

Responsible Learning about Uncertain Risks arising from Emerging Biotechnologies

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Responsible Learning about Uncertain Risks arising from Emerging Biotechnologies

Dissertation

for the purpose of obtaining the degree of doctor
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Summary

The current regulatory regime for genetically modified organisms (GMOs) in the Netherlands and Europe places great emphasis on ensuring safety. In particular, the operationalization of the Precautionary Principle (PP) in European GMO legislation has led to a strong precautionary culture with little room for research that involves uncertain risks. While safety must be highly regarded, this culture also hinders innovation because emerging biotechnologies often come with new, uncertain risks. Innovation in biotechnology is crucial to contribute to solving global problems such as pollution and CO₂ emissions and global warming. Current policy is therefore subject to a dilemma between safety and innovation. To break free from this impasse, researchers must be able to learn what uncertain risks entail, for example through Safe-by-Design (SbD). The main question posed in this thesis is: *"How to create an environment that is suitable to learn safely and responsibly what uncertain risks associated with emerging biotechnologies entail?"*.

First, **Chapter 1** provides an overview of the history of safety concerns of biotechnology. The first genetic engineering techniques were discovered in the 1970s, raising concerns within the research community itself about how to ensure safety. Later, concerns were also expressed by society in the form of protests, mainly aimed at applications of biotechnology to plants and crops. These concerns and events have contributed to a strong precautionary culture within GMO legislation which is subject to debate about the balance between safety and innovation. Second, this chapter discusses the definitions used in this thesis regarding risks, uncertain risks and uncertainties – and the difference in lack of knowledge of these types of risks. These are important for the discussions on how to create an environment suitable for responsible learning so that innovation can take place but without compromising safety, and for the degree of responsibility that would be placed on researchers. After all, they are the ones working with biotechnology, who innovate and are therefore directly confronted with uncertainties. Finally, this chapter introduces SbD; an iterative risk management strategy that can enable learning what uncertain risks entail in a controlled and responsible way. Operationalizing SbD comes with several challenges, such as that researchers can not solely determine what is safe 'enough', it is difficult to estimate all potential risks arising from a new biotechnology during the early development stages, and the lack of knowledge to be able to anticipate potential risks. However, SbD has a lot of potential to go hand-in-hand with innovation, which has already been demonstrated in other domains such as nanotechnology.

Safe and responsible learning about uncertain risks succeeds or fails with responsible handling of the knowledge gap between risks and uncertain risks – we do not know exactly what an uncertain risk entails. It is, therefore, necessary to involve a range of stakeholders in the development of a biotechnology. This way, several aspects can be discussed (for example from an ecological, (bio)ethical, and social perspective), and a broader set of risks can be identified than, for example,

only technical risks. **Chapter 2** shows how notions of safety and risk are interpreted differently by actors associated with emerging biotechnologies, and what this means for the implementation of SbD in research practices. Through interviews and a workshop, differences are revealed about what constitutes an acceptable level of risk, the meaning of inherent safety, and SbD's expectations in terms of achieving inherently safe biotechnologies. Different views are also discussed about the degree of responsibility that could or should be placed on researchers when applying SbD. **Chapter 3** analyzes how responsibilities are allocated to stakeholders with regard to identifying and managing risks and uncertain risks. This demonstrates that there is currently no assigned responsibility for identifying and communicating uncertain risks (forward-looking responsibility). This leads to the current regime being one of compliance; researchers must meet the set standards for safety, which leaves no room for research involving uncertainties. To enable responsible learning about uncertain risks, we argue for more flexibility in regulation, and co-responsibility between policy, risk managers and researchers. To operationalize such learning by means of SbD, it is crucial that all actors involved are aware of potential risks arising, and that knowledge (e.g. data derived from experiments) is shared openly.

Chapter 7 examines tensions between stakeholder groups, in particular regarding the assignment of responsibilities to researchers and whether this responsibility should pertain to both the short and long term ('forward-looking' responsibility). Some risks only become apparent once a technology is embedded in society. It is therefore important that a wide range of potential risks is discussed and strategies are developed to lower or mitigate these risks. A workshop format has been developed that can contribute to creating a suitable environment for a constructive, open discussion about potential risks with stakeholders from various fields. During this workshop, anticipatory strategies are also collectively developed, thereby offering researchers insight into how these strategies can be implemented in research practices. In addition, the discussions in the workshop make clear where there are still knowledge gaps, and where specific risk research is therefore required.

Now that the management of risks within biotechnology has become clear, how are risks managed in another, similar field? We first take on a technical perspective and compare SbD with the Inherent Safety Principles (ISPs) – another risk mitigation strategy applied in chemistry – using a case study that entails miniaturized processes using hydrogen cyanide (**Chapter 4**). This case illustrates that designing for safety by means of SbD leads in practice to value conflicts and therefore a trade-off must be made between other relevant values, e.g. sustainability, circularity, and efficiency. In addition, the ISPs seem to be better equipped to deal with such conflicts. We, therefore, argue that SbD is better suited for early-stage research (e.g. fundamental research) and the ISPs for existing products and processes (e.g. applied research).

Then, in **Chapter 5**, the risk management regime for biotechnology is compared with that of chemistry. This shows that although both regimes have a very different focus (biotech focuses on uncertain risks and chemistry on known risks), neither creates an environment suitable for (pro)active learning about new, uncertain risks. We argue that the current responsibilities should be allocated differently. For both industries, we must arrive at shared responsibility (co-responsibility) between policy, risk managers and researchers/industry. This means that some responsibilities must be taken away from the chemical industry and biotechnology should have more responsibility assigned. In addition, we make policy recommendations to stimulate openness, transparency and cooperation in the industry – in particular for the conventional chemical industry – for example by making extra funding available for the development of safer(er) products and processes. In addition, a higher level of safety can also be enforced from the industry by applying the 'polluter-pays' principle to a greater extent.

Finally, designing for safety is limited if one has little or no awareness of potential emerging risks. In Chapters 6 and 7 examples are given on how to increase awareness of risks and thus safety. **Chapter 6** presents two iGEM¹ projects executed by students from TU Delft and illustrates how more emphasis on safety issues in education has stimulated students to take safety more into account in their design choices. **Chapter 7** presents a script for researchers to organize a workshop with a broad group of participants. This also increases awareness of risks and safety among (senior) researchers. In addition, we argue that the research community should value risk research equally with technically-innovative research. A culture change is therefore also needed at universities, knowledge institutions and within the publication culture, in which research focused on risks and safety is valued more.

Based on the obtained results, I conclude in **Chapter 8** that three conditions must be met to enable responsible learning through SbD: *regulatory flexibility*, *co-responsibility* and *awareness*. Otherwise, SbD cannot be fully operationalized and is limited to providing guidelines to lower or mitigate risks and uncertainties, rather than actively learning what they entail. As a result, there will remain a knowledge gap between known and uncertain risks, which inhibits innovation and hinders risk management to ensure future safety for humans, animals and the environment. Finally, I mention the limitations of this study and make recommendations for future research based on the presented results.

¹ International Genetically Engineered Machine (iGEM); International competition for students in synthetic biology.

Samenvatting

In het huidige regelgevingsregime voor genetisch gemodificeerde organismen (GGO's) in Nederland en Europa wordt veel nadruk gelegd op het waarborgen van veiligheid. Met name de operationalisatie van het Precautionary Principle (PP) in de Europese GGO-wetgeving heeft geleid tot een sterke voorzorgscultuur waarin weinig ruimte is voor onderzoek waaraan onzekere risico's kleven. Hoewel veiligheid hoog in het vaandel dient te staan belemmert deze voorzorgscultuur ook innovatie omdat opkomende biotechnologieën vaak gepaard gaan met nieuwe, onzekere risico's. Echter is innovatie in de biotechnologie cruciaal om bij te dragen aan het oplossen van globale problemen zoals vervuiling, CO₂ uitstoot en de opwarming van de aarde. Het huidige beleid is dus onderhevig aan een dilemma tussen veiligheid en innovatie. Om deze te doorbreken moeten onderzoekers kunnen leren wat onzekere risico's inhouden, bijvoorbeeld via Safe-by-Design (SbD). De hoofdvraag die gesteld wordt in dit proefschrift is: *"Hoe kunnen we een omgeving creëren die geschikt is om veilig en verantwoord te leren wat onzekere risico's verbonden aan opkomende biotechnologieën inhouden?"*.

Als eerste geeft **Hoofdstuk 1** een overzicht van de geschiedenis van zorgen omtrent veiligheid van biotechnologie. De eerste genetische manipulatie technieken werden ontdekt in de jaren 70, waarbij binnen de onderzoeksgemeenschap zelf zorgen ontstonden over de veiligheid van deze nieuwe technieken. Later werden zorgen vanuit de maatschappij geuit in de vorm van protesten die vooral gericht waren op toepassingen van biotechnologie op planten en gewassen. Deze zorgen en gebeurtenissen hebben bijgedragen aan een sterke voorzorgscultuur binnen de GGO-wetgeving, en sindsdien wordt veel discussie gewijd aan de spanning tussen veiligheid en innovatie hierin. Ten tweede behandelt dit hoofdstuk de definities van risico's, onzekere risico's en onzekerheden die in dit proefschrift worden gebruikt. Daarbij worden ook verschillen in gebrek aan kennis van deze typen risico's belicht. Deze zijn belangrijk voor de discussies over hoe we leerprocessen op een verantwoorde manier dienen in te steken zodat innovatie kan plaatsvinden maar daarbij niet de veiligheid in het gedrang komt, en voor de mate van verantwoordelijkheid die daarbij op onderzoekers komt te liggen. Immers zijn zij degenen die met biotechnologie werken, hierin innoveren en dus direct te maken krijgen met onzekerheden. Als laatste introduceert dit hoofdstuk SbD; een iteratieve risicomanagement strategie die het mogelijk kan maken om op een gecontroleerde en verantwoorde manier te leren wat onzekere risico's inhouden. SbD komt met diverse uitdagingen zoals dat onderzoekers niet alleen kunnen bepalen wat veilig 'genoeg' is, het lastig is om alle potentiële risico's van een nieuwe biotechnologie al in te schatten tijdens de vroege ontwikkel stadia, en het gebrek aan kennis om te kunnen anticiperen op potentiële risico's. Echter heeft SbD veel potentie om veiligheid hand-in-hand te laten gaan met innovatie, wat al is aangetoond in andere domeinen zoals in de nanotechnologie.

Veilig en verantwoord leren over onzekere risico's valt of staat met verantwoord omgaan met de kenniskloof tussen risico's en onzekere risico's – we weten niet precies wat een onzeker risico inhoudt. Daarom is het nodig om meerdere actoren bij de ontwikkeling van een biotechnologie te betrekken. Zo kunnen er meerdere kanten worden belicht (bijvoorbeeld een ecologisch, (bio)ethisch, maatschappelijk perspectief), en een bredere set aan risico's worden geïdentificeerd dan bijvoorbeeld alleen technische risico's. **Hoofdstuk 2** laat zien hoe noties met betrekking tot veiligheid en risico's verschillend worden geïnterpreteerd door actoren gelieerd aan opkomende biotechnologieën, en wat dit betekent voor de implementatie van SbD in onderzoekspraktijken. Door middel van interviews en een workshop komen verschillen aan het licht over wat een acceptabel niveau van risico's en veiligheid is, de betekenis van inherente veiligheid, en de verwachtingen die SbD schept over het bereiken van inherent veilige biotechnologieën. Hierbij komen ook verschillende visies aan bod over de mate van verantwoordelijkheid die op onderzoekers zou komen te liggen bij het toepassen van SbD. **Hoofdstuk 3** analyseert hoe verantwoordelijkheden zijn verdeeld met betrekking tot het identificeren en managen van risico's en onzekere risico's. Dit laat zien dat er op dit moment geen toegeschreven verantwoordelijkheid is voor het identificeren en communiceren over onzekere risico's ('vooruitkijkende' verantwoordelijkheid of 'forward-looking responsibility'). Dit leidt ertoe dat het huidige regime er één van naleving is; onderzoekers moeten aan de gestelde normen voor veiligheid voldoen wat geen ruimte laat voor onderzoek met onzekerheden. Om in dit regime ruimte te creëren voor verantwoord leren wat onzekere risico's inhouden pleiten wij voor meer flexibiliteit in de regelgeving en medeverantwoordelijkheid (co-responsibility) tussen beleid, risico managers en onderzoekers. Om dergelijke leerprocessen te operationaliseren met behulp van SbD is het essentieel dat alle betrokken actoren zich bewust zijn van potentiële risico's, en dat kennis (bijvoorbeeld data afkomstig van experimenten) openlijk wordt gedeeld.

Hoofdstuk 7 gaat in op spanningen tussen groepen actoren, met name betreffende het toewijzen van verantwoordelijkheden aan onderzoekers zelf en of deze op zowel korte- als op lange termijn zouden moeten gelden ('vooruitkijkende' verantwoordelijkheid). Sommige risico's worden nu eenmaal pas duidelijk wanneer een technologie is ingebed in de maatschappij. Daarom is het van belang dat er een breed scala aan potentiële risico's wordt besproken en daarop strategieën worden ontwikkeld om deze risico's te verlagen of te omzeilen. Hiervoor is een workshop-format ontwikkeld wat kan bijdragen aan het creëren van een geschikt milieu voor een constructief, open gesprek over potentiële risico's met actoren uit diverse vakgebieden. Tijdens deze workshop worden ook gezamenlijk anticiperende strategieën ontwikkeld, en biedt het onderzoekers daarbij inzicht in hoe deze strategieën geïmplementeerd kunnen worden in onderzoekspraktijken. Daarnaast maken de discussies in de workshop duidelijk waar nog kennishiaten zitten, en waar dus specifiek risico-onderzoek nodig is.

Nu het risicobeheer binnen de biotechnologie in kaart is gebracht, hoe wordt er met risico's omgegaan in een ander, vergelijkbaar vakgebied? Hierbij nemen we eerst een technisch perspectief aan en vergelijken we SbD met de Inherent Safety Principles (ISP's) – een andere risico-verlagende strategie toegepast in de chemie – met behulp van een casus over geminiaturiseerde processen met waterstofcyanide (**Hoofdstuk 4**). Deze casus illustreert dat het ontwerpen voor veiligheid door middel van SbD in de praktijk leidt tot waarde conflicten en er dus een afweging moet worden gemaakt tussen andere relevante waarden, b.v. duurzaamheid, circulariteit, en efficiëntie. Daarbij lijken de ISP's beter uitgerust om om te gaan met dergelijke conflicten. Daarop stellen we dat SbD beter geschikt is voor onderzoek in een vroeg stadium (bijvoorbeeld fundamenteel onderzoek) en de ISP's voor reeds bestaande producten en processen (bijvoorbeeld toegepast onderzoek).

Daarna wordt in **Hoofdstuk 5** het beleid voor risicomanagement van biotechnologie vergeleken met dat voor de chemie. Hieruit blijkt dat hoewel beide regimes een heel verschillende focus hebben (biotech is gericht op onzekere risico's en chemie op bekende risico's), geen van beide een milieu creëert wat geschikt is voor (pro)actief leren over nieuwe risico's. Daarop beargumenteren we dat de huidige verantwoordelijkheden anders moeten worden toegewezen. Voor beide industrieën moeten we uitkomen op medeverantwoordelijkheid tussen beleid, risico managers en onderzoekers/industrie. Dat wil zeggen dat er bij de chemie verantwoordelijkheden moeten worden afgenomen bij de industrie, en de biotechnologie meer verantwoordelijkheid moet worden toegewezen. Daarnaast doen we beleidsaanbevelingen om openheid, transparantie en samenwerking in de industrie te stimuleren – in het bijzonder voor de conventionele chemische industrie – bijvoorbeeld door het beschikbaar stellen extra financiering voor het ontwikkelen van veilige(re) producten en processen. Daarnaast kan een hoger niveau van veiligheid ook worden afgedwongen bij de industrie door het principe van 'de vervuiler betaalt' breder en strenger toe te passen.

Als laatste, ontwerpen voor veiligheid is beperkt als iemand zich niet tot weinig bewust is van mogelijke opkomende risico's. In Hoofdstuk 6 en 7 worden voorbeelden gegeven over hoe bewustzijn van risico's en dus veiligheid kan worden vergroot. **Hoofdstuk 6** presenteert twee iGEM²-projecten uitgevoerd door TU Delft-studenten en illustreert hoe meer nadruk op veiligheidskwesties in onderwijs ertoe heeft geleid dat studenten hun ontwerpkeuzes meer hebben toegespitst op veiligheid. **Hoofdstuk 7** presenteert een script voor onderzoekers om een workshop met een brede groep deelnemers te organiseren. Hierdoor wordt vooral ook het bewustzijn van risico's en veiligheid onder (senior) onderzoekers vergroot.

² International Genetically Engineered Machine (iGEM); Internationale wedstrijd voor studenten in de synthetische biologie.

Daarnaast pleiten we ervoor dat de onderzoeksgemeenschap risico-onderzoek en technisch-innovatief onderzoek gelijk gaan waarderen. Er is dus ook op de universiteiten en kennisinstituten, en binnen de publicatiecultuur een verandering nodig zodat onderzoek gericht op risico's en veiligheid meer wordt gewaardeerd.

Op basis van de verkregen resultaten concludeer ik in **Hoofdstuk 8** dat er aan drie voorwaarden moet worden voldaan om verantwoord leren door middel van SbD mogelijk te maken: *flexibiliteit van de regelgeving*, *medeverantwoordelijkheid* en *bewustzijn*. Zo niet kan SbD niet volledig worden geoperationaliseerd en is het beperkt tot het geven van richtlijnen om risico's en onzekerheden te verlagen of te omzeilen, in plaats van actief te leren wat ze inhouden. Het gevolg hiervan is dat er een kenniskloof blijft bestaan tussen bekende en onzekere risico's, wat innovatie remt en risicobeheer belemmert voor het waarborgen van toekomstige veiligheid voor mens, dier en milieu. Als laatste noem ik de beperkingen van dit onderzoek en doe ik op basis van de gepresenteerde resultaten aanbevelingen voor toekomstige studies.

Chapter 1

General Introduction

1.1. Introduction

In 2020, Emmanuelle Charpentier and Jennifer Doudna were both awarded the Nobel Prize in Chemistry for developing the revolutionary CRISPR³-Cas9 genome editing technology (Ledford & Callaway, 2020). CRISPR had already been discovered in 1987, but only in 2012, the sequences were combined with the Cas-9 protein which opened up a new world of precise gene editing possibilities. While this technique comes with many beneficial applications such as gene therapy, diagnostics or the development and production of biobased materials and bioenergy, it also gives rise to new risks and uncertainties – instances for which we currently lack knowledge about the possible detrimental effects and their severity. To ensure safety for society and the environment and taking into account the knowledge gaps we currently have, we must proceed with caution.

In Europe, proceeding with caution has so far been categorized by *precaution* in current regulation of biotechnological applications such as CRISPR. Precautionary measures for safety are taken based on partial data, assumptions and expectations, rather than on specific data and knowledge resulting from something actually gone wrong, which would derive measures to act with caution to ensure safety. Particularly the way the Precautionary Principle (PP) is operationalized in respective GMO legislation has resulted in a strict regime with a strong focus on ensuring safety. Thereby, little room is provided for experiments that might involve uncertain risks e.g. using CRISPR. Due to the normative character of the regulatory regime, one has to provide conclusive evidence that an experiment is safe which cannot be done for uncertain risks as there is a knowledge gap. However, the vast pace of developments in this field and the potential these techniques have to contribute to solving global problems related to pollution or global warming have led to a dilemma in regulation between safety and innovation. To break free from this impasse, researchers should be able to learn what uncertain risks entail. Learning would allow us to gain knowledge and to decide, in response, what appropriate (regulatory) measures should be taken to ensure safety, while innovation is not being stifled. However, while risks might emerge during this learning (i.e. uncertain risks), we must be careful that these are kept to a minimum so that people, animals or the environment do not become exposed to detrimental effects. Therefore, this should be done in a controlled and responsible way, for instance through Safe-by-Design (SbD) – a promising risk management approach to anticipate and mitigate uncertain risks.

This thesis explores how we can learn what uncertain risks associated with emerging biotechnologies entail, and how to manage them safely and responsibly.

³ Clustered Regularly Interspaced Short Palindromic Repeats – a family of DNA sequences derived from bacteriophages. In combination with the Cas9-enzyme, the technique can be used for finding and altering a specific piece of DNA, or for turning specific genes on or off without altering a sequence.

To do so, I have studied how the current risk management regime ensures safety, how to reconcile ensuring safety with innovation given the vast pace of developments in this field, and how to enable a responsible learning process regarding uncertain risks. To place the research question into context, this chapter briefly elaborates on the history of concerns about biotechnology and how these shaped the current regulatory regime for Genetically Modified Organisms (GMOs) in Europe. Then, I elaborate on the definitions used in this thesis concerning risks, uncertain risks and uncertainties, and introduce the concept of SbD. Lastly, in Section 1.6, I present the main research question and the respective sub-questions that will be answered in this thesis.

All content Chapters (i.e. 2 to 7) have been either published or are in review for peer-reviewed academic journals. Literature studies, conceptual analyses, performed data collection (i.e. interviews, organization of workshops), data analyses, processing of the obtained results, and the writing of all chapters have been performed by the author of this thesis. For all empirical data collection, permission was granted by the TU Delft Human Research Ethics Committee. All transcripts, interview guides, lists of interviewees and workshop participants, and respective coding are made available on the DANS⁴ data repository and are accessible via a DOI provided in the relevant chapters' method section (i.e. Chapters 2, 3, 4 and 7). Due to confidentiality and privacy, this data is restricted but access can be requested from the author of this thesis. Lastly, the empirical material regarding Chapter 4 was supplemented with work conducted for a BSc. thesis (i.e. interviews) for which the respective student has been made co-author of this paper. Also, the conducted workshops presented in Chapter 7 were co-developed with the co-authors. Further analysis of the outcomes of the workshops and the writing of the paper was performed by the first author.

1.2. A Very Brief History of Biotech Regulation

Biotechnology regulation has been shaped by safety concerns coming from both society and the research community. Initial concerns were already expressed in the 1970s when the first discoveries of genetic engineering techniques made researchers question how to ensure safety regarding these 'new' applications. Therefore, the 'Asilomar Conference on Recombinant DNA' was organized in 1975 to address 'new' biohazards associated with this new technology (Berg et al., 1974). The result of this conference was a voluntary moratorium on experiments regarding the cloning of recombinant DNA, and an endeavor to bring science more to the public domain. Furthermore, guidelines were established to ensure working safely with recombinant DNA technologies, for instance, using biological containment,

⁴ DANS (Data Archiving and Networked Services) is an institute of the Royal Netherlands Academy of Arts and Sciences (KNAW) and the Dutch Research Council (NWO).

biological barriers, and the use of additional safety factors such as physical containment. Measures derived from the Asilomar Conference are perceived as an early application of the PP (Capron & Schapiro, 2001; Peacock, 2010), which was further developed in the Montreal Protocol (1987), the United Nations Rio Declaration on Environment and Development (1992), and the Cartagena Protocol (2003).

The PP is widely implemented in regulation to ensure safety and to justify taking precautionary measures when emerging technologies give rise to possible threats to human health and/or the environment (United Nations, 1992). But the way this principle has been operationalized in GMO regulation within the European Union (EU) is controversial with many proponents and opponents (Anyshchenko, 2019; Anyshchenko & Yarnold, 2020; Van Asselt & Vos, 2006). Thereby criticisms mostly pertain to how the principle is operationalized in comparison to its first defined implementation described in the 1992 Rio Declaration on Environment and Development (Hansson, 2008; Sandin et al., 2002) and that it is ambiguous in the distinction between risk and uncertainty (Hopster, 2021; Van Asselt & Vos, 2008). Also, there are different versions of the PP tailored to distinct sets of circumstances which leads to that no normative conclusion can be taken solely based on the PP (Hartzell-Nichols, 2013). Therefore, the PP should be considered as a midlevel principle that should be complemented with other principles before a decision can be made on what precautionary measures would be appropriate (Sandin & Peterson, 2019).

For biotechnology, the ambiguity and debates about the scope, definition and practical consequences of the PP have lead to discussions on the defined scope of a GMO (Tagliabue, 2015, 2016), the resulting length and duration of procedures and inadequate decision-making, particularly regarding the market authorization of plant engineering techniques and applications (Zetterberg & Björnberg, 2017). Currently, the debate within the European Union (EU) focuses on how ‘new’ genetic engineering techniques such as CRISPR should be assessed in comparison to recently exempted techniques such as traditional mutagenesis⁵ (Parisi & Rodriguez Cerezo, 2021). However, any regulatory changes could be more than five years away or may not happen at all, which is illustrative of the current regime not being resilient in dealing with emerging techniques.

⁵ Mutagenesis is a process that changes an organism's genetic information. This can occur naturally, or is induced by exposure to mutagens. In terms of *traditional* mutagenesis, physical or chemical agents (e.g. X-ray or UV radiation) make (random) permanent changes to genetic material. These forms of mutagenesis techniques have been known since the beginning of the 20th century. In comparison, CRISPR is a form of *directed* mutagenesis, which makes site-specific mutations in a targeted manner.

1.3. Distinctions in Applications of Biotechnology

In addition to concerns coming from the research community itself, social scrutiny and protests against certain applications of biotechnology have also impacted regulation. In particular, GM crops faced many protests due to the perceived potential risks involved, mostly associated with these being ‘unnatural’ (van Haperen et al., 2011) and possibly irreversibly damaging (local) ecosystems (Blaine et al., 2002; Krinsky, 2005). This has led to GMO regulation differentiating a) contained and non-contained use, b) the application of biotechnology, and c) the process by which GMOs are obtained. This is reflected in specific procedures or exemptions that can apply.

Biotechnology is divided into three⁶ application-oriented fields: industrial (beer brewing, biobased compound production, etc.), applications to plants and crops, and (bio)medical purposes (vaccine development, insulin production, gene therapy etc.). Industrial applications mostly involve micro-organisms such as yeasts, bacteria and fungi which are growing contained (i.e. closed reactor vessels), plant engineering or agricultural purposes can be contained, semi-contained (i.e. controlled greenhouses) or non-contained (field trials), and (bio)medical applications are contained during lab stages (insulin production or vaccine development) but are non-contained in specific cases when used to treat patients (for instance gene therapy or vaccination).

Particularly semi- and non-contained use is regulated on a strict base and needs to undergo a case-by-case environmental risk assessment; a permit is required to make sure that no or only negligible risks emerge that might result in humans or the environment being exposed to possible detrimental effects. In that regard, while new, emerging applications may have great potential benefits, e.g. improving the global food supply by means of engineering plants and crops, these benefits are not weighed-in in the risk assessment – only risks and whether these would be acceptable. In contrast, (bio)medical applications such as gene therapy are also heavily controlled during developmental stages (National Institute for Public Health and the Environment, n.d.), but their development is less stifled as the respective risk assessment does allow for potential benefits to be taken into account (European Medicines Agency, n.d.) – which is not the case for industrial and plant applications of biotechnology. Besides, while these types of applications also undergo public scrutiny i.e. interfering with nature and ‘playing God’ (Delhove et al., 2020), the associated risks are perceived differently; they mostly pertain to an individual’s level

⁶ There are also many other applications distinguished, e.g. to living aquatic organisms, for nutrition, or bioinformatics (Kafarski, 2012). Industrial, plant engineering, and (bio)medical applications are the most profound.

instead of e.g. altered plants possibly affecting their local ecosystem⁷ (Abels, 2005; Bauer, 2002, 2005). Nevertheless, Delhove et al. (2020) illustrate that one's perception and the acceptability of applications such as gene therapy is still highly dependent of public engagement and one's knowledge, e.g. the amount of information provided by scientists and/or medical staff and the extent of knowledge patients have – which is applicable to all uses of biotechnology.

Since the discovery of CRISPR-Cas9 in 2012, the debate on how to manage and assess new gene-editing techniques once again gained momentum. Thereby, 'playing for God' (Locke, 2020) or organisms and plants altered through CRISPR being 'unnatural' (Schultz-Bergin, 2018) were again arguments used to call for more strict regulatory measures. In 2018, the Court of Justice of the EU (ECJ) ruled that organisms obtained by directed mutagenesis methods such as CRISPR should be subjected to strict GMO legislation while conventional techniques with a long safety record such as crossbreeding or traditional mutagenesis are to be exempted (European Court of Justice, 2018). The ECJ and EC argue that as new genetic engineering techniques such as CRISPR can produce GMOs that do not occur naturally at a high rate and in large quantities, these should be distinguishable from organisms obtained by conventional techniques (European Commission, 2018). Also, the EC argues that as these 'new' techniques are still in development, there is *lack of* knowledge and therefore the use of these new techniques should be regulated strictly – we should be *precautious*.

The ruling of the ECJ sparked discussion as now, in theory, identical organisms can be either exempted or subjected to GMO regulation due to the use of a specific technique (Wasmer, 2019). Particularly opponents of the ECJ's ruling argue that gene-editing techniques, and specifically point mutations by means of CRISPR-Cas9, are very precise in terms of initiating specific mutations in an organism's DNA (Callaway, 2018b; Grohmann et al., 2019; Kupferschmidt, 2018). Therefore they argue that these techniques are comparable in their precision and thus as safe as classical breeding techniques (crossing and selection) – which are exempted. In addition, other exempted forms of mutagenesis using radiation or treatment by chemicals are less accurate – particularly compared to CRISPR-Cas9 – as these cause random mutations of which we only get to see the phenotypical results (e.g. plant characteristics) and mutations on a molecular level remain unknown. Nevertheless, the traditional forms of mutagenesis have a long safety record and in that sense have provided conclusive evidence that they are safe. For 'new' techniques, although they may be equally safe or safer (i.e. more accurate)

⁷ Nevertheless, also (bio)medical applications such as antibiotics can affect (local) ecosystems. In particular wastewater treatment facilities provide environments that are at risk for supplying antibiotic resistance or horizontal gene transfer (Karkman et al., 2018). However, compared to applications to plants, the pros and cons of (bio)medical applications are associated more strongly with the individual level.

compared to the traditional routes, this has not been proven yet and therefore, they are subjected to GMO legislation.

1.4. Defining Risks

Emerging technologies are often, if not always, accompanied by risks, uncertain risks and uncertainties. Though all these notions pertain to the association of ‘having the possibility of something bad happening’, they do differ in their meaning and the extent of having knowledge about the possibility of something happening, or the severity of the possible event.

As this thesis covers risk management and regulation, risks related to technicalities and societal issues, and differing (societal) perceptions of risks, I adopt the broad definition of a risk referring to *the possible consequential adverse effects of an activity or event with respect to something that humans value* (IRGC, 2019). However, this definition applies to a wide range of risks, and risks differ in their meaning between domains, i.e. technical sciences, social sciences and society and regulatory organizations (risk communication). In this thesis, I mostly focus on the technical definition of a risk on which I elaborate below. The societal interpretation of a risk which is often associated with ‘the absence of danger or being safe from danger’, is touched upon in Chapter 7 (Section 7.3.1.) and discussed in Chapter 8 – the conclusions and recommendations.

When referring to a *technical risk*, I refer to its definition of already having extensive knowledge about a hazard’s probability of occurrence and the severity of that hazard doing harm, i.e. the impact, or effect (Hansson, 2009). Therefore, a risk is quantifiable and defined as: $\text{Risk} = \text{Effect} * \text{Probability}$ ⁸. For *uncertain risks*, we have knowledge about the possible effects, but lack knowledge in terms of the probability, or the severity of the effects. For *uncertainties*, we only know that there is a possibility of ‘something bad happening’ (see Figure 1.1). Using CRISPR-Cas9 again as an example, applying this technique may lead to off-target effects – unexpected and only partially understood effects of which some may be harmless, and some could have more severe consequences. In that sense, some off-target effects may be considered an uncertain risk – we know the effect but have difficulty estimating the probability of this effect occurring – or an uncertainty in case we lack knowledge of both aspects. Lastly, an *emerging risk* can refer to both an uncertain risk and an uncertainty as emerging risks are considered ‘new’ and in that sense, knowledge is limited.

⁸ In Chapters 2 and 4, I refer to a risk with: $\text{Risk} = \text{Hazard} * \text{Probability}$, as in these cases, the source of potential harm-doing is addressed.

In this thesis, I also use the terms *known knowns* and the *known unknowns*⁹ (Aven & Renn, 2009) to refer to the extent of knowledge we have of risks and uncertain risks. The known knowns adhere to known risks – we know that we have extensive knowledge. The known unknowns refer to uncertain risks and uncertainties; matters of which we have limited knowledge – we may not know the potential hazard's effect or the severity of this effect, or may only know that something 'bad' might happen.

The majority of scientific research is devoted to studying the known unknowns, i.e. through hypothesis testing. However, in such research, it is expected that a hypothesis is either accepted or rejected based on known possibilities, so on existing knowledge even though it may be limited (Logan, 2009). But, sometimes, a result can be completely unexpected which refers to a third category of uncertainties; the *unknown unknowns*. This category is associated with the so-called 'black swan' type of events, which are surprising extreme events relative to present knowledge (Flage & Aven, 2015). While considered outside the scope of this thesis, there is also a fourth category, the 'unknown knowns' – things of which we have knowledge and data but do not understand their relevance or applicability (Sarewitz, 2020). Figure 1.1 provides a schematic illustration of the extent of knowledge and understanding referring to all four categories mentioned above.

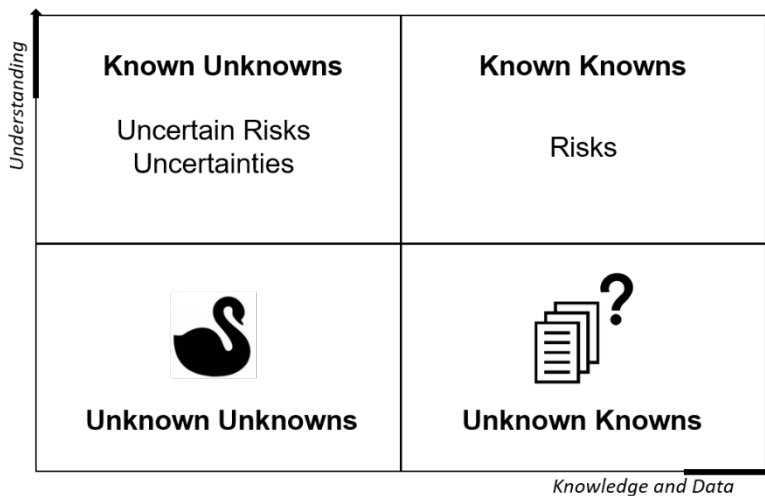


Figure 1.1: Schematic overview of the extent of available knowledge and data, plotted against the extent of understanding, illustrating the positioning of the known unknowns, known knowns, unknown unknowns and unknown knowns.

⁹ Referring to uncertainties by having known knowns, known unknowns and unknown unknowns was initiated by United States Secretary of Defense, Donald Rumsfeld during a 2002 press briefing addressing the absence of evidence linking the government of Iraq with the supply of weapons for mass destruction to terrorist groups.

1.5. Safe-by-Design

Uncertain risks and uncertainties are subject to knowledge gaps and may be understood and/or interpreted differently by various stakeholders – they are ambiguous. These matters complicate determining whether an uncertain risk should be regarded and assessed as a risk, and deriving norms for the acceptability of such risk. *Risk governance* entails the multitude of stakeholders and procedures that lead up to such decision-making processes (Van Asselt & Renn, 2011). Thereby, the aim is to provide a conceptual as well as a normative basis for how to deal responsibly with risks that are uncertain, complex, and/or ambiguous. To do so, multiple ‘dynamic’ approaches have been developed that aim to deal with numerous involved stakeholders, and take their respective values into account in decision-making processes regarding emerging technologies. Examples of such are Responsible Research and Innovation, Adaptive Risk Management and more recently for the field of biotechnology, *Safe-by-Design* (SbD). In particular the latter holds the promise of being able to deal with uncertain risks associated with emerging technologies, which has already been demonstrated in literature in the field of nanotechnology (Gottardo et al., 2021; Kelty, 2009). As the field of biotechnology, and in particular synthetic biology, is also highly associated with ‘new’ risks, the SbD approach is believed to be very suitable to continue safe and responsible development of this field (Van de Poel & Robaey, 2017).

The concept of SbD originated in the domains of chemical and civil engineering and has recently been thoroughly applied in emerging fields such as nanotechnology and synthetic biology (Schwarz-Plaschg et al., 2017; Van de Poel & Robaey, 2017; Van Gelder et al., 2021). By using and integrating knowledge of materials’ (possible) adverse effects on human health, animals and/or the environment into the early stages of a design process, risks can be anticipated and mitigated early on. Thereby, a broad range of stakeholders should be involved to be able to identify and anticipate a range of possible issues, also ensuring safety on a broader level (i.e. also beyond technical issues). As such it provides a socially broad approach to learning about uncertain risks and how to manage them responsibly. However, as SbD is still a relatively new approach in biotechnology and synthetic biology, some challenges need to be overcome to make this approach operational and workable for associated stakeholders such as researchers, risk assessors, policy makers etc. These challenges are addressed below and pertain to the question of whether SbD is an adequate way to identify and address uncertain risks and uncertainties associated with emerging biotechnologies, which is analyzed in Chapters 2 – 7 and discussed in Chapter 8 of this thesis – the conclusions and recommendations.

The first challenge relates to having no agreed-upon definition of SbD for its application in biotechnology yet, which may lead to miscommunication between

involved stakeholders and therefore differences in application. Therefore, we must gain insights into how SbD and notions related to this approach (e.g. safety, uncertain risks, inherent safety) are perceived and understood by different stakeholders.

Secondly, the designers (i.e. researchers) of a biotechnology application cannot solely determine what level of safety would be acceptable and which aspects or values besides safety should also be highly regarded when designing for safety. This requires input from other stakeholders as well to determine what trade-offs should be made (Robaey et al., 2017). In addition, when dealing with new biotechnology applications, it is difficult to foresee all safety issues during the early stages of development, e.g. during research and development (R&D). These issues give rise to questions regarding the applicability of SbD, mostly in terms of responsibility allocation to researchers and other stakeholders, and how to deal with value conflicts, i.e. how to balance the value of safety with other relevant values in design choices, e.g. sustainability, efficiency, economy, etc.

Lastly, SbD focuses on knowledge of materials' (e.g. organisms, vectors, applied techniques, etc.) possible adverse effects and aims to use this knowledge to lower or mitigate risks and uncertain risks. Thus, this would be knowledge we already have obtained – we have (some) knowledge regarding the effect and/or possibility. However, this also gives rise to the question of to what extent SbD is able to identify and deal with uncertainties – matters of which we do not know the effect nor the possibility; we only know some harm might be inflicted. Therefore, we need to gain insights into these issues and determine whether SbD could be an approach for safe and responsible learning.

1.6. Research Questions and Approach

The discussion so far illustrates that Europe's risk management on biotechnology is very much focused on ensuring safety, and therefore on lowering or mitigating *known* risks. Thereby, little room is provided for experiments that might involve learning about uncertain risks due to the embeddedness of the PP in GMO legislation, and the resulting prescriptive character of the regulatory regime. However, given the vast pace of developments in this field, and the potential biotechnology has to contribute to solving global problems related to pollution and global warming, we need to find a way to continue the development of this field in a safe and responsible way. One way to do so is by learning what uncertain risks and uncertainties entail, which led to the main research question to be answered in this thesis: *How to create an environment that is suitable to learn safely and responsibly what uncertain risks associated with emerging biotechnologies entail?*

To answer this question, and considering the subjects touched upon in this introductory chapter, three sub-questions were derived.

1. How are notions of risk, safety, inherent safety and Safe-by-Design perceived by different stakeholders associated with emerging biotechnologies?

The first sub-question revolves around shedding light on the differing perceptions of stakeholders towards notions related to safety and risks, and the SbD approach. These need to be researched first as this thesis mostly uses empirical findings, qualitative data through interviews and workshops, and contextual analyses which need to be placed in the right context. In addition, differing interpretations or understandings of the notions of risk, safety and inherent safety also contribute to one's understanding of SbD and thus affect the implementation and operationalization approach – which is necessary information for sub-question 3.

Chapters 2, 3 and 7 present an analysis of stakeholders' differing perceptions, associations and interpretations of risks, safety and SbD, based on interviews and/or workshops. Chapters 3 and 7 also further explore to what extent having different interpretations result in tensions between stakeholder groups, and what this would mean for identifying and managing uncertain risks, and thus the operationalization of SbD to enable responsible learning.

2. How is safety ensured in the current governance ecosystem for biotechnology, and how resilient is this system given the expected future developments in this field?

First, with 'governance ecosystem', I refer to the collection of institutions, administrative and societal processes and actors, in which the interplay and interactions between this complex set of actors is crucial for the proper functioning of the system. As I focus on the implementation of biosafety governance in the Netherlands, these actors comprehend, amongst others, the responsible Ministry, policy makers, regulators, risk assessors and managers, knowledge and research institutions, scientists, engineers, biosafety officers and actors adhering to the societal domain. On an EU level, actors and institutions involved in GMO regulation e.g. the European Commission, are also considered part of the ecosystem.

To enable responsible learning about uncertain risks and uncertainties associated with emerging biotechnologies, we must first gain insights into a) how the current system aims to ensure safety, b) how it manages uncertain risks and uncertainties, and c) how responsibilities are allocated. Thereby, we also compare the biotechnology governance ecosystem to a comparable field, in this case, the field of chemical engineering. From this comparison recommendations are provided

for policy changes and how responsibilities should be redistributed to ensure safe future developments in both biotechnology and chemistry.

First, through interviews and a literature review, Chapter 3 provides an overview of the current governance ecosystem for biotechnology in the Netherlands, and elaborates on how different applications of biotechnology are regulated. This chapter also illustrates that currently there is little room for researching uncertain risks and research that has uncertain risks and uncertainties involved. This has led to a precautionary culture¹⁰ in which compliance prevails; a linear system with very little interactions between stakeholders e.g. researchers and policymakers/regulators, and the circumvention of uncertain risks. It is concluded that this is mostly due to the strong embeddedness and the operationalization of the precautionary principle in GMO regulation and illustrates that the current system is 'not fit for purpose' with an eye on future developments in this field.

Following upon, Chapter 4 analyzes differences in applying the Inherent Safety Principles (ISPs) – which are commonly used in the field of chemical engineering – and SbD; two approaches aiming to lower risks and increase safety. For this, a case study regarding miniaturized processes using Hydrogen Cyanide is used. The regulatory system for biotechnology is compared to regulation that applies to chemicals in Chapter 5. In this chapter, we argue that the fields' respective risk management regimes are at odds with each other – biotechnology regulation places great emphasis on uncertain risks, and regulation concerning chemical products and processes focuses on known risk, while both types of risks emerge in either field. We conclude that for both fields learning about uncertain risks is necessary to work towards safe(r) industries, but is stifled in either. In biotechnology due to there being little room to study uncertain risks and uncertainties, and in chemistry due to lack of incentives to make products and processes safer.

In terms of current and future responsibility allocation for identifying and managing uncertain risks, Chapter 3 analyzes the notion of forward-looking responsibility in the current regulatory regime within the Netherlands. Chapter 5 compares the allocated responsibilities in biotech regulation with the respective regulation for chemicals and the chemical industry. Here, we argue for policy changes and for redistributing responsibilities for managing uncertain risks. For biotechnology there should be some responsibility given to researchers and industry so that a learning environment can be created – resulting in co-responsibility. For the domain of chemical engineering responsibilities should be mostly taken away from the industry itself as this appears to create little incentive for (the conventional) industry to work on the development of safer chemicals and chemical products.

¹⁰ In this context, a culture refers to the way actors behave and act, defined by 'written' (e.g. norms, policy, regulation) and 'unwritten' rules (e.g. shared beliefs, values and communication practices).

Thereby, for both risk management regimes the playing fields should be levelled so that safe and responsible development of new products and processes prevails, and that biotechnology can compete with long-established chemical products and processes.

3. To what extent is the Safe-by-Design approach capable of contributing to responsible learning about uncertain risks, and what is needed to operationalize this approach?

As already discussed, SbD would be a suitable approach to learn what uncertain risks entail. But, it also comes with multiple challenges as addressed in Section 1.5 above. Stakeholders' different expectations and associations with SbD are analyzed in Chapter 2 (sub-question 1). Chapter 7 analyses how to enable an environment that would be suitable for learning processes, for instance through SbD. Here, we focus on communication between stakeholder groups, and in particular tensions between these groups that complicates this communication. In response, we have developed a workshop format for researchers to organize a stakeholder workshop in line with the notion of 'social learning'. By means of this workshop, and as stakeholders from different areas of expertise are involved in this workshop, researchers can identify a range of possible issues, develop anticipatory strategies to lower or mitigate these, and gain insights into setting up additional research concerning uncertain risks and uncertainties.

Designing for safety through SbD comprehends (pro)actively lowering, mitigating and anticipating possible risks. Thereby being aware of potential risks is crucial. To study awareness in research practices, we have focused on both senior and junior researchers. Chapter 6 illustrates how awareness of safety issues is created among students and how 'designing for safety' can be embedded in education. We do this by showcasing two different iGEM¹¹ projects executed by students from TU Delft, in which safety and security issues have been thoroughly analyzed and anticipated in each project's respective design choices. Creating awareness of senior researchers is addressed in Chapter 7 where we share our findings about a workshop that provides researchers with tools to identify and anticipate risks. Also, through this workshop, we aim to incentivize researchers to set up research that specifically addresses risks.

Lastly, the above-stated sub-questions and main research question will be reflected upon in Chapter 8 – the 'Conclusions and Recommendations'. Based on

¹¹ International Genetically Engineered Machine (iGEM); International competition for students in synthetic biology. The iGEM foundation is dedicated to the advancement of synthetic biology, the development of an open, collaborative, and cooperative community, aiming to tackle global challenges by means of synthetic biology (iGEM Foundation, n.d.-a).

the results, the limitations of this research are elaborated on and recommendations for regulation, industry and researchers, and future research are provided.

Chapter 2

Safe-by-Design: Stakeholders' Perceptions and Expectations of How to Deal with Uncertain Risks of Emerging Biotechnologies in the Netherlands

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2.1. Introduction

Developments in the field of biotechnology have been a topic of discussion since the emergence of genetically modified organisms (GMOs) at the beginning of the 1970s (Paul Berg et al., 1975). Public debate reached its peak during the mid-1990s around the issue of unknown consequences (Hanssen et al., 2018). Although most debates revolved around applications of agricultural (i.e. green) biotechnology, these discussions also negatively affected the image of industrial (i.e. white) biotechnology. Today, gene editing techniques are causing societal turmoil due to their uncertain risks. In terms of white biotechnology, the application of Clustered Regularly Interspaced Short Palindromic Repeat (CRISPR) technology may offer endless possibilities but could also be accompanied by unforeseen risks, for example off-target mutations (Gorter de Vries et al., 2018). Such undesired consequences could negatively affect the public, animals and the environment, and these concerns have reignited the ongoing GMO debate, especially with regard to risk governance applied to all strands of biotechnology, that is, red, green and white. For the sake of clarity, in this paper we use the term *risk governance* to refer to the broad notion of risk-related decision-making processes regarding emerging biotechnologies (van Asselt & Renn, 2011).

In the summer of 2018, the Court of Justice of the European Union (ECJ) in Luxembourg, ruled that organisms treated with CRISPR technology should be classified as GMOs (Purnhagen et al., 2018). The main concern arising from this decision is that the focus is too much on quantifiable risks (Callaway, 2018a). This narrow focus offers little flexibility for the further development of CRISPR applications and for dealing with uncertain risks that might accompany this type of biotechnology. As a result, this ruling rekindled the discussion about the development of adequate governance, especially in terms of risk assessment and the proper classification thereof (Callaway, 2018b). Although many have called for measures to shift the focus from quantifiable risks to uncertain risks (Callaway, 2018a; Kupferschmidt, 2018), there is no consensus on the best way to establish adequate risk governance in practice. However, suggestions have been made that adequate risk governance should entail collaboration and co-development of knowledge between governmental decision-makers and other stakeholders such as scientists, risk assessors or other experts in the field (Linkov et al., 2018; Trump et al., 2019). This way, when information regarding quantifiable risks is lacking in early stages of development, quantitative data can be complemented with insights and experimental data from experts (e.g., researchers) in order to gain insight in the balance between the known risks, and possible societal implications (Linkov et al., 2018). However, as there also tends to be a 'disciplinary culture' among experts (Ndoh et al., 2020), a broad inclusion of perspectives would be important to establish appropriate risk governance.

Several policy advisory bodies in the Netherlands have suggested that the concept of Safe-by-Design (SbD) could lead us towards the appropriate governance of emerging biotechnologies (Bureau KLB, 2018; Cogem, 2009; Ministerie van Infrastructuur en Waterstaat, 2019; Stermerding & de Vriend, 2018). Theoretically, this approach can include a wide range of stakeholders, establishing co-development of knowledge to learn about the biotechnologies' potential impacts. The SbD approach is already applied in the domains of chemical engineering and nanotechnology, and comprises both engineered and procedural safety by “using materials and process conditions which are less hazardous” (Bollinger et al., 1996; Khan & Amyotte, 2003). This refers to the idea of designing specifically for the notion of safety by iteratively integrating knowledge about the adverse effects of materials (Van de Poel & Robaey, 2017). Within the domain of biotechnology, the SbD approach is still relatively new and its application should be different from the traditional applications. Yet, there is no concrete definition of the concept for biotechnology, nor an explication of how exactly the approach could be applied within this domain. As mentioned, safe biotechnology is a contentious issue on which various stakeholders have different perspectives that need to be teased out in order to arrive at a meaningful use of SbD.

In this paper we pose the question: ‘How do various stakeholders perceive notions of risk, safety and inherent safety, and what does this imply for the applicability of SbD for risk governance in industrial biotechnology in the Netherlands?’ We found that stakeholders hold widely diverging views on the notion of acceptable risk, the allocation of responsibilities, and whether the focus should be on the product or the process, or perhaps both. Because these notions are not aligned, it is hard to reach agreement on what level of risk is acceptable, making it more difficult to apply SbD in an appropriate way. In addition, results illustrate that defining SbD within the context of (white) biotechnology is complex, and would require more research.

2.2. Methods

2.2.1. Design

This study used a three-step research approach comprising a literature study, semi-structured interviews and a stakeholder workshop¹². The first step focused on studies devoted to perceptions of risk and safety in relation to biotechnology, and on the concept of SbD applied in different engineering fields (e.g. chemical engineering, nanotechnology). Studies in the field of biotechnology are mainly associated with perceptions of and attitudes towards GMOs, relevant to the field of

¹² All data (e.g., form of consent, interview protocol, coding protocol and transcripts) are available upon request via <https://doi.org/10.17026/dans-z8a-7p5p>.

white (industrial) and green (food and agriculture) biotechnology. Results from the literature study functioned as input for the interviews.

2.2.2. Interviews

The interviews were carried out in the light of a bigger project, and served the goal of gaining insight in: (1) current policies involving biotechnology and synthetic biology; (2) safety and risks in the development of synthetic biology applications; (3) current interactions between science, policy and society; and (4) tasks and responsibilities within the overall development process of biotechnologies. For this study, the set of questions was complemented with an extra set of questions specifically focusing on the concept of SbD and perceptions of risks, safety and inherent safety. Given that the interviewees are working in different domains (i.e., industry, societal sphere, regulatory body, or academia), this helped clarifying how these notions are addressed and used by the interviewees, how these notions relate to the concept of SbD in their perspective, and whether there are differences in these. The interviews followed a semi-structured approach that left enough room for interviewees to go into detail when the researchers felt that such was necessary.

Interviews (N_{tot}=12) with experts in the field of industrial biotechnology from the Netherlands were conducted in the period May–July 2018 and in February 2019. The interviewees were selected based on their experience (all holding senior positions) and professional domain, namely industry (ID) (N=2), societal sphere (SO) (N=1), policymaking or regulatory body (PM) (N=4), academia or independent consultancy (AE) (N=5). At the start of each interview, the interviewee signed a form giving consent to record the interview. After the interview, a transcript was sent to the interviewee for any remarks or corrections. Upon receiving the interviewee's approval, the transcript was coded and analyzed accordingly.

2.2.3. Stakeholder workshop

The results from the interviews functioned as input for a stakeholder workshop that was held in November 2018 in The Hague, the Netherlands. The aim of the workshop was to clarify recent and future challenges posed by the current regulatory framework for biotechnologies in the Netherlands and to explore the merits of an SbD strategy as a solution to these challenges. The output and preliminary results from the interviews were discussed with all participants and functioned as a reflection on the results obtained so far.

A variety of stakeholders (N_{tot}=22) active in the fields of academia (N=7), Dutch governance institutes (N=8), consultancy (N=3), NGOs (N=2) and industry (N=2) participated in the stakeholder workshop, of which most of the interviewees¹³. All

¹³ Nine of the twelve interviewees participated in the stakeholder workshop.

participants were selected based on their knowledge of and experience in the field of industrial biotechnology in the Netherlands, all holding senior positions in their designated profession, except for one PhD researcher.

2.3. Theory

2.3.1. Safe-by-Design

SbD is an engineering concept for risk management that originated in the field of chemical engineering and is heavily applied in the field of nanotechnology (Kelty, 2009; Schwarz-Plaschg et al., 2017; Van de Poel & Robaey, 2017). SbD comprises both engineered and procedural safety (Khan & Amyotte, 2003), and is usually referred to as “reducing or eliminating hazards by using materials and process conditions which are less hazardous” (Bollinger et al., 1996; Kahn & Amyotte, 2003). This refers to the idea of designing specifically for the notion of safety by integrating knowledge about the adverse effects of materials (e.g. chemicals or nanomaterials) on human health, animals and the environment into the design process of a technology (Schwarz-Plaschg et al., 2017). Literature regarding SbD in the context of chemical engineering or nanotechnology assumes that there is (adequate) knowledge of the used chemicals or nanomaterials (Nau & Scholz, 2019) and that safety can be treated like a property of materials or products. However, the actual usage of such materials in later stages is hereby excluded (Schwarz-Plaschg et al., 2017). Therefore, for cutting-edge technologies such as nanomedicines, it can be hard to adopt SbD principles as these technologies have not reached the same level of maturity as common nanomaterials (Yan et al., 2019). In terms of industrially applied biotechnologies, emerging gene editing techniques such as CRISPR have also not reached the level of matureness to already oversee all (possible) consequences.

Dealing with uncertainties calls for measures different from those used in traditional risk assessment, which addresses and regulates technologies assuming these are fully developed and ready to enter the market (Schwarz-Plaschg et al., 2017). In that perspective, SbD can be seen as a strategy to shift regulatory and political decisions towards scientists or other engaged stakeholders. Recalling that adequate risk governance should comprise co-development of knowledge, specifically when data about risks turns out to be insufficient in the early stages of development (Linkov et al., 2018), the concept of SbD enables this by iteratively engaging different stakeholders throughout a biotechnology's development process. When collectively designing with safety in mind, different stakeholders might see different issues arising due to their differing perceptions (Ndoh et al., 2020; Robaey, 2018). However, when many stakeholders are involved in a biotechnology's development process and the focus is on designing for safety, it is important that all the stakeholders' expectations, notions and perceptions are known and aligned. Any mismatches in notions (feelings of safety and security,

sustainability) or expectations ('high' or 'low' levels of safety) might lead to difficulties in choosing 'the right' design options, making it difficult to reach a collective design with an adequate safety level.

It is currently being explored how the concept of SbD can be applied in technical domains such as biotechnology and synthetic biology. In order to get a better idea about the suitability of this concept for use in these domains, two types of SbD applications must be distinguished: upstream and downstream (Doorn et al., 2013; Powell, 2007; Schwarz-Plaschg et al., 2017).

2.3.2. Product Applied Safe-by-Design

Literature coming from chemical engineering or nanotechnology describes the concept of SbD as safety measures specifically applied upstream; aimed at the product itself or the technical components. Examples of these types of measures are the replacement of hazardous chemicals, or adaptation of the process or product synthesis (Kraegeloh et al., 2018; Schwarz-Plaschg et al., 2017; Van de Poel & Robaey, 2017). The choice between two chemical compounds having comparable properties but e.g. different levels of toxicity, can be made in a quantifiable way. Regarding safety, the compound having the lower level of toxicity would be preferred in this case. Within this paper, we refer to these types of measures with product-applied SbD. Within the field of biotechnology and synthetic biology, measures such as biocontainment (i.e. building in genetic safeguards) are examples of product-applied SbD applications (Robaey, 2018).

2.3.3. Process Applied Safe-by-Design

In addition to safety measures specifically applied to technical components, there are also measures that are applied downstream and might involve decision making at other levels, e.g. policy level. Examples of such measures are licensing and monitoring – and in that sense, weighing risks against benefits – , or any other measure that would require the active involvement of multiple stakeholders. Within this paper, we refer to such measures with process-applied SbD.

The biggest difference between product and process applied SbD lies in the decision-making process on what is an acceptable level of risk. From a product (upstream) perspective, these decisions are mostly routinely and can be dealt with quantitatively, as it is usually known which risks accompany the usage of certain raw materials or synthesis pathways. From a process (downstream) perspective, the decision regarding what level of risks is acceptable can be more complex, as more uncertainties have to be taken into account. When dealing with new biotechnologies e.g. CRISPR, it is difficult to foresee any future issues or risks due to a lack of experience (Van de Poel & Robaey, 2017), complicating the decision-making process in terms of the 'ideal' balance between risks and safety and making it more subjective. In addition, although a certain usage is devised for a

biotechnology, in practice, this can turn out differently because different users are involved. In that respect, we can argue that although the norms and values applied to a biotechnology's development process in general will not change, the weight given to them can. For example, whereas safety can be given more weight in the early stages of development, sustainability could become more important at a later stage. And as many stakeholders are involved, reaching a consensus about what weight should be given to which norms and values might be difficult.

2.3.4. Inherent safety

In literature, strategies and measures for early and iterative safety considerations throughout a technology's development process are frequently referred to as inherent safety (Amyotte et al., 2007; Kletz, 1996, 2003; Nau & Scholz, 2019; Schwarz-Plaschg et al., 2017; Yan et al., 2019). In the domains where SbD is already being applied, for example chemical engineering, the term inherent refers to the focus on changing the process at an early stage to eliminate hazards, rather than developing add-on features to control them (Khan & Amyotte, 2003). In relation to SbD, both notions aim to act upon safety issues by adapting processes during early stages of development to reduce or eliminate potential uncertain risks. However, there is reason to believe that the term inherent creates differing expectations and notions among stakeholders, for example in terms of 'lower' or 'higher' levels of safety, leading to complications with regard to collectively establishing acceptable levels of safety in practice.

Literally translated, inherent safety refers to something being intrinsically or built-in 'safe', hinting at absolute safety. The suggestion of something being absolutely, namely 100%, safe is contrary to an engineering point of view, which acknowledges that achieving 100% safety is currently not possible (Khan & Amyotte, 2003; Schmidt, 2008). In addition, it appears that inherent safety has different meanings in different engineering disciplines. Within the traditional engineering disciplines, inherent safety has a rather straightforward definition: "In safety engineering, inherent safety refers to the elimination of hazards, for example, by replacing dangerous substances or processes by less dangerous ones" (Van de Poel & Robaey 2017, p. 299). Although this principle can also be applied within the field of biotechnology, for instance by using less hazardous organisms, there is a difference in that these principles are being applied to living organisms which can, therefore, act unpredictably (Robaey, 2018). In that sense, Robaey (2018) underlines that the first step in *doing* SbD in the field of biotechnology is to formulate strategies and measures beforehand (choice of organism, biocontainment, designing warning mechanisms) in order to be able to approach inherent safety.

2.4. Results

Four themes were derived from the interviews and the stakeholder workshop. These themes help to clarify and structure the results in terms of differences in stakeholder perceptions of risks and safety, and expectations with regard to the concept of SbD. The identified themes are: (1) *Risks and safety*, (2) *Responsibility allocation*, (3) *Inherent safety* and (4) *The citizen's role*.

Section 2.4.1 provides an overview of the current regulatory setting according to the interviewees, and whether this corresponds to the state of affairs outlined in the literature. Each of Sections 2.4.2–2.4.5 provide a detailed overview per identified theme where any issues arose, and whether there were any contradictions between the interviewees' statements¹⁴. At the end of each section, the findings are linked to the concept of SbD. What implications this might have for future policymaking, as interpreted by the present researchers, are then discussed.

2.4.1. Current situation

In the Netherlands, current legislative settings for biotechnology can be described as a precautionary culture, meaning that the Dutch government is held (end)responsible for inducing risks towards society, even unknown risks (Helsloot et al., 2010), assuming that research facilities or industry have complied with regulation. These regulations, which were developed in the mid-1990s, base their classification (GMO/non-GMO) and the type of risk assessment needed on the process, rather than on the end product (as is done in the United States). A synthesis can derive exactly the same end product, but the path travelled – for example via traditional mutagenesis or a synthetic pathway – is decisive for classification (GMO/non-GMO).

According to all the interviewees, the current regulations for industrial biotechnologies in the Netherlands are unfit for future risk governance. In line with European legislation, the Dutch government uses the following definition of a GMO: “an organism with the exception of human beings in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination” (Ministerie van Infrastructuur en Milieu, 2014). This means that altered organisms that do not occur *naturally* need to be assessed on what risks they might pose to human health, animals and the environment, and fall under the Dutch GMO legislation. As techniques for genetic modification are developing rapidly and becoming increasingly more complex, basing the required type of risk assessment on the technology's process and its *naturalness* can become

¹⁴ The interviews were held in Dutch, and the quotations from them have been translated into English. The original quotations can be requested from the corresponding author.

questionable. In that sense, we could argue that the definition of a GMO itself has become outdated.

This was acknowledged by several interviewees active in academia [AE] and policymaking [PM]. For example, one of the interviewees [AE5] stressed that risk assessment in line with the current GMO regulation has become inadequate in terms of the technical details needed for proper risk assessment, that is, risk assessment tools for host organisms or vector list¹⁵. Thus, regulation no longer matches with what is being or is planned to be done in laboratory settings; it is lagging behind.

“The end product can be the same, although different regulations may apply, which creates tension amongst researchers. Current governance is perceived as a burden by researchers.” [PM1]

“The standard vector list is no longer adequate; it is outdated. The researcher himself has been using vectors that they have tinkered with much more, so the list no longer matches [with reality].” [AE5]

The inadequate governance can be explained by the rapid developments in the field of biotechnology over the last decade. In particular CRISPR applications have led to an increased pace in developments within this field. In addition, the ruling of the European Court to classify CRISPR applications as GMOs has also increased the complexity of handling such classifications, as such techniques do not match with the GMO classifications the GMO directive is based on. Although there was a consensus amongst the interviewees that current policy should be updated to conform with current biotechnologies, they also said that they expect that the rapid pace of these developments will continue, or perhaps even accelerate in the coming years. Interviewees from the domain of policy making (PM) mentioned the SbD concept as a strategy to be able to anticipate future developments in industrial biotechnology responsibly, in addition to an update of current regulation. However, interviewee PM1 asks the question: “If SbD would become fully integrated, will policy become redundant?”.

2.4.2. Risks and safety

The first identified theme revolves around perceptions of and the balance between risks and safety.

2.4.2.1. How safe is safe enough?

Regulation is an effective way to deal with technological risks. However, people from different contexts and different worldviews tend to have different perceptions of risks and safety (Adams, 1995, 2011; De Witt et al., 2017; Hansson, 1989; Merad,

¹⁵ Practical tools for risk assessment: identification of what risks accompany the use of certain host organisms or vectors. Offered by the Dutch GMO office (in Dutch: Bureau GGO). <https://www.ggo-vergunningverlening.nl/ingeperkt-gebruik/hulpmiddelen-bij-de-risicobeoordeling/doorzoekbare-lijsten>

2020): what one person considers an unacceptable risk, another can find perfectly acceptable. Especially when dealing with uncertain risks, finding a balance in what level of risk is acceptable and coming to an agreement on this is very context dependent and can differ between stakeholders. Illustrative of this difference in perceptions are the responses from the interviewees representing academia [AE], industry [ID] and society [SO]. The decision that industrial companies have to make about how 'safe' they want their products to be is often based on the costs of 'adding' safety to a product, and whether this addition outweighs another addition. "Where should the balance be between a safe product and an affordable one?" [ID1] Although it is hard to answer this question, when a product already complies with safety standards it is often a matter of the company drawing up a balance sheet. In academia, it is acknowledged that a technology can never be safe in an absolute sense: there will always be some risks that we have to accept. In that sense, some interviewees argue that current GMO regulation is too strict; too much emphasis within debates is put on risks while the risks are actually very small [AE1]. The focus is too much on "safety on paper" [AE2].

Interviewees also pointed out that in societal debates, the emphasis is mostly on uncertainties that accompany a biotechnology, rather than the quantifiable risks. For the broader audience, accepting that a biotechnology can potentially harm the ones they love, directly or indirectly via the environment, is more complex due to people's values, and their perceptions of risks and safety, and of biotechnology in general [SO1]. Emphasizing uncertain risks in the public debate might increase feelings of unsafety and lead to more reluctance to accept biotechnologies, thus hindering further development. In that sense, for society, determining what is not acceptable is easier than determining what would be acceptable. Interviewees from the field of policymaking acknowledged this difficulty in determining 'what is safe' [PM3].

"The extremes of something not being acceptable is easy. Within society, we are now in search of this level of acceptance [when something can be considered acceptable]." [PM3]

2.4.2.2. How to communicate about safety?

Although the formal decision-making process (i.e. licensing) on whether a technology is acceptably safe is based on legislation, peoples' perception of what would be acceptable is also based on emotions, feelings and personal experiences. Despite the complete absence of reported accidents in the field of white biotechnology in recent decades, some organizations still claim that biotechnology is an unsafe domain to operate in. These claims often rely on reported incidents or raised concerns coming from other strands of biotechnology, e.g. gene drives (Scudellari, 2019) or germline editing (Rossant, 2018). Although these claims can sometimes be considered controversial, we can never guarantee that there will be no negative side-effects in the long run, also for white biotechnology. Therefore

these organizations cannot be told that they are completely wrong. An interviewee active in the field of governance [PM3] addressed this when questioning whether we (the public) are actually concerned about safety itself or more about whether we feel safe, and to what extent this is influenced by the amount of discussion devoted to these topics.

"Is it about safety or more about feelings of safety? These can be at odds with each other. For example, a fence around a prison can guarantee safety, while giving a sense of insecurity to local residents at the same time. Feelings of unsafety can sometimes increase more when more social debate is dedicated to it." [PM3]

A proposed solution to overcome this is to involve people more in the decision-making process, thereby making them critically rethink the technology [SO1]. A representative from industry [ID1] stressed that when a technology has undergone a sufficient risk assessment, it should be ready to be introduced into the market and within society. Elaborately informing people was not specifically mentioned by this interviewee, while all the other interviewees did mention this to a certain extent.

Other interviewees, however, pointed out the decreasing credibility of objective (scientific) information due to the increasing influence of industry within this domain [SO1], thereby questioning whether informing the general audience is effective. SO1 argued that, with an eye on SbD, industry influences the values associated with what would be acceptably safe. This raises a moral issue: "How critical do you have to be with regard to company interests within research?" [SO1].

2.4.2.3. When to consider safety?

The interviewees held widely diverging perceptions on the acceptability of risks. In addition, another issue arises: when or where in the development process of biotechnology should safety aspects be considered? Although all interviewees acknowledged that safety aspects should be considered and acted upon during development, differences emerged in relation to emphasizing safety measures at the beginning or at the end of the development process. AE1 stressed that measures for safety should be taken into account throughout the process, thereby being adequately met by the end of the development process, namely when the technology enters the market stage. AE5 commented that the emphasis should be put on safety measures at the beginning of a biotechnology's development process, that is, during the design and idea phase. With regard to uncertain risks, this implies that the responsibility for determining what to identify as safety issues, what measures to take and what would be safe enough, would mostly be allocated to researchers. In contrast to AE5, AE1 specifically mentioned that you cannot expect only researchers to decide what would be safe enough. A different perspective was put forward by interviewee SO1, who argued that the negative or positive consequences of biotechnologies are often caused by people, not the technology

itself. Although certain values may be embedded in a technology, this cannot guarantee that there will not be any misuse or different usage than originally intended. In that sense, SO1 emphasized that safety issues should mainly be addressed during the later stages of a biotechnology's development process, when a product is being introduced into society.

2.4.2.4. Weighing risks and benefits during the development process

When dealing with uncertain risks, one way to determine what would be acceptable is to weigh the societal benefits of a technology against the known and unknown risks of a technology. Following this line of thought, PM2 argued that the specific moment at which risks are assessed during a technology's development process also calls for different standards. In that sense, benefits can be assigned a greater role depending on when risk assessment takes place, possibly creating a more appropriate balance between risks and benefits. For example, in the case of antibiotics, "The social benefit of this technology turned out to be huge" [AE4]. However, a challenge would then be to determine what can and cannot be considered huge [PM1], and what we as a society "would be willing to give up for a certain matter" [AE1].

2.4.3 Responsibility allocation

The second identified theme is allocating responsibility. When applying SbD as a way to anticipate uncertain risks, who should be accountable for the decision making on what is and what is not safe enough? Recalling the theoretical assumptions regarding SbD, a shared responsibility among stakeholders is desirable so that risks and safety aspects are fully taken into account throughout a technology's development process (Robaey et al., 2017; Stermerding & De Vriend, 2018; Van de Poel & Robaey, 2017).

2.4.3.1. An equal share?

The interviewees acknowledged that all stakeholders involved in the research, development and further implementation of a biotechnology should have a shared responsibility for being open. Specifically, transparency in terms of raw materials, used products, processes and techniques, and the subsequent risks and safety measures related to these. Although the interviewees agreed upon a shared responsibility, this does not mean that the weight of this responsibility should be equally divided. AE1 argued that, depending on the technical complexity of a biotechnology, researchers or stakeholders at the beginning of a biotechnology's development process should have a higher degree of responsibility. SO1 mentioned some concerns with regard to the "techno-optimism" amongst researchers. Allocating higher degrees of responsibility to those considered experts in a technically complex matter (e.g. researchers) does not contribute to transparency

in the decision-making process on what would be acceptable in terms of safety and risks. In that sense, putting higher degrees of responsibility on these stakeholders would not necessarily lead to increased levels of safety, as societal concerns might be overlooked.

“Everyone [should be held responsible]. But that is also dependent on what you’re dealing with, how technically complicated that is, or the amount of expert knowledge necessary to make these decisions.”
[AE1]

2.4.3.2. Allocating responsibility

While some interviewees argued that researchers should have a higher degree of responsibility in terms of anticipating uncertain risks as they are situated at the ‘cradle’ of a technology [AE1, AE5], others argued that, in this case, the Dutch government should be held responsible and take the lead in imposing regulation [AE4, PM1, PM3]. In this way, the government functions as a controlling agent for researchers [AE4], thereby reflecting society’s norms and values (democratic system). In addition, ID1 argued that industry should have a higher degree of responsibility, implying that also companies active in the field of industrial biotechnology should have the responsibility to be open about their products and processes. However, this might become problematic as not every company would want to go along with this level of openness for financial reasons or because of issues of confidentiality.

“New developments create new uncertainties and therefore require reflection and new learning processes. Organizing these processes around these new risk questions is where industry and scientists have a high degree of responsibility. But, for that, you will need an active government to stimulate it.” [AE4]

“You see, the industry naturally has responsibility for producing safe products. I think it would help if a company takes social responsibility into account and should therefore also provide information.” [ID1]

Graphically speaking, this means that higher degrees of responsibility are allocated to the beginning (idea and development phase) and the end (regulation and market implementation) of a biotechnological development process (Figure. 2.1).

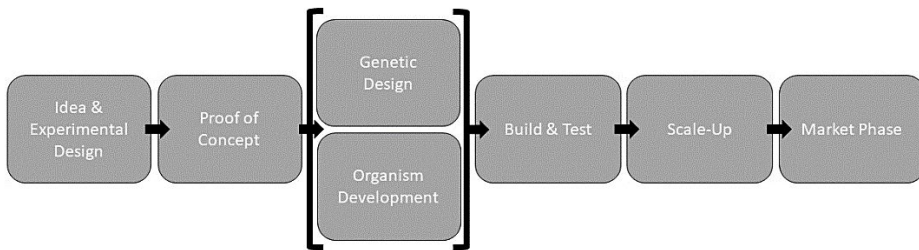


Figure 2.1: A simplified version of a biotechnology's development process. Phases with higher levels of responsibility would be upstream - the idea and proof of concept phase (e.g. researchers from both academia and industry), and downstream - the scale-up and market phase (e.g. governmental regulation).

2.4.4 Inherent Safety

As mentioned, strategies and measures for early and iterative safety considerations throughout a technology's development process are frequently referred to as inherent safety, even though a collective meaning of this notion is not shared by all stakeholders. Although all the interviewees acknowledged that technology can never be absolutely safe as the term inherent might suggest, their notions differed. Recalling the distinction we have made between product and process applied SbD, inherent safety also conjures two different applications: one focusing on the product, the other on the process. This also leads to complexities in how we deal with risks; in a more quantitative way relying on known risks, or more subjectively relying on differing perceptions and values with regard to uncertain risks.

2.4.4.1. Product vs. process

SO1 argued that SbD is already being applied in industry, referring to the fact that their products should always be safe. This implies that, in this case, inherent safety is more associated with the product's technical aspects, and SbD is applied product-wise. Within the domain of governance, inherent safety is considered a strategy to do SbD. In this sense, inherent safety is associated with process-wise SbD, aiming to get as close as possible to the creation of absolute safety [PM3].

"We have been working on Safe-by-Design for some time now. We define it more as a process. It is about taking safety into account as a value within a technological development. It is about thinking about safety during the development of products, which always includes safety." [PM3]

Although the distinction between these perceptions of inherent safety may seem a small one, it can have major consequences for how uncertain risks should be dealt with and for future risk governance. Interviewee AE3 mentioned that safety is always a dynamic, iterative process where multiple actors have to be taken into account, which is exactly where the challenge lies. "Applying the 'helicopter perspective' to incorporate all stakeholders' perspectives and opinions calls for prioritizing some

over others” [AE3]. However, AE3 also pointed out that scientists are under pressure to publish and therefore sometimes have to take risks. “Someone else will be ahead of you if you want to do it in a safe and good way”[AE3], illustrating the tension between the two mentioned notions: product and process applied. From a researchers’ perspective (product applied), prioritizing safety measures imposed by others (process applied) might result in safety measures that researchers may find excessive for the goal they have in mind. Finding a good balance in these prioritizations is crucial to ensure safety in a responsible way.

2.4.4.2. Mismatches and expectations

As an explanation for these differing perceptions of inherent safety, it is suggested that stakeholders simply have, or have access to different types of knowledge. From an academic’s perspective [AE3, AE4, AE5], it was argued that policymakers can lack technological and/or scientific knowledge of the technologies for which they are preparing regulations. From a policymaker’s perspective [PM1, PM2], it was argued that engineers might tend to focus too much on solely technical aspects, thereby overlooking unknown outcomes and uncertain risks that may occur later. However, policymakers putting pressure on researchers to take societal aspects into account is illustrative of the intertwining of the product and process application of SbD and inherent safety. This also raises the question whether researchers can, or should, consider safety issues arising from the process application, at the product application stage.

The interviewees argued that there are various reasons why researchers focus too much on the technology itself and too little on the societal implications. First, within industry, employees initially think of the interests of the company they are working for. “Their needs are simply put first” [ID1]. Secondly, an incentive for researchers to actively think about “the unknown” is lacking [PM1]. “What’s in it for the researcher?” [AE5]. Researchers are convinced that the technologies they are working with can be considered safe. “Tons of money coming from society is lost on unnecessary paperwork that does not necessarily contribute to safety” [AE2]. This shows that for researchers, there is lack of understanding why emphasis should be put already at the beginning of the development process on safety issues that may not be relevant until later. Thirdly, although risk assessment is currently also being done by researchers themselves, the preconditions have been formulated by others, namely policymakers. Because of this, the relevance or purpose of the conditions might not always be clear to them. In addition, PM3 argued that current regulations for risk assessment are not necessarily ‘risk-based’, but more aimed at ‘legal risk assessment’. This lack of relevance originates, according to the interviewees, in academia, because researchers do not have a clear incentive to proactively think about future, uncertain risks. These examples strongly suggest that there is a

mismatch between the perceptions of SbD and inherent safety between stakeholders, be it more technically or process applied.

2.4.4.3. *Expectations*

We found indications that the term *inherent* can evoke expectations that might not be realized in practice. Especially for society, inherent safety could lead to high expectations of levels of safety. Although all the interviewees acknowledged these high or unrealistic expectations, a change in referring to this term differently has not been witnessed. For governmental institutions and policy bodies, the continued use of this specific term probably has some desired effects.

Either way, it has become clear that the perceptions and notions related to SbD are not aligned between stakeholders. In addition, the two applications of SbD and inherent safety (i.e. product and process) create tension between stakeholders at the beginning (researchers) and at the end of a biotechnology's development process (policymakers). This gives rise to the question of the extent to which SbD can act upon this by creating a dynamic, iterative environment in which stakeholders can communicate effectively. However, there is no clear agreement yet on how this could be established in practice. One step in the right direction would be to ensure that all stakeholders speak the same language.

2.4.5. The Citizen's Role

The last identified theme is the role of the citizen, namely the general public. Should the citizen have a role in the decision-making process regarding the risks and safety measures related to industrial biotechnologies? One of the main questions that emerged from the interviews is whether the active involvement of citizens is often sought to push acceptance rather than to promote discussion. What is, or should be, the main reason to involve the public in these debates? And, more importantly, who should represent 'the public'?

To start with, all the interviewees agreed that information regarding biotechnologies should be accessible to everyone who would like to be informed. However, opinions differed regarding the role that should be assigned to these people: the role of accepting or the role of choosing [SO1]? One interviewee from academia stressed that the only influence the general public should have on decision making is via the Netherlands' democratically elected government [AE2]. Another interviewee [AE1] applied a similar though slightly more nuanced perspective, arguing that it is the responsibility of parliament to express the citizens' perspective one way or another, which can be done via debate, but also via the direct influence of citizens. However, both AE1 and AE5 stressed that the direct involvement of citizens is difficult as they cannot be considered experts in the field of biotechnology and would have difficulty understanding highly technical aspects.

Thus, arriving at a consensus on the right balance between risks and benefits becomes complex. “A thorough background is needed to be able to correctly assess risks”(AE5). In addition, interviewee AE3 acknowledged that most citizens are not experts and therefore might have trouble indicating the right balance between risks and benefits. However, they would have a higher level of acceptance than ‘the professional’ who had actually done the risk analysis and managed the process. In other words, it would be harder for citizens to accept as their threshold is higher.

“Yes, vote! That is the only role [for the citizen]. We are a parliamentary democracy.” [AE2]

“A shared responsibility perhaps; citizen collectives and government. Reciprocity is essential to achieve safety.” [PM1]

“The citizen has certain values and thoughts, but these are often not included, or too late if they are included. Here it is assumed that the matters and discussions within biotechnology are too complex for the public.” [SO1]

PM1, from the field of policymaking, argued that it is difficult to involve citizens in the decision-making process regarding risks and safety, because they have very different perceptions of biotechnologies and risks. This difficulty in involving the citizen was also acknowledged by an interviewee from the societal domain [SO1], but was not stated as something that is impossible to achieve. SO1 stressed that the citizen has certain values and thoughts that should be taken into account in discussions revolving around biotechnology, but doubted whether and, if so, how these are included now. “It is often assumed that the subject matter is too complex for citizens anyway” [SO1]. According to SO1, it is the role of policymakers to find out what these values of the public are and how to include these in policies. “Yes, the domain of biotechnology is complex, which makes it difficult but not impossible to have a broad discussion about this” [SO1].

No clear answer can be derived from the interviews and stakeholder workshop as to what the desirable role of the public should be within this debate. The interviewees’ opinions differed in terms of involving the public directly, or indirectly via representatives (e.g. the House of Representatives or the Senate – which comprise the bicameral legislature of the Netherlands, namely the States General). As including everyone would not be very practical, others who adhere to the second perspective argued that only the States General should be involved. This parliament is democratically elected by the public and has the means and desire to acquire the necessary knowledge and information to incorporate the citizens’ perceptions. Following that line of thought, the only true role for citizens would then be just to vote. However, when only the House of Representatives and the Senate are involved in such discussions, the public’s trust (and access to knowledge) can become extremely important. Again, matters of trust are crucial here, as people vote for those they feel they can trust. Although there is no consensus on what exact role

the public should have, we can say that within this debate the key should be facilitation, not pushing acceptance.

2.5. Conclusions and Future Work

This study explored the different perceptions and associated notions of 'risks', 'safety' and 'inherent safety', and the implications of these for applying SbD as a governance instrument to anticipate uncertain risks. First of all, although SbD does show potential to deal with and anticipate uncertain risks that accompany emerging biotechnologies (e.g. CRISPR), the concept seems to create diverging expectations in terms of the aforementioned. Points of attention that arose from the conducted interviews and stakeholder workshop are the differences in the direct meaning and usage of SbD (i.e. process and product applied) and the notions created in relation to inherent safety by different stakeholder groups (science, policy and society). Stakeholders that apply an SbD perspective product-wise seem to put more emphasis on product specifications in terms of what would be safe enough, while stakeholders that apply SbD process-wise put more emphasis on the process itself and the societal issues that accompany this process. This finding also applies to whether the public should be involved in these decision-making processes, which makes more sense from a process-applied perspective. These differences in applying SbD product- or process-wise also lead to different judgements in terms of balancing risks, safety issues and possible benefits, complicating collectively designing for safety. In addition, where this decision-making should take place within a biotechnology's development process and who should be responsible for it remains unclear. There is a consensus that all stakeholders involved in this process should be responsible, but there is no agreement on whether the degrees of responsibility should also be equally divided, or whether some groups should bear greater responsibility than others.

Secondly, stakeholders' expectations of SbD are not aligned. One way to resolve this issue would be to make others' perceptions and expectations transparent to one another, thus enabling communication between stakeholder groups. However, more research is needed to establish whether there is indeed a lack of communication between these groups, and if so whether this relates to the two different applications of SbD and whether more transparency could solve this. But, most importantly, could SbD create an environment that enables this?

Thirdly, in order to temper the high expectations that accompany the use of SbD and the term *inherent safety*, perhaps referring to, for example, Safer-by-Design would be more appropriate in practice as this might create a more realistic idea of safety. However, it can be questioned whether this would solve the issue of the high expectations that accompany SbD and inherent safety, or whether the same problem would still exist, but then under a new name.

Lastly, the concept of SbD is already being applied in other technical fields, namely nanotechnology and chemical engineering. Future research could explore applications of SbD in these domains and investigate the extent to which these findings can be translated to the domain of industrial biotechnology, possibly contributing to defining SbD within this context.

2.6. Limitations

We want to emphasize that all interviews were conducted within the Netherlands and can therefore only be associated with Dutch regulation concerning white biotechnologies (contained use). Although Dutch regulation is based on EU policy, we acknowledge that there are differences in regulation between EU member states. Also, although a broad range of stakeholders from the domain of biotechnology was interviewed, only a few of them have expert knowledge concerning risk governance within the EU. Therefore, findings from this study cannot be generalized and applied to regulation of biotechnologies in Europe or in general.

Chapter 3

Responsible Learning About Risks Arising from Emerging Biotechnologies

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3.1. Introduction

In 2012, the scientific community was astounded when researchers discovered a new advanced gene-editing technique: CRISPR/Cas9. Due to its ability to edit almost any organism's DNA material, it opened up many new possibilities for research and development (R&D) in a broad range of applications. For the fields of synthetic biology and biotechnology, this advanced technique means new possibilities for innovations using living organisms. But, it might also lead to more uncertain risks, i.e. 'known unknowns' – although knowledge might still be limited, it does contain indications that a new type of event could occur in the future with possibly severe consequences (Flage & Aven, 2015). For biotechnology, these could range from technical issues (e.g., off-target mutations) (Gorter de Vries et al., 2019) to societal or environmental concerns (e.g., climate change or bioweapons) (Asveld et al., 2019; Ouaghran-Gormley & Fye-Marnien, 2019). Although most debates concerning uncertain risks revolve around applications of non-contained (i.e. agricultural or 'green') biotechnology, this has also put emphasis on managing uncertain risks for contained (i.e. industrial or 'white') biotechnology, even though the associated uncertainties of these strands of biotechnology may differ, for example, their influence on natural ecosystems.

From a European risk governance perspective, currently, uncertain risks are covered in GMO-legislation by the embeddedness of the Precautionary Principle (PP). This 'better safe than sorry' principle provides guidelines for risk managers to take precautionary measures that are justified when dealing with important values such as threats for (societal) health or the environment (Sandin et al., 2002). An example of the embedded precautionary culture is the ruling of the European Court of Justice (ECJ) in the summer of 2018, that organisms treated with CRISPR-Cas technology should be classified as Genetically Modified Organisms (GMOs) (Purnhagen et al., 2018) in accordance with existing legislation on GMOs in the European Union (EU). Although CRISPR-Cas applications are still under development and therefore its associated risks are not completely known yet, the main concern arising from this ruling is the focus being too much on quantifiable risks instead of discovering what these uncertain risks might entail (Callaway, 2018b). Considering the fast pace of developments and the associated uncertain risks within the field of biotechnology, a too strong focus on quantifiable risks might lead to a lack of incentive for researchers to discover and learn what these risks encompass, and possibly to a knowledge gap in risk governance to anticipate these unknown risks.

Given the normative approach and the embeddedness of the PP in GMO-legislation, room to learn what uncertain risks might entail is limited as uncertain risks do not meet the set norms. Effective risk governance should contain a flexible assessment procedure that takes into account that risks can be complex, uncertain

and/or ambiguous (Hansson, 2016; Van Asselt & Renn, 2011; Van Asselt & Vos, 2008). But, to discover the complexity of uncertain risks responsibly, a controlled learning environment would be needed in which risks, step-by-step, can be identified. This gradual, controlled learning of what uncertain risks encompass is what we refer to as responsible learning. An approach that has been gaining attention over the past years and could enable such controlled learning is Safe-by-Design (SbD). As this approach aims to address safety issues already during early-stage development by stimulating engagement of a broad range of stakeholder iteratively (e.g., by feedback-loops), a variety of issues could already be brought up in these early stages of development and anticipated on in design choices made by researchers (Robaey, 2018; Van de Poel & Robaey, 2017). For example, researchers, engineers, ecologists, biologists and policymakers might identify different (possibly long-term) issues that might come up during, and after a biotechnology has been developed. By already addressing and acting on these possible issues in the initial experimental design, these could be tackled early on. This would make it possible coming to a collective experimental design with safety in mind (Khan & Amyotte, 2003; Van de Poel & Robaey, 2017). However, learning about uncertain risks would call for some regulatory flexibility since the established norms for known risks cannot be met during the set-up of an experiment as there is insufficient information available. Theoretically, the iterative character of SbD for making design choices can offer such flexibility to discover what these unforeseen risks possibly entail, in a responsible way. Also, this new information can help risk managers to amend the set norms of what is considered an acceptable risk to the state-of-the-art in biotechnology.

This paper addresses the following question: What conditions would be needed to enable an environment for responsible learning about new and uncertain risks of emerging biotechnologies? For the sake of clarity, although biotechnology can be classified in different ‘colors’ (i.e., red - biopharmaceuticals, white – industrial, green – agricultural), our study focuses on industrial biotechnology. In addition, although uncertain risks could emerge throughout a biotechnology’s development cycle (i.e. design-build-test-upscale-market phase), we focus on the early design stages up to building and testing as, ideally, we would want newly emerging risks to be anticipated on in the initial design choices of a biotechnology. Our study is structured as follows. First, we provide an overview of the current risk management regime in the Netherlands and the embeddedness of the PP, and the notion of forward-looking responsibility assigned to different groups of stakeholders, building upon Van de Poel & Nihlen-Fahlquist (2012) (Section 3.3). Secondly, we analyze which conditions would be needed to create an environment suitable for responsible learning about uncertain risks. We identified the following three conditions: 1) regulatory flexibility, (2) co-responsibility between researchers and risk managers, and (3) openness towards all stakeholders (Section 3.4). These conditions are elaborated by using an illustrative discussion tool, i.e. a 3D cube (Section 3.4.2).

Thirdly, we argue to what extent the SbD approach (Section 3.5) could provide guidelines for responsible learning and what would be required to do so considering the embeddedness of the PP in GMO legislation.

3.2. Methods

This study comprises an empirically informed conceptual analysis of responsibility, uncertain risks and what would be needed to establish an environment for responsible learning. Literature studied for the conceptual analysis focused on the notion of forward-looking responsibility, the PP and its embeddedness in managing uncertain risks. For clarifying the context in which this study takes place, interviews were conducted with relevant stakeholders to gain insight in the current GMO permit application process from both a regulatory and practical perspective, how this relates to the interviewees' perceived and assigned notion(s) of responsibility, and how we could or should take appropriate measures to anticipate uncertainties that might come along during the development of a biotechnology. From these interviews, three conditions were established that would be necessary to conduct an environment suitable for responsible learning. Based on literature, we discuss to what extent these conditions could be met by applying SbD, and whether this could be implemented considering the embeddedness of the PP in the risk management regime.

Interviews (Ntot=9) were conducted between May and October 2019 and generally focused on two types of stakeholders. The first type is active as 'applicants' – stakeholders who conduct experiments and are involved in risk assessment and permit application processes. These interviewees (N=5) are employed as a principal investigator (PI), Postdoc researcher (PD), PhD researcher (PhD), technician/ designated responsible employee (DRE)¹⁶, and a Biosafety Officer (BSO)¹⁷. The second type is active in the risk management stage (e.g., regulatory settings), consisting of interviewees (N=3) employed by the Dutch GMO Office (BGGO)¹⁸, and the Dutch Human Environment and Transport Inspectorate (ILT)¹⁹. Also, one interview was conducted with an independent consultant, who could elaborate on the communication between applicants and risk managers.

The interviews followed a semi-structured approach that left enough room to go into detail when the researchers felt this was necessary for clarification or context.

¹⁶ In Dutch: verantwoordelijk medewerker. This employee assists in conducting risk assessments and is seen as the 'bridge' between researchers and the Biosafety Officer.

¹⁷ Biosafety Officers (BSOs) have a coordinating, motivating and signaling responsibility for biological safety when working with GMOs. BSOs provide support to researchers and research staff by providing information and advice on experimental designs and license applications from the BGGO.

¹⁸ In Dutch: Bureau Genetisch Gemodificeerde Organismen (BGGO).

¹⁹ In Dutch: Bureau Inspectie Leefomgeving en Transport (ILT).

The interviewees were selected based on their experience in the domain of biotechnology and field of profession, and all hold senior positions, except for the PhD and Postdoc researcher. At the start of each interview, a form of consent was signed to approve recording of the interview. After the interview, a transcript was sent to the interviewee for any remarks or corrections. Upon receiving the interviewee's approval, the transcript was coded and analyzed. In terms of the conceptual analysis, since this takes place within a specific context (i.e., contained use of industrially applied biotechnologies), the empirical input from the interviews helped to clarify relevant concepts for this study. Lastly, 3 out of 9 interviews were conducted in English, the others were conducted in Dutch. Therefore, some quotations in-text have been translated into English²⁰. In addition, although all information provided by the interviewees is based on Dutch GMO legislation, it is still relevant to other countries or EU Member States. Albeit there are some legislative differences within the EU, all States have to adhere to the uniform EU directives. Also, issues associated with discovering uncertain risks responsibly are everywhere at stake, also outside the EU.

3.3. European Risk Governance

The regulation of biotechnologies within the EU has been active since the 1990s. The main principle that underlies EU legislation is the PP which originated in German domestic law during the 1970s and 1980s and has been incorporated in many international environmental treaties and agreements since then (P Berg et al., 1974; Jelsma, 1995; Marchant & Mossman, 2004). In 1992, the EU committed to conform their environmental policy with the PP in the Maastricht amendments (Article 174.2²¹). Later, EU policy was followed by many individual European nations (e.g., Germany, France and the Netherlands), leading to an integrated 'precautionary process' within risk assessment and management (Stirling, 2007). In 2003, European GMO legislation was complemented with the Cartagena Protocol on Biosafety. Particularly the safe distribution of GMOs between countries is emphasized in this protocol, but it also addresses possible adverse effects on the conservation and sustainable use of biological diversity, and risks to human health (Kinderlerer, 2004).

In terms of the PP, there has been disagreement about its measures for biosafety and in terms of its effectiveness. For more than a decade, opponents have argued that the way the PP is embedded in the regulatory regime is confusing (Manson, 2002), too complex (Sandin et al., 2002), primarily designed to stop the use of modern biotechnology - hindering Europe to realize the benefits that

²⁰ All data (i.e. form of consent, interview protocol, transcripts) can be requested from the corresponding author via <https://doi.org/10.17026/dans-x9u-g6u4>.

²¹ <https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:12002E174:EN:HTML>

biotechnology could bring (Kinderlerer, 2004), or implemented differently than originally intended (Tagliabue, 2015, 2016) and an update would be required (Hansson, 2016). More recently, proponents have argued that the PP can confine risks, although it can restrict opportunities as well (Anyshchenko, 2019), or that it is a way to use information about known risks in the best possible way and can help to create public acceptance of biotechnologies (European Union, 2017; Taleb et al., 2014).

Although the PP inherently can provide researchers and risk managers with guidelines to avoid taking unnecessary risks, the way this principle is operationalized now appears to withhold them from exploring what any 'new' uncertain risks might entail. Considering the fast developments in biotechnology, there needs to be room to explore what uncertain risks these might bring, to learn what these entail and how to anticipate these responsibly. In the Netherlands, although certain procedures allow researchers to explore these uncertainties to some extent, the way the PP is currently embedded does not stimulate conducting such research.

3.3.1. National Risk Governance

In the Netherlands, risk governance is influenced by many different groups of stakeholders, e.g., the European Commission, Dutch Parliament, citizens, researchers, etc. However, from an executive perspective, risk governance processes generally involve three groups of stakeholders: risk managers, risk assessors, and applicants. Risk managers, e.g., policymakers or regulators, focus on the management of risks which comprises more normative questions e.g., how 'big' these uncertain risks are? or how acceptable these would be, and to whom? (Asveld, 2007; Asveld et al., 2019). In other words, risk managers set the norms for risk assessments; a measure for the normative conception of risks. Risk assessors determine whether a submitted risk assessment meets the set norms, e.g., are the risks involved in an experiment acceptably safe? (Kermisch, 2012). Although this group of stakeholders is active within Governmental organizations (e.g., the Dutch GMO Office or BGGO), they are not considered regulators. Applicants, e.g., researchers and BSOs, must conduct a risk assessment and submit these to the designated governmental agency before starting their experiments. When dealing with uncertain risks, quantitative data for risk assessment can remain incomplete or limited due to lack of experience or knowledge (Collingridge, 1982; Genus & Stirling, 2018). As risk managers and risk assessors generally do not conduct experimental research themselves, it can be difficult for them to determine when and how to act on uncertain risks appropriately and responsibly. Therefore, stakeholders who do conduct experiments, i.e., researchers, could provide necessary knowledge by devoting research specifically to what these uncertain risks could entail (Linkov et al., 2018). For the sake of clarity, although we acknowledge the differences in

executive duties pertaining to risk managers and risk assessors, within this paper we will refer to both groups of stakeholders as Risk Managers. Those who conduct risk assessments (e.g., researchers and BSOs) are referred to as applicants.

3.3.1.1. Procedure

Based on all interviews, we have derived a schematic representation of the risk assessment and permit application procedure for contained use of GMOs in the Netherlands – see Figure. 3.1. At the start of this procedure, researchers are requested to do a risk assessment in which already set norms by risk managers are embedded, for example, societal or environmental implications of components. The risk assessment is conducted by the involved researchers and BSO and is often based on literature or previous permit applications (Figure 3.1 – level 1). When no new components or elements are introduced, the risk assessment procedure automatically assigns an appropriate Biosafety Level (BSL) and a corresponding Microbiological Laboratory (ML) class in which researchers can conduct their experiment (Figure 3.1 – level 3). In this case, researchers must only make notification of their experiment(s) to BGGO (applicable for BSL I-II). When there are new elements introduced or the assigned BSL is above level II-notification, researchers must request a permit from BGGO. However, due to the ‘newness’ of such elements or technologies, there might be inadequate knowledge about the technology’s possible risks at that moment. When such a situation occurs, BGGO could prohibit the experiment, examine whether it is possible to approve an experiment but with a higher BSL (e.g. level IV²²) and additional conditions, or could ask the applicants to adjust their experimental set-up so it would fit the current BSL-norms. In response, applicants can apply for the so-called ‘2.8 procedure²³’ (Figure 3.1 – level 2a) when they believe that, for example, a lower containment level would also be sufficient or when they do not have access to a laboratory with the assigned ML-class. When such procedure becomes active, applicants have to provide more information which shows that a lower level would also be acceptable. Based on this, risk managers from BGGO (Figure 3.1 – level 2a) can ask the Commission on Genetic Modification (COGEM) for advice. Based on this, BGGO could approve the 2.8 application with a lower designated BSL, or reject it and remain to the initially assigned BSL. In response, researchers can follow this decision, or adjust their experiment and go through the process again by filing a new application.

²² There are no level IV laboratories in the Netherlands.

²³ <https://www.ggo-vergunningverlening.nl/ingeperkt-gebruik/procedures/bijzondere-procedures>

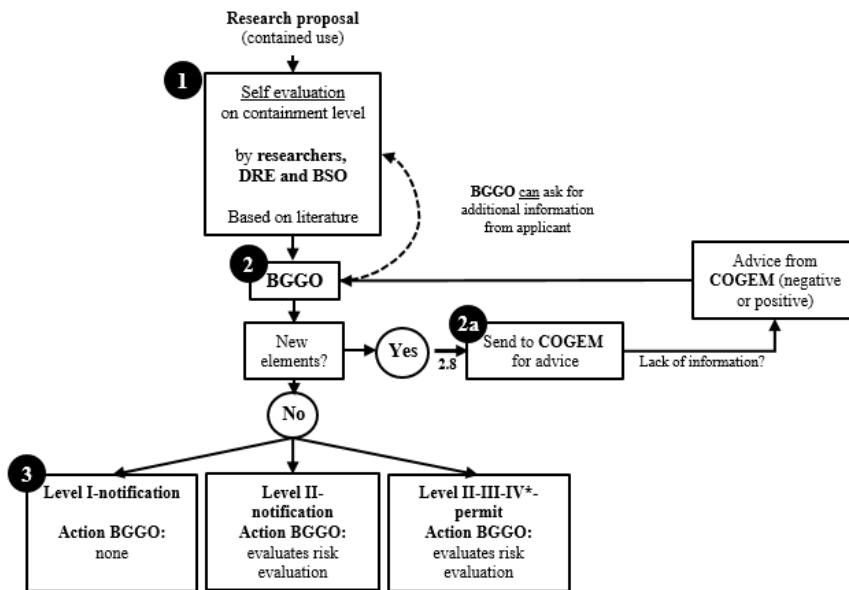


Figure 3.1: Schematic representation of the Risk Governance system for GMOs (contained use) in the Netherlands. Illustration produced in collaboration with Rathenau Instituut, The Hague, the Netherlands.

3.3.1.2. Procedure in Practice

On March 1st 2015, a change was implemented regarding the GMO procedure²⁴. Where prior to this date the risk assessment procedure was conducted by BGGO, from this date on, research institutions have the responsibility to carry out this assessment themselves and have to determine whether additional regulations apply (only for level I and level II-notification). This renewal was based on vast experience with historical permit requests and aimed to lighten the administrative burden for institutions. Interviewees [PI; PD; PhD: BSO] acknowledge that it has accelerated research as they do not have to await formal approval, but it has also made the risk assessment a slightly routinized procedure. Interviewed risk managers [BGGO1; BGGO2], however, acknowledge that the workload for researchers has increased as a result of this renewal. Furthermore, interviewee PhD also mentions that when 'new' elements are introduced and additional information is requested by BGGO, the decision-making process of whether this would be acceptably is also dependent on the researchers' input, which implies them to also have responsibility. "We have all kind of micro-organisms and viruses in here. So they [BGOO] don't know what biosafety level [to assign]. I have level 1 micro-organisms, but also level 3. [...] so basically, all I had to say was 'Okay, biosafety 3

²⁴ <https://www.infomil.nl/onderwerpen/integrale/omgevingsloket/versies/wijzigingen-eerdere/versie-2-11/versie-2-12/inhoudelijke/besluit-regeling-ggo/>

level micro-organisms are really low in terms of abundance'. I just had to present it and prove that nothing dangerous is happening here" [PhD]. Taking into account that the executive risk assessment for level I and II-notification also lies with researchers, trust and openness become important for responsible risk management. Although there is currently little reason to question researchers' integrity, we should still be alert that this does not lead to a false sense of safety. "Yes, for [level] 2 and 3, the risk assessment is carried out by the institution and BGGO checks it. Not for [level] 1, this level is let go [sic] as there is also lower risk and we do not assume that people [researchers] who work on level 1 should actually work at level 3. We don't have that feeling" [ILT].

Ideally, researchers should take safety and possible emerging risks already into account during the early developmental stage of a biotechnological product or process and (re)consider their design choices accordingly, e.g., while composing a research proposal. However, the way the PP is currently being operationalized in risk assessment procedures appears to withhold relevant actors from exploring any new, uncertain risks. If such risks are arising, researchers are asked to adjust their experimental set-up (or safety level) so it fits the current BSL norms. In that sense, we can say that the established risk management regime is a regime of compliance. Researchers are assigned a form of forward-looking responsibility to prevent risks from occurring, but no such responsibility is assigned to them for knowing, assessing and communicating uncertain risks.

3.3.2. Forward-looking Responsibility

Forward-looking responsibility entails measures that aim for that something does happen – taking appropriate preventive measures (Van de Poel, 2011). Therefore, in terms of preventing risks from occurring, forward-looking responsibility plays a crucial role in dealing with uncertain risks and exploring what these specifically entail. Building upon forward-looking responsibility for risks as described by Van de Poel & Nihlen-Fahlquist (2012), we subdivide this notion into four main categories. These are (1) Responsibility for risk reduction, (2) Responsibility for risk assessment, i.e. establishing risks and their magnitude, (3) Responsibility for risk management, including decisions about what risks are acceptable and the devising of regulations, procedures and the like to ensure that risks remain within the limits of what is acceptable, and (4) Responsibility for communication about risks (Van de Poel & Nihlen-Fahlquist, 2012). However, considering the rapid developments in the field of biotechnology, we believe that the notion of forward-looking responsibility should not only comprise 'known' risks, but also uncertain risks. In the following section, we first provide an overview of which subcategory of forward-looking responsibility can currently be assigned to risks managers and applicants and argue that the forward-looking responsibility for knowing, assessing and communicating about uncertain risks is not specifically assigned to either of them.

3.3.2.1. Forward-looking Responsibility

Risk managers are forward-looking responsible for establishing the norms of what would be acceptably safe, and what would not. Therefore, risk management involves questions of values, e.g., what is safe ‘enough?’ and is based on a trade-off of what would be considered acceptably safe and what not e.g., assigning an appropriate BSL. In the Netherlands, current legislative settings for biotechnology can be described as a precautionary culture where the Dutch government is held accountable for inducing risks towards society or the environment, even unknown risks (Helsloot et al., 2010), thereby assuming that research facilities or industry have complied with regulation. In addition, as risk managers are also involved in assessing and anticipating uncertain risks, they can also be ascribed a form of forward-looking responsibility which refers to making sure the ‘right’ precautionary measures are taken to anticipate any uncertain risks.

Table 3.1: Subcategories of forward-looking responsibilities assigned to risk managers and applicants (known and uncertain risks), built upon Van de Poel & Nihlen-Fahlquist (2012).

Subcategory of Forward-looking Responsibility	Known risk	Uncertain risk
Responsibility for setting standards for acceptable risks	Risk managers (e.g., BSL levels)	Risk managers (Precautionary Principle)
Responsibility for knowing and assessing risks	Risk Managers & Applicants	<i>Not assigned</i>
Responsibility for reducing risks	Applicants	Applicants
Responsibility for communication about risks	Risk Managers & Applicants	<i>Not assigned</i>

Within current regulation, applicants (i.e., researchers, BSOs or designated responsible employees) are also assigned forward-looking responsibility. As already touched upon in the previous section, applicants have the responsibility to do a risk assessment before the start of their experiment(s) meaning that they must make design choices based on the established norms by risk managers. However, in terms of uncertain risks – also possible unforeseen issues that may arise while already conducting experiments, the assigned responsibilities are unclear. Table 1 summarizes the assigned forms of forward-looking responsibility of risk managers and applicants for known and uncertain risks and illustrates that currently, there is no assigned form of forward-looking responsibility for knowing, assessing and communicating uncertain risks.

3.4. From Compliance to Responsible Learning

Within this study, we refer to responsible learning as stimulating researchers to proactively (re)consider their experimental design choices for the sake of safety, while also being able to explore what any uncertain risks might entail. As discussed in the previous section, the current risk management regime seems to be one of compliance in which no forward-looking responsibility is assigned to researchers for knowing, assessing and communicating uncertain risks. But, considering the fast pace of biotechnological development, (more) uncertain risks can be expected to arise. Therefore, ideally, researchers should proactively identify and anticipate uncertain risks and (re)adapt their experimental design by taking appropriate measures. In this section, we argue that three conditions should be met to create an environment for responsible learning, derived from the not assigned forms of forward-looking responsibility (see Table 3.1): regulatory flexibility, co-responsibility and openness. An overview of the derived conditions needed for responsible learning is provided in Table 3.2.

3.4.1. Conditions for Responsible Learning

Although experiments should always be designed and executed with caution, the degree of uncertain risks can only become known by experimenting and learning. Therefore, we introduce the first needed condition for responsible learning: regulatory flexibility. Recalling current GMO regulation and biosafety rules for confined use of GMOs within the Netherlands as described in Section 3.3, experimental designs need to be determined before conducting a risk assessment. When there are too many uncertainties in terms of risks, researchers are asked to provide more information concerning the elements of their experimental design. If there would be no or little literature available, this can create complications in terms of approving the experiment and the possibility of exploring and learning about possible uncertain risks. Therefore, we should transition to a more balanced form of risk management in which there is more room (and more stimuli) to discover what uncertain risks entail, in a responsible way. However, in addition to regulatory flexibility, two other conditions would be crucial for anticipatory, inclusive and responsive learning about new and uncertain risks: co-responsibility and openness.

As touched upon earlier, trust and openness appear to be important matters regarding safety. Interviews conducted with researchers and academic staff [PI, PD, PhD, BSO, DRE] indicate that they do perceive a strong responsibility in this respect. They mention that, based on their experience and awareness of the state-of-the-art in biotechnology, they should be capable of estimating whether an experiment might come with any unforeseen risk and whether these would be acceptable or not. However, they argue that the norms established within the current risk assessment are becoming outdated due to the fast developments within this field (Bouchaut & Asveld, 2020), and a regulatory update would be necessary. They

also point out that they need room to explore uncertain risks to take on more forward-looking responsibility but that this is sometimes stifled by current regulation and regulatory practices. So, if researchers would also be assigned a form of forward-looking responsibility – creating co-responsibility – both parties can see to it that the ‘right’ measures are taken to prevent any harm done while it would also contribute to researchers carefully (re)consider their experimental design choices based on them also being accountable (though not in a legal sense) (Van de Poel & Robaey, 2017).

However, some of the interviewed risk managers indicate that they believe that researchers might have different motives to conduct their research and do not always prioritize safety to the same extent, thereby complicating stakeholders having co-responsibility. “I think there are different kinds of researchers, some are operating on a more fundamental level. [...] If you continue such research and try to answer such related questions, it’s not so much about ‘how do you design something inherently safe?’. Well no, one wants to know an answer to that question and if that can be done quickly via a [biosafety]level 3 way, then they do it via a [biosafety]level 3 way. Another type of researcher, if they already have an application in mind, something like ‘I want to make a vaccine’, then they already know ‘my vaccine must be safe’, otherwise, it will never enter the market” [BGGO1]. In that sense, both parties having co-responsibility calls for openness – the third condition needed for responsible learning. Researchers should be open and responsive towards risk managers or any other associated stakeholders about any unclear or ambiguous experimental results (Sonck et al., 2020). Also, both parties trusting each other would be of great importance here. By early addressing unforeseen issues and opening up a dialogue, these issues can be anticipated on and appropriate measures can be taken of which risk governance can also benefit. However, practically, we do not envision these interactions to happen for every step taken within the design process. Instead, researchers should structurally reflect on the decisions to be made, thereby applying perspectives of other stakeholders by means of, for example, having occasional awareness exercises. A culture should be established where this is ‘common practice’ as has been happening in, for example, healthcare and the aviation industry (Singh, 2009), or more recently, in the field nanotechnology (Rerimassie et al., 2018).

Table 3.2: Overview of the not-assigned forms of forward-looking responsibility to researchers and risk managers, and the derived conditions needed for responsible learning.

Subcategory of Forward-looking Responsibility	Known risk	Uncertain risk	Derived Conditions for Responsible Learning
Responsibility for setting standards for acceptable risks	Risk managers (e.g., BSL levels)	Risk managers (Precautionary Principle)	<i>Regulatory Flexibility</i>
Responsibility for knowing and assessing risks	Risk Managers & Applicants	<i>Risk Managers & Applicants</i>	<i>Co-Responsibility</i>
Responsibility for reducing risks	Applicants	Applicants	<i>Co-Responsibility</i>
Responsibility for communication about risks	Risk Managers & Applicants	<i>Applicants</i>	<i>Openness</i>

In summary, to find a balance between taking appropriate precautionary measures and ‘proceeding with caution’, some regulatory flexibility would be needed for researchers to be able to discover what uncertain risks might entail. Also, researchers should actively (re)consider their design choices for the sake of safety which can be stimulated by assigning them co-responsibility (Van de Poel & Robaey, 2017). However, as Bouchaut and Asveld (2020) point out, perceptions of risks and safety tend to differ between stakeholders. This can be based on their worldview, experience, or professional position (De Witt et al., 2017). As researchers find themselves in a different position than risk managers, their perspective on what would be an acceptable risk might differ. Besides, researchers holding different positions (i.e., PIs, Postdocs or PhD researchers) might also have a different perception of what would be acceptably safe and whatnot, due to their professional experience. Therefore, researchers must be open towards other stakeholders about their experimental findings or any unforeseen issues they might foresee or might arise during the experiments. But, the conditions we have identified to enable responsible learning can occur in different degrees. For example, how open should researchers be about issues they might expect but haven’t encountered yet as this could cause unnecessary turmoil? In the section below, some ‘extreme’ scenarios are elaborated, illustrating that all conditions should be present to some extent to enable an environment for responsible learning.

3.4.2. Scenarios for Responsible Learning

We can establish different scenarios where the three identified conditions for responsible learning would have a ‘low’ or ‘high’ degree. In this paper, we use a 3D

cube (Figure 3.2) as a discussion tool where each axis represents one of the three conditions, clearly illustrating a specific scenario that might occur when differing degrees of these conditions would be present. As we would like researchers to proactively (re)consider their design choices in early experimental settings, the needed conditions for responsible learning are argued from an applicant's perspective. Therefore, the condition of co-responsibility between risk managers and applicants is illustrated as a shared degree of forward-looking responsibility to assess and reduce risks, regulatory flexibility in terms of the normative assessment of risks, and openness as the extent researchers should be open about their experimental findings, and to what extent they would be aware of potential implications of their experiment by e.g. incorporating various stakeholders during the experimental design phase and including their perspectives in design choices.

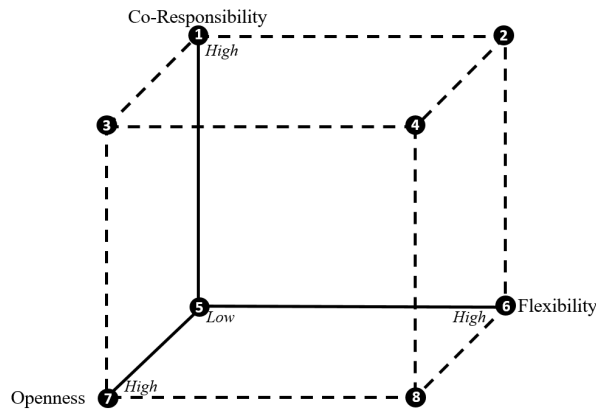


Figure 3.2: Graphical representation of the 'low' or 'high' degrees of openness, (regulatory) flexibility and co-responsibility (X,Y,Z-axis) needed to enable an environment suitable for Responsible Learning.

As mentioned earlier, having all conditions present in some degree would be prerequisite for an environment for responsible learning. Would one of the conditions not be present, or only in low degrees (e.g., vertexes 2, 3 or 8), this would limit responsible learning. Vertex 2 illustrates both co-responsibility and regulatory flexibility to be present, but no, or only little openness and responsiveness of researchers concerning their experiments' potential implications. As this could result in researchers applying for potentially 'high-risk' experiments, the high degree of regulatory flexibility may also lead to them being approved. Although this would already go against our understanding of responsible learning or responsible behavior in general, this could also result in an extra burden for risk managers. Also, as there would be co-responsibility between researchers and risk managers, the latter would be accountable and blameworthy might this have detrimental effects on society or the environment. Considering these could be 'high-risk' experiments, there is a chance this will be the case. Vertex 3 illustrates high degrees of openness

and co-responsibility, but no, or only a low degree of regulatory flexibility. If there would be only very little room within regulation to learn what uncertain risks might entail, and which could also take up considerably more time in terms of getting their experiments approved (i.e. 2.8 procedure), it would sound superfluous for researchers to specifically devote experiments to this type of research, nor would assigning a form of responsibility to researchers seem reasonable. Vertex 8 illustrates both openness and regulatory flexibility being present, but no co-responsibility. In this case, researchers would not be held accountable which could incite them to be less open about potential uncertain risks, which would not contribute to researchers designing their experiments more responsibly.

Although all conditions should be present, not all should be met at their highest degree. For example, vertex 4 illustrates all three conditions present in their highest degree. Considering the condition of openness, not only would this seem not feasible (i.e., when can you be fully open of matters you possibly cannot know yet or may only slightly expect?), it might also hinder researchers from conducting research. When researchers would be ‘fully’ open of all possible consequences their research might have, would it still be worth the time and effort to research these? This scenario also applies to vertex 7, where only openness is present in the highest degree, compared to low degrees of regulatory flexibility and co-responsibility.

3.5. Safe-by-Design for Responsible Learning

Recalling our definition of responsible learning and the defined conditions to enable such an environment, in theory, the SbD approach could provide guidelines for a controlled, iterative, step-by-step exploration of what uncertain risks could consist of, what consequences they might have, and how to anticipate these accordingly. This section first briefly explains the SbD approach and thereafter elaborates how this approach could provide guidelines for the earlier identified conditions needed for responsible learning. Secondly, we argue to what extent implementing SbD would be hindered by the embeddedness of the PP in the current risk management regime.

3.5.1. Safe-by-Design

SbD is an approach that comprises both engineered and procedural safety by “using materials and process conditions which are less hazardous” (Bollinger et al., 1996; Khan & Amyotte, 2003) and finds its origin in the domain of chemical engineering. More recently, this approach has gained attention in the fields of nanotechnology (Kelty, 2009; Kraegeloh et al., 2018; Schwarz-Plaschg et al., 2017), synthetic biology (Asin-Garcia et al., 2020) and biotechnology (Robaey et al., 2017; Van der Berg et al., 2020). The SbD approach is associated with learning processes that aim for designing specifically for the notion of safety by iteratively integrating knowledge about the adverse effects of materials (Van de Poel & Robaey, 2017).

In particular the iterative character (i.e., feedback loops) of this design approach and the inclusion of a wide range of stakeholders could provide a way to gradually discover uncertain risks (Bouchaut & Asveld, 2020). By including different stakeholders throughout the experimental design process, different issues can be identified and active anticipation of possible risks is stimulated. This might broaden the scope of possible risk-related issues, and could impact experimental design choices. For example, may a possible risk be identified during the Build & Test phase, one could go steps back in the design process, and try to anticipate these beforehand by making adaptations in the design choices (Figure 3.3). By implementing these so-called feedback loops, eventually, a collective 'safe' design could be achieved. Still, when dealing with emerging biotechnologies, it can become difficult to foresee future implications of the technology due to researchers' lack of experience or the biotechnology could be used differently than devised (Collingridge, 1982).

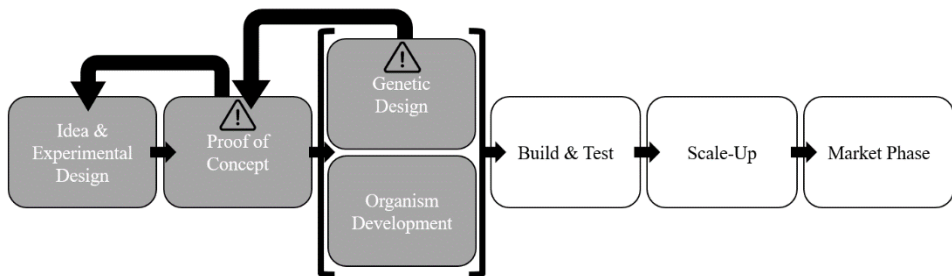


Figure 3.3: Schematic illustration of a (simplified) biotechnology's development process, and the iterative character of Safe-by-Design. The parts from 'scale-up' onwards (in white) are left out of consideration as the focus within this study is on experimental design choices and not on upscaling or market implementation.

3.5.2. Guidelines for Responsible Learning

In terms of the earlier identified conditions needed for responsible learning, the SbD approach could provide guidelines to enable these – in particular the conditions of co-responsibility and openness. In terms of regulatory flexibility, SbD cannot enable such, but it could help to monitor such a more flexible risk management regime.

The conditions of co-responsibility and openness could be met to a certain extent by applying the SbD approach. The SbD approach stimulates active stakeholder participation, openness and responsiveness, creating a dialogue between parties where we can reach agreement on what would be considered acceptably safe and what measures would be appropriate to take. Might any unforeseen (and unacceptable) issues arise, researchers could anticipate these in their experimental design accordingly. This iterative character also provides

flexibility in terms of design, however, no regulatory flexibility. Still, we believe that the SbD approach could be a suitable candidate for responsible learning, provided that regulation would allow so. However, one of the challenges would then also become how to monitor these types of research devoted to exploring uncertain risks in a proper way. Assigning researchers co-responsibility to assess and reduce uncertain risks might help tackle this challenge.

3.5.3. Barriers for Safe-by-Design

Recalling the different 'extreme' scenarios described in Section 3.4.2. illustrate that the conditions of regulatory flexibility, co-responsibility and openness should all be present, but to some degree. However, placing these findings in the perspective of the current embeddedness of the PP in GMO regulation, and the focus herein on quantifiable risks, the condition of regulatory flexibility cannot be met to the desired degree (Hansson, 2016; Stirling et al., 1999). Recalling Section 3.3.1.1, when dealing with 'new' elements, the 2.8 procedure comes into force. The advice of COGEM and the decision-making of BGGO is mainly based on literature – albeit partly provided by the applicants. Although depending on the 'newness' of these elements or processes, when there is no sufficient literature available, this leads to different scenarios; researchers are required to provide more information (which would not be possible in this case), or given the option to reconsider their experimental set-up and adjust these accordingly so it does meet the set standards and an appropriate BSL can be assigned. So, when the set-up of an experiment would already be prohibited due to the risks being 'too' uncertain, this would limit room for learning what these uncertain risks exactly are. In other words, when no research can be conducted to exploring what uncertain risks entail, no literature can be devoted to these matters, leading to a vicious circle where research devoted to exploring uncertain risks is obstructed. As a result, the SbD approach cannot be implemented to its fullest potential, specifically the iterative character of SbD to anticipate uncertain risks.

3.6. Conclusion

This study explored what conditions would be needed to enable an environment for responsible learning about new and uncertain risks of emerging (white) biotechnologies. First of all, we described the risk management regime in the Netherlands and argued that this is currently a regime of compliance in which researchers are assigned forward-looking responsibility to prevent risks from occurring, but not for knowing, assessing and communicating uncertain risks. Therefore, there is a need to create room for exploring uncertain risks and thus to create conditions for anticipatory and responsible learning about these risks.

To enable an environment suitable for responsible learning, we identified three conditions that should be met: (1) regulatory flexibility, (2) co-responsibility between risk managers and applicants, and (3) openness.

Lastly, we analyzed how the SbD approach could provide guidelines for responsible learning in a controlled, iterative and step-by-step fashion and for considering design choices accordingly. In terms of the established conditions, SbD can provide a framework for co-responsibility and openness by active stakeholder engagement and the iterative character of SbD. Might any unforeseen (and unacceptable) issues arise, researchers could anticipate these in their experimental design choices. This iterative character also provides flexibility in terms of design, however, no regulatory flexibility. Still, we believe that the SbD approach could be a suitable candidate for responsible learning, provided that regulation would allow so. However, one of the challenges would then also become how to monitor these types of research devoted to exploring uncertain risks in a proper way. Assigning researchers co-responsibility to assess and reduce uncertain risks might help tackle this challenge. Also, stimulating openness and responsiveness amongst researchers about their experimental findings – after and during their experiments – could also help both groups to gain more trust in each other.

We are not advocating that researchers should have the freedom to take unacceptable risks. But, we believe that responsible learning could be a way for researchers to design experiments more responsibly, while also stimulating research specifically devoted to exploring uncertain risks of which risk governance can benefit as well.

3.7. Limitations

This study was carried out within the Netherlands and focuses on Dutch legislation regarding contained use of GMOs. However, as the issue of managing and anticipating newly emerging risks is at stake globally, we believe that our findings are not limited to the Dutch context only. In terms of EU policy, although we acknowledge that there are differences between the EU Member States, all have to adhere to the uniform EU directives. Also, the conditions we defined to enable an environment for responsible learning are not necessarily bounded to EU legislation (on which Dutch legislation is based), and could therefore be applied to other contexts. However, as our analysis of the applicability of the SbD approach is based on the embeddedness of the PP in EU legislation, this cannot be generalized outside the EU.

Chapter 4

Value Conflicts in Designing for Safety: Distinguishing Applications of Safe-by-Design and the Inherent Safety Principles

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4.1. Introduction

One of the most acknowledged values in the fields of chemical engineering, biochemistry and biotechnology is safety. To ensure (bio)chemical processes to be acceptably safe for society, animals and the environment, multiple approaches have been developed over the last decades. Examples of such are the 12 principles of Green Chemistry (Anastas & Warner, 1998; Anastas & Eghbali, 2010), Safety Management Systems (Reniers et al., 2009), Inherent Safety (Kletz, 1996) and the Inherent Safety Principles (ISPs) (Khan & Amyotte, 2003). In the field of chemical engineering, in particular, the ISPs are widely known (Kletz, 2003) and aim at eliminating or minimizing the risks of hazardous chemicals or syntheses by using conditions or chemicals with less dangerous properties. The Safe-by-Design (SbD) approach, which is derived from the notion of inherent safety, has been gaining foot in the field of nanotechnology (Kelty, 2009; Van de Poel & Robaey, 2017), biotechnology and synthetic biology (Bouchaut & Asveld, 2020; Robaey et al., 2017) over the last decade. Although both approaches revolve around measures for safety, the derived measures differ to some extent. That is, the ISPs provide guidelines for risk-reducing measures or the development of add-on safety features (Amyotte et al., 2007; Khan & Amyotte, 2003), while SbD questions the initial use of certain chemicals or carriers during the early stages of development more strongly (Robaey, 2018). However, although there is a difference between the derived measures, both approaches suffer from internal value-conflicts (e.g., safety vs. performance or sustainability) during implementation (Bollinger et al., 1996; Edwards, 2005). However, in terms of lock-ins – external barriers such as company culture or established infrastructure that hinder implementation or adoption of an alternative process or technology—mostly SbD is affected. As the ISPs provide add-on safety measures (Amyotte et al., 2007; Khan & Amyotte, 2003), they would be, to a certain extent, able to take lock-ins into account. The SbD approach, however, may call for more drastic changes in terms of design choices (e.g., choice of raw materials) and can therefore experience more hindrance of external barriers (e.g., would call for a change in process set-up and/or infrastructure). In addition, although the approaches differ in optional measures for safety, there also seems to be some overlap. For example, it could be argued that the SbD strategy of developing kill switches (Robaey, 2018) also fits within one of the ISPs as its goal is to reduce any possible negative consequences might anything unforeseen happen. The other way around, the ISP of substitution—the replacement of hazardous chemicals with less hazardous ones (Khan & Amyotte, 2003; Kletz, 1996) – could also be classified as a SbD strategy.

Although the ISPs are considered an already established approach for risk reduction and SbD is considered a relatively new approach, the distinction between these approaches seem to be somewhat blurry. Therefore, this paper aims to define the differences between these approaches and to shed light on which approach

would be better applicable to a specific type of research: either applied or fundamental research. Although internal conflicts occur in both types of research, external conflicts such as lock-ins are more heavily present in applied research stages. Therefore, either approach might be better able to deal with a specific type of conflict.

In order to analyze these differences and the applicability of both approaches, we have chosen a case study from the field of biochemistry that focuses on the miniaturization of processes (i.e., the use of micro-reactors) using Hydrogen Cyanide (HCN) (Coloma, Guiavarc'h, et al., 2020; Coloma, Lugtenburg, et al., 2020; Van der Helm et al., 2019). HCN, a commonly used C1-building-block within industry, is an extremely toxic compound for humans and animals with possibly lethal consequences when exposure occurs in low concentrations (Keim, 2012). However, the compound also comes with great benefits in terms of its low number of by-products, its broad applicability for syntheses (due to it only having one carbon atom), and its relatively easy and cheap production. By applying the concept of miniaturization, this leads to an increase in (industrial) safety as the smaller reactors assure that less toxic cyanide would be present at any given time. Therefore, the idea of minimization, one of the ISPs, lowers the hazard (i.e., exposure to a lethal dose of cyanide) and therefore the associated risk. However, the notion of SbD would already question the initial usage of such an extremely toxic compound and would encourage using or searching for alternatives that would be less toxic (Robaey et al., 2017). Considering that HCN is widely used in industry and has been since its discovery by the end of the 18th century, currently, there are hardly any alternatives (with the same properties and similar benefits), and incentives for researching alternatives seem to be lacking. Especially the latter sheds light on the applicability of the ISPs and SbD to already established syntheses and processes and raises the question of which approach would be more suitable for different research stages.

This paper is structured as follows. First, we introduce miniaturization processes using HCN and provide an overview of the concepts of inherent safety, the ISPs and SbD. Second, by applying either approach to the case study, this sheds light on their applicability for a specific research stage. We identified some internal value-conflicts in terms of safety, sustainability, and efficiency, and external conflicts or lock-ins, such as (company) culture and already established safety measures. These results indicate that multiple values should be taken into account when designing for safety and that either approach differs in their applicability for a specific research stage. By applying Technology Readiness Levels (TRLs) specifically defined for the chemical industry (Buchner et al., 2019), we can identify the technology's development stage and whether a product or process may already suffer from certain barriers or lock-ins that might lead to value conflicts in choosing measures for safety. We argue that SbD would be more suitable for early-stage

development or fundamental research (TRLs 1–5). As applied research (TRLs 5–9) may already suffer from lock-ins, this complicates application of the SbD approach, and the ISPs would be more appropriate here. Last, we conclude that neither of the approaches should be associated with a specific domain, but instead with the emergence of known or uncertain risks.

4.2. Methods

This study comprises three components: (1) A literature study focusing on inherent safety, the ISPs and SbD, (2) semi-structured interviews that helped to clarify the specific context of the case study regarding miniaturized processes using HCN, and (3) analysis of the suitability of the ISPs and SbD by applying either approach to the case study. This means that this study comprises an empirically informed conceptual analysis, in which the conducted interviews mostly provided information concerning the miniaturized processes, and what it would entail to implement this type of technology in industry. The analysis part of this study is mostly based on existing literature from which we defined the relevant concepts for this study, but complemented with information derived from the interviewees.

The reason we chose miniaturized processes using HCN as a case study is the availability of comprehensive knowledge and of many safety procedures that make it possible to work with this compound safely. However, coming from a SbD-perspective, we might be questioning whether we should be working with such a hazardous substance at all considering its lethal properties. This case study allows us to research what effects applying the SbD approach would have, what its bottlenecks would be and what the differences are between applying the ISPs and SbD in practice.

In terms of empirical input, interviews ($N_{\text{tot}}=7$) were conducted from October to December 2019 with a range of relevant stakeholders that gave more information about (technical) details of the miniaturization of HCN processes itself, (national) regulation in terms of safety measures from a governance and knowledge institution's perspective, the current usage of HCN within industry and whether and which values are at stake for different stakeholders. Interviewees from academia are employed as a Principal Investigator (PI) ($N=2$), PhD researcher ($N=1$) and a Safety Officer ($N=1$). Furthermore, two interviews were conducted with representatives of a global industrial (bio)chemical concern [BCM1; BCM2], and one interview with a risk assessor employed by the Dutch National Institute for Public Health and the Environment²⁵.

²⁵ In Dutch: Rijksinstituut voor Volksgezondheid en Milieu (RIVM)

The interviews followed a semi-structured approach that left enough room for interviewees to go into detail when the researchers felt this was necessary for clarification or context. The interviewees were selected based on their experience in the domain of (bio)chemistry and field of profession. In addition, all interviewees hold senior positions, except for the PhD researcher. At the start of each interview, we asked the interviewee to sign a form of consent to approve recording the interview. After the interview, a transcript was sent to the interviewee for any remarks or corrections. Upon receiving the interviewee's approval, the transcript was anonymized, coded and analyzed. All data (i.e., form of consent, interview protocol, interview transcripts) can be requested from the corresponding author²⁶.

4.3. Cyanide Research

C-1 chemistry entails the field of research that uses one-carbon reagents. Examples of such are methane (CH_4), carbon monoxide (CO), methanol (CH_3OH) and hydrogen cyanide (HCN). In particular the latter is considered the cheapest and most versatile building block within this specific domain (Bracco et al., 2016). However, although this compound comes with great benefits such as its low costs and relatively easy production coupled with its high efficiency for syntheses with a low number of by-products, it also poses a health threat due to its toxic properties. That is, compared to other toxic gasses (e.g., CO), its lethal concentration is extremely low, i.e. HCN : 110 mg/m³ (RIVM, n.d.-c) compared to CO : 2.000 mg/m³ (RIVM, n.d.-b) —10 min exposure meaning that the chance of a fatality is very high. Therefore, many safety measures and procedures have been developed such as the usage of closed reactors or specific safety protocols and equipment to handle HCN safely. More recently, increasing interest is given not only to novel techniques for safety but also to positively impact the energy efficiency and environmental aspects. One of such techniques is miniaturization; a type of process intensification that leads to substantially smaller and more efficient chemical processes and synthesis pathways (Stankiewicz & Moulijn, 2000).

4.3.1. Miniaturization

As the name 'miniaturization' already implies, micro-reactors are used to intensify processes and to reduce the scale of equipment (Figure 4.1a,b). In these types of processes, low(er) volumes (e.g., 500 μL –2 mL) are used that make it possible to, for example, enable reactions under higher temperature or using higher concentrations, as well as better process control and heat management (Löwe & Ehrfeld, 1999; Stankiewicz & Moulijn, 2000). Furthermore, as micro-reactors require fewer materials, equipment and installation costs would be lower, fewer demands in laboratory infrastructure would be necessary, better process performance could

²⁶ All data can be accessed via <https://doi.org/10.17026/dans-x9n-prcm>

be achieved, and the process by itself would be inherently safer (Sie, 1996). In particular, the latter is advantageous when working with highly toxic compounds.

As micro-reactors make the overall process more controllable (van der Helm et al., 2019), these are especially interesting for industry, in particular when outscaling is applied. This means that several micro-reactors are coupled in parallel (Figure 4.1c) in order to achieve higher throughput or a larger production volume. Due to the improved controllability per micro-reactor, this also leads to a higher level of safety (Van der Helm et al., 2019). In addition, miniaturized processes are also generally regarded as highly efficient because batch processes (a finished lot or quantity after one production cycle) can be converted into miniaturized continuous systems. However, converting batch processes into continuous processes also calls for finding an effective method of immobilization for the used enzyme, which can be problematic.

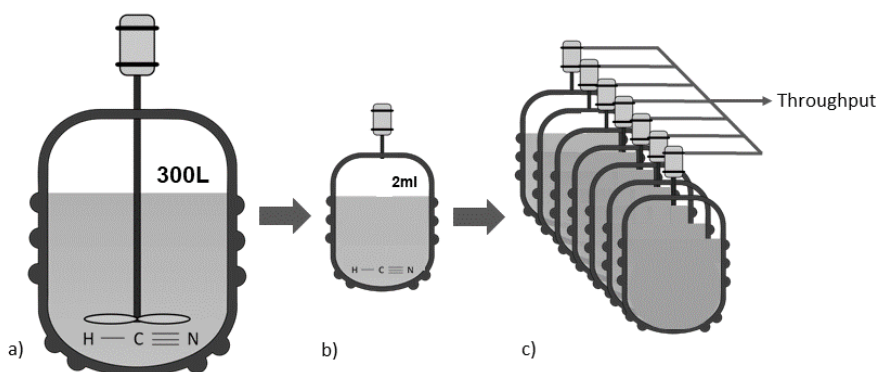


Figure 4.1: Simplified, schematic representation of the concept of miniaturization. (a) Illustration of a batch reactor (300L), (b) a miniaturized reactor (2mL), and (c) outscaling—the coupling of multiple micro-reactors in parallel for higher throughput

4.4. Designing for Safety

Miniaturized processes can be regarded as a safer alternative to already established syntheses and processes as they provide a lower volume of HCN to be present at any given time. However, as HCN is still being used, the risk of incurring a lethal dose is still present. In that sense, a ‘true’ inherently safe design would not make use of any hazardous substances in the first place, which is exactly the idea behind the SbD approach.

Within the chemical industry, safety measures are generally applied to already existing techniques and are mostly focused on technicalities. In general, these measures are classified as (1) engineered safety, (2) procedural safety, and (3)

inherent safety (Amyotte et al., 2007). Engineered safety involves add-on safety features that do not perform any fundamental operation within the process itself, but only become active when an issue within the process occurs. Procedural safety entails measures for safety, such as safety protocols, that reduces risks for safe work practices. Inherent Safety comprises using the properties of a material or process to eliminate or reduce the hazard (i.e., the potential for harm) itself (Kletz, 1996). Given the definition of risk (i.e., $\text{risk} = \text{hazard} * \text{probability}$), this means that the risk is also lowered although the probability that anything might happen would remain the same. This reduction or elimination of hazards is also exactly what makes inherent safety different from engineered or procedural safety; it seeks to minimize the hazard at the source instead of accepting the hazard and taking add-on safety measures (Amyotte et al., 2007).

4.4.1. Inherent Safety

In order to approach inherent safety, the Inherent Safety Principles (ISPs) have been developed, which, mostly with a technical approach, function as guidelines for safe product and process design (Khan & Amyotte, 2003; Kletz, 1996). The four general principles are (1) Minimization: Using smaller quantities of hazardous substances, (2) substitution: Replacing hazardous chemicals with less hazardous ones, (3) moderation: Using less extreme reaction conditions, a less hazardous form of a material or use facilities that minimize the impact of a hazardous material, and (4) simplification: Designing facilities in such a way that any unnecessary complexity is eliminated and makes operating errors less likely to occur. Although all four principles have the goal of making products or processes safer, these cannot be applied simultaneously (Bollinger et al., 1996; Khan & Amyotte, 2003; Rusli et al., 2013; Turney, 2001). As we will elaborate in Section 4.5.1, applying miniaturized processes using HCN (the ISP of minimization) can be deleterious for other ISPs, thereby leading to internal conflicts.

4.4.2. Safe-by-Design

Safe-by-Design (SbD) is an approach for (experimental) process design focusing on procedural and technical risk management and is currently gaining foot in the fields of nanotechnology and biotechnology (Kelty, 2009; Robaey et al., 2017; Turney, 2001). Although compared to the ISPs, SbD has a more socio-technical approach as it encourages active stakeholder engagement and communication about design choices and implementing measures for safety, associations with both approaches seem to overlap (Bouchaut & Asveld, 2020) as they both refer to the idea of designing specifically for safety by integrating knowledge about the adverse effects of materials in the technology's design process (Bollinger et al., 1996). However, when applying the ISPs, it is assumed that sufficient knowledge is available about the adverse consequences or risks of using such chemicals or production routes – as illustrated in the previous section. As SbD already questions

the initial use of hazardous chemicals and the design principles are solely focused on the value of safety, SbD tends to focus more on issues related to uncertain risks (Schwarz-Plaschg et al., 2017). For example, technologies that are still under development can be prone to uncertain risks as they have not reached a certain level of maturity to oversee all possible consequences. When knowledge about possible consequences turns out to be insufficient, the SbD approach can enable an iterative process in which many stakeholders are involved. That way, a range of different issues can be addressed, reflected on and incorporated in design choices, coming to a collective design with safety in mind (Bouchaut & Asveld, 2020). Therefore, in contrast to the ISPs that mostly have a technical focus, SbD can also incorporate socio-technical implications. However, this also means that although SbD can initially put more weight on the value of safety, later, other values such as sustainability might become relevant too as we will elaborate in Section 4.5.2.

4.5. Comparative Analysis

This paper aims to define the differences between the ISPs and SbD and which approach would be more suited for either fundamental or applied research. First of all, the conducted interviews helped to clarify the specific context in terms of our case study. Following that, by applying either approach to our case study and based on literature, we found that both the ISPs and SbD suffer from internal conflicts and external barriers, or lock-ins. However, in terms of the latter, we found that SbD finds more hindrance from these lock-ins and the ISPs would be more able to deal with these as they provide ‘add-on’ measures for safety, in comparison to SbD. For the sake of clarity, this study entails an empirically informed conceptual analysis, meaning that the presented results in this section are partly derived from the conducted interviews (context) and supported by literature (concepts) (All data is available upon request, see Section 4.2).

4.5.1. Internal Conflicts within the ISPs

As already touched upon in Section 4.4.1, not all ISPs can be applied simultaneously as this would cause internal conflicts. In the following sections, we provide a deeper analysis of occurring value-conflicts in line with (Bollinger et al., 1996; Khan & Amyotte, 2003), who have described these extensively. Using our case study, analysis of these conflicts illustrates what trade-offs would have to be made to achieve an inherently safer design from a technical perspective and whether this would be feasible. Besides, the latter also sheds light on the applicability of the ISPs in terms of such internal conflicts.

4.5.1.1. *Inherent Safety vs. Performance*

Inherently safer chemicals or synthesis pathways might not always perform to the same extent as less safe alternatives. However, whether something can be

deemed more efficient is dependent on what the comparison is made with, which also applies to miniaturization processes using HCN. For example, when such processes are compared with batch processes, miniaturization can indeed contribute to a more efficient (and safer) process. Batch processes are most commonly used for applications that have to be made under sterile conditions such as raw materials for food supplements. Therefore, such processes are conducted in a closed reactor vessel in which no substances are added or discarded during synthesis except for oxygen for pH adjustment. However, due to the mixing/stirring of substances in the vessel, heat is being released, which can affect process efficiency. If we would move from batch reactors to miniaturized, continuous flow processes, the efficiency would indeed increase as no energy would be required for stirring anymore and the temperature within the vessel would remain constant, meaning that no energy would be required for cooling.

Although miniaturized processes could help us improve safety, interviewees pointed out that a trade-off between safety and other relevant values would have to be made when transitioning to miniaturized processes. For example, industry already using continuous processes would take little or no benefit from miniaturization in terms of process efficiency. In addition, according to interviewees from a global (bio)chemical company, production routes and syntheses performed in industry are already deemed safe. As these firms have to comply with regulation, provide training for their staff and apply preventive safety measures to ensure a responsible and safe work environment, a question to them would be how much could be gained in safety when miniaturized processes would be implemented, and at what cost? In addition, according to the interviewees, if mini-reactors would be used, it would become more difficult to monitor the quality of raw materials with possible negative effects for the end-product's quality.

4.5.1.2. Inherent Safety vs. the Environment

Miniaturized processes can contribute to more environmentally friendly processes as they are more efficient and therefore lower amounts of toxic chemicals are used. However, as the CN-groups from HCN would still be inherently toxic, alternatives should be sought in order to contribute to a safer environment. For HCN, alternative forms can indeed be found that would expose a lower risk, for example, forms where the CN-groups would be retained to salts such as potassium hexacyanoferrate (III) ($K_3Fe(CN)_6$) or potassium hexacyanoferrate (II) ($K_4Fe(CN)_6$) (Grundke & Opatz, 2019). As the CN-groups form a strong bond with the iron in these salts, in theory, these would even be safe enough to be consumed by humans. However, as was pointed out by interviewees [PI1, PI2], in terms of the environment, to break the strong bond between the iron and the CN-groups, more extreme reaction conditions are required such as a higher temperature (and thus more energy) and a higher pH, which can lead to the formation of more residual products,

which would not be favorable from a sustainability perspective. Besides, a higher temperature might lead to certain enzymes no longer functioning when an enantiomer (optical isomer—right- or left-handed) is targeted. Because of this, the suggested alternatives $\text{K}_3\text{Fe}(\text{CN})_6$ and $\text{K}_4\text{Fe}(\text{CN})_6$ would be limited to only a number of syntheses or could only be used when a racemic mixture (equal parts of optical isomers) is targeted and enzymes are not required.

4.5.1.3. Inherent Safety vs. the Inherent Safety Principles

Given the limited range of alternatives to HCN, and that the ones available may be at the expense of other relevant values (i.e., energy efficiency, sustainability), it is clear that application of the ISPs can lead to internal value-conflicts. As already touched upon in Section 4.4.1 and 4.5.1.2, substitution of HCN with, for example, CN-salts would require more energy, would call for more extreme reaction conditions (i.e., higher temperature) and could result in more residual products. The same conflict occurs within one of the ISPs itself; moderation. Although we would be using a less hazardous material, this would not result in using less extreme reaction conditions. Of course, we could also exclude using CN-groups and search for other C-1 chemicals such as CO or CH_4 . However, as these compounds also have toxic properties and are harmful to the environment, these would still be deleterious in terms of the other ISPs.

4.5.1.4. Hazard vs. Hazard

Other, alternative compounds could also just induce different hazards. For example, we could also be using sodium cyanide (NaCN), which is far less hazardous than HCN and would create a safer environment for laboratory personnel to handle this compound. However, in an acidic environment, NaCN could easily form the gaseous HCN and still pose the same risk. Therefore, researchers need to assure that all work is conducted in a basic environment ($\text{pH} > 11$), which would require extra control measures, thereby also creating the probability for potential failure.

4.5.2. Internal Conflicts within Safe-by-Design

Technical designs often have to fulfil more requirements than, in this case, solely safety. In terms of SbD, as this approach places more weight on the value of safety, this can turn out to be detrimental for other values. For example, using CN-salts such as $\text{K}_3\text{Fe}(\text{CN})_6$ or $\text{K}_4\text{Fe}(\text{CN})_6$ (Grundke & Opatz, 2019) as described in Section 4.5.1.2. These compounds might be safer in terms of usage, they turn out to be deleterious in terms of sustainability. Such internal value conflicts would call for a trade-off (Van Gorp & Van De Poel, 2001). In that sense, we can assign two distinctions of applying SbD: Product-applied and process-applied (Bouchaut & Asveld, 2020). Product-applied SbD entails safety measures specifically applied

upstream, aimed at the technical components or the product itself. Process-applied SbD entails measures applied downstream, aimed at design decisions regarding scaling-up and further implementation. In terms of value trade-offs, transferring from product- to process-applied SbD might call for a different balance (i.e., safety vs. sustainability). However, in terms of creating inherent safety, safety would still be the core value at stake. If certain design requirements would call for a value trade-off, this would also imply that we would possibly have to 'give in' on safety. Although designers often have to accept such a trade-off for certain reasons, they could also look for new or alternative technical options minimizing the trade-offs that would have to be made (Van Gorp & Van De Poel, 2001).

4.5.3. Lock-ins

Application of both approaches to our case study of miniaturized processes already illustrated some internal conflicts and value trade-offs, which are mostly technically focused. However, devoting research to alternative, inherently safe raw materials (SbD approach) or implementation of miniaturized processes (ISP) also encounters other barriers than solely technical ones. Based on conducted interviews with representatives from industry, these barriers were identified as company culture, infrastructure, regulation and IPR, to which we refer as lock-ins.

From a company's perspective, devoting research to and eventually implementing alternative production methods or radically different synthesis pathways requires investments. However, when existing methods or pathways are already considered satisfactory in terms of their efficiency, costs, safety and the end-product's quality, and it is yet not clear what an alternative could add to one of these factors, incentives could be lacking (Edwards, 2005). In addition, although the industrial sector has been paying attention to creating inherently safe(r) processes over the past years, interviewees from industry pointed out that some companies may have outdated plants and installations. They mention that investments in infrastructure are often made for 20–40 years, and measures for safety are often add-on measures to already existing processes and conditions. If one would like to take a very different path, for example by implementing miniaturized processes and outscaling, this would not always be possible for existing plants. These, or other even more radically different processes could be best implemented when building a new production site, but this would require a consensus (BCM1). As corporate cultures are not always set to make fast decisions on such rigorous changes, accepting and implementing these changes often takes more organizational time [BCM1; BCM2]. Along the lines of these barriers, Turney (2001) argues that inherent safety is a radical departure from the traditional approach of looking at additional safety features first, as recommended by conventional safety codes and standards. Therefore, time would be needed to encourage people to change their thinking and practice to create inherent safety.

Creating inherent safety would take more than holding on to existing safety codes and standards as people's behavior and actions can also influence safety. For example, the more experienced people get, the more they learn and can become (more) aware of any induced risks, leading to behaving in a certain way and adhering to safety protocols. However, more experience could also lead to habituation where people spend less attention to, or disobeying protocols. "A researcher working with HCN for the first time will be more attentive than someone who has done this already a 100 times" [PI2]. From a SbD perspective, experience can be of great importance for creating an inherently safer environment. As SbD encourages stakeholder involvement (Van de Poel & Robaey, 2017), more discussion and engagement between relevant parties is invited, and more experience is brought in to anticipate potential risks (Swuste et al., 2020). As a broad range of stakeholders can share their vision and perspectives, measures could be designed collectively that would anticipate a wide range of potential risks. In terms of open communication for the sake of safety, mostly the domains of healthcare and the aviation industry are described in literature (Rutherford, 2003; Singh, 2009), in particular creating awareness and developing anticipatory measures such as 'learning from each other'. As parties can share data and information about, for example 'almost incidents', better, faster and anticipatory solutions can be developed (Groeneweg et al., 2018). However, although the chemical industry would like to transition to a more 'open' culture, many seem to struggle to enable such (ibid.). Interviewees [BCM1; BCM2] indicated that companies tend to be reluctant in being open and transparent—"they do not necessarily feel the need to share information with others". The reason they give for this lack of transparency is that they possess all the necessary expertise and experience to be able to deal with safety measures responsibly. In addition, related to patent due, any information released could lead to ownership issues, jeopardizing patent filing.

4.5.3. Differentiating the ISPs and SbD

Working towards inherently safer products and processes turns out to be not so straight-forward and depends on many factors such as people's way of thinking and acting, work culture and certain lock-ins such as infrastructure and IPR. When comparing application of the ISPs to the SbD approach, the ISPs offer more technically oriented risk-reducing measures. Therefore, the ISPs would be a better fit to deal with lock-ins as they provide guidelines that already take into account certain initial product- and process design choices (i.e., choice of chemicals, synthesis pathway, plant design). SbD calls for a different attitude to critically (re)think initial design choices (i.e., searching for alternatives to highly toxic chemicals). Therefore, we argue that SbD is more about inherent safe design while the ISPs focus more on safe process design.

4.6. Assigning Types of Research

Although the chemical industry is often more associated with applied research and knowledge institutions such as academia with fundamental research, we must not simply base the suitability of the ISPs and SbD on this association. Instead, we should look at a technology's development stage and the rise of known or uncertain risks to distinguish the approaches' applicability.

4.6.1. Technology Readiness Levels

The Technology Readiness Levels (TRLs) could offer a systematic structure that supports assessment of the maturity of technologies for the chemical industry (Buchner et al., 2019). Within this study, we build upon the TRLs specifically defined for the chemical industry (Table 4.1) by (Buchner et al., 2018).

Building upon the defined TRLs and descriptions provided in Table 1, it is important we first make a distinction between fundamental and applied research. For the levels 1–5, we feel that fundamental research would be more fitting as the technology is still in its early developmental stage within laboratory settings, thereby giving rise to more uncertain risks. In addition, we do acknowledge a difference for levels 1–3, which are mostly technically focused in terms of design choices, and levels 4–5, which also entail preparations for developing process design and scaling-up. The levels 5–9 consist of more advanced testing of process design, pilot trials and the operation of full-scale plants, which we associate more with known risks and applied research. Therefore (and recalling Section 4.5.4), we associate the TRLs 1–5 more with inherent safe design as it entails early (experimental) design choices (SbD approach) that would make the product or process already inherently 'safe', and the TRLs 5–9 more with safe process design (ISPs) as it involves add-on measures for safety.

In terms of assigning a fitting approach to the early research stages, the SbD approach can also make a distinction between the early developmental stages (TRLs 1–3) and the early process design (TRLs 4–5). In that sense and recalling Section 4.5.2, we can assign product-applied, and process-applied SbD strategies (Bouchaut & Asveld, 2020) such as the choice of raw material (e.g., chemicals) or develop built-in warning mechanisms might anything unforeseen develop. That would imply that for all TRLs, the value of safety is most prominent, but a balance could be found with other values that might become relevant when transitioning to later stages (TRLs 4–5), such as the values of sustainability or efficiency. For research that would be classified TRLs 5–9, certain design choices have already been established in e.g., infrastructure (existing chemical plants). Therefore, implementing measures for safety should be able to take these into account, and application of the ISPs would be more suitable here. For clarity, we constructed

Figure 4.2, which illustrates the distinction between the types of research based on the TRLs, and their associated approaches and possible measures for safety.

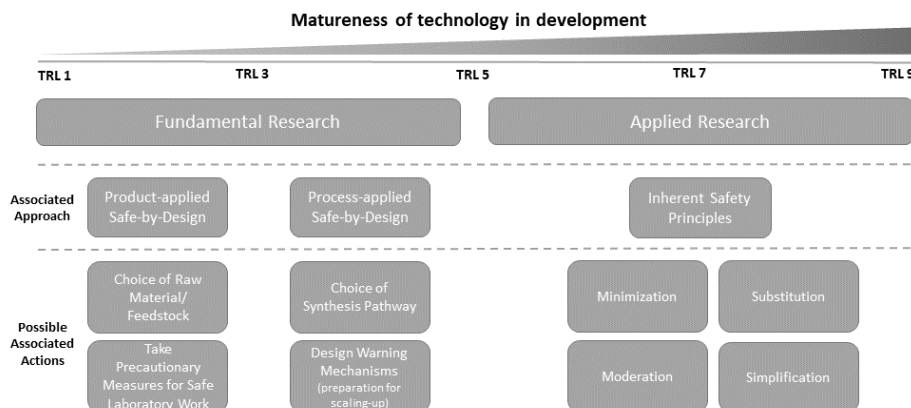


Figure 4.2: Defined Technology Readiness Levels with the associated type of research, approach (Safe-by-Design (SbD) or the Inherent Safety Principles (ISPs)) and possible safety measures to take.

4.6.2. Applicability to Domains

Although the field of chemical engineering is generally more associated with applied research and ‘newer’ fields such as biotechnology and nanotechnology more with fundamental research, application of either the ISPs or the SbD approach should not be decided upon the specific domain but should be considered on the stage of research and what types of risk arise.

The domain of chemical engineering constitutes a more traditional field with decades of knowledge and experience. Therefore, this field, and in particular process design, is often more associated with applied research and known risks, which makes it very suitable for application of the ISPs. For the fields of biotechnology and synthetic biology, the SbD approach has been gaining foot (Asin-Garcia et al., 2020; Robaey et al., 2017; Van der Berg et al., 2020). As these fields are ‘newer’ compared to the chemical domain, this can give rise to uncertain risks. For example, unexpected operating conditions during bio-energy production causing the release of hazardous substances (Casson Moreno et al., 2016), or the possibly accidental release and spread of synthetic cells and carriers (Knapland & Knaplund, 2011; Maurer et al., 2006; Regårdh, 2011; Schmidt et al., 2011). However, uncertain risks are not solely limited to ‘new’ domains of engineering, but can also still arise in the domain of chemical engineering, e.g., pesticides or PFOA (Domingo & Nadal, 2019). Therefore, neither of the approaches should be associated with a specific domain as known and uncertain risks also do not limit themselves to a specific field of interest.

4.7. Conclusions

This paper aimed to define the differences between the ISPs and SbD and to shed light on which approach would be better applicable to what type of research: Either applied or fundamental research. For both approaches, we identified internal conflicts and external lock-ins that called for some value trade-offs. However, especially SbD appeared to be less able to cope with external barriers in comparison to the ISPs as they provide guidelines for add-on safety measures. In contrast, as SbD assigns more weight to the value of safety in early design choices, this can lead to more radical measures for safety. Therefore, we argue that SbD is more about inherent safe design while the ISPs focus more on safe process design.

Our case study on miniaturized processes using HCN illustrated that a trade-off within the ISPs can only be made when risks (and benefits) are known. As known risks are more associated with applied research (TRLs 5–9), we argued that the ISPs would be more suitable for this type of research as they take into account certain lock-ins and provide guidelines for safety measures from thereon. In case of uncertain risks, making a trade-off between the ISPs would be impossible. As SbD encourages stakeholder involvement and calls for a different attitude to critically (re)think initial design choices, this approach would be more suitable for early-stage, or fundamental research (TRLs 1–5). Although taking appropriate measures to anticipate uncertain risks is challenging, it could give the opportunity to already find the safest possible pathway at the beginning of a technology's development. As it does not suffer from lock-ins (yet), this could help to create incentive for devoting research to alternatives.

4.7.1. Concluding Remarks

This study entails an empirically informed conceptual analysis, meaning that the conducted interviews mostly functioned to gain understanding of the relevant context (i.e., miniaturized processes, safety measures and possible barriers for implementation from an industry perspective). The interviews were mostly carried out with people employed in the Netherlands (e.g., Dutch research institute) although interviewees did have different nationalities and working experience outside the Netherlands. The interviewees from a global biochemical firm have senior international experience and are not stationed in the Netherlands. Therefore, the knowledge derived from these interviews is partly based on Dutch regulation (i.e., Safety Officer complying with Dutch legislation) but not limited to this. In addition, all interviewees were from within the EU, so the overarching set of rules is identical. Furthermore, technicalities or process design related to miniaturized processes or syntheses using HCN are not limited to a specific country or region and are therefore representative of safety and design issues, even beyond the European context.

Safety is and will remain a contentious issue within the chemical and biotechnical domain, and does not only encompass technicalities or safety measures in terms of process and/or plant design. Although procedural safety aims to capture human behavior (and failure) to a large extent, human mistakes cannot be fully omitted. In terms of future research, Artificial Intelligence (AI) and machine learning could be implemented for processes where human behavior is a concern. However, such automated processes could also give rise to a new dimension with regard to engineered safety, in case such systems fail and would be in need of human interference.

Table 4.1: Definition of Technology Readiness Levels (TRLs) for the Chemical industry. Adapted from (Buchner et al., 2018).

TRL	1	2	3	4	5	6	7	8	9
Title	Idea	Concept formulated	Proof of Concept	Preliminary Process Development	Detailed Process Development	Pilot Trials	Final Engineering	Commissioning	Production
Description	Opportunities identified, basic research translated into possible applications (e.g., by brainstorming, literature study)	Technology concept and/or application formulated, patent research conducted	Applied laboratory research started, functional principle/reaction (mechanism) proven, predicted reaction observed (qualitatively)	Concept validated in laboratory environment, scale-up preparation started, conceptual process design (e.g., based on simulation with simple models)	Shortcut process models found, simple property data analyzed, detailed simulation of process and pilot plant using bench scale information	Pilot plant constructed and operated with low rate production, products tested in application	Parameter and performance of pilot plant optimized, (optional) demo plant constructed and operating, equipment specification including components that are type conferrable to full-scale production	Products and processes integrated in organizational structure (hardware and software), full-scale plant constructed, start-up initiated	Full-scale plant audited (site acceptance test), turn-key plant, production operated over the full range of expected conditions in industrial scale and environment, performance guarantee enforceable
Workplace	Sheets of paper (physical or digital), whiteboard or similar	Sheets of paper (physical or digital), whiteboard or similar	Laboratory	Laboratory/ Miniplant	Laboratory/ Miniplant	Pilot plant, technical centre	Pilot plant, technical centre, (optional) demo plant (potentially incorporated in production site)	Production site	Production site

Chapter 5

Differences in Barriers for Controlled Learning about Safety between Biotechnology and Chemistry

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5.1. Introduction

The planetary boundary for production and release of new chemicals and plastics (Persson et al., 2022), rising CO₂ levels, depletion of fossil-based raw materials and geo-political dependencies present an urgent call for an industrial transition toward a biobased economy. Industrial biotechnology (and the associated field of green chemistry) aim to find more sustainable alternatives to conventional chemical manufacturing routes. Particularly the development of CO₂-negative approaches (e.g. CO₂ conversion into chemicals and fuels (Aresta et al., 2016)) and biobased alternatives to fossil resources-derived chemicals, polymers and plastics (Carlozzi & Touloupakis, 2021; Liu et al., 2019) show great potential to fight today's problems and for countries or regions to become less dependent on others. However, biotechnology is struggling to compete with conventional chemical methodologies (Chen, 2012; Fritsche et al., 2020). This can be explained by the history, size (Chemicals | Internal Market, Industry, Entrepreneurship and SMEs, n.d.; Haaf & Hofmann, 2020) and influence (e.g. having a strong lobby in terms of policy measures (Maxwell & Briscoe, 1997; Reibstein, 2017)) of the chemical industry, and the simple fact that these industries are already established and matured compared to the biobased industries. However, it also appears that the respective risk management cultures in each industry differ greatly, which hinders the development of biotechnology and the biobased industry in becoming technically and economically feasible

The risk management culture in biotechnology emphasizes uncertain risks and is subject to a strong precautionary regime, particularly in Europe, leaving little room for development when uncertain risks are involved. In contrast, for chemistry, the focus is on known risks which has resulted in a culture of passive learning (i.e. through accidents) and many examples of regrettable substitution (Blum et al., 2019; Sweetman, 2020). The two risk management regimes seem to be at odds with each other even though both types of risk emerge in each field. If we want to tackle the global challenges of today, we need to develop new, safer products and processes that may require new types of chemistry in which biotechnology could play a pivotal part. This requires a middle way between the risk management regimes of chemistry and biotechnology: one that stimulates awareness of uncertain risks and also creates room to gain new knowledge of these risks. Therefore, we need to put designated procedures and institutions in place solely for the aim of learning about uncertain risks, i.e. active, or controlled learning, so new products and processes can be developed safely. Safe by Design (SbD) approaches could provide a framework to achieve such controlled learning, as has already been demonstrated in biotechnology (Robaey, 2018) and nanotechnology (Yan et al., 2019). SbD is an emerging approach that entails adaptive and iterative risk management by providing strategies to make researchers and research institutions question the initial usage of (possibly) hazardous compounds and/or encourages to

(completely) rethink a technology's design process already during the very early stages of development (e.g. during R&D) for the sake of safety (Robaey, 2018; Robaey et al., 2017). Thereby, the approach focuses on learning what possible risks might emerge and encourages alternative design choices to circumvent the earlier identified emerging risk. This is no guarantee that safety is ensured, but it does place more emphasis on designing for safety. Therefore, we propose it to also be implemented in the conventional chemical industry – as we will elaborate in this article. In addition, although we focus on safety, other notions such as circularity can also be included when considering design choices (i.e. Safe and Circular by Design (Slootweg, 2020)).

5.2. Known and Uncertain Risks

While societal concerns have had consequences for regulation and managing risks in both industries, each field's respective regime places emphasis on a different type of risk. This seems to be at odds with each other as both uncertain and known risks emerge in either field. With uncertain risks, we refer to risks that are not completely known, for instance, it might not be known what the order of magnitude is of a possible detrimental effect, or it might not be known what the possible detrimental effects are to begin with (Aven & Renn, 2009).

The field of industrial biotechnology is associated with known and particularly with uncertain risks. In terms of known risks and in response to public concerns, measures such as containment have been taken to lower or mitigate these risks. In terms of uncertain risks, applications such as CRISPR are still under development and can give rise to possible issues such as mutations or off-target effects (Gorter de Vries et al., 2019) that are difficult and complex to identify and anticipate. Other forms of engineering organisms and subsequently applying them in industrial processes also give rise to uncertain risks. Strategies for reducing and anticipating risks for these types of applications are well developed, e.g. by auxotrophy (Wright et al., 2013) or building in a conditional dominant lethal gene (Wise De Valdez et al., 2011). Even though these strategies may not be perfect (Hirota et al., 2017; Zhao et al., 2020), they do show that the field is actively dealing with uncertain risks.

In contrast, the chemical industry relies strongly on existing knowledge of risks. Chemical engineering's history as a scientific discipline goes back to the early 18th century and since then, many incidents have occurred. Therefore, there is vast knowledge and experience of the tragic consequences of these incidents (i.e. through passive learning) such as global pollution by micro-plastics (Law & Thompson, 2014) or the widespread occurrence of PFAS (Beans, 2021; Domingo & Nadal, 2019). While part of the industry has devoted itself to designing safer products and processes by utilization of the green chemistry principles (Anastas & Eghbali, 2010) or SbD strategies (Zimmerman & Anastas, 2015), still there are many reported cases of regrettable substitution (Drohmann & Hernandez, 2020;

Zimmerman & Anastas, 2015) – replacing a hazardous chemical with an alternative that is suitable in technical and economic terms, but just as harmful or potentially worse as the replaced chemical. Here we particularly emphasize regrettable substitutions by negligence (e.g. PFAS (Grandjean, 2018)), which often appeared to have been induced by the conventional chemical industry. Despite calls for a more ethical, greener chemistry (Gibb, 2022; Mehlich et al., 2017; Reibstein, 2017), the latter illustrates that this part of the industry hasn't been able, or unwilling, to deal with known or uncertain risks effectively.

5.3. Risk Management in Biotechnology and Chemistry at Odds

Each discipline's respective risk management approach provides little room or incentive to learn what uncertain risks entail. Europe's highly precautionary regime in biotechnology results in a culture of compliance (Bouchaut & Asveld, 2021) meaning that when no conclusive evidence can be provided that an emerging uncertain risk would be acceptably safe, innovations might be put on hold until safety can be guaranteed. In chemistry, managing risks is based on conclusive evidence that a new product or application is not safe, creating little incentive for the conventional chemical industry to actively research uncertain risks (or provide data concerning known risks) as this can lead to their new technology becoming prohibited or market entry postponed.

For clarity, this next section focuses mostly on differences in regulation between either field in Europe, and differences between Europe and the US. However, the problems we face today illustrate that risk management in biotechnology and chemistry is of importance on a global scale. The sections below can also provide insights for regulation in other parts of the world.

5.3.1. Chemistry

Regulation concerning chemicals in both Europe and the United States actively promotes and calls for the progressive substitution of the most dangerous chemicals when suitable alternatives have been identified. Although this, in theory, seems solid regulation to increase safety, several problems have been encountered. While a precautionary approach has been embedded in US regulation concerning chemicals (i.e. TSCA), the approach's operationalization fails to lead to higher safety. Mostly as current legislation in the US calls for conclusive evidence that a new product or process cannot be considered safe for it to be banned or strictly regulated. This results in little incentive for the conventional industry to test on safety for the vast majority of chemicals. On the other hand, a small subset of chemicals is subjected to a highly precautionary culture but has resulted in "an inequitable barrier to entry for newer, safer chemicals" (Wagner, 2000). It discourages industry to develop new and possibly safer chemicals, chemical products and processes as information about 'new' risks could be used against them in a later stage (Wagner, 2000). This

also relates to other regulatory problems such as the conventional industry filing incomplete dossiers, necessary information not being available due to confidentiality issues (Baltic Eye, 2015; Chemical Watch, 2013), or issues concerning regrettable substitution (by negligence). Particularly the latter illustrates the passive learning, or 'learning by doing' aspect, of which the so-called 'forever chemicals' or 'Generation-X chemicals' are the most illustrative (Beans, 2021; Drohmann & Hernandez, 2020; Strodder, 2020).

For European regulation (i.e. REACH), Drohmann and Hernandez (2020) have already called for regulatory changes to tackle regrettable substitution and point out several reasons why this is still an ongoing problem. The main reasons they put forward are (1) absence of information regarding hazard properties of the substitute substance, (2) inconsistencies in the implementation of the European Chemicals Regulations, and (3) lack of interest of some part of the industry to manage stringent classifications. In addition, incomplete dossiers and necessary information not being available due to confidentiality issues (Baltic Eye, 2015; Chemical Watch, 2013) lead to the scenario of "no data, no problem" (Drohmann & Hernandez, 2020) where the industry seems to be working towards innovating for circumventing existing environmental norms and legislation, instead of working on truly safer alternatives. Lastly, regulation calling for the progressive substitution of dangerous chemicals when suitable alternatives have been identified gives rise to another problem. To find safer alternatives to hazardous compounds, industry has to engage in active research. However, incentives appear to be lacking. As already referred to with the issue of regrettable substitution, economic and technical feasibilities are given great value instead.

5.3.2. Biotechnology

In contrast with chemicals, biotechnology is regulated more strictly. In Europe particularly, biotechnology is regulated based on precaution which gives rise to a completely different way of handling risks. First of all, in terms of allocated responsibility, initial stakeholders (researchers/engineers, companies) are responsible for providing conclusive evidence that their experiments and innovations only involve acceptable risks, and thus can be deemed safe. But, in terms of managing uncertain risks, this responsibility lies with risk managers and assessors and ultimately the government (Bouchaut & Asveld, 2021). This results in a culture of compliance: if there are uncertain risks involved, one has to redesign the technology or process to comply with the set norms. While for chemicals, the responsibility for managing uncertain risks is allocated to the industry which does not incentivize them to provide data, nor comply with the norms when uncertainties are involved.

Both US and EU regulations regarding biotechnology value safety and therefore regulation is strict. But US regulation does differ in having a product-based

assessment instead of process-based in Europe. Thereby, in the US, the innovative character of biotechnology is more emphasized. Since 2019, the USDA has implemented exemptions for GE crops that could have also been produced through conventional breeding techniques. This change now allows crop developers to self-determine whether such an exemption applies to their product, but does not influence the outcome of the USDA's review process for crops created by GE techniques (Regulatory Status Review). The motivation for this regulatory change was to stimulate innovation and make governmental oversight more effective and efficient (Hoffman, 2021; SGS Agriculture and Food, 2020). Also, this change has contributed to levelling the playing fields between conventional breeding and crop improvement using biotechnology – crops with the same outcome should not be regulated differently (product-based assessment). However, it appears that this revised regulation for GE crops has also led to businesses avoiding disclosure of e.g. methods and genes due to confidentiality issues (George et al., 2022) – which might give rise to new 'no data, no problem' issues we already know from chemistry.

Although US regulation allows more room for innovation in biotechnology compared to the EU, this is no guarantee that as a result the conventional chemical industry will adopt products and processes derived from biotechnology. As mentioned, the conventional industry shows a lack of incentive and seems to be mostly profit-driven. While green chemistry can also be profitable, this would still require substantial investments, differently set-up research, development and implementation. Therefore, as long as changes are not enforced, it is plausible that the conventional industry will stick to what they have been doing for many years.

5.4. Controlled learning about Uncertain Risks

It has become clear that the risk management cultures in biotechnology and chemistry either do not provide much room or incentivize learning what uncertain risks entail. For the sake of safe and responsible development of new products and processes, regimes where a culture of passive learning prevails (i.e. the conventional chemical industry) need to become ones of active, controlled learning (Van de Poel, 2017). And regimes in which learning is currently stifled (mostly pertaining to European biotech regulation), regulation should change to allow room for such learning about uncertain risks. To enable active, controlled learning in all industries, SbD could provide a suitable framework.

SbD is an adaptive and iterative risk management approach and focuses on learning what possible risks might emerge and encourages alternative design choices to circumvent the earlier identified emerging risk. Depending on how much room regulation allows for uncertain risks, these strategies are based on mitigating or lowering known risks, or can be applied to gradually learn in a step-by-step way what uncertain risks entail. As mentioned before, controlled learning about uncertain risks through SbD needs designated procedures and institutions to be put in place

specifically for the aim of learning about uncertain risks (Van de Poel, 2017). Not only would this require organizations and research to be set up differently but also a culture change. The latter will be very hard to accomplish without incentives that provide a shift from economic motives to safety. In that sense, this would require (1) changes in the chemical industry i.e. higher attention for safety by enforcement, holding companies accountable for damage and stimulating transparency, (2) changes in education and academic research, and (3) governmental measures in terms of policy adaptations.

First of all, to incentivize or enforce adoption of SbD-thinking in industry, developers should be made accountable for negative externalities resulting from their products or processes. Also, regulation could provide additional funding or research grants to companies to research safer alternatives. Partnerships could be stimulated to innovate and share information about new products with the industry hopefully sparking a broader adoption. Thereby, it could become more appealing for e.g. the conventional chemical industry to adopt SbD and actively work on the creation of safer products and processes.

Secondly, the 'learning about uncertain risks' should be reflected in how research is being valued in awarding research grants. Currently, the supporting academic system (e.g. funding organizations, research institutions and universities) does not seem to be very supportive of risk research as mostly technically innovative research is awarded. That way, we are missing out on important knowledge and data concerning potential risks in biotechnology and chemistry, and of which risk governance could benefit as well. In that sense, academic scholars should also embrace this different way of thinking to a greater extent and become more focused on risk research. And vice-versa, publishing agents (peer-reviewed academic journals) should value risk research the same as technical research. Also, we can work towards a culture wherein safety is embraced to a larger extent by targeting the 'engineers of tomorrow' and embedding the 'designing for safety' way of thinking already in education. To do so, knowledge institutions engaged in education should also devote part of their curriculum to the SbD-way of thinking – examples can be coming from iGEM (International Genetically Engineered Machines; IGEM.org), a yearly student competition in synthetic biology that highly regards safety and SbD. Only through education, we can reach the future engineers and embed this way of thinking in future company- and industry cultures and risk management.

Still, bringing drastic change culture-wise can often not be achieved from a solely bottom-up initiation. Therefore, policy should no longer place the responsibility of managing uncertain risks with industry as the current allocation appears to be too tempting for misuse by part of the industry. Therefore, responsibility needs to be redistributed leaning toward a regime of compliance. That would mean that industry would be responsible for providing conclusive evidence

that a new product or process is safe, thereby hopefully sparking an incentive to conduct more risk research. However, for that, total transparency would be needed – eliminating the current ‘no data – no problem’ issue. Therefore, regulation needs to put requirements for transparency into place, not only concerning known risks but also uncertain risks. Also, society must have independent testing so that the provided information can be relied upon, and companies should be required to report on their use of chemicals and their efforts to reduce hazards (by SbD), and pay support systems that recover post-use products. Not only for the sake of safety itself but also for people and animals having the right to a healthy and safe living environment.

Chapter 6

Integrating Designing for Safety in Education: An iGEM Showcase

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6.1. Introduction

The Safe-by-Design (SbD) approach is portrayed as a promising approach to identify and anticipate risks associated with emerging applications of synthetic biology (e.g. Asin-Garcia et al., 2020; Robaey et al., 2017; Van de Poel & Robaey, 2017). However, in literature, SbD is often conceived as a broad notion of incorporating safety and responsibility (Krouwel et al., 2022), thereby differing in terms of suitable strategies for safety per field of application (van Gelder et al., 2021). In that sense, few reports and publications explicitly describe examples of how SbD-strategies have been implemented in biotechnology and synthetic biology. Therefore, the notion remains abstract, in particular for stakeholders who would have to actively engage with this approach, namely researchers and engineers. In addition, amongst this group, there are differences in what is perceived as SbD and the approach's associated notions such as inherent safety and measures to work towards this (Bouchaut & Asveld, 2020). To make SbD more tangible for this group, we provide two concrete examples of how SbD and its derived anticipatory strategies to mitigate emerging risks have been incorporated in each example's respective design choices. The two examples provided are projects executed by students participating in the annual international Genetically Engineered Machines²⁷ (iGEM) competition at Delft University of Technology (TU Delft), the Netherlands. The iGEM competition is dedicated to the advancement of synthetic biology and aims to tackle every-day or global problems related to, amongst others, human health, climate change, environmental pollution or agricultural challenges (iGEM Foundation, 2021a).

Even though the field of synthetic biology is considered relatively new, there is already over a decade of experience in terms of safety and (bio)security (Millett et al., 2020). Still, the field is developing at a vast pace, and therefore, safe and responsible development must be ensured (Stemerding, 2015). The iGEM foundation regards safe and responsible design highly, and therefore participating teams have to ensure that their project is developed in such a way. To do so, an expert committee on safety and security provides advice to participating student teams, and teams have to go through multiple steps, of which, amongst others, a risk assessment. Also, students have to demonstrate to iGEM that they are working safely (i.e. adhere to safety rules, proper lab training), adhere to rules and policies (e.g. projects may not be tested or released outside the laboratory), and teams have to proactively mitigate potential associated risks that may arise during their projects (iGEM Foundation, 2021b).

Concerning the latter, to help students identify and anticipate uncertain risks during the development of their project, Value Sensitive Design (VSD) and SbD are

²⁷ www.igem.org

integrated into education related to the iGEM project at TU Delft. First, VSD sheds light on relevant moral values that must be taken into account by students during the development of their project. From there on, students zoom in on the value of safety by means of SbD and develop and apply anticipatory strategies to mitigate earlier identified emerging risks.

In this paper, first, we provide some context on safety within iGEM and how this is related to other relevant aspects of such a project. Secondly, we elaborate on VSD and SbD and explain how both approaches are integrated into education concerning iGEM. Lastly, we showcase two iGEM projects executed by students from TU Delft, illustrating how each has operationalized VSD and SbD and how that led to the project having been developed safely and responsibly. Thereby, the contribution of this paper is two-fold. Firstly, we aim to provide concrete examples of how SbD strategies have been implemented and to contribute to the knowledge base concerning SbD in bio-engineering. That way, we hope to raise awareness about ‘designing for safety’ amongst researchers and engineers and to provide them with some hands-on tools to incorporate such measures in their research. Secondly, by illustrating how both VSD and SbD have been incorporated in education related to iGEM, we hope to inspire other lecturers to do so too, and thereby contribute to an increased awareness of the importance of designing for safety amongst future engineers.

6.2. Safety in iGEM

Safety is dependent on and related to many other aspects that are relevant in an iGEM project. That is besides technical features, matters related to ethics and social responsibility, science communication and public outreach, and examining relevant policy, regulation and law (iGEM Foundation, n.d.-b). Students must become aware of this interrelatedness at the start of their project as certain design choices (i.e. choice of organism, vector, DNA plasmid) can be very desirable in a technical sense (e.g. high efficiency or accuracy) but can give rise to an emerging risk or bottleneck coming from a different angle. For instance, when implemented outside the controlled environment of the laboratory²⁸, a genetically modified organism (GMO) or certain type of genetic modification could lead to undesirable competition with a local ecosystem, possible gene transfer, or could simply turn out to be undesirable from a (local) societal perspective.

Insights of such kind can be derived from e.g. interviews with associated stakeholders (human practices) or result from lab experiments (wetlab), and have to be fed back in the design of the project and result in an alternative design choice to ensure safety. Figure 6.1 illustrates such iterations within the design process of

²⁸ Although iGEM does not allow projects to be brought outside the contained environment of the laboratory, students must think about a possible, eventual application of their project in real-life.

an iGEM project. In practice, although students are each assigned responsibility for a specific aspect (e.g. Wetlab or Safety & Security manager), their work all feeds into others' and therefore, working and discussing findings and results collectively is emphasized.

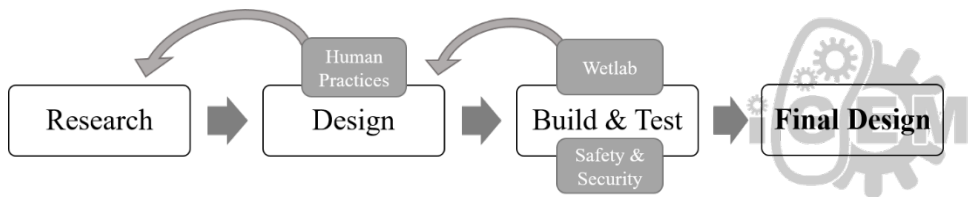


Figure 6.1: Simplified, schematic illustration of an iGEM project's iterative design process. This figure illustrates that findings in terms of human practices, safety & security and/or wetlab experiments can result in adaptations in design choices. Hence the arrow indicating going one or two step(s) back in the design process. Of course, the steps Research – Design – Build & Test are not a linear process and call for multiple iterations until the final design is obtained.

6.3. Safety in Education

As mentioned, students first have to become acquainted with identifying relevant (moral) values that need to be taken into account in their project's design. Therefore, at the start of their project, iGEM students have to enroll in the MSc. course 'Ethical, Legal and Societal Aspects of Biotechnology (ELSIB)'. Here, the students familiarize themselves with tools for identifying and prioritizing relevant values (e.g. sustainability, safety, equity) and how to incorporate these findings in their projects' design choices. We do this first by means of VSD in the course, on which SbD builds. As the value of safety is often also addressed in VSD, SbD derives knowledge and insights from VSD concerning the notion of safety. In this paper, we emphasize the notion of safety and therefore particularly focus on the operationalization of SbD in iGEM. However, as VSD forms the basis for SbD, we also briefly illustrate findings from VSD when showcasing the executed iGEM projects at TU Delft (i.e. PHOCUS and AptaVita).

6.3.1. Value Sensitive Design

VSD provides a method to conduct responsible research and innovation by shedding light on moral values that need to be (proactively) taken into account throughout a design process (Friedman, 1996; Friedman et al., 2013, 2008). However, incorporating relevant values implies that a very broad set of values would have to be accounted for, which raises the question of how to prioritize these values? The concept of Values Hierarchy enables translating values to specific contexts and design requirements. The Values Hierarchy is a simple tool that, as the word already suggests, puts order in a list of indicated values for design choices by performing three types of analyses: conceptual, empirical and technical (Friedman et al., 2008; Van de Poel, 2013, 2015)

The first step, the conceptual investigation, entails identifying all relevant stakeholders (direct and indirect) within the design process. This first step does not limit itself to solely determining who the affected stakeholders are and what values they consider to be of importance, but also tries to engage itself within trade-offs of competing values (Friedman et al., 2013; Van de Poel, 2013). An advantage of the conceptual investigation is that it immediately clarifies any issues or conflicts (e.g. between values or stakeholders) and forms a basis for comparison (Friedman et al., 2013; Miller et al., 2007). The second step within this process is to investigate empirically how earlier identified values are being applied to human contexts. This can be done by conducting interviews or surveys, but also by performing observations (Van de Poel, 2013). The third step, the technical investigation, aims to translate earlier identified values and empirical data into tangible design requirements. However, this last step is usually conducted in two forms: one focusing on how existing technological properties support or may hinder human values, and one focusing on how the design can support values. Although the empirical and technical investigations seem to overlap, what must be clear is that the technical investigation focuses solely on technology, while the empirical step also includes social factors. A matter of importance during these steps is that one should not get stuck in a moral overload; where one is burdened by conflicting obligations or values that hold the same hierarchy, but cannot be realized at the same time (Van den Hoven, 2013).

6.3.2. Safe-by-Design

In line with VSD, literature suggests that if we can design for a range of values, we can also specifically design for the value of safety (Fahlquist et al., 2015; Robaey et al., 2017; Van de Poel & Robaey, 2017). In that sense, SbD is a risk management approach that focuses on safety and provides anticipatory strategies to mitigate emerging uncertain risks (Robaey, 2018). It does so by encouraging actors involved in the design process of a technology (i.e. researchers, engineers) to take responsibility for future safety during the idea and design phase of a technology (Fahlquist et al., 2015) by providing anticipatory strategies to mitigate emerging risks. Active stakeholder involvement and communication about optional design choices is hereby crucial.

SbD has been implemented thoroughly in the field of nanotechnology (Khan & Amyotte, 2003; Schwarz-Plasch et al., 2017; Van de Poel & Robaey, 2017), and is gaining foot in biotechnology and synthetic biology (Asin-Garcia et al., 2020; Kapuscinski et al., 2003; Robaey, 2018). As these fields are relatively new, there can be insufficient knowledge in terms of the technology itself or the eventual application (Collingridge, 1982), which calls for an iterative process in which emerging risks can be anticipated, with emphasis on uncertain risks.

Anticipating uncertain risks utilizing SbD focuses on both technical aspects (upstream) and aspects related to further upscaling or eventual implementation of the technology (downstream). Of course, both are related as any possible issues may only be discovered when the technology already finds itself in a later stage of development (e.g. during upscaling) and technical measures need to be taken in response (Bouchaut & Asveld, 2020). Also, other conflicting values with the value of safety might require different design choices (Bouchaut et al., 2021). For example, the value of safety can be given more weight in initial technical design choices but could lead to a value conflict with e.g. sustainability in a later stage of development. Also, other matters related to security, e.g. privacy issues or dual-use (Millett et al., 2020; Vennis et al., 2021) might call for a different choice of design in which safety is still ensured but no conflict emerges with another value.

6.4. Safety in Practice: An iGEM showcase

As mentioned, first, students have to conduct a VSD analysis which is embedded in the ELSIB-course. In line with the first level (conceptual investigation), the students have to identify relevant stakeholders in their project and determine which are the most powerful or influential using a power-interest grid. Following upon, students have to identify relevant values for all associated stakeholders which is done by reviewing literature, relevant websites (e.g. company or organisation's website) or through interviews. Secondly, the empirical phase of VSD sheds light on possible value conflicts, and how identified values are or aren't met in the current design, thus giving insight into where there's room for improvement in terms of the initial design. Lastly, all identified stakeholders' values are analysed and reviewed in terms of their potential to be translated into design requirements. For instance, values related to notions such as 'respect' or 'integrity' are mostly dependent on human behavior and are therefore difficult to translate into tangible technical design choices. Other values that have the potential to be translated to norms are translated into design requirements to which the project's design should adhere. Finally, students hand in a report of the VSD analysis which is assessed (and graded) by the responsible teacher of the ELSIB-course, and by one of the iGEM supervisors involved in safety & security and human practices.

After the VSD analysis, insights are derived about possible value conflicts and bottlenecks. This provides the starting point for students to start building and 'testing' their project, taking into account the established norms and design requirements for their project. However, as the development of an iGEM project is never linear and issues or uncertain risks may also emerge during the process, SbD comes into play to ensure safe and responsible design. As mentioned, issues might arise based on data from wetlab experiments, from conducted interviews with experts in the field or at the site of prospected implementation. To ensure safety, these insights have to be fed back into the design process and alternative design

choices should be made accordingly by applying certain SbD-strategies (e.g. Robaey, 2018) while keeping on taking the initial design requirements into account.

In the next sections, we will elaborate on how SbD is put into practice by showcasing two iGEM projects. We will first shortly illustrate the conducted VSD analyses, on which we thereafter zoom in on the value of safety and elaborate SbD and the implemented SbD strategies more elaborately for each iGEM project. To be clear, the work described below is the iGEM students' work. The authors have acted as supervisors, providing regular feedback on the students' work and guiding them in their work.

6.4.1. PHOCUS – Target Locusts from within

“Locust plagues currently threaten food security in the Horn of Africa, the Arabian peninsula and South Asia, devastating croplands and pasture. We, the TU Delft iGEM team PHOCUS, aim to tackle locust crises by developing a targeted, fast-working and safe bio-pesticide based on engineered bacteriophages. Upon bacteriophage ingestion by the locust, toxic molecules will be produced by targeted bacteria in the locust gut, killing it from within.” (TU Delft iGEM PHOCUS, 2020b)

6.4.1.1. Value Sensitive Design

PHOCUS aims to tackle locust swarms caused by gregarious-state desert locusts (*Schistocera gregaria*) by using modified bacteriophages that secrete a toxin in the locust's gut – thereby killing it from within. To do so safely and responsibly, the first step was to conduct a VSD analysis to identify relevant stakeholders and derive their most important values. Based on this first analysis, norms and design requirements are formulated that formed the starting point for the development of PHOCUS. To be clear, to keep the number of associated stakeholders realistic, students have chosen a specific country (in this case Kenya) that functions as a pilot site for the hypothetical implementation of PHOCUS. Below, we now provide a summary of the conducted VSD analysis. A more detailed overview is provided in Appendix A: Table A.1 and Table A.2. Table A.1 provides the listed identified stakeholders in order of priority (i.e. using a power/interest grid) and their associated values. Table A.2 gives an overview of the selected values, the derived norms and design requirements.

As the proposed site of implementation is Kenya, the most important identified stakeholder is the Ministry of Agriculture, Livestock, Fisheries and Irrigation of Kenya. Also, as PHOCUS provides a way to eradicate harmful locust swarms to prevent crops from being destroyed, several stakeholders are considered of great importance too: the Food and Agriculture Organization, the Desert Locust Control Organization East Africa, and of course, Kenyan farmers and herdsmen. Additionally, stakeholders were identified that might be competitors for PHOCUS

(i.e. chemical companies currently producing pesticides), and the iGEM Foundation itself.

Secondly, associated values were derived from the list of associated stakeholders. This list of values contains universal values such as 'equality' and 'health', but also other values such as 'family', 'cooperation', 'innovation' and 'passion'. As especially the latter set of values are difficult to translate into tangible design requirements, these were omitted from the third step (technical investigation). However, of course, where possible these values were taken into account during the composition of norms and design requirements of other values. For instance, although 'Respect' or 'Honesty' are difficult to translate to norms and requirements for design, these have been taken into account with 'Accessibility' and 'Equity'.

The technical investigation included values such as 'health', 'food safety', 'accessibility' and 'environmental safety' but a more detailed overview can be found in Appendix A, Table A.1. Here, we shortly address two (one related to technical aspects, and one to social aspects) and explain what norms and design requirements were derived from these. For example, in response to the value of 'health', the derived norm is 'No effects on physical or mental health' for all people (or animals involved, except for the locusts). To adhere to this norm, the following (technical) design requirements were established: (1) Using bacteriophages as genetic carriers as this type of virus is only able to infect a very specific bacterial genus or strain and thus cannot cause infections in humans, (2) No delivery of bacteriophages under acidic conditions to reduce the risk of bacteriophages entering human intestines as the digestive system of locusts is far less acidic than the human stomach, (3) Use a non-toxic, non-pathogenic host microorganism that is not present in humans to reduce the risk of infecting human gut bacteria, or prevent depletion of beneficial bacteria, and (4) The produced toxin must be non-pathogenic to humans and degradable in the human digestive system. In addition, a concern that was strongly discussed during the design stage of PHOCUS was the generation (and release) of a GMO. To reduce the risk of potential recombination of the heterologous DNA in the genome of the bacteriophage with the host genome, a non-toxic and non-pathogenic host microorganism should be chosen, for instance, a lytic phage. This way, the integration of the DNA into the bacterial genome can be avoided as the host will be lysed after viral replication.

In response to the value of 'accessibility', the following norms were constructed (see also Appendix A, Table A.2): (1) Access to the product (i.e. PHOCUS) at all times, and (2) Access to knowledge about the product. In line with these norms, the following design requirements were established: (1) There needs to be a robust distribution network, (2) Local production, (3) Affordable, (4) Simple and easy to use, and (5) Sufficient knowledge should be provided to end-users for them to make

an educated decision to use, or not use, our product. The argumentation behind these requirements is that to make adequate quantities of food available to people in the affected area(s), PHOCUS must reach local farmers and landowners. Therefore, a robust distribution network should be set up, but to limit the dependence on such large channels, production sites should be developed locally. That way, the product can reach the customers faster and with fewer intermediates. Also, the economic capacity of local stakeholders (i.e. farmers and land workers) must be taken into account. As most countries that are being affected by locust swarms show low mean income, PHOCUS should be as inexpensive as possible. Lastly, although levels of education differ per country, a sufficient level of information should be provided to the potential users of PHOCUS, enabling them to make an informed decision about whether to use, or not use PHOCUS.

After the third step in VSD, the technical investigation, some value conflicts and other clashes between norms and design requirements were encountered. These were, for example, Food Security vs. Environmental, Health and Food Safety, and Accessibility vs. Responsibility and Integrity. In response, this had some implications for the technical design options within the project, such as whether to go for a lytic or lysogenic cycle of the bacteriophage, if a kill-switch should be added, whether locusts should be sprayed directly with the bacteriophages or the crops instead, or whether the locusts should indeed be killed or could be prevented from swarming first of all? These questions were considered from a SbD perspective and anticipatory strategies were developed to ensure safe and responsible development of PHOCUS.

6.4.1.2. Safe-by-Design

The identification of uncertain risks or possible issues concerning the bio-pesticide PHOCUS, and the development of anticipatory strategies was achieved through several interviews with technical experts, (bio)ethicists and local stakeholders, extensive literature reviews, and feedback from the Dutch National Institute for Public Health and the Environment (in Dutch: RIVM) which has extensive knowledge on SbD and biosafety & security (RIVM, n.d.-a). Figure 6.2 illustrates a selection of the SbD measures that were considered during the design of PHOCUS (TU Delft iGEM PHOCUS, 2020a), on which we elaborate below.

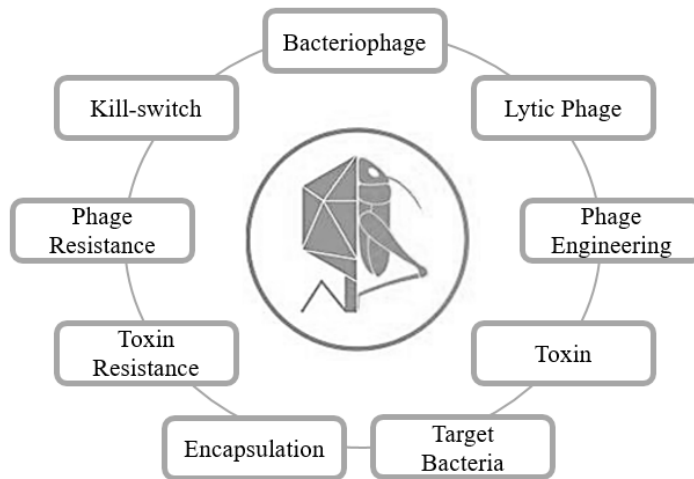


Figure 6.2: Schematic overview of SbD measures considered for the design of PHOCUS. Adapted from TU Delft iGEM PHOCUS, 2020a.

Bacteriophage: As previously mentioned, a potential issue that needs to be circumvented is that engineered bacteriophages might be dangerous to humans. However, based on interviews with experts in the field and literature, this risk turned out to be negligible due to phages not being able to infect human cells (Kutter & Sulakvelidze, 2004). Also, the bacteriophage needs to be stable in the locust gut (pH 7-8), meaning that if they would be swallowed by humans, they won't survive in the acidic environment of the human stomach (i.e. pH 1-2) (Evans et al., 1988; Ganeshan & Hosseinioust, 2019; Ventura et al., 2011). Still, the intended type of bacteriophage could be dangerous to animals or other insects besides the locusts (De Paepe et al., 2014). Although some studies have been conducted in terms of the influence of phages on animal microbiota, the impact is not yet well understood. Therefore, more research needs to be conducted. Lastly, the bacteriophages mustn't remain for long when being released in nature. However, this issue turned out to be negligible as phages turn out to become unstable when exposed to levels of UV (i.e. sunlight) (Iriarte et al., 2007). Still, to gain certainty about whether the aforementioned potential issues would be indeed negligible, more data on these issues would have to be collected before PHOCUS would even be admissible for field trials.

Lytic Bacteriophages: One of the questions that arose from the VSD analysis was whether to go for the lytic or lysogenic cycle of a bacteriophage. Based on extensive literature review, PHOCUS will use a lytic bacteriophage as it will minimize the risk of horizontal gene transfer and/or phage mediated transduction (Paul & Jiang, 2001; Soucy et al., 2015; Verheust et al., 2010; Yutin, 2013). Also, the lytic cycle ends with cell lysis, thus cell death that reduces the risk of creating a new

GMO. And, bacteriophages that reach their target bacteria will propagate quickly due to properties of the lytic cycle.

Bacteriophage Engineering: Engineered bacteriophages led to several concerns: (1) Phage dissemination into the environment, (2) Production of harmful proteins, and (3) Persistence of the applied mutation in nature. Based on literature, several design choices were made to mitigate these potential issues (Nobrega et al., 2016; Verheust et al., 2010). Firstly, the bacteriophage should be engineered with a naturally narrow host range, so the propagation chance of the bacteriophage outside the locust is reduced. Secondly, no potentially harmful sequences for humans, animals or the environment should be inserted in the bacteriophage. And lastly, to examine the stability of the mutation in the engineered genes, the engineered bacteriophage should be propagated in its host for several generations, where after the presence of the mutation can be confirmed (or not) by PCR after each generation. If this is confirmed, this would mean that the insert is extremely stable and thus the mutation could spread through multiple genetic populations. In response, appropriate measures should be taken.

Toxin: Literature described the Cry toxin Cry7Ca1 to be effective against locusts of the species *Locusta migratoria manilensis* by puncturing the gut lining (Song et al., 2008; Wu et al., 2011). Also, Cry toxins turn out to be highly specific to their target insects and therefore only kill a limited number of species (within the locust range of species) (Pardo-Lopez et al., 2013). Also, the specificity of the Cry toxins is provided by the mid-gut environment of the insect (Nester et al., 2002). Recalling that humans do not have the same gut conditions as insects (e.g. pH), this toxin should not affect humans when ingested.

Target Bacteria: Bacteria present in the locust gut must be targeted specifically by the bacteriophage. As the locust gut contains multiple bacterial species (*Enterobacter*), PHOCUS must contain a cocktail of bacteriophages that specifically target the bacteria. However, the species *Enterobacter* can also be present in the human microbiome giving rise to the risk of PHOCUS infecting human's bacteria. But, interviews with technical experts and literature review revealed that this risk might be very small as, as mentioned before, the pH in the human stomach is much more acidic compared to the pH in the locusts gut (Zelasko et al., 2017), the bacteriophages are equipped with non-pathogenic bacteria, and the Cry toxin is highly specific to locusts. Nonetheless, more knowledge should be gained through studies on different gut microbiomes.

Encapsulation: Encapsulation acts as a physical barrier to control the environment of a single molecule, thereby preventing off-target infection. For PHOCUS, a physical barrier would be needed to avoid ecological imbalances in vegetation the bacteriophages are sprayed upon. However, interviews, literature

studies and research performed by the students did not result in finding an appropriate encapsulation method (Hof et al., 2002; Jha et al., 2011).

Toxin Resistance: When exposed to (bio)pesticides for a long time, locusts can become resistant as they have slightly varying genetic alterations, of which the strongest (thus being resistant) are being passed on to offspring. For the Cry7Ca1 toxin, locusts ultimately becoming resistant is very likely as a large number of locusts is being exposed to the Cry toxin, and they reproduce quickly. Therefore, the genomes of the locusts should be monitored closely. An anticipatory strategy could be to only spray PHOCUS in particular areas (Jutsum et al., 1998), or by developing a novel toxin with a different mode of action. Still, more research would be needed to ensure safety in this regard.

Phage Resistance: Not only locusts can develop resistance to PHOCUS, but gut bacteria can too. This will result in no toxins being produced and the locusts not being killed. However, as PHOCUS uses lytic bacteriophages, all target bacteria are lysed and therefore resistance development is limited. Still, the students have developed a mathematical model (Team:TU Delft/Model/Toxin Production - 2020.Igem.Org, n.d.) that studies the development of resistant bacteria and shows that the selected bacteriophage would kill the entire bacterial population (i.e. *Enterobacter*) within hours. Due to this short timeframe, the bacteria would not be able to develop resistance to PHOCUS.

Kill-switch: A kill-switch could be built in to terminate the engineered bacteriophages might they propagate in nature (Robaey, 2018). However, building in such a biocontainment measure was deemed unnecessary as the engineered phages will decrease naturally over time (Schmerer et al., 2014). That is because PHOCUS depends on a selective advantage over the wildtype, and would therefore lose competition with the wildtype bacteriophage. Also, the genetic inserts will be lost over time and the bacteriophage will turn back to its wildtype sequence. In addition, and as mentioned earlier, the engineered bacteriophages become unstable due to exposure to UV and high temperatures (Jończyk et al., 2011), and the lytic nature of the bacteriophage functions as self-limiting (Clark & March, 2006; Ul-Haq et al., 2012).

However, as safety regarding such an innovative technique is an iterative process, and as the SbD analysis also revealed, more research needs to be conducted before we can ensure safe transfer of PHOCUS to the stage of field trials. Before that, more data should be gathered from laboratory experiments. In particular, experiments should be devoted to studying PHOCUS' toxicity to non-target organisms, pathogenicity to non-target organisms, stability and potential to accumulate, uniqueness of sequence targeted, potential gene flow of insert, and the specificity of locusts.

6.4.2. AptaVita – On a mission to tackle hidden hunger

“Vitamin deficiencies, also known as “Hidden Hunger”, impact the health and quality of life of people around the world, particularly in Sub-Saharan Africa and South Asia. Insufficient data on its occurrence impedes developing proper strategies against it. Therefore, TU Delft iGEM 2021 is developing AptaVita: a modular, cheap, and quantitative paper-based test that allows detecting vitamin deficiencies at the point-of-care using RNA biosensors and colorimetric readouts through a cell-free system.” (TU Delft iGEM AptaVita, 2021b)

6.4.2.1. Value Sensitive Design

AptaVita aims to target vitamin deficiencies, also known as ‘hidden hunger’. Currently, there is insufficient data concerning the number of people that suffer from such deficiency. Although the World Health Organization (WHO) is monitoring vitamin deficiencies through the Micronutrient Deficiency Information System (MDIS), this database is not up to date due to the types of analysis needed to gather necessary data. Now, data is obtained by techniques such as High-Performance Liquid Chromatography (HPLC) and Mass Spectrometry (MS). But, as these techniques are quite expensive and can only be performed in a laboratory setting, this results in a slow-updating database. In addition, regions where vitamin deficiencies appear to be the highest, are mostly rural and economically poor. To tackle these problems, Aptavita has developed a modular and cheap Rapid Diagnostic Test (RDT) that is able to rapidly and accurately diagnose micronutrient deficiencies at the point-of-care. It does so by using aptamers, which are small RNA molecules, that specifically bind to target vitamins.

Also for this project, first, a VSD analysis was conducted that sheds light on relevant moral values that needed to be taken into account during the development of this project. To do so, Aptavita chose Uganda as a hypothetical country of application, to keep focus within the VSD. We here provide a summary of the VSD, but a more detailed overview is provided in Appendix B.

As Aptavita aims to contribute to efficient and accurate data delivery concerning vitamin deficiencies, their most important stakeholder is the WHO. Additionally, the Center for Disease Control and Prevention, the Food and Agriculture Organization, and the Government of Uganda were identified as important stakeholders. Furthermore, local Ugandan communities and point-of-care clinics are considered of importance, mostly based on the proposed implementation. And, lastly, possible collaborators for the production of the RDT (i.e. Astel Diagnostics) and the iGEM Foundation itself were listed as relevant stakeholders.

From this list of relevant stakeholders, their associated values were retrieved using the respective institutions’ and organizations’ websites and reports, or from interviews. The most prominent values were ‘health’, ‘safety’, ‘accessibility’, ‘efficiency’, ‘sustainability’, ‘equality’, and ‘education’ of which a more detailed

overview is provided in Appendix B, Table B.1. Here, we illustrate two values, namely ‘Quality’ (technical aspect) and ‘accessibility’ (societal aspect) and explain what norms and design requirements were derived (see also Appendix B, Table B.2).

As AptaVita aims to deliver accurate and reliable results quickly, the value of ‘quality’ includes both aspects. To ensure ‘quality’ (thus accuracy and reliability) in AptaVita, the following norms were derived: (1) Measurements should reflect the true value, and (2) Measurements should be consistent. In line with these norms, the following design requirements were derived: (1) the RDT should have a control with a containing ligand at a known concentration that is not naturally present in the sample, (2) implementing a mobile readout will provide a more accurate result compared to a readout with the naked eye, (3) using blood as a sample will provide a more accurate result compared to other bodily fluids such as saliva due to vitamin presence, (4) as AptaVita makes use of aptamers that specifically bind to target vitamins, sensible aptamers biosensors are required to accurately detect vitamin concentrations, and to avoid interference with other molecules present in the blood samples, and (5) a robust cell-free system should be used to ensure consistent measurements.

In response to the value of ‘accessibility’, the following norms were derived: (1) the RDT should be available at the point-of-care, (2) it should be affordable, and (3) it should be understandable to everyone who makes use of it. In response, the test mechanism in the RDT should be freeze-dried to ensure that no particular measures for safe transport should be taken. This also enables easy transport to remote or rural areas and thus access at all points-of care. Secondly, for the RDT to be affordable, cheap (but accurate) reactives and small reactor volumes should be used. Lastly, an understandable user manual should be included containing all necessary knowledge for healthcare workers to perform the test.

Also, AptaVita encountered several value conflicts that led to questions arising about alternative design choices. Conflicts emerged, amongst others, between the values of ‘acceptability’ and ‘quality’, mostly pertaining to the type of sample to be used in the RDT. Although initially blood was selected as a suitable sample to obtain accurate results, it turned out that this can be perceived as painful by patients and would require skilled professionals to withdraw the blood from patients. Also, interviews revealed that in some communities, blood has a symbolic meaning that may give rise to resistance. So, while blood may provide a more accurate result as the level of vitamins is higher, other samples such as saliva or urine might be more readily accepted. On the other hand, interviews with other experts in the field revealed that using blood might also contribute to having more trustworthiness from the community. Eventually, AptaVita aimed to make a compromise in this trade-off and went for using blood, but only a small amount by a finger prick. This way,

resistance from people can be omitted as venepuncture will not be needed, while still using blood as a sample will promote trustworthiness and provide accurate results. In addition, other conflicts emerged concerning the type of cell-free system to be used, where the RDT should be produced (i.e. local or in Western Europe) and the reactants to be used.

6.4.2.2. Safe-by-Design

Emerging uncertain risks and respective anticipatory strategies were identified through interviews with technical experts, (bio)ethicists and local stakeholders, extensive literature reviews, and feedback from the Dutch National Institute for Public Health and the Environment (in Dutch: RIVM). (RIVM, n.d.-a) Figure 6.3 illustrates the SbD measures that were considered during the design of AptaVita (TU Delft iGEM AptaVita, 2021a), on which we elaborate below.

Biosensor Design: in AptaVita, both safety and security aspects were taken into consideration to ensure safe development – from project design to prospected implementation. First of all, AptaVita would use GMOs which poses a risk in terms of biocontainment, particularly concerning reproduction of these organisms in the environment. To eliminate this issue, AptaVita uses a cell-free system to avoid any usage of GMOs in their system. Secondly, the reporting system uses a paper-based detection kit for which literature suggests two reactants, namely pyrocatechol and chlorophenol red-B-D-galactopyranoside (CPRG) (Lin et al., 2020). However, although pyrocatechol would be more desirable from an economic perspective, it is hazardous to humans during exposure or accidental consumption (U.S. Environmental Protection Agency, 2000). Therefore, AptaVita would make use of CPRG.

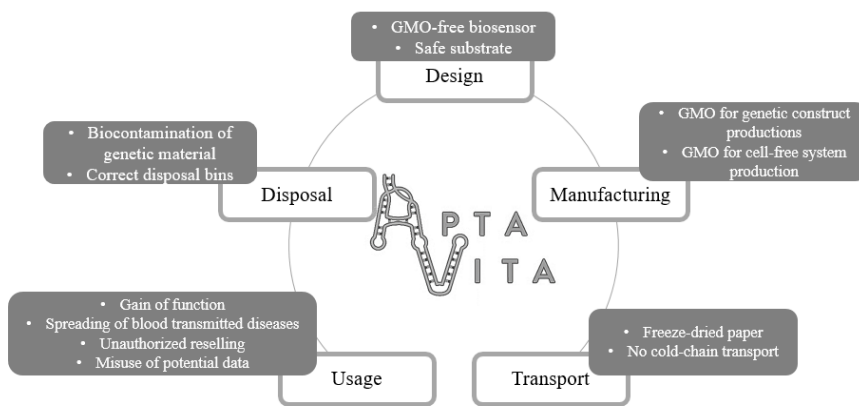


Figure 6.3: Schematic overview of SbD measures considered for the design of AptaVita. Adapted from TU Delft iGEM AptaVita, 2021a.

Manufacturing: although AptaVita avoids using GMOs by using a cell-free biosensor, *E.coli* bacteria is used for the amplification of the genetic material containing the reporter gene. Therefore, GMO legislation should be adhered to, both in Uganda (if AptaVita would be produced as the site of implementation) and in the Netherlands (if AptaVita would be produced in Western Europe). However, as it turned out that Uganda does not have clear legislation concerning biosafety and biosecurity, AptaVita will be produced in the Netherlands, thereby adhering to the EU's (strict) GMO legislation.

Transport: potential issues could emerge during the transport of AptaVita, in particular when produced in the Netherlands and transported to Uganda. Freeze-drying can increase biosafety during transportation and ensures a sterilized and abiotic test (Pardee et al., 2014). In addition, because freeze-dried devices can be stored at room temperature, no special transport would be required. Once arrived at the location of usage, the freeze-dried test can be rehydrated by simply adding a patient's sample to the biosensor.

Usage: considering the usage of the RDT, several emerging risks need to be anticipated. Firstly, as the RDT contains a plasmid with an ampicillin resistance gene, this could lead to microorganisms getting a gain-of-function such as antibiotic resistance. This mostly adheres to proper disposal of the RDT, which is elaborated in the section 'disposal'. Secondly, using blood as a sample gives rise to the risk of spreading blood infectious diseases. Therefore, obtaining blood samples should be done by trained personnel who are well informed, and by using sterilized needles (although obtaining the sample would only require a finger prick). As these measures would already be present in healthcare facilities, AptaVita should be implemented there. Also, WHO guidelines for obtaining samples should be adhered to (WHO, 2010). Thirdly, as AptaVita should be implemented within healthcare facilities, the RDT should not be distributed via unauthorized sellers as this could lead to people having insufficient information regarding the RDT, or knowledge in general. This could give rise to issues such as the spreading of blood infectious diseases by e.g. incorrect disposal. However, circumventing the risk of having unauthorized sellers is difficult but could be done by heavy monitoring. Lastly, and more adhering to biosecurity instead of biosafety, risks emerge in terms of privacy in health databases. One way to circumvent this issue and thereby ensure the privacy of the users of AptaVita is to develop a dedicated hardware device that will collect patients' data and subsequently upload the data to the vitamin deficiency database. For the WHO's database, data will be stored and shared anonymously, and will only be made relevant to determining high-risk areas in terms of vitamin deficiencies. However, more research would be needed to become confident privacy issues could be tackled this way. Also, decent data infrastructure and continuous maintenance and updating would be pivotal for this to work.

Disposal: a conflict with the value of ‘sustainably’ emerges if Aptavita would be developed as a single-use and thus non-recyclable RDT. However, the values of ‘health’ and ‘safety’ are regarded higher (i.e. preventing possible spread of blood infectious diseases), and thus will Aptavita not be recyclable. However, to somewhat limit the considerable amount of waste generated by the RDT, proper disposal is crucial (The Republic of Uganda - Ministry of Health, 2009) – thus in addition to proper disposal needed for the sake of health and safety.

6.5. Concluding Remarks

With this paper, we mean to contribute to the SbD knowledge base by providing concrete examples of how this approach is operationalized in practice, and to illustrate how we have embedded ‘designing for safety’ in education. Thereby, we hope to have inspired and provided tools for researchers and lecturers working in the field of synthetic biology to implement the SbD approach in their research and/or education. An important aspect of ‘designing for safety’ is awareness. We hope that emphasis being placed on this notion and embedding both VSD and SbD in education helps to increase students being aware of such and to make design choices accordingly. In addition, students participating in iGEM are also incentivized to pay great attention to safety aspects through the iGEM Foundation itself. As they regard safety and security highly, they award one project with the ‘Best Safety & Security’ every respective year. Also, to win the ‘Grand Prize’, projects should be ‘overall excellent’ and need to score high on all aspects, in addition to technical achievements.

This paper focused mostly on biosafety measures through SbD, but both iGEM projects also considered biosecurity aspects to a great extent, in particular the risk of misuse. As imagining different usage can be hard, both iGEM teams contacted the Biosecurity Office, part of the Dutch National Institute for Public Health and the Environment (in Dutch: RIVM). Recently, they have developed a tool for dual-use research of concern evaluation, the ‘Dual-Use Quicksan’ (Biosecurity Office, n.d.; Vennis et al., 2021). This web-based tool consists of a questionnaire that enables identification of potential issues regarding dual-use of the product, but also again uses this data to contribute to the general awareness of dual-use.

6.6. Additional notes

Both PHOCUS (2020) and Aptavita (2021) have been either nominated or have won the iGEM special awards for Best Safety & Security and Best Integrated Human Practices, besides receiving additional nominations and awards. For more information on the projects: PHOCUS: <https://2020.igem.org/Team:TUdelft>, and Aptavita: <https://2021.igem.org/Team:TUdelft>.

Chapter 7

Uncertainties and Uncertain Risks of Emerging Biotechnology Applications: A Social Learning Workshop for Stakeholder Communication

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7.1. Introduction

Already in 2017, Hogervorst and colleagues pointed out various developments in biotechnology for which no adequate environmental risk assessment (ERA) could be performed at that moment (Hogervorst et al., 2017). In particular, the increasing complexity associated with new genomic techniques, and lack of knowledge thereof, gives rise to debate on how to execute an ERA in such cases (Parisi & Rodriguez Cerezo, 2021). Currently, Europe's risk management regime regarding biotechnology seems to be one of compliance (Bouchaut & Asveld, 2021), which provides little room to learn what uncertainties and uncertain risks entail. With these types of uncertainty, we refer to the so-called 'known unknowns' – instances of which we know we are missing information about the probability or severity of a harmful effect, or of which we do not know if there are any possible harmful effects to begin with (Aven & Renn, 2009). Due to the strong embeddedness and operationalization of the precautionary principle (PP), potentially having a risk involved is sufficient to take cost-effective measures to prevent environmental degradation. In other words; uncertainty does not justify inaction, or ultimately limits research (United Nations, 1992). However, these measures should be based on an examination of the potential benefits and costs, or lack of action, and be subject to review in the light of new scientific data (Commission of the European Communities, 2000).

The way the PP has been operationalized in Europe has resulted in a normative framework in which the biological safety protocol is currently subjected to a dilemma between safety and innovation. While it ensures safety on known and acceptable risks, it also hinders innovation as it stifles research with uncertainties involved. Indeed, present regulation based on the PP only allows very little room for learning about uncertainties and how to mitigate uncertain risks, and thus also whether uncertainties should be regarded as uncertain risks, and uncertain risks as (unacceptable) risks (Flage & Aven, 2015; M. B. A. van Asselt & Vos, 2006; M. van Asselt & Vos, 2008). In addition, learning being limited also results in maintaining a lack of knowledge regarding the potential benefits, which also creates a deadlock for reviewing earlier taken precautionary measures in the light of new knowledge.

To break free from this impasse, the process of ERA must create more room to learn what uncertainties and uncertain risks entail, and based on this information, define how to assess and regard these. But this learning may be complicated by differing perspectives from stakeholders on uncertainties and uncertain risks (Bouchaut & Asveld, 2020). So foremost, we need to increase mutual understanding of differing perspectives. A new approach to facilitating learning about uncertainties (both potential risks and benefits) would require extensive communication and mutual learning between various stakeholders. Although dependent on the partaking stakeholders' fields of expertise (e.g. technical, regulatory or societal

domain), we must ensure that this learning is conducted in line with possible (societal) concerns and that any results are taken up swiftly by relevant stakeholders to allow for some form of adaptive risk management. The question that emerges from this is how to organize such a learning process with a variety of stakeholders. This paper's aim is therefore twofold: develop a tool that enables a learning process regarding emerging uncertain risks and uncertainties, and evaluate whether learning has occurred. To do so, we organized five stakeholder workshops with participants from a range of expertise (e.g. technical researchers, social scientists, risk assessors, policymakers), building upon the International Risk Governance Council (IRGC) framework and the notion of 'social learning' by Van de Poel (2017).

The importance of learning processes is acknowledged by the IRGC framework that provides guidelines for dealing with situations characterized by a mix of complexity, uncertainty and/or normative ambiguity (IRGC, 2017; Renn & Walker, 2008). Particularly the framework's first step, the pre-assessment, involves relevant stakeholder groups to capture differing perspectives on potential risks, their associated opportunities and potential strategies to address these (IRGC, 2017). For our workshops, we complemented the IRGC's pre-assessment with three levels of 'social learning' about uncertainties and relevant technical, governmental and societal aspects (Van de Poel, 2017). These levels are (1) impact learning, which addresses uncertainties associated with the social impacts of a new technology, which can be both positive and negative; (2) normative learning, referring to what 'we' think would be desirable or not and calls for a balance between ensuring safety and being able to take some risk to gain knowledge of uncertainties; and (3) institutional learning addressing responsibility allocation, e.g. who decides what risk would be acceptable? And who establishes norms?

During the workshops, we made use of a case study that focuses on an emerging biotechnology application with several associated uncertainties and uncertain risks. Through this case and implementing the three levels of social learning, the discussions conducted in the workshops provided insights into tensions between the partaking stakeholder groups in terms of how to manage uncertainties and uncertain risks, what would be needed to overcome these tensions, and what would be needed to organize a learning process about these potential risks from emerging biotechnology applications? Based on these insights, we developed a tool – a script and guidelines – for researchers to organize a stakeholder workshop that enables a suitable environment in which learning processes can take place. Via this learning process, a range of partaking stakeholders can collectively identify different estimates of emerging risks and develop anticipatory strategies to lower or mitigate these. As a result, adaptations in (experimental) research designs can be defined to ensure safety, and knowledge gaps are identified for which complementary risk research should be set up.

7.2. Materials and Methods

A total of five workshops were conducted; one in March 2021, two in June 2021, one in January 2022 and one in February 2022. Due to COVID-19, all workshops were conducted in an online environment with a maximum duration of 2.5 hours. From all workshops, an anonymized transcript was made which was coded and analyzed accordingly. Prior to all workshops, participants signed a form giving consent to record the workshop (audio and video). Furthermore, of the five workshops, two (March and June 2021) were held in English, and three (June 2021, January 2022 and February 2022) were conducted in Dutch as all participants in these workshops were native Dutch-speaking. Therefore, quotes from these latter three workshops have been translated into English. All transcripts and original quotations are available upon request from the corresponding author²⁹.

7.2.1. Design

There is a need for a constructive discussion about emerging risks and how to assess them/ learn about them responsibly. Using a case study, which is elaborated on in the next section, we first wanted to identify tensions between stakeholder groups that might complicate further communication and knowledge exchange between these groups. This mostly pertained to differing perspectives on emerging uncertainties and differences in the acceptability of these, possibly causing difficulty in progressing with experimental research safely and responsibly. All workshops were dedicated to gaining such insights.

As already mentioned, the workshops were built upon the pre-assessment step within the IRGC framework. But, to make this step more concrete for our workshop and to gain a more holistic approach, we have implemented the notion of social learning. Particularly its three levels of learning about uncertainties, namely: normative, impact and institutional (Van de Poel, 2017). In the two workshops conducted in March and June 2021, a (plenary) discussion was devoted to each level of learning. Table 7.1 provides an overview of the organization of these workshops in the form of a short script. For the next 'normative learning' step, we made use of an online discussion platform (i.e. ConceptBoard) that would make this step more interactive. Within the workshop, participants were divided into two 'break-out' sessions and each was moderated either by MOD or by one of the present observers (OBS).

Based on derived insights from the workshops conducted in March and June 2021, we developed the first set-up of the tool to enable an environment suitable for discussing and learning about uncertainties and uncertain risks. The workshops conducted in January and February 2022 were also dedicated to the validation of

²⁹ <https://doi.org/10.17026/dans-zta-6zz2>

the tool, and therefore, these were slightly modified compared to the previous workshops. For instance, we decided to not use the interactive platform anymore as it turned out that participants were facing problems managing it in an online environment. Also, the workshops had more concrete steps which were: (1) identifying uncertainties and/or uncertain risks, (2) developing anticipatory strategies to lower or mitigate the earlier identified potential issues, and (3) determining what would be needed to implement the developed strategies in a researcher's experimental set-up. Step 2 – developing anticipatory strategies – adheres to the notion of Safe-by-Design (SbD), a promising iterative risk management approach to deal with potential risks of biotechnology applications by using materials and process conditions that are less hazardous (Bollinger et al., 1996; Khan & Amyotte, 2003; Robaey, 2018). This choice was based on providing the partaking stakeholders with more concrete guidelines for developing suitable strategies, which also came up during the evaluation of the first two workshops. Table 7.2 provides a short script of these workshops.

All conducted workshops provided insights into tensions and/or differing perspectives between stakeholder groups about the identification of uncertainties and uncertain risks, and what would be needed to anticipate or mitigate these. In response, themes were derived that helped clarify and structure these insights, of which a detailed overview is provided in Section 7.3. Section 7.4 elaborates on the utilization of the developed tool and to what extent this format can be used to initiate an active discussion between stakeholders about uncertainties and uncertain risks associated with emerging biotechnology applications.

Table 7.1: Script for Workshops conducted in March and June 2021. MOD = Moderator of the workshop; OBS = Observant (x3); 'ConceptBoard' is an online platform which was used as an interactive discussion tool during these workshops.

Program part	Approx. Time	Content
Introduction	15	Welcome by MOD; Introduction of the workshop's program and room for questions; Introduction and more information regarding the case 'Genetic Engineering and the Rhizosphere' by MOD.
<i>Impact learning</i> Identifying Possible Issues	30	<i>In breakout sessions in ConceptBoard:</i> What issues do the participants foresee based on the case? Can be both positive (opportunities) and negative (possible risks). MOD and OBS1-3 help structure the identified issues by grouping them.
<i>Break</i>		
<i>Normative Learning</i>	30	<i>In breakout sessions in ConceptBoard:</i>

Prioritizing Issues		MOD and OBS 2 help the participants to provide argumentation concerning the importance of the identified values based on relevant values; Results in a group of associated values; In four rounds, participants are asked to prioritize the earlier identified values in terms of importance. To do so, participants have to explain why they feel that a certain value is more important than another? Every round, each participant can move one value one level up, and one value one level down. This results in an illustration of how each value is prioritized (low importance – moderate importance – high importance) <i>Plenary</i> discussion is devoted to the outcomes of the breakout sessions.
<i>Institutional Learning</i>	30	A <i>plenary</i> discussion devoted to the following questions: <i>How to balance (uncertain) risks and (potential) benefits?</i> <i>How to establish norms for uncertain risks?</i> <i>Who should be responsible to ensure safety?</i> <i>To what extent is the current risk management system able to cope with the identified issues?</i>
Closure	15	MOD asks all participants what their take-home message is; Thank you to all participants and request for feedback; Closure of workshop.

Table 7.2: Script for Workshops conducted in January and February 2022. MOD = Moderator of the workshop.

Program part	Approx. Time	Content
Introduction	30	Welcome by MOD; Introduction of the workshop's program and room for questions; Introduction and more information regarding the case 'Genetic Engineering and the Rhizosphere' by MOD.
Identification and Prioritization of Risks	20	In <i>breakout</i> sessions:

	15	Participants identify and discuss possible issues they foresee based on the case. In these groups, they try to come to a top-3, in which the possible issues are listed in order of importance (e.g. dependent on estimated severity or magnitude). <i>Plenary:</i> Each 'break out group' presents their top-3. Each group is invited to pose questions to the other.
Break		
Formulating Anticipatory Strategies	15	In <i>breakout</i> sessions: Participants discuss and develop SbD strategies that might lower or mitigate the earlier identified issues. MOD stresses that these measures do not all have to be technically oriented, but can also focus on e.g. procedural or organizational matters. <i>Plenary:</i> Each 'breakout group' presents their strategies and explains how these would mitigate or lower the earlier identified issues. Each group is invited to pose questions to the other.
Identify Needs of a Researcher	20	This part revolves around the question: What do researchers need to implement (the earlier identified) SbD strategies in their research? Participants are given 5 minutes to put things in the chat, where after each participant is allowed to elaborate on the matters they've put in the chat. Plenary discussion about what of the listed matters are found most important – can we reach a consensus?
Closure	15	MOD asks all participants about their take-home message; Thank you to all participants and request for feedback; Closure of workshop.

7.2.2. Case: Genetic Engineering in the Rhizosphere

As already mentioned, in 2017, Hogervorst and colleagues pointed out several developments in the biotechnology field for which, at that moment, no adequate environmental risk assessment could be conducted. One of these developments is

the genetic engineering of plants' root exudates and their impact on the rhizosphere. The latter comprises the zone of soil around plants' roots that is influenced by root activity and consists of micro-organisms that feed on sloughed-off plant cells, proteins and sugars released by the roots; the root exudates (Walker et al., 2003). By manipulating a plant's root exudates, we can reduce our reliance on agrochemicals. Influencing the soil acidity in the plant root area can improve a plant's productivity (Bais et al., 2006; Ryan et al., 2009). For example, in papaya and tobacco plants, researchers have overexpressed the enzyme citrate synthase which is responsible for the production of citric acid in the plant. This acid is excreted through the roots of the plant and causes an acidifying effect on the plant's root zone. This effect can improve the availability of phosphate in the root zone, stimulating the plant's growth. Also, it can cause partial alleviation of aluminum toxicity stress, a frequently occurring problem in soils that inhibits plant growth (De La Fuente et al., 1997).

The rhizosphere is a complex environment with plants, microbes, soil and climate conditions interacting. As many of these interactions are not yet well understood, performing an adequate risk assessment is impossible at the moment. Therefore, such genetic engineering approaches have never progressed beyond experiments demonstrating the proof of principle. However, recently, scientists noted that they believe CRISPR-Cas9-based genetic screening can help future studies of plant-microbiome interactions and discover novel genes for biotechnological applications (Barakate & Stephens, 2016). Also, others argue that new tools and resources can be applied to introduce complex heterologous pathways – that encompass both natural and biosynthetic routes – into plants. Such would allow for building synthetic genome clusters from microbiomes to enable stacking and shuffling of disease resistance and stress tolerance traits between crop plants (Shih et al., 2016).

At the start of each workshop, the case described above was introduced to all participants, which illustrated the dilemma of having insufficient knowledge about such a complex system while it is also a technique that has potentially great societal benefits such as improving the global food supply. This set the stage for the workshop and formed the starting point for an active discussion on how to manage associated uncertainties and uncertain risks safely and responsibly.

7.2.3. Participants

As genetic engineering in the rhizosphere is a case with high complexity, many interactions between variables and insufficient knowledge on many aspects, a broad variety of stakeholders were invited to take part in this workshop – see Table 7.3. The aim hereby was to retrieve a holistic approach to uncertainties associated with the case and to develop a range of anticipatory strategies to lower or mitigate these

uncertainties while taking into account both impact, moral and institutional aspects of risk management.

A total of 32 stakeholders from a range of expertise participated in the workshops. Participants' fields of expertise pertained to the technical sciences (i.e. microbiologists, biotechnologists, ecologists and Biosafety Officers), social sciences (i.e. (bio)ethicists, scholars working at the intersection of research and policy), regulatory organizations (i.e. risk assessors, policy officers) and the National Government (i.e. the Ministry responsible for national biotech regulation). We made sure that in every workshop a variety of stakeholders was partaking (see Table 7.3).

All participants were selected based on their knowledge of and/or experience with biotechnology applications and the regulation thereof. All hold senior positions in their designated professions, except for participant [RIT3] who was an MSc. Student Biotechnology and [RIT1] and [RIT6] were both PhD Candidates at the time of the workshop. Also, [RIS1] and [RIT12] are both professor emeritus. Lastly, MOD, OBS1, OBS2 and OBS3 were present in all workshops.

Table 7.3: Participants' Sectors and Code

Organization	
MOD	Moderator
OBS1	Observer
OBS2	Observer
OBS3	Observer/ Moderator
Workshop March 16th 2021	
RIT1	Research Institute – Technical Sciences
RIT2	Research Institute – Technical Sciences
RIT3	Research Institute – Technical Sciences
BSO1	Research Institute – Biosafety Officer
RIS1	Research Institute – Social Sciences
RO1	Regulatory Organization
RO2	Regulatory Organization
NG2	National Government
Workshop June 3rd 2021	
RIT4	Research Institute – Technical Sciences
RIT5	Research Institute – Technical Sciences
RIS2	Research Institute – Social Sciences
RO3	Regulatory Organization
RO4	Regulatory Organization
Workshop June 7th 2021	
RIT6	Research Institute – Technical Sciences
RIT7	Research Institute – Technical Sciences
RIT8	Research Institute – Technical Sciences
RIS3	Research Institute – Social Sciences

RO5	Regulatory Organization
RO6	Regulatory Organization
Workshop January 25th 2022	
RIT9	Research Institute – Technical Sciences
RIT10	Research Institute – Technical Sciences
NG3	National Government
RO7	Regulatory Organization
BSO2	Research Institute – Biosafety Officer
RIS4	Research Institute – Social Sciences
Workshop February 7th 2022	
RIT11	Research Institute – Technical Sciences
RIT12	Research Institute – Technical Sciences
RIS5	Research Institute – Social Sciences
BSO3	Research Institute – Biosafety Officer
NG4	National Government
NG5	National Government
RO7	Regulatory Organization

7.3. Results

All discussions in the workshops were transcribed, coded and analyzed in line with the three levels of ‘social learning’ (see Section 7.2 Materials and Methods). These levels formed the three themes that need to be addressed to arrive at responsible learning about uncertainties. These themes are (1) Institutional learning entailing responsibilities, (2) Impact learning considering uncertainties and uncertain risks, and (3) Normative learning adhering to balancing uncertain risks with potential benefits. Furthermore, as part of the workshops was devoted to developing anticipatory measures, the notion of SbD was also discussed. However, as SbD is not considered the main focus of this paper, insights from these discussions are integrated into the other themes. Sections 7.3.1 – 7.3.3 elaborate on the tensions and differing perspectives between stakeholder groups in line with the identified themes. Section 7.3.4 provides an evaluation of the conducted workshops and to what extent these have led to social learning, and a summary of the ‘lessons learned’. These lessons functioned as input for the final design of the tool (i.e. the workshop script) which is elaborated in Section 7.4.

7.3.1. Institutional learning: Responsibility

The first identified theme revolves around responsibility concerning safety. With this, we refer to three matters; 1) researchers should apply a broad perspective on issues arising when developing a new technique or application thereof and taking anticipatory measures; 2) whether this should be done for both fundamental and applied research, and 3) unrealistic expectations concerning safety and the association with something being ‘natural’ or not.

During the workshops, it became apparent that there is a consensus that researchers should make sure that their experiments are developed and conducted safely and responsibly. However, there were differences in how willing researchers would be to do so concerning possible long-term effects. On the one hand, participants [RIT9; RIS4; RO7] mentioned that researchers are probably not very willing to do so as they want to focus on answering the fundamental questions in research and generating new knowledge. In terms of long-term effects related to applications of their findings, stakeholders from other expertise might be better equipped to do so [RIT4].

"The assumption here is somewhat that researchers want that too [talk and identify uncertainties], and I often find that very sobering when I speak to biotechnologists from [University], for example, who simply see that, that specific type of thinking is not their job at all. They mainly see the development of new knowledge as their task, and what risks there are, that is outsourced to, for example, for [sub department of University]. Or for a [regulatory organization] member. [RIS4]

"I must also honestly say that I always try to keep myself a bit off from all the difficult follow-up things and think well, there are all [other] people who really like that and study bioethics, they can say useful things about it" [RIT4]

Particularly in the light of the Asilomar Conference where researchers themselves took responsibility for ensuring the safe development of recombinant techniques (Abels, 2005; Berg et al., 1975; Berg & Singert, 1995), this was surprising. However, it was also argued that there certainly is a willingness amongst researchers, but tools need to be provided to do so [RIT10].

"I do think that it is the researcher's responsibility to think about this [emerging risks or other use than intended], not just the university's. And I also think, on the one hand, there is some trust needed, that we [researchers] are certainly committed to... The whole purpose of the research we do is to make something better whether it's global health, the environment or whatever. So the benevolence is there. So, I need questions to be asked, for someone to point out a blind spot through a question, that makes me start to think about such. That's what I need!" [RIT10]

In terms of these tools, discussions in the workshops of January and February 2022 were devoted to SbD strategies mitigating or limiting identified risks. Researchers would probably bear the most responsibility to 'do' SbD as they are working with emerging techniques, but that would require to know when this should be done [RIT11], and to what it specifically pertains [NG4]. Would that only be when an application is already foreseen, or also during fundamental stages of research [RO7]?

"It's important, when should you do this? And certainly if you are an academic researcher you have a fundamental question. And should you immediately start applying SbD because an application may result from your research? And when should you build in those reflection moments? And how do you build it in?" [RIT11]

"From 'I make sure that I work safely, so protect myself as a researcher and then I'm working on SBD'. But that's not what we mean. [...] But then you can say: when is it, and when is something not SbD?"

Does that mean you're always improving? Or will there come a point where you say: look, we're here. Those are, I think, questions that are important for a researcher' [NG4]

Some stakeholders pertaining to the social sciences domain argue that, from their perspective, researchers working on fundamental matters are not concerned with matters they consider outside their scope. For instance, [RIS4] argues that when researchers are working on a fundamental matter, this would be value-neutral from their perspective, and therefore there is no need yet to consider whether this would be a good or bad idea. Only in the next steps e.g. when there is an envisioned application “we will look at what harm can it do?” [RIS4]. However, this was nuanced by a participant from the technical sciences [RIT7] who argues that there are two stages “We try to understand the world and then we try to change the world, to make our lives better”. Thereby, [RIT7] acknowledges that applying insights one gained from understanding the world and trying to modify the world based on that knowledge are two different matters.

Also, there were discussions on what responsibility researchers have towards society in terms of communicating about risks and the meaning of safety – as biotechnology is still subject to public discourse. The discussion revealed two interpretations of safety, and how this is used and understood differently by different stakeholders. First of all, safety is often a technical matter in which a quantifiable chance of hazard (something that can cause harm) and how serious that harm could be is embedded – a definition that is frequently used by researchers from the technical sciences. However, the societal association with risks turns out to be ambiguous. Particularly in terms of risk communication, the societal interpretation of risk adheres more to the ‘absence of danger’ [RO7; NG4]. In line with Beck et al., (1992), this association seems to be a response to society not being ‘in control’, but instead, organizations and governmental bodies responsible for the progress of biotechnological techniques and applications (Burgess et al., 2018). So, while technically safety refers to something having an acceptable risk involved, the societal interpretation is different.

“Safety is also a concept defined by technicians, which is often where it comes from. And if we define safety as ‘the chance is so small that something will happen’ so we accept that, or we accept that because there is an advantage. But citizens understand safety as the absence of danger. So if you start talking about risks when you don’t even know if they are there - they are always there of course - But, then you already have a negative communication frame. And at the same time, you cannot guarantee safety” [RO7]

“So we as a government think that we cover everything with [acceptable] risks, but in principle, the citizen says ‘no, I want full protection’. Which of course is not realistic, you can never completely protect someone against something” [NG4]

Also, there was some frustration detected in line with society’s stance on biotechnologies. Not necessarily due to safety concerns – whether that would be having an acceptable risk involved or by being ‘fully protected from danger’ – but

due to the association made with naturalness (de Graeff et al., 2022). And, in that respect, when something is 'natural' that it would be safe(r). [RIT4] mentions that the distinction between what is natural and what is not has become a bit blurry. It is mentioned that putting a UV lamp on crops is still natural as it is just "...putting the sun on it a little harder" and people tend to think very quickly that 'natural is safe': "At least in the case when I talk to people about it, that's the biggest difference. If it's natural, then you can sell it. If it's not natural, alarm bells will start ringing!". However, this association might be skewed as, given the recent pandemic, "corona is also natural and the vaccine we all receive is not natural" [RIT4].

7.3.2. Impact learning: Uncertainties and uncertain risks

Discussions also pertained to questions on appropriate strategies or measures to anticipate emerging risks, both short- and long-term. First of all, for short-term risks, strategies can be applied that limit possible risks. For example, one could ensure containment [RIT11; RIS5; RIT11; RIT1] or "that the plant is just one generation, or that you deprive the plant of the ability to reproduce" [NG4]. But for the long term, it might be a bit more difficult to understand issues arising and how to anticipate these properly. "So something is, typically in the lab, you will test something in the relatively short term, but we really rarely test for something in the long term. So there is lack of knowledge, usually for the long term effects" [RIT6]. On the other hand, participant [BSO3] mentions that taking heavy measures could be a strategy in itself to anticipate long-term risks. Lastly, [RIT11] questions how realistic this 'testing for the long term' would be. In particular when a commercial party is involved: "How much time can you use to do this research? Especially if there is a commercial component to it. Ehm [sic], and that's why I think that long-term effects are especially difficult to capture in research, so to speak. You won't have 50 years to study those effects!" [RIT11]

Also, there was discussion about anticipatory strategies mostly being risk avoidant. Although that would be a way to ensure safe research, it doesn't solve the problem of learning about uncertain risks. Therefore, participants argued that there should be a distinction between strategies by which you aim to reduce uncertainties as much as possible, and strategies that make it possible to learn about the risks involved [RIS5]. However, some tension is expressed by stakeholders from the National government. On the one hand, although they prefer to choose the safest option from the start of a study, sometimes one does not know what the safest form is without researching it [NG4]. On the other hand, they [respective Ministry] are end-responsible for ensuring safety: "My role as a policy officer is to ensure that if something is genetically modified, it does not lead to a greater than a negligible risk to people, the environment and the living environment [sic]" [NG5] In that sense, learning about uncertain risks gives rise to a dilemma: ensuring safety and learning what the safest form is.

Following the discussion regarding strategies for avoiding risks and learning what uncertain risks entail, it was discussed whether uncertainties should always be regarded as uncertain risks, and when uncertainties can be deemed a risk. It was mentioned that there can be a knowledge gap in such instances which can create tension in risk management. For example, for one material we know that we lack very specific information concerning the long-term toxicity levels in humans. While for another material, we might not even know yet whether or not this would be toxic to humans in the short term. This higher degree of uncertainty illustrates that there are varying degrees of missing information regarding uncertainties. But, this does not mean that all uncertainties should already be considered an uncertain risk (Flage & Aven, 2015; M. B. A. van Asselt & Vos, 2006; M. van Asselt & Vos, 2008). This is also addressed by participant [RO7]: “Look, if we don't know at all whether something has an effect, does it make sense to talk about risks? The fact that you say that there are risks, also means that you recognize that something is going on, and in this case, you don't know that at all!” [RO7].

Furthermore, it is mentioned that with uncertain risks we tend to focus on ‘known unknowns’. However, given the vast pace of developments in the biotechnology field, it is expected that we will also have to deal with the ‘unknown unknowns’ shortly – matters which we do not know yet. From a precautionary perspective, it would be justified to “keep our hand on the tap, and only open it when we know for sure what will come out!” [NG4]. Also, [RO2] mentions that as long you have insufficient data to obtain a proper view of the severity of risks, you should always assume the worst-case scenario. In other words: “if you don't have all data to be sure that something does not happen, you should assume that this will happen so the risk assessment generates that you should be more careful with taking the next steps (i.e. from lab to environment)” [RO2]. However, it is also argued that the best way to deal with these upcoming uncertainties is to work together and organize the systems in such a way that we are equipped to deal with new uncertainties:

“In other words, you should set up the systems in such a way that if those [new] uncertainties arise, that you all [technical scientists, social scientists, regulatory organization, national government] know and trust each other enough to find solutions together. And which one [new uncertainty] you will encounter is indeed unknown, but at least then you have the structure to do something with it” [RIS4]

“Yes, so gather more brainpower from different perspectives to get a clear picture of what those new risks [of the new uncertainties] are” [RO7]

In terms of working together, participants discussed examples coming from other disciplines where organizations are collaborating to learn about uncertainties. For instance, participant [RIS4] referred to a study once conducted about antibiotic resistance that could be possibly passed on by micro-organisms, and [RO7] to the ‘safe-innovation approach’ in the field of nanotechnology.

"There was one study about antibiotic resistance that could possibly be passed on by micro-organisms. This actually showed that a researcher could not come up with the question that the employee [a risk assessor from a regulatory organization] asked him, [presumably] based on his [the researcher's] own culture and knowledge and technological training. At the same time, that employee [from a regulatory organization] had no idea what was actually going on at a fundamental, technical level of research. So in that [project's] user committee, the two of them seemed to really hit it off and thought: 'yes, we have [complementary] knowledge, we can only answer this question together!'"
[RIS4]

"Yes, I'm thinking now, that comes from the 'nano-world'. That's what they call the safe-innovation approach. I don't know if it's quite the same, but it is the commitment to...Let's say, the innovator and the people who have risk knowledge, to bring them together faster, so that you can have that conversation [about uncertainties]. And then it's just a question of whether those two are good enough, or whether you should include even more perspectives? So that's one of those thoughts that lives there and actually also in a protected environment, so to speak. So let's say 'Chatham House rules' or something. That you can just talk openly without company secrets just being exposed on the table, so to speak." [RO7]

Lastly, participants mention that using nature as a threshold could help to indicate whether an uncertainty should be regarded as an uncertain risk. "To know whether something involves a risk, you should also try to compare it to already known, you know, similar cases. [...] Also looking at what is already known about the type of changes that it might induce. And is that something that is already there in the environment?" [RO5]. However, discussions emerged about to what extent you could use nature as a reference, particularly if you are looking at a mechanism that is already present in nature, but that is also precisely the subject of intervention. "To what extent are they then [after intervention] comparable to mechanisms you find in natural systems?" [RIS5]. Also, how representative are tests performed under contained use? "For example, a soil in the greenhouse would already be tested there or say several soils: but how representative are they for the outside world, where it will eventually end up? It seems very complex to me to simulate a soil life and everything in the soil, so I think there is a modelling issue?" [NG3]. And, how desirable is it to mimic natural processes anyway? "Are natural processes always desirable and safe? So, is that always suitable to imitate? Nature has also developed enough dangerous situations and toxins, so what do we want to learn from nature and evolution?" [NG5].

7.3.3. Normative learning: Balancing risk and benefits

In all workshops, the potential benefits of developing technologies were mentioned and how these should be balanced with uncertain risks. In particular for emerging technologies where there is a (societal) benefit associated, emphasis is often placed on not being able to guarantee that something is safe [RO2]. Gene drive technology is discussed – a technological application with possible great societal benefits by for instance altering or eradicating disease-causing insects such as mosquitos. For such technologies, society seems to be reluctant to accept possible associated risks even though the benefit would be large [RO1]. For

(bio)medical applications (red biotechnology), this balance seems different which can be mostly explained by to who the risks and benefits are attributed [RO2; RO7; NG3].

"For health care, this balance would be different as the benefits and risks would all be for the same person" [RO2]

"And whose benefits are they?" [RO7] "Yes, whose benefits and whose risks? [NG3]

"Of course, it's about whose benefits and whose risks it is, isn't it? So if the risks are for society, but the benefits are only for the [producer], then you have a different story than if it were equally divided. Then you have a different weighting framework" [NG3]

So, there appears to be a difference in how society perceives the risks associated with red biotechnology, and therefore, there might be less societal scrutiny for this strand of biotechnology. From a regulatory perspective, this strand is also regulated differently (Abels, 2005; Bauer, 2002, 2005) and benefits (e.g. a life-saving treatment) are included in the respective risk assessment. For white (industrial) and green (plant) biotechnology, benefits are not taken into account during the risk assessment [RO2]. However, according to [RIS1], there is always a risk-benefit analysis performed, albeit implicitly. "One continues with these [research/experimental] activities because there are benefits. So, in every risk assessment, benefits are underlying because why would we proceed with them if there weren't any? So, implicitly there is always a risk/benefit weighing going on" [RIS1]. However, questions that emerged from this statement pertained to who makes, or should make, this (implicit) trade-off, and based on what information considering that the potential benefits are also uncertain. As justly mentioned by [NG3], "How should we account for these?". Following up on this remark, it was discussed that instead of trying to assign weight to the potential benefits and focusing on emerging risks, we could also look at what happens if we do nothing. For instance, related to the case, an expected benefit of engineering plants' rhizosphere is contributing to improving the global food supply: "What happens when we don't do it? Instead of well, just looking at what happens if we do it?", and "Perhaps exactly by intervening we can maintain an existing ecosystem, while otherwise, we would lose it, for example. So not intervening with nature can also lead to a loss of biodiversity and so on" [RIT4]. However, other participants were sceptical of the ideas introduced by [RIT4]:

"And there is also seldom talked about the uncertainties in advantages, it is always said: we can do this and it all yields this nicely. I've never heard of any uncertainty about the benefits" [NG3]

"No, the premise is usually it's going to save the world. As long as the risks are manageable, we will save the world!" [RIS4]

Also, if we would include potential benefits in the risk-benefit balance, and therefore proceed with these technologies, we might eventually be able to solve the

global food problem. But, this could give rise to new problems – perhaps no direct risks to one's health, but more related to one's livelihood and quality of life, i.e. economic and financial independence.

"Suppose this becomes the staple crop in some country that normally doesn't have such crops, say, will that displace other crops economically? Don't know if you understand what I'm saying, I'll give the example of Vanillin. You know, you can also do [produce] that with micro-organisms, but that means that in Madagascar suddenly [...] money is made with vanilla, and they suddenly have no income anymore, so that are other kinds of impact you could think about" [ROT]

7.3.4. Evaluation and Lessons Learned

Based on the conducted workshops and the derived results presented in the previous sections, we first list the main findings and provide an evaluation of to what extent these workshops have contributed to social learning. Following upon, we formulate some 'lessons learned' that formed the basis for the development of the final form of the tool to enable learning about uncertain risks which is presented in Section 7.4.

First of all, discussions associated with institutional learning entailed tensions about 3 matters: 1) responsibility allocation in the sense of researchers anticipating emerging risks, 2) whether these responsibilities should pertain to both short- and long-term risks and 3) apply to both fundamental and applied research. There was a consensus that ensuring safety is a responsibility that all associated stakeholders of an emerging technique or application should bear. In addition, researchers should be responsible to take anticipatory measures to lower or mitigate emerging risks, for instance through SbD. Based on this, some learning took place in the sense that participants are now aware of others' stance and perception on allocating responsibilities. However, as no consensus was reached in terms of what responsibility should be assigned to which actor, we can conclude that the conducted workshops have led to limited learning in terms of institutional learning.

Secondly, impact learning has taken place in the sense that emerging uncertain risks and uncertainties associated with the case study were identified. For instance; "I think that for me the take home message is that, indeed, that SbD is looked at very differently". And also: "When is something an uncertainty or a certain risk? And how should we as researchers deal with this?" [PIW], or: "So very often topics like this [the case study on engineering plants' rhizosphere] don't come up, but to participate in this discussion is certainly valuable. And if in the future, if these kinds of subjects become more topical for me, it will help me a lot" [RIT9]. However, participants were not able to come to a consensus in terms of the possible impacts or severity of these uncertainties. This could be due to the different fields of expertise of the partaking stakeholders, e.g. some having less technical insight into the possible effects of the identified uncertainties. Furthermore, participants agreed that researchers should be equipped with tools to be able to anticipate 'new'

uncertainties. For instance, different stakeholders working together and reorganizing the internal system as the external system (i.e. GMO regulation with a strong emphasis on the PP) currently provides little room to conduct research with uncertainties or uncertain risks involved – which also reflects institutional learning.

Lastly, normative learning took place during the workshop as the participants gained insights into the dilemmas accompanying emerging technologies, and balancing their pros and cons. Particularly concerning the latter, the participants had to weigh the pros and cons associated with the case study to list what potential risks they considered the most severe or probable, and how to anticipate these. However, learning in terms of establishing new norms or reshaping the process of ERA did not take place. There were suggestions made and discussions devoted to these matters but without concrete results. While this could be partly explained by the partaking stakeholders having little influence on these matters (i.e. EU-level decisions), it can also be attributed to how the current regulatory system is operationalized, in particular in terms of the PP. Although this principle could stimulate learning (i.e. specifically setting up risk research as a precautionary measure) which is argued by the European Commission (Commission of the European Communities, 2000), it now provides a very normative approach to risks in the risk assessment system. This has resulted in a system that allows learning about known risks (albeit limited as there is already extensive knowledge of these risks) but only very limited learning what uncertain risks entail – depending on the extent of knowledge that is missing. Research involving uncertainties, thus having very little to no knowledge about the extent, is limited as it cannot be proven to be safe, i.e. having acceptable risks.

The main findings of the conducted workshops formed the basis for the development of a workshop format that enables a constructive discussion about emerging risks with a broad range of stakeholders. First of all, we should focus on researchers and provide them with tools to create a mutual learning environment to identify and anticipate emerging risks, and set up research devoted to learning what uncertain risks entail. An important condition for this, however, is that such discussions take place in an informal, non-institutional setting. This way, a truly free exchange of views and perspectives can take place without shared insights immediately having implications in terms of (societal) perception or in terms of (stricter or less strict) regulation. Fear of such consequences or implications can result in stakeholders keeping information or opinions to themselves. Such issues have already emerged in the (conventional) chemical industry, where there is little incentive for industry to share knowledge and data about possible adverse effects (Bouchaut et al., 2022; Drohmann & Hernandez, 2020).

Secondly, in the workshop format, SbD should not be specifically mentioned as this notion is understood differently by stakeholders. This was mentioned in the

workshops and is also argued in literature (Bouchaut & Asveld, 2020; Kallergi & Asveld, 2021). We want researchers to have an open vision to develop anticipatory strategies to lower or mitigate identified risks. If we would mention SbD specifically, this could lead to a ‘tunnel vision’ in which strategies would only pertain to e.g. technical measures. Also, it is important that stakeholders have a shared vocabulary, or that it is accommodated that stakeholders elaborate on what they specifically mean with certain jargon. During the workshops, there were sometimes misunderstandings between stakeholders when using e.g. technical terms or jargon from the policy or regulatory domain. Although such misunderstandings were addressed, and partaking stakeholders that needed some explanation did ask for this, it does illustrate that stakeholders must feel comfortable with each other. While this is a challenge, we expect this to become more feasible once discussions of these matters have become more common. Also, referring back to ‘new’ uncertainties emerging in the (near) future, making such constructive discussions common practice will be good preparation to be able to deal with these accordingly.

7.4. Enabling Stakeholder Communication

Based on the lessons drawn from the conducted workshops (Section 7.3.4), we developed a final workshop format intending to enable a constructive discussion about emerging uncertain risks and to develop anticipatory strategies for ensuring safety. To do so, we chose the format of a protocol that facilitates researchers to organize a stakeholder workshop themselves. First, we envision the workshop to be organized by researchers who are working with (emerging) biotechnologies or biotechnological applications and invite researchers from other relevant areas of expertise such as ecology and toxicology, as well as stakeholders from the regulatory regime and other scientific disciplines such as (bio)ethics, social sciences and Biosafety officers. Thereby, it’s the intention that the organizing party composes a case of their own (as we have used genetic engineering of plants’ rhizosphere). For instance, the development of a new type of application or proceeding from a laboratory environment (contained) to a non- or semi-contained environment (e.g. field trials or clinical trials) where new uncertainties or uncertain risks can emerge. Secondly, by organizing this workshop, insights are gained into; 1) different estimates of uncertain risks, which risks are identified, on what basis, degree and nature of uncertainty, 2) defining anticipatory strategies to mitigate or lower the identified uncertain risks, and 3) determining what is needed to implement the defined strategy/strategies in their research practices.

Also, during the workshops and based on the evaluation with all partaking stakeholders, it turned out that there needs to be some incentive for researchers to place more emphasis on the identification and anticipation of risks (both short- and long term). Therefore, we would like to stress that this workshop brings value to researchers by not only ensuring safe and responsible research design but a greater

emphasis on identifying and anticipating uncertain risks could also speed up research later in the process. For instance, when an experiment is initiated, additional information on possible risks may be required by an organization's BioSafety Officer or a Member State's respective GMO Office. Having already invested in a more extensive analysis of emerging risks, such processes might be accelerated or even prevented. However, it can also occur that a risk assessment (e.g. at the start of a new experiment) reveals that the experiment involves uncertain risks and that more data or research would be needed. This would also be a moment to initiate a workshop that would complete the risk assessment more thoroughly. Also, consultation with an organization's BSO throughout the application process could create an incentive for organising this workshop. Therefore, we suggest researchers to organize this workshop when: researching emerging biotechnology applications; before composing or submitting a research proposal; when a risk assessment asks for extra information on emerging risks; and after consultation with an organization's BSO.

A detailed script to organize this workshop is provided in Appendix C, listing all preparatory measures for the workshop, organizational and practical matters e.g. hosting the workshop online or in a physical setting, and the elaborate steps that need to be taken for the execution of the workshop. For instance, one or multiple moderators need to be appointed as the workshop largely consists of discussions. In addition, we have created a flowchart (Figure 7.1) that schematically illustrates the protocol and briefly lays out the three main steps that need to be followed during the workshop. This flowchart can also be used by the organization to keep an overview during the workshop. The first step in Figure 7.1 entails the identification and prioritization of risks. Here, after the case is introduced at the beginning of the workshop, participants identify and discuss potential risks in small groups. Following upon, a plenary discussion is devoted to each group's respective findings which are listed in terms of what potential risks are estimated the most important, which are considered less important, and why. In the second step, participants again discuss in small groups what anticipatory strategies could be applied to lower or circumvent the identified risks in step 1. The groups then return to a plenary setting in which participants decide on what strategies are considered the most effective, efficient, or suitable considering the research set-up. The final step is a plenary discussion devoted to discussing what would be needed to implement the earlier developed anticipatory strategies and whether these would lead to an acceptably safe research design. If not, the participants identify the knowledge gaps and how these could be filled in by setting up additional (risk) research.

7.5. Discussion

In this paper, we presented the development of a tool, i.e. a script for researchers, to organize a workshop to identify emerging risks and anticipatory

strategies associated with emerging biotechnologies utilizing the notion of social learning and its three levels of learning about uncertainties (i.e. impact, normative and institutional). Also, integrating notions associated with the SbD-approach provides researchers insights into adaptations concerning their research design for increased safety and setting up additional risk research specifically for learning about 'new' risks. The following aspects deserve attention as they have an influence on the execution and the outcomes of the workshop: 1) stakeholder representation, 2) free knowledge exchange and actors in bad faith, 3) expertise in moderating, observing and reporting, 4) the choice of the case, 5) the use of definitions and jargon, and 6) some limitations of our proposed method.

First of all, stakeholder representation is crucial for obtaining a holistic overview of any potential issues arising, and the extent to lower or mitigate these. For example, when specific techniques or applications with a geographically broad focus are discussed, the participants must have the experience and knowledge to discuss the case study in such a broad context. The organizers of the workshop must be aware of and should not underestimate the needed diversity of participants in order to arrive at a constructive, inclusive and broad discussion. As this workshop is tailored to biotechnology research and developments, it makes sense to especially invite stakeholders who are associated with the technical aspects related to this field. However, evaluations after our conducted workshops revealed that also the presence of social scientists and policymakers is crucial to arrive at safe biotechnology development beyond technical aspects and measures, and was even greatly appreciated by the partaking stakeholders from the technical sciences. Considering the set-up of our workshop, the organizers will be from the technical sciences, who might not have stakeholders from the regulatory or societal domain in their direct network. Therefore, identifying and inviting these stakeholders might take up some considerable time and calls for extra preparations, which must be taken into account by the organizing party.

Following upon, having an informal setting is needed to arrive at 'free' knowledge exchange in which stakeholders from differing domains exchange their thoughts and experiences, and can pose critical questions. This is particularly relevant when working with a controversial technique or application. Therefore, inviting a wide range of stakeholders, including both proponents and opponents, is crucial to arrive at applications that will not be rejected by society (von Schomberg, 2013). However, knowledge exchange can also be exploited by actors who will attempt to block every process that does not fit the direction they desire. This places organizers in a difficult position. Whose input is considered valuable, and who to exclude from the discussion? As this allows for selectivity, it also gives rise to another misuse of the knowledge exchange processes, namely that researchers can choose to only invite stakeholders who fit exactly with their research aims.

As discussion is a key element of the workshops, the organizers must have considerable expertise in moderating, observing and reporting. Although we provide the methods to organize a workshop, the organizers are responsible for the execution and thus the outcomes. Therefore, we recommend having a moderator with a neutral stance on the discussed technology or application. While it can be advantageous that the moderator is affiliated with the same lab that is developing the discussed technique (i.e. having specific technical knowledge), we do not recommend this as this may result in bias. This also applies to the observer(s) and reporter(s).

Usually, a case will be highly specific to a certain technique – as was the case used in our workshops. While this brings focus to the discussion, one should be careful about subsequently generalizing the outcomes of the discussions. Also, due to the high specificity of the case, it may be difficult for some stakeholders to grasp the content as it's not their field of expertise. On the other hand, the case being outside their 'comfort zone' can also lead to obtaining new insights. Another issue concerns the timing of the introduction of the case to the participants. If already introduced before the workshop, the participants will be able to already think about the case and look up additional information. On the other hand, and also related to participants' own field of expertise, they may decline the invitation as they feel that this would be beyond their expertise, thereby risking that valuable new insights will be missed.

Discussions in our workshops also revealed that there was some confusion in terms of used jargon and stakeholders' definitions of e.g. uncertainty or risk, were not aligned. While having clear definitions is needed for effective communication, having differing definitions and interpretations can be used to shed light on stakeholders' different perceptions of notions related to risks and uncertainties – which could also be valuable for the organizing party.

Finally, organizers should be aware that the method we present here also has limitations. First of all, the case used for the conducted workshops pertained to a highly complex environment. Although this contributed to making the dilemma clear of having insufficient knowledge, and continuing with promising developments, this may have caused some difficulties for participants to come up with concrete foreseen issues and anticipatory strategies. Secondly, in the case of the workshops we conducted, all stakeholders are associated with Dutch legislation. Although EU legislation is guiding, all EU Member States have their view on biotechnology and value different matters, and therefore, there might be a bias toward the Dutch perception. Thirdly, caution should be exercised when generalizing the outcomes of the workshop. Nevertheless, we believe that this tool is not only suitable to the field of emerging biotechnologies and can be used for other emerging fields such as nanotechnology or geo-engineering as well.

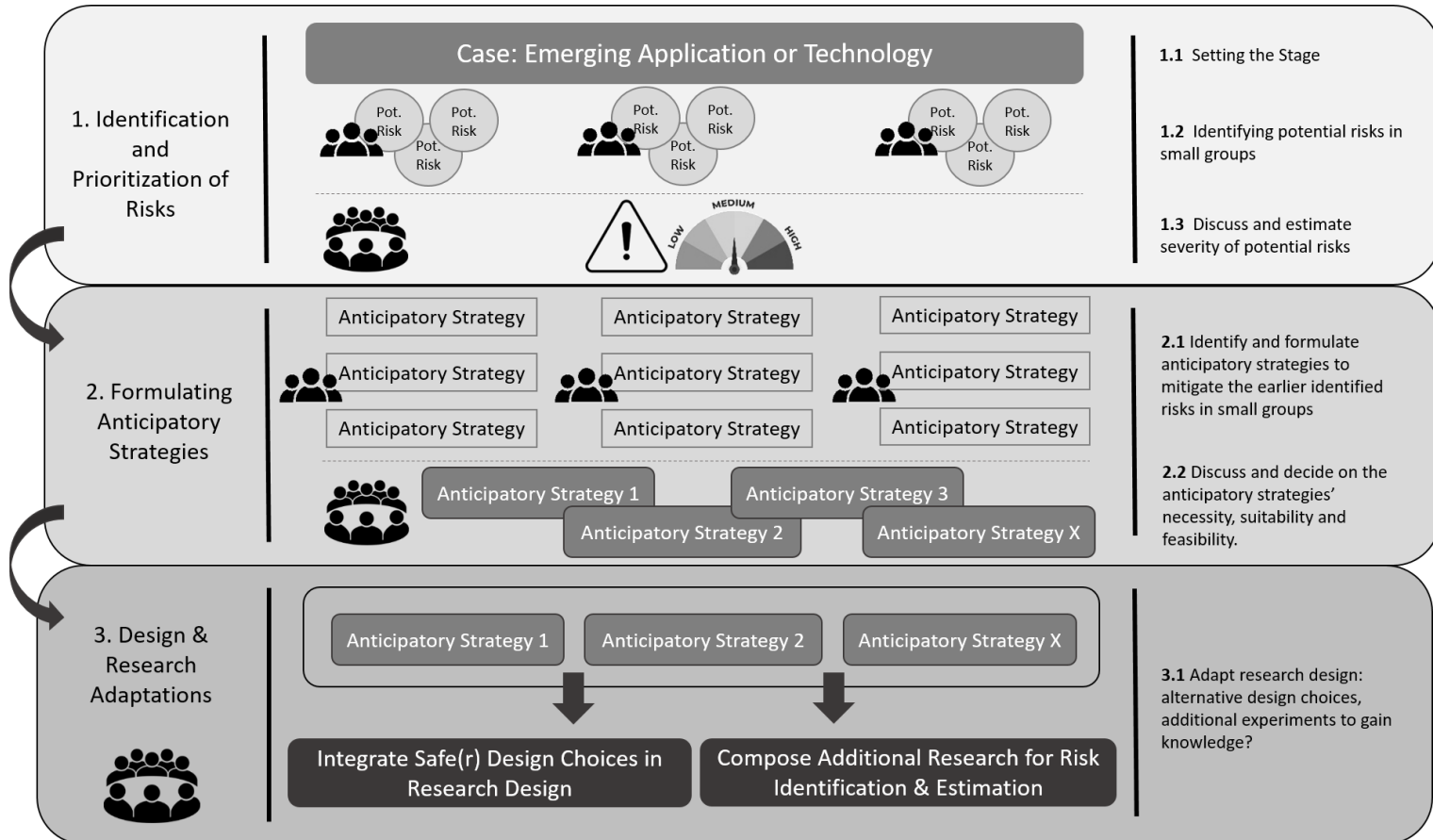


Figure 7.1: Flowchart for steps to follow during the social learning workshop.

Chapter 8

Conclusions and Recommendations

8.1. Introduction

In this thesis, it was explored how notions pertaining to safety, risks and SbD are perceived differently by associated stakeholders, how safety is ensured and uncertain risks are dealt with in the current governance ecosystem for biotechnology and how this is managed in the field of chemistry, and to what extent SbD is capable of enabling responsible learning about uncertain risks and uncertainties. I will first provide answers to the sub-questions as formulated in Chapter 1, and then conclude on the main research question addressed in this thesis: *How to create an environment that is suitable to learn safely and responsibly what uncertain risks associated with emerging biotechnologies entail?* Lastly, I discuss the limitations of this thesis (Section 8.7) and provide recommendations for future research to specific stakeholders (e.g. regulators, risk managers, researchers and SbD scholars) (Section 8.8).

8.2. Differing Perceptions

How are notions of risk, safety, inherent safety and Safe-by-Design perceived by different stakeholders associated with emerging biotechnologies?

Crucial for a constructive and fruitful discussion about uncertain risks with a range of partaking stakeholders is them having a shared association and/or understanding of notions on risks and safety. The research in this thesis (Chapters 2, 3 and 7) revealed some differences in the perceptions of technical researchers, social scientists, (bio)ethicists, policymakers and risk assessors. Differences were mostly found in proposed strategies to lower or mitigate risks, and avenues to improve or ensure safety. That is, differences in perceptions mostly adhered to implementing technical measures in response to technical issues, or implementing such measures as a result of issues coming from the societal domain. Chapter 7 touched upon the societal association of risks and safety, in which we found the biggest difference in terms of these notions' meanings and their ambiguity.

In the (technical) sciences, risks and safety have a normative character. Thus, norms are established that determine whether a risk would be acceptable, thereby ensuring safety for society, animals and the environment. However, the societal interpretation (mostly used in risk communication) is ambiguous and risks are perceived as an 'absence of danger' (Chapter 7) and a product of human activity (Beck et al., 1992). In Beck et al.'s 'Risk Society: Towards a new modernity' (1992), the authors argue that we as a society are suffering from 'the latent side-effects' of the 'victories of modernity' (e.g. CO₂ emissions and climate change, hazardous pesticides, antibiotic resistance). Initially, we as a society celebrate the achievements modernity has brought us, but only later come to realize that we have to deal with the associated risks of modern innovations too. In that sense, people

feel they are not in control and therefore institutions responsible for development are also the institutions that should protect our society from these ‘latent side-effects’. As a result, the societal interpretation of risks and safety can be seen as a response to this ambiguity and is therefore associated with the ‘absence of risks or danger’ (Beck et al., 1992). This illustrates that the societal interpretation of risks and safety is very different from other stakeholders’, which mostly adheres to the technical interpretation (i.e. $\text{risk} = \text{effect} * \text{probability}$) and in response, technical measures. Debates regarding uncertain risks and emerging biotechnologies need to include societal actors to arrive at applications that will not be rejected by society (Von Schomberg, 2013), and therefore, all partaking stakeholders must be aware of the different interpretations and associations of safety and risks to realize a constructive debate.

Different perceptions of Safe-by-Design (SbD) adhere to the first two challenges of this approach described in Chapter 1; having no-agreed upon definition, and researchers not being able to solely determine what measures should be taken to arrive at an acceptable level of safety. Considering SbD’s definition, research conducted in this thesis shows that while there are (minor) differences in interpretations of the approach, they all have in common that SbD calls for a (pro)active mindset to lower or mitigate risks. There is a consensus that a broad range of stakeholders should be involved to be able to identify a wide range of possible issues and develop anticipatory strategies to reduce or circumvent these. We cannot put this responsibility solely on researchers.

Differences were found in the expectations stakeholders have in the sense of SbD leading us toward inherently safe designs – referring to ‘absolute’ or 100% safety. While stakeholders pertaining to the social sciences and regulatory domain appeared to be somewhat positive, stakeholders from the technical sciences acknowledged that achieving 100% safety will never be possible from an engineering point of view. Nevertheless, for all stakeholders, the notion does create associations of *working toward* this ‘absolute’ safety. This can be explained by the iterative character of SbD, and the promise of identifying and anticipating potential risks already during the *very early* design stages of a technology. Indeed, in theory, this could pave the way for safe(r) processes and designs. But we have to keep in mind that for being able to make *safer* design choices or to enable iterations in the design, knowledge is crucial. And, as we lack sufficient knowledge of uncertain risks and uncertainties, we cannot make directed choices for safer designs – we can only implement precautionary measures with the accompanied inherent risk of thereby stifling knowledge creation.

8.3. Safety and Resilience in Regulation

How is safety ensured and uncertain risks dealt with in the current governance ecosystem for biotechnology, and how resilient is this system given the expected future developments in this field?

Chapter 3 provided oversight of the current regulatory regime concerning GMOs in the Netherlands. Based on this, I conclude that the regime focuses largely on ensuring safety as a result of how the Precautionary Principle (PP) is operationalized in GMO legislation and has led to a highly precautionary culture. In terms of managing uncertain risks, (environmental) risk assessments prescribe that only research activities entailing acceptable risks are conducted. When research involves uncertain risks or uncertainties, the governance ecosystem calls for measures to mitigate or exclude risks or issues of which we have no or only limited knowledge. In that sense, the current system ensures safety by focusing on known risks, and calls for conclusive evidence for having only acceptable risks involved – it is a regime of compliance. Additionally, as the Dutch regulatory system is based on EU legislation, I also conclude that the European governance ecosystem focuses on ensuring safety by precaution.

Furthermore, due to the regime being highly precautionary and one of compliance, it is currently not resilient in dealing with emerging techniques and applications of biotechnology. However, given the current and expected developments in biotechnology, it should become more flexible, and allow room for research involving uncertain risks – which can be done. As illustrated by the COVID-19 pandemic, when stakes are high and societal benefits are expected to be significant, the system can be altered to provide room for having uncertain risks and uncertainties involved (i.e. vaccine development) (Council of the EU, 2020; Wesseler & Purnhagen, 2020). Thereby, safety is not neglected, but also other important factors are given significant weight in the balance between safety and innovation. As already touched upon in this thesis though, risk assessments for (bio)medical applications already allow for potential benefits to be weighed-in to some extent. Regarding the other applications of biotechnology (industrial and plant engineering), (environmental) risk assessments prescribe that only research activities entailing acceptable risks are conducted, illustrating that the system is currently not very able to deal with the vast pace of developments in biotechnology. On a personal note, compared to regulatory adjustments due to COVID, one wishes that pressing matters such as global warming and the Paris Climate Accords would provide enough incentive for governments to reshape regulation to enable responsible development of the field of biotechnology, and to enforce highly polluting industries to take on a radically different approach (Chapter 5).

When considering responsibility allocation of researchers and risk managers, I showed that the current regime has not-assigned forms of forward-looking responsibility concerning uncertain risks (Chapter 3). In response, I argue that the

responsibility for knowing and assessing uncertain risks should be allocated to both risk managers and researchers, and the responsibility of communicating about uncertain risks to researchers. Thus, I call for co-responsibility between risk managers and assessors, and researchers. As these stakeholders have different knowledge they should complement each other when dealing with uncertain risks. I call for a better understanding of the uncertain risks from a technical perspective, and knowledge of how to manage and regulate these risks responsibly from a regulatory and societal perspective. In addition, if researchers would be made co-responsible, they should be equipped with tools to do so accordingly (Chapter 7). We cannot expect researchers to be solely able to estimate the possible severity of an uncertain risk or potential issue. This also pertains to implementing appropriate SbD measures – strategies to lower or mitigate potential issues –: complementary knowledge is crucial.

Compared to biotechnology, responsibilities are allocated differently in the chemical industry (Chapter 5). Also for this industry, responsibility for managing uncertain risks should be redistributed. As already mentioned above, for biotechnology, there should be some responsibility given to researchers and industry; thus arriving at co-responsibility. For the chemical industry and the regulation of new chemicals or chemical substances, responsibilities should be mostly taken away from the industry itself and allocated to governmental institutions responsible for assessing and managing risks. That may prevent future regrettable substitutions from happening. In addition, for both risk management regimes the playing fields should be levelled so that safe and responsible development of new products and processes prevails, and that chemistry can be challenged by novel, more sustainable products and production methods.

Research conducted in this thesis also shed light on differences between risk management in biotechnology and other fields such as nanotechnology and chemistry. First, biotechnology and in particular synthetic biology are comparable to nanotechnology as these are emerging fields with uncertain risks involved. The management of uncertain risks in nanotechnology (while this was not explicitly described in this thesis) has also been studied as a significant body of literature concerning SbD comes from this field. Regulation of nanotechnology in the EU is done through REACH (as are chemicals) in which nanomaterials are covered by the definition of a ‘substance’ (European Commission, n.d.). While nanotechnology is also regulated strictly like biotechnology, there are instances known where nanomaterials have exposed society to negative health effects (Jacobs et al., 2010). Those cases show that learning has occurred about uncertain risks, but in a *passive* form, thus by learning-by-doing, or through incidents. This ‘room for learning’ can be attributed to REACH in which conclusive evidence is needed to prove that a product is *not* safe – as with chemicals (Chapter 5). For the chemical industry, this

has resulted in cases of regrettable substitution, either by accident or by negligence of which PFAS is the most illustrative example. This illustrates that currently REACH does allow room for learning, but not the type of learning one would like to pursue (i.e. through incidents). Instead, we must arrive at *active* learning meaning that designated procedures and institutions should be put in place specifically for learning what uncertain risks entail in a safe and responsible way.

8.4. Safe-by-Design

To what extent is the Safe-by-Design approach capable of contributing to responsible learning about uncertain risks, and what is needed to operationalize this approach?

As already referred to (sub-question 1), there is a consensus that SbD is an approach that encourages associated stakeholders of an emerging (bio)technology to critically (re)consider design choices specifically to enhance or increase safety. Thereby, SbD's iterative character (feedback loops) and the inclusion of a wide range of stakeholders would allow for gradual, step-by-step learning of what uncertain risks and uncertainties entail. In addition, the risk-lowering or mitigating strategies that SbD provides could ensure that research entailing uncertainties is conducted in a safe and responsible way. Therefore, in theory, SbD is very much capable of creating and guiding an environment suitable for responsible learning.

However, considering SbD in practice, it now seems to mostly provide strategies to lower or mitigate risks based on knowledge we already have – this pertains to the third challenge of SbD as discussed in Chapter 1. Due to the prescriptive character of the current risk management regime, this barely allows research involving uncertain risks and/or uncertainties to be conducted. As a result SbD can hardly provide strategies to deal with matters that we do not understand yet – only ways to possibly circumvent these. This is where the problem lies for operationalizing SbD; learning about uncertain risks can be done through SbD, but managing them responsibly and thereby ensuring safety can only be done with having extensive knowledge – there are knowledge gaps that have inherent uncertainty for ensuring safety. Until something 'bad' has happened, this uncertainty will remain. In addition, foreseeing all potential safety issues during the R&D or design phase of a technology is difficult as some may only become known or fully understood once the innovation is introduced to society – which are matters that SbD cannot solve.

The problem mentioned above is not only applicable to the field of biotechnology; also e.g. nanotechnology and chemistry face problems in dealing with knowledge impasses concerning uncertain risks. Thereby, the challenges of SbD related to balancing the value of safety with other values and the need for

knowledge to be able to make adequate trade-offs also pertain to these fields – and perhaps to all domains where SbD is implemented. As uncertain risks can be complex and ambiguous, it calls for multiple stakeholders to be involved to bring different perspectives, to make an adequate joint trade-off in design choices, and to determine what level of uncertainty to allow, and where additional risk research is needed. In this process potential benefits of a technology or application could be weighed-in too. Urgently, SbD could incorporate moral responsibility which need is illustrated by many incidents in the conventional chemical industry.

Thus, while the current operationalization of SbD is limited to mainly lowering and mitigating known risks – mostly due to the way the PP is operationalized. The applicability of SbD leading us toward safety would mostly depend on researchers being aware of potentially arising issues, and then sharing any related knowledge openly with all associated stakeholders (Chapter 3), thus one's *mindset* – as discussed in Chapters 6 (iGEM) and 7 (stakeholder communication). When researchers are not aware that any potential issues might arise, or if one does not intend to make design choices for safer processes and products to begin with, the identification of potential risks (and the range they apply to) would already become very limited. So, implementing SbD including awareness and identification would force great responsibility on researchers. But as we have already argued, researchers cannot solely bear this responsibility, so they should be made co-responsible and provided with suitable tools to do so (Chapters 3 and 7). Consulting a range of stakeholders will provide researchers (and others) with valuable insights to set up or continue research activities safely. This is most effective when this takes place in an informal, non-institutional setting (Chapter 7). Only then a truly free exchange of views and perspectives can take place without fear of shared insights immediately having implications in terms of (societal) perception or (stricter or less strict) regulation. Such problems have already emerged in the (conventional) chemical industry (Chapter 5), where there is little incentive for industry to share knowledge and data about possible adverse effects (Drohmann & Hernandez, 2020). However, extensive exchanges of knowledge are prone to two difficulties. First, they cannot always take place; this would be unrealistic, take up too much time, and would make the working conditions for researchers stressful. Also in this, a balance should be found in which the respective researchers decide whether a (new) research project has uncertain risks and uncertainties which call for knowledge exchange. Secondly, knowledge exchange can also be exploited by actors with agendas to subvert such processes. Including a wide range of stakeholders is crucial to arrive at applications that will not be rejected by society (Von Schomberg, 2013) which implies that, for instance, also opponents of biotechnology should be invited to partake in these knowledge exchanges. Although scientists can choose for themselves who they would invite in the proposed workshop as described in Chapter 7, this also puts them in a difficult position to

choose whose input they would consider valuable, and which not. In addition, such selectivity would also allow for misuse of the knowledge exchange processes as researchers can choose to only invite stakeholders who fit exactly with their own research aims.

In conclusion, and applicable to all engineering domains, implementing SbD does not guarantee the development of safe products. Due to ill-equipped science or differently oriented mindsets, there may be a lack of incentive or difficulty to address novel risks and we may be only generating partial knowledge (Maynard et al., 2006). In addition, some novel risks can only be assessed once introduced to society (Jacobs et al., 2010). Therefore, while learning about uncertain risks and uncertainties should be enabled, these processes must remain to some extent precautionary and monitored. Regarding this monitoring, we must have co-responsibility for transparency and knowledge sharing between researchers *and* regulators and risk assessors.

8.5. How to create an environment suitable for responsible learning?

Based on the discussion and presented results so far, I will now conclude on *How to create an environment that is suitable to learn safely and responsibly what uncertain risks associated with emerging biotechnologies entail?* It has become clear that current regulation for biotechnology does not create a suitable environment for responsible learning about uncertain risks and uncertainties. It struggles in balancing ensuring safety with innovation. In particular, the way the PP is operationalized in GMO legislation has resulted in a highly precautionary culture in which there is little room to conduct research with associated uncertain risks or uncertainties, or to learn what these types of risk entail – it has resulted in a culture of compliance. Although studies by the EU are being devoted to how ‘new’ genetic engineering techniques such as CRISPR should be assessed in comparison to recently exempted techniques (Parisi & Rodriguez Cerezo, 2021), the outcome might not have any consequences for GMO regulation at all. These issues do not only stifle innovation but also illustrate that the current regime is not resilient in dealing with emerging techniques.

To break free from the impasse between safety and innovation, researchers should be able to learn what uncertain risks entail, for instance, through Safe-by-Design (SbD). To do so, I conclude that three conditions are needed to create an environment that allows for such learning: *regulatory flexibility*, *co-responsibility* between regulators, risk assessors and researchers, and (increased) *awareness* amongst researchers. Regulatory flexibility will allow SbD to be operationalized to its fullest extent, enabling learning of what uncertain risks and uncertainties entail in a controlled, step-by-step way. Thereby, co-responsibility between researchers, risk assessors and managers and regulators is needed to ensure monitoring and

responsible development of emerging biotechnologies. Lastly, awareness of safety and risks is crucial for implementing SbD in research practices to begin with, particularly regarding uncertainties. While SbD provides some strategies to lower or mitigate issues arising (e.g. auxotrophy, kill-switches, etc.) (Robaey, 2018), these are based on knowledge we already have. For uncertainties or other unexpected issues one's awareness and mindset also heavily influence design choices and what anticipatory measures to take to manage these risks responsibly and safely.

The listed conditions will enable an environment suitable for responsible learning and will derive new knowledge, data and understanding of risks and uncertain risks. But – emphasizing 'responsible' in responsible learning – we must be aware that there is and will remain a knowledge gap regarding these types of risks. Yes, obtaining more knowledge will help to close this gap, but it also has the inherent risk of only learning after an incident has occurred; thus learning through accidents, or passive learning. Therefore, we must be careful (and in that sense remain precautionary) about what risk(s) we are taking (establish how 'big' is the knowledge gap), and also place it in the perspective of the innovation and its potential benefits – what is there to win and on what level (e.g. individual, society, global)? Therefore, potential (and realistic benefits – not every innovation is going to save the world) should be weighed-in in respective risk assessments to see if potential risks are in balance with societal and/or environmental gains. Thereby it must be noted that information regarding benefits should also be considered by a multitude of stakeholders.

Being able to learn about uncertain risks and uncertainties will allow the field of biotechnology to mature and become competitive with the conventional chemical industry's (often fossil-based and polluting) products and processes, contributing to transitioning toward a biobased economy and the creation of safer and more sustainable (bio)chemical products and processes. In addition, as biotechnology is developing at a vast pace, Europe must make sure that it does not miss out on the field's potential benefits. In particular compared to e.g. the United States which has a regulatory regime that is more focused on innovation (Chapter 5). Europe must stay on top of the state-of-the-art in biotechnology, and must closely monitor the developments to see to it that these are done safely and responsibly. Might a development have detrimental effects – such as PFAS – we must be able to act and restrict early and swift, and not be dependent on or awaiting other countries to take action. In that sense, regulation being flexible and resilient is key to boosting innovation in biotechnology safely and responsibly.

8.6. Concluding Remarks

Designing for safety comprehends (pro)actively lowering, mitigating and anticipating possible risks. Thereby, awareness of potential risks plays a major role

as well as specifically devoting research to study these risks. It should become 'common practice' for researchers to discuss risk-related matters with a range of stakeholders. To ensure this, safety and being aware of risks should become embedded in education to equip the engineers of tomorrow. Chapter 6 illustrated how safety is strongly embedded in education for students partaking in the iGEM competition. However, this competition is not compulsory and it is important that safety is embedded in compulsive engineering courses, ideally complemented with insights from the social sciences (e.g. stakeholder analysis, relevant values and how to account for these in design choices). Not all students partake in iGEM, and outside TU Delft, the Netherlands or Western Europe, a lot of universities do not have sufficient funds or facilities to be part of this competition. Therefore, while iGEM is a nice example of how safety can be strongly embedded in educational practices, it should be implemented more broadly and most importantly in an accessible way. Furthermore, we should be able to learn about uncertain risks and uncertainties and hence research on the uncertain risks and uncertainties. This should be made transparent and shared and therefore should be awarded equally with technical innovative research, e.g. included for funding by funding organizations, part of required data for publications by academic journals etc. as argued in Chapter 5. To realize the embedding of responsible learning for safety in education and the joint learning of responsible researchers and risk managers, the academic system needs to be reshaped so it values research on risk uncertainties equally with technically innovative research.

For senior researchers, we also developed a workshop that contributes to increasing awareness and stimulating risk research (see Chapter 7 and Appendix C). The aim hereby is to identify possible emerging risks and develop suitable anticipatory strategies to lower or mitigate these. Through this workshop, we can create or increase awareness and enable a mutual learning process between a range of partaking stakeholders for identifying possible issues. As researchers cannot decide alone on the extent of acceptability of potential issues, this learning process needs stakeholders from other areas of expertise as well. Although the current regulatory regime currently stifles risk research associated with uncertain risks and uncertainties and any regulatory changes may be more than 5 years away or may not happen at all, it is still important that learning environments become embedded in research practices. If there, eventually, are no regulatory changes mutual learning processes will still contribute to safer research practices, products and techniques. If changes will be implemented, we are well prepared as a research community to take up risk research to a greater extent, safely and responsibly.

Lastly, it is promising that over the last years, the EC has become supportive of implementing SbD or related notions such as Safe-and-Sustainable-by-Design (European Commission, 2020), or Safe-and-Circular-by-Design (Slootweg, 2020).

To increase safety, the EC is right in incentivizing industries to adopt this approach. But to avoid SbD becoming a check-box as we have witnessed, this should be done via providing additional funding or grants to companies to research safer alternatives, or it should be enforced by means of the 'Polluter-Pays' principle. And, to see to it that companies truly implement SbD the EC should require companies to report on their use of harmful substances (e.g. chemicals) and their efforts to reduce accompanied hazards by means of SbD.

8.7. Limitations

As in all studies, also this study has many limitations. I focus on two. First of all, although societal interpretations of risks and uncertain risks are touched upon in this work, this research did not include societal actors in interviews and workshops. While all interviewees and partaking stakeholders in the conducted workshops are part of society, their viewpoint regarding society is, of course, influenced by their expertise coming from the technical and social sciences.

Secondly, this work focused on Europe and in particular the Netherlands and its respective risk governance ecosystem. Only in Chapter 5, we have looked into US legislation and regulation. Therefore, the majority of the findings in this study cannot be generalized outside Europe, which also pertains to the needed conditions for SbD as these have been based on the operationalization of the PP in EU legislation. Nevertheless, difficulties pertaining to learning what uncertain risks entail and how to do that safely and responsibly are not limited to solely Europe, but applicable to all parts of the world.

8.8. Recommendations

The conducted research and outcomes in this thesis provided answers but also gave rise to new questions. Therefore, some suggested actions and recommendations for future research are presented below, specified to certain stakeholders.

For MEPs³⁰ and the EC:

As there are differences between EU and US regulation of biotechnology (i.e. one focused on ensuring safety by precaution, one focused on innovation), it should be explored (either by the EC itself or by e.g. Innovation Sciences scholars) to what extent this influences the rate of innovation (and economic value), effects on the environment, and safety issues in both the EU and US. This may provide the EU with insights into any coherence between specific types of biotechnology applications, and any possible rise in safety issues. In addition, such research may

³⁰ Members of European Parliament

also contribute to the knowledge base regarding governance and the economics of innovation, and risk governance.

For Regulators and Risk Managers:

In terms of (environmental) risk assessments of emerging biotechnologies, regulation should allow potential benefits to be included. The COVID pandemic illustrated that this is possible, and when stakes are high, it could provide a way to allow innovation. However, the question here becomes one of how to assess these potential benefits, and who is providing this information and/or data? For instance, if such responsibility would be allocated to the industry itself, every innovation might be presented and framed as saving the world which would make the risk-benefit assessment subjective and misbalanced.

Building upon Chapter 5, to prevent more pollution by PFAS (or comparable compounds), in July 2021, several countries (i.e. the Netherlands, Germany, Sweden, Denmark and Norway) have already called for a total ban on these substances in the EU (NOS, 2021). However, whether this ban will come into effect will depend on several factors. A scientific assessment and consultation round are needed to identify which products contain PFAS, and which of these may be considered essential. As a result, some PFAS that would be 'essential' may be exempted from the ban, giving rise to questions in terms of what would be considered 'essential' by the European Commission and Parliament? And whether such exemptions would just lead to the development of 'new' PFAS and thereby completely miss the aim of preventing regrettable substitution from happening? If we truly want to prevent regrettable substitution (particularly by negligence) from happening in the future, the conventional chemical industry must drastically change. We must work toward a more ethical chemistry; the question is, how? By incentivizing industry through e.g. additional funding or grants to develop safe and sustainable alternatives to commonly used products and processes from e.g. a radically different feedstock? Or by enforcement and holding 'the polluters' accountable for negative externalities? However, for the latter case, the damage has already been done which is exactly what we want to initially prevent from happening. Also, if a cultural change towards safety will be enforced and regrettable substitution will still take place, it would require extensive research to determine the extent of accountability, i.e. whether this has occurred by accident or by negligence.

For Researchers and Lecturers (SbD-scholars, social sciences, philosophy)

Not all risks can be determined during the development of a technique or application, and in particular the severity of such a risk due to knowledge gaps. Some may only become clear once embedded in society and widely used. For instance, pollution by micro-plastics or global warming as a result of CO₂ emissions.

In terms of allocating responsibilities and blameworthiness when uncertain risks turn out to have detrimental effects, this could be difficult and complex as such effects can be regarded as a ‘problem of many hands’ (Van de Poel et al., 2012; Van de Poel et al., 2015). As ensuring safety is also dependent on many actors, institutions, organizations and local and global regulations, future studies could be dedicated to exploring to what extent safety can be regarded as a problem of many hands. Such studies could provide insights into what would be needed to ensure safety on a broader level, and how to act might anything unforeseen happen (also of value for risk managers and regulators).

In this thesis, I argued that we must arrive at co-responsibility for transparency and knowledge sharing between researchers *and* regulators and risk assessors. However, more research should be set up exploring what a good balance should be in these assigned responsibilities, and if and how this should be monitored. For instance, while a researcher would have the assigned responsibility to share knowledge about potential risks, there remains a knowledge gap to determine whether or not such risks should be regarded as a risk. Therefore, can one be held accountable when they would’ve failed – in hindsight – to provide sufficient information about such potential issues arising? And, to prevent such from happening, how to shape and assign responsibilities for monitoring such decision-making? The latter also pertains to how to shape free knowledge exchange processes (as discussed in Chapter 7), and who to invite to participate in such? With monitoring, such processes may lose their informal and ‘free’ character, while without, there is a risk that only selected viewpoints will be invited to take part in the knowledge exchange.

This thesis also showed that SbD can deal with known and uncertain risks, in theory. A valuable insight would be to what extent SbD could also manage and anticipate ‘black swan’ type of events (i.e. unknown unknowns). Also, this thesis provided insights into how to deal with emerging risks arising from biotechnology and synthetic biology. As the industry concerning synthetic chemicals is also emerging, it could be studied what lessons derived from this thesis can apply to this field.

Lastly, it has become clear that individuals such as researchers, lecturers and students also have a part in the creation of safe industries, and safer products and processes. Therefore, all must adopt and embed a mindset that also addresses safety in addition to other factors such as sustainability and efficiency. As mentioned, one can ‘do’ SbD, but the extent of thoroughness and comprehensiveness is also determined by one’s mindset and attitude towards safety. Therefore, this notion must become more strongly embedded in students’ education and in research cultures in which knowledge institutions play a pivotal part.

Appendices

Appendix A - PHOCUS

Table A.1: Identified stakeholders and derived values. From: iGEM 2020 'PHOCUS' VSD Assignment – ELSIB course. *Values were retrieved from organization's respective website. **Values were interpreted from other sources (e.g. media) or from empirical findings (i.e. interviews).

<i>Stakeholder</i>	<i>Values</i>
Ministry of Agriculture, Livestock, Fisheries and Irrigation of Kenya*	Professionalism Integrity Efficiency and Responsiveness Partnerships Gender Equity
Food and Agriculture Organization (FAO)**	Health Equality Accessibility Food Safety Food Security Environmental Safety Sustainability Innovation
Desert Locust Control Organizations East Africa**	Cooperation Food Security Innovation
Kenyan farmers and herdsman**	Family Health Economic Benefit Status Food Security Personal Autonomy
Sumitomo Chemical*	Integrity Passion Innovation Collaboration Responsibility Economic Benefit
iGEM*	Integrity Good Sportsmanship Respect Honesty Celebration Cooperation Effort Excellence

Table A.2: Translation of selected values into norms and design requirements. Only values that can result in tangible design requirements are included in this Table. From: iGEM 2020 'PHOCUS' VSD Assignment – ELSIB course.

<i>Value</i>	<i>Norm(s)</i>	<i>Design Requirement(s)</i>
Health	No effects on physical or mental health	• Bacteriophages as genetic carriers • No delivery of bacteriophages under acidic conditions • Non-toxic, non-pathogenic host microorganism that is not present in humans • Produced toxin non-pathogenic to humans and degradable in human digestive tract
Accessibility	Access to the product at all times Access to knowledge about the product	• Robust distribution network • Local production • Affordable • Simple and easy to use • Provide sufficient knowledge to end used for an educated decision
Food Safety	Low or limited presence of hazardous compounds	• No toxin production outside the locust • Toxin should be non-toxic to humans and livestock, and degrade when exposed to the outside environment
Environmental Safety	Production is not harmful for the environment Usage is not harmful for the environment	• Production in cell-factories • Toxins very specific to locusts • Use virulent bacteriophages • Insertion of a kill switch driven by light • Physical barrier between the environment and the bacteriophages
Sustainability	No irreversible effect on the environment	• Production cell-factories • Agricultural waste as feedstock

		• Storage system based on sunlight • Local production of bacteriophages • Product unstable outside locusts
Integrity	Business interest should be in harmony with public interest Adherence to your values no matter the circumstances No underlying agenda	• Actions taken to achieve the goals should always be in accordance with the values stated, no matter the contact or situation faced • Should not be affected by political instability or misconduct • Decisions made in the design process should be transparent and clearly communicated
Efficiency and Responsiveness	The product should be producible and deployable on short notice Measures against locusts should be highly efficient	• Easily scalable cell-factories for production • Minimise required amount of toxin • High level of toxin production in a short amount of time • Use of anchoring proteins to increase the specificity
Collaboration	Collaborate with stakeholders Earn trust of stakeholders	• Approval for local, regional and cross-border use • Adjusted to needs of different stakeholders • Transparent design choices and knowledge sharing
Food Security	Upsurge of plagues should be controlled Adequate resources for nutritious food should be available	• Highly toxic and specific toxin • Tackle locusts before they are swarming and/or kill them efficiently • No negative effect on the growth of the crops

		• Toxin should not reduce the nutritional value of the food
Economic Benefit	Users should benefit economically Producers should benefit economically	• Cheaper than current products • Large yield of toxic per quantity of phage • Rapid spread of the phage amongst locusts • Fast replicating phage • Profitable production and sale
Personal Autonomy	Being able to make own decisions Users willingly use the products	• Sufficient information about the product's availability • Deciding not to use the product does not result in punishment in what so form • No higher power or legislation influences potential users
Responsibility	Cannot be used in a harmful way Beneficial to society	• Highly specific bacteriophage which cannot be tuned and used for other purposes • Regularly re-evaluate the design • Involve different stakeholders in design process and use their input to improve design • Inform the public about the product

Appendix B – AptaVita

Table B.1: Identified stakeholders and derived values. From: iGEM 2020 ‘AptaVita’ VSD Assignment – ELSIB course. ¹ The values are retrieved from their respective websites and reports. ² The values are derived from other sources, i.e. interviews. ³ Quality is referred to as accuracy and reliability.

<i>Stakeholder</i>	<i>Values</i>
World Health Organization ¹	Health Equality Inclusivity Honesty Trustworthiness Sustainability Accessibility Safety Quality ³
Center for Disease Control and Prevention ¹	Health Equality Prevention Efficiency Quality ³ Safety
Food and Agriculture Organization ¹	Food Safety Health Sustainability Equality
Government of Uganda ²	Health Equality Food Safety Education Efficiency Accountability
Local Ugandan Communities ²	Trustworthiness Acceptability Accessibility Health
Point-of-care clinics ²	Health Safety Accessibility Trustworthiness
Astel Diagnostics ¹	Quality ³ Health Accessibility Trustworthiness
iGEM Foundation ¹	Integrity Excellence Respect

	Effort Honesty Cooperation
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Table B.2: Translation of selected values into norms and design requirements. Only values that can result in tangible design requirements are included in this Table. From: iGEM 2020 'PHOCUS' VSD Assignment – ELSIB course.

<i>Value</i>	<i>Norm(s)</i>	<i>Design Requirement(s)</i>
Health	Avoid any negative impact on physical, mental and social well-being of people	The value health stands at the core of all other values. Therefore, the design requirements below are also the design requirements for health as a value.
Quality (Accuracy & Reliability)	Measurements should reflect the true value Measurements should be consistent	• Control with a ligand at known concentration • Mobile readout • Use of blood • Develop sensible and selective aptamers • Use of a robust cell free system
Efficiency	Avoid wasting materials, efforts, money and time while achieving the desired result	• Ready-to-use RDT • Use of a fast-expression cell free system • Inexpensive materials • Small reaction volumes
Safety	Production, use and disposal of the RDT should not be harmful to the environment Production, use and disposal of the RDT should not harmful to the user	• Non-GMO, use of cell-free system • Provide use and disposal instructions • Use of non-toxic components
Equality & Inclusivity	Everyone should have equal access to RDT Production and use of RDT should not lead to discrimination on any basis	• Frugal innovation • Manual should be in native language • Include local community in production/value chain

Trustworthiness & Acceptability	The device should inspire confidence and reliance in the user The device should be readily approved by the user, should be willing to use the device	• Use blood as sample • Reliable producer • Use of cell-free system • Use of urine or saliva as sample
Accessibility	RDT should be available at the point of care (physical) RDT should be affordable (economic) RDT should be understandable (information)	• Freeze-dried system stable at ambient temperatures • Use of cheap reactives and small reaction volumes • Include a user manual
Sustainability	Reduce ecological footprint Reduce social dependency	• Freeze-dried system stable at ambient temperatures • Use recycled/biodegradable packaging materials • Small reaction volume • Local/regional production

Appendix C – Protocol for Workshop

As researchers find themselves at the cradle of emerging biotechnologies, it is important that safe and responsible development is ensured. By accommodating this workshop, researchers can see to it that this is done. This would be beneficial not only because safe and responsible development is highly endorsed by funding organizations, but also, in later experimental stages, it could prevent research to be delayed due to unforeseen issues arising, complicating matters such as conducting an adequate risk assessment and permit application. For instance, an issue could occur for which no policy is equipped yet. By identifying and anticipating these issues during early stages of experimental development, such delay or complication could be circumvented. Therefore, we provide a script that elaborates each step, the respective stages of thought to go through and the desired outcome or deliverable of each step. As mentioned, the ideal results of the workshop are a list of potential issues or uncertainties that need to be anticipated, suitable strategies to do so, and a list of design adaptations and/or requirements.

Eight notes of importance prior to the workshop:

1. First of all, when inviting participants it should be clear why they are invited for the workshop, how their specific contribution would be meaningful for the researchers and vice-versa (what's in it for them?). Thereby, the subject of the meeting and what will be discussed during the meeting should be clearly explained in the invitation.
2. As to avoid very general discussions about risks and uncertainties that lead to unclear recommendations, the subject of the meeting (i.e. the reason for organizing this workshop) should be presented as a specific case that is in line with the (intended) research and forms the framework for the discussions. So, for instance, the development of a new type of application or proceeding from a laboratory environment (contained) to a non- or semi-contained environment (e.g. field trials) where new types of uncertainties can emerge.
3. The case should be sent to all participants prior to the workshop. Thereby, a balanced amount of information must be provided. It should be balanced in a way that experts can form a realistic idea of the different factors that may lead to new risks, and non-experts with less technical knowledge can place the 'case' in a broader picture.
4. Thirdly, it must be decided if an external moderator or discussion leader will be needed or whether one directly involved in the research project will act as discussion leader. We would recommend an external moderator due to the ability to act and summarize the discussions neutrally and who can create a positive and relaxed atmosphere. However, depending on the specific content the workshop will be focusing on, the moderator might require to have relevant

(technical) knowledge considering the topic(s) for discussion. If this is not found to be possible, someone directly involved in the research project can act as discussion leader but should bear in mind to mostly focus on guiding, summarizing and reflecting on the discussion itself, instead of (perhaps subconsciously) letting one's opinion influence the discussions. Another option is to have a moderator that focuses on the discussions and have a 'second moderator' who focuses more on technical related matters. However, when choosing this option, the two moderators must make good arrangements of who answers/moderates what aspects.

5. Appoint a rapporteur with good reporting skills before the workshop for making a written report of the discussions.
6. Determine the composition of break-out groups (preferably balanced with different types of expertise in each group).
7. Make sure you are well prepared and have everything properly installed and tested: whiteboards, post-it notes, (felt-tip) pens, a camera to photograph results, tools for online support etc.
8. Lastly, if making recordings or if personal information will be used in the meeting's written report, ask participants for their permission using a form of consent³¹. This form of consent can be sent to the participants with the official invitation and should be handed in before the start of the workshop.

In addition to the script provided below, Figure 7.1 illustrates all steps to be followed and can be used as a supplementary tool during the workshop.

	<i>Explanation</i>	<i>Outcome/ Deliverable</i>
Welcome	The discussion leader welcomes all participants. Also, participants can be reminded of filling in the form of consent for making recordings during the workshop.	-
Introductions	All participants, including the discussion leader, shortly introduce themselves and indicate how they are involved with biotechnology and/or the relevant context under discussion.	-
Step 1: Identification and Prioritization of Risks		

³¹ For informed consent templates, see <https://www.tudelft.nl/en/about-tu-delft/strategy/integrity-policy/human-research-ethics/informed-consent-templates-and-guide>

1.1 Introduction of aim/content workshop	The discussion leader or researcher from the project introduces the program for the day and the aims of the workshop. Participants can ask questions regarding the aims, set-up or other details concerning the workshop. Thereafter, the discussion leader or researcher from the project pitches the case on which the participants will focus during the workshop (point 2 above). Ideally, the case should be explained through several bullet points on a slide, thereby clearly stating the context (contained use or introduction to the environment, rationale of the research) and the central problem (complexities, uncertainties). Participants can ask questions to clarify matters regarding the case.	-
1.2 Identifying potential risks	Participants discuss in small groups (max 5 people in a physical setting and max 4 people when organized online) what possible risks are emerging according to their view or perspective. For this, participants are given 20 minutes to come to a consensus of 3 emerging issues, listed in order of importance. Before the discussion starts, one of the participants should be appointed to make notes of the top-3 of potential issues. After the discussion in small groups, the lists will be discussed plenary. For online settings, members of the research group can act as 'discussion leader' for the smaller groups to stimulate discussion and to provide more (technical)	A top-3 list (per group) of identified potential issues or uncertain risks

	information when asked for by the participants.	
1.3 Plenary discuss and estimate severity of potential risks	Every group briefly presents their top-3 plenary. If groups weren't able to reach a consensus regarding a top-3, they should elaborate on the issues they ran into. Other participants can ask questions for clarification. A plenary discussion (15 minutes) is devoted to the plausibility and severity of the identified issues, led by the moderator.	Overview of all listed potential issues. Written report (by the rapporteur) with details concerning the estimated plausibility and severity of the identified potential risks, and an overview of issues that did not make the 'top-3' or was a lot of disagreement on.
Step 2: Formulating Anticipatory Strategies		
2.1 Defining strategies	Each small group (same composition as in step 1) discusses what anticipatory strategies they can think of for circumventing their top-3 of identified issues. To stimulate or help discussion, the moderator can point out several technical strategies, e.g. kill-switches, auxotrophy, choice of an organism or implementing control mechanisms using, for instance, light. In addition, other measures on (work)organization can also be mentioned to spark discussion, e.g. proper lab training of staff. Again, one of the participants in each small group should be appointed to provide a summary in the plenary session that follows. Note: one strategy can anticipate multiple possible issues. For more information and examples, see Robaey (2018).	List with anticipatory strategies for each respective group's top-3.

2.2 Plenary discussion of anticipatory strategies	Every group briefly presents their defined anticipatory strategies plenary. Other participants can ask questions for clarification. A plenary discussion (15 minutes) is devoted to the effectiveness and feasible implementation of each strategy, and which would be the most effective to circumvent the earlier identified risks. Thereby, the defined anticipatory measures are also placed in the context of current regulation and legislation. Participants identify where there might be a lack of knowledge to adhere to the established norms to ensure safety.	Overview of all anticipatory strategies, and a list of which strategies are the most suitable. Identification of knowledge gaps necessary to adhere to existing legislation and thereby ensuring safety. Written report (by the rapporteur) with details concerning the estimated effectiveness and implementation of the defined strategies, and details concerning what strategy was deemed more suitable than another.
Step 3: Design & Research Adaptations		
3.1 Formulating design adjustments	First, participants are given 5 minutes to think of how the earlier identified strategies can be implemented in research. Or in other words, what would have to be adjusted in terms of the research design? For instance, there might be a need for more knowledge and/or additional risk research, more budget required for setting up the needed risk research, hiring extra staff, or more intense collaboration with the organization's BSO, etc. Participants put their suggestions in the chat (online environment) or write them down for themselves (physical meeting). Following up, a plenary discussion is devoted to	Proposal for adjustments in the research design and complementary experiments specifically devoted to risk research.

	all suggestions made. The discussion leader addresses the participant's suggestions one-by-one, either from the chat or from what each participant has written down, and asks the participants to elaborate. Participants are encouraged to respond to each other's proposed adjustments.	
Lessons learned and action points	All participants share their thoughts about the workshop and its outcomes. Also, participants formulate a take-home message and suggestions for follow-up steps. The rapporteur makes notes of all suggestions.	List with suggestions for follow-up steps and/or research. Feedback from participants on the workshop and the outcomes.
Summary workshop	The discussion leader provides a recap of the workshop, and briefly summarizes the main outcomes of the meeting. Participants are allowed to respond and/or ask questions.	-
Thank you & closure	The discussion leader thanks the participants and concludes the workshop by summarizing how this workshop may contribute to adjusting the research (proposal).	-

Based on the outcomes of the workshop and the written report containing more detail concerning the discussions, the organizers of the workshop (i.e. the research consortium/PI/main applicants) should decide on what measures to take and implement them in their research design accordingly.

References

- Abels, G. (2005). The long and winding road from Asilomar to Brussels: Science, politics and the public in biotechnology regulation. *Science as Culture*, 14(4), 339–353. <https://doi.org/10.1080/09505430500369087>
- Adams, J. (1995). *Risk* (University College London (Ed.)). Routledge. <http://www.john-adams.co.uk/wp-content/uploads/2017/01/RISK-BOOK.pdf>
- Adams, J. (2011). Not 100% sure? The “public” understanding of risk. In D. J. Bennet & R. C. Jennings (Eds.), *Successful Science Communication - Telling it like it is* (pp. 90–100). Cambridge University Press.
- Amyotte, P. R., Goraya, A. U., Hendershot, D. C., & Khan, F. I. (2007). Incorporation of Inherent Safety Principles in Process Safety Management. *Process Safety Progress*, 26(4), 333–346. <https://doi.org/10.1002/prs>
- Anastas, P., & Warner, T. (1998). *Green Chemistry: Theory and Practice*. Oxford Univeristy Press.
- Anastas, P., & Eghbali, N. (2010). Green chemistry: Principles and practice. *Chemical Society Reviews*, 39(1), 301–312. <https://doi.org/10.1039/b918763b>
- Anastas, Paul, & Eghbali, N. (2010). Green Chemistry: Principles and Practice. *Chemical Society Reviews*, 39(1), 301–312. <https://doi.org/10.1039/b918763b>
- Anyshchenko, A. (2019). The Precautionary Principle in EU Regulation of GMOs: Socio-Economic Considerations and Ethical Implications of Biotechnology. *Journal of Agricultural and Environmental Ethics*, 32(5–6), 855–872. <https://doi.org/10.1007/s10806-019-09802-2>
- Anyshchenko, A., & Yarnold, J. (2020). From ‘mad cow’ crisis to synthetic biology: challenges to EU regulation of GMOs beyond the European context. *International Environmental Agreements: Politics, Law and Economics* 2020 21:3, 21(3), 391–404. <https://doi.org/10.1007/S10784-020-09516-1>
- Aresta, M., Dibenedetto, A., & Quaranta, E. (2016). State of the art and perspectives in catalytic processes for CO₂ conversion into chemicals and fuels: The distinctive contribution of chemical catalysis and biotechnology. *Journal of Catalysis*, 343, 2–45. <https://doi.org/10.1016/J.JCAT.2016.04.003>
- Asin-Garcia, E., Kallergi, A., Landeweerd, L., & Martins dos Santos, V. A. P. (2020). Genetic Safeguards for Safety-by-design: So Close Yet So Far. *Trends in Biotechnology*, 38(12), 1308–1312. <https://doi.org/10.1016/j.tibtech.2020.04.005>
- Asveld, L. (2007). Autonomy and Risk: Criteria for International Trade Regimes. *Journal of Global Ethics*, 3(1), 21–38. <https://doi.org/10.1080/17449620701219790>
- Asveld, L., Osseweijer, P., & Posada, J. (2019). Societal and Ethical Issues in Industrial Biotechnology. In *Advances in Biochemical Engineering/ Biotechnology* (pp. 1–21). https://doi.org/10.1007/10_2019_100

References

- Aven, T., & Renn, O. (2009). On risk defined as an event where the outcome is uncertain. *Journal of Risk Research*, 12(1), 1–11. <https://doi.org/10.1080/13669870802488883>
- Bais, H. P., Weir, T. L., Perry, L. G., Gilroy, S., & Vivanco, J. M. (2006). The role of root exudates in rhizosphere interactions with plants and other organisms. *Annual Review of Plant Biology*, 57, 233–266. <https://doi.org/10.1146/ANNUREV.ARPLANT.57.032905.105159>
- Baltic Eye. (2015). *Major shortcomings in the EU regulation for chemicals in goods - Baltic Eye*. Stockholm University. <https://balticeye.org/en/pollutants/reach-report-2018/>
- Barakate, A., & Stephens, J. (2016). An overview of crispr-based tools and their improvements: New opportunities in understanding plant-pathogen interactions for better crop protection. *Frontiers in Plant Science*, 7, 765. <https://doi.org/10.3389/FPLS.2016.00765/BIBTEX>
- Bauer, M. W. (2002). Controversial medical and agri-food biotechnology: a cultivation analysis. *Public Understanding of Science*, 11(2), 93. <https://doi.org/10.1088/0963-6625/11/2/301>
- Bauer, M. W. (2005). Distinguishing Red and Green Biotechnology: Cultivation Effects of the Elite Press. *International Journal of Public Opinion Research*, 17(1), 63–89. <https://doi.org/10.1093/IJPOR/EDH057>
- Beans, C. (2021). News Feature: How “forever chemicals” might impair the immune system. *Proceedings of the National Academy of Sciences*, 118(15). <https://doi.org/10.1073/PNAS.2105018118>
- Beck, U., Lash, S., & Wynne, B. (1992). *Risk Society: Towards a new modernity* (Vol. 17). Sage.
- Ben Ouagrham-Gormley, S., & Fye-Marnien, S. R. (2019). Is CRISPR a Security Threat? In *Defense Against Biological Attacks* (pp. 233–251). Springer Nature Switzerland. https://doi.org/10.1007/978-3-030-03053-7_12
- Berg, P., Baltimore, D., Boyer, H. W., Cohen, S. N., Davis, R. W., Hogness, D. S., Nathans, D., Roblin, R., Watson, J. D., Weissman, S., & Zinder, N. D. (1974). Potential Biohazards of Recombinant DNA Molecules. *Science*, 185(4148), 303. https://www.mcdb.ucla.edu/Research/Goldberg/HC70A_W10/pdf/BergLetter.pdf
- Berg, Paul, Baltimore, D., Brenner, S., Roblin, R. O., Singer, M. F., Bergt, P., Baltimore, D., Roblin, R. O., & Singer, M. F. (1975). Summary Statement of the Asilomar Conference on Recombinant DNA Molecules. *National Academy of Sciences*, 72(6), 1981–1984. <https://doi.org/10.1073/pnas.72.6.1981>
- Berg, Paul, & Singert, M. F. (1995). The recombinant DNA controversy: Twenty years later. *Proceedings of the National Academy of Sciences of the United States of America*, 92(20), 9011–9013. <https://www.pnas.org>
- Biosecurity Office. (n.d.). *Biosecurity - Dual-Use Quickscan*. Retrieved February 21, 2022, from <https://dualusequickscan.com/>
- Blaine, K., Kamaldeen, S., & Powell, D. (2002). Public Perceptions of Biotechnology. *Journal of Food Science*, 67(9), 3200–3208. <https://doi.org/10.1111/J.1365->

2621.2002.TB09566.X

- Blum, A., Behl, M., Birnbaum, L. S., Diamond, M. L., Phillips, A., Singla, V., Sipes, N. S., Stapleton, H. M., & Venier, M. (2019). Organophosphate ester flame retardants: are they a regrettable substitution for polybrominated diphenyl ethers? *Environmental Science & Technology Letters*, 6(11), 638–649. <https://doi.org/10.1021/acs.estlett.9b00582>
- Bollinger, R. E., Clark, D. G., Dowell, R. M., Webank, R. M., Hendershot, D. C., Kletz, T., Lutz, W. K., Meszaros, S. I., Park, D. E., & Wixom, E. D. (1996). *Inherently safer chemical processes: a life cycle approach*. Center for Chemical Process Safety of the American Institute of Chemical Engineers.
- Bouchaut, B., & Asveld, L. (2020). Safe-by-Design Stakeholders' Perceptions and Expectations of How to Deal with Uncertain Risks of Emerging Biotechnologies in the Netherlands. *Risk Analysis*, 40(8), 1632–1644. <https://doi.org/10.1111/risa.13501>
- Bouchaut, B., & Asveld, L. (2021). Responsible Learning About Risks Arising from Emerging Biotechnologies. *Science and Engineering Ethics*, 27(2), 22. <https://doi.org/10.1007/s11948-021-00300-1>
- Bouchaut, B., Asveld, L., Hanefeld, U., & Vlierboom, A. (2021). Value Conflicts in Designing for Safety: Distinguishing Applications of Safe-by-Design and the Inherent Safety Principles. *International Journal of Environmental Research and Public Health*, 18(4), 1963. <https://doi.org/10.3390/ijerph18041963>
- Bouchaut, B., Hollmann, F., & Asveld, L. (2022). Differences in barriers for controlled learning about safety between biotechnology and chemistry. *Nature Communications*, 13(1), 1–4. <https://doi.org/10.1038/s41467-022-31870-8>
- Bracco, P., Busch, H., Von Langermann, J., & Hanefeld, U. (2016). Enantioselective synthesis of cyanohydrins catalysed by hydroxynitrile lyases-a review. *Organic and Biomolecular Chemistry*, 14(27), 6375–6389. <https://doi.org/10.1039/c6ob00934d>
- Buchner, G. A., Stepputat, K. J., Zimmermann, A. W., & Schomäcker, R. (2019). Specifying Technology Readiness Levels for the Chemical Industry. *Industrial & Engineering Chemical Research*, 58(17), 6957–6969. <https://doi.org/10.1021/acs.iecr.8b05693>
- Buchner, G. A., Zimmermann, A. W., Hohgräve, A. E., & Schomäcker, R. (2018). Techno-economic Assessment Framework for the Chemical Industry - Based on Technology Readiness Levels. *Industrial & Engineering Chemical Research*, 57(25), 8502–8517. <https://doi.org/10.1021/acs.iecr.8b01248>
- Bureau KLB. (2018). *De stand van de gedachtewisseling over modernisering van het biotechnologiebeleid. Eindrapport met de opbrengsten van een gedachtewisseling tussen betrokken maatschappelijke partijen van maart tot en met oktober 2018*.
- Burgess, A., Wardman, J., & Mythen, G. (2018). Considering risk: placing the work of Ulrich Beck in context. *Journal of Risk Research*, 21(1), 1–5. <https://doi.org/10.1080/13669877.2017.1383075>
- Callaway, E. (2018a). Gene Editing. EU law deals blow to CRISPR crops. *Nature*, 560, 2016. <https://doi.org/10.1038/d41586-018-05814-6>

- Callaway, E. (2018b). CRISPR plants now subject to tough GM laws in European Union. *Nature*, 560(7716), 16. <https://doi.org/10.1038/D41586-018-05814-6>
- Capron, A. M., & Schapiro, R. (2001). Remember Asilomar? *Perspectives in Biology and Medicine*, 44(2), 162–169. <https://doi.org/10.1353/pbm.2001.0022>
- Carlozzi, P., & Touloupakis, E. (2021). Bioplastic production by feeding the marine *Rhodovulum sulfidophilum* DSM-1374 with four different carbon sources under batch, fed-batch and semi-continuous growth regimes. *New Biotechnology*, 62, 10–17. <https://doi.org/10.1016/J.NBT.2020.12.002>
- Casson Moreno, V., Papasidero, S., Scarponi, G. E., Guglielmi, D., & Cozzani, V. (2016). Analysis of accidents in biogas production and upgrading. *Renewable Energy*, 96, 1127–1134. <https://doi.org/10.1016/j.renene.2015.10.017>
- Chemical Watch. (2013). *The weaknesses of the REACH review*. <https://chemicalwatch.com/14167/ngo-platform-the-weaknesses-of-the-reach-review>
- Chemicals | Internal Market, Industry, Entrepreneurship and SMEs. (n.d.). Retrieved September 21, 2021, from https://ec.europa.eu/growth/sectors/chemicals_en
- Chen, G.-Q. (2012). New challenges and opportunities for industrial biotechnology. *Microbial Cell Factories* 2012 11:1, 11(1), 1–3. <https://doi.org/10.1186/1475-2859-11-111>
- Clark, J., & March, J. (2006). Bacteriophages and biotechnology: vaccines, gene therapy and antibacterials. *Trends in Biotechnology*, 24(5), 212–218. <https://doi.org/10.1016/j.tibtech.2006.03.003>
- Cogem. (2009). *Trendanalyse Biotechnologie 2009* (Issue april).
- Collingridge, D. (1982). *The social control of technology*.
- Coloma, J., Guiavarc'h, Y., Hagedoorn, P. L., & Hanefeld, U. (2020). Probing batch and continuous flow reactions in organic solvents: Granulicella tundricolahalohydroxynitrile lyase (GtHNL). *Catalysis Science and Technology*, 10(11), 3613–3621. <https://doi.org/10.1039/d0cy00604a>
- Coloma, J., Lugtenburg, T., Afendi, M., Lazzarotto, M., Bracco, P., Hagedoorn, P.-L., Gardossi, L., & Hanefeld, U. (2020). Immobilization of Arabidopsis thaliana Hydroxynitrile Lyase (AtHNL) on EziG Opal. *Catalysts*, 10(8), 899. <https://doi.org/10.3390/catal10080899>
- Commission of the European Communities. (2000). *Communication from the Commission on the precautionary principle*. <https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2000:0001:FIN:EN:PDF>
- Council of the EU. (2020). *Vaccine against COVID-19: Council adopts measures to facilitate swift development - Consilium*. <https://www.consilium.europa.eu/en/press/press-releases/2020/07/14/vaccine-against-covid-19-council-adopts-measures-to-facilitate-swift-development/>
- de Graeff, N., Buijsen, M. B., & Bredenoord, A. (2022). *On the nature of nature: A study on the use and meaning of nature and (un)naturalness in the literature on genetic*

- modification. <https://cogem.net/publicatie/on-the-nature-of-nature-a-study-on-the-use-and-meaning-of-nature-and-unnaturalness-in-the-literature-on-genetic-modification/>
- De La Fuente, J. M., Ramírez-Rodríguez, V., Cabrera-Ponce, J. L., & Herrera-Estrella, L. (1997). Aluminum tolerance in transgenic plants by alteration of citrate synthesis. *Science*, 276(5318), 1566–1568. <https://doi.org/https://doi.org/10.1126/science.276.5318.1566>
- De Paepe, M., Leclerc, M., Tinsley, C. R., & Petit, M. A. (2014). Bacteriophages: An underestimated role in human and animal health? *Frontiers in Cellular and Infection Microbiology*, 5(MAR). <https://doi.org/10.3389/FCIMB.2014.00039>
- De Witt, A., Osseweijer, P., & Pierce, R. (2017). Understanding public perceptions of biotechnology through the Integrative Worldview Framework. *Public Understanding of Science*, 26(1), 70–88. <https://doi.org/10.1177/0963662515592364>
- Delhove, J., Osenk, I., Prichard, I., & Donnelley, M. (2020). Public Acceptability of Gene Therapy and Gene Editing for Human Use: A Systematic Review. *Human Gene Therapy*, 31(1–2), 20–46. <https://doi.org/10.1089/hum.2019.197>
- Domingo, J. L., & Nadal, M. (2019). Human exposure to per- and polyfluoroalkyl substances (PFAS) through drinking water: A review of the recent scientific literature. *Environmental Research*, 177, 108648. <https://doi.org/10.1016/J.ENVRES.2019.108648>
- Doorn, N., Schuurbijs, D., Van de Poel, I., & Gorman, M. E. (2013). Early engagement and new technologies: opening up the laboratory. In *Journal of Responsible Innovation* (Vol. 1, Issue 2). <https://doi.org/10.1080/23299460.2014.924240>
- Drohmann, D., & Hernandez, F. (2020). Risk of Regrettable Substitution under EU REACH: Level Playing Field in the EU Regulatory Context. *ICRL - International Chemical Regulatory and Law Review*, 2020. <https://heinonline.org/HOL/Page?handle=hein.journals/icrl2020&id=30&div=&collection=>
- Edwards, D. W. (2005). Are we too risk-averse for inherent safety? An examination of current status and barriers to adoption. *Process Safety and Environmental Protection*, 83(2 B), 90–100. <https://doi.org/10.1205/psep.04309>
- European Commission. (n.d.). *Nanomaterials in REACH and CLP - Environment - European Commission*. Retrieved May 13, 2022, from https://ec.europa.eu/environment/chemicals/nanotech/reach-clp/index_en.htm
- European Commission. (2018). *Statement by the Group of Chief Scientific Advisors A Scientific Perspective on the Regulatory Status of Products Derived from Gene Editing and the Implications for the GMO Directive*. European Commission. <https://curia.europa.eu/jcms/upload/docs/application/pdf/2018->
- European Commission. (2020). *Chemical Strategy for Sustainability: Towards a Toxic-Free Environment*. Communication from the Commission to the European Parliament, The Council, The European Economic and Social Committee and the Committee of the Regions.
- European Court of Justice. (2018). *Court of Justice of the European Union PRESS*

- RELEASE No 111/18. www.curia.europa.eu
- European Medicines Agency. (n.d.). *Benefit-risk methodology*. Retrieved May 10, 2022, from <https://www.ema.europa.eu/en/about-us/what-we-do/regulatory-science-research/benefit-risk-methodology>
- European Union. (2017). *The precautionary principle: decision-making under uncertainty* (Issue 18). <https://doi.org/10.2779/709033>
- Evans, D. F., Pye, G., Bramley, R., Clark, A. G., Dyson, J., & Hardcastle, J. D. (1988). Measurement of gastrointestinal pH profiles in normal ambulant human subjects. *Gut*, 29(8), 1035–1041. <https://doi.org/10.1136/gut.29.8.1035>
- Fahlquist, J. N., Doorn, N., & Van de Poel, I. (2015). Design for the Value of Responsibility. In J. Van den Hoven, P. E. Vermaas, & I. Van de Poel (Eds.), *Handbook of Ethics, Values, and Technological Design* (pp. 473–490). Springer, Dordrecht. https://doi.org/10.1007/978-94-007-6970-0_18
- Flage, R., & Aven, T. (2015). Emerging risk - Conceptual definition and a relation to black swan type of events. *Reliability Engineering and System Safety*, 144, 61–67. <https://doi.org/10.1016/j.ress.2015.07.008>
- Friedman, B. (1996). Value-sensitive design. *Interactions*, 3(6), 16–23. <https://doi.org/10.1145/242485.242493>
- Friedman, B., Borning, A., Davis, J. L., Gill, B. T., Kahn, P. H., Kriplean, T., & Lin, P. (2008). Laying the Foundations for Public Participation and Value Advocacy: Interaction Design for a Large Scale Urban Simulation. *Proceedings of the 2008 International Conference on Digital Government Research*, 305–314.
- Friedman, B., Kahn, P. H., Borning, A., & Hultdtgren, A. (2013). Value Sensitive Design and Information Systems. In N. Doorn, D. Schuurbiers, I. Van de Poel, & M. E. Gorman (Eds.), *Early engagement and new technologies: Opening up the laboratory* (pp. 55–95). https://doi.org/10.1007/978-94-007-7844-3_4
- Fritsche, U., Brunori, G., Chiaramonti, D., Galanakis, C., Hellweg, S., Matthews, R., & Panoutsou, C. (2020). *Future transitions for the bioeconomy towards sustainable development and a climate-neutral economy : knowledge synthesis : final report*. [Publications Office of the European Union, Luxembourg]. <https://doi.org/http://dx.doi.org/10.2760/667966>
- Ganeshan, S. D., & Hosseinidoust, Z. (2019). Phage therapy with a focus on the human microbiota. *Antibiotics*, 8(3). <https://doi.org/10.3390/antibiotics8030131>
- Genus, A., & Stirling, A. (2018). *Collingridge and the dilemma of control: Towards responsible and accountable innovation*. <https://doi.org/10.1016/j.respol.2017.09.012>
- George, D. R., Hornstein, E. D., Clower, C. A., Coomber, A. L., Dillard, D., Mugwanya, N., Pezzini, D. T., & Rozowski, C. (2022). Lessons for a SECURE Future: Evaluating Diversity in Crop Biotechnology Across Regulatory Regimes. *Frontiers in Bioengineering and Biotechnology*, 0, 667. <https://doi.org/10.3389/FBIOE.2022.886765>
- Gibb, B. C. (2022). Sustaining chemistry. *Nature Chemistry*, 14(5), 477–479.

<https://doi.org/10.1038/s41557-022-00938-9>

- Gorter de Vries, A. R., Couwenberg, L. G. F., Van den Broek, M., de la Torre Cortés, P., ter Horst, J., Pronk, J. T., & Daran, J.-M. G. (2019). Allele-specific genome editing using CRISPR–Cas9 is associated with loss of heterozygosity in diploid yeast. *Nucleic Acids Research*, 47(3), 1362–1372. <https://doi.org/10.1093/nar/gky1216>
- Gorter de Vries, A. R., F Couwenberg, L. G., Van den Broek, M., de la Torre Cortés, P., ter Horst, J., Pronk, J. T., & Daran, J.-M. G. (2018). Allele-specific genome editing using CRISPR-Cas9 causes off-1 target mutations in diploid yeast 2. *BioRxiv*, 397984. <https://doi.org/10.1101/397984>
- Gottardo, S., Mech, A., Drbohlavová, J., Malyska, A., Bøwadt, S., Riego Sintes, J., & Rauscher, H. (2021). Towards safe and sustainable innovation in nanotechnology: State-of-play for smart nanomaterials. *NanoImpact*, 21, 100297. <https://doi.org/10.1016/J.IMPACT.2021.100297>
- Grandjean, P. (2018). Delayed discovery, dissemination, and decisions on intervention in environmental health: A case study on immunotoxicity of perfluorinated alkylate substances. *Environmental Health*, 17(1), 1–6. <https://doi.org/10.1186/S12940-018-0405-Y/TABLES/2>
- Groeneweg, J., Mors, ; E Ter, Van Leeuwen, E., & Komen, S. (2018). The Long and Winding Road to a Just Culture. *SPE International Conference and Exhibition on Health, Safety, Security, Environment, and Social Responsibility.*, 16–18. <https://doi.org/10.2118/190594-MS>
- Grohmann, L., Keilwagen, J., Duensing, N., Dagand, E., Hartung, F., Wilhelm, R., Bendiek, J., & Sprink, T. (2019). Detection and identification of genome editing in plants: Challenges and opportunities. *Frontiers in Plant Science*, 10, 236. <https://doi.org/10.3389/FPLS.2019.00236/BIBTEX>
- Grundke, C., & Opatz, T. (2019). Strecker reactions with hexacyanoferrates as non-toxic cyanide sources. *Green Chemistry*, 21(9), 2362–2366. <https://doi.org/10.1039/C9GC00720B>
- Haaf, A., & Hofmann, S. (2020). *MEASURING THE ECONOMIC FOOTPRINT OF THE BIOTECHNOLOGY INDUSTRY IN EUROPE Prepared for EuropaBio-The European Association for Bioindustries*. https://www.europabio.org/wp-content/uploads/2021/02/201208_WifOR_EuropaBIO_Economic_Impact_Biotech_FINAL.pdf
- Hanssen, L., Dijkstra, A. M., Sleenhoff, S., Frewer, L. J., & Gutteling, J. M. (2018). Revisiting public debate on Genetic Modification and Genetically Modified Organisms. Explanations for contemporary Dutch public attitudes. *Journal of Science Communication*, 17(4), A01. <https://doi.org/10.22323/2.17040201>
- Hansson, S. O. (1989). Dimensions of Risk. *Risk Analysis*, 9(1), 107–112. <https://doi.org/10.1111/j.1539-6924.1989.tb01225.x>
- Hansson, S. O. (2009). Risk and Safety in Technology. In A. Meijers (Ed.), *Handbook of the Philosophy of Science. Volume 9: Philosophy of technology and engineering sciences*. (pp. 1069–1102). Elsevier. <https://doi.org/10.1016/B978-0-444-51667-1.50043-4>

- Hansson, S. O. (2016). How to be Cautious but Open to Learning: Time to Update Biotechnology and GMO Legislation. *Risk Analysis*, 36(8), 1513–1517. <https://doi.org/10.1111/risa.12647>
- Hartzell-Nichols, L. (2013). From “the” Precautionary Principle to Precautionary Principles. *Ethics, Policy & Environment*, 16(3), 308–320. <https://doi.org/10.1080/21550085.2013.844569>
- Helsloot, I., Pieterman, R., & Hanekamp, J. C. (2010). *Risico's en redelijkheid. Verkenning naar een rijksbreed beoordelingskader voor de toelaatbaarheid van risico's*.
- Hirota, R., Abe, K., Katsuura, Z. I., Noguchi, R., Moribe, S., Motomura, K., Ishida, T., Alexandrov, M., Funabashi, H., Ikeda, T., & Kuroda, A. (2017). A Novel Biocontainment Strategy Makes Bacterial Growth and Survival Dependent on Phosphite. *Scientific Reports* 2017 7:1, 7(1), 1–10. <https://doi.org/10.1038/srep44748>
- Hof, F., Craig, S., Nuckolls, C., & Rebek, J. (2002). Molecular encapsulation. *Angewandte Chemie International Edition*, 41(9), 1488–1508.
- Hoffman, N. E. (2021). Revisions to USDA biotechnology regulations: The SECURE rule. *Proceedings of the National Academy of Sciences*, 118(22). <https://doi.org/10.1073/pnas.2004841118>
- Hogervorst, P. A. M., Van den Akker, H. C. M., Glandorf, D. C. M., Klaassen, P., Van der Vlugt, C. J. B., & Westra, J. (2017). *Beoordeling van risico's voor mens en milieu van nieuwe ontwikkelingen in de moderne biotechnologie*. <https://www.rivm.nl/bibliotheek/rapporten/2017-0178.html>
- Hopster, J. (2021). Climate Uncertainty, Real Possibilities and the Precautionary Principle. *Erkenntnis* 2021, 1–17. <https://doi.org/10.1007/S10670-021-00461-2>
- iGEM Foundation. (n.d.-a). *iGEM*. Retrieved June 23, 2022, from <https://igem.org/>
- iGEM Foundation. (n.d.-b). *Impact/Beyond-The-Lab - igem.org*. Retrieved February 8, 2022, from <https://old.igem.org/Impact/Beyond-The-Lab>
- iGEM Foundation. (2021a). *iGEM Giant Jamboree*. <https://jamboree.igem.org/>
- iGEM Foundation. (2021b). *Safety.igem.org*. <https://2021.igem.org/Safety>
- IRGC. (2017). Introduction to the IRGC Risk Governance Framework, revised version. *Lausanne: EPFL International Risk Governance Center*. <https://doi.org/10.5075/epfl-irgc-233739>
- IRGC. (2019). *Risk Governance*. <https://irgc.org/risk-governance/what-is-risk-governance/>
- Iriarte, F. B., Balogh, B., Momol, M. T., Smith, L. M., Wilson, M., & Jones, J. B. (2007). Factors affecting survival of bacteriophage on tomato leaf surfaces. *Am Soc Microbiol*, 73(6), 1704–1711. <https://doi.org/10.1128/AEM.02118-06>
- Jacobs, J. F., Van de Poel, I., & Osseweijer, P. (2010). Sunscreens with Titanium Dioxide (TiO₂) Nano-Particles: A Societal Experiment. *NanoEthics* 2010 4:2, 4(2), 103–113. <https://doi.org/10.1007/S11569-010-0090-Y>
- Jelsma, J. (1995). Learning about learning in the development of biotechnology. In

- Managing Technology in Society* (pp. 141–165).
<https://www.narcis.nl/publication/RecordID/oai:ris.utwente.nl:publications%2F244a5f00-6c0e-4ef7-9eba-e2f074c5048e>
- Jha, C. K., Aeron, A., Patel, B. V., Maheshwari, D. K., & Saraf, M. (2011). Enterobacter: Role in Plant Growth Promotion. *Bacteria in Agrobiolgy: Plant Growth Responses*, 159–182. https://doi.org/10.1007/978-3-642-20332-9_8
- Jończyk, E., Kłak, M., Międzybrodzki, R., & Górski, A. (2011). The influence of external factors on bacteriophages-review. *Folia Microbiologica*, 56(3), 191–200. <https://doi.org/10.1007/S12223-011-0039-8>
- Jutsum, A., Heaney, S., Perrin, B., & Wege, P. (1998). Pesticide resistance: assessment of risk and the development and implementation of effective management strategies. *Pesticide Science*, 54(4), 435–446. [https://doi.org/10.1002/\(SICI\)1096-9063\(199812\)54:4%3C435::AID-PS844%3E3.0.CO;2-K](https://doi.org/10.1002/(SICI)1096-9063(199812)54:4%3C435::AID-PS844%3E3.0.CO;2-K)
- Kafarski, P. (2012). Rainbow code of biotechnology. *Chemik*, 66(8), 811–816.
- Kallergi, A., & Asveld, L. (2021). *Perceptions of Safe-by-Design for biotechnology*. <https://doi.org/http://dx.doi.org/10.13140/RG.2.2.24999.62889>
- Kapuscinski, A. R., Goodman, R. M., Hann, S. D., Jacobs, L. R., Pullins, E. E., Johnson, C. S., Kinsey, J. D., Krall, R. L., La Viña, A. G., Mellon, M. G., & Ruttan, V. W. (2003). Making “safety first” a reality for biotechnology products. *Nature Biotechnology* 2003 21:6, 21(6), 599–601. <https://doi.org/10.1038/nbt0603-599>
- Karkman, A., Do, T. T., Walsh, F., & Virta, M. P. J. (2018). Antibiotic-Resistance Genes in Waste Water. *Trends in Microbiology*, 26(3), 220–228. <https://doi.org/10.1016/J.TIM.2017.09.005>
- Keim, W. (2012). *Catalysis in C1 chemistry* (W. Keim (Ed.)). Springer Science & Business Media.
- Kelty, C. M. (2009). Beyond Implications and Applications: the Story of “Safety by Design.” *NanoEthics*, 3, 79–96. <https://doi.org/10.1007/s11569-009-0066-y>
- Kermisch, C. (2012). Risk and Responsibility: A Complex and Evolving Relationship. *Science and Engineering Ethics*, 18(1), 91–102. <https://doi.org/10.1007/s11948-010-9246-y>
- Khan, F. I., & Amyotte, P. R. (2003). How to Make Inherent Safety Practice a Reality. *The Canadian Journal of Chemical Engineering*, 81(1), 2–16. <https://doi.org/10.1002/cjce.5450810101>
- Kinderlerer, J. (2004). The regulatory system in the EU and further afield. *Journal of Commercial Biotechnology*, 10(3), 248–257. <https://doi.org/10.1057/palgrave.jcb.3040080>
- Kletz, T. . (1996). Inherently Safer Design: The Growth of an Idea. *Process Safety Progress*, 15(1), 5–8. <https://onlinelibrary.wiley.com/doi/pdf/10.1002/prs.680150105>
- Kletz, T. A. (2003). INHERENTLY SAFER DESIGN ITS SCOPE AND FUTURE. *Process Safety and Environmental Protection*, 81(6), 401–405.

- <https://doi.org/10.1205/095758203770866566>
- Knapland, K. S., & Knaplund, K. S. (2011). Synthetic Cells, Synthetic Life, and Inheritance. *Valparasio University Law Review*, 45, 47–72. <https://scholar.valpo.edu/vulr/vol45/iss4/3>
- Kraegeloh, A., Suarez-merino, B., Sluijters, T., & Micheletti, C. (2018). Implementation of Safe-by-Design for Nanomaterial Development and Safe Innovation : Why We Need a Comprehensive Approach. *Nanomaterials*, 8(4), 239. <https://doi.org/10.3390/nano8040239>
- Krimsky, S. (2005). From asilomar to industrial biotechnology: Risks, reductionism and regulation. *Science as Culture*, 14(4), 309–323. <https://doi.org/10.1080/09505430500368998>
- Krouwel, S. J. C., Dierickx, E. R., Heesterbeek, S., & Klaassen, P. (2022). Adopting Safe-by-Design in Science and Engineering Academia: The Soil May Need Tilling. *International Journal of Environmental Research and Public Health*, 19(4), 2075. <https://doi.org/10.3390/ijerph19042075>
- Kupferschmidt, K. (2018). EU verdict on CRISPR crops dismays scientists. *Science (New York, N.Y.)*, 361(6401), 435–436. <https://doi.org/10.1126/science.361.6401.435>
- Kutter, E., & Sulakvelidze, A. (2004). *Bacteriophages: biology and applications* (E. Kutter & A. Sulakvelidze (Eds.)). Crc Press. <https://www.taylorfrancis.com/books/mono/10.1201/9780203491751/bacteriophages-elizabeth-kutter-alexander-sulakvelidze>
- Law, K. L., & Thompson, R. C. (2014). Microplastics in the seas. *Science*, 345(6193), 144–145. <https://doi.org/https://doi.org/10.1126/science.1254065>
- Ledford, H., & Callaway, E. (2020). Pioneers of revolutionary CRISPR gene editing win chemistry Nobel. *Nature*, 586(7829), 346–347. <https://doi.org/10.1038/D41586-020-02765-9>
- Lin, X., Li, Y., Li, Z., Hua, R., Xing, Y., Advances, Y. L.-R., & 2020, U. (2020). Portable environment-signal detection biosensors with cell-free synthetic biosystems. *Royal Society of Chemistry Advances*, 10(64), 39261–39265. <https://doi.org/10.1039/D0RA05293K>
- Linkov, I., Trump, B. D., Anklam, E., Berube, D., Boisseasu, P., Cummings, C., Ferson, S., Florin, M. V., Goldstein, B., Hristozov, D., Jensen, K. A., Katalagarianakis, G., Kuzma, J., Lambert, J. H., Malloy, T., Malsch, I., Marcomini, A., Merad, M., Palma-Oliveira, J., ... Vermeire, T. (2018). Comparative, collaborative, and integrative risk governance for emerging technologies. *Environment Systems and Decisions*, 38(2), 170–176. <https://doi.org/10.1007/s10669-018-9686-5>
- Liu, Y., Jiang, X., Cui, Z., Wang, Z., Qi, Q., & Hou, J. (2019). Engineering the oleaginous yeast *Yarrowia lipolytica* for production of α -farnesene. *Biotechnology for Biofuels* 2019 12:1, 12(1), 1–11. <https://doi.org/10.1186/S13068-019-1636-Z>
- Locke, L. G. (2020). The Promise of CRISPR for Human Germline Editing and the Perils of “Playing God.” *The CRISPR Journal*, 3(1), 27–31. <https://doi.org/10.1089/CRISPR.2019.0033>

- Logan, D. C. (2009). Known knowns, known unknowns, unknown unknowns and the propagation of scientific enquiry. *Journal of Experimental Botany*, 60(3), 712–714. <https://doi.org/10.1093/JXB/ERP043>
- Löwe, H., & Ehrfeld, W. (1999). State-of-the-art in microreaction technology: concepts, manufacturing and applications. *Electrochimica Acta*, 44(21–22), 3679–3689. [https://doi.org/10.1016/S0013-4686\(99\)00071-7](https://doi.org/10.1016/S0013-4686(99)00071-7)
- Manson, N. A. (2002). Formulating the precautionary principle. *Environmental Ethics*, 24(3), 263–274.
- Marchant, G., & Mossman, K. (2004). *Arbitrary and capricious: The precautionary principle in the European Union courts*. American Enterprise Institute.
- Maurer, S., Lucas, K., & Terrell, S. (2006). From understanding to action: Community-based options for improving safety and security in synthetic biology. In *Berkely: University of California*.
- Maxwell, J., & Briscoe, F. (1997). There's money in the air: The CFC Ban and Dupont's regulatory strategy. *Business Strategy and the Environment*, 6(5), 276–286. [https://doi.org/10.1002/\(SICI\)1099-0836\(199711\)6:5](https://doi.org/10.1002/(SICI)1099-0836(199711)6:5)
- Maynard, A. D., Aitken, R. J., Butz, T., Colvin, V., Donaldson, K., Oberdörster, G., Philbert, M. A., Ryan, J., Seaton, A., Stone, V., Tinkle, S. S., Tran, L., Walker, N. J., & Warheit, D. B. (2006). Safe handling of nanotechnology. *Nature*, 444(7117), 267–269. <https://doi.org/10.1038/444267a>
- Mehlich, J., Moser, F., Van Tiggelen, B., Campanella, L., & Hopf, H. (2017). The Ethical and Social Dimensions of Chemistry: Reflections, Considerations, and Clarifications. *Chemistry - A European Journal*, 23(6), 1210–1218. <https://doi.org/10.1002/CHEM.201605259>
- Merad, M. (2020). Highlights on the Risk Governance for Key Enabling Technologies: From Risk Denial to Ethics. In *Synthetic Biology 2020: Frontiers in Risk Analysis and Governance* (pp. 399–408). https://doi.org/10.1007/978-3-030-27264-7_18
- Miller, J. K., Friedman, B., Jancke, G., & Gill, B. (2007). Value tensions in design: The value sensitive design, development, and appropriation of a corporation's groupware system. *GROUP'07 - Proceedings of the 2007 International ACM Conference on Supporting Group Work*, 281–290. <https://doi.org/10.1145/1316624.1316668>
- Millett, P., Isaac, C. R., Rais, I., & Rutten, P. (2020). The synthetic-biology challenges for biosecurity: examples from iGEM. *Nonproliferation Review*, 27(4–6), 443–458. <https://doi.org/10.1080/10736700.2020.1866884>
- Ministerie van Infrastructuur en Milieu. (2014). Besluit genetisch gemodificeerde organismen milieubeheer 2013. In *Staatsblad 2014, nr 157*.
- Ministerie van Infrastructuur en Waterstaat. (2019). *Voortgangsbrieven modernisering veiligheidsbeleid biotechnologie*.
- National Institute for Public Health and the Environment. (n.d.). *Gene Therapy Office*. Retrieved May 10, 2022, from <https://loketgentherapie.nl/en/gene-therapy-office/history>

- Nau, K., & Scholz, S. G. (2019). Safe by Design in 3D printing. *Safe By Design in 3D Printing*, 341–350. <https://doi.org/10.1007/978-981-13-9271-9>
- Ndoh, C., Cummings, C. L., & Kuzma, J. (2020). The Role of Expert Disciplinary Cultures in Assessing Risks and Benefits of Synthetic Biology. In *Synthetic Biology 2020: Frontiers in Risk Analysis and Governance* (pp. 351–370). Springer, Cham. https://doi.org/10.1007/978-3-030-27264-7_15
- Nester, E., Thomashow, L., Metz, M., & Gordon, M. (2002). 100 Years of *Bacillus thuringiensis*: A Critical Scientific Assessment. *American Society for Microbiology, Washington DC*. <http://europemc.org/books/NBK559445>
- Nobrega, F. L., Rita Costa, A., Santos, J. F., Siliakus, M. F., Van Lent, J. W. M., Kengen, S. W. M., Azeredo, J., & Kluskens, L. D. (2016). Genetically manipulated phages with improved pH resistance for oral administration in veterinary medicine. *Scientific Reports*, 6(1), 1–12. <https://doi.org/10.1038/srep39235>
- NOS. (2021). *Nederland zet met vier andere landen eerste stap naar PFAS-verbod*. <https://nos.nl/artikel/2389382-nederland-zet-met-vier-andere-landen-eerste-stap-naar-pfas-verbod>
- Pardee, K., Green, A. A., Ferrante, T., Cameron, D. E., Daleykeyser, A., Yin, P., & Collins, J. J. (2014). Paper-based synthetic gene networks. *Cell*, 159(4), 940–954. <https://doi.org/10.1016/J.CELL.2014.10.004/ATTACHMENT/6FCFDFA4-CB11-4B7A-A72C-2769499AEC77/MMC2.XLSX>
- Pardo-Lopez, L., Soberon, M., & Bravo, A. (2013). *Bacillus thuringiensis* insecticidal three-domain Cry toxins: mode of action, insect resistance and consequences for crop protection. *FEMS Microbiology Reviews*, 37(1), 3–22. <https://doi.org/10.1111/j.1574-6976.2012.00341.x>
- Parisi, C., & Rodriguez Cerezo, E. (2021). *Current and future market applications of new genomic techniques*. <https://doi.org/10.2760/02472>
- Paul, J., & Jiang, S. (2001). Lysogeny and transduction. *Methods in Microbiology*, 30, 105–125. [https://doi.org/10.1016/S0580-9517\(01\)30042-9](https://doi.org/10.1016/S0580-9517(01)30042-9)
- Peacock, K. W. (2010). *Biotechnology and genetic engineering*. Infobase Publishing. <https://books.google.com/books?hl=en&lr=&id=GwpsVDKQcSUC&oi=fnd&pg=PP1&ots=j7Ui4ALOME&sig=oQKLCepeE1ITzIMwTs5UAQXpGIw>
- Persson, L., Almroth, B. M. C., Collins, C. D., Cornell, S., Wit, C. A. de, Diamond, M. L., Fantke, P., Hassellöv, M., MacLeod, M., Ryberg, M. W., Jørgensen, P. S., Villarrubia-Gómez, P., Wang, Z., & Hauschild, M. Z. (2022). Outside the safe operating space of the planetary boundary for novel entities. *Environmental Science & Technology*, 56(3), 1510–1521. <https://doi.org/10.1021/ACS.EST.1C04158>
- Powell, M. C. (2007). New risk or old risk, high risk or no risk? How scientists' standpoints shape their nanotechnology risk frames. *Health, Risk & Society*, 9(2), 173–190. <https://doi.org/10.1080/13698570701306872>
- Purnhagen, K. P., Kok, E., Kleter, G., Schebesta, H., F Visser, R. G., & Wesseler, J. (2018). *The European Union Court's Advocate General's Opinion and new plant breeding techniques*. <https://doi.org/10.1038/nbt.4174>

- Regårdh, P. (2011). *Safe, secure and ethical?: assessing and regulating risks associated with synthetic biology* [Doctoral Dissertation, Massachusetts Institute of Technology, Boston (MA), USA]. <https://dspace.mit.edu/handle/1721.1/65509>
- Reibstein, R. (2017). A more ethical chemistry. *Current Opinion in Green and Sustainable Chemistry*, 8, 36–44. <https://doi.org/10.1016/J.COGSC.2017.09.004>
- Reniers, G. L. L., Ale, B. J. M., Dullaert, W., & Soudan, K. (2009). Designing continuous safety improvement within chemical industrial areas. *Safety Science*, 47(5), 578–590. <https://doi.org/10.1016/J.SSCI.2008.07.003>
- Renn, O., & Walker, K. (2008). Global risk governance. Concept and Practice using the IRGC framework. In O. Renn & K. Walker (Eds.), *Springer International*. <https://link.springer.com/content/pdf/10.1007/978-1-4020-6799-0.pdf>
- Rerimassie, V., Stermerding, D., de Bakker, E., & Van Est, R. (2018). *Beyond public acceptance: Design of a societal incubator for promising (nano)technologies*. [https://www.rathenau.nl/sites/default/files/2018-07/Beyond Public Acceptance_1.pdf](https://www.rathenau.nl/sites/default/files/2018-07/Beyond%20Public%20Acceptance_1.pdf)
- RIVM. (n.d.-a). *Education and Safe by Design | Biotechnologie*. Retrieved February 17, 2022, from <https://biotechnologie.rivm.nl/safe-by-design>
- RIVM. (n.d.-b). *koolmonoxide | | Risico's van stoffen*. Retrieved February 17, 2021, from <https://rvszoeksysteem.rivm.nl/stof/detail/859>
- RIVM. (n.d.-c). *waterstofcyanide | | Risico's van stoffen*. Retrieved February 17, 2021, from <https://rvszoeksysteem.rivm.nl/stof/detail/1325>
- Robaey, Z. (2018). *Dealing with risks of biotechnology : understanding the potential of Safe-by-Design* [Report commissioned by the Dutch Ministry of Infrastructure and Water Management, The Hague, The Netherlands]. <https://doi.org/10.13140/RG.2.2.13725.97769>
- Robaey, Z., Spruit, S., & Van de Poel, I. (2017). The Food Warden: An Exploration of Issues in Distributing Responsibilities for Safe-by-Design Synthetic Biology Applications. *Science and Engineering Ethics*. <https://doi.org/10.1007/s11948-017-9969-0>
- Rossant, J. (2018). Gene editing in human development: Ethical concerns and practical applications. *Development (Cambridge)*, 145(16 Special Issue), 2017–2019. <https://doi.org/10.1242/dev.150888>
- Rusli, R., Shariff, A. M., & Khan, F. I. (2013). Evaluating hazard conflicts using inherently safer design concept. *Safety Science*. <https://doi.org/10.1016/j.ssci.2012.09.002>
- Rutherford, W. (2003). Aviation safety: a model for health care? *Quality and Safety in Health Care*, 12(3), 162. <https://doi.org/10.1136/qhc.12.3.162>
- Ryan, P. R., Dessaux, Y., Thomashow, L. S., Weller, D. M., Ryan, P. R., Dessaux, Y., Thomashow, L. S., & Weller, D. M. (2009). Rhizosphere engineering and management for sustainable agriculture. *Plant and Soil* 2009 321:1, 321(1), 363–383. <https://doi.org/10.1007/S11104-009-0001-6>
- Sandin, P., & Peterson, M. (2019). Is the Precautionary Principle a Midlevel Principle?

- Ethics, Policy & Environment*, 22(1), 34–48.
<https://doi.org/10.1080/21550085.2019.1581417>
- Sandin, P., Peterson, M., Hansson, S. O., Rudén, C., & Juthe, A. (2002). Five charges against the precautionary principle. *Journal of Risk Research*, 5(4), 287–299.
<https://doi.org/10.1080/13669870110073729>
- Sarewitz, D. (2020). Unknown knowns. *Issues in Science and Technology*, 37(1), 18–19.
- Schmerer, M., Molineux, I. J., Ally, D., Tyerman, J., Cecchini, N., & Bull, J. J. (2014). Challenges in predicting the evolutionary maintenance of a phage transgene. *Journal of Biological Engineering*, 8(1), 21. <https://doi.org/10.1186/1754-1611-8-21>
- Schmidt, M., Dando, M., & Deplazes, A. (2011). Dealing with the outer reaches of synthetic biology biosafety, biosecurity, IPR and ethical challenges of chemical synthetic biology. *Chemical Synthetic Biology*, 321–342.
<https://onlinelibrary.wiley.com/doi/pdf/10.1002/9780470977873#page=323>
- Schmidt, Markus. (2008). Diffusion of synthetic biology: A challenge to biosafety. *Systems and Synthetic Biology*, 2(1–2), 1–6. <https://doi.org/10.1007/s11693-008-9018-z>
- Schultz-Bergin, M. (2018). Is CRISPR an Ethical Game Changer? *Journal of Agricultural and Environmental Ethics* 2018 31:2, 31(2), 219–238.
<https://doi.org/10.1007/S10806-018-9721-Z>
- Schwarz-Plaschg, C., Kallhoff, A., & Eisenberger, I. (2017). Making Nanomaterials Safer by Design? *NanoEthics*, 11(3), 277–281. <https://doi.org/10.1007/s11569-017-0307-4>
- Scudellari, M. (2019). Hijacking Evolution. *Nature*, 571, 160–162.
<https://doi.org/10.1093/iclqaj/22.1.183>
- SGS Agriculture and Food. (2020). *What Effect Will the US Reduction in Biotechnology Regulations Have on Food Exports?* | SGS.
<https://www.sgs.com/en/news/2020/06/what-effect-will-the-us-reduction-in-biotechnology-regulations-have-on-food-exports>
- Shih, P. M., Vuu, K., Mansoori, N., Ayad, L., Louie, K. B., Bowen, B. P., Northen, T. R., & Loqué, D. (2016). A robust gene-stacking method utilizing yeast assembly for plant synthetic biology. *Nature Communications* 2016 7:1, 7(1), 1–8.
<https://doi.org/10.1038/ncomms13215>
- Sie, S. T. (1996). Miniaturization of Hydroprocessing Catalyst Testing Systems: Theory and Practice. *AIChE Journal*, 42(12), 3498–3507. <https://doi.org/10.1002/aic.690421219>
- Singh, N. (2009). On a wing and a prayer: surgeons learning from the aviation industry. *Journal of the Royal Society of Medicine*, 102(9), 360–364.
<https://doi.org/10.1258/jrsm.2009.090139>
- Slootweg, J. C. (2020). Using waste as resource to realize a circular economy: Circular use of C, N and P. *Current Opinion in Green and Sustainable Chemistry*, 23, 61–66.
<https://doi.org/10.1016/J.COGLSC.2020.02.007>
- Sonck, M., Asveld, L., & Osseweijer, P. (2020). Meta-Responsibility in Corporate Research and Innovation : A Bioeconomic Case Study. *Sustainability*, 12(1), 38.

- <https://doi.org/https://doi.org/10.3390/su12010038>
- Song, L., Gao, M., Dai, S., Wu, Y., Yi, D., & Li, R. (2008). Specific activity of a *Bacillus thuringiensis* strain against *Locusta migratoria manilensis*. *Journal of Invertebrate Pathology*, 98(2), 169–176. <https://doi.org/10.1016/j.jip.2008.02.006>
- Soucy, S., Huang, J., Genetics, J. G.-N. R., & 2015, U. (2015). Horizontal gene transfer: building the web of life. *Nature Reviews Genetics*, 16(8), 472–482. <https://doi.org/10.1038/nrg3962>
- Stankiewicz, A. I., & Moulijn, J. A. (2000). Process intensification: Transforming Chemical Engineering. *Chemical Engineering Progress, January*, 22–34. https://doi.org/10.1007/978-3-319-26695-4_34
- Stemerding, D. (2015). iGEM as laboratory in responsible research and innovation. *Journal of Responsible Innovation*, 2(1), 140–142. <https://doi.org/10.1080/23299460.2014.1002171>
- Stemerding, D., & de Vriend, H. (2018). Nieuwe risico's, nieuwe aanpak. *Milieu*, 10–11.
- Stirling, A. (2007). Risk, precaution and science: towards a more constructive policy debate. Talking point on the precautionary principle. *EMBO Reports*, 8(4), 309–315. <https://doi.org/10.1038/sj.embor.7400953>
- Stirling, A., Renn, O., Klinke, A., Rip, A., & Salo, A. (1999). *On science and precaution in the management of technological risk. Volume 1 - A synthesis report of case studies*. <http://agris.fao.org/agris-search/search.do?recordID=GB2013202687>
- Strodder, C. (2020). The “Forever” Chemicals: PFAS and the Maritime Industry. *Australian and New Zealand Maritime Law Journal*, 34, 60. <https://heinonline.org/HOL/Page?handle=hein.journals/ausnewma34&id=60&div=&collection=>
- Sweetman, A. (2020). A grand challenge for environmental organic chemistry: how can we avoid regrettable substitution? *Frontiers in Environmental Chemistry*, 1(7). <https://doi.org/10.3389/FENV.2020.00007>
- Swuste, P., Groeneweg, J., van Gulijk, C., Zwaard, W., Lemkowitz, S., & Oostendorp, Y. (2020). The future of safety science. In *Safety Science* (Vol. 125, p. 104593). Elsevier B.V. <https://doi.org/10.1016/j.ssci.2019.104593>
- Tagliabue, G. (2015). The nonsensical GMO pseudo-category and a precautionary rabbit hole. *Nature Biotechnology*, 33(9), 907–908. <https://doi.org/10.1038/nbt.3333>
- Tagliabue, G. (2016). The Precautionary principle: its misunderstandings and misuses in relation to “GMOs.” *New Biotechnology*, 33(4), 437–439. <https://doi.org/10.1016/J.NBT.2016.02.007>
- Taleb, N. N., Read, R., Douady, R., Norman, J., & Bar-Yam, Y. (2014). *The Precautionary Principle (with Application to the Genetic Modification of Organisms)*. <http://arxiv.org/abs/1410.5787>
- Team:TU Delft/Model/Toxin Production - 2020.igem.org. (n.d.). Retrieved February 18, 2022, from https://2020.igem.org/Team:TU Delft/Model/Toxin_Production

- The Republic of Uganda - Ministry of Health. (2009). *Making Medical Injections Safer (MMIS) Project - Approaches to health care waste management*.
<https://www.health.go.ug/docs/Approaches for HCWM 2009.pdf>
- Trump, B. D., Cegan, J., Wells, E., Poinssatte-Jones, K., Rycroft, T., Warner, C., Martin, D., Perkins, E., Wood, M. D., & Linkov, I. (2019). Co-evolution of physical and social sciences in synthetic biology. *Critical Reviews in Biotechnology*, 39(3), 351–365.
<https://doi.org/10.1080/07388551.2019.1566203>
- TU Delft iGEM AptaVita. (2021a). *Team: TUDelft/Safety - 2021.igem.org*.
<https://2021.igem.org/Team:TUDelft/Safety#Safe-by-Design>
- TU Delft iGEM AptaVita. (2021b). *TUDelft: AptaVita (2021) - Project Promotion [English] - iGEM Video Universe*. <https://video.igem.org/w/wet5194egUCbH7ay4ka6bQ>
- TU Delft iGEM PHOCUS. (2020a). *Team: TUDelft2020/Safety*.
<https://2020.igem.org/Team:TUDelft/Safety#safety>
- TU Delft iGEM PHOCUS. (2020b). *TUDelft: PHOCUS (2020) - Project Promotion Video [English] - iGEM Video Universe*.
<https://video.igem.org/w/arSaDiV4GkH5CMV3AGFY96>
- Turney, R. D. (2001). Inherent Safety: What can be done to increase the use of the concept. *HJ Pasman: Loss Prevention and Safety Promotion in the Process Industries - 10th International Symposium*, 519–528.
- U.S. Environmental Protection Agency. (2000). *Health Data from Inhalation Exposure - Pyrocatechol*. <https://www.epa.gov/sites/default/files/2016-09/documents/catechol-pyrocatechol.pdf>
- UI Haq, I., Chaudhry, W. N., Akhtar, M. N., Andleeb, S., & Qadri, I. (2012). Bacteriophages and their implications on future biotechnology: A review. *Virology Journal*, 9(1).
<https://doi.org/10.1186/1743-422X-9-9>
- United Nations. (1992). The Rio Declaration on Environment and Development. In *The United Nations Conference on Environment and Development*.
https://doi.org/10.1007/978-1-4020-9160-5_648
- Van Asselt, M. B. A., & Renn, O. (2011). Risk governance. *Journal of Risk Research*, 14(4), 1466–1461. <https://doi.org/10.1080/13669877.2011.553730>
- Van Asselt, M. B. A., & Vos, E. (2006). The Precautionary Principle and the Uncertainty Paradox. *Journal of Risk Research*, 9(4), 313–336.
<https://doi.org/10.1080/13669870500175063>
- Van Asselt, M. B. A., & Vos, E. (2008). Wrestling with uncertain risks: EU regulation of GMOs and the uncertainty paradox. *Journal of Risk Research*, 11(1–2), 281–300.
<https://doi.org/10.1080/13669870801990806>
- Van Asselt, M., & Renn, O. (2011). Risk Governance. *Journal of Risk Research*, 14(4), 431–449. <https://doi.org/10.1080/13669877.2011.553730>
- Van Asselt, M., & Vos, E. (2008). Wrestling with uncertain risks: EU regulation of GMOs and the uncertainty paradox. *Journal of Risk Research*, 11(1–2), 281–300.

<https://doi.org/10.1080/13669870801990806>

- Van de Poel, Ibo. (2011). The Relation Between Forward-Looking and Backward-Looking Responsibility. In N. A. Vincent, I. Van de Poel, & J. Van den Hoven (Eds.), *Moral Responsibility* (pp. 37–52). Springer. https://doi.org/10.1007/978-94-007-1878-4_3
- Van de Poel, Ibo. (2013). Translating Values into Design Requirements. In D. P. Michelfelder, N. McCarthy, & D. E. Goldberg (Eds.), *Philosophy and Engineering : Reflections on Practice , Principles and Process* (pp. 253–277). Springer, Dordrecht.
- Van de Poel, Ibo. (2015). Conflicting Values in Design for Values. In J. Van den Hoven, P. E. Vermaas, & I. Van de Poel (Eds.), *Handbook of Ethics, Values, and Technological Design: Sources, Theory, Values and Application Domains* (pp. 89–116). Springer, Dordrecht. https://doi.org/10.1007/978-94-007-6970-0_5
- Van de Poel, Ibo. (2017). Society as a Laboratory to Experiment with New Technologies. In D. M. Bowman, E. Stokes, & A. Rip (Eds.), *Embedding new technologies into society: A regulatory, Ethical and Societal Perspective* (pp. 978–981).
- Van de Poel, Ibo, Fahlquist, J. N., Doorn, N., Zwart, S., & Royakkers, L. (2012). The Problem of Many Hands: Climate Change as an Example. *Science and Engineering Ethics*, 18(1), 49–67. <https://doi.org/10.1007/S11948-011-9276-0>
- Van de Poel, Ibo, & Nihlen-Fahlquist, J. (2012). Risk and Responsibility. In S. Roeser, R. Hillerbrand, M. Peterson, & P. Sandin (Eds.), *Handbook of Risk Theory: Epistemology, Decision Theory, Ethics, and Social Implications of Risk* (pp. 878–907). Springer. <https://doi.org/10.1007/978-94-007-1433-5>
- Van de Poel, Ibo, & Robaey, Z. (2017). Safe-by-Design: from Safety to Responsibility. *NanoEthics*, 1–10. <https://doi.org/10.1007/s11569-017-0301-x>
- Van de Poel, Ibo, Royakkers, L., & Zwart, S. D. (2015). Moral responsibility and the problem of many hands. In I. Van de Poel, L. M. Royakkers, & S. D. Zwart (Eds.), *Moral Responsibility and the Problem of Many Hands*. Taylor and Francis Inc. <https://doi.org/10.4324/9781315734217>
- Van den Hoven, J. (2013). Value Sensitive Design and Responsible Innovation. In R. Owen, J. Bessant, & M. Heintz (Eds.), *Responsible Innovation: Managing the Responsible Emergence of Science and Innovation in Society* (pp. 75–83). John Wiley and Sons. <https://doi.org/10.1002/9781118551424.CH4>
- Van der Berg, J. P., Kleter, G. A., Battaglia, E., Bouwman, L. M. S., & Kok, E. J. (2020). Application of the Safe-By-Design Concept in Crop Breeding Innovation. *International Journal of Environmental Research and Public Health*, 17(17), 6420. <https://doi.org/10.3390/ijerph17176420>
- Van der Helm, M. P., Bracco, P., Busch, H., Szymańska, K., Jarzębski, A. B., & Hanefeld, U. (2019). Hydroxynitrile lyases covalently immobilized in continuous flow microreactors. *Catalysis Science and Technology*, 9(5), 1189–1200. <https://doi.org/10.1039/c8cy02192a>
- Van Gelder, P., Klaassen, P., Taebe, B., Walhout, B., van Ommen, R., Van de Poel, I., Robaey, Z., Asveld, L., Balkenende, R., Hollmann, F., van Kampen, E. J., Khakzad, N., Krebbers, R., de Lange, J., Pieters, W., Terwel, K., Visser, E., Van der Werff, T., &

- Jung, D. (2021). Safe-by-design in engineering: An overview and comparative analysis of engineering disciplines. *International Journal of Environmental Research and Public Health*, 18(12), 6329. <https://doi.org/10.3390/ijerph18126329>
- Van Gorp, A., & Van de Poel, I. (2001). Ethical considerations in engineering design processes. *IEEE Technology and Society Magazine*, 20(3), 15–22. <https://doi.org/10.1109/44.952761>
- Van Haperen, P. F., Gremmen, B., & Jacobs, J. (2011). Reconstruction of the Ethical Debate on Naturalness in Discussions About Plant-Biotechnology. *Journal of Agricultural and Environmental Ethics* 2011 25:6, 25(6), 797–812. <https://doi.org/10.1007/S10806-011-9359-6>
- Vennis, I. M., Schaap, M. M., Hogervorst, P. A. M., de Bruin, A., Schulpen, S., Boot, M. A., van Passel, M. W. J., Rutjes, S. A., & Bleijs, D. A. (2021). Dual-Use Quicksan: A Web-Based Tool to Assess the Dual-Use Potential of Life Science Research. *Frontiers in Bioengineering and Biotechnology*, 9, 1156. <https://doi.org/10.3389/FBIOE.2021.797076/BIBTEX>
- Ventura, M., Sozzi, T., Turrone, F., Matteuzzi, D., & Van Sinderen, D. (2011). The impact of bacteriophages on probiotic bacteria and gut microbiota diversity. *Genes and Nutrition*, 6(3), 205–207. <https://doi.org/10.1007/S12263-010-0188-4>
- Verheust, C., Pauwels, K., Mahillon, J., Helinski, D. R., & Herman, P. (2010). Contained use of Bacteriophages: Risk Assessment and Biosafety Recommendations. *Applied Biosafety*, 15(1), 32–44. <https://doi.org/10.1177/153567601001500106>
- von Schomberg, R. (2013). A Vision of Responsible Research and Innovation. In *In: R. Owen, M. Heintz and J Bessant (eds.) Responsible Innovation* (pp. 51–74). London: John Wiley, forthcoming. <http://onlinelibrary.wiley.com/doi/10.1002/9781118551424.ch3/summary>
- Wagner, W. E. (2000). The Precautionary Principle and Chemical Regulation in the U.S. *Human and Ecological Risk Assessment: An International Journal*, 6(3), 459–477. <https://doi.org/10.1080/10807030091124572>
- Walker, T. S., Bais, H. P., Grotewold, E., & Vivanco, J. M. (2003). Root Exudation and Rhizosphere Biology. *Plant Physiology*, 132(1), 44–51. <https://doi.org/10.1104/PP.102.019661>
- Wasmer, M. (2019). Roads forward for European GMO policy-uncertainties in wake of ECJ judgment have to be mitigated by regulatory reform. *Frontiers in Bioengineering and Biotechnology*, 7(JUN), 132. <https://doi.org/10.3389/FBIOE.2019.00132/BIBTEX>
- Wesseler, J., & Purnhagen, K. (2020). Is the Covid-19 Pandemic a Game Changer in GMO Regulation? *EuroChoices*, 19(3), 49–52. <https://doi.org/10.1111/1746-692X.12301>
- WHO. (2010). *WHO guidelines on drawing blood: best practices in phlebotomy WHO Library Cataloguing-in-Publication Data WHO guidelines on drawing blood: best practices in phlebotomy.*
- Wise De Valdez, M. R., Nimmo, D., Betz, J., Gong, H. F., James, A. A., Alphey, L., & Black IV, W. C. (2011). Genetic elimination of dengue vector mosquitoes. *Proceedings of the National Academy of Sciences of the United States of America*, 108(12), 4772–

4775. <https://doi.org/10.1073/PNAS.1019295108>
- Wright, O., Stan, G. B., & Ellis, T. (2013). Building-in biosafety for synthetic biology. *Microbiology*, 159(PART7), 1221–1235. <https://doi.org/10.1099/MIC.0.066308-0/CITE/REFWORKS>
- Wu, Y., Lei, C., Yi, D., Liu, P., environmental, M. G.-A. and, & 2011, undefined. (2011). Novel *Bacillus thuringiensis* δ -endotoxin active against *Locusta migratoria manilensis*. *Am Soc Microbiol*, 77(10), 3227–3233. <https://doi.org/10.1128/AEM.02462-10>
- Yan, L., Zhao, F., Wang, J., Zu, Y., Gu, Z., & Zhao, Y. (2019). A Safe-by-Design Strategy towards Safer Nanomaterials in Nanomedicines. *Advanced Materials*, 1805391, 1–33. <https://doi.org/10.1002/adma.201805391>
- Yutin, N. (2013). Horizontal Gene Transfer. *Brenner's Encyclopedia of Genetics: Second Edition*, 530–532. <https://doi.org/10.1016/B978-0-12-374984-0.00735-X>
- Zelasko, S., Gorski, A., & Dabrowska, K. (2017). Delivering phage therapy per os: benefits and barriers. *Expert Review of Anti-Infective Therapy*, 15(2), 167–179. <https://doi.org/10.1080/14787210.2017.1265447>
- Zetterberg, C., & Edvardsson Björnberg, K. (2017). Time for a New EU Regulatory Framework for GM Crops? *Journal of Agricultural and Environmental Ethics*, 30(3), 325–347. <https://doi.org/10.1007/s10806-017-9664-9>
- Zhao, Y., Schetelig, M. F., & Handler, A. M. (2020). Genetic breakdown of a Tet-off conditional lethality system for insect population control. *Nature Communications* 2020 11:1, 11(1), 1–9. <https://doi.org/10.1038/s41467-020-16807-3>
- Zimmerman, J. B., & Anastas, P. T. (2015). Toward substitution with no regrets. *Science*, 347(6227), 1198–1199. <https://doi.org/10.1126/science.aaa0812>

List of Publications

Journal Articles

Bouchaut, B. & Asveld, L. (under review). Integrating Designing for Safety in Education: An iGEM Showcase. *Journal of Responsible Innovation*.

Bouchaut, B., de Vriend, H. & Asveld, L. (2022). Uncertainties and Uncertain Risks of Emerging Biotechnology Applications: A Social Learning Workshop for Stakeholder Communication. *Frontiers in Bioengineering and Biotechnology*. 10:946526. doi:10.3389/fbioe.2022.946526.

Bouchaut, B., Hollmann, F. & Asveld, L. (2022). Differences in Barriers for Controlled Learning about Safety between Biotechnology and Chemistry. *Nature Communications*, 13(1), 1-4. doi:10.1038/s41467-022-31870-8.

Bouchaut, B. & Asveld, L. (2021). Responsible Learning About Risks Arising from Emerging Biotechnologies. *Science and Engineering Ethics*, 27(2), 1-22. doi:10.1007/s11948-021-00300-1.

Bouchaut, B., Asveld, L., Hanefeld, U. & Vlierboom, A. (2021). Value Conflicts in Designing for Safety: Distinguishing Applications of Safe-by-Design and the Inherent Safety Principles. *International Journal of Environmental Research and Public Health*, 18 (4), 1963. doi:10.3390/ijerph18041963.

Bouchaut, B. & Asveld, L. (2020). Safe-by-Design Stakeholders' Perceptions and Expectations of How to Deal with Uncertain Risks of Emerging Biotechnologies in the Netherlands. *Risk Analysis*. 40 (8), 1632-1644. doi:10.1111/risa.13501.

Published Works & Opinion

Bouchaut, B. & Asveld, L. (2022) Let's Talk About Risks! A Workshop for Identifying and Anticipating Uncertain Risks for Safe Biotechnology Applications. *Rathenau Instituut, Den Haag*.

Bouchaut, B. (2021) Verantwoord leren over onzekere risico's in biotechnologie. *Podium voor Bio-ethiek*, 28 (4), 27-30. <http://doi.org/10.13140/RG.2.2.19686.29762>

Lotte Asveld, Britte Bouchaut & Frank Hollmann. (2021) Opinion 'Recycling moet veilig gebeuren, anders haken burgers af'. *Dagblad Trouw*

Opinion 'De 'echte' Ingenieur' by Britte Bouchaut. (2020) *University Magazine Delta of TU Delft*.

Bouchaut, B., Asveld, L. & Hanefeld, U. (2019) 'Veilige en Duurzame (Bio)Chemie met Blauwzuur?' *Ministerie van Infrastructuur en Waterstaat, Den Haag*.

Opinion 'Klimaatlast in Balans' by Britte Bouchaut. (2019). *University Magazine Delta of TU Delft*.

Conference Proceedings

'Biosafety by Design: Mere Control or Room for Serendipity?' Symposium by Britte Bouchaut, Lotte Asveld, Laurens Landeweerd, Ruth Mampuys, Vitor Martins Dos Santos, Enrique Asin Garcia, Kyra Delsing and Dirk Stemerding at 4TU.Ethics bi-annual Conference on Ethics and Technology 'It's Alive!', Wageningen University & Research (WUR), Wageningen, NL, 2021.

'Value Conflicts in Designing for Safety: A Case Study of Miniaturization Processes using Hydrogen Cyanide'. Oral presentation at the Society for Risk Analysis-Europe (SRA-E) Benelux Conference – TU Eindhoven, Eindhoven, NL, 2021.

'The Thinkers and the Doers: Safe-by-Design as Operationalization of the Precautionary Principle'. Oral presentation at 4TU.Ethics Conference on the 'Ethics of Disruptive Technologies' – TU Eindhoven, Eindhoven, NL, 2019.

'Safe-by-design: Perceptions and expectations of how to deal with risks of emerging biotechnologies. Findings and next steps' Oral presentation at Netherlands Biotechnology Congress – The sound of Biotech, Ede, NL, 2019.

'Safe-by-design: Perceptions and expectations of how to deal with risks of emerging biotechnologies. Findings and next steps' Oral presentation at the 25th SPRU PhD Forum - University of Sussex, Falmer, Brighton, UK, 2019.

'Perceptions of Inherent Safety: A comparison study from the bioengineering field'. Oral presentation at the 19th International Conference on Systems Biology (ICSB), Lyon, France, 2018.

'Perceptions of Inherent Safety: A comparison study from the bioengineering field'. Oral presentation at S.NET Conference, Maastricht University, NL, 2018

Curriculum Vitae

Britte Bouchaut was born on June 12th, 1989 in Kloosterzande, part of the former municipality Hontenisse, the Netherlands. After completing her HAVO program at the 'Reynaert College' in Hulst, Britte started with the Chemistry program at HZ University of Applied Sciences in Vlissingen, the Netherlands. As part of this program, she did an internship at an environmental laboratory in Vancouver, Canada, and conducted her Bachelor thesis research at the Reactor Institute Delft, TU Delft, the Netherlands.

During her Bachelors, Britte decided that it was not her goal to start working in the chemical industry after getting her degree. Instead, she wanted to gain more insights into why certain (polluting) domains or industries remain as they are, and why some innovations (Safer! More sustainable!) do not become adopted in society. She moved from TU Delft to TU Eindhoven where she initially started a pre-master program in Sustainable Energy Technology but quickly changed to Innovation Sciences which provided her more insights into policy and regulation. In addition to the standard curriculum, Britte followed the Philosophy certificate program and devoted one full year to educational affairs as part of the respective study association's Board. To complete the MSc. Innovation Sciences program, she traveled to Bintan, Indonesia to conduct fieldwork for her thesis.

After obtaining her MSc. degree in December 2017, Britte returned to TU Delft for a PhD at the Biotechnology and Society (BTS) group in January 2018. During this time, she developed her interest in responsible research and innovation and risk management further, and returned to her roots by focusing on biotechnology and (bio)chemistry. Besides research, Britte is a passionate educator and has been one of the proud supervisors of the TU Delft iGEM teams 2019-2022.

While she is a chemist by training, Britte is also a truly interdisciplinary researcher and is dedicated to bring all her education and experiences together to work toward a more ethical chemistry the coming years. Since July 2022, Britte is a Postdoctoral researcher in the EU Horizon 2020 'Water Mining' project at BTS and a 'Van Rijn'-junior lecturer at the faculty of Applied Sciences – TU Delft. In her free time, she enjoys writing (satirical) opinion articles, building and collecting LEGO® and taking care of her many plants and cat.



The acknowledgements are besides fun to read also a reflection of one's process, so why not first listen to an appropriate tune and sing along?

Acknowledgements

If someone told me, three years ago
Half of my PhD from my home
I would've told you, three years ago
That's okay, now leave me alone

I just wanna write on some stuff
Too many brainfarts to turn in a paper
I don't want Lotte to be stressed – No!
Too little time for her to keep up...

GMO, policy, how to gain safety?
Just too many insecurities
The PP, precaution, how to gain knowledge?
I try to keep it on...

Responsible learning
How to make innovation also safe?
Responsible learning
It is my PhD spent half inside..!

Adapted from: Content – Bo Burnham

If you've sang along (or just read the text), you're now aware that I conducted my PhD partly from home. Mostly due to obtaining a concussion and the BT-offices being flooded after a water connection broke down in one of the laboratories. And, oh yeah, a global pandemic, which was also a good reason to not travel to Delft for a significant period. Nevertheless, while working from home was sometimes challenging, the thesis in front of you illustrates that I managed to finish! But, of course, I never could've done this on my own so here we go.

First of all, thank you, **Lotte**. Not only for giving me the possibility to pursue a PhD, but mostly for being an awesome co-promotor, a critical and constructive reviewer of my work, a dear colleague and a true friend. After my Masters, I needed to regain some confidence, and you believed in me. The amount of trust you had in me was sometimes frightening, but it always worked out. So, I guess you were right! Thank you very much for making this PhD a very nice journey and I'm looking forward to continue working with you. **Zoë** – we met at my interview and I immediately felt a connection to you. You have been my mentor, my uplifting spirit and also a true believer in what I thought I could never achieve. Although you've transferred to Wageningen, I'm so happy that I may still call you my friend, and that we get to celebrate so many joyful moments together!

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