National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Safe, sustainable and circular design in industrial biotechnology

Guidance for researchers and developers

Contents

Introduction

To address global challenges such as climate change, pollution and an expected shortage of natural resources, there is a growing awareness that the economy as a whole needs to transform to be more sustainable and more circular (see box 1). Technological innovations, including biotechnology can help to conserve resources, limit pollution and mitigate climate change.

Industrial biotechnology for the production of bio-based materials is expected to play an increasingly important role in accelerating the transition towards a circular (bio)economy. With industrial biotechnology the use of renewable resources can be increased, bio-based materials with improved properties can be designed, and better lifecycles can be created with options for re-use, upcycling or compostability.

However, this requires not only technological innovations, but also a good understanding of the entire product chain as well as knowledge on safety, sustainability and circular design. Whether you are currently studying in silico biotechnology processes, testing a set-up in a laboratory or are planning to scale up your process, in each stage you can consider safety, sustainability and/or circularity. This information guide is meant to help Dutch designers in industrial biotechnology to integrate safety, sustainability and circularity in process or product design. It also provides a rough guide on legal frameworks for safety, sustainability and circularity in industrial biotechnology.

Box 1: Policy moves towards safe, sustainable and circular

Developments towards safe, sustainable and circular products and industries are seen in multiple policy initiatives. The European Commission (EC) wants Europe to become the first climate-neutral continent, combat climate change and protect biodiversity while remaining a competitive economy [1]. To realise these goals, the Commission is targeting sectors (including industry, agriculture, transport, and finance) with policy frameworks including the Chemicals Strategy for Sustainability[2], Circular Economy Action Plan[3], and Zero Pollution Action Plan[4].

A globally important initiative is the United Nations' (UN) resolution *Transforming our World: the 2030 Agenda for Sustainable Development*[5]. The resolution brings together goals and targets related to human rights, planetary health, and the economy[6], commonly referred to as the Sustainable Development Goals. Several Sustainable Development Goals are relevant for industry in general: goals 9 and 12 focus on sustainable and circular industries[7]. Industrial biotechnology process may contribute to one or more of the other goals.

Several countries including the Netherlands have policy initiatives to combat global problems like climate change, biodiversity loss, or threats to food and energy security. Examples are the Dutch Klimaatakkoord (Climate Agreement)[8] and the circular economy policy[9].

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1 European Commission (2022) Delivering the European Green Deal | European Commission (europa.eu).

2 European Commission (2021) Chemicals Strategy for Sustainability, Strategy.pdf (europa.eu).

3 European Commission (2020) A new Circular Economy Action Plan. For a cleaner and more competitive Europe, EUR-Lex - 52020DC0098 - EN - EUR-Lex (europa.eu)

4 European Commission (2021) EU Action Plan: Towards Zero Pollution for Air, Water and Soil, EUR-Lex - 52021DC0400 - EN - EUR-Lex (europa.eu).

5 UN (2015) Transforming our World: the 2030 Agenda for Sustainable Development (Resolution A/res/70/1)

6 "[The Sustainable Development Goals and targets] are integrated and indivisible and balance the three dimensions of sustainable development: the economic, social, and environmental" (UN, 2015, page 1).

7 Goal 9 is 'build resilient infrastructure, promote inclusive and sustainable industrialization and foster innovation' and goal 12 is 'ensure sustainable consumption and production patterns' THE 17 GOALS | Sustainable Development (un.org).

8 https://www.klimaatakkoord.nl/binaries/klimaatakkoord/documenten/publicaties/2019/06/28/klimaatakkoord/klimaatakkoord.pdf

9 Nederland circulair in 2050 | Circulaire economie | Rijksoverheid.nl

Safe, sustainable and circular design

Designing with safety and sustainability in mind is a precondition for realizing circular design[10]. See box 2 for a description of safety, sustainability and a circular economy and how these terms interrelate. The European Commission claims that "up to 80% of products' environmental impacts are determined at the design stage"[11]. In other words, it is important to take safety and sustainability into account already in early design stages of a product or process, because the most important decisions are made at the design stage. An upcoming approach for this is called Safe-and-Sustainable-by-Design[10,12]. It aims to identify and minimise, in an early phase of the innovation process, the impacts concerning safety for humans and the environment and for sustainability, minimizing the environmental footprint, in particular regarding climate change and resource use, and protecting ecosystems and biodiversity, taking a lifecycle perspective[13]. This life cycle perspective is also crucial for circular design. A product that is to be part of the circular economy needs to be designed for either reuse and recycling (in a so-called 'technical cycle') or a safe return to the biosphere for products that abrade or are consumed during use (e.g. tyres, shampoo).

In order to design out waste and create a circular product chain, it is important to consider the whole life cycle, including all the steps of the research and development phase, production, use, recycling and/or composting. In the case of industrial biotechnology, especially for biobased chemicals and polymers, the biotech product is generally an intermediate ingredient that is used for further production of an end product. Therefore, there are often other product designers in the supply chain. Design of the end product is not the primary focus of this information guide. However, to be able to contribute to a safe and sustainable circular design it is important to take into account the entire product (development) chain and adapt the design of a product in a way that safety, sustainability and circularity can be pursued throughout the product chain. This requires a process of mapping the entire product chain and including all relevant stakeholders to co-create i) a safe, sustainable and circular production process, with optimal use of by-products without the production of waste, and ii) safe, sustainable and circular products that are ideally not used once, but over and over again. This process is further elaborated on page 5.

[10] About Safe-by-Design - Safe-by-Design (safe-by-design-nl.nl).

[11] EC (2020). *A new Circular Economy Action Plan for a cleaner and more competitive Europe*. COM(2020)98, section 2.1.

[12] JRC Publications Repository - Safe and Sustainable by Design chemicals and materials Review of safety and sustainability dimensions, aspects, methods, indicators, and tools (europa.eu)

[13] OECD, 2022. Sustainability and Safe and Sustainable by Design: Working Descriptions for the Safer Innovation Approach. Series on the Safety of Manufactured Nanomaterials No. 105

Box 2: how circular economy, sustainability and safety relate to each other

In a circular economy we handle raw materials, materials and products more efficiently and carefully[14]. A circular economy means that in the economic system the preservation of natural capital and regeneration of natural systems is taken as the starting point, thereby using renewable and generally available resources as much as possible. To this end, resources are optimally used and re-used without risks to health and the environment, and finite resources are used as little as possible.

A circular economy by definition also meets the needs of sustainable development. Sustainability was defined by the United Nations Brundtland Commission in 1987 as "meeting the needs of the present without compromising the ability of future generations to meet their own needs". This definition was used for deriving the UN Sustainable Development Goals (SDGs). These 17 SDGs are a blueprint for people, planet and prosperity and recognize that ending poverty and other deprivations must go hand-in-hand with strategies that improve health and education, reduce inequality, and spur economic growth – all while tackling climate change and working to preserve our oceans and forests[15].

Safety for human health and the environment are important requirements for reaching a circular economy and/or sustainable development. In a circular economy, as the material loops are closed to prevent waste, any health or environmental hazards will remain 'in the loop'. For example, if a product contains a substance of (very) high concern (SVHC), people and the environment can be exposed to those chemicals through-out its initial use, re-uses, and possibly in products that are made from its recycled materials. Unsafe technologies also don't meet sustainable development goals. With safety for human health and the environment being an indispensable part of sustainability or a circular economy, one could strictly argue that sustainability is part of the circular economy, or the other way around. However, in this information guide they are approached as a trinity that cannot be seen separately.

[14] Circular Dutch economy by 2050 | Circular economy | Government.nl

[15] THE 17 GOALS | Sustainable Development (un.org)

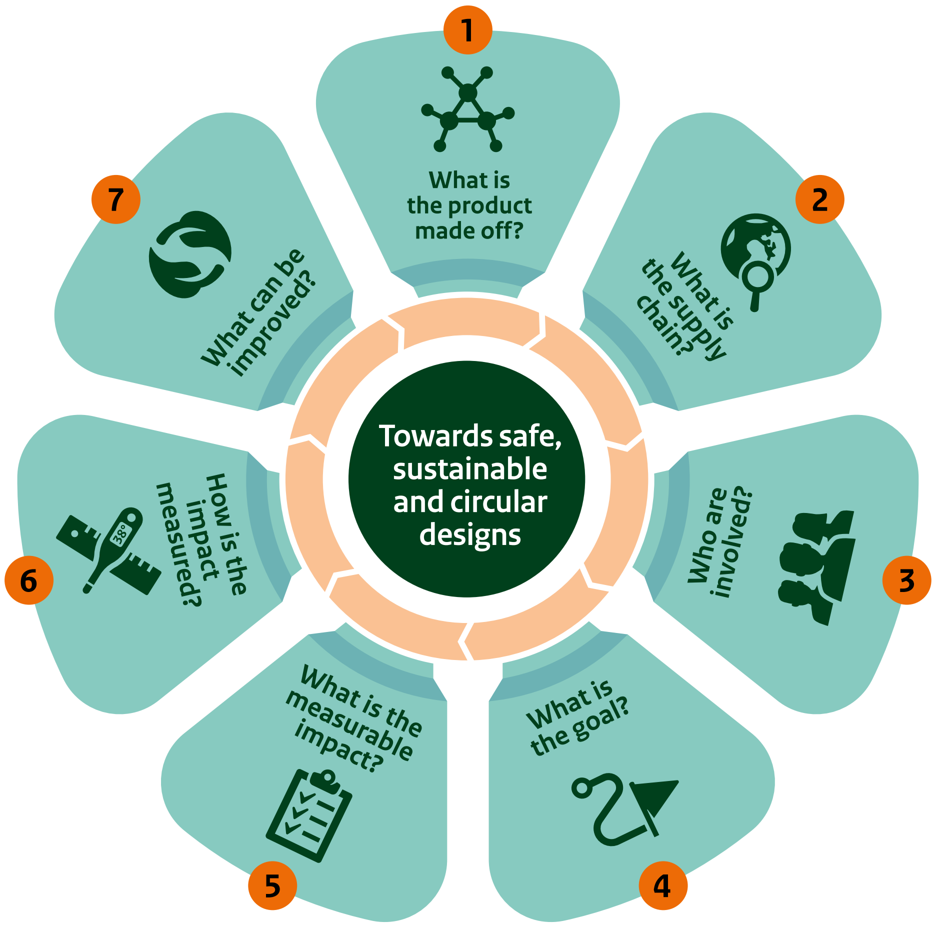

Figure 1. Iterative steps towards safe, sustainable and circular design and improvement of processes and products

A general guide to safe, sustainable and circular design can be found in the iterative steps in figure 1[16]. Following the seven steps, you are guided through a design or optimisation process that enables you to focus on suitable changes in your workflow that contribute to safety, sustainability or circularity.

1. Here, you look at all the resources a process uses or a product is made off, which include raw materials, intermediate ingredients, products, or even waste streams.
2. Mapping and analysing the supply chain: who can supply the required materials and do they differ with regards to safety, sustainability, and/or circularity? Are there other important differences between suppliers, such as ethics or working conditions?
3. Here, you map who are involved in which step of the production process. Who are the parties and stakeholders involved? Can they help (or hinder) in realizing a safer, more sustainable or more circular process or product?
4. Determine what you want to improve: which part(s) of your process or product are most relevant to improve the safety, sustainability and/or circularity, based on the previous step? As the section 'Indicators for safety, environmental impact and circularity' will show, there are many indicators for safety, sustainability, and circularity in the industrial biotechnology, so you will have to decide which one(s) you will focus on.
5. Choose which measurable impact you would like to achieve and select the indicator(s) and tool(s) to assess that impact.
6. Determine the impact a change in your process or product will have using the tool(s) selected in step 5.
7. In the last step, bringing all information together, you will decide what can be improved to make your process or product safer, more sustainable and/or more circular. After improvements are made it is important to validate if the results have the desired effect.

Following the steps and using the information below, you can improve your industrial biotechnology process and product. Ideally, you will use the seven steps iteratively to identify more ways to improve your process or product. For instance, each time you alter your process to gain a higher yield or include new features in your product, you can simultaneously improve the safety, sustainability and circularity. The next sections will provide guidance on how to assess and improve safety, sustainability or circularity.

[16] A detailed description of the seven steps for safe, sustainable and circular design can be found at www.rivm.nl/direct.

Design in industrial biotechnology

In industrial biotechnology modern biotechnology is applied for the production of materials, chemicals, and fuels from renewable resources. Microorganisms or enzymes are used to produce products that are useful to a broad range of industrial sectors, including chemical, pharmaceutical, human and animal nutrition, materials and polymers, textiles, and energy. Even though every production process is different, we have schematically represented the generic process of industrial biotechnology in five steps (figure 2).

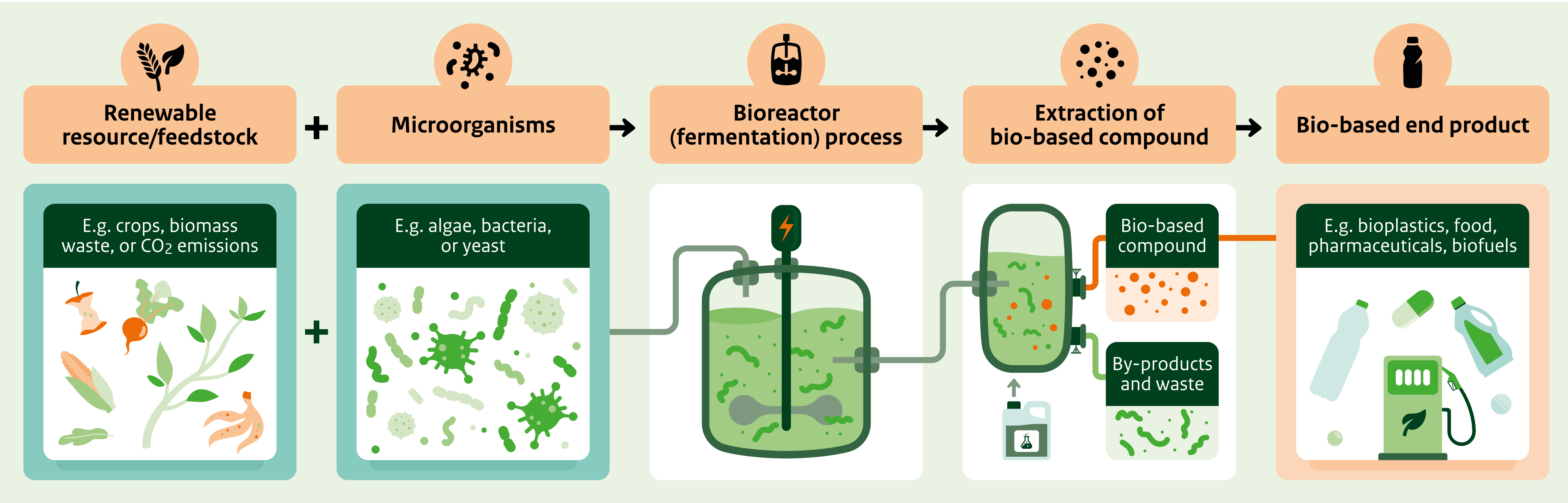

Figure 2. Steps in the industrial biotechnology process

The process of industrial biotechnology

To assess the safety, sustainability and circularity, it is best to split up the process of industrial biotechnology into the most important generic steps. For each of the steps we can then analyse which aspects have most impact. Based on this we can derive more specific indicators for safety, sustainability and circularity. Industrial biotechnology is broken down into the following steps (see figure 2):

A **feedstock/renewable resource** is needed as input for the process. This can be an agricultural product such as sugar beet or sugar cane, but preferably a residual flow is used, such as plant residues, organic waste or even CO_2 emissions from factories.

Microorganisms (from nature or designed/modified) convert the feedstock into the desired (intermediate) product. Sometimes a mixture of natural microorganisms is used, but often the microorganism is genetically modified to insert new metabolic pathways or to increase its efficiency.

In the **bioreactor (fermentation) process** the conversion of the feedstock into the desired (intermediate) product by the microorganisms takes place. The conditions in the bioreactor are optimised for this process.

Extraction of bio-based compound takes place in downstream processing. The bio-based (intermediate) product is separated from the microorganisms and purified. For this process chemicals, such as solvents, are often used. The process also generates organic side streams and by-products.

In the following production process, the bio-based intermediate is converted into a **bio-based end product**, such as bioplastics, medicines, feed or biofuels. This process no longer falls under the industrial biotechnology process itself and is, therefore, not specifically considered in this information guide. However, the end product and its production process determine the requirements for the bio-based compound. This should be taken into account in the design process of the industrial biotechnology process, as well the requirements for the next life cycle phase of the product (reusability, compostability or recyclability of the product).

Development stages for the production process of a bio-based compound

Before a bio-based compound can be commercially produced with an industrial biotechnology process, several development stages are passed through. In the early stages not much data about the production process are available for assessing safety and environmental impact. During product development more data are gathered, but the freedom to adapt the production process (e.g. regarding feedstock, synthesis route, purification, by-product treatment) decreases. It is therefore important to conduct suitable assessments throughout all stages, so that process designers can optimize new production processes for safety and sustainability. We distinguish three stages:

In the **Concept stage**, a synthesis route to a desired chemical is developed in silico (in silico strain development) and then tested in the lab. In this stage, only stoichiometric information[17] is available, as practical yields are not yet known.

During the **Process design stage**, the synthesis route is tested at laboratory scale to produce small amounts of purified (intermediate) product. Information on the real-world performance of the main reaction(s) is gathered, such as conversion, selectivity, performance of catalysts, formation of by-products, and heat of reaction. During process design a (usually small-scale) lab scale set-up for the synthesis route is developed. This goes beyond the main reaction(s) considered in the previous stage by including the design of the purification of the main (intermediate) product, process waste treatment, preparation of reactants, etc. This step yields the first data on a future facility, for example in terms of productivity, input materials, utilities, emissions, and waste.

In the **Piloting stage**, small-scale production facilities are established based on the process design. The real-world performance of the production process is measured and optimized to prepare for future industrial up-scaling. In piloting trials, production data simulated by the process design is validated and technological experience is gained.

[17] Information on how the feedstock is biochemically converted to the desired chemical

Foto: Shutterstock

Indicators for safety, sustainability and circularity

Modern industrial biotechnology employs microorganisms to turn renewable nutrients (such as plants or biomass waste) into intermediate ingredients suitable for medicines, plastics, detergents, etc. This raises questions such as i) How does the CO_2 footprint compare to the fossil-based counterparts? ii) How much energy is needed in the process? iii) What is the environmental impact of the solvents necessary to extract the desired chemicals from microorganisms? iv) Does the output of the biotechnology process have the potential for safe reuse, recycling or composting in the circular economy?

The table on the next page describes which indicators for safety, sustainability and circularity are most important in each development stage and in each step of the industrial biotechnology process. For the purpose of this information guide, sustainability is narrowed down to environmental impact. The table of indicators was composed based on desk research and expert consultation.

This overview is meant as a general guide and can, therefore, not be exhaustive. It is advised to scrutinise your own situation and evaluate if all indicators are relevant and if some indicators are still missing.

Table 1. Indicators for safety, sustainability and circularity in an industrial biotechnology process

Process step ***Design stage***	**Renewable resource/ feedstock (biomass)**	**Microorganisms used (or designed)**	**Bioreactor (fermentation) process**	**Extraction of biobased compound in downstream processing**
Concept stage: *in silico* development of microorganism • Design phase 'desktop design'. • No data available of the process itself • Important design choices	Choice of the use of a feedstock. Criteria for selection of a biomass resource: • Renewable resource • Preferably waste stream / by-product • Land occupation, use of (fresh) water and synthetic fertilizers (and pesticides) for production • Low carbon footprint and/or energy demand for production and transport • Availability of resource • Pre-processing of feedstock	Safe design of microorganism: • Pathogenicity of the organism • Horizontal gene transfer • Vertical gene transfer Safe design of metabolic pathway: • Antibiotic resistance marker usage • Harmful gene products (e.g. toxins, allergenicity) • Presence of properties to survive, sustain or interact with the environment	Design for a production process with: • Low energy demand (e.g. the temperature of process) • Low water usage • High resource efficiency (high selectivity) • Non-harmful cleaning agents	Design for a downstream process with: • Low energy demand • Use of renewable energy sources • Low chemical usage • Use of non-harmful chemicals • Low water usage
Process design stage: lab scale development • Testing in practice • On lab scale (small scale) • Adjusting design choices, based on first test results	Investigate presence of pathogens, toxins, pesticides, medicines or other chemicals or heavy metals in biotic waste stream. Collect rough data on the environmental impact of the renewable resources you use: • Carbon footprint and/or energy demand • Land usage • Soil quality and erosion • Water usage • Eutrophication • Acidification Adapt design choices according to results, thereby considering possible difference in environmental impact depending on geographic region.	Resource efficiency of the microorganism when scaling up (optimise microorganism or colony to handle feedstock fluctuations).	Collect data on and optimise the production process: • Toxin production or other secondary metabolites • Sensitisation/irritation (relevant for worker safety) • Fumes during production (including explosion risk, smell) • Energy usage • Water usage • Resource efficiency in the process	Collect data on the production process: • Chemical (solvents, biocides, antibiotics and other chemicals) usage (safe for humans and environment, renewable chemicals) • Sensitisation/irritation (relevant for worker safety) • Fumes during production (including explosion risk, smell) • Energy usage • Water usage • Water quality (of waste water) • Reusability, compostability or recyclability of by-products and waste

Table 1 (continued)

Process step ***Design stage***	**Renewable resource/ feedstock (biomass)**	**Microorganisms used (or designed)**	**Bioreactor (fermentation) process**	**Extraction of biobased compound in downstream processing**
Piloting stage: • Larger scale testing • More data available on process • Preparing for commercial production	Study fluctuations in biomass feedstock. Presence of pathogens, toxins, pesticides, medicines or other chemicals or heavy metals can vary. Collect more precise data on the environmental impact of the renewable resources you use: • Carbon footprint and/or energy demand • Land usage • Soil quality and erosion • Water usage • Eutrophication • Acidification • Availability of raw material	Resource efficiency of the microorganism when scaling up (optimise microorganism or colony to handle feedstock fluctuations).	Study potential infection or pollution risk (of the process) and further optimisation. Collect more precise data on the environmental impact of the production process at larger scale (including location of production plant and transport): • Carbon footprint and/or energy usage • Water usage • Resource efficiency in your process	Collect more precise data on the environmental impact of the production process at larger scale (including location of production plant and transport): • Carbon footprint and/or energy usage • Water usage • Water quality (of waste water) • Smog (photochemical oxidant formation) • Ecotoxicity (air, water, soil) • Ozone depletion • Reusability, compostability or recyclability of by-products and waste

Tools

This section suggests a selected number of tools for measuring and/or assessing the safety, sustainability and circularity of an industrial biotechnology process. An inventory of tools was done based on previous work[18], desk research and expert consultation. Table 2 shows a selection of tools to assess the indicators from table 1. The tools are further described on page 13 and 14.

A wide range of sustainability tools is available, for a variety of scopes and timescales. Full assessment methods such as Life cycle assessment (LCA) have a broad coverage of environmental impacts, but are data-intensive and thus difficult to apply during the concept stage and process design stage. Therefore, methods with lower data requirements have been suggested for the early stages. By applying the suggested tools, critical issues can be identified early-on in the development process and steered in the right direction. Some tools (such as LCA) may require involvement of sustainability experts.

18 https://www.rivm.nl/publicaties/environmental-assessment-of-bio-based-chemicals-in-early-stage-development-a-review-of

Table 2. Guidance and tools to evaluate safety, sustainability and circularity in an industrial biotechnology process

Process step / *Design stage*	Renewable resource/ feedstock (biomass)	Microorganisms used (or designed)	Bioreactor (fermentation) process	Extraction of biobased compound in downstream processing
Concept stage	Choice of a feedstock. **Tool 1:** Circular evaluation framework (Wageningen University). **Tool 2:** Assessing sustainability of residual biomass applications (RIVM). **Tool 3:** WAIR (Athena Instituut).	Safe design of organism and metabolic pathway. **Tool 5:** Safety framework.	Safety and environmental impact of production process. **Tool 6:** Ecoscale.	Environmental impact of downstream processing. **Tool 8:** Information on legal frameworks and chemical hazards.
Process design stage	Presence of pathogens, toxins, pesticides, medicines or other chemicals or heavy metals in biotic waste stream. Contact a laboratory for further information on sampling and analytical methods.	Resource efficiency of the microorganism when scaling up. This is part of optimisation processes.	Safety and environmental impact of the production process. **Tool 6:** Ecoscale. Assessment of risks for workers **Tool 7:** Arboportaal.	Safety and environmental impact of downstream processing. **Tool 8:** Information on legal frameworks and chemical hazards. Reusability, compostability or recyclability of by-products and waste. **Tool 9:** Circular Transition Indicators (CTI).
Piloting stage	Fluctuations in biomass waste stream. Contact a laboratory for further information on sampling and analytical methods. Environmental impact of the renewable resources. **Tool 4:** Life cycle assessment (LCA).	Resource efficiency of the microorganism when scaling up. This is already part of optimisation processes.	Assessment of risks for workers. Environmental impact of the production process at larger scale. **Tool 4:** Life cycle assessment (LCA).	Environmental impact of the production process at larger scale. **Tool 4:** Life cycle assessment (LCA).

Tools to evaluate the use of the biomass resource

For assessing the environmental impact of the use of biomass resources, it is important to take into account the effects on the entire system:

- To achieve a resource-efficient biomass use, the value pyramid or cascading principles can used as a rule of thumb (see figure 3). The Biomass Value Pyramid shows the many opportunities to create value from agricultural crops (and residues) and other left over bio-materials. The lowest value is achieved by burning the biomass and converting it into heat and electricity. The value is low because we do not exploit the structures of the biomass - only the energy content. Higher value products can be achieved by converting the biomass in for example industrial biotechnology processes.
- When using an agricultural feedstock, take into account the land occupation, use of (fresh)water and synthetic fertilizers and energy demand for production.
- When using a side or waste stream, this is considered better from a life cycle perspective than using an agricultural source or biomass stream with a higher economic value. However, be aware of potential unwanted side effects. What are the consequences of the use of a side or waste stream for the system? E.g. when using straw as a feedstock, this can't be used as a soil fertilizer any more and more synthetic fertilizer will potentially be used. This would be an adverse effect of using this waste stream.
- Does the feedstock need to be transported? Short transportation distances will lead to lower CO_2 emissions.

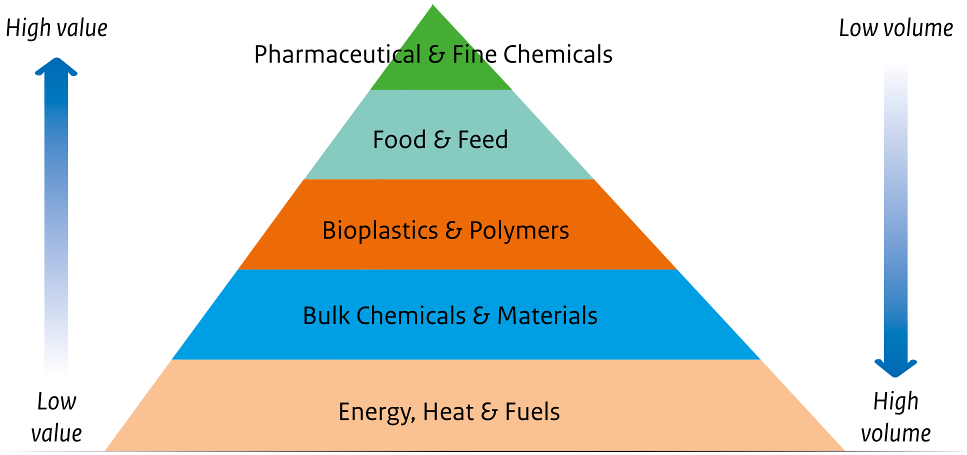

Figure 3: The value pyramid for biomass

Tool 1: Circular evaluation framework (Wageningen University)
The report "Identifying and implementing circular applications of agri-residues" describes and explains a Circular Evaluation Framework that supports the decision making process in the implementation of processes for the valorisation of agri-residues or by-products. The framework enables to perform a quantitative comparison of circularity, socio-economic impact, environmental impact and implementability for alternative processes. This report includes the quantification of circularity. Finally, a quick description of the process of using the framework is given in a decision tree, and a flyer summarizes the most important aspects of using this framework on one page.

Tool 2: Assessing sustainability of residual biomass applications (RIVM).
The RIVM has published a report "Assessing sustainability of residual biomass applications". In the study you will find an inventory of the issues related to the optimization of residual biomass flows. It also includes a review of the existing indicators and methods for assessing their environmental impact and sustainability. Table 1 on page 32 of the RIVM report provides a classification of residual biomass flows according to availability, risks, economics and application. Potential risks for pathogens and contaminants are displayed.

Tool 3: WAIR (Wheel of Action, Interaction and Reflection)
WAIR is a learning tool to help (student) biotechnologists to anticipate potential environmental, social and safety impacts of their project. The tools is set up to practice anticipation, and design and reflection from a transdisciplinary perspective.

Tool 4: Life cycle assessment
Life cycle assessment (LCA) enables the assessment of the pressure a certain (production) process places on the environment. The assessment comprises all phases needed to produce and use a product, from the initial development to the treatment of waste (the total life cycle). The goal of LCA is, for example, to compare alternatives or to identify phases in the production process that place a relatively high level of pressure on the environment. Based on this knowledge, production processes can be optimized. LCA is a suggested tool in the piloting stage to assess the environmental impact of the renewable resources, the production process at a larger scale for both the bioreactor (fermentation) process and the extraction of the biobased compound for downstream processing. All three can be included in one LCA. For an LCA you can either consult specialists or use a tool such as ReCiPe. Within LCA, 'life cycle impact models' (LCIA) are used to estimate the environmental impact. The RIVM developed a life cycle impact (LCIA)-model, called ReCiPe.

A life cycle impact assessment results in an 'environmental profile': a score list with different environmental effects, such as climate change, water use, land use and soil acidification. This list provides information about the environmental effects that score relatively well or poorly within the life cycle of a product and about the phases in the life cycle that contribute most to the different environmental effects.

Tools for evaluating the microorganisms used

Safety is an important aspect when working with biotechnology. Modern biotechnology techniques such as genetic modification and synthetic biology require a specific safety approach. To gain insight into microbiological risks for the environment and human health one needs to assess the hazards: the potential adverse effects that could arise from the biotechnology. The RIVM report "Classification of biological agents" provides an overview of biological agents that can cause disease in humans.

For assessing the risks, the probability of a hazard occurring, and the severity of its effect, need to be considered. If the risks are assessed, risk reduction measures can be determined and taken.

Tool 5: Safety framework
The document Safety framework Biotechnology, published by RIVM, will help to understand why the environmental safety aspect of biotechnology is important. It explains how to assess environmental safety using the principles of a risk assessment, and gives insight in how risk management relates to the required biosafety level (BSL) of the laboratory. It also gives insight into the regulations that apply to activities with genetically modified organisms.

Tools for the assessment of the bioreactor (fermentation) process

Material efficiency is an important parameter to assess the environmental sustainability during the concept stages. Material efficiency is how much material is required to produce a unit of output. An overview of some methods to calculate material efficiency can be found in the scientific article "Environmental assessment of bio-based chemicals in early-stage development": a review of methods and indicators. A good score for material efficiency indicators could signal that a process does not waste a lot of feedstock which limits the environmental impact of biomass cultivation. Low scores can indicate substantial by-product formation, which could signal that more purification is required to isolate the main product.

Another indicator to consider, is the generation of hazardous substances and their potential impact to humans (e.g. workers) and the environment.
Tool 6 and tool 7 are addressing these topics.

Tool 6: Ecoscale
Ecoscale is a semiquantitative tool which evaluates the quality of the organic preparation (in a laboratory practice). It is based on assigning a range of penalty points to six parameters: yield, cost, safety hazards, technical setup, reaction conditions, and ease of downstream processing. The proposed approach is based on assigning a range of penalty points to these parameters.

Tool 7: Arboportaal
The Arboportaal website is an initiative of the Ministry of Social Affairs and Employment. The website has been set up as a starting point for employers, employees and occupational health professionals who are looking for information about healthy and safe work.

Tools related to the extraction of biobased compound (intermediate product) in downstream processing

Tool 8: Information on chemical safety
In a biotechnology process, the biobased compounds are recovered and purified by solvent extraction. The following information sources are useful to get informed on the legal frameworks and chemical hazard properties of chemicals (including solvents).

- Risico's van stoffen (in Dutch)
- ECHA Information on chemicals

Tool 9: Circular Transition Indicators
Biological resources are embedded in the natural biological cycle, which is regenerative and without waste. Using biomaterials is therefore viewed as contributing to the circular economy. However, this general notion does not account sufficiently for sustainability issues, as a shift to biomaterials may exacerbate the overexploitation of natural resources or the disturbance of nutrient cycling. Furthermore, processed biological resources are not necessarily biodegradable, as is the case for some bioplastics.

The Circular Transition Indicators (CTI), is a simple, objective and quantitative framework that can be applied to businesses. The version CTI v2.0 is updated with a bio-economy Guidance: CTI v2.0 includes an instruction and interpretation on the bioeconomy across all indicators and process steps.

Dutch legal requirements for safety and sustainability

Safe, sustainable and circular design in industrial biotechnology is a process of iterative improvement, together with all stakeholders involved. Dutch legislation already sets requirements for ensuring safety for people and protecting the environment. Safe, sustainable and circular design takes place in the context of, but is not limited to these legal requirements.

For industrial biotechnology, many different laws and regulations can be applicable. For (startup) companies in biotechnology it can be complicated to get an overview of which legislation related to safety and sustainability could be applicable to their industrial biotechnology process. Therefore, a general overview of laws and regulations that may apply in the different parts of the process of industrial biotechnology is given in the schedule below (figure 4). More information on specific legislation applicable can be found by clicking on the names in the schedule. In box 3 the general structure of Dutch legislation is explained.

Box 3: Structure of Dutch legislation

Dutch legislation can be an implementation of EU legislation. An EU *regulation* is directly binding in all Member States. National legislation can add to EU regulations. An EU *directive* must be implemented in the national law. Directives set standards and Member States have to implement or adjust legislation to achieve those standards.

Dutch legislative hierarchy is structured as follows: *Act* of Parliament, Governmental *Decree*, ministerial *Order*. Acts of Parliament often only address the main aspects of a subject. Implementation regulations, such as Governmental Decrees, then lay down further rules on practical aspects. The Act and Decree can also stipulate that more detailed rules can be laid down in a Ministerial Order or in provincial or municipal regulations.

The EU's ambition for sustainability and circularity policy and legislation has been formulated in the EU action plan 'The European Green Deal' (COM(2019)640). It aims to have a sustainable economy and achieve climate neutrality by 2050. New EU directives and regulations are being developed to achieve the goals of the Green Deal. Examples that may be relevant for industrial biotechnology are:

- The Renewable Energy Directive (2018/2001/EU) aims to promote the renewable energy usage at 32% in 2030, which pushes biofuels into the market. It also provides guidelines on the sustainability of feedstocks, sets out to compare greenhouse gas emissions from fossil fuels and biofuels, and sets targets for greenhouse gas savings for biofuels.
- The Single-Use Plastics Directive (2019/904/EU) considers biodegradable and bio-based plastics to be plastics. As part of the EU Circular Economy Action Plan, the Commission announced the adoption of a policy framework on the sourcing, labeling and use of bio-based plastics, and the use of biodegradable and compostable plastics.
- In March 2022 the Commission has proposed a new Directive called the Ecodesign for Sustainable Products Regulation (ESPR) that would establish a framework to set ecodesign requirements for specific product groups to improve their circularity, energy performance and other environmental sustainability aspects. It will enable the setting of performance and information requirements for almost all categories of physical goods placed on the EU market.
- In December 2022 the European Commission adopted the Recommendation for safe and sustainable chemicals. The 'safe and sustainable by design' framework encourages innovation to replace hazardous substances in products and processes. It provides authorities, scientists and companies with guidance on the design of chemicals and materials and assessment of safety and sustainability throughout their entire lifecycle. This recommendation is part of the EU Chemicals Strategy for Sustainability.

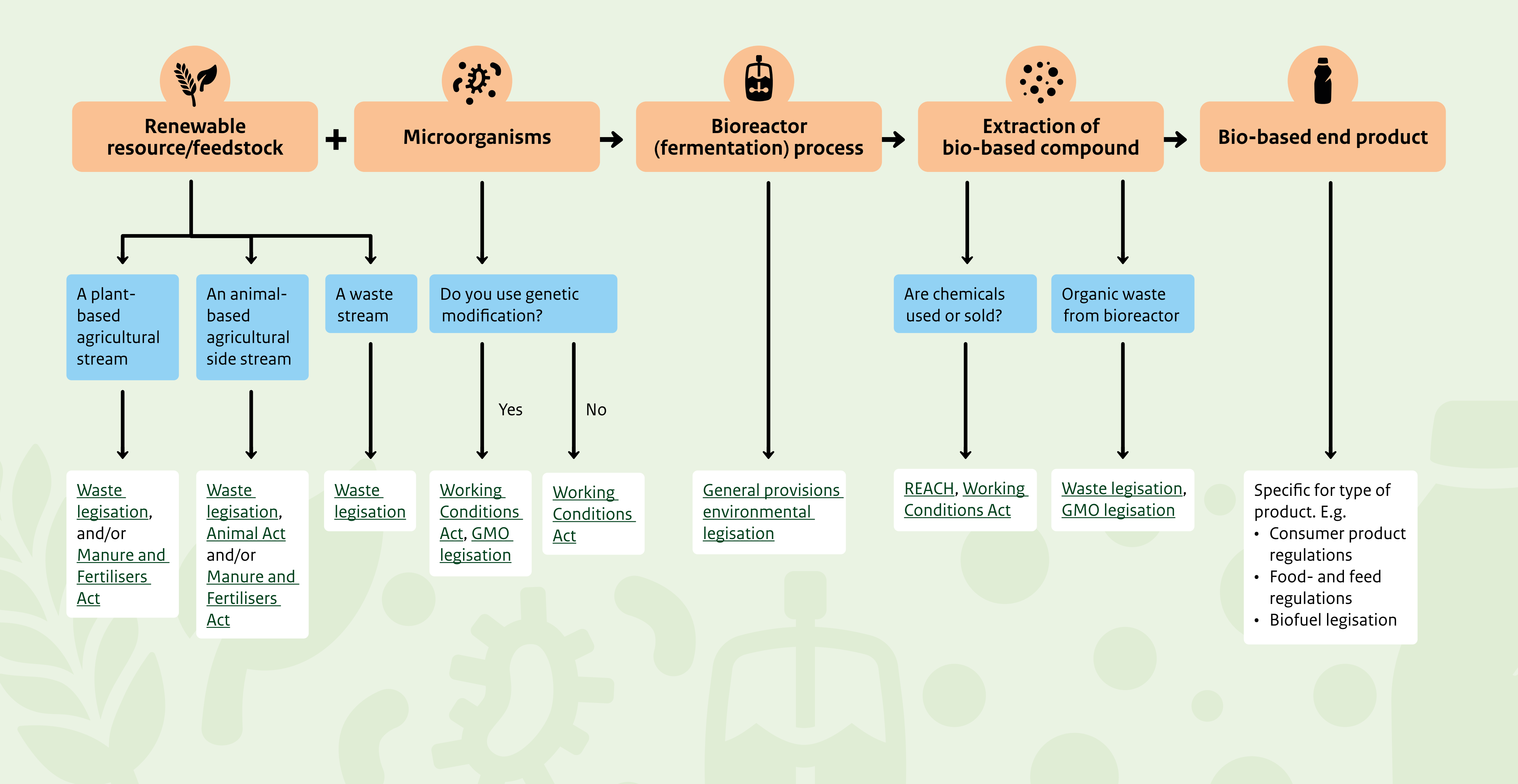

Figure 4. Industrial biotechnology processes and Dutch legal requirements for safety and sustainability

Environmental and Planning Act (Omgevingswet)

Preparations are being made to replace the Environmental Management Act (Wet Milieubeheer) for the new Environmental and Planning Act (Omgevingswet). Preparations are being made for the Enviromental and Planning Act to come into effect in 2023. It will combine and modernise laws for spatial planning, housing, infrastructure, the environment, nature and water, and focuses on a healthy physical environment that meets the needs of society. Until the new Act comes into effect, the legislation it replaces will remain in effect.

Waste legislation
If an entrepreneur 'discards' a residual flow, this is considered to be waste. However, if the residual flow has a clear destination – directly as a product or indirectly as a raw material for a second production process (not being waste processing) – the entrepreneur can substantiate this and thus avoid the status of waste. For each individual material or residual flow, it needs to be determined whether it is 'waste', 'by-product' or 'end-of-waste'. If the residual flow is considered to be waste, the (administrative) rules for waste transport and processing apply. These are laid down in the National Waste Management Plan 3 (Landelijk Afval Plan; MWMP3).

Certain organic residual flows have a legal status as waste, which limits the type of processing and application of products. The reason is that the composition of the biomass cannot always be controlled and the biomass may be microbiologically or chemically contaminated. For the processing of an organic flow, a permit for the processing of waste is often required.

The MWMP3 will be replaced by a more circular management plan (Circular Materials Plan 1), which is supposed to come into effect in 2023.

EU legislation EU Waste Framework Directive 2008/98/EC	**Responsible authority in the Netherlands** Rijkswaterstaat
National legislation Omgevingswet *(information in English)* Preparations are made for this Act to come into effect in 2023. Also new waste legislation (Circular Materials Plan 1) is under preparation. Until then, legal requirements are laid down in the National Waste Management Plan 3 that falls under the Environmental Management Act (Wet Milieubeheer).	**Useful links/documentation** The Greenhouse Horticulture Innovation Foundation (SIGN) made a flyer about how to get started with agricultural residual flows. The 'Leidraad afvalstof of product' of the Ministry of Infrastructure and Water Management contains guidelines and jurisprudence for the most uniform application of the concepts 'waste', 'by-product' and 'end-of-waste status'.

GMO legislation
The Netherlands GMO Decree and the GMO Order provide legislative guidance for avoiding risks to human health or the environment of working with genetically modified organisms (GMOs). A distinction is made between "introduction in the environment" (introductie in het milieu, IM) and "contained use" (ingeperkt gebruik, IG).

In the case of industrial biotechnology, GMOs are generally kept under controlled conditions within fermentation tanks in a confined space, and thus regulated under the contained use. For this confined space a Wabo permit is required. This might change at some point in the coming years under the Environmental and Planning Act.

A risk assessment is required for all applications of GMOs under contained use and focuses on keeping the organism contained and thus preventing contact with the environment. The severity of potential adverse effects as a result of possible contact with the environment determines the level of the containment regime.

Introduction in the environment occurs when activities involving genetically modified organisms (GMOs) take place outside a confined space of physical containment. Field trials with genetically modified plants are an example of this, but an open tank with GM phototrophic cyanobacteria would usually also be regulated under introduction in the environment. For all applications of GMOs under release into the environment an environmental risk assessment and notification or permit is required. In addition, a trained and approved on-site biosafety or environmental safety officer, employed by the company or organization, needs to be in place. The GMO legislation also has specific requirements for importing, transporting, discarding or destroying GMOs.

EU legislation Directive 2009/41/EC on the contained use of genetically modified micro-organisms Directive 2001/18/EC the deliberate release of genetically modified organisms	**Responsible authority in the Netherlands** Ministry of Infrastructure and Water Management and GMO office of the National Institute for Public Health and the Environment
National legislation Omgevingswet *(information in English)* Preparations are made for this Act to come into effect in 2023. Besluit ggo milieubeheer 2013 Regeling ggo milieubeheer 2013	**Useful links/documentation** GGO Vergunningverlening

General provisions environmental legislation (Wabo)
An environmental permit is required for the establishment of laboratories. An application must be submitted to the Wabo competent authority. In most cases, the Wabo competent authority is an environmental agency (Omgevingsdienst). The environmental permit might change at some point in the coming years under the Environmental and Planning Act.

When working with biological agents, a company must draw up rules of conduct and make provisions aimed at preventing the release of the biological agent. Wabo also specifies in which cases waste water containing biological agents may be discharged. The purpose of the rules of conduct and provisions is to prevent the (uncontrolled) release of biological agents.

EU legislation -	**Responsible authority in the Netherlands** Municipality (often outsourced to the Omgevingsdienst)
National legislation Omgevingswet *(information in English)* Preparations are made for this Act to come into effect in 2023. Until then the Wet algemene bepalingen omgevingsrecht (Wabo) and Activiteitenbesluit are in effect.	

Animal Act (Wet dieren)
Animal by-products are products of animal origin that are not used for human consumption. Examples of animal by-products are carcasses and blood. The recycling of animal by-products is subject to legislation to prevent diseases. In many cases, registrations, approvals or permissions are required for working with animal by-products. These are granted by the NVWA. It is also regulated in which cases companies may deviate from the rules of the EU regulations, and which rules they must adhere to instead.

EU legislation Regulation (EC) No 1069/2009 Regulation (EC) No 142/2011	**Responsible authority in the Netherlands** Netherlands Food and Consumer Product Safety Authority (NVWA)
National legislation Wet dieren Besluit dierlijke producten Regeling dierlijke producten	**Useful links/documentation** Regelgeving over dierlijke bijproducten | Dierlijke bijproducten | NVWA

Manure and Fertilisers Act (Meststoffenwet)
The Manure and Fertilizers Act (Meststoffenwet) sets requirements for the processing of manure. In addition, approval is required for companies that compost, ferment or process manure in another way. The law makes a distinction between different types of fertilizers: animal fertilizers, sewage sludge, compost, other organic fertilizers, inorganic fertilizers (chemical fertilisers).

EU legislation Directive 91/676/EEC	**Responsible authority in the Netherlands** Netherlands Food and Consumer Product Safety Authority (NVWA) en Netherlands Enterprise Agency (RVO)
National legislation Meststoffenwet Uitvoeringsbesluit meststoffenwet Uitvoeringsregeling meststoffenwet	**Useful links/documentation** Meststoffenwet - Kenniscentrum InfoMil

Working conditions Act (Arbowet)
As part of the Risk Inventory and Evaluation that is imposed by the Working Conditions Act (Arbeidsomstandighedenwet), an employer must assess exposure to biological agents. This means that the nature, extent and duration of exposure is assessed with the aim of determining the risks for the worker. This inventory must include, among other things, the biosafety levels of the biological agents to which the employees may be exposed and information about illnesses, allergic or poisoning effects that the employees may experience as a result. Protective measures should also be included. Information, training and good internal supervision are mandatory. Should an infection (or other incident) nevertheless occur, this must be registered or reported.

EU legislation -	**Responsible authority in the Netherlands** Ministry of Social Affairs and Employment
National legislation Arbeidsomstandighedenwet Arbeidsomstandighedenbesluit Arbeidsomstandighedenregeling	**Useful links/documentation** Biologische agentia in de wet | Arboportaal

Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)
Companies that manufacture, distribute, import or use chemicals can be required to demonstrate how the chemicals can be used safely, which is authorized by the European Chemical Agency. Registration and labelling of the chemical can be required, depending on the role of the company in the supply chain.

The REACH Regulation aims to protect humans and the environment from chemical risks while ensuring a level playing field for EU companies. The Regulation covers the registration, evaluation, authorization and restriction of chemicals. EU-based biotech companies that manufacture, import or use chemicals will have duties under REACH depending on their role in chemicals supply chains. They can have multiple roles depending on how they use chemicals. In any case they will have duties to communicate upstream or downstream in the supply chain on how the chemicals are used safely.

EU legislation Regulation (EC) No 1907/2006	**Responsible authority in the Netherlands** Ministry of Infrastructure and Water Management
National legislation Omgevingswet *(information in English)* Preparations are made for this Act to come into effect in 2023.	**Useful links/documentation** Reach I RIVM

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Published by

National Institute for Public Health and the Environment
P.O. Box 1 | 3720 BA Bilthoven
The Netherlands
www.rivm.nl/en

February 2023

Committed to *health and sustainability*

014194