Perceptions of Safe-by-Design for biotechnology

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Safe-by-design (SbD) is een concept dat van ontwikkelaars van nieuwe technologie vraagt om veiligheid vroeg in een ontwerpproces mee te nemen. Nieuwe technologieën ontwikkelen zich snel. Om te zorgen dat deze innovaties op een verantwoorde wijze bijdragen aan de samenleving, is een overweging van verschillende veiligheidsaspecten nodig. SbD plaatst de verantwoordelijkheid voor veiligheid in de handen van de ontwikkelaars. Het vraagt hen om de risico's van een nieuwe technologie vroegtijdig te identificeren en om deze risico's zo goed mogelijk te voorkomen. SbD bouwt voort op bestaande veiligheidspraktijken in de techniek maar is vooral relevant voor opkomende technologieën zoals biotechnologie.

Biotechnologie behelst de wetenschap en technologie voor de toepassing van levende organismen voor verschillende doeleinden. Medicijnontwikkeling, landbouw en groene chemie zijn enkele gebieden die baat hebben bij ontwikkelingen in dit vakgebied. Biotechnologie kan duurzame oplossingen bieden voor maatschappelijke uitdagingen en bijdragen aan duurzame ontwikkelingsdoelstellingen. Net als met iedere andere technologie, gaat biotechnologie gepaard met risico's en onzekerheden. Een SbD-benadering kan in theorie bijdragen aan de veiligheid van nieuwe biotechnologie, maar de relevantie van een dergelijke benadering is nog niet goed onderzocht.

In deze studie onderzochten we de percepties van verschillende belanghebbenden van SbD voor biotechnologie. Welke verschillende visies bestaan er op het concept SbD? Welke SbD strategieën worden als effectief beschouwd? En onder welke voorwaarden zouden de belanghebbenden SbD overtuigend en betrouwbaar vinden? Om deze vragen te beantwoorden, interviewden we deelnemers van drie verschillende belangengroepen, namelijk het maatschappelijk middenveld, het bedrijfsleven en de academische wereld. We benaderden individuen van wie we verwachtten dat zij SbD gaan toepassen in hun werk, zoals bio-ingenieurs en vertegenwoordigers van biotechnologiebedrijven. We benaderden ook mensen die niet direct betrokken zijn bij technologie ontwikkeling, zoals vertegenwoordigers van politieke partijen of NGO's. Daarnaast spraken we met academici die een bredere expertise hebben dan biotechnologie, bijvoorbeeld ecologen, communicatiewetenschappers en ethici. De reacties van onze respondenten duiden op diverse voordelen, risico's en zorgen die geassocieerd worden met SbD. Met name maken ze duidelijk dat er een noodzaak is om te reflecteren op de doelstellingen en ambities van SbD.

Onze respondenten waren over het algemeen positief over de doelstellingen en de filosofie achter SbD. Niemand wil onveilige producten, en nadenken over veiligheid in een vroeg stadium werd gezien als logisch en slim. Geïnterviewden zetten echter vraagtekens bij de praktische implementatie van SbD. Belanghebbenden van de biotechnologie bedrijfstak stellen dat SbD al standaard praktijk is in hun sector. Daarom zien ze weinig toegevoegde waarde in het SbD initiatief. Ze maken zich ook zorgen dat het SbD-initiatief bij sommige mensen tot de conclusie zal leiden dat biotechnologie toepassingen nu niet veilig zijn. Andere deelnemers zien wel ruimte voor 'extra' veiligheidsinspanningen, maar vrezen dat SbD verkeerd begrepen zal worden. Het zou bijvoorbeeld een vals gevoel van veiligheid op kunnen roepen of tot een verkeerde interpretatie leiden van een 'keurmerk' of een garantie van veiligheid. Zulke misvattingen moeten op alle niveaus voorkomen worden: voor de overheid (die geen absolute veiligheid zou moeten aanbieden of eisen), voor ontwikkelaars (die niet gesust zouden moeten worden

door een vals gevoel van veiligheid) en voor gebruikers en burgers (die SbD niet zouden moeten interpreteren als absolute garantie).

Het probleem van absolutie garantie heeft directe gevolgen voor de betrouwbaarheid van een SbD benadering. Onze deelnemers zouden elke bewering dat alle risico's zijn vermeden, wantrouwen: zulke beweringen zijn niet realistisch en daarom niet geloofwaardig. Desalniettemin schrijven onze deelnemers SbD inspanningen niet af als zinloos, integendeel. Zij steunen SbD als een doelstelling voor ontwikkelaars en als een stimulans voor toenemend bewustzijn over veiligheid. Daarbij waarderen veel deelnemers SbD als een brede benadering die verder gaat dan technische maatregelen. Technische veiligheidsmaatregelen gericht op het genetische aspect van een organisme hebben hun waarde, maar kunnen het complexe probleem van veiligheid niet volledig omvatten. Onze deelnemers wijzen op de noodzaak om veiligheid vanuit meerdere invalshoeken te benaderen en benadrukken een interdisciplinaire aanpak, communicatie met burgers en transparantie over (toekomstige risico's) en de handelingen van bedrijven.

De reacties van onze respondenten maken verder duidelijk dat veiligheid essentieel is, maar niet de enige relevante morele waarde bij het ontwerpen of evalueren van een nieuwe technologie. Voor sommige geïnterviewden vormen gezondheidsrisico's en milieurisico's alleen een deel van het verhaal. Andere effecten op de samenleving, zoals ongelijkheid in toegang tot een nieuwe technologie, moeten ook aandacht krijgen. Anderen merken op dat veiligheid vaak subjectief is: wat als veilig genoeg wordt beschouwd, hangt af van persoonlijke waarden en wereldbeschouwing. SbD kan bijkomende geruststelling geven ten aanzien van veiligheid, maar een dergelijke nadruk kan ook contraproductief werken. Een werkelijk verantwoorde innovatiebenadering vereist een breed debat waarbij verschillende waarden op de agenda staan, niet enkel veiligheid. Het vereist ook een open gesprek over hoe voordelen op moeten wegen tegen risico's, of hoe innovatie moet opwegen tegen voorzorg.

Concluderend wordt SbD beschouwd als een goedbedoeld initiatief, dat onbedoelde bijeffecten kan hebben. De doelstelling en filosofie van SbD zijn sympathiek, maar de praktische toepasbaarheid is niet vanzelfsprekend. Hoe kunnen we dan de voordelen van SbD behouden zonder in de valkuilen te vallen? Om te beginnen vereist SbD een duidelijke en niet ambigue interpretatie die ook de relatie met huidige veiligheidspraktijken in de biotechnologie verheldert. Dit vraagt om reflectie op de doelstellingen en ambities van SbD. Wat is het probleem dat SbD wil oplossen? Wiens probleem is het? Voor welke toepassingsgebieden van biotechnologie is SbD urgent? Hoe realistisch zijn de voorstellen? Ontwikkelaars en beleidsmakers moeten heel duidelijk zijn over de grenzen van SbD toepassingen, zowel tegen zichzelf als tegen anderen. Ze hebben ook duidelijke afspraken nodig over waar ieders verantwoordelijkheden beginnen en eindigen. Tenslotte moet SbD deel uitmaken van een brede maatschappelijke dialoog en een besluitvormingsproces over nieuwe biotechnologische ontwikkelingen. Samen kunnen dergelijke processen helpen om onze samenleving te laten profiteren van veiligere en meer verantwoorde innovaties, ondanks de onvermijdelijke onzekerheden.

Public summary

Safe-by-Design (SbD) is a concept that urges the developers of new technologies to integrate safety early on in their design process. New technologies are developing rapidly. For these innovations to contribute in a responsible way to society, various safety aspects must be considered. SbD places more responsibility for safety in the hands of the developers. It asks them to take early actions to identify the risks of a new technology and to prevent these risks to the extent possible. SbD borrows ideas from established safety practices in engineering but is especially relevant for emerging technologies such as biotechnology. Biotechnology is the science and technology of using living organisms for useful purposes. Medicine, agriculture and sustainable industry are some areas that have profited from developments in this field. Biotechnology can provide innovative solutions to societal challenges and contribute to sustainable development goals. As with any technology, however, its products come with risks and uncertainties. A SbD approach could -in theory- enhance the safety of novel biotechnologies but the relevance of such approach remains unexamined.

In this study, we explored the views of various stakeholders on SbD for biotechnology. How do different stakeholders understand the concept of SbD? Which SbD strategies do they consider effective? And under which conditions would they consider a SbD approach feasible and trustworthy? To answer these questions, we interviewed participants from three stakeholder groups, namely civil society, industry and academia. We approached people who are expected to integrate SbD in their work, such as bioengineers or representatives of biotechnology companies. We also approached people who are not directly involved with technology development, such as members of political parties or civil society organizations. Finally, we talked to academics with a broader expertise than biotechnology such as ecologists, communication scientists or ethicists. The responses of our participants reveal several benefits, risks and concerns associated with SbD. Importantly, they point to a need for reflection about the aims and claims of SbD.

Our participants were overall positive about the aims and philosophy behind SbD. Nobody wants unsafe products and thinking about safety early was praised as a logical and smart thing to do. Yet, participants were unsure about the practical implementation of SbD. For example, participants from the biotechnology industry believe that SbD is already a standard practice in their sector. Therefore, they have difficulties finding an added value for the initiative of SbD. Sometimes, they also worry that this initiative could make others think that existing biotechnological applications are not already safe. Other participants may see a use for “extra” safety efforts but worry that SbD could be misunderstood. For example, it might encourage a false sense of safety or be mistaken as a “stamp” or guarantee of absolute safety. Such misconceptions must be prevented at all levels: for the government (who should neither offer nor demand absolute guarantees), for the developers (who should not be reassured by a false sense of safety) and for the users and citizens (who should not interpret SbD as absolute guarantees).

The problem of absolute guarantees has direct consequences for the trustworthiness of a SbD approach. Our participants would distrust any claims to prevent all risks: such claims are unrealistic and therefore not credible. Still, our participants do not dismiss SbD efforts as futile, quite the contrary. They favour SbD as an objective for the developer and as an attitude of increased attentiveness to safety. In addition, many participants appreciate SbD as a comprehensive approach that goes beyond taking technical measures. Technical measures like increasing safety at the genetic level of an organism have

their uses but cannot fully cater for the complex problem of safety. Our participants stress the need to examine safety from multiple perspectives and emphasize interdisciplinary collaboration, communication with citizens and transparency about (future) risks or a company's doings.

The responses of our participants also remind us that safety is essential but not the only relevant value when designing or evaluating a new technology. For some interviewees, health and environmental risks are only part of the story. Other impacts on society, such as injustice due to limited access to a new technology, must be examined too. Other interviewees comment that safety is often subjective: what is considered as "safe enough" may depend on personal values or worldviews. SbD can offer extra reassurances on safety but such emphasis may not be always productive. Rather, responsible innovation in biotechnology needs a broad debate that takes additional societal values into account, not only safety. It may also need an open conversation on how to best balance benefits versus risks, or innovation versus precaution.

In conclusion, SbD is understood as a well-meant initiative but one which could have undesirable effects. The aims and philosophy behind SbD are very relatable but its practical implementation is not always straightforward. How could we, then, maintain the benefits of SbD while avoiding its pitfalls? To begin with, SbD needs a clear and unambiguous interpretation that will also clarify its relation to current safety practices in biotechnology. This demands reflection over the aims and claims of SbD. *What* is the problem that SbD aspires to solve? *Whose* problem is it? *For which* areas of biotechnology is SbD urgently needed? *How realistic* are its propositions? Developers and policy makers must be absolutely clear about the limits of SbD efforts, both to themselves and to others. They also need proper agreements about where one's role and responsibilities start and end. Finally, SbD must be part of a broader deliberation and decision-making process about new biotechnological developments. Combined, such efforts may allow our societies to profit from safer and more responsible innovations, despite our inevitable uncertainties.

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1 Introduction

Safe-by-Design (SbD) is a novel concept that urges developers of new technologies to integrate safety early on in the design process (van de Poel and Robaey, 2017; Ministry of Infrastructure and Water Management, 2019). It emphasizes the prevention of risks over risk management and suggests that the safety of new technologies can be increased if appropriate design choices are made at early stages of technology development. The term Safe-by-Design originates from the field of nanotechnology (Kelty, 2009) but shows potential for other emerging technologies as well. This is especially true for (modern) biotechnology (Robaey, 2018), understood here as the use of biological systems and parts thereof for the development of new products. Biotechnology is a domain of economic and societal relevance as it can provide technological solutions for, among others, medicine, agriculture and sustainable industrial production. However, new biotechnologies emerge at a rapid pace and are characterised by a high degree of uncertainty over their risks. This situation poses considerable challenges to their risk assessment and regulation. As it is often the case with emerging technologies, current regulatory frameworks are struggling to stay up-to-date and fit for purpose.

A SbD approach implies that more responsibility for safety is placed in the hands of bioengineers (and other developers of novel biotechnologies) who take pre-emptive actions to increase the safety of their innovations. SbD can thus be understood as a response to societal demands for safer technologies, on the one hand, and the societal need for innovative technological solutions, on the other. As such, it is indicative of a series of shifts at the interface between science and society, advocating increased attention to the impacts of technologies and promoting research agendas defined in collaboration with stakeholders. The latest formalization of these shifts can be found in Responsible Research and Innovation (RRI) (Stilgoe *et al.*, 2013; von Schomberg, 2013), a policy framework prominent in EU policy discourse. Amidst these developments, SbD constitutes a manifestation of an RRI methodology, i.e. one that guides innovation via early stakeholder engagement, mutual learning and mutual responsibility in order to deliver innovations that align with societal values (in this case: safety).

By urging developers to act upon safety at the onset of innovation, SbD could potentially lead to safer and more responsible biotechnologies. Nevertheless, SbD is a concept that is yet to gain traction in research, development and innovation practice. Formal implementations of SbD in biotechnology are still scarce and may not provide sufficient ground for evaluation. Moreover, despite SbD being a strongly institutionalized concept with references in policy papers, policy communications and academic literature, little is known about how it is perceived by various stakeholders involved in or affected by novel biotechnologies. This project addresses this knowledge gap by investigating the perceptions of a broad range of stakeholders of SbD for biotechnology.

1.1 Why study stakeholder perceptions?

Stakeholder perceptions of SbD matter both for practical reasons and for reasons of legitimacy. First, the perceptions of stakeholders are likely to affect their actions: whether relevant stakeholders will endorse SbD (or products developed via a SbD approach) will largely depend on their perception of this concept. Second, SbD is worth pursuing if and only if relevant stakeholders decide that it is a worthwhile development that can satisfy societal needs for (more) safety. Third, SbD is still a fluent concept that could benefit from incorporating the perspectives of relevant stakeholders into its conceptualization.

Finally, empirical research on stakeholder perceptions could also inform communication and education activities to address potential concerns or misconceptions about SbD.

Obviously, practitioners in the field of biotechnology, in either academia or industry, should be convinced of the *feasibility* of SbD if they are to integrate it in their practice. At minimum, these stakeholders should agree that a SbD approach is effective, i.e. increases safety. Alternatively, disagreements over the effectiveness of SbD can be insightful regarding the exact notion of safety that can be maximized via a SbD approach. Next, practitioners may agree that a SbD approach is effective and desirable but they may still feel restricted to implement it. Their perceptions can thus point to concrete barriers that must be addressed before SbD can be implemented successfully in practice.

Stakeholders who do not implement a SbD approach can still be affected by it or by its derived products. These stakeholders may or may not believe that a SbD approach is *feasible* and may or may not consider that a SbD approach is *trustworthy*, i.e. worthy of their trust and confidence. It is also plausible that these stakeholders support the concept in specific circumstances only or provided that specific (process) conditions are met. Obviously, their perceptions are likely to affect the success of products or producers who implement a SbD approach. Moreover, SbD implementations are likely to require input from stakeholders, whose perceptions may also affect their willingness and motivation to join corresponding participatory activities.

Stakeholder perceptions are thus significant but why would one expect them to vary across stakeholder groups? After all, the aims of SbD (i.e. to develop safer technologies) are generally agreed as noble and desirable. To begin with, the concept of SbD is entangled with the notions of risk and safety. SbD is also a specific form of governance with its own normative assumptions over the "proper" way of doing things. Notoriously, perception of technological risks as well as one's preferred mode of risk governance vary greatly according to one's values and worldviews. It is therefore reasonable to expect that different stakeholders may hold different views over SbD. Secondly, SbD is a concept that has attracted considerable criticism from social scientists, who are rather sceptical about its aims and practice (Schwarz-Plaschg *et al.*, 2017; van de Poel and Robaey, 2017). These analyses remind us that the seemingly straightforward concept of SbD is far from unproblematic. It is interesting to investigate whether this criticism is shared by other (non-academic) stakeholders too and whether new points of attention will emerge thanks to their perspectives. Finally but importantly, the context in which SbD is applied (in the case: biotechnology) is bound to affect the way SbD is perceived; this necessitates an examination of stakeholder perceptions specific to SbD for biotechnology.

1.2 Research questions

This project explores the views and perceptions of a broad range of stakeholders regarding SbD in biotechnology. The main research question asked is as follows:

"How do various relevant stakeholders perceive the trustworthiness and feasibility of the concept of Safe-by-Design (SbD) for biotechnology?"

The above research question was tackled through the following three sub-questions:

1. How do relevant stakeholders understand the concept of SbD?
2. Which SbD strategies do they consider effective for biotechnologies?
3. Under which process conditions would they consider SbD trustworthy and feasible?

These sub-questions were addressed by means of literature review (cf. Section 2) and semi-structured interviews with representatives from three major stakeholder groups, namely civil society, industry and academia (cf. Section 3).

The remainder of this report is organized as follows: Section 2 reviews related work on stakeholder perceptions and examines the concept of trustworthiness in more detail. In Section 3, we explain our rationale behind the identification of relevant stakeholders and describe our interview procedures. Results are presented in Section 4. Section 5 discusses our findings and reflects on their implications, with conclusions provided in Section 6.

2 Related work

2.1 Literature on stakeholder perceptions of SbD for biotechnology

What is presently known about the ways SbD for biotechnology is perceived by various stakeholders? In this subsection, we review related work in the domain of biotechnology. Studies pertaining to SbD in different domains (e.g. nanotechnology) or studies about comparable frameworks (e.g. RRI) are only selectively discussed, e.g. when reflecting on studies with a primary focus on biotechnology.

Bouchaut and Asveld (2020) discuss perceptions of stakeholder from four professional domains (industry; societal sphere; policy making or regulatory body; academia) in relation to inherent safety and SbD in industrial biotechnology. The study reported varying understandings of risk and safety, with participants expressing different opinions on when a biotechnological innovation is *safe enough*. In times, the study participants also seem to doubt that more safety is objectively needed. With regard to SbD practice, different expectations were observed, with participants further questioning *when* safety can or should be maximized. In addition, the term "inherent safety" was met with dissatisfaction as it raises unrealistic expectations of absolute safety. We note that different understandings of risk and safety are likely to affect whether a SbD approach is perceived as feasible*:* whether such an approach can indeed enhance safety largely depends on *which* safety one hopes to see enhanced (and to what extent). Similarly, different views on *who*, *when* and *how* is supposed to maximize safety correspond with different conceptualizations of SbD and are likely to affect perceptions of its feasibility. Interestingly, some of the responses documented in Bouchaut and Asveld (2020) question whether researchers are the most suited actors to be tasked or trusted with the maximization of safety. This further motivates our interest in the (process) conditions necessary for a trustworthy implementation of SbD. Finally, the study participants had mixed feelings over an active role of citizens in decision making. This indicates that process conditions related to citizen participation may be prioritized differently by different stakeholder groups.

Schuurbiers (2021) interviewed researchers active in the domain of biotechnology and safety over the role of safety and SbD in their practice. This study also reported varying understandings of safety across the interviewees. It should be noted that the study participants were not supposed to implement SbD in their practice but to contribute with their research to the domain of biosafety. Still, their varying interpretations of safety (and of the research efforts that contribute to it) suggest that SbD affords multiple interpretations even within the same stakeholder group. Moreover, the study reported both positive and negative perceptions of the concept of SbD among academics. Some researchers conceived SbD as a restraining development while others welcomed it as a useful guiding principle or as a means to assume social responsibility. However, responses further revealed a tension between safety and novelty

(of scientific discovery), with safety initiatives not yet or not always treated (and rewarded) as an integral part of the scientific enterprise. This tension corresponds with practical challenges identified by Soeteman-Hernández *et al.* (2020) when implementing SbD for nanotechnologies in academia, specifically a lack of awareness (and appreciation) of SbD by primary investigators and a lack of time (for SbD-related activities) by PhD researchers. Moreover, a tension between safety and novelty indicates cultural barriers to implementing SbD for the specific stakeholder group (academics). Here, we follow van Hove and Wickson (2017) who distinguish between practical and cultural barriers to the adoption of a framework such as RRI. In their study of the perceptions of RRI by academics, the authors conclude that the reasons why RRI is not enacted in practice are not always practical but may relate to deeply rooted convictions about the role and nature of scientific practice.

Asin-Garcia *et al.* (2021) interviewed stakeholders from academia, industry and the policy sector over the utility of a specific SbD technology, namely genetic safeguards. The study focused on the domain of industrial biotechnology and reported both negative and positive opinions regarding the feasibility and future opportunities of genetic safeguards in this sector. Some interviewees perceive genetic safeguards as redundant or as broadcasting a wrong message of unsafety to the public. Others seem to perceive a real potential but mostly in relation to future application scenarios, i.e. beyond contained settings. The authors attribute the identified differences to different biosafety norms held by individual participants (i.e. not uniformly held across stakeholder groups). In other words, while safety is the prevailing value underlying any SbD effort, stakeholders maintain different norms on how the value of safety should be manifested. This affirms that perceptions of SbD are subject to different understandings of risk and safety, as also suggested by the abovementioned studies.

In a reflection over the future of the same SbD strategy, namely genetic safeguards, Asin-Garcia *et al.* (2020) sketch a gloomy picture of misaligned stakeholder expectations over the role of SbD and genetic safeguards. The authors note that SbD in biotechnology is often accompanied by implicit assumptions over its persuasive power and over its capacity to foster innovation; these assumptions abound in academic discourse but may not be valid or equally shared across stakeholders. The absence of concrete application scenarios, in particular, means that the utility of genetic safeguards remains vague for non-academic stakeholders; this gap was made explicit in the abovementioned study by Asin-Garcia *et al.* (2021). Finally, the authors highlight specific technical challenges that hinder the development of genetic safeguards into mature SbD solutions, including challenges due to mutations and evolution. This raises concrete questions about the feasibility of this specific strategy from both a technical and conceptual point of view.

In an analysis of a similar SbD strategy, namely xenobiology, Aparicio (2021) further scrutinize the expectations associated with SbD. Based also on the notion of synbio-phobia-phobia (Marris, 2015), i.e. the fear of the public's fear, the author describes xenobiology and other biocontainment technologies as interventions that are expected or hoped to lead to the acceptance of synthetic biology. Let us stress here that SbD need not be motived by an imagined hostile public but by genuine safety concerns by both policy makers and civil society. However, the legitimacy of SbD presupposes some agreement across stakeholders over the usefulness of SbD. Otherwise, the risk that SbD is perceived as a top-down initiative of questionable motives or as a PR stand is tangible. This further necessitates a mapping of the prevailing understandings of SbD and of the conditions under which a SbD approach can be trustworthy.

The abovementioned studies share considerable commonalities. First, they confirm that perceptions of safety play a significant role in one's perception of the concept of SbD, including both its feasibility and its utility. Second, existing studies point to slightly negative dispositions toward the concept in general and/or specific implementations (c.f. biocontainment strategies). In particular, academic stakeholders may not always perceive the concept favourably while industrial stakeholders may not be fully convinced of its usefulness, at least given present application scenarios. While *assumptions* about the reactions of societal stakeholders to the concept of SbD are frequent, the views of societal stakeholders remain underrepresented in the literature. Finally, concrete technical, practical and cultural obstacles to implementing SbD in biotechnology are exposed.

2.2 On trustworthiness

Trust is a relationship between two parties in the presence of a risky situation. It is the willingness of party A to interact with party B in spite of the possibility that the outcome of this interaction may disadvantage party A. Definitions of trust abound but the notion of vulnerability, which one acknowledges and accepts voluntarily, is proposed by many scholars as central to trust (PytlikZillig and Kimbrough, 2016). Obviously, the trusting party A does not wish neither expects that the disadvantageous outcome will materialize. Rather, party A is willing to take a so called "leap of faith" (Möllering, 2006), hoping that the actual outcome (as resulting from the actual behaviour of party B) will prove them right. Trust governs virtually every human transaction at both personal and organizational levels: a human or an organization may trust another human, organization or institution. In trust literature, the party who grands trust is called the *trustor* while the one who receives it is called the *trustee*; we will employ the same terminology in this report.

Trustworthiness is theoretically distinct from trust. It is an assessment made by party A of whether party B is worthy of their trust. From the several factors that affect trust, trustworthiness captures the characteristics of the trustee (Mayer *et al.*, 1995). In their seminal work, Mayer *et al.* (1995) offer a conceptualization of trustworthiness as a function of perceived benevolence, ability and integrity. Benevolence reflects the general goodwill of the trustee towards the trustor, while ability and integrity assess the trustee's capacity to perform the task at hand (ability) and in accordance with accepted norms (integrity). It should be noted that the model put forth by Mayer *et al.* (1995) is applicable to multiple levels of analysis. For example, it can describe trust relations between individuals or between organizations (Schoorman *et al.*, 2007). Likewise, Caldwell and Clapham (2003) explicate the factors of benevolence, ability and integrity into 7 duties "owed by" organizations, namely competence, legal compliance, responsibility to inform, quality assurance, procedural fairness, interactional courtesy, and financial balance.

Obviously, the trustworthiness of a specific actor who promotes or implements a SbD approach is to be assessed based on their perceived benevolence, ability and integrity. That said, we note that SbD is also an initiative that makes concrete propositions about (responsible) professional practice. Ideally, the approach advocated should become an established institution, i.e. a shared (formal or informal) pattern of behaviour. This motivates us to investigate trust and trustworthiness in less personified terms. Trust at the level of institutions can be approached in two ways. On the one hand, one can still talk about trust *in* an institution; the trustworthiness of this institution remains relevant. On the other hand, Bachmann and Inkpen (2011) offer a different conceptualization of institutional trust, or more precisely of institutional-based trust. Rather than a relationship between a party A and an institution B, the

authors focus on a relationship between a party A and a party C, "*in the face of*" an institution B (Bachmann and Inkpen, 2011). In other words, institutional-based trust emphasizes the role of institutions (such as a SbD approach) in enhancing trust *between* actors. We propose that a SbD approach could help establish institutional-based trust *between* different stakeholders, e.g. a provider of a technology and a user of this technology, enabling them to engage in transactions that they would have otherwise considered too risky.

3 Materials and methods

The primary data collection method of this study was semi-structured interviews with stakeholders from three major stakeholder groups, namely civil society, industry and academia. In this section, we explicate our understanding of "relevant" stakeholders and document our interview procedures.

3.1 Stakeholder identification

For the purposes of this study, we distinguished stakeholders across two dimensions. First, we considered one's relation (*internal* or *external*) to the processes that institutionalize SbD. Internal stakeholders refer to actors who formally and directly influence the concept of SbD[1]. Consider as example actors in the policy and regulatory domains who actively promote and institutionalize SbD. Scientists who develop SbD methods and strategies are also directly involved in making this concept a reality. More often than not, the perceptions of internal stakeholders are aligned with the official SbD discourse or are already embedded in it. Thus, our focus was on external stakeholders, i.e. participants who are not formally affiliated with SbD initiatives. Of course, this distinction is not watertight as the concept of SbD is being shaped interactively and in consultation with external stakeholders, who indirectly contribute to its development.

External stakeholders interact with the concept of SbD in varying degrees. For the purposes of this study, we further distinguished between *direct* and *indirect* stakeholders, based on their degree of involvement when implementing a SbD approach. Direct stakeholders are called upon, urged or encouraged to implement a SbD approach in their practice[2]. Bioengineers working in academic labs or in R&D sections in the industry, alongside their lab leaders, regulatory affairs officers, managers or directors are typical examples of direct stakeholders. Direct stakeholders are often providers of biotechnologies and likely to have some biotechnological knowledge. Nevertheless, SbD is envisioned as a comprehensive approach that integrates interdisciplinary knowledge. Therefore, we also considered experts with a broader academic expertise of relevance to safety, such as ecology, ecotoxicology, risk communication, responsible innovation and ethics. Such experts may not initialize a SbD trajectory directly but may still contribute (data or advice) to it and can, thus, be seen as direct stakeholders.

Indirect stakeholders may have no to minimum involvement with R&D in biotechnology but are likely to be affected by it. Consider as an example users of biotechnologies or of their derivatives. This means both industrial users (e.g. a producer who employs a compound produced by a microorganism) and end

[1] The distinction between internal and external stakeholders is typically used to describe a stakeholder's (contractual) position in an organization. Our slightly idiosyncratic use of the terms corresponds with our understanding of SbD as an institution, rather than as an organization. We also believe that an emphasis on (the degree of implication with) the formalization of SbD is better suited to the present situation, as SbD is still to become a commonly acknowledged institution.

[2] The distinction between direct and indirect stakeholder largely corresponds with stakeholder classifications based on impact or influence. Consider as an example, Freeman's (1984) classic definition of a stakeholder as "any group or individual who *can affect* or *is affected by* the achievements of the organization's objectives" (emphasis ours)

users (i.e. consumers). Again, the distinction between direct and indirect stakeholders does not mean that indirect stakeholders have no say in a SbD trajectory. Their input is often required but the responsibility for (planning and implementing) a SbD trajectory remains with direct stakeholders. Finally, safety in biotechnology involves the interests of specific groups such as workers or local communities, as well as broader entities such as society as a whole or the environment. To capture the perspectives of such stakeholders, we had to rely on proxy organizations from the domain of civil society, namely political parties, religious associations, and NGOs.

3.2 Participant recruitment

Direct invitations for an interview were sent via email to 38 professionals active in the domain of civil society (C=15), industry (I=13) and academia (A=10); in addition, 9 organizations (C=5, I=4) were approached via their online contact forms or info email accounts. Useful roles and relevant expertise across the three stakeholder groups were identified together with our problem owner in an early meeting; an initial list of contacts was provided by our problem owner at the same meeting. Additional contacts were identified and recruited via publicly available information. It should be noted that the variety of biotechnological applications pertaining to white, red and green biotechnology considerably complicated our work. Whenever possible, we tried to recruit participants active in or knowledgeable about any of these branches. In our search for representatives from the biotech industry, the Holland Bio database of Dutch biotech companies was an indispensable resource[3]. Social media (i.e. Linkedin) were occasionally used to search for suitable candidates. Few of the contacted professionals forwarded our invitation to other relevant contacts; for practical reasons, these contacts are not calculated in our reported total; besides, we secured no interviews via this route. Few contacts were suggested by interviewees (snowball sampling). Invitations to these contacts are included in our reported total and we secured 1 interview via snowball sampling.

Out of the total 47 contact initiatives (C=20, I=17, A=10), we received 15 positive replies. One invitee declined our invitation but provided some written feedback, which we incorporate as appropriate. In practice, 13 interviews were scheduled and conducted (response rate ~28%), with 1 positive response never receiving a follow-up and 1 scheduled interview being cancelled due to illness.

3.3 Interviews

We conducted 13 semi-structured interviews with 15 participants out of 12 organizations; two organizations requested a joint interview (2x2 interviewees). The distribution of interviews per stakeholder group was approximately equal (C=4, I=4, A=5). Table 1 provides an anonymized overview of all interviewees, their corresponding roles and associated expertise.

*Table 1: Interviewees' roles and expertise (in terms of biotechnology branches). C= civil society, I= industry, A= academia. *A link to a specific branch was noted but the participant's work or research reportedly relates or is applicable to any branch.*

ID	Role	Branch
C1	Committee member youth wing- social liberal	Environmental
C2	Committee member youth wing- social liberal	Environmental; Medical
C3	Member think tank- green	[non conclusive]
C4	Representative religious association	[non conclusive]

[3] https://www.hollandbio.nl/business-solutions/dutch-life-science-database/

I1	Biochemist/ regulatory affairs officer- biotech company	Industrial
I2	Biochemist/ innovation consultant- biotech company	Environmental
I3a	Representative professional association	Environmental; Industrial
I3b	Representative professional association	Medical; all*
I4a	Representative professional association	Agricultural
I4b	Representative professional association	Agricultural
A1	Soil ecologist	Environmental; Agricultural
A2	Medical ethicist	Agricultural; Medical
A3	Biochemist/ synthetic biologist	Environmental; all*
A4	Communication scientist	[non conclusive]
A5	Microbial ecologist	All

Interviews were conducted online (via Microsoft Teams) in the period between October 9th, 2021 and November 1th, 2021. The sessions were video recorded and a total of 12 hours and 34 minutes of recordings were obtained, with an average of 58 minutes per interview. Appendix 1 provides the participant information sheet and consent form emailed to the participants. Notes, automatically generated transcripts and videos were used to write anonymized summaries shortly after each interview session.

The interview was pilot-tested twice and few adjustments were made for clarity and brevity. During the interviews, we strove to remain flexible and attentive to the expertise and background of each participant. In particular, varying levels of familiarity with the concept of SbD called for some improvisation in the explanations and background information provided. Despite expected variations, all interviews covered the three main blocks indicated in the interview guide, namely:

1. Questions about SbD in general, e.g. prior knowledge, first impression/own definition, risks and benefits.
2. In-depth discussion of a biocontainment example. The example and infographic used were developed by RIVM (the Dutch National Institute for Public Health and the Environment) for educational purposes (RIVM, 2021) and were used with permission.
3. Questions related to different types of SbD actions. A set of SbD cards previously developed by the authors (Kallergi and Asveld, 2021) was used as a probe. In the context of the present study, these cards were meant to generate additional input on the effectiveness of SbD strategies and on specific process conditions.

Issues of feasibility and trustworthiness were further tackled at opportune moments or via dedicated questions when approaching the end of the interview. All visual materials used in the interview are provided in Appendix 2.

4 Results

In this section, we present our results organized according to the three sub-questions of the study (cf. subsection 1.2). We report on our participants' conceptualizations of SbD, including the benefits and risks they associate with the concept (subsection 4.1); their evaluation of technical and non-technical

SbD actions (subsection 4.2); and issues directly related to feasibility and trustworthiness (subsection 4.3).

4.1 Understandings of SbD

The majority of our interviewees had little to no prior knowledge of SbD: some (n=4) have never heard the term prior to the interview, others (n=5) report having encountered the term but being uncertain about its meaning and some (n=4) consider themselves familiar with it. While not all participants were professionally active in the field of biotechnology, all appeared to be positively dispositioned towards it, provided that it contributes to societal wellbeing. Participants refer (and appreciate) applications that contribute to sustainability, sustainable development goals, health or sustainable agriculture (i.e. in the form of pest resistant crops or biocontrol measures). However, interviewees from civil society sometimes question whether biotechnology is a necessary solution for the given problem and ask that alternative (i.e. non-biotechnological) solutions be also considered. For these participants, the primary question should not be about the safety of a biotechnological application but about the problem it solves.

Asked for their first association with SbD or their own definition of SbD, participants choose to highlight different elements. Most focus on the (early) identification of risks while others underline the enhanced role of developers and producers. A few participants emphasize that SbD occurs at earlier stages of a technology development trajectory. Interestingly, a couple of interviewees equal SbD with the implementation of genetic safeguards while two participants explicitly associate SbD with the deliberate release of (potentially harmful) organisms.

In general, all participants agree with the overall objective of SbD to develop safer biotechnologies; as poignantly said by one interviewee, it is hard to disagree with this objective, unless one has questionable morals. Moreover, SbD is commonly perceived as a reasonable, logical and smart way of working. However, this observation resonates differently across participants. On the one hand, several interviewees emphasise that SbD is not a new concept or approach but corresponds with established practices in the biotech industry (**business as usual**). On the other hand, several interviewees see SbD as a logical next step for the sector. This difference is also reflected in the risks and benefits associated with SbD (cf. subsection 4.1.1 and 4.1.2). Finally, while the overall aims and philosophy behind SbD appear to be well received, the responses of our participants reveal several philosophical and practical discontents, which we discuss under risks (cf. subsection 4.1.2) and barriers (cf. subsection 4.3.1).

The articulations of our interviewees indicate that the SbD mandate to anticipate, identify, or -at least- think about safety issues early is apparent to them. Yet, several participants complain that the concept is vague, fuzzy, not concrete or even artificial. Moreover, many associate SbD with an early identification of risks but few offer suggestions on how to respond to these risks. A couple of participants call for fundamental research on the envisioned adverse effects while two participants refer to risk management measures to be prepared in advance. Concrete design choices are seldom mentioned; this may be in line with the expertise of our interviewees, few of which engage in bioengineering practice. Interviewees involved with product development typically refer to internal protocols and checkpoints that affect decision-making, and less frequently to specific design actions.

4.1.1 Benefits of SbD

An obvious benefit highlighted by participants is that SbD supports the development of safe products; this benefit is self-explanatory for those who suggest that SbD is a standard practice in the biotech industry. In addition, several interviewees attribute SbD with the capacity to accelerate innovation in the sector or ease the transition from lab to real life. Some participants find that an increased emphasis on safety will be beneficial for actors (i.e. companies or scientists) who are too market-driven or too technology- focused. Others directly refer to regulations lagging behind technological developments or to a history of late regrets (i.e. harms identified too late). The abovementioned responses suggest that SbD is perceived as an initiative that goes beyond existing safety practices or as an initiative that could support the development of (what one participant described as) "futureproof" technologies. Finally, few participants contemplated potential benefits which they nevertheless did not expect to materialize. These benefits were the possibility of reducing administrative burdens at a later stage (i.e. at registration) and the possibility of generating more (public) trust in the sector.

4.1.2 Risks of SbD

Several participants express concerns about a negative impact of SbD on innovation. A too strict interpretation of SbD is clearly seen as detrimental to progress, a concern that is comparable to typical criticism of the precautionary principle. At least two interviewees draw attention to the value of innovation, which should be equally weighted or even prioritized. Moreover, a couple of participants fear that SbD could pose too much burden on smaller companies who may lack the administrative or financial resources for it. In the context of green biotechnology, this risk is further associated with a negative effect on biodiversity, with two participants (academia; industry) speculating that large companies are likely to focus on a limited set of profitable crops. Others worry that the concept of SbD may evolve into a nonsense certification. This corresponds with concerns about a "checklist mentality" as well as concerns about carelessness. For example, it was remarked that SbD might make developers overconfident of their capacity to prevent all risks and, subsequently, careless, while one participant (civil society) described biocontainment (cf. section 4.2.1) as wearing a helmet and running off a cliff.

A different but prominent set of concerns refers to the impact of the initiative of SbD on the public perception of biotechnology. Participants are repeatedly concerned that SbD propagates a wrong and even dangerous message to the public. Two distinct types of "wrong messages" were identified. Firstly, it is feared that SbD inadvertently implies that biotechnology is not already safe. It was suggested that (an emphasis on) SbD may lead to the conclusion that existing biotechnological products are unsafe or that the innovation practices of the sector differ from SbD. One participant (industry) further mentioned that repeated references to safety might have a reverse psychological effect. Interviewees from the industry are very vocal about unintended messages of unsafety and often refer to a tainted relationship with the public, which calls for cautious communications. Secondly, it is feared that the concept of SbD may raise false or unrealistic expectations about absolute safety, 100% safety or zero risks. Interviewees are aware that absolute safety is unattainable but notice that societal stakeholders may reason about risks differently. They also worry that the SbD may in fact promise too much. Claims of absolute safety are bound to backfire, causing even more distrust towards the sector. Noticeably, misconceptions over **absolute guarantees** are not exclusive to societal stakeholders. In fact, several responses indicate that the pitfall of absolute guarantees may apply to developers too. Consider as an example the abovementioned comments on overconfidence and carelessness or the issue of mutations discussed in subsection 4.1.2. Moreover, one participant (civil society) directly associated SbD to worldviews: what

one expects or aspires to achieve with SbD may depend on what one thinks about the capacity and right of humans to transform nature.

4.2 Perceptions of SbD strategies

Perceptions of (the effectiveness of) different SbD strategies were tackled via a biocontainment example, illustrating the strategy of synthetic auxotrophy, and via a set of SbD cards, illustrating different types of SbD actions (cf. Appendix 2). Synthetic auxotrophy, i.e. a built-in dependency of a microorganism on artificial nutrients, was discussed as a SbD measure to prevent risks associated with the escape of modified cyanobacteria grown in a semi-open pond.

4.2.1 Biocontainment

The strategy of biocontainment was met with mixed feelings. Initial reactions tend to appreciate the ingenuity of the solution, which is described as neat, elegant, clever or smart. Yet, most participants are unsure about the effectiveness and usefulness of the strategy. To begin with, several participants doubt whether such a strategy can be properly validated. Some interviewees are positive about a stepwise validation but others maintain that the possibility of mutations that will enable the organism to bypass the dependency cannot be excluded. The issue of mutations is recurring but is reflected differently by participants: some suggest that biology (and biotechnology) is a unique discipline in that respect[4] while others conclude that uncertainties are anyway inherent to any innovation or intervention. Either way, such responses indicate that SbD as a form of control or as a form of risk elimination is perceived as fundamentally flawed. Finally, one interviewee commented that further modifying an organism for the sake of safety is conceptually strange, as genetic modification is seen by many as unsafe.

Assuming that the strategy is sufficiently validated, its usefulness is not readily acknowledged either. In situations that would benefit from a semi-open setting, some consider biocontainment as a valid alternative to physical containment, while others prefer a combination of biological and physical containment (e.g. a glass cover over the pond; a basin around the pond). Other complementary measures mentioned are monitoring (i.e. both of leakages and of the concentrations of the leaked organism in the natural environment) and the layering of biocontainment strategies, including strategies to prevent horizontal gene transfer. Some participants expressed a general preference for physical containment and questioned the semi-open setting as the default deployment mode. Oftentimes, biocontainment is discussed as a redundant measure (i.e. in case physical containment fails), a measure to reduce residue risk (i.e. exclude the tiniest chance of escape) or a measure to reassure public opinion (if other measures are not deemed sufficient by the local community). These responses are in dissonance with the view that biocontainment would be excessive in contained settings, as stated by one participant (industry).

A reluctance to rely on biocontainment alone indicates that the strategy is perceived by several participants as just **not enough**. Yet, many responses suggest exactly the opposite, i.e. that the strategy is in fact **too much**. For example, one participant explained their preference for physical containment as a preference for less complicated measures that are also proportional to the risks. In fact, several participants consider biocontainment as complicated and note that it introduces complications at various levels: for the operation of the company (costs, more permits needed), for risk assessment

[4] Consider as an example comments by two interviewees (academia; industry) who were introduced to the history of the term SbD and who immediately remarked that ideas from nanotechnology cannot be directly applicable to biotechnology.

(more components to be evaluated) and for the organism (reduced efficiency). What is more, many participants would like to know how severe the environmental risks are at the first place, with some arguing that the organism would not survive in natural settings anyway. Only one participant described biocontainment as simpler than other safety measures while another participant expressed a slight preference for biological containment for risks of a biological nature.

Inquiries on the "actual" adverse effects of the modified organism are in dissonance with previous comments that absolute guarantees are not possible. Moreover, no references were made to biocontainment as a possible measure against uncertainties. This might be because the strategy is in itself subject to uncertainties due to mutations. We also hypothesise a different explanation: several participants are pessimistic about the positive impact of (additional) safety measures to the public perception of biotechnology. As such, participants may be disheartened to plan for every conceivable uncertainty. Instead, they would rather have a conversation about safety on an entirely different basis, namely one that knowingly weighs benefits and risks. This sentiment is also traceable in our participants' prioritization of SbD actions, as further discussed in the next subsection.

4.2.2 (Non-technical) SbD actions

When discussing different types of SbD actions, most participants recognize the need for a more comprehensive SbD approach. Several participants identify all illustrated types of actions (technical actions; organizational actions; (early) stakeholder engagement; coordination across the value chain) as essential and interconnected. Others highlight non-technical actions such as interdisciplinary teams, stakeholder involvement, education (including education of citizens), organizational support (including freedom to raise safety concerns), information exchange, and responsibility allocation. Nevertheless, replies that primarily associate SbD with technical actions (including scientific expertise) were also provided. Regardless of their preferences, many participants explicitly state that technical actions alone cannot be successful, as experience has painfully taught us. For some, technical actions may (objectively) increase the safety of an innovation but this is irrelevant if not perceived positively by societal stakeholders. For others, safety is a complex problem that needs to be addressed from multiple perspectives. References to blind spots, own bubbles and tunnel vision were also made. Noticeably, interdisciplinary teams seem to be the action of choice to counter these shortcomings. Stakeholder and citizen involvement are less prominent, with some participants being sceptical about citizen involvement, which they consider unproductive. Only one participant (civil society) explicitly asked for stakeholder involvement to be an obligatory component of SbD. That said, interactions with citizens are widely acknowledged as essential, with (effective) communication being frequently mentioned as a required component. Closely related to communication is a requirement for transparency raised by participants from all stakeholder groups. This may refer to transparency about (future) risks, transparency about a company's doings (e.g. methods, procedures) and transparency as accessible information about both risks and doings.

4.3 Feasibility and trustworthiness

4.3.1 Is a SbD approach feasible?

Overall, participants agree that a (comprehensive) SbD approach can improve safety and should be feasible in practice. Again, the feasibility of a SbD approach is self-explanatory for those who understand SbD as the norm in the biotech industry. Possible barriers to (the success of) a SbD approach range from practical to conceptual. Some participants question how exactly the concept of SbD will be interpreted

and enforced in practice and ask that the flexibility of developers (to choose fitting measures) be maintained. Others wonder about variable implementations across competitors; differences in safety cultures worldwide were also mentioned. In response, participants call for clarity both in the definition of SbD and in associated obligations. One participant (civil society) sees low awareness of SbD as a possible barrier, while another interviewee (academia) emphasizes a lack of funds and time. Academic and civil interviewees also see challenges in implementing SbD under market pressures, with one interviewee (academia) identifying political will as a relevant factor. Next to these pragmatic challenges, some participants (academia; industry) doubt whether SbD is fitting to biotechnology, as living systems are distinct from engineering projects. Finally, one participant (civil society) reflected on issues of responsibility: could a developer be held responsible for the safety of a biological mechanism that already exists in nature (cf. CRISPR)?

4.3.2 (When) is a SbD approach trustworthy?

Direct inquiries on trustworthiness[5] are typically followed by replies that involve some sort of control, check or regulation. Again, concerns that the concept of SbD will be variably interpreted (and potentially misused) by practitioners are noted. A clear and commonly shared definition, the involvement of some overseeing authority and some form of certification are proposed as possible counter measures. However, the exact governance of SbD remains unclear. For some, a SbD approach need not be explicitly validated as regulations on the final product would be sufficient. In this case, SbD may be best materialized as best practices, professional codes or guidelines to support developers or project leaders. Next, existing structures of auditing are often proposed as sufficient, should a SbD approach need to be explicitly validated. Finally, dedicated SbD certifications were also proposed. Parallels are drawn with schemes such as the CE mark, certification marks in general (in Dutch: *keurmerk*) or the ISO certification. In all cases, a clear set of steps or obligations and an independent and knowledgeable authority would be required. Obviously, concerns about unnecessary bureaucracy are raised, especially by industrial stakeholders, who often question the need for additional safety schemes.

At the same time, several participants shift attention from specific process conditions, such as external validation, and directly relate the question of trustworthiness to the aims of SbD. Some interviewees respond that a SbD approach (as implemented by a producer or promoted by an authority) will be deemed trustworthy, if and only if it does not overpromise on its aims. For these participants, absolute safety guarantees, as also implied by certification marks, are by default untrustworthy. Process conditions and/or the characteristics of the trustee may be secondary (or even in contradiction) to this requirement. Finally, and for the sake of completeness, we note a few additional elements associated with trustworthiness. The endorsement of SbD by established companies or by actors who are trusted by consumers (NGOs, the media) was attributed a positive role while one participant saw a use for cases that were suspended (for the time being) thanks to a SbD approach.

[5] Articulation on trustworthiness may refer to whether claims to a SbD approach can be trusted or to whether the approach advocated by SbD is trustworthy. For the purposes of this study, both are understood as reflections on the trustworthiness of a SbD approach.

4.3.3 Can SbD instil (public) trust?

Given that the majority of participants referred to a concerning lack of public trust towards biotechnology, the potential of SbD to build or repair public trust was also inquired[6]. Our participants are clearly split on the subject. On the one hand, several participants believe that a SbD approach could affect public trust positively by manifesting that safety has been properly considered in an intentional or proactive manner. Naturally, previously discussed actions remain relevant, including the need for transparency, proper communication and a comprehensive approach. In a way, SbD is understood as propagating a message of care: an "additional story about safety", a commitment to safety (as opposed to what is technically achievable) and a proactive stance. On the other hand, several participants are of the opinion that a SbD approach cannot repair or increase public trust because distrust of biotechnology is not always motivated by safety concerns. Some comment that safety improvements are never deemed satisfactory while others remark that safety concerns may have been over-represented in the public debate (being the only concerns acknowledged as valid). All seem to agree that the discussion around biotechnology must be conducted on a different basis, i.e. one that addresses a broader range of concerns and a broader range of societal values than safety alone.

5 Discussion

5.1 Study limitations

This study set out to map the perspectives of relevant stakeholders by means of semi-structured interviews. Our sample included interviewees from various backgrounds and professional interests, some of whom have never encountered the concept of SbD before. Major stakeholder groups (civil society; industry; academia) were equally represented and a saturation of responses was observed in our sample. Yet, it should be noted that all of our interviewees were positively dispositioned towards biotechnology. Despite our efforts to invite stakeholders from a wider ideological spectrum, our findings do not reflect the perceptions of those who may be less sympathetic towards biotechnology. We can speculate on the reasons why invited organizations declined our invitations but, eventually, we understand this as a limitation of our study design: in the absence of an existing network of contacts, our approach did not provide sufficient room to interact with organizations in a manner that would build trust.

The question of representation is urgent to any effort to capture stakeholder perceptions. Specific to our study is the complication that biotechnology encompasses a broad set of technologies and applications. Identifying relevant stakeholders becomes quickly problematic, especially when one moves further down the value chain of a future biotechnological innovation. Our sample included stakeholders with varying roles and with expertise in various branches of biotechnology. Yet, it did not exhaustively cover all roles per branch. It is thus plausible that some of the particularities of each branch were missed. Finally, citizens and consumers were represented only via proxy organizations (e.g. political parties), a solution that was fitting to our research method (i.e. interviews). A more accessible data collection method (e.g. a workshop or a public event) can further inform the questions put forth by this study.

[6] Our interest in SbD as a facilitator of institutional-based trust concerned trust relations between various actors across a value chain, not *per se* interactions with the public. Yet, the issue of public trust (or lack thereof) dominated the responses of our participants.

Lastly, a mention is due to the methodological constraints of this study. All interviews were conducted in English, which was understood to be a non-native language for our participants. For this reason, we decided to rely less on the exact wording used by interviewees and to permit a more interactive conversation during the sessions. This decision was further motivated by the fact that SbD was understood to be an unfamiliar concept for our participants and one to be assigned meaning during the interviews. Finally, our unit of analysis (i.e. summaries) unavoidably introduces an interpretative step early on in the process. In conclusion, our study and findings should be understood as interpretive and constructivist in nature, not as descriptive. Different methodological approaches are certainly possible and applicable.

5.2 Putting it all together: what do relevant stakeholders think of SbD?

While the general disposition of our interviewees towards the aims and philosophy behind SbD is positive, our findings reveal both positive and negative perceptions of the concept. It should be noted that the concerns and objections of our participants are often conditional to the way SbD will be interpreted in practice. This may be due to the absence of a concrete SbD methodology at the first place or due to our generalized explanations. In any case, participants seem to understand SbD as an external initiative that is still to be formalized into concrete obligations for the sector. A first conclusion of our study is, thus, that the feasibility and trustworthiness of a SbD approach will greatly depend on how SbD will be interpreted by both citizens and the government.

The majority of our participants are negative towards "strict" interpretations of SbD as "exhaustive" risk identification or as absolute prevention. They stress that no effort can ever identify and eliminate all risks and that the absence of risk cannot be proven scientifically. This may be common knowledge for risk managers and risk theorists but it is useful to note the diffusion of these views across all stakeholder groups. The unfortunate association of SbD with absolute guarantees is often reported in relation to the term "inherent safety" (Bouchaut and Asveld, 2020; Schuurbiers, 2021); our study indicates that refraining from the term "inherent safety" does not necessarily improve the situation. At present, we are unable to tell whether this association stems from the term "Safe-by-Design", our explanations[7], biased fears for extra regulatory obligations, or ongoing debates about safety. We hypothesize that our participants' sensitivity towards absolute guarantees is (partially) linked to current debates around safety. Note that the safety of biotechnology, in general, and the interpretation of the precautionary principle, in particular, are a matter of much debate between (some) policy makers, on the one hand, and scientists and the biotech industry, on the other. Thus, the concept of SbD cannot be perceived independently of these debates while dissatisfaction with the current regulation of biotechnology unavoidably affects the perception of SbD by academic and industrial stakeholders.

In their denunciation of absolute guarantees, our participants acknowledge that the subject of safety is entangled with uncertainty. Our capacity to predict and eliminate all risks is impeded by uncertainties caused by, among others, the evolvability of living organisms or the fact that new knowledge about adverse effects may emerge in the future. Despite this realization, participants do not dismiss SbD efforts as futile. Instead, they propose conceptualizations of SbD that steer away from the pitfalls of absolute safety. In particular, participants favour an understanding of SbD as a mind set or as an attitude of increased awareness of safety issues. SbD as such is primarily oriented at the developer or producer.

[7] While we cannot exclude unfortunate formulations from our side, we nevertheless note that concerns about "zero risk" were already raised in writing by one contact who shared their previously documented views on SbD.

Correspondingly, many participants operationalise SbD as a stepwise protocol or as a framework of best practices; these practices may not necessarily eliminate all risks but could demonstrate that safety issues were adequately considered during the development process. An appreciation for a more comprehensive approach was noted but, ironically, the content of this framework remains inconclusive. Only one participant (civil society) defined SbD as a framework of obligations related to (assuming) responsibility, (obtaining) knowledge and (maintaining) transparency (about risks). In addition, we note that larger companies appear confident in their internal procedures and workflows while smaller companies underscore the need for clarity (about any required steps) and for support in the form of accessible advisors.

While not dismissive of SbD, our participants voiced several concerns and discontents. Our findings align with common concerns and a (slightly negative) perception of SbD by direct stakeholders as reported in literature (Bouchaut and Asveld, 2020; Asin-Garcia *et al.*, 2021; Schuurbiers, 2021). This study further indicates that major concerns (e.g. about absolute guarantees) may be shared by indirect stakeholders too. At the same time, our findings cautiously suggest that indirect, civil society stakeholders may be more positive about the added value of SbD than direct stakeholders. Continuous feedback on how societal stakeholders perceive SbD is further needed, as also suggested by one participant. Finally, we note that the industry domain is typically treated indiscriminately in the literature; we propose that dedicated studies based on company size or maturity could provide additional insights in the needs and requirements of industrial stakeholders.

External validation as a means to increase trust between actors loosely corresponds with typical mechanisms in the development of institutional-based trust, namely certification and legal regulation (Bachmann and Inkpen, 2011). We note, however, that an emphasis on external validation may have been overrepresented given the direct formulation of our questions. Repeated references to transparency and communication (cf. subsection 4.2.2) may correspond with Caldwell and Clapham (2003)'s dimension of honest communication, a factor of organizational trustworthiness that conflates elements of procedural fairness and responsibility to inform. The trustworthiness model by Mayer *et al.* (1995), however, seems to only partially explain our findings. Broadly speaking, participants do not seem to doubt the good intentions of the SbD initiative (cf. benevolence): no responses would suggest that SbD is perceived as ill intended, although concerns were raised about its unintentional negative effects. The proposition that trustworthiness is conditional to the objective of SbD could be interpreted as a valuation of ability by the trustor. Nonetheless, this valuation does not refer to the ability (skills, competence or expertise) of an actor or institution but to a shared (epistemological) limitation. In other words, the question asked by the trustor is not whether the trustee can do what they promise to do but whether what is being promised can be done at the first place. It follows that dedicated measures to increase trustworthiness may be premature at this stage and as long as scepticism over unrealistic claims remains.

5.3 Where to go next: points for further consideration

5.3.1 Which biotechnology?

The view that SbD is not a new concept but business as usual is often accompanied by remarks about the exact field of practice targeted by the initiative of SbD. Specifically, participants speculate that SbD may implicitly refer to radical practices such as synthetic biology or novel methods such as gene drives. Others note that SbD may be predominantly addressing environmental risks (of transgenic products).

Finally, one interviewee directly asked: In which domains is SbD urgently needed? We are of the view that SbD can be relevant to any product under development, in either research or industrial settings. Yet, it is possible that implicit assumptions have crawled into the official SbD discourse[8]. The question begs to be asked: What exactly do we have in mind when we talk about (a need for) a SbD approach in biotechnology? Do we interpret biotechnology as, mostly, genetic engineering? Do we already refer to newer genomic editing techniques? Are we making the leap to practices such as synthetic biology? Obviously, if we conclude that SbD is motivated by challenges *specific* to emerging biotechnologies, this should be explicated accordingly.

The same question may apply to the biotechnological applications assumed in SbD discourse. Reportedly, already deployed applications (e.g. industrial applications in closed containment) are sufficiently regulated and streamlined. Consider also the conclusion of one participant that SbD "makes sense" only for environmental applications for deliberate release. For most industrial interviewees, radically novel applications are far ahead in the future while their safety will need to be tackled in a stepwise manner. Moreover, it was remarked that many biotechnological applications are already achievable, known to be safe and yet not fully utilized. This slightly bitter comment could suggest that SbD may be a sensible preparation for the future but does not help with the barriers currently perceived by the sector.

5.3.2 What problem does SbD solve?

An objective to develop safe technologies would appear to be straightforward but the exact problem that SbD aspires to solve is rather ambiguous, as different understandings of SbD illustrate. Obviously, understandings of SbD as standard industrial practice assume that a SbD approach works. Conspicuously, though, the only way to explicate the success of a SbD trajectory is a product that complies with existing safety regulations. SbD works because it enables the development of safe products *according to* the current regulation. Embracing a SbD approach may make this process easier or faster and may increase a producer's chances of success but the contribution of SbD remains utilitarian: it is a means to an end, the end being a certifiable and marketable product. In this case, the problem that SbD aspires to solve is one of process: it strives to reduce unnecessary effort, eliminate false starts and increase the effectiveness and efficiency of a development process. This gain is readily relatable for producers but requires an appropriate regulatory framework in place. It also subjects SbD to an obvious criticism: insofar as safe products are produced, the path to their development may be irrelevant.

The juxtaposition of SbD with emerging technologies and their corresponding uncertainties points to a different problem. Understandings of SbD as extra safety or as safety for the future assume that existing regulatory frameworks may not be completely adequate or futureproof. This may be due to the speed of technological developments or because existing safety norms cannot yet capture future risks. Thus, the producer is urged, encouraged or expected to consider safety issues *beyond* what is legally required in a given moment in time. In this case, the problem that SbD aspires to solve is one of time: it strives to limit damage while safety research and policy is busy catching up with the future. From the point of view of producers, SbD emerges as a strategic choice: the producer is willing to take the extra mile in exchange for some competitive advantage. This could be a competitive position in the future (e.g. if updated

[8] In this study, we were confronted with our own assumptions behind the relevance of SbD during the recruitment of participants, especially when navigating the various biotechnology companies currently active in the field.

regulations are enforced) or the opportunity to fulfil their social corporate responsibility. Suggestions about dedicated SbD certifications could help visualize commitments to social corporate responsibility, if so desirable. Unfortunately, these certifications are the most vulnerable to criticism over absolute guarantees and a false sense of safety.

5.3.3 SbD at the interface between biotechnology and society

Concerns about the effects of SbD on the public perception of biotechnology are previously noted in the literature (Asin-Garcia *et al.*, 2021) and stem from a history of polarized interactions between societal groups and the biotechnology sector. Strictly speaking, however, such concerns are yet to be validated empirically. In this study, we can only confirm that civil stakeholders ask questions or raise concerns about SbD being interpreted as absolute safety guarantees by authorities or by developers; this is an interesting but indirect association of SbD with absolute safety guarantees by civil stakeholders. In the meantime, it is striking to observe that the initiative of SbD inadvertently places direct stakeholders in an impossible position. Embrace SbD and you risk admitting that biotechnology is not already safe or that there is good reason for extra safety measures. Oppose SbD and you risk confirming that the sector is not serious about safety or wants to avoid control. Given this catch-22 situation, it is not surprising that the only reasonable response from the sector would be to co-opt the term of SbD. Efforts to differentiate SbD from existing safety practices will unavoidable stumble upon this communication deadlock.

A positive contribution of SbD as a facilitator of public trust remains disputable. What is more, while some responses indicate that SbD may project a message of care (i.e. proactively thinking about safety), most participants conclude that safety can never be enough. This can be interpreted in two ways. On the one hand, the safety of biotechnology will never be deemed satisfactory by some. The imaginary of a hostile public is traceable here as well as in corresponding comments that attribute deeply rooted mistrust and suspicion to specific societal groups. Unfortunately, the present Covid-19 circumstances only reinforce this perception, with the majority of our participants referring to the wave of distrust towards Covid-19 vaccines. On the other hand, safety can never be enough simply because it is only part of the story. References to indirect societal risks (e.g. related to issues of power and access) and to other values or worldviews that may affect one's evaluation of biotechnology were frequently made by our participants. In effect, our participants suggest that responsible innovation in biotechnology requires a societal debate on a different basis. This means both: a need to approach safety concerns differently (e.g. by deliberating over acceptable risks) and a need to address other concerns beyond safety. Interestingly, while some stakeholders see SbD as a step that precedes broader deliberation over the desirability of a biotechnological innovation, responses by civil stakeholders may suggest the opposite, i.e. that broader deliberation precedes SbD efforts. All in all, the risk that SbD diverts our attention (back) to an unproductive discussion on (absolute) safety must be taken seriously.

6 Conclusion

This study explored stakeholder perceptions of the concept and practice of SbD for biotechnology. We encountered both positive and negative perceptions of the initiative and captured risks, benefits and barriers associated with it. Our participants offered multiple interpretations of the concept, reflected on various SbD strategies and expressed preferences and discontents. Findings indicate that not all stakeholders are convinced of the need for an extra emphasis on safety in the domain of biotechnology while others do see a function for it but remain sceptical about its practical implementation. Next, it was

concluded that the feasibility and trustworthiness of a SbD approach would greatly depend on its interpretation. This conclusion may sound trite but it demands reflection over the aims of the SbD initiative. *What* is the problem that SbD aspires to solve? *Whose* problem is it? *How realistic* are its propositions? It follows that the process conditions or regulatory structures needed for a successful implementation of SbD cannot be delineated before a unanimous conceptualization of SbD is reached. In this study, SbD as an objective for the developer and as an attitude of increased attentiveness to safety issues was proposed by most as the most reasonable conceptualization.

The *philosophy* underlying the concept of SbD sounds logical and relatable for most but its practical implementation remains surprisingly hard to imagine. We suspect that this may be due to vested interests rather than a lack of know-how or imagination. To begin with, safety is a notoriously complex subject that demands attention to, among others, differences in risk perception, the value-laden nature of risk, the impact of worldviews and our uncomfortable relation with uncertainty. It is plausible that a practical interpretation of SbD asks too much from developers. Secondly, we note that SbD is entwined with thorny and currently unresolved issues, such as the current regulation of biotechnology, the public acceptance of biotechnology and the balance between precaution and innovation. It follows that, despite its benevolence, SbD cannot be perceived as a neutral initiative but is negotiated together with speculations over its political aims and practical consequences.

This study passes no judgement over the safety of biotechnology and over the current regulatory framework. Similarly, we believe that whether SbD is "business as usual" in the biotechnology sector is a matter of interpretation. However, if we agree that SbD is indeed "business as usual" and that it should (continue to) be the norm in the sector, then companies who are confident in their implementation of a SbD approach may have an obligation to share their expertise and help standardize SbD into a pragmatic and workable framework. This would be particularly beneficial for smaller companies and may help address concerns over variable implementations of the concept. Tools and platforms to share domain knowledge and best practices can be of enormous help, while it is worth noticing the promising role of internal documentations as a medium to encourage safety sensibilities. Finally, the possibility that SbD becomes a vehicle to standardize or at least explicate tacit knowledge and unarticulated safety expertise by professionals deserves further consideration.

A loud message from this study is that misconceptions over absolute guarantees must be prevented for actors at all levels: for the government (who should neither offer nor demand absolute guarantees), for the developers (who should not fall into the pitfalls of a false sense of safety) and for the public (who should not interpret SbD as absolute guarantees). As already discussed, this calls for reflection about the epistemological assumptions behind this initiative. Obviously, it also demands cautious communication. It may be the case that all communications on SbD must be accompanied by an introduction to basic risk concepts. Activities in educational or professional settings and materials meant for public outreach could certainly benefit from this. Nevertheless, spontaneous encounters with SbD will remain problematic. We believe that discussions on safety and SbD require a more radical shift in the way scientists and producers communicate about and relate to risk and uncertainty. In other words, nuanced communications on SbD need to be accompanied by transparency over risks and uncertainties in all interactions with society.

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Appendix 1 – Participant information sheet and inform consent form

TU Delft

Participant information sheet – Stakeholder interviews

Research project title:	**Perceptions of Safe-by-Design for Biotechnology**
Primary Researcher:	Dr. Amalia Kallergi (A.Kallergi@tudleft.nl)
Supervisor:	Dr. Lotte Asveld (L.Asveld@tudelft.nl)
Last edited on:	10 September 2021

You are being invited to participate in a research project. Before you decide to take part in this study it is important for you to understand why the research is being done and what participation will involve. Please take time to read the following information carefully and discuss it with others if you wish. You can contact us if there is anything that is not clear or if you would like more information. Take time to decide whether you wish to take part or not.

Thank you for reading this.

Purpose of this study

Safe-by-design is a new concept that urges the developers of new technologies to integrate safety early on in the design process. A Safe-by-design approach could be especially relevant for biotechnology as it could provide a practical solution to the safety concerns and uncertainties that come with rapidly emerging biotechnologies. However, it is unclear how different stakeholders perceive the concept of Safe-by-design and under which conditions they would consider this approach feasible and trustworthy.

This study aims to uncover the perceptions of a broad range of stakeholders over the feasibility and trustworthiness of Safe-by-design for biotechnology. We want to know what *you* think about the concept of Safe-by-design in general, whether you find it relevant or useful and whether you have specific requirements before Safe-by-design can be trustworthy. Any views expressed will be considered your own, will be treated with confidentiality and will *not* be understood as reflecting your institute's official position.

What will the study involve?

You are being invited to a semi-structured interview. The researcher has a list of topics that would like to discuss with you but may ask you additional questions as the conversation unfolds. In compliance with the RIVM guidelines, the interview will be conducted online using the Microsoft Teams platform.

Your interview will be video-recorded: this recording will be used to produce a de-identified summary of your interview. This de-identified summary will be assigned a code and will be used for further analysis.

TU Delft

Why am I asked to take part?

You are invited to this study because you are active in a field of practice that is related to biotechnology. No prior experience with the concept of Safe-by-design is required.

Do I have to take part?

No, it is up to you to decide whether to take part or not. Participation is voluntarily and your decision will not be disclosed to anyone, now or in the future.

What will happen if I take part?

If you decide to participate, the researcher will schedule an online session with you. The researcher will also ask you to sign a consent form; this form must be submitted by email the latest 1 day prior to the interview.

At the start of the online session, we will check again whether you have any questions and whether you want to participate; joining the online session does not oblige you to proceed with the interview. If you decide to proceed, the researcher will ask you to orally repeat your consent to start the video recording. The interview will proceed with a few background questions followed by open-ended questions on the feasibility and trustworthiness of Safe-by-design for biotechnology. Remember that you can refuse to answer questions and can stop at any moment without giving a reason. The online interview is expected to last approximately 1 hour.

Are there possible disadvantages and/or risks in taking part?

There are no foreseeable risks or discomforts for those participating in the project.

Benefits

There are no direct benefits for those participating in the project.

Reimbursements

There are no reimbursements for those participating in the project.

Confidentiality

Your participation to this project will be kept strictly confidential and all data will be treated and analysed anonymously. Your interview summary will be written without any direct or indirect identifiers to your person or organization. No person other than the primary researcher will have access to the original video recordings, which will be destroyed at the end of the project.

This research will record personal data about your affiliation and function. This data will be stored in a secure network drive during the project's lifetime and will not be shared with anyone outside the research team. We will use this data to assign you a profile, expressed in generic categories. This profile will be used to aggregate results and to compare views of

different stakeholder groups. Any communications about the results of this study will only refer to your assigned profile. You will not be identified in any publication from this study.

You can request and review any personal data stored in relation to this project and you can ask for this data to be changed or erased at any moment after your participation.

What will happen to the results of the research project?

The results of this research will be used to write a report for the funder of this project. You can request a copy of this report from the primary researcher (A.Kallergi@tudelft.nl). The results of this research may also be communicated in scientific publications. The de-identified summary your interview will be stored in an internal data storage service (TU project drive) for 10 years per university policy and may be shared with other researchers for future research and learning.

Right to Refuse or Withdraw

You can refuse to answer questions and you can stop at any moment without giving a reason; the remainder of your responses will be processed unless you also choose to withdraw your consent. You can withdraw your consent verbally during your interview or by emailing the primary researcher (A.Kallergi@tudelft.nl). We can process this request for as long as it is reasonable to do so (i.e. prior to communication of results).

Who is organising and funding this research?

This research project is organised is by Delft University of Technology and funded by the Ministry of Infrastructure and Water Management.

Ethical review of the study

This research project has been reviewed and approved by the Human Research Ethics Committee of TU Delft.

Whom to Contact

For inquiries about this research project, the interview procedure and the processing, storing or sharing of data and research results, you can contact the primary researcher: Dr. Amalia Kallergi (A.Kallergi@tudelft.nl). For inquires made after the project's lifetime (i.e. December 2021), you can contact Dr. Lotte Asveld (L.Asveld@tudelft.nl). For inquiries about your personal data, you can contact the privacy team (privacy-tud@tudelft.nl). Should you have felt uncomfortable in any stage of your participation or should you have a complaint about this research project, please contact Dr. Lotte Asveld (L.Asveld@tudelft.nl)

TU Delft

Informed Consent Form
"Perceptions of Safe-by-Design for Biotechnology"
Stakeholder interviews

Please tick the appropriate boxes	**Yes**	**No**
Taking part in the study		
I have read and understood the study information dated 10/09/2021. I have been able to ask questions about the study and my questions have been answered to my satisfaction.	○	○
I consent voluntarily to be a participant in this study and understand that I can refuse to answer questions and I can withdraw from the study at any time, without having to give a reason.	○	○
I understand that taking part in the study involves a video-recorded interview conducted online.	○	○
Use of the information in the study		
I understand that information I provide will be used for writing a report and that results may be communicated in scientific publications.	○	○
I understand that personal information collected about me that can identify me, such as my affiliation and function, will not be shared beyond the study team; personal information collected about me will be destroyed at the end of the project.	○	○

Signatures

_____	_____	_____
Name of participant [printed]	Signature	Date

I have provided the information sheet to the potential participant and, to the best of my ability, ensured that the participant understands to what they are freely consenting.

_____	_____	_____
Researcher name [printed]	Signature	Date

Study contact details for further information: Dr A. Kallergi (A.Kallergi@tudelft.nl)

Appendix 2 – Visual materials

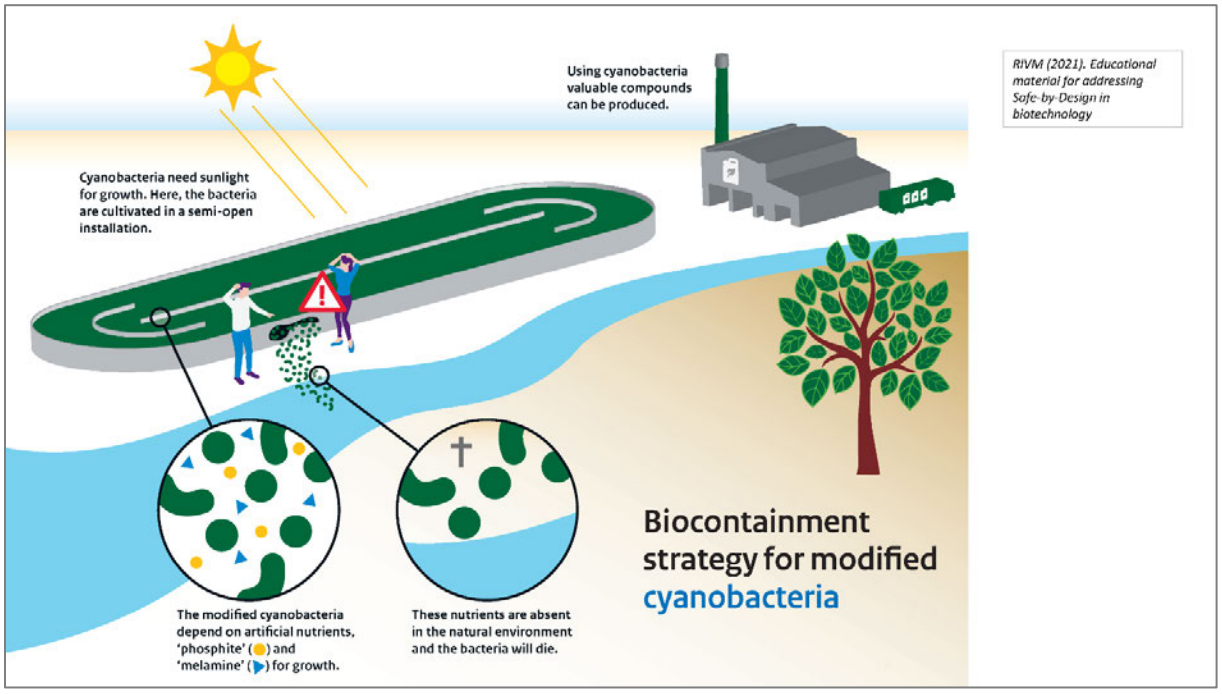

Figure 1: Biocontainment case, courtesy of RIVM, used with permission. The infographic illustrates the use of synthetic auxotrophy as a SbD measure to prevent risks associated with the escape of modified cyanobacteria grown in a semi-open pond.

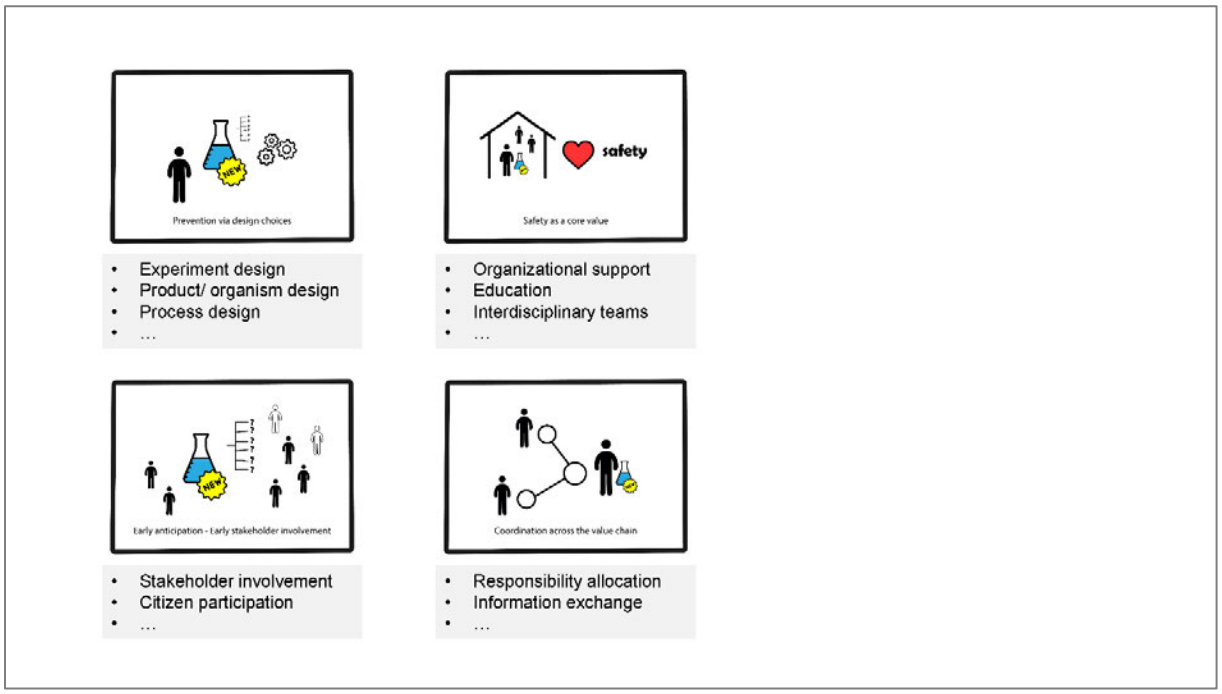

Figure 2: SbD cards (own material). The cards provide suggestions for different types of SbD actions: technical actions; organizational actions; (early) stakeholder involvement; coordination across the value chain.