AN EXPLORATORY STUDY ON EMBEDDING SAFE-AND-SUSTAINABLE-BY-DESIGN (SSbD) IN CIRCULAR BIOECONOMY RESEARCH

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This report outlines the findings of an exploratory study on Safe-and-Sustainable-by-Design for circular bioeconomy research. This research specifically focuses on understanding how the values of safety and sustainability could be implemented in the design process. It also addressed how focus on the network of relations with other experts and stakeholders can be embedded and can hopefully lead to better practices for safety and sustainability. The report concludes with a workflow for considering safety and sustainability by biotechnology practitioners.

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Table of Contents

Samenvatting

Safe-by-Design (SbD) is het streven om veiligheidsoverwegingen mee te nemen in het gehele ontwikkelingsproces van nieuwe technologieën, ook met het oog op toekomstig gebruik en het eind van de levenscyclus. Er zijn al meerdere onderzoeken naar SbD uitgevoerd, waaronder onderzoek naar SbD specifiek voor biotechnologie. Dit rapport draagt op twee manieren bij aan voorgaand onderzoek.

Ten eerste adresseert dit rapport de kritiek dat veiligheid niet de enige belangrijke waarde is die een rol moet hebben in SbD. Duurzaamheid is een voorbeeld van een waarde inherent aan onderzoek in de circulaire bioeconomie die nog niet verankerd is in SbD kaders en hulpmiddelen. Een principe van de circulaire economie is dat duurzaamheid en veiligheid van materialen essentieel zijn voor circulariteit. Safe-and-Sustainable-by-Design (SSbD) is recent geïntroduceerd in de nanotechnologie en groene chemie sector, zoals in de Duurzame Chemicaliënstrategie van de Europese Commissie, met name om bij te dragen aan de Europese Green Deal. Dit onderzoek zet de eerste stappen in het verankeren van duurzaamheid, naast veiligheid, als belangrijke waarde in het gehele ontwikkelingsproces van circulaire biotechnologieën.

Ten tweede adresseert dit rapport de kritiek dat SbD waardevol is op theoretisch vlak, maar lastig toe te passen in de praktijk. Onderzoek naar SbD is vaak theoretisch van aard en geeft weinig concrete toepassingsmogelijkheden voor relevante belanghebbenden in de biotechnologie. Dit rapport bouwt voort op eerder werk, maar geeft daarnaast ook een praktisch toepasbaar werkproces. Dit werkproces kan gezien worden als een middel dat relevante belanghebbenden kan helpen om SSbD effectief toe te passen in hun werk. Het werkproces richt zich voornamelijk op het netwerk van relaties, dat helder in kaart gebracht moet zijn om veiligheid en duurzaamheid een integraal onderdeel te laten zijn van projecten in de circulaire bioeconomie.

De onderzoeksvraag van dit verslag luidt daarom: welke elementen zijn noodzakelijk voor de implementatie van Safe-and-Sustainable-by-Design in circulair biotechnologie onderzoek? De onderzoeksvraag wordt beantwoord aan de hand van zowel literatuuronderzoek als data uit interviews en een workshop georganiseerd met biotechnologie beoefenaars werkzaam aan Wageningen University & Research. De interviewvragen zijn gestructureerd aan de hand van verschillende vragen: wie, hoe, wat en wanneer vragen. Uit de interviews zijn terugkerende thema's gedestilleerd. Vervolgens is er een workshop georganiseerd om de onderzoeksresultaten te bespreken met een deel van de geïnterviewden. De resultaten van het onderzoek worden geïnterpreteerd in een zorg-ethisch kader voor Safe-by-Design en integreren enkele van de meest recente en relevante instrumenten in een werkproces dat dicht bij de biotechnologische praktijk staat: het Ontwerp Bouw Test Leer-kader Dit werk is daarom bijzonder relevant voor biotechnologen. Tenslotte presenteren we aanbevelingen voor de inbedding van SSbD voor industriële biotechnologie en de rol ervan in de circulaire bio-economie.

Summary

Safe-by-Design (SbD) aims to embed safety considerations throughout the whole design, research and development phase of new technologies, while anticipating their use and disposal. Previous studies have already been done on SbD, as well as on SbD specifically for the biotechnology sector. This report adds to the work already done on SbD in two ways.

Firstly, this report addresses the criticism that next to safety, other values are also of importance and should be embedded in the design process. Sustainability is a value that is already inherent to circular bioeconomy research, but not explicitly included in SbD measures. Principles of the circular economy indicate that sustainability and safety of materials is primordial for circularity. Safe-and-sustainable-by-Design (SSbD) has recently been introduced in the field of nanotechnology and chemicals developments, as in the European Commission's Chemicals Strategy for Sustainability, particularly to contribute to the European Green Deal. This report will take the first steps in embedding sustainability, next to safety, as an important design value guiding circular bioeconomy research.

This report secondly addresses the criticism that SbD is appreciated and useful in theory, but difficult to put into practice. A lot of work on SbD is theoretical in nature and does not provide concrete guidelines for practitioners to work with. This report brings a practical addition to previous work on SbD by providing a workflow. The workflow should be understood as a tool that can help relevant stakeholders with embedding SSbD in their work. The focus of the workflow is on the network of relationships with other experts and stakeholders that need to be in place to ensure that the values of safety and sustainability are thoroughly embedded in the design and R&D phases of circular bioeconomy research.

Therefore, the research question of this report goes as follows: “which basic elements are necessary for the implementation of Safe-and-Sustainable-by-Design measures in circular biotechnology research for industrial biotechnology applications?" This question is answered by means of desk research as well as interviews and a workshop with biotechnology practitioners affiliated with Wageningen University & Research. The interview questions are structured in four categories: who, how, what and when questions. Recurring themes have been distilled from the interviews and were discussed with some of the interviewees during a workshop. The outputs of the research are interpreted under a care ethics framework for Safe-by-Design and integrate some of the most recent and relevant tools into a workflow close to biotechnology practice: the Design Build Test Learn framework. This work is therefore particularly relevant to biotechnology practitioners. Finally, we present recommendations for embedding SSbD for industrial biotechnology and its role in the circular bioeconomy.

Introduction

1.1. Context: what is Safe-by-Design?

The concept of Safe-by-Design (SbD) finds implementation in several fields of engineering (van Gelder et al. 2021). Constitutive elements of the concept include risk identification, life cycle assessment, risk assessment, risk management, stakeholder engagement and reflections on risk perception. At the same time SbD implies early decisions in design that aim towards risk minimization, and therefore places a larger responsibility for safety on designers and engineers (Robaey et al. 2017). In this report we understand SbD to be practices and measures that aim to embed safety considerations throughout the whole design, research and development phase of new technologies, with its future use and end of life in mind.

Such a development means more responsibility for engineers and designers. While it is desirable to address safety issues upstream, it is also challenging to implement them in practice. Some of these challenges can be categorized as pertaining to mere technological choices directly: what can be done? And other challenges can be more broadly understood as who should do what throughout the research and innovation process?
Next to that, some work has also recently been done on integrating the value of sustainability in the design process in order to contribute to the European Green Deal, specifically in the field of nanotechnology (Gottardo et al. 2021; Mech et al. 2022), as well as for chemical substances and materials (Caldeira et al., 2022; European Commission's Chemicals Strategy for Sustainability). Safe-and-sustainable-by-Design (SSbD) takes "[...] a systems approach by integrating safety, circularity and functionality of advanced materials, products and processes throughout their life cycle" (Gottardo et al., 2021, p. 8). Little research has however been done so far on SSbD for industrial biotechnology applications in the bioeconomy.

Transitioning from SbD to SSbD should not simply be seen as merely adding sustainability considerations on top of an already existing SbD process. Rather, SSbD should be seen as using a systems perspective that highlights how safety and sustainability are inherently intertwined (Mech et al., 2022, 4). For this report, we understand SSbD to encompass practices and measures that aim to embed safety as well as sustainability considerations throughout the whole design, research and development phase of new technologies, with considerations for use and end of life of an innovation. In this way, products can truly contribute to a circular bioeconomy. This is not without challenges.

Some of the main challenges that can be distilled from recent research into the concept of SbD are the following: using SbD can give rise to value conflicts (Bouchaut et al. 2021; Ishmaev et al., 2021; Kallergi & Asveld 2021), safety should not be the only value that is considered (Kallergi & Asveld 2021), a broader context and specific applications need to be considered to define what SbD should achieve (Kallergi et al 2021). Moreover, it is difficult to implement SbD methods and theories into practice (Kallergi & Asveld 2021), considering that there is a lot of ambiguity when it comes to understanding what is meant with SbD (Kallergi & Asveld 2021), there is little attention to how roles and responsibilities are allocated (Kallergi & Asveld 2021), and there is little understanding of how various stakeholders working with biotechnologies perceive SbD (Schuurbiers, 2021). Several publications also point to a need to focus on SbD as a concept of responsibility for safety, rather than designing for safety alone (van de Poel & Robaey 2017; Huijs et al 2022; Bouchaut & Asveld 2021).

We have distilled two main challenges from this previous research: challenges in communication across disciplines that we coin as the alignment challenge, and challenges in going from values to common understanding of design, that we coin as the specification challenge. Both challenges bear impact with regard to responsibility ascription and distribution.

1.1.1. The Alignment Challenge: communication across disciplines

Aligning several stakeholders, and various types of experts around an important societal value such as safety, or sustainability, brings about challenges in communicating and collaborating across disciplines and among stakeholders. This alignment in communication and collaboration could concern various challenges. Here we focus on safety and sustainability.

A recently published report by the Rathenau Institute (2022) on strengthening policy implementation for biosafety emphasizes that communication between practitioners and governmental institutions is crucial for maintaining the current governance-ecosystem for biosafety in the future. They identify five characteristics of strong communication: clarity regarding roles, clear allocation of responsibility and accountability, effective communication, inclusive two-way communication and learning capacity & flexibility. According to the report, strong communication leads to trust in biosafety and risk governance, enables stakeholders to understand risk- and safety considerations and enables them to have a voice in decisions on acceptable risk and safety. Bad communication can lead to incomprehension and deprive people of the possibility to understand and react to decisions, which can eventually lead to a complete misunderstanding of risk and safety and distrust in the institution making the decisions. The report furthermore recognizes the necessity of strong communication for the goal of SbD implementation, precisely because SbD puts more responsibility for safety on researchers. This demands an active role in thinking through safety consideration during the whole R&D process (rather than being merely compliant in following protocols), and requires strong communication between relevant stakeholders in order for stakeholders to align with important issues.

When it comes to aligning stakeholders, Bouchaut & Asveld (2020) find that the concept of SbD leads to different expectations amongst stakeholders. In biotechnology, SbD creates an expectation of inherent safety, which is not realistic or possible, and therefore complicates the communication about dealing with risks. They suggest that other domains that have studied SbD more extensively, such as nanotechnology and chemical engineering, could inspire SbD's implementation by means of communication. This underlines the importance of aligning expectations amongst stakeholders and experts from different disciplines.

Recent literature also offers ways out of the alignment challenge in facilitating exchanges between experts, and also including stakeholders.

Schuurbiers (2019) has evaluated and compared five models of embedding a reflexive component in SbD research. He shows that each model has advantages and disadvantages but concludes by stating that no model can be successful if practitioners are not willing to think through and integrate values that go beyond their technical work. He therefore highlights the importance of reflexive abilities of practitioners to successfully embed SbD, and with that also the ability of innovators to understand and include insights from the social sciences or philosophy in their work.
Bouchaut & Asveld (2021) also argue that a responsible learning environment should be facilitated for biotechnology practitioners. Responsible learning should stimulate researchers to proactively consider safety and potential risks of their research and thereby move beyond mere compliance with protocols and rules. Stakeholders should therefore communicate openly and honestly.

This leads us to the next connected challenge of specification. Let us assume that models such as these of Schuurbiers and Bouchaut & Asveld would be successful, there is another layer of challenge associated with value specification.

1.1.2. The Specification Challenge: going from values to design

Another challenge has to do with practically implementing SbD, in other words value specification in terms of design requirements. This challenge has two components: how to specify, who should specify the values at hand.
In dealing with how to do value specification, there is a gap in skills and resources. The recent Rathenau report (2022) states that researchers currently have little time, resources and knowledge needed to implement SbD in their work. The report furthermore underlines that low awareness for safety amongst researchers, according to biosafety officers, is a challenge to carrying responsibility for safety, in other words they are not equipped to make design choices that would fit the goal of safety. In relation to this, Kallergi & Asveld (2021a) argue that it is necessary to move on from seeing SbD merely as a technical act if we want to successfully implement it in the circular economy. Going beyond the technical also requires a certain set of skills and resources, like by hiring other experts (as suggested in the models discussed by Schuurbiers). These skills also require understanding how to deal with possible tensions between safety and sustainability as values. Kallergi & Asveld (2021a) present this but do not elaborate on that extensively.

In addressing who should do SbD, there are issues with incentives and lack of clear roles and responsibilities in SbD. In relation to this, there is a lack of recognition and reward in academia for researchers who embed safety and risk considerations into their work early on, because there is more recognition for spectacular innovative results than showing that there are little or acceptable safety risks for a certain study (Rathenau, 2022). In addition, while practitioners are positive about the aims of SbD, practitioners find it hard to put into practice. This is linked to the lack of clear definitions as well as agreement on roles and responsibilities (Kallergi & Asveld, 2021b).

1.2. Research questions and background

These challenges found in previous studies were used to shape the research question and design of this report. This study aims to better understand these challenges and offers a set of recommendations and a workflow that can help address these challenges, with the aim of guiding practitioners to implement SSbD in circular bioeconomy research. This research takes academic research as a start. The research question that we will answer in this report is:

> "Which basic elements are necessary for the implementation for Safe-and-Sustainable-by-Design measures in circular biotechnology research for industrial biotechnology applications?"

With basic elements, we mean the network of people and institutions that need to be in place for SSbD to be able to be put into practice. By measures, we mean frameworks, guidelines and tools that have previously been designed for SbD and/or SSbD. The question is answered by means of a combination of desk research, semi-structured interviews, and a workshop with the interviewees, who consist of practitioners in the field of circular bioeconomy research within Wageningen University & Research (WUR).

We will specifically look at what is needed for a practical implementation of SSbD in circular bioeconomy research by using the perspectives of biotechnology practitioners as a basis. There will be a focus on understanding how biotechnology practitioners relate to each other and on how responsibility for safety and sustainability is understood and communicated amongst them. Based on the basic elements that we have identified in the interviews, we have designed a workflow that may help biotechnology practitioners with implementing SSbD. As stated before, this is our focus because allocating responsibility has been identified as problematic in previous SbD research (Rathenau Institute, 2022), but in-depth research and solutions have not yet been provided. When there is unclarity about roles and responsibilities connected to them, it leads to difficulties with implementing SSbD. When there is more clarity on roles and responsibilities, safety and sustainability can be included better. Trade-offs between these different values can always occur but are also always project dependent. Therefore, clear communication about the implementation of safety and sustainability and possible trade-offs between these values is crucial (Asin-Garcia, 2022). This report does not explicitly focus on circularity in order to focus on the values of safety and sustainability. Circularity is, however, an engineering goal that is part of our interviewees research. Safety and sustainability are necessary values for a Circular Economy (Ellen MacArthur Foundation). If we want to reuse materials in order to achieve circularity, it needs to be known that the materials and involved production processes are safe and sustainable. Circularity can therefore also be understood as a driver for taking into account the combination of the values safety and sustainability.

For example, given the questionable sustainability of using sugar or starch as carbon sources in biotechnological processes, the number of investigations exploring alternative sources becomes larger every day. These mainly focus on the bioprocessing and biorefinery of waste biomass, an approach intrinsically integrated with circular bioeconomy which helps tackle carbon management and greenhouse gas emissions (Leong et al. 2021). Carbon management is exemplary of having sustainability concerns in mind in the design.

Safety and sustainability, however, do not necessarily go hand in hand: there can be trade-offs that have to be made between them. For instance, choosing one certain material over another can be more sustainable, but less safe. A specific example would be the use of hydrogen as electron donor in bioproductions. Reduced inorganic or one-carbon (C1) electron donors can support microbial CO_2 fixation, while being sustainably obtained from waste streams or regenerated by using unlimited resources, such as light or water. As one of these compounds, molecular hydrogen represents a sustainable option for industrial biotechnology. However, hydrogen is quite insoluble and also explosive, which represents a safety risk in terms of bioreactor design and operation (Claassens et al., 2018). For this report we understand research in the circular bioeconomy to aim for:

> "[…] sustainable, resource-efficient valorization of biomass in integrated, multi-output production chains (e.g. biorefineries) while also making use of residues and wastes and optimizing the value of biomass over time via cascading." (Stegman et al., 2020).

Where circular bioeconomy research already has aims that are sustainable, the question remains whether sustainability is implemented in each phase of the research and design process and how this relates to later phases in the journey of an innovation. Before going into the details of the methods, we breakdown our research question above in a set of sub-questions. In turn, these relate to a care ethics framework for SbD presented by Baas et al. 2022. They write:

> "Approaching the concept of Safe-by-Design from a care ethics perspective draws attention to the fact that achieving safety is a process that requires work and commitment, and thereby focuses on the responsible subjects (i.e., the stakeholders involved), instead of on the safety of the object (i.e., the technology itself). As it further emphasizes that the responsibility for safety has to be shared by all stakeholders involved with the technology, from its very first conceptualization to its disposal as waste, it highlights that safety is not only the burden of engineers and designers, but of all those involved, including institutions and individual users."

In our work, we seek to move towards implementation, we therefore aim to combine the subjects, and the objects. We find the care framework adapted to SbD helpful in that it helps making explicit the relationships between stakeholders that are needed to achieve safe objects.

Baas et al. identify different ways in which care ethics can contribute to the conceptualization of SbD based on care ethicist's Joan Tronto's five circles of care.

Table 1: Five ways in which care ethics can contribute to SbD (Baas et al., 2022)

1) Situated Safety and Sustainability	Recognizing that safety considerations happen in the contexts and surroundings of a technology and is not something that is embedded in the technology itself.
2) Building Circles of Care for Safety and Sustainability	Recognizing the need to build 'circles of care' where relevant stakeholders share responsibility for safety within a project.
3) Safety as an Ongoing Commitment	Recognizing that maintaining safety requires ongoing work: it is not something that can be implemented at the start of a project and then forgotten about.
4) Relating with Care: Minding Your Language	Recognizing that the way we talk about promises and expectations of a technology shape the way we understand and implement safety measures.
5) Recognizing Moral Emotions and Affect	Recognizing that emotions play a role (i.e.: how safe do we feel implementing a certain technology in society?).

For simplicity, we present ways as who, how, what and when. In the next sections, we explicate these and connect it to recent literature. These are then the basis of the interview guide we present later.

1.2.1. Who-questions

The who-questions focus on understanding how collaborations work out in practice between different stakeholders, and on understanding how participants perceive who has the most influence when it comes to safety and sustainability efforts and decision-making. This also allows identifying who participants perceive as relevant, and who is forgotten. The who-questions stem from Baas et al.(2022) paper on including a care ethics perspective for SbD. Care ethics sees people and the relationships of care and responsibility they have for each other as central to acting ethically.

1.2.2. How-questions

The how-questions focus on understanding how awareness of safety and sustainability is currently raised among participants, and how this could be done differently. The how-questions also focus on understanding in what way (imagined) expectations of the public play a role in defining safety and sustainability. These how-questions stem from Asin-Garcia et al.'s (2020) research that states that stakeholders have false expectations and idealized assumptions of what SbD can do.

1.2.3. What-questions

The what-questions focus on what is understood by safety and sustainability, and in what ways they are included in current research and innovation processes, as well as in understanding what challenges arise if both values have to be taken into account. These what-questions are based on studies that focus on the practical implementation of SbD (Schuurbiers 2019, Bouchaut & Asveld 2021, Kallergi & Asveld 2021).

1.2.4. When-questions

Lastly, the when-questions focus on the timing when decisions about safety and sustainability are being made. These questions also build on studies focusing on the practical implementations of SbD.

2. Methodology

2.1. Recruitment of participants

The participants (N=12) for the interviews and workshop were recruited based on their involvement with circular bioeconomy research at Wageningen University & Research. A list of potential interviewees was written up by prof. dr. Vitor Martins dos Santos and dr. Enrique Asin-Garcia based on their network in the Wageningen University & Research biotechnology sector. We included people from three different chair groups to get diversity in perspectives. These are the laboratories of Systems and Synthetic Biology, Microbiology and Bioprocess Engineering. Out of eighteen contacts, two contacts did not respond, and four other contacts were unable to participate. One contact forwarded us to somebody else who ended up being a participant in our study (snowball sampling). During the research, more potential participants were identified, but due to time constraints they were not all included. Table 1 presents an overview of participants and their degree of professional experience.

Table 1: Overview of interviewees

Role and experience level	Number of respondents	Codes for qualitative analysis
Advanced PhD students	2	PhD1, PhD2
Postdoctoral researchers	1	PD1
Senior scientists	2	SS1, SS2
Assistant professors	2	AP1, AP2
Professors	1	P1
Lab technicians	2	LT1, LT2
Program managers	2	PM1, PM2

2.2. Interviews

The goal of the interviews was to take stock of where participants are now in terms of practices that are relevant to SbD and potentially discover practices that are relevant to SSbD.
The interviews were conducted in a semi-structured manner, meaning that the same set of questions were used for each participant, but that the interviewer also maintained flexibility to ask follow-up questions or dive deeper into themes specific to the experience of the participant. All interviews have been conducted via Microsoft Teams (online) in the period

between October 17th, 2022, and October 28th, 2022. The sessions have all been recorded and the automated transcription software in Microsoft Teams was used. Appendix 1 contains the interview guide that was used, that connects to the background theory presented in section 1. The interviews lasted between 45 and 90 minutes, with an average of approximately one hour. Participants' identities and transcripts are anonymized in order to create an atmosphere of trust and openness.

Each interview started with a question to get a brief background of the participant and understand their knowledge and previous experience with SbD/SSbD. This guide was built based on insights from the existing literature on SbD and the gaps and potential issues that have already been identified. The interview guide was built around four groups of questions: who, how, what and when questions. For each group of questions, participants were asked to describe the current ways in which safety and sustainability considerations are embedded in their work. Secondly, participants were asked how they think safety and sustainability should be embedded in their work as well as in biotechnology research more generally.

2.3. Workshop

As a follow-up to the interviews, we organized a two-hour workshop at the campus of Wageningen University & Research in a hybrid format. The goal of the workshop was to reflect main findings back to the interviewees and engage them in reflecting on their practice for integrating safety and sustainability considerations in their work.
All interviewees were invited to participate. Four of them ended up participating in the workshop (PhD1, LT2, PM1, PD2). The other interviewees declined due to conflicting appointments or not being able to make the time for the workshop. The workshop started by providing the participants with more background of the aim and framework of the study. Afterwards, we had a discussion of the preliminary results of the interviews based on the who, how, what and when questions used for the interviews. Did they see their views reflected in the results? Were they surprised by certain findings?
We also discussed their understanding of the meaning of safety and sustainability together. Finally, we discussed input for the workflow together with the participants. The workflow is built on the Design, Build, Test and Learn (DBTL) framework commonly used in synthetic biology (Biofoundries.org). We asked each participant to work out where they would place themselves and their responsibilities when it comes to safety and sustainability in the framework. We also asked them to reflect on who they would ask for assistance in phases of the process that they are not themselves responsible for. Finally, we asked the participants for feedback on the workshop and the idea of the workflow.

3. Results

3.1. Findings from interviews

Recurring themes were distilled based on the input of the interviewees. While we started with an initial organization of themes through the interview guide, after the interviews, we found new emerging themes relevant to embedding safety and sustainability in biotechnology research.

Table 2: Interview themes

Interview guide	Emerging themes
Who?	Work culture
	Hierarchy
	Responsibility
	Role models
How?	Awareness for sustainability is lacking
	Communication & education
	Long term vision
What?	Definitions
	Protocols & systems
	Common sense
When?	Too late
	End products

3.1.1. Who-questions

Work culture

Interviewees generally agree that the working culture matters when it comes to ensuring safe working practices (PD1, LT1, LT2). For instance, interviewees mentioned that the laboratory should be a place where people dare to approach others who do not follow certain safety practices and remind them of the protocols in place. There should be an environment where people dare to ask questions when they are uncertain about safety risks or have sustainability concerns, and they should know who they can turn to for help. Making minor mistakes should also not be reproached but rather seen as an opportunity to learn, both for the person who made the mistake as well as lab technicians and fellow students or researchers. A lab technician gave an example of how they try to create this work culture:

> *What if your experiment fails terribly, and you feel very disappointed and sad by that. What do you do? Most students answer something along the lines of: I just continue with my work. However, the right answer is: you go home for the afternoon, do something that makes you happy and you try it again tomorrow together with your supervisor. You are here to learn, so you should not be afraid to make mistakes. (LT1, translated by author).*

Other examples mentioned were providing visible and understandable information and reminders on safe working practices that are available to everyone (LT2). Regular social activities can also be organized that help to see coworkers as people who are just like you (PD1). A practical example that was mentioned by one interviewee is a WhatsApp group that was created for a laboratory. Researchers and lab technicians communicated about potential safety risks in this group.

Hierarchy

In general, interviewees do not experience strong hierarchical relations with their coworkers. They also do not experience major communication problems with people in different positions or disciplines. However, one interviewee (LT1) mentioned that it is sometimes the case that professors have a strong influence on laboratory and safety procedures, even though they do not actively work in the lab themselves. This interviewee understood that as problematic because these procedures do not always match with what people working in the lab understand to be the best procedures. During the workshop, we returned to this point and participants indicated that sometimes professors change protocols because they have a different idea about a given experiment or process but that it is not always the most practicable. No specific example was provided by participants.

Responsibility

Interviewees agree that everyone should be responsible for safety and sustainability in their own role. There is also consensus amongst the interviewees that people do not always take this responsibility for a variety of reasons: people do not want to be held accountable in general because responsibility is not pleasant to bear (PM2), people are led by passion for their own research topic or career advancements in the first place and therefore do not think of safety and sustainability (AP1), people feel lost on how to practically implement safety and sustainability therefore do not do it (PM2), people feel overwhelmed by the complexity of safety and sustainability considerations (PM1) and people do not think safety and sustainability must play a major role in each study (AP2), specifically when it comes to fundamental research.

Interviewees in general agree that the government should mainly be responsible for providing researchers with the tools and knowledge to make sure that research happens safely and sustainably. Suppliers of materials should be responsible for producing sustainable materials (P1). What your responsibility should be therefore depends on your role. It was also repeatedly mentioned that researchers already have a lot on their plate, so they cannot and should not be solely responsible for safety and sustainability (PhD1).

A positive example of a clear allocation of responsibility for safety when it comes to working in a laboratory was mentioned by an interviewee (PhD2). Some machines in the lab have an information card posted on them, stating who is responsible for the experiment running in the machine, and how this person can be reached in case of an emergency. Safety in generally understood within the realm of actions of interviewees.

Role models

Some interviewees mentioned that people are herd animals (LT1, LT2), and that they are likely to follow the crowd when it comes to following safety procedures while working in the laboratory. Role models and positive examples are necessary because people tend to copy each other’s behavior.

An interviewee (LT1) mentioned that students generally look up to researchers who are higher up in the hierarchy. Some students tend to think that these researchers do not make any mistakes anymore. Therefore, students are afraid of making mistakes themselves and admitting to these mistakes. If senior researchers, however, own up to their mistakes publicly and share them with others, students will be encouraged to do the same.

3.1.2. How-questions

Awareness for sustainability is lacking

Interviewees generally agreed that although biotechnology research generally has sustainable aims, people are not aware enough of including sustainability considerations as a concrete step in the whole research and design process (AP2). Interviewees generally agree that there is more awareness for safety than for sustainability. They also agreed that there is a lot of awareness for safety, for instance when it comes to laboratory protocols and using safe materials (LT2).

Communication & education

It was repeatedly stated by interviewees that clear and constructive communication between colleagues is of key importance. An example of this is the need to be constructive, open and not overly critical when people make mistakes. Interviewees also agree that educating future researchers on safety and sustainability as integral parts of their work is key to facilitating long-term systemic change (AP1). Interviewees mentioned that younger generations tend to care about sustainability and want to know how they can make their research sustainable (PhD1, AP2, AP1).

Picture 1: Posters at the coffee corners of one of the WUR laboratories explaining the reasoning behind safety measures.

Picture 2: Slide on contacting Biosafety Officers at the coffee machine

Long term vision
Different interviewees mentioned the problem that governments as well as universities lack long term visions with regard to values of safety and sustainability. Long term thinking is understood by these interviewees as necessary to create systemic change. Many projects only run for brief amounts of time, which makes it difficult for systemic change to take place. Safety and sustainability should be values that are embedded in the system (PM1, PM2, AP2).

3.1.3. What-questions

Definitions
Interviewees agree that it is difficult to define concepts such as safety, circularity and sustainability, and that understandings of these concepts vary between different disciplines and projects. Some interviewees state that generally agreed upon top-down definitions should be constructed by European and national governmental institutions (PM2). Other interviewees emphasize the necessity of having some flexibility in definitions so they can be shaped to suit specific projects (AP1).

Protocols & systems
Interviewees in general agree that safety is mainly regulated and maintained by means of protocols and regulations (internal to the group and conform to regulation). Most interviewees do not see this as problematic, because protocols provide clarity and ensure that there is a standard that all research should adhere to (LT1, LT2). They do mention that the protocols should not be overly restrictive and allow for room to adjust to the context of a specific project.

Next to protocols, interviewees also see other ways to embed safety and sustainability considerations in the work culture and system. One interviewee mentions that long term risks can be hard to foresee in advance, and that in addition, disastrous events are impossible to quantify in a reliable way (SS1, SS2). It is therefore beneficial to design the system in a way so that negative effects stay manageable and that risks can be contained within the system. Here we see that considerations go beyond the laboratory.

Common sense
Different interviewees stated that caring for safety and sustainability does not have to be rocket science. Using ‘boerenverstand’ (common sense) is of importance and should not be underestimated (LT1, SS1, AP1). This common sense should however be developed and practiced and does not appear out of the blue. Interviewees mentioned common sense because they wanted to emphasize that embedding safety and sustainability should not be overcomplicated.

3.1.4. When-questions

Too late
Interviewees agree that safety and sustainability insights generally come too late in the process and could be included earlier on in the process (PM2). Interestingly, efficiency was repeatedly mentioned as a driver for safety and sustainability. When a sustainable alternative becomes cheaper, it is preferred over the less sustainable option (LT1, LT2). One interviewee also mentioned that safety and sustainability should not be included too early in the process, specifically when it comes to fundamental research. This could limit fundamental studies too much and therefore lead to less valuable results (AP2). Safety and sustainability should be considered when it is known how the research will be applied.

End products
Some interviewees mentioned that they feel that their responsibility ends when they have delivered the final product. The company is responsible for what happens to the product when it enters the market; this is particularly the case when the research is commissioned by a company, on other research projects partners carry out necessary life cycle assessments . (SS1, P1). However, one interviewee states that it should not be like this, and that there should be more focus on the end-of-life of all materials and chemicals used in the research and design process. (PM2).

3.2. Insights from the workshop

Workshop participants in general recognized their experiences in the outcome of the interviews. For the who-questions, a participant also recalled being afraid of making mistakes as a student out of a fear of being penalized. It was also repeated that researchers themselves cannot be fully responsible for safety and sustainability because they already have a lot on their plate.

Discussion of the how-questions lead to the idea that the framework for safety has been developed more extensively than a framework for sustainability, but that sustainability is more present in the zeitgeist. It was also mentioned that as a researcher, you tend to not think about safety and sustainability when you do not experience directly visible problems regarding them. You are first and foremost focused on your own experiments and research. It was also mentioned that using sustainable alternatives for materials makes some activities with tools more difficult to execute. It was also mentioned that reusing materials (i.e., washing cups) is not always more sustainable than using throwaway cups. Measuring sustainability is therefore not easy as there are many variables present.

The what- and when questions lead to the idea that sustainable alternatives must become cheaper or more efficient for them to be an attractive option. A participant also highlighted the difficulty of changing systems: people might experience themselves in a lock-in situation and feel overwhelmed and unsure about how to make changes. The point was also raised that researchers do not feel responsible anymore when a product has entered the market.

The second part of the workshop was used to discuss understandings of safety and sustainability. Discussing safety led to a discussion on what role risks play: is it about the reduction of risk, the absence of risk or about reducing harm instead of reducing risk? The practical sides of safety (i.e., wearing a lab coat) were discussed, as well as psychological safety in the work culture. Safety was also seen in a broader context: the risk of farmers losing their work when biotechnologies alter food production processes, as well as the role of supermarkets in recalling products that, for instance, contain salmonella. The discussion on sustainability was more brief (due to time constraints) but lead to the idea that the concepts of safety and sustainability can be intertwined and overlapping.

We furthermore noticed that the build and test phases of the process were understood by the participants as phases where they were mostly compliant with the rules because most decisions would be made in the design and learn phases (see section 4.2). An encouraging finding is that most participants found themselves active in all parts of the DBTL model, meaning that decisions can also rely on those enacting them, though this is not always the case.

4. Discussion

4.1 Addressing the Alignment and Specification challenges

At the beginning of this report, we presented two challenges: the alignment and specification challenges. A first finding of this report confirms that these challenges are very much present. At a small scale of the twelve participants we interviewed, the alignment challenge comes forth with the need for communication being mentioned at several moments. At the same time, we find the specification challenge is still very much there with participants struggling to define safety and sustainability requirements beyond the lab.

In order to address these challenges, several available tools should be employed. We refer to these in the next section at appropriate moments where they can have impact. In that sense, we see that existing tools mentioned in section 1.1.1 for the alignment challenge can be used and we suggest that it is more a matter of knowing when to use them. We find that the specification challenge is one that needs more active commitment from several stakeholders to work together towards specifying what safety and sustainability should mean for a given project. We think the workflow we present in the next section can help in addressing this challenge.

4.2. Using the DBTL cycle for SSbD implementation

Using Baas et al.'s (2022) work on including a care ethics perspective for SbD we aim to reconcile questions pertinent to people who have to apply SSbD to products (strains, processes, compounds) which have to be safe and sustainable. We have chosen this theoretical framework because it adds to the discussion on designing for responsibility in SbD (van de Poel and Robaey, 2017) by emphasizing our interdependence and the importance of concrete relationships with other experts and stakeholders when it comes to making ethical decisions. A care ethics perspective is also critical of the idea that ethical problems can be solved by means of protocols and regulations alone. SbD can therefore be understood as a practice of caring for and feeling responsible for ethically sound technological innovations that will benefit the network of people who are involved with these developments. The framework also leaves room to include sustainability as an essential value, as humans are inherently connected to the environment, which makes sustainability a core value that needs to be protected for us and the planet to thrive.

Baas et al. argue that this understanding of care ethics leads to a philosophically better grounded as well as a more practically applicable understanding of SbD. Even though Baas et al. mention that van de Poel and Robaey's study does not include what responsibility for safety would look like in practice, Baas et al. do not include views of practitioners in their work, and therefore also keep their study on a theoretical level. In order to build on their studies, we include views of practitioners in order to contribute to bridging the gap between practice and theory. We have this focus because we think that focusing on relationships can help to make long-term changes in work processes in biotechnology, rather than only creating moments of awareness without leading to structural change.

In the course of our research, it became clear that the circles of care presented by Baas et al. (2022) needed to be anchored in an on-going practice. For this, the most promising avenue we found was to connect questions relevant to practitioner's responsibility to a safe and sustainable product through the Design-Build-Test-Learn (DBTL) framework used in biotechnological research and development. It can help practitioners to structure a project in a way that is the most efficient. It consists of four phases. The Design phase consists of formulating ideas and approaches for a project, including workflows, sequences, engineering approaches and models (see table 4.1). The Build phase can include picking and storing strains for later use, modifying organisms and sequencing (see table 4.2). The Test phase is used for testing constructs and strains. This phase usually generates great amounts of data (see Table 4.3). During the Learn phase the data and experiences collected during the DBTphases are analyzed and potential new hypotheses or points of improvement are formulated for the next DBTL cycle (see table 4.4).
A challenge of this framework is that it mostly considers strain design. However, in the Learn phase of the cycle, questions relevant to the process, and the produced compounds find their relevance.

As a first step, we present state-of-the art tools relevant to practitioners at different moments, and specify from our findings what kind of relationships to other practitioners, and stakeholders are already in place for safety, and sustainability separately. The following tables are by no means exhaustive. They present what we found in this project. Looking at them critically invites defining areas for attention in further research.

*Table 4.1 Integrating SSbD in the **Design phase** of the DBTL cycle*

Dimension of care	Specification for safety	Specification for sustainability	Existing tools
Situated Safety and Sustainability	*Project acquisition by senior staff* leads to recognizing the need of society for a safe future.	*Project acquisition by senior staff* leads to recognizing the need of society for a sustainable future.	To improve situated safety, tools like the anticipation workshop (Bouchaut et al. 2022) can provide a better understanding of challenges. The implementation routes presented in the LabServant report (Chmarra et al., 2021) can also be a good basis to start a conversation on situated safety.
Building Circles of Care for Safety and Sustainability	Principlal Investigators have the responsibility to hire people with the right skills to address different aspects. Professors have responsibility for protocols that are then implemented by others. PhDs have the responsibility to turn to both professors and lab technicians to check when they need to do something that differs from the protocol.	Similar considerations can be extended to sustainability.	Here, the models presented by Schuurbiers (2019) can be helpful in determining either what skills are needed in a team, or who are other experts that can help. This is a decision that should be lead by PIs and professors, and informed by the rest of the staff.

Safety as an Ongoing Commitment	Program managers have a long-term view and are able to set requirements for safety More generally, if every project includes a SbD work package for the integration of these issues, this can facilitate an on-going commitment.	Program managers have a long-term view and are able to set requirements for sustainability More generally, if every project includes a work package for the integration of these issues, this can facilitate an on-going commitment. Lab technicians are in a good position to help make day to day decisions to be aware of resource use and disposal.	RIVM report on the value chain can be valuable for program managers to know how to allocate resources to points of attention with regard to safety and sustainability. (Hogervorst el al. 2023)
Relating with Care: Minding Your Language	Safety is often spoken about in terms of compliance with protocols.	Sustainability is sometimes used as a buzzword. This can be problematic, because it obscures what is concretely meant by sustainability. In the design phase, it is important to communicate clearly about safety and sustainability goals.	Internal communication within department. Communication from regulatory instances on expectations regarding sustainability and safety. Here leadership in a research group can really set the tone for how safety and

			sustainability are considered. RIVM SbD education (Biotechnologie Website)
Recognizing Moral Emotions and Affect	Enthusiasm of researchers for their project and its scientific goals can lead to negligence of safety considerations.	Enthusiasm of researchers for their project and its scientific goals can lead to negligence of sustainability considerations.	Using methods that iGEM teams use to talk about their project to the wider public could help identifying broader issues relevant to integrating values in their work.

*Table 4.2 Integrating SsbD in the **Build phase** of the DBTL cycle*

Dimension of care	Specification for safety	Specification for sustainability	Tools
Situated Safety	Understanding the context necessary of a specific project at different stages. When possible substitute building with modelling	Understanding the context necessary of a specific project. When possible substitute building with modelling	People with modelling skills can help determine whether modelling can replace experiments. Here context can be at different scales (R&D, use, end of life) and this can be facilitated by modelling.
Building Circles of Care for Safety	n/a	n/a	n/a
Safety as an Ongoing Commitment	Having a clear link to the design phase	Having a clear link to the design phase	Practitioners could make it clear as to when they are moving to the build phase, in order to clarify any issues and requirements in relation to safety and sustainability criteria
Relating with Care: Minding Your Language	n/a	n/a	n/a
Recognizing Moral Emotions and Affect	n/a	n/a	n/a

Table 4.3 Integrating SsbD in the ***Test phase*** *of the DBTL cycle*

Dimension of care	Specification for safety	Specification for sustainability	Tools
Situated Safety	n/a	n/a	n/a
Building Circles of Care for Safety	n/a	n/a	n/a
Safety as an Ongoing Commitment	n/a	n/a	n/a
Relating with Care: Minding Your Language	n/a	n/a	n/a
Recognizing Moral Emotions and Affect	PhD students and postdocs are often the ones on the work floor, together with lab technicians/managers. Being able to share mistakes with colleagues is important for improving safety overall	n/a	Having proper contact details easily available. Having role models who lead by example in showing how mistakes should be dealt with – keeping in mind that the university is an educational environment.

Table 4.4 Integrating SsbD in the ***Learn phase*** *of the DBTL cycle*

Dimension of care	Specification for safety	Specification for sustainability	Tools
Situated Safety	Impact for the broader context of the innovation – not only technological but also socio-economical Consider unexpected results from the Test phase and their impacts.	Impact for the broader context of the innovation – not only technological but also socio-economical Consider unexpected results from the Test phase and their impacts.	Role playing games (Surf website)
Building Circles of Care for Safety	All relevant stakeholders are part of the learn phase: society,	All relevant stakeholders are part of the learn phase: society, researchers, policy makers.	Schuurbiers (2019) presents model 5 of interaction which calls for integrating all stakeholders and

	researchers, policy makers.		experts which would be most relevant for the learn phase.
Safety as an Ongoing Commitment	Build meaningful relationships to relevant stakeholders before scaling up from the R&D phase and repeating the next DTBL cycle	Build meaningful relationships to relevant stakeholders before scaling up from the R&D phase and repeating the next DTBL cycle	Existing concepts of living labs, or societal incubators are meant specifically for learning throughout an innovation process.
Relating with Care: Minding Your Language	Co-constructing a language about the innovation where definitions of safety are shared and agreed on.	Co-constructing a language about the innovation where definitions of sustainability are shared and agreed on.	Undertaking a value-sensitive design approach can help explicit the language. (VSD website)
Recognizing Moral Emotions and Affect	Engaging with stakeholders who are not experts in the field requires different modes of communication	Engaging with stakeholders who are not experts in the field requires different modes of communication	Methods Participatory Value Evaluation as developed by Populytics can provide new insights in what matters to stakeholders (Populytics website)

4.3 Limitations of the study

A first limitation of the study is our scope. Our study has only included biotechnology practitioners who are involved with Wageningen University & Research. This means that a certain bias can be found amongst the people who were interviewed, who all work for the same organization. However, this was at the same time also necessary and useful for our focus on mapping the network of relationships because we had a proper understanding of the network that the interviewees people are operating in. We did interview people in a variety of functions as well as different biotechnology labs to still get a varied perspective. Citizens and policy makers were not included as participants in the study because our focus was on creating a workflow for practitioners of biotechnology. Not including citizens and policy makers could also be understood as a limitation of the study.

A second limitation of the study is the role of the value of sustainability. Only including sustainability as a value next to safety can also be understood as a limitation of the study. This choice was made for two reasons. Firstly, this is an exploratory study with a limited timeframe. Secondly, including all potentially important values (i.e., justice, accessibility) would have made the workflow too extensive and practical applicability might be lost.

A third limitation our study is that not all the interviewees were familiar with SSbD as a methodology. This meant that throughout the interviews, context on what is currently understood as SbD and how sustainability could also play a part in that was sometimes provided.

A fourth limitation of our study is that we are merely suggesting a workflow. While we see this as a step closer to implementation of a SSbD, this remains yet to be tested and finetuned with the goals of practicability and efficacy.

5. Recommendations

Based on previous studies on SbD and input of biotechnology practitioners, this report innovates in that it tries to situate existing work within a workflow known to biotechnology practitioners, DBTL. By mapping connections, practitioners can better situate and embed safety and sustainability in their work. Follow-up research should be done to expand the workflow, and see whether the workflow functions well in practice, and whether the workflow can also be of help in, for instance, the fields of nanotechnology and green chemistry. The recommendations that stem from our research are as follows:

- Education on Safe-by-Design and on Safe-and-Sustainable-by-Design should be further embedded in courses for students at Wageningen University & Research. Education should also be offered to other relevant practitioners: lab technicians, program managers and senior researchers who are unfamiliar with the methodology can benefit.
- Communicate clearly and early-on about responsibility for safety and sustainability for a project, for instance with the help of the workflow designed in this project.
- Create opportunities for practitioners to engage with the tools that allow meaningful participation with other stakeholders and experts.
- Support practitioners in defining relevant metrics for safety and sustainability for their specific project.
- Sustainability should be discussed systematically along Safety and relevant tools like life cycle assessment should be integrated especially in the Design and Learn phases of the DBTL cycle either by means of working with other experts, or by gaining this expertise in-house.
- The workflow we present as tables could benefit from being developed as an easy to use and accessible tool for practitioners.
- The workflow should be tested over a longer period of time to be assessed for efficacy.

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Appendix

1. Interview guide

Warm up question: Can you tell me a little bit about yourself, as well as your experience and background with safety and sustainability in your work?

1. Who?
1.1) Who has mainly been targeted with efforts for safety and sustainability in your experience?
1.2) Who do you think has the most influence when it comes to safety and sustainability efforts, and why?
1.3) With whom are you working most closely together, and how do you talk and communicate?
1.4) Do you perceive a difference between a hierarchical relationship you might have with them and what happens on the floor?

2. How?
2.1) How is awareness about safety and sustainability currently being raised among biotechnology researchers and other relevant stakeholders along the whole lifecycle of products and processes, particularly beyond complying with lab safety rules?
2.2) Should awareness be raised differently than the way it is done now? If so, how?
2.3) How do you include the (imagined) expectation of public ideas on safety and sustainability in your work?
2.4) How do you think these expectations should be included in your work?

3) What?
3.1) What is your general understanding of safety and sustainability in your work?
3.2) In what way is safety being considered when it comes to making technological choices and in the research and innovation process (figure 1)?
3.3) In what way is sustainability included when it comes to making technological choices and in the overall research and innovation process (figure 1)?
3.4) What challenges are currently there to apply measures that contribute to safety and sustainability, and what would help address these challenges?

4) When?
4.1) When are decisions about safety and sustainability currently being made?
4.2) Do you think this is working well? If not, when would be the best moments and places to take these decisions together with stakeholders?

Round-up: Ask whether the interviewee has any more questions for me/us, let the interviewee know that they can always reach me by email and thank them for their time.

2. Author biographies

Mrs. Maaike van der Horst has a master's degree in the Philosophy of Science, Technology and Society from the University of Twente. She is the main author of this report and worked as a junior researcher on this project for Safe-and-sustainable-by-Design. She will start her PhD in Philosophy of Technology at the University of Twente in January 2023.

Dr. Zoë Robaey is Assistant Professor in Ethics of Technology at the Philosophy Group of Wageningen University. Her work investigates moral responsibility under conditions of uncertainty in the field of biotechnology in agriculture. In 2019, she received a VENI grant from the Dutch Research Organization for her research on the virtues for innovation in practice. In this work, she combines conceptual and empirical investigations to develop a notion of responsibility under uncertainty that builds on the practices of practioners. Prior to joining Wageningen University, Zoë was postdoctoral researcher at the Biotechnology and Society Group at Delft University of Technology, working on the project "Inclusive Biobased Innovations" (2017-2019). She also worked as a researcher on synthetic biology at the Rathenau Institute on the "SYNENERGENE" project (2016-2017). She defended her PhD thesis titled "Seeding Moral Responsibility in Ownership: How to Deal with Uncertain Risks of GMOs" in January 2017 at Delft University of Technology.

Dr. Enrique Asín-García is postdoctoral researcher with the Biomanufacturing and Digital Twins at the Department of Bioprocess Engineering at Wageningen University.
Enrique studied Biotechnology at the University of Salamanca (Salamanca, Spain) from which he obtained his BSc in 2015. In 2017, he completed a MSc in Cellular and Molecular Biotechnology at Wageningen University & Research. Enrique graduated from his PhD research project in 2022 at the Laboratory of Systems and Synthetic Biology of Wageningen University under the supervision and mentorship of Professor Vitor Martins dos Santos. By means of synthetic biology tools, genome recoding and metabolic engineering, his work has been the main foundation of the NWO-funded project "SafeChassis: Implementing and Assessing Safeguards for Lifestyle Engineering of a Versatile Industrial Chassis", focused on biosafety tools for safe-by-design industrial bioprocesses. At the beginning of 2022, Enrique founded SynBioNL, the Synthetic Biology Association of The Netherlands, with the position of treasurer as part of the Executive Board.

Prof. Dr. Ir. Vitor Martins dos Santos did a MSc Food Biotechnology at the School of Biotechnology, Porto, Portugal, after which he did his PhD in Environmental Bioprocess Engineering, Wageningen University. After work in Belgium (von Karman Institute for Fluid Dynamics) and Spain (National Science Council), he did a postdoc and founded a group on Systems & Synthetic Biology at the German Centre of Biotechnology, Braunschweig, Germany. In 2009 he was appointed holder of the new Chair Systems & Synthetic Biology, Wageningen University, and since January 2022 he took the position of Professor of Biomanufacturing and Digital Twins at the Department of Bioprocess Engineering at Wageningen University.