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IMPLEMENTING SAFE BY DESIGN IN PRODUCT DEVELOPMENT THROUGH COMBINING RISK ASSESSMENT AND LIFE CYCLE ASSESSMENT

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November, 2021

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This research was funded by the Dutch Ministry of Infrastructure and Water Management (IenW). The Ministry is neither responsible nor liable for the content of this document.

Acknowledgements: We gratefully acknowledge the inputs of Willie Peijnenburg (CML, RIVM), Martina Vijver (CML), Carlos Blanco Rocha (CML) , Stefano Cucurachi (CML) and Bart Walhout (RIVM) to earlier versions of this deliverable.

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Publieksamenvatting

Als antwoord op de milieuvraagstukken van deze tijd, worden in hoog tempo nieuwe materialen en producten ontwikkeld om bij te dragen aan duurzaamheid. Het Safe by Design-concept richt zich op het waarborgen van een veilig gebruik van chemicaliën die een rol spelen in het materiaal- en productontwerp. Safe by Design wordt beschouwd als een veelbelovende aanpak om de ecologische en menselijke gezondheidsrisico's van producten gedurende hun levenscyclus te verminderen en doet een beroep op de verantwoordelijkheid van ontwerpers van materialen en producten om al in een vroeg stadium rekening te houden met deze risico's. De gecombineerde toepassing van een risicoanalyse van de gebruikte chemische stoffen en een levenscyclusanalyse van producten wordt veelal gezien als een waardevolle invulling van Safe by Design. Echter, praktische methoden die gebruik maken van een gecombineerde risico- en levenscyclusanalyse waarbij hele nieuwe chemicaliën of materialen toegepast worden, ontbreken nog grotendeels. In dit project hebben we voorbeelden uit de literatuur opgespoord die risico- en levenscyclusanalyse combineren bij het evalueren van de risico's van nieuwe materialen en producten. We hebben uiteindelijk tien studies gevonden die risico- en levenscyclusanalyse combineren in een productontwikkelingscontext. Deze hebben we beoordeeld op basis van een aantal criteria waarbij we het volgende te weten wilden komen:
1) Welke benaderingen en methoden zijn er op dit gebied momenteel beschikbaar voor ontwerpers? 2) Wat kunnen ontwerpers momenteel bewerkstelligen met deze methoden en benaderingen? en 3) Welke hiaten en uitdagingen moeten nog worden aangepakt zodat deze methoden ontwerpers beter kunnen faciliteren?

Onze bevindingen laten zien dat productontwerpers al in een vroeg stadium van het ontwerpproces een aantal relatief eenvoudige checks kunnen doen. Zo kunnen ze levenscyclus-denken toepassen en lijsten met bekende gevaarlijke stoffen raadplegen om mogelijke bronnen van risico's in hun ontwerp te ontdekken. Indien nodig, kunnen ze dan op zoek gaan naar veilige alternatieven voor gevaarlijke chemicaliën. Het toepassen van deze vereenvoudigde benaderingen en richtlijnen kan een volwaardige risico- of levenscyclusanalyse weliswaar niet vervangen, maar het kan helpen om enkele voor de hand liggende bronnen van risico's te vermijden. Ontwerpers kunnen ook met experts op het terrein van risico- en levenscyclusanalyse samenwerken om zodoende een completere evaluatie van het ontwerp te maken om gezondheidsrisico's over de gehele levenscyclus van het product op te sporen. Voorbeelden hiervan zijn echter nog schaars. Om deze situatie te verbeteren zou er meer ervaring opgedaan moeten worden met Safe by Design door voorbeeldstudies uit te voeren. Hierbij zouden deze methoden moeten worden toegepast in de context van een concreet productontwerp. Om de drempel voor toepassing van de methoden te verlagen, zouden tools en databases moeten worden ontwikkeld vanuit het perspectief van productontwerpers. Dit vergt een intensieve samenwerking tussen ontwerpers, onderzoekers op het terrein van risico- en levenscyclusanalyse en bedrijven.

List of Abreviations

AF: Assessment Factor

BMD: Benchmark Dose

CB: Control Banding

DMEL: Derived Minimal Effect level

DNEL: Derived No-Effect Level

ECHA: European Chemicals Agency

EEA: European Environmental Agency

EHS: Environmental Health and Safety

ERA: Ecological Risk Assessment

EU: European Union

GSD: Goal and Scope Definition

HHRA: Human Health Risk Assessment

IenW: Infrastructuur en Waterstaat

ISO: International Standards Organisation

LC: Life Cycle

LCA: Life Cycle Assessment

LCI: Life Cycle Inventory

LCIA: Life Cycle Impact Assessment

LCRA: Life Cycle Risk Assessment

NOAEL: No Observed Adverse Effect Level

OECD: Organisation for Economic Co-operation and Development

PEC: Predicted Environmental Concentrations

PHRA: Public Health Risk Assessment

PNEC: Predicted No Effect Concentration

RA: Risk Assessment

REACH: Registration, Evaluation, Authorisation and Restriction of Chemicals

SbD: Safe by Design

SME: Small and Medium Enterprise

SRA: Society of Risk Analysis

SSbD: Safe and Sustainable by Design

TRL: Technological Readiness Level

ZZS: Zeer Zorgwekkende Stoffen

1.Introduction

There is significant commitment to transform the EU economy to become resource efficient, climate neutral and less polluting. This is evident with recent initiatives like the European Green Deal (COM/2019/640), the European Commission's new Action Plan for a Circular Economy (COM/2020/98), the new European Industrial Strategy and the Chemicals Strategy for Sustainability (COM/2020/667). Several emerging technologies and products (including materials and chemicals) are considered promising toward supporting this transition. While it is challenging to evaluate the environmental risk and impacts in advance of products that are not yet produced commercially, there is greater flexibility and lower cost for design modification at earlier stages of product development (Collingridge, 1982). Systematic evaluation of ecological and human health risks during early product development can also facilitate risk governance and enhance regulatory preparedness as novel products approach commercial production (OECD, 2021a; Isigonis et al., 2019) as well as give opportunities to choose consciously where the safety responsibility is situated in the design process (Van de Poel and Robaey, 2017).

Safe by Design (SbD) is considered a viable approach to mitigate the ecological and human health risks of products through their lifecycle thereby enabling the sustainable transition envisioned in recent policy commitments. Based on the review of SbD research in the context of nano-enabled products in EU Horizon 2020 projects, the Organisation for Economic Co-operation and Development (OECD) defines SbD as: "The SbD (Safe-by-Design, Safer-by-Design, or Safety-by-Design) concept refers to identifying the risks and uncertainties concerning humans and the environment at an early phase of the innovation process so as to minimize uncertainties, potential hazard(s) and/or exposure. The SbD approach addresses the safety of the material/product and associated processes through the whole life cycle: from the Research and Development phase to production, use, recycling and disposal." (OECD, 2021a). Köhler and Som (2013) note that while product development teams have established processes to handle some types of risks (e.g., technical and electrical safety, fire hazards, biocompatibility), this is not the case for ecological and human health risks of novel products. There is a need to create SbD guidance and methods for product development teams to assess and mitigate such risks.

The above definition of SbD implies the value of risk assessment (RA) based approaches throughout a product's life cycle (also known as Life Cycle Risk Assessment (LCRA)) to ensure safety of products. It has been extensively argued that joint application of RA and Life Cycle Assessment (LCA) can provide a comprehensive assessment of risks and impacts during early product development (Guinée et al., 2017; Subramanian et al., 2016; Shatkin et al., 2008). Various configurations of using these methods in combination have been reviewed (Grieger et al., 2012; Guinée et al., 2017; Harder et al., 2015; Kobayashi et al., 2015), while Linkov et al. (2017) and Guinée et al (2017) remind us that conceptual differences between the RA and LCA do not permit a complete integration of the two methods. Nonetheless data interpretation of both quantitative methods can support transparent decision making. RA has been adapted to low Technological Readiness Level (TRL) in so-called screening RA approaches that are less specific and with lower data needs (see Isigonis et al. (2019) for a review of approaches for nanomaterials). Ex-ante LCA is an adaptation of LCA using diverse data sources that scale-up an emerging technology using likely scenarios of future performance at full operational scale and comparing them with incumbent technology at the same point in time (Cucurachi et al., 2018).

These adaptations of RA and LCA can steer product development towards lower risks and environmental impacts.

The aim of this review is to synthesize literature (conceptual approaches, methods, data) on how ex-ante LCA and screening RA have been jointly used for technological systems design, with the goal of supporting SbD design teams (product designers, materials scientists, chemists). Hence, the focus is explicitly on the low TRLs (1-6) of a technology or product, starting from basic concept (TRL 1-4) to laboratory scale (TRL 5-6). Performing RA and LCA at higher TRLs departs from the scope of SbD and product design teams typically do not have the expertise to apply these more advanced methods. This review thus focusses on the state-of-the-art of these methods at low TRL, and what gaps need to be addressed to improve rigor and relevance for supporting design teams. Specifically, we seek to answer these questions:

a) What approaches and methods for combining RA and LCA at TRL 1-6 can designers currently use?
b) What is the scope and quality of what designers can currently accomplish with these methods and approaches?
c) What gaps and challenges remain to be addressed to facilitate RA and LCA application by product design teams?

This review paper is organized as follows. Section 2 provides a background on the RA and LCA processes, including their adaptations at low TRL, and what combinations are relevant to SbD. Section 3 describes the method used to conduct the review, including search strategy and review criteria. Section 4 presents the key findings of the review, and Section 5 extrapolates our findings to implications for SbD practice. Section 6 summarizes the key conclusions from the review.

2.Background on LCA and RA and their Combination

2.1 Risk Assessment

RA has been defined as “the quantitative and qualitative evaluation of the risk posed to human health and/or the environment by the actual or potential presence of an exposure to particular pollutants” (UN, 1997). Chemical RA for regulatory purposes uses two assessments: Ecological Risk Assessment (ERA, assessment of risk to species in ecosystems of interest) and Human Health Risk Assessment (HHRA, assessment of risk to workers, consumers and general public). The RA process is shown in Figure 1 which will be elucidated in the subsequent paragraphs.

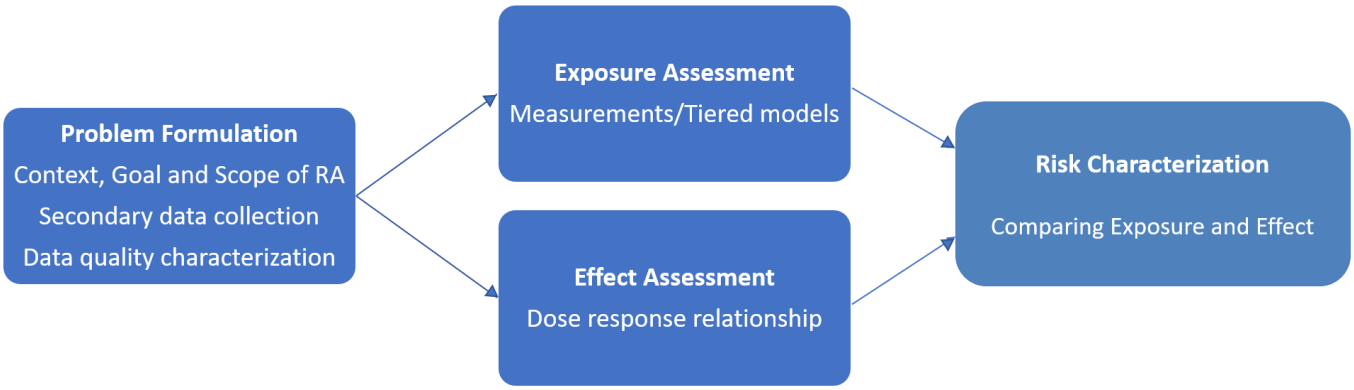

Figure 1 Phases of RA

(Adapted from ECHA (2015a))

2.1.1 Problem Formulation

The problem formulation phase establishes the goal and scope of the RA by identifying potential risks in an environmental or human health context. Factors like representation of the taxonomic diversity, ecotoxicological endpoints, spatial and temporal scales, and exposure routes are considered for ERA (Traas and van Leeuwen, 1995). All of these factors contribute to a conceptual model of stressors and observed effects in an ecosystem (Norton et al., 1992). Problem formulation for HHRA is referred to as "hazard identification" and involves data collection on physicochemical properties and toxicological effects of the chemical" (European Chemicals Agency (ECHA) ,2015a).

While *in vivo* data are typically used to make regulatory decisions on chemicals, data from *in vitro* assays and *in silico* methods such as Quantitative Structure Activity Relationships (OECD Report, 2007), grouping and justified read across (ECHA, 2015b) offer clues on potential risks. The REACH Annex XI recommends a Weight of Evidence approach (Weed, 2005) to integrate expert judgement and available data (ECHA, 2010) in situations with insufficient knowledge and data. Alternatives assessment can also be used by product design teams to comprehensively assess chemicals used for specific functional properties in terms of toxicological, economic and technical criteria (OECD, 2021b; OECD, 2013).

Data quality is another key concern, and its characterization can guide further data collection and evaluation. The Klimisch score is most commonly used to evaluate the quality of data in RA based upon relevance, reliability and adequacy (Klimisch et al., 1997). Other information criteria frameworks include OECD Guidance Document 34 (OECD Report, 2005) and European Centre for the Validation of Alternative Methods criteria for a pre-validation study and for assessment of test validity (Worth et al, 2004). The Society of Risk Analysis (SRA) has a Risk Analysis Quality test with a battery of questions to assess if RA is framed and designed and will be eventually useful for risk management decision making (SRA Working Group, 2021).

2.1.2 Effect Assessment

The goal of the effect assessment phase is characterization of the relationship between the chemical dose and the incidence of adverse effects in the exposed ecological or human targets (Van Leeuwen, 1995). Generally, this phase involves choosing a dose descriptor from dose response relationships for relevant endpoints, and applying assessment factors (AFs) to account for uncertainties.

For ERA, effect assessment involves the determination of the Predicted No Effect Concentration (PNEC) for an environmental compartment (e.g., aquatic, terrestrial, sewage treatment) during long-term and/or short-term exposure. In low data availability situations (e.g. at low TRL), PNEC is assessed by applying AFs to the ecotoxicological endpoint concentration of the most sensitive organism within the environmental compartment (Traas and van Leeuwen, 1995). AFs in ERA are based on uncertainties in intra- and inter-laboratory variation of ecotoxicity data, intra- and inter-species variations, short-term to long-term toxicity extrapolation, and laboratory data to field impact extrapolation (ECHA, 2008).

Effect assessment for HHRA involves the determination of the Derived No-Effect Level (DNEL) for threshold effects and the Derived Minimal Effect level (DMEL) for non-threshold effects (e.g., carcinogens). DNEL and DMEL are derived for each exposed population (workers, consumers, general population) exposure route (inhalation, oral and dermal), and expected exposure duration (acute, sub-chronic, chronic). Determination of the DNEL begins with establishing a point of departure on the dose response curve (e.g., the no observed adverse effect level (NOAEL) (Vermeire et al., 1995). Subsequently, HHRA AFs are applied to account for intra-species (exposure to workers, sensitive sub-populations) and inter-species (metabolic rate and other factors) variation, nature and severity of the effect, duration of exposure, uncertainty in chosen dose descriptor (e.g., NOAEL versus (true) no adverse effect level), data quality and high to low dose extrapolation (ECHA, 2012a; 2012b). DMEL is derived using an exposure level that represents a risk level of very low concern (usually set in the order of 10^{-5} and 10^{-6}) (Vermeire et al., 1995), and is based on policy prescription (e.g., As Low as Reasonably Achievable, Best Available Technology, etc.) or on high to low dose extrapolation.

At low TRLs the most appropriate endpoints and dose ranges may not be known, but (eco)toxicological assays on a broad range of endpoints may provide useful insights on relevant endpoints and dose ranges. Another dose descriptor that can be used in the case of poor mechanistic understanding or data quality is the Benchmark Dose (BMD), which corresponds to a measurable effect size. Uncertainty in dose response relationships can also be quantified in the BMD approach using the lower and upper limits of the BMD (EFSA, 2009).

2.1.3 Exposure Assessment

In the third phase of exposure assessment, the intensity, frequency and duration of the ecological or human exposure to the chemical is measured or estimated. Precise and comprehensive measurement of exposure in actual contexts, while ideal, is expensive and hence a tiered approach is recommended. Exposure assessment within ERA assesses Predicted Environmental Concentrations (PEC) using actual measurements in environmental matrices or using multimedia

fate models simulating release and transfer processes (Van de Meent and de Bruijn,1995). Simplified estimates in the case of novel chemicals/materials may be obtained using mass-balance models (Mueller and Nowack, 2008; Gottschalk et al., 2009; O'Brien and Cummins, 2010).

HHRA exposure assessment involves the determination of exposure levels for relevant routes of exposure (e.g., inhalation, dermal, oral) depending on exposure scenarios. Many lower tier tools currently available for exposure assessment follow a control banding (CB) approach, which involves a qualitative hazard and exposure assessment, and matches a set of control measures to a range or "bands" of hazards and exposures (Brower, 2012). Higher tier exposure assessment tools follow a source-receptor approach, where chemical emission sources are linked to identified receptors. Examples include the Near Field/Far Field model (Cherrie, 1999), ConsExpo (Delmaar et al., 2006) and the Advanced REACH tool (Fransman et al., 2011).

2.1.4 Risk Characterization

In the risk characterization phase, the results of the exposure and effect assessments are compared (Van Leeuwen,1995). Risk characterization for ERA involves the comparison of PEC and PNEC, for HHRA exposure and DNEL, and for Public Health Risk Assessment (PHRA) PEC is compared to DNEL. Risk is considered acceptable when exposure is lower than the no-effect threshold (Van Leeuwen, 1995).

2.2 Life cycle thinking and Life Cycle Assessment

Life cycle thinking (LCT) implies the assessment of the whole life cycle of a technology system according to several environmental criteria, in order to pinpoint hotspots and avoid burden shifting across life cycle stages, impact categories and regions (Pennington et al. 2007). LCA is the operationalization of LCT into a consistent method, and can guide product development towards lower resource intensity, toxicity and other environmental impacts. The ISO 14040-44 series of standards (ISO, 2015a-d) delineates LCA into four phases shown in Figure 2.

Many forward looking LCAs have been defined, and sometimes these terms are used interchangeably. In this paper, we focus on ex-ante LCA which compares the future, upscaled version of a technology and its incumbent at that point in time (Cucurachi et al., 2018). Ex-ante LCA follows the same phases and steps as LCA but implementation of the steps comes with some additional challenges which have been identified by several authors (Van der Giesen et al, 2020; Arvidsson et al., 2018). Below, we briefly summarize the key characteristics of each phase and the main challenges of each phase for ex ante LCA.

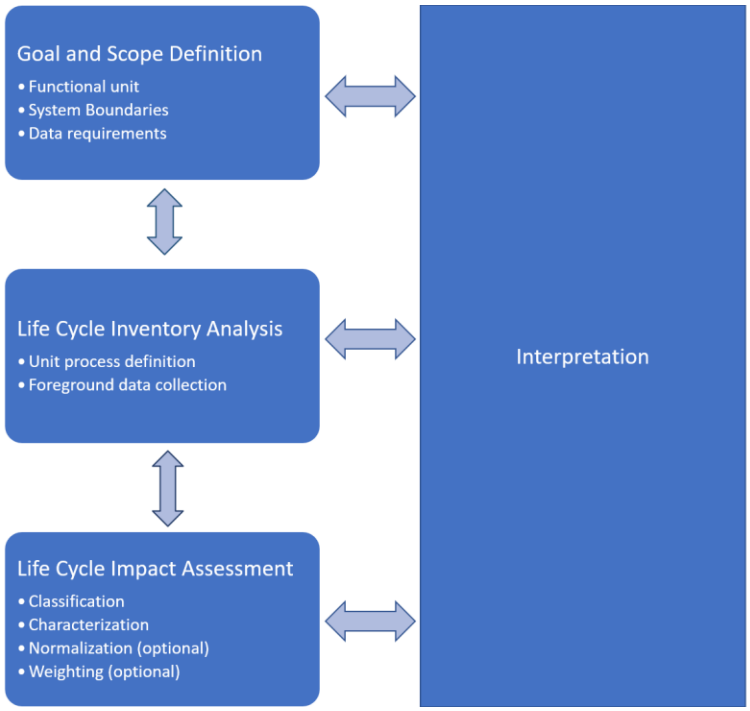

Figure 2 Phases of LCA (Adapted from ISO 14041)

2.2.1 Goal and Scope Definition

Goal and Scope Definition (GSD) sets up the framework for the study can be refined through product design. The goal of an LCA study addresses the intended application, the reasons for performing the study and target users (Heijungs and Guinee, 2012). In defining the scope, this description is extended to the functional unit, system boundaries and data requirements. The functional unit is the operationalization of functional performance of the product system (indicating the focus on the entire life cycle of a product and not just the product itself). System boundaries determine which unit processes (component processes within a product system) shall be included within the study. Data requirements broadly specify the data needed, including temporal aspects, geographical aspects, technology coverage and level of detail, and data completeness and representativeness (ISO 14040, 2015a). This phase of LCA requires the greatest input from the product design team, especially on technical and market assessment aspects. Van der Giesen et al. (2020) specify the additional questions that ex ante LCA must address in this phase: 1. At what moment in time is the new technology to be expected to be operational at which level of maturity? 2. How does the functional unit need to be defined so that the new and the incumbent technology provides the same (similar) functionality? 3. What is the incumbent technology (if available)?

2.2.2 Life Cycle Inventory Analysis

This phase involves the collection, compilation and quantification of inputs and outputs (the so called Life Cycle Inventory (LCI)) for a product throughout its life cycle (Heijungs and Guinee, 2012; ISO 14040, 2006). A unit process is the smallest element considered in the life cycle

inventory analysis for which input and output data can be collected and quantified (Heijungs and Guinee, 2012). Input data include material, energy and resource consumption information, and output data may include intermediate product flows, waste and emission (air, water and soil) data. Ex-ante LCA challenges for this phase concern the technical and market performance of the technology and its (incumbent) alternative at a given time in the future (Van der Giesen et al., 2020). Data needed to model the product lifecycle can be foreground data (specific data collected by LCA practitioner) and background data (data from the LCI databases to model the context). The hierarchy of data collection strategies to obtain foreground data for ex ante LCA have been described (Pavatkar and Eckelman, 2009), but updating the background data to a future stage remains a challenge.

2.2.3 Life Cycle Impact Assessment

Life Cycle Impact Assessment (LCIA) aims at assessing the magnitude of the potential environmental impacts for a product system by transforming LCI results to contributions to midpoint and endpoint impact categories. The key steps in this phase include classification, characterization, normalization and weighting. Classification involves the grouping of LCI results to midpoint or endpoint impact categories (Heijungs and Guinee, 2012). Impact categories represent environmental issues of concern to which LCI results are assigned, e.g., climate change, loss of biodiversity (Guinée et al., 2002). Impact categories can be defined early on or at a later point of an impact pathway. For example, climate change involves a long pathway of causal mechanisms including emissions of greenhouse gases → changes in the composition of the atmosphere → changes in the radiation balance → changes in the temperature distribution → changes in climate → etc. Midpoint impact categories focus at an early point of this pathway, e.g. ozone depletion, greenhouse effect, while endpoint impact categories focus at the final points of this pathway, e.g. resource depletion, ecological health impact, human health impact. Classification is followed by characterization, which is the calculation of midpoint or endpoint results for different impact categories. LCI results are multiplied with a multiplier for contribution of each unit mass toward the impact category. Normalization and Weighting are considered optional steps (ISO 14040, 2015). The challenges for ex ante LCA for LCIA include accounting for novel impacts and missing characterization factors (Van der Giesen et al., 2020), the latter being a significant factor for toxicity related impact assessment.

2.2.4 Interpretation

In the interpretation phase, the GSD, LCI and LCIA results are evaluated with respect to the initial goal and scope of the analysis. Contribution analysis, a presentation of impacts or processes in terms of their percentage contribution, may be useful to identify hotspots. While uncertainty analysis and explorative scenarios are helpful to eliminate some sources of uncertainty, new technology systems and their future projections are particularly challenging in this regard because it is inherently tedious to quantify uncertainties of such future projections (Van der Giesen et al., 2020).

2.3 Combining and integrating RA and LCA

Combining RA and LCA can provide methods to operationalize SbD. There are several reviews on the topic of combining LCA and RA (Grieger et al., 2012; Guinee et al., 2017; Harder et al., 2015; Kobayashi et al., 2015). Guinée et al. (2017) distinguish four schools for combining and integrating RA and LCA: 1) Knowledge integration (adopting specific elements of knowledge from RA into the impact assessment phase of LCA, e.g., in defining characterization factors for human and ecotoxicological impacts); 2) Chain perspective (looking at chemical risks through the product life cycle) or what is known as LCRA; 3) RA for LCA-hotspots (performing a full LCA and doing an RA only for risk hotspots identified therein); 4) Combining results (combine the results of RA and LCA, rather than combining or integrating parts of the analytical methods themselves as in 1-3). The relevant ways of combining LCA and RA for SbD include LCRA (School 2) and combining the results of independent application of RA and LCA (School 4).

It is worthwhile to reiterate that there is a fundamental constraint that prohibits a full integration of the methods. It is beyond the scope of this review to explore in depth, but Guinee et al. (2017) do this with the example of nanosilver socks. Briefly put, LCA has a global, relative and mass flow based perspective whereas RA has a highly contextual, threshold and concentration based perspective. By combing these methods, researchers avoid problem shifting across life cycle/risk receptors/geographical boundaries and make transparent trade-offs.

With this background, we move forward with describing the methods for literature search and review (Section 3) and findings (Section 4) of the review, and how they serve the goals of SbD in practice (Section 5).

3.Methods

The literature search followed a three-tiered keyword strategy to explore literature on Web of Science and Google Scholar databases. First, we sought to identify papers that combine LCA and RA in prospective mode. Next, we focused more broadly upon the papers actually combining risk assessment and life cycle assessment. As a final check for relevant methodological approaches, papers in ex ante LCA and screening RA were identified. No publication year or geographical delimiters were used. Figure 3 shows the keywords used for the search.

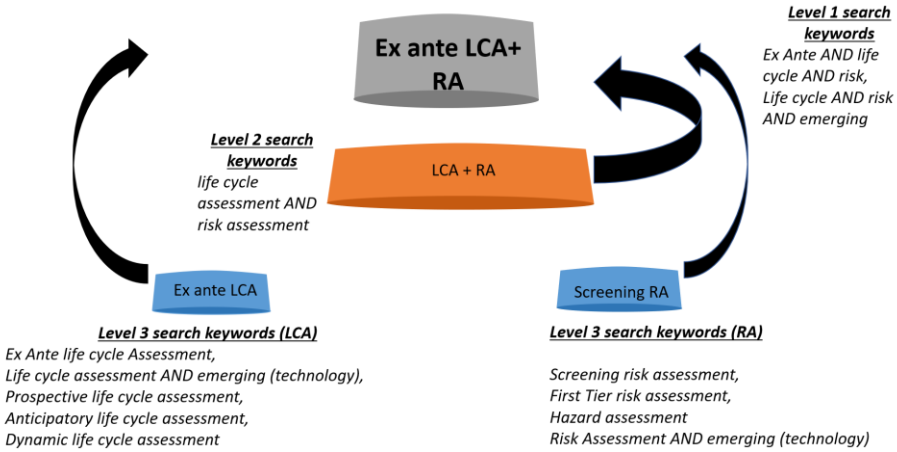

Figure 3: Keywords used for search strategy

The review followed the following process. First, the abstracts were screened manually and 255 papers were extracted. Next, the core number of papers was reduced to 35 papers, which combined RA and LCA (Appendix 1). In a following evaluation step, papers were reduced to ten most relevant papers at TRL 1-6 and described using relevant criteria (Table 1).

Table 1 Criteria to describe literature combining RA and LCA at TRL 1-6

Criteria	**Description**
TRL	Scope of this review is the concept (1-4) and laboratory scale (4-6). Definitions from Da Costa et al. (2019) for Concept proven and initial process chemistry[1] is followed for TRL 1-4 and Lab Scale/Advanced process chemistry and Design[2] is followed for TRL 5-6.
Application Domain	What field of applied research (e.g., bio- or nanotechnology) is the product development context in?
SbD focus	Does the paper focus on the assessment of hazard, exposure or risk?
Type of Risk	Does the paper focus on ERA/HHRA/PHRA?

[1] The idea of a new synthesis route for a chemical is determined by brainstorming of possible alternatives. The reaction is proven in the laboratory, the stoichiometry is gathered, and a rough estimation of the required technology is generated. Small amounts of purified product are obtained and data on the main reaction(s) is collected in laboratory experiments

[2] Synthesis route is defined, and the entire production process is designed at a theoretical, commercial-scale level including main reaction and separation steps. The mass and energy balance of the production process including information on process stream composition, pressure and temperature can be obtained.

LC approach	What elements of LC are present in the study?
Technology system	Does the paper focus on risk of a chemical/material, product or process?
System boundaries	What life cycle stages does the paper focus on?

TRL: Technology Readiness Level SbD: Safe by Design ERA: Ecological Risk Assessment HHRA: Human Health Risk Assessment PHRA: Public Health Risk Assessment LC: Life Cycle LCA: Life Cycle Assessment

4.Results

The papers chosen for detailed review are described as per criteria (Table 1) in Table 2. Ten papers were found in TRL 1-4 and two papers were found in TRL 5-6, with Da Costa et al (2019) and Tan et al. (2019) including in both classes. Papers (column 2) are classified as per review criteria described in Table 1. Brief Description (column 3) provides a concise explanation of the main focus of the paper. More information can be found in Appendix 2. Advantages (column 10) and Disadvantages (column 11) describe the ease of application of the approach by a product design team.

Table 2 Classification of literature based on the pre-selected criteria

TRL	Paper	Application Domain	Brief Description	SbD Approach	Type of Risk	LC approach	Technology system	System boundary	Product development context	
									Advantage	Disadvantage
1 -4	Askham, et al. (2013)	Chemistry	Hazard and exposure indicators of coating ingredients using REACH risk phrases[3]	Hazard	HHRA	Risk metrics integrating with LCI	Product	Production	Simple	Not applicable to novel chemicals, no standar-dized information source for risk phrases Risk phrases are obsolete [4]
	Korevaar et al. (2019)	Nanotechnology	Decision tree for applying ex ante LCA with recommending green chemistry indicators for early stages	Hazard	HHRA	Ex-ante LCA	Product	Cradle to grave	Simple	Not applicable to novel chemicals
	Fernandez-Dacosta et al. [5](2019)	Biotechnology	Review of toxicity and environmental impact metrics for lactic acid production at various TRLs	Hazard	HHRA	LCT	Product	Production	Simple	Not applicable to novel chemicals
	Wardak, A., et al. (2008)	Nanotechnology	Expert elicitation based CB of nano-enabled	Risk	HHRA	LCT	Product	Use-Disposal	Simple	Laborious for design teams Variable expert input

[3] R-phrases are short phrases that describe the hazard level of the substance on a mass basis

[4] They have been replaced by hazard statements in Classification, Labelling and Packing

[5] This review provides methods at each TRL

TRL	Paper	Application Domain	Brief Description	SbD Approach	Type of Risk	LC approach	Technology system	System boundary	Product development context	
									Advantage	Disadvantage
			products in the market							
	Van Harmelen et al.(2016)	Nanotechnology	Screening tool for product development based on LCA and RA tools	Risk	ERA, HHRA, PHRA	LCT [6]	Material	Cradle to grave	Comprehensive risk and impact metrics	Time consuming
	Som, C., et al. (2010)	Nanotechnology	Smart textile case study illustrating application of LCT to gene-rate risk hotspots	Risk	ERA, HHRA	LCT	Material	Cradle to grave	Simple	Qualitative
	Sweet and Strohm (2006)	Nanotechnology	State of art on nanomaterial risk and discusses application of LCT	Risk	ERA, HHRA	LCT	Material	Cradle to grave	Simple	Qualitative
	Shatkin and B. Kim (2015)	Nanotechnology	Expert judgement on hazard and exposure criteria + a toxicology gap analysis of safety data sheets for cellulose	Risk	ERA, HHRA	LCT	Material	Cradle to grave	Systematic Prioritizes data gaps	Labor intensive

[6] Relative comparisons between novel product and incumbent technology.

TRL	Paper	Application Domain	Brief Description	SbD Approach	Type of Risk	LC approach	Technology system	System boundary	Product development context	
									Advantage	Disadvantage
			nanomaterials							
	Tan et al. [7](2018)	Nanotechnology	Ingredients in cellulose nanocrystal foam are scanned against substances identified in 15 environmental regulations	Hazard	HHRA	Ex ante LCA	Product	Production	Addressed hazard at product level	Not applicable to novel chemicals
	Kralisch [8](2013)	Biotechnology	Ex-ante LCA for biodiesel production at lab scale with Hazard based metrics applied	Hazard	ERA, HHRA	Ex ante LCA	Process	Cradle to grave	Simple	Not applicable to novel chemicals
5 - 6	Fernandez-Dacosta et al. (2019)	Biotechnology	Review of toxicity and environmental impact metrics for lactic acid production at various TRLs	Hazard	HHRA	LCT, Ex ante LCA	Product	Production	Simple	Not applicable to novel chemicals

[7] One strategy described in this study (block list scan) is at TRL 1-4 while another (in vivo assay) is at TRL 5-6

[8] The ex ante LCA used in this study is at TRL 5-6 but RA is at TRL 1-4

TRL	Paper	Application Domain	Brief Description	SbD Approach	Type of Risk	LC approach	Technology system	System boundary	Product development context	
									Advantage	**Disadvantage**
	Tan et al. (2018)	Nanotechnology	*In vivo* assay of product samples with zebrafish embryos (*Danio rerio*) and waterfleas (*Daphnia magna*)	Hazard	ERA	Ex ante LCA	Product	Production	Applicable to novel products	Toxicological expertise needed

TRL: Technology Readiness Level SbD: Safe by Design ERA: Ecological Risk Assessment HHRA: Human Health Risk Assessment PHRA: Public Health Risk Assessment LC: Life Cycle LCT: Life Cycle Thinking. It should be noted that LCT stands for all types of Life Cycle Thinking including LCA CB: Control Banding

Seven papers were classified as belonging to the domain of nanotechnology, two as biotechnology and one as chemistry. The larger proportion of papers in nanotechnology can be attributed to the substantial work combining RA and LCA in this application domain.

There are five hazard-based approaches and five-risk based approaches. No exposure-based approaches were found, though exposure was included in risk-based approaches. Ten papers focus on HHRA, five papers focus on ERA and one paper focusses on PHRA.

Hazard-based approaches at TRL 1-6 are applying green chemistry metrics or checking against (eco)toxicity of chemicals identified in existing chemical regulations. Korevaar et al. (2019) use green chemistry indicators recommended by Anastas and Eghbali (2009) to assess consumption of solvent, electricity, heat and emissions of pollutants and wastes. Kralisch et al. (2013) uses the Environmental Health and Safety (EHS) tool described by Koller et al. (1999) to estimate risks of specific volumes of chemicals. Existing chemical regulations regularly publish lists of chemicals of potential or known (eco)toxicity, as illustrated by Tan et al. (2018) in their use of a "block list" scan, and by Askham et al. (2013) in their use of REACH risk phrases. The "block" list approach of Tan et al. (2018) based on the Dutch list of "Zeer Zorgwekkende Stoffen" (ZZS)[9] is particularly a good start for product design teams to check product constituents. While the Askham et al. (2013) approach of comparing product ingredients with REACH risk phrase (now called hazard phrase) concentration limits is useful, this information is not collated.

Novel chemicals whose hazard is not well characterized cannot be assessed through hazard-based approaches at TRL 1-6, but this may be possible through the approach of Tan et al. (2018) which describes an *in vivo* assay with zebrafish embryos (*Danio rerio*) and waterfleas (*Daphnia magna*) to assess ecotoxicity when product samples can be produced. While in principle such assays can provide a dose descriptor that can provide an indication of potential (eco)toxicity especially by comparing with similar chemicals, contextual features needed for a full risk assessment (i.e., ecosystem aspects in ecotoxicology) are missing.

Among risk based approaches, LCT approaches look at risks over a product's life cycle (see 3.2). Methods used include literature review (Som et al., 2016; Sweet and Strohm, 2006) for understanding risks of products through the life cycle and CB (Shatkin and Kim, 2015; Wardak et al., 2008; Van Harmelen et al., 2016). Som et al. (2016) and Sweet and Strohm (2006) present guidelines and case studies that guide the application of LCT to a nano-enabled product to gain insights on potential hotspots, and can be easily applied by product design teams. An important contribution of their approach is to use state-of-the art information on hazard, fate and transport, exposure, existing regulation, etc. to identify sources of risk. Van Harmelen et al. (2016) present the software program LICARA nanoSCAN, a product development tool that uses CB based tools such as Stoffenmanager (Van Duuren-Stuurman, et al., 2011), Precautionary matrix (Höck et al., 2013) and Nanoriskcat (Hansen et al, 2011) for RA. While the LICARA nanoSCAN is simplified to enable use by SMEs, product design teams are commonly unfamiliar with RA and LCA and may need additional guidance to use it. Expert elicitation can also play an important role in filling knowledge gaps at low TRL, as demonstrated by Wardak et al. (2008) and Shatkin and Kim (2015), but few product development teams may have the technical and facilitation expertise to employ these methods.

[9] The ZZS list includes the most dangerous substances for the environment and human beings.

In terms of LCT/LCA used in the literature examined, six papers are based on LCT (i.e., LCRA), and four papers include ex ante LCA combined with RA. LICARA nanoSCAN presents a qualitative comparison of novel product with its incumbent on impacts (e.g., energy consumption, materials consumption, water use, waste generation) for each lifecycle stage. Ex ante LCA is applied from TRL 4 onward.

In terms of technology systems, five papers focus at the product level, four at the material level and one at the process level. The difference between chemical and product lifecycle is important in LCRA. The product lifecycle includes the life cycle of all the product constituents whereas a chemical lifecycle includes the lifecycle of a particular chemical of interest as it is included in the manufacturing, use and end of life of a product. Except for Tan et al. (2018), the four nanotechnology papers are interested only in the risks of the nanomaterials within the product. Six papers focus on the cradle to grave life cycle, three focus on the production phase and one focuses on the use-disposal phases only.

5. Discussion

While the concept of SbD has been receiving increasing attention over the past years, clear methodological guidance by product design teams is missing.

This review contributes to the recent interest in implementing SbD (Peijnenburg et al., 2021; Gottardo et al., 2020) by examining how RA and LCA have been combined in the product development context at TRL 1-6. Some useful examples of combining RA and LCA in the reviewed literature include:

- Van Harmelen et al. (2016) combining RA and LCA comprehensively at low TRL;
- Tan et al. (2018) presenting a two-step hazard screening at product level and combining it with ex ante LCA;
- Kralisch et al. (2013) using ex ante LCA for process design;
- Shatkin and Kim (2015) using expert elicitation effectively for prioritization of data gaps.

However, except for Van Harmelen et al. (2016) and Tan et al. (2018), the papers usually focus more on one of the methods (RA or LCA) and the full possibilities of combining them are not exploited. These two publications are also among the most novel of the approaches reviewed. In the LICARA nanoSCAN tool, the novel features include translating LC impacts into relative comparisons between novel product and its market alternative and combining LCA and RA into a product development decision matrix. Tan et al. (2018) use a two-step hazard screening process including a “block list” to remove or substitute chemicals on the regulatory radar, followed by toxicological screening of product samples.

We present the findings for each research question in the sub-sections below.

5.1 Research Question 1: What approaches and methods for combining RA and LCA at TRL 1-6 can designers currently use?

Hazard based approaches (Askham et al., 2013; Fernandez Dacosta et al., 2019; Kralisch et al., 2013; Tan et al., 2018) can guide product design teams to avoid or minimize concentrations of known or suspected hazardous substances. LCT (Som et al., 2010; Sweet and Strohm, 2006) can be used by product design teams to identify risk hotspots. Simple

indicators such as those by Anastas and Eghbali (2009) for consumption of solvent, electricity, heat and emissions of pollutants and wastes can also be directly applied by product design teams.

Even as many methods found in our review are highly simplified adaptations of RA and LCA, product design teams may still lack expertise to apply them. The application of the LICARA nanoSCAN has been reported to be challenging for SMEs (Van Harmelen et al., 2016) due to lack of experience in RA and LCA. Expert elicitation is a laborious process, and conducting a robust expert elicitation process and resolving inconsistent findings (e.g. Wardak et al., 2008; Shatkin and Kim, 2008) requires training that product design teams may not possess. Assessment and prioritization of gaps (e.g., Shatkin and Kim, 2008) requires technical RA expertise that product design teams in small companies do not possess. Predictive toxicology using in-vitro and in vivo methods (Tan et al., 2018) also need to be performed by (eco)toxicologists while also being laborious and costly.

In summary, product design teams can minimize hazards and apply LCT on their own, but they need to collaborate with RA/LCA experts or professionals trained in expert elicitation to apply other methods. Figure 4 shows the role for RA and LCA at various TRLs based on this review and our knowledge and experience from other projects not (yet) published or at TRLs outside the scope of this review. Weight of Evidence, Grouping/Read Across and uncertainty estimation have been mentioned in Section 2 as being predecessors to regulatory RA, but they are out of the scope of this review due to lacking LCT and being relevant at laboratory to pilot scale range.

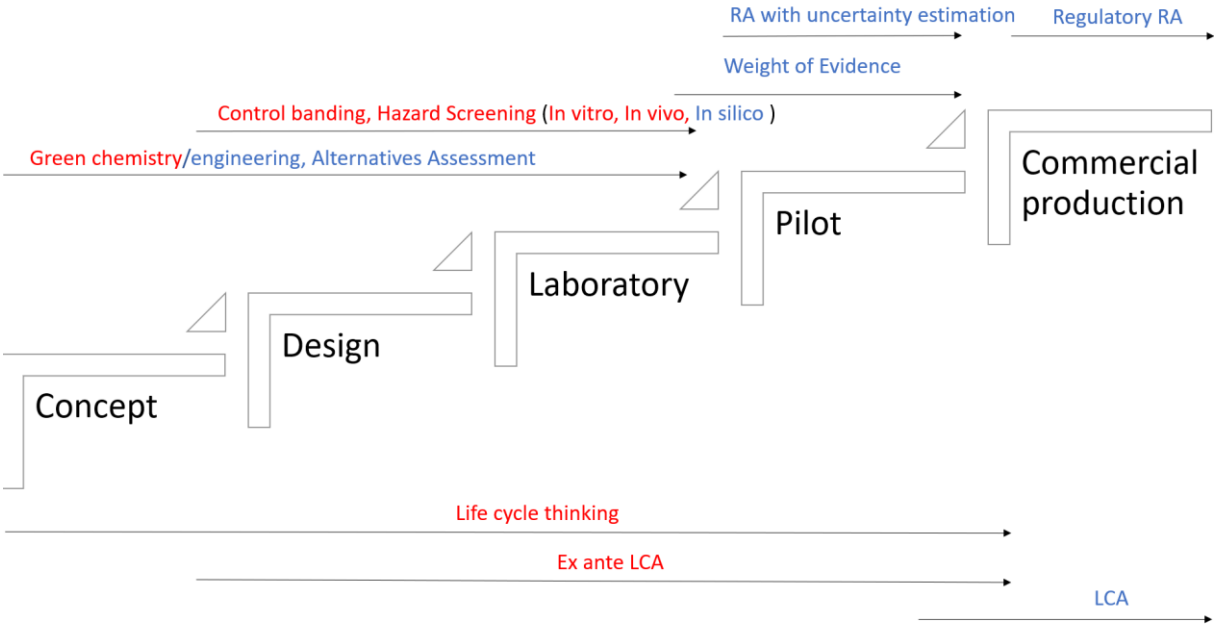

Figure 4: Application of LCA and RA at various TRLs for Product Design

Text in red: Method found in review Text in Blue: Not found in review but potentially useful for SbD

5.2 Research Question 2: What is the scope and quality of what designers can currently accomplish with these methods and approaches?

Product Designers can apply LCT and assess risk hotspots, i.e., potentially harmful product ingredients, emissions and wastes through the lifecycle, and mitigate them. The application of low TRL approaches and guidelines cannot substitute a full-fledged RA or LCA at a later stage but they may help avoid some obvious sources of risks and impacts in an early stage of product development.

A life cycle-based approach enables product designers to pinpoint risk hotspots in cases of novel materials and technologies. The case studies in Som, et al. (2010) and Sweet and Strohm (2006) illustrate how a life cycle-based approach to risks of materials/technologies through reviewing literature on RA and LCA can provide hints on risk hotspots.

A challenging aspect for applying RA and LCA at different TRLs is the consistency of the results. One part of it is the granularity of the low TRL models, and another part of it is upscaling that occurs through the TRLs (e.g., energy requirements are higher at laboratory scale than commercial scale). Van Harmelen et al. (2016) report that while there is good agreement of the LiCARA screening and full RA/LCA for the fuel cell and façade coating case studies, screening RA/LCA produced results later on appeared to be either more positive (in the case of antimicrobial fiber cloth due to detailed information on the reference product) or more negative (in the case of antibacterial coating due to magnitude of social benefit) than full RA/LCA results. For both LCA and RA at low TRL, the observation of Villares et al. (2017) that results should not be considered as conclusive due to several assumptions and high uncertainty in these models, is relevant. Rather, incorporating SbD within the design process should be viewed as an evaluation of a scenario based on best available knowledge and data that establishes comparative benchmarks, clarifies the goal and scope of the analysis, drives data collection to build more realistic models, and ultimately drives technology developers to design more sustainable technology systems.

5.3 Research Question 3: What gaps and challenges remain to be addressed to better facilitate RA and LCA application by product design teams?

While a variety of tools has been developed for screening RA, the potential of ex ante LCA has not yet been fully utilized in SbD. Ex-ante LCA in the reviewed literature is applied at TRL 4, but has outside the specific SbD literature also been applied at TRL as low as 2 (e.g. Villares et al. (2017) apply ex ante LCA to bioleaching of electronic waste to pinpoint hotspots). “Safety” in a product development context requires tradeoffs between risks, environmental impacts, functionality, costs, while meeting any applicable regulatory requirements, and involves relative assessments (OECD, 2020). The first phase of LCA – the Goal and Scope Definition - at TRL 1-2 could be a good starting point for SbD via understanding technical and economic aspects of product functionality and existing alternatives at various TRLs.

Most publications in the current review focus upon the risks within a product’s life cycle of a single chemical or material. However, product design teams should consider all chemical risks of products, which may involve various applications, chemicals and derivative exposure scenarios. A comprehensive assessment of all chemical risks in a product context is missing in the literature thus far and it should be investigated how the scope of current approaches could be expanded.

Among the reviewed papers, only Van Harmelen et al. (2016) collaborated with Small and Medium Enterprises (SMEs) to develop the LICARA nanoSCAN tool. More studies of using RA and LCA at various TRLs in product design practice are needed. Researchers note the poor understanding of how to integrate ecodesign tools in product design practice (Brones et al., 2014; Le Pochat et al., 2007), and a major research gap is how ecodesign can be integrated with project management. SbD, like ecodesign, can impact several product design aspects such as tradeoffs between cost, quality , safety, other environmental impacts, supply chain aspects and competitive advantage due to environmental performance. While the stage gate model has been proposed as a process model of including safety aspects in product design (e.g., Gottardo et al. (2017)), more studies are needed focusing on the application of tools and implications on these cross-cutting issues.

The Dutch ministry of Infrastructure and Water Management (IenW) points out that SbD requires a focus on interdisciplinary collaboration between teams and across companies (IenW Safe by Design flyer, 2020). Marcoluaki et al. (2021) emphasize collaboration between risk assessment researchers and companies and propose a blueprint for a European Centre for Safe and Sustainable by Design (SSbD). The approach of Shatkin and Kim (2008) has been used by a consortium including the value chain of cellulose nanomaterials to coordinate meeting regulatory requirements for novel materials [10]. Similarly, many ex ante LCA studies have emphasized this interdisciplinary collaboration too (Tsoy et al., 2020; Villares et al., 2017).

The data gap is another critical issue that needs to be addressed. The European Environmental Agency (EEA) estimate that of about 100,000 chemicals in the market, hazard and exposure are poorly characterized for about 70% (EEA, 2020). There should be clearly organized sources of risk information (hazard information, basic exposure scenarios) on chemicals that non-chemists can understand, interpret, and handle in their daily practices. Some information exists in the ECHA website[11] and other public databases (e.g. the SIN List[12]) for RA experts, but it is does not cater to the knowledge and perspective of the product designer (e.g., including function of chemicals, cost, example lifecycle pathways and risk identification for product types). There currently exist no tools that can estimate emissions of novel processes, as needed as a starting point to assess risk. Most of the recent early TRL projects perform experimental measurement of emissions across the life cycle. However, this is unrealistic in the product design context and needs to be addressed through informatics and modelling approaches (Tsoy et al., 2020; Ma et al., 2019). There are more tools to assess human health exposure in the manufacturing context than in the use and end of life stages of products, and this gap should also be filled.

Finally, SbD currently focuses on risks only, while current and future policy goals - in addition to risks - also include climate neutrality, circular economy concepts and consideration of other environmental impacts, and on top of that economic and social impacts. This motivated the European Commissions' Joint Research Centre to coin the term SSbD (Gottardo et al., 2020). While getting more experience with SbD approaches we might also want to move from SbD towards more SSbD-oriented approaches in order to address the challenges mentioned above. However, while LCA studies can provide information on environmental impact categories beyond risk-related impact categories, full SSbD requires more and other practical approaches that are beyond the scope of our current review.

[10] https://www.youtube.com/watch?v=5jPkomUeJBE
[11] https://echa.europa.eu/information-on-chemicals
[12] https://sinlist.chemsec.org/

6.Conclusions

Early assessment of safety issues arising during product design is important to ensure EHS and non-hazardous material cycles in circular economy. We therefore reviewed the combination of RA and LCA at low TRLs for SbD, and found several useful approaches like LCRA, control banding, in vivo toxicological screening, ex ante LCA, etc. Product designers are able to apply some hazard-based approaches and LCT, but need expert support to be able to apply ex ante LCA, expert elicitation and predictive toxicology approaches. The application of low TRL approaches and guidelines cannot substitute a full-fledged RA or LCA but they may help avoid some obvious sources of risks and impacts. Further, as observed in this and other publications, incorporating SbD within the design process should be viewed as an interdisciplinary collaborative process, repeated over different TRLs of a design, and ultimately driving technology and product developers and RA/LCA experts to design more sustainable technology systems.

However, important preconditions are not met to combine these methods comprehensively at low TRLs, in particular lack of SbD in product design context, interdisciplinary collaboration between designers and RA/LCA researchers , organized data and tools workable with the knowledge of product designers and policy discussion on the expansion from SbD to SSbD.

To conclude, the current state of combined LCA and RA for SbD is that some methods and approaches are available, but application in real situations is still challenging and requires further development of all concepts involved.

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Van Harmelen, T., Zondervan-van den Beuken, E.K., Brouwer, D.H., Kuijpers, E., Fransman, W., Buist, H.B., Ligthart, T.N., Hincapié, I., Hischier, R., Linkov, I., Nowack, B., Studer, J., Hilty, L. and Som, C. (2016) LICARA nanoSCAN - A tool for the self-assessment of benefits and risks of nanoproducts. *Environment International*, 91:150–160.

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Villares, M., Işıldar, A., van der Giesen, C., and Guinée, J. (2017) Does ex ante application enhance the usefulness of LCA? A case study on an emerging technology for metal recovery from e-waste. *The International Journal of Life Cycle Assessment*, 22(10), 1618-1633.

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Weed, D. L. (2005) Weight of evidence: a review of concept and methods. *Risk Analysis*, 25: 1545- 1557.

Worth, A. P., Hartung, T. and van Leeuwen, C. J. (2004) The role of the European centre for the validation of alternative methods (ECVAM) in the validation of (Q) SARs. *SAR and QSAR in Environmental Research*, 15: 345-358.

Appendix 1 Preliminary List of Literature

Paper	Prospective?	Classification as per Guinee et al (2017) (Knowledge Integration category omitted)				Methods	Case study
		LCRA	LCA for risk hotspots	Combining LCA and RA Results	Unclear		
Askham, C., et al. (2013). "Linking chemical risk information with life cycle assessment in product development." Journal of Cleaner Production 51: 196-204.	Yes				Yes	Yes	Yes
Barberio, G., Scalbi, S., Buttol, P., Masoni, P., and Righi, S. (2014). Combining life cycle assessment and qualitative risk assessment: The case study of alumina nanofluid production. Science of the Total Environment, 496, 122-131.	Yes			Yes		Yes	Yes
Benetto, E., Tiruta-Barna, L., and Perrodin, Y. (2007). Combining lifecycle and risk assessments of mineral waste reuse scenarios for decision making support. Environmental Impact Assessment Review, 27(3), 266-285.	No			Yes		Yes	Yes
Cappuyns, V., and Kessen, B. (2014). Combining life cycle analysis, human health and financial risk assessment for the evaluation of contaminated site remediation. Journal of Environmental Planning and Management, 57(7), 1101-1121.	No			Yes		Yes	Yes
Carpenter, A. C., et al. (2007). "Life cycle based risk assessment of recycled materials in roadway construction." Waste Manag 27(10): 1458-1464.	No			Yes		Yes	Yes
Fernandez-Dacosta, C., Wassenaar, P. N., Dencic, I., Zijp, M. C., Morao, A., Heugens, E. H., and Shen, L. (2019). Can we assess innovative bio-based chemicals in their early development stage? A comparison between early-stage and life cycle assessments.	Yes	Yes				Yes	Yes

Journal of Cleaner Production, 230, 137-149.							
Fransman, W., et al. (2017). "Comparative Human Health Impact Assessment of Engineered Nanomaterials in the Framework of Life Cycle Assessment." Risk Anal 37(7): 1358-1374.	Yes	Yes		Yes		Yes	Yes
Harder, R., et al. (2015). "Review of Environmental Assessment Case Studies Blending Elements of Risk Assessment and Life Cycle Assessment." Environ Sci Technol 49(22): 13083-13093.	No			Yes		No	Yes
Hristozov, D., et al. (2018). "Quantitative human health risk assessment along the lifecycle of nano-scale copper-based wood preservatives." Nanotoxicology 12(7): 747-765.	Yes	Yes				Yes	Yes
Grieger, K. D., et al. (2012). "Analysis of current research addressing complementary use of life-cycle assessment and risk assessment for engineered nanomaterials: have lessons been learned from previous experience with chemicals?" Journal of Nanoparticle Research 14(7).	Yes	Yes		Yes		No	Yes
Guinee, J. B., et al. (2017). "Setting the stage for debating the roles of risk assessment and life-cycle assessment of engineered nanomaterials." Nat Nanotechnol 12(8): 727-733.	Yes	Yes	Yes	Yes		No	Yes
Hou, D., Qi, S., Zhao, B., Rigby, M., and O'Connor, D. (2017). Incorporating life cycle assessment with health risk assessment to select the 'greenest'cleanup level for Pb contaminated soil. Journal of Cleaner Production, 162, 1157-1168.	No			Yes		Yes	Yes
Kobayashi, Y., Peters, G. M., Ashbolt, N. J., Heimersson, S., Svanström, M., and Khan, S. J. (2015). Global and local health burden trade-off through the hybridisation of quantitative microbial risk assessment and life cycle assessment to aid water management. Water research, 79, 26-38.	No			Yes		Yes	Yes

Kobayashi, Y., et al. (2015). "Towards More Holistic Environmental Impact Assessment: Hybridisation of Life Cycle Assessment and Quantitative Risk Assessment." Procedia CIRP 29: 378-383.	No	Yes	Yes	Yes		No	Yes
Köhler, A. R. and C. Som (2014). "Risk preventative innovation strategies for emerging technologies the cases of nano-textiles and smart textiles." Technovation 34(8): 420-430.	Yes	Yes				No	Yes
Korevaar,G. et al. (2019). "De toepassing van Safe-by-Design en Life Cycle Assessment in de ontwerpfase van het innovatieproces Lessons learnt: de casus van op nano-titania gebaseerde fotokatalyse"IENW report	Yes		Yes			Yes	Yes
Kralisch, D., Staffel, C., Ott, D., Bensaid, S., Saracco, G., Bellantoni, P., and Loeb, P. (2013). Process design accompanying life cycle management and risk analysis as a decision support tool for sustainable biodiesel production. Green chemistry, 15(2), 463-477.	Yes			Yes		Yes	Yes
Linkov, I., et al. (2017). "Integrate life-cycle assessment and risk analysis results, not methods." Nat Nanotechnol 12(8): 740-743.	Yes			Yes		No	Yes
Liu, K. F. R., Ko, C. Y., Fan, C., and Chen, C. W. (2012). Combining risk assessment, life cycle assessment, and multi-criteria decision analysis to estimate environmental aspects in environmental management system. The International Journal of Life Cycle Assessment, 17(7), 845-862.	No		Yes			Yes	Yes
Nishioka, Y., et al. (2006). "Integrating Air Pollution, Climate Change, and Economics in a Risk-Based Life-Cycle Analysis: A Case Study of Residential Insulation." Human and Ecological Risk Assessment: An International Journal 12(3): 552-571.	No			Yes		Yes	Yes

Pant, R., van Hoof, G., Schowanek, D., Feijtel, T. C., De Koning, A., Hauschild, M., ... and Rosenbaum, R. (2004). Comparison between three different LCIA methods for aquatic ecotoxicity and a product environmental risk assessment. The International Journal of Life Cycle Assessment, 9(5), 295.	No			Yes		Yes	Yes
Pizziol,L., et al. (2019). "SUNDS probabilistic human health risk assessment methodology and its application to organic pigment used in the automotive industry." NanoImpact 13: 26-36.	Yes	Yes				Yes	Yes
Ribera, G., et al. (2014). "Life cycle and human health risk assessments as tools for decision making in the design and implementation of nanofiltration in drinking water treatment plants." Sci Total Environ 466-467: 377-386.	Yes			Yes		Yes	Yes
Sharratt, P. N., and Choong, P. M. (2002). A life-cycle framework to analyse business risk in process industry projects. Journal of Cleaner Production, 10(5), 479-493.	No		Yes			Yes	Yes
Shatkin, J. A. (2008). "Informing Environmental Decision Making by Combining Life Cycle Assessment and Risk Analysis." Journal of Industrial Ecology 12(3): 278-281.	Yes		Yes			No	Yes
Shatkin, J. A. and B. Kim (2015). "Cellulose nanomaterials: life cycle risk assessment, and environmental health and safety roadmap." Environmental Science: Nano 2(5): 477-499.	Yes		Yes			Yes	Yes
Shih, H. C. and H. W. Ma (2011). "Life cycle risk assessment of bottom ash reuse." J Hazard Mater 190(1-3): 308-316.	No					Yes	Yes
Som, C., et al. (2010). "The importance of life cycle concepts for the development of safe nanoproducts." Toxicology 269(2-3): 160-169.	Yes	Yes				No	Yes
Sweet, L. and B. Strohm (2006). "Nanotechnology—Life-Cycle Risk Management." Human and Ecological Risk Assessment: An International Journal 12(3): 528-551.	Yes	Yes				No	Yes

Tan, L., Mandley, S. J., Peijnenburg, W., Waaijers-van der Loop, S. L., Giesen, D., Legradi, J. B., and Shen, L. (2018). Combining ex-ante LCA and EHS screening to assist green design: A case study of cellulose nanocrystal foam. Journal of Cleaner Production, 178, 494-506.	Yes			Yes		Yes	Yes
Tsang, M. P., et al. (2017). "Evaluating nanotechnology opportunities and risks through integration of life-cycle and risk assessment." Nat Nanotechnol 12(8): 734-739.	Yes			Yes		Yes	Yes
Van Harmelen, T., Zondervan-van den Beuken, E. K., Brouwer, D. H., Kuijpers, E., Fransman, W., Buist, H. B., ... and Som, C. (2016). LICARA nanoSCAN-A tool for the self-assessment of benefits and risks of nanoproducts. Environment international, 91, 150-160.	Yes	Yes		Yes		Yes	Yes
Walser, T., Juraske, R., Demou, E., and Hellweg, S. (2014). Indoor exposure to toluene from printed matter matters: complementary views from life cycle assessment and risk assessment. Environmental science & technology, 48(1), 689-697.	No			Yes		Yes	Yes
Wardak, A., et al. (2008). "Identification of Risks in the Life Cycle of Nanotechnology-Based Products." Journal of Industrial Ecology 12(3): 435-448.	Yes	Yes				Yes	Yes
Weyell, P., Kurland, H. D., Hülser, T., Grabow, J., Müller, F. A., and Kralisch, D. (2020). Risk and life cycle assessment of nanoparticles for medical applications prepared using safe-and benign-by-design gas-phase syntheses. Green Chemistry, 22(3), 814-827.	Yes			Yes		Yes	Yes
Xue, M., Kojima, N., Zhou, L., Machimura, T., and Tokai, A. (2019). Trade-off analysis between global impact potential and local risk: A case study of refrigerants. Journal of Cleaner Production, 217, 627-632.	No			Yes		Yes	Yes