Overview state of the art knowledge and regulations for pesticides with a lower risk profile

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Including more low-risk pesticides of biological origin as alternatives to chemical pesticides in agriculture is considered an important way forward to reach the Farm to Fork strategy targets. Low-risk pesticides, as defined by the current European Union (EU) plant protection Commission Regulation EC No 1107/2009, include pesticides of biological origin, but not all biological pesticides meet the low-risk profile requirements. In order to be granted low-risk status they must meet low-risk criteria defined by Regulation (EC) No 1107/2009. However, risk assessment procedures are designed for synthetic products with an expected high risk, which complicates the approval of products with an expected or known lower risk. Important steps forward have been taken in the past years, for example the acceptance of uniform principles and data requirements that facilitate the approval of microbial pesticides (Regulation [EC] No 1107/2009). Nonetheless, for other low-risk pesticides of biological origin, specific requirements are lacking. Biopesticides are still slow in obtaining approval, which hinders the replacement of toxic synthetic chemicals. This limits the choices for farmers and encourages derogations for toxic synthetic compounds. This paper summarises the bottlenecks encountered when performing a risk assessment for the authorization of biological pesticides and low-risk pesticides. It also lists recommendations on how to foster the use of pesticides with a lower environmental impact and potential next steps in the research agenda.

Keywords: low-risk, risk assessment, biopesticide, microbial pesticide, semiochemical, botanical, biostimulant

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Preface

This report provides an overview of the different groups of substances that are classified as low-risk under the pesticide Regulation (EC) No 1107/2009, which guidance documents apply to the various groups of substances, what problems are encountered with the authorization of these substances and which research questions are still open. The different groups of substances include microbial pesticides (which do not contain chemical molecules as an active ingredient, but organisms such as bacteria, viruses, fungi, macrophages, etc.), botanicals (natural substances of plant origin) and pheromones (or semiochemicals, i.e. substances that are excreted by an organism and influence the behaviour of other organisms) as three important groups of potential low-risk substances.

Voorwoord

Dit rapport geeft een overzicht van de verschillende groepen stoffen die onder laag-risico middelen worden gerangschikt, welke verordeningen en richtlijnen van toepassing zijn op de verschillende groepen stoffen en welke problemen worden ondervonden bij de toelating van deze stoffen. De verschillen groepen stoffen omvatten o.a. microbiële gewasbeschermingsmiddelen (die geen chemische moleculen als actief ingrediënt bevatten maar organismen zoals bacteriën, virussen, schimmels, macrofagen o.a.), botanicals (natuurlijke stoffen van plantaardige oorsprong) en feromonen (of semiochemicals, i.e. stoffen die door een organisme worden uitgescheiden en het gedrag van andere organismen beïnvloeden) als drie belangrijke groepen binnen laag-risico middelen.

Summary

Including more low-risk pesticides of biological origin as alternatives to chemical pesticides in agriculture is considered an important way forward to reach the Farm to Fork strategy targets. Low-risk pesticides, as defined by the current European Union (EU) plant protection Commission Regulation EC No 1107/2009, include pesticides of biological origin, but not all biological pesticides meet the low-risk profile requirements. In order to be granted low-risk status they must meet low-risk criteria defined by Regulation (EC) No 1107/2009. However, risk assessment procedures are designed for synthetic products with an expected high risk, which complicates the approval of products with an expected or known lower risk. Important steps forward have been taken in the past years, for example the acceptance of uniform principles and data requirements that facilitate the approval of microbial pesticides (Regulation [EC] No 1107/2009). Nonetheless, for other low-risk pesticides of biological origin, specific requirements are lacking. Biopesticides are still slow in obtaining approval, which hinders the replacement of toxic synthetic chemicals. This limits the choices for farmers and encourages derogations for toxic synthetic compounds. This paper summarises the bottlenecks encountered when performing a risk assessment for the authorization of biological pesticides and low-risk pesticides. It also lists recommendations on how to foster the use of pesticides with a lower environmental impact and potential next steps in the research agenda.

Key words: low-risk, risk assessment, biopesticide, microbial pesticide, semiochemical, botanical, biostimulant

1 Introduction

1.1 Contents of this report

This report focuses on the state-of-the-art knowledge and regulations for all substances with a potential lower risk profile that fall under Regulation (EC) No 1107/2009. Active substances with identified lower risks might be registered as basic substances or low-risk substances. Currently, both categories only include naturally occurring substances (later called biopesticides) such as microorganisms, semiochemicals, or natural extracts (for instance from plants). This report highlights the specific challenges to these biopesticides being approved as active substances with identified lower risks. Moreover, the plant biostimulants regulation, which is relevant and adjacent, is discussed. This regulation has recently been renewed and now excludes products which include any plant protection product. This report aims at helping decision makers understand the multiple facets of pesticides with a potential lower risk profile. It clarifies definitions and provides key elements to navigate within the existing regulatory tools. Recommendations are drawn which can help these substances reach the market and provide farmers with multiple tools and alternatives to most harmful pesticides. The report concludes with a research agenda.

Chapter 1 presents the context of the topic of this report. Chapter 2 discusses the definitions of categories and terminology, as applied to active substances with a lower risk profile, in more detail. Chapter 3 describes the new regulation for plant biostimulants. Chapter 4 describes the recently adapted regulation and data requirements for microbial pesticides. It summarizes the changes which were and were not adopted in the new data requirements. Chapter 5 discusses the current regulation and guidance for botanicals and discusses how approval of botanicals as active substances can be improved. Chapter 6 presents the current guidance and regulation for semiochemicals. Chapter 7 describes natural substances other than botanicals. Chapter 8 presents discussion, conclusions and recommendations. Chapter 9 includes all references.

1.2 Context

The EU Chemicals Strategy for Sustainability[1] aims for the reduction of the use of chemicals as part of the EU's zero pollution ambition, which is a key commitment of the European Green Deal. With the aim to better protect citizens and the environment and boost innovation for safe and sustainable chemicals, the EU Chemical Strategy requires the application of the Integrated Pest Management (IPM) principles. Pesticides with a lower basic risk profile are part of an IPM approach. Indeed, the ambition of the European commission is to halve the use of pesticides in agriculture in 2030 and to halve the use of the most hazardous pesticides in 2030. However, the European Parliament has not approved this ambition, so it is uncertain if Member States will proceed with setting their own national reduction targets. While a proposal for the SUR (Regulation on the Sustainable Use of Plant Protection Products) was adopted by the European Commission in June 2022, on 21 November 2023 the European Parliament has rejected the Commission proposal on sustainable use of plant protection products.

The European commission states that: "less acceptance of toxic chemicals on the market and the approval of plant protection products with low risk are two paths towards a toxic free environment" (European Commission, 2021). Regulation (EC) No 1107/2009 concerns the placing of plant protection products (PPP) on the market. It was adapted to include two categories of substances used for plant protection, low-risk and basic, which are expected to have a lower basic risk profile. Pesticides classified as low-risk must adhere to extra criteria in addition to that set for all substances under Regulation (EC) No 1107/2009.

[1] European Commission. Chemical Strategy. URL: https://environment.ec.europa.eu/strategy/chemicals-strategy_en (last accessed 29/11/2023).

In contrast to low-risk and basic substances, which are terms defined in a regulatory context, green pesticides is not a defined category in EU regulations. However, it is used in the context of the Green Deal. In this context it refers to products of natural origin or identical products of synthetic nature, with a supposedly lower risk to man, animal, the environment and non-target organisms. The Green Deal promotes the use of low-risk pesticides as defined by Regulation (EC) No 1107/2009. There is not a clear definition of biopesticides nor botanicals in Regulation (EC) No 1107/2009, and they are therefore not legally binding terms. "Green pesticide", "biocontrol / biocontrol agent" and "biological pesticide" are sometimes used as equivalents to describe a plant protection product of biological origin (e.g. containing microorganisms (including viruses), botanicals or semiochemicals as active ingredient). At other times, however, these refer only to living organisms. This leads to confusion. Biopesticides might also include macro-organisms (e.g. insects), but these are not the subject of this report as they are not part of Regulation (EC) No 1107/2009. Macro-organisms are regulated per Member State and are not under the remit of the Ctgb (Dutch Board for the Authorisation of Plant Protection Products and Biocides) but under that of Netherlands Enterprise Agency (Ministry of Agriculture, Nature and Food Quality).

According to the definitions published by Balog et al. (2017) and Villaverde et al. (2014), who consider both living organisms used for pest control as well as naturally occurring substances used for pest control as biopesticides, biopesticides are:

1. living organisms, including microorganisms;
2. naturally occurring substances that include plant extracts, semiochemicals (insect pheromones) and certain minerals.

Definition of terms used in this report:

Biopesticides are living organisms, as well as substances from biological or natural origin, used as plant protection products in agriculture. They include:

- Microorganisms (bacteria, algae, protozoa, viruses, fungi, baculoviruses);
- Natural organic substances (botanicals [i.e. plant extracts], salts, minerals, blood, chitin);
- Semiochemicals (pheromones);
- RNA-based low-risk pesticides.

In this report, we will exclude macro-organisms (e.g. insects) as they are not regulated under the Regulation (EC) No 1107/2009.

Low-risk pesticides are active substances that meet both the regular approval criteria and the low-risk criteria following Annex II, point 5 of Regulation (EC) 1107/2009.

Basic substances are active substances that are not on the market as plant protection products but as other product classes, for instance as foodstuff, feed, or cosmetics. Their safe use is easy to prove. One example is vinegar, used as fungicide, herbicide or pH modifier, but available on the market as foodstuff or cleaning agent.

Green pesticides are not defined in regulations, but in the context of the Green Deal they refer to products of natural origin or identical products of synthetic nature, with a supposedly lower risk to man, animal, the environment and non-target organisms.

Natural substances are substances of plant origin (also called botanicals) and substances from mineral and animal origin.

Biostimulants are natural products which influence the growth of plants without releasing fertilizers. They are regulated by the EU Fertilising Products Regulation (FPR) that went into force in July 2019 (European Commission 2019).

Only biopesticides were granted the status of low-risk and basic substances. In order to increase the number of low-risk pesticides, it is important to identify the challenges met by biopesticides in being approved as active substances and, when applicable, to acquire low-risk status. As illustrated above, biopesticides are a heterogeneous group of substances with no clear definition in the regulations. They are based on a diverse group of active living and non-living ingredients[2]: microorganisms, plant extracts, pheromones, viruses,

[2] OECD (URL: https://www.oecd.org/env/ehs/pesticides-biocides/biological-pesticides.htm, last accessed 04/12/2023) lists the following categories: microbials (bacteria, algae, protozoa viruses, fungi), pheromones and semiochemicals, macrobials/invertebrates such as insects and nematodes, and plant extracts/botanicals.

RNA-based low-risk pesticides and minerals. Their potential hazards are new and different from chemical pesticides. They are expected to have a lower level of impact on the environment and human health and to be of low risk. Nevertheless, a biopesticide is not necessarily a low-risk pesticide. Before these substances are allowed on the market, they need to go through a proper risk assessment process, as laid down in several regulations. Regulation (EC) No 1107/2009 coversmicroorganisms, pheromones, biological products (e.g. plant extracts, botanicals), and spray-induced gene-silencing products (SIGS). SIGS are RNAi-based products, applied exogenously through spray application. The registration of these RNAi-based products follows the same regulatory framework as for classical synthetic pesticides (Regulation (EC) No 1107/2009). Biostimulants, i.e. natural products which influence the growth of plants without releasing fertilizers, are not covered by Regulation (EC) No 1107/2009, but, rather, by the EU Fertilising Products Regulation (FPR) that went into force in July 2019 (European Commission, 2019). In this report the risk assessment for the substances covered by Regulation (EC) No 1107/2009 are described, except for the SIGS, and in addition also the biostimulants.

2 Active substances with lower risks under 1107/2009

2.1 Definitions and terminology used by several regulations/agencies

A short overview of often used terms is presented here. It is specifically pointed out when there are differences (or similarities) in the interpretation by agencies like the Dutch Board for the Registration of Plant Protection Products and Biocides (Ctgb), the European Commission (EC) or the United States Environmental Protection Agency (U.S. EPA).

2.1.1 Green pesticides

"Green pesticides" is not a defined category in EU regulations, and hence the term "green products" (*groene middelen*) as used in the Green Deal (Werkgroep Green Deal, 2017) is not clearly defined in regulatory terms. In the context of the Green Deal it refers to products of natural origin (plants, animals, microorganisms or certain minerals) or identical products of synthetic nature, with an assumed low risk to man, animal, the environment and non-target organisms. It is assumed that they all belong to the class of low-risk pesticides as defined by Regulation (EC) No 1107/2009.

In a similar fashion, the U.S. National Pesticide Information Centre (NPIC, a cooperative agreement between Oregon State University and the U.S. Environmental Protection Agency) points out that the term "green" in "green pesticide" is not defined by any regulatory agency, which makes it open to interpretation by the consumer and marketing companies.

2.1.2 Low-risk pesticides

According to the definition used in Regulation (EC) No 1107/2009, and amended by EU Regulation 2017/1432, low-risk active substances are expected to pose a low risk to human and animal health and the environment, as provided for in Article 47(1). This article then specifies that a low-risk plant protection product should: 1) contain only approved low-risk active substances, safeners and synergists, 2) not contain a substance of concern, 3) be sufficiently effective, 4) not cause unnecessary pain and suffering to vertebrates to be controlled, and 5) should comply with certain provisions of Article 29(1) (mainly dealing with adherence to technical specification and the availability of sufficiently accurate methods for qualitative and quantitative analysis of its content).

The Ctgb adheres to these definitions, identifying low-risk active substances following the same method as prescribed by EU regulations[3].

The U.S. EPA uses a somewhat different terminology, referring to "minimum risk pesticides". These are defined as posing little to no risk to human health or the environment, and are therefore exempted from the requirement to be registered, under the Federal Insecticide, Fungicide, and Rodenticide Act. A minimum risk product must meet six conditions listed by the EPA[4], which are basically that: 1) active and inert ingredients must have been listed in 40 CFR 152.25(f)2 and 40 CFR 180,950(e), resp., and 2) the labelling of the material must meet certain requirements with regards to claims and information provided.

[3] CTGB. Basic substances (*Basistof*). URL: https://www.ctgb.nl/onderwerpen/basisstoffen (last accessed 29/11/2023).
[4] U.S. EPA (April 2023). Minimum Risk Pesticides. URL: https://www.ctgb.nl/onderwerpen/basisstoffen (last accessed 29/11/2023).

2.1.3 Microbial agents/pesticides

Regulation (EC) No 1107/2009 applies to substances, including microorganisms, having general or specific action against harmful organisms or on plants, parts of plants or plant products, referred to as active substances (see definition in section 2). In this regulation, microorganisms are defined as any microbiological entity, including lower fungi and viruses, cellular or non-cellular, capable of replication or of transferring genetic material (Regulation (EC) No 1107/2009, and see chapter 4). This implies that dead microorganisms (except for viruses) are not considered to be microorganisms but, rather, should be considered as chemical active substances. The European Chemicals Agency (ECHA) Ad hoc Working Group - Microorganisms adheres to a similar definition, as given in article 3 of the Biocidal Products Regulation EU No 528/2012. Hence, only viable microbiological entities (cellular or non-cellular) capable of replication or of transferring genetic material are considered microorganisms. This includes: lower fungi, viruses, bacteria, yeasts, moulds, algae, protozoa and microscopic parasitic helminths. Non-viable microbiological entities are not covered by the ECHA guidance[5].

The U.S. EPA uses a very similar definition of microbials or microbial pesticides: microorganisms that produce a pesticidal effect. These have pesticidal modes of action that often include competition or inhibition, toxicity and even use of the target pest as a growth substrate. They may be:

- Eukaryotic microorganisms, including, but not limited to, protozoa, algae, and fungi
- Prokaryotic microorganisms, including, but not limited to, bacteria
- Autonomous replicating microscopic elements, including, but not limited to, viruses

The FAO/WHO guidelines, on the other hand, give a definition of a microorganism active substance which indicates that it may contain viable and/or non-viable microorganisms (OECD 2014, Arche Consulting 2018).

2.1.4 Biological control agents

Microbial agents are also referred to as Microbial Pest Control Agents (MPCAs). The Organisation for Economic Co-operation and Development (OECD) refers to these compounds as microbial Biological Control Agents (mBCAs). Products, as opposed to agents, are referred to as Microbial Pest Control Products (MPCPs) or microbial Biological Control Products (mBCPs). The main groups of MPCAs are bacteria, fungi, viruses, protozoa and microsporidia (European Commission 2012). This implies that in OECD terminology microbial pesticides are part of a larger family of biological control agents.

The New Zealand Environmental Protection Agency uses a similar interpretation of the term "biological control agents" (BCAs). They define them as "agents that are introduced into the environment to target a pest species, with the aim of reducing the pest's population or abundance in the environment." On their website[6] they give numerous examples of species that are included in this wide definition of BCAs. This includes, amongst others, organisms such as the mistflower gall fly (*Procecidochares alani*, used to control the weed mistflower), the boneseed leafroller (used to control the weed boneseed), the mite *Aceria genistae*, the broom shoot moth (*Agonopterix assimilella*) and broom leaf beetle (*Gonio olivacea*) (all three are used to control the weed broom). However, they also include fungi such as the leaf spot fungus (*Kordyana sp.*, used to control the plant *Tradescantia*), and several rust fungi (*Puccinia lantanae*, *Propodium tubuculatum*) used to control the weed *Lantana camara*. Hence, in the terminology of the New Zealand EPA the phrase "biological control agents" includes microorganisms.

The U.S. EPA does not use the term "biological control agent" in their description of the risk assessment of microbial agents (see above section on microbial agents/pesticides). This is in line with the practical distinction made by Marrone (2007), who limits the use of the term to macro-organisms by saying, "Biological control agents (BCAs) are living organisms that infect and kill the pest or pathogen and are predators of pests and weeds. For the purposes of this review, BCAs are macro-organisms such as predators and parasites. Microorganisms that some may consider as BCAs (e.g. *Bacillus subtilis* for controlling plant diseases) are considered (microbial) bio-pesticides (MPCAs) but in this review referred to as microbial pesticides."

[5] ECHA. Ad hoc Working Group – Microorganisms. URL: https://echa.europa.eu/about-us/who-we-are/biocidal-products-committee/working-groups/ad-hoc-wg-microorganisms (last accessed: 29/11/2023).

[6] Environmental Protection Authority of New Zealand (2023). Biological control agent. URL: https://www.epa.govt.nz/industry-areas/new-organisms/biological-control-agents/ (last accessed: 29/11/2023).

2.1.5 Biopesticides

The Ctgb defines biological pesticides as plant protection products that contain microorganisms (including viruses), botanicals, or semiochemicals as an active ingredient.

The U.S. EPA uses the term "biopesticides", which they define as pesticides derived from natural materials such as animals, plants, bacteria and certain minerals (Leahy, Mendelsohn et al., 2014). Typically, biological pesticides have unique modes of action and are considered reduced-risk pesticides. They fall into three major classes: biochemical pesticides, microbial pesticides and plant-incorporated protectants.

Besides the term biopesticides (or biological pesticides) the U.S. EPA uses the term "biochemical pesticides" to denote naturally occurring substances, or synthetically derived equivalents, that have a non-toxic mode of action to the target pest(s) and have a history of exposure to humans and the environment demonstrating minimal toxicity. Synthetically derived biochemical pesticides are equivalent to a naturally occurring chemical which fits this category. Biochemical pesticides include, but are not limited to, semiochemicals (insect pheromones and kairomones), natural plant and insect regulators, naturally occurring repellents and attractants, induced resistance promoters, and enzymes. Biochemical pesticides typically degrade rapidly and are not persistent in the environment. Apart from pheromones, they tend to have much less species-specificity and have a broader spectrum than the microbials.

Additionally, the U.S. EPA uses the term "organic pesticides". These are clearly defined and must comply with specific standards set by the USDA National Organic Program[7]. They cannot contain man-made chemicals or genetically modified organisms. Some of these products are low in toxicity and considered minimum-risk pesticides. However, being certified as organic does not necessarily mean that a product is 100% safe[8].

The U.S. EPA also has the term "plant-incorporated protectants" (PIPs) for pesticidal substances produced by plants (e.g. Bt Cry proteins) and the genetic material that has been added to the plant (e.g. Cry genes).

2.1.6 Biostimulants

The definition of a plant biostimulant, as given by Arcadia International (Traon, Amat et al., 2014), that is used for regulation within the European Union is as follows. "Any substance or microorganism, in the form in which it is supplied to the user, applied to plants, seeds or the root environment with the intention to stimulate natural processes of plants to benefit their nutrient use efficiency and/or their tolerance to abiotic stress, regardless of its nutrients content, or any combination of such substances and/or microorganisms intended for this use."

The EU biostimulants regulation defines biostimulants as products that stimulate plant nutrition processes independently of the product's nutrient content with the sole aim of improving one or more of the following characteristics of the plant or the plant rhizosphere: 1) nutrient-use efficiency, 2) toleration of abiotic stress (i.e. difficult growing conditions, such as extreme temperatures, drought or water logging, among others), and 3) crop quality[9].

The distinction between biostimulants and plant protection products can be summed up in the following statement. Biostimulants are intended to "stimulate the natural processes of plants" rather than have any direct action against pests or diseases. To clarify the differences, the definition of biostimulants and the regulation related to them is presented section 3.

[7] US EPA (30/05/2023) Labelling of Pesticide Products under the National Organic Program https://www.epa.gov/pesticide-labels/labeling-pesticide-products-under-national-organic-program (last accessed: 29/11/2023).

[8] National pesticide information center. "Natural or Green?" What does it mean? http://npic.orst.edu/capro/greenmyths.html (last accessed: 29/11/2023).

[9] European biostimulants industry council. EU Regulation Ensures that Biostimulants Are Safe and Effective. URL: https://biostimulants.eu/highlights/eu-regulation-ensures-that-biostimulants-are-safe-and-effective/# (last accessed: 29/11/2023).

2.1.7 Definitions of active substance and plant protection product

An active substance is any chemical, plant extract, pheromone or microorganism (including viruses), that has action against pests or on plants, parts of plants or plant products. Before an active substance can be used within a plant protection product in the EU, it must be approved by the European Commission (https://food.ec.europa.eu/plants/pesticides_en).

Plant protection products are pesticides that protect crops or desirable or useful plants. They are primarily used in the agricultural sector but also in forestry, horticulture, amenity areas and in home gardens. They contain at least one active substance (see definition above) and may also contain other components including safeners, synergists and dilutants. EU countries are responsible for the authorization of plant protection products in their territory and ensuring compliance with EU rules and Member State regulation (https://food.ec.europa.eu/plants/pesticides_en).

Definitions under EC Regulation No 1107/2009

Active substance: any chemical, plant extract, pheromone or microorganism (including viruses), that has action against 'pests' or on plants, parts of plants or plant products.

Plant protection product: a product including the active substance(s) and any formulations, safeners, synergists and/or dilutants used to protect crops or desirable or useful plants in agriculture, horticulture and gardens.

2.2 Regulations for low-risk and basic substances

2.2.1 Low-risk active substances

Within Regulation (EC) No 1107/2009 an active substance can be approved as a low-risk substance if it meets the regular approval criteria and the low-risk criteria in Annex II, point 5 of the regulation. Low-risk substances are included in Part D of the list of approved active substances in the Annex to Commission Implementing Regulation (EU) No 540/2011.

The list of criteria for low-risk substances was recently revised in order to facilitate the approval of naturally occurring substances, semiochemicals and microorganisms (European Commission 2017):

- Semiochemicals and microorganisms are now (with some limitation) automatically considered as low-risk substances
- Persistence and accumulation criteria are lifted for naturally occurring substances (which includes metals or minerals)

A list of potentially low-risk substances is available (European Commission 2018a). Note that the term "naturally occurring substances" mentioned in 5.1.2 is not clearly defined in Regulation (EC) No 1107/2009 which can leave ground for interpretation (Vekemans and Marchand 2020).

The criteria for low-risk substances, as of 2017, are as follows (Annex II, point 5):

5.1. Actives substances other than microorganisms

Article 5.1.1 An active substance, other than a microorganism, shall not be considered as being of low-risk where it corresponds to any of the following:

a. it is or has to be classified in accordance with Regulation (EC) No 1272/2008 as any of the following:
   - carcinogenic category 1A, 1B or 2,
   - mutagenic category 1A, 1B or 2,
   - toxic to reproduction category 1A, 1B or 2,
   - skin sensitiser category 1,
   - serious damage to eye category 1,
   - respiratory sensitiser category 1,
   - acute toxicity category 1, 2 or 3,
   - specific Target Organ Toxicant, category 1 or 2,
   - toxic to aquatic life of acute and chronic category 1 on the basis of appropriate standard tests,
   - explosive,
   - skin corrosive, category 1A, 1B or 1C.
b. it has been identified as priority substance under Directive 2000/60/EC;
c. it is deemed to be an endocrine disruptor;
d. it has neurotoxic or immunotoxic effects.

Article 5.1.2. An active substance, other than a microorganism, shall not be considered as being of low-risk where it is persistent (half-life in soil is more than 60 days) or its bio-concentration factor is higher than 100. However, a naturally occurring active substance which does not correspond to any of points (a) to (d) of point 5.1.1 may be considered as being of low-risk, even if it is persistent (half-life in soil is more than 60 days) or its bio-concentration factor is higher than 100.

Article 5.1.3. An active substance, other than a microorganism, emitted and used by plants, animals and other organisms for communication, shall be considered as being of low-risk where it does not correspond to any of points (a) to (d) of point 5.1.1.

5.2. Microorganisms

Article 5.2.1. An active substance which is a microorganism may be considered as being of low-risk unless at strain level it has demonstrated multiple resistance to anti-microbials used in human or veterinary medicine.

Article 5.2.2. Baculoviruses shall be considered as being of low-risk unless at strain level they have demonstrated adverse effects on non-target insects.

Products that contain only low-risk substances can then be authorized as a low-risk plant protection product. Note that the criteria used for deciding on low-risk are hazard-criteria, implying that the substance should meet these criteria.

2.2.2 Market for low-risk substances

The development and placing on the market of low-risk substances and products is encouraged by several regulatory incentives. Low-risk substances are approved for 15 years instead of 10, and data protection on the studies submitted for the approval and subsequent authorization is prolonged from 10 to 13 years. Moreover, a fast-track authorization procedure with reduced timelines (120 days instead of one year) is intended to ensure that low-risk products can be placed on the market quickly. For more information on the substances approved as low-risk substances, see the EU Pesticides Database (https://food.ec.europa.eu/plants/pesticides/eu-pesticides-database_en).

At the EU level there have been 30 Microorganisms and 27 other substances registered as low risk (European Commission 2018a). In the Netherlands, the Ctgb has approved 13 low-risk plant protection products (CTGB 2023). While the status of low-risk is not exclusively meant for natural substances, no synthetic pesticide is currently registered as a low-risk pesticide. Several potential low-risk substances were already approved before the change of the criteria for facilitating the approval as low-risk in 2017. Of these, 29 substances which could potentially get low-risk approval must wait for their renewal in order to be approved as low-risk (reference year 2022) (Robin and Marchand 2022).

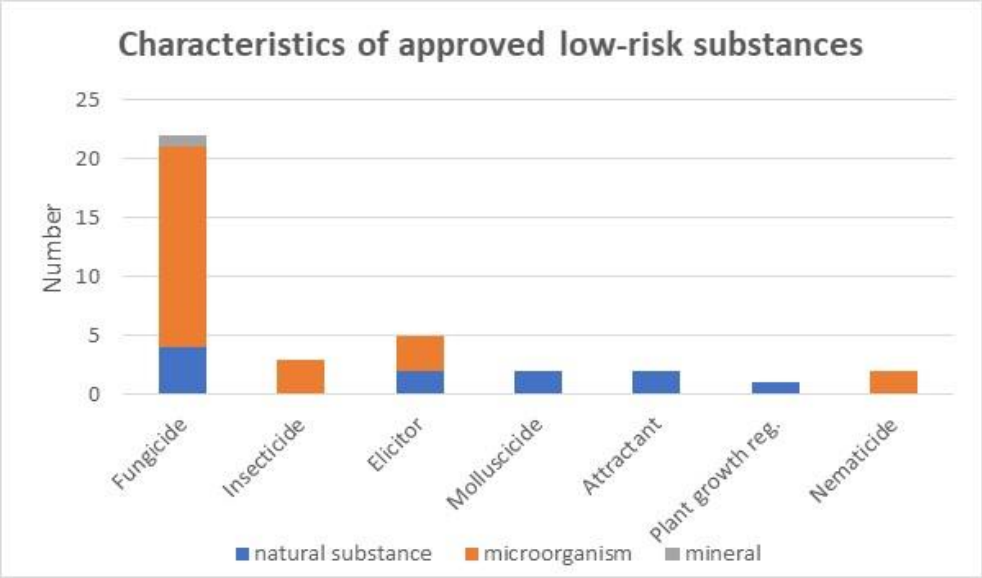

Figure 1 *Characteristics of EU approved low-risk substances (based on data from Robin and Marchand, 2022).*

The diversity of already approved low-risk pesticides is limited (Robin and Marchand 2022), and they present a limited number of functions: 61% are fungicides, 15% are elicitors (compounds which activate chemical defence in plants), and only a few are insecticides, molluscicides, attractant, nematicides and plant growth regulators (Figure 1). The number of potential usages is also limited.

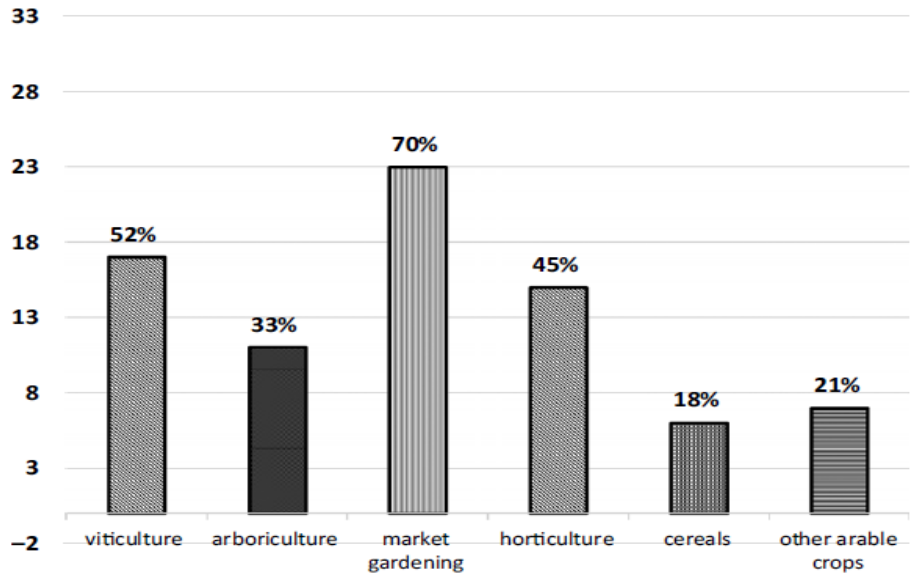

Figure 2 *Crop usages and distribution of low-risk substances, % expressed in kg uses (Robin and Marchand 2022).*

The distribution of crop usages for approved low-risk substances shows that field usages are not the main domain for low-risk substance (only 18% and 21% for cereal and other arable crops, respectively). Low-risk biocontrol agents are mainly usable for market gardening (70%) and viniculture (52%) (Figure 2). Regulatory unpredictability, high costs and long approval times in Europe negatively impact investments and how industries select projects and markets.

2.2.3 Basic substances

Basic substances refer to active substances that are not on the market as PPP but for other product classes, for instance as foodstuff[10], feed (relative to animal feeding), or cosmetics. Their safe use is easy to prove. One example is vinegar, used as fungicide, herbicide or pH modifier, but available on the market as both foodstuff and cleaning agent. For these substances no residue concerns apply (therefore no maximum residue limit nor preharvest intervals[11]). Active substances that can be defined as foodstuff are intrinsically considered as basic substances, following Article 2 of Regulation (EC) No. 178/2002 (Romanazzi, Orçonneau et al., 2022).

Basic substances may be of value for plant protection in areas in which the economic interest in applying for approval may be limited. As long as the substance does not have an immediate or delayed harmful effect on human and animal health nor an unacceptable effect on the environment, it can be legally used in the EU after having been approved as "basic" under Regulation (EC) No 1107/2009[12] (via derogation). In the application procedure for a basic substance status, justification of the simplified risk assessment should be provided (e.g. based on its use as food or feed).

Under the following conditions, an active substance can be approved with a simplified approach as a basic substance, for which the properties are described in Article 23 (European Commission 2009):

a. *is not a substance of concern; and*
b. *does not have an inherent capacity to cause endocrine disrupting, neurotoxic or immunotoxic effects; and*
c. *is not predominantly used for plant protection purposes but nevertheless is useful in plant protection either directly or in a product consisting of the substance and a simple diluent; and*
d. *is not placed on the market as a plant protection product.*

Specific guidance is available for the submission of applications concerning active substances that can be approved as "basic substances": SANCO/10363/2012 rev11. While all but one basic substance is of natural origin, there is only one specific guideline for naturally occurring substances: "the predicted environmental concentrations should be compared to the natural background concentrations. It should be demonstrated that the substance will not have 'an unacceptable effect on the environment'."

Unfortunately, no clear definition has yet been provided for "naturally occurring substances" (IBMA 2022).

Romanazzi et al. (2022) presented an overview of 24 basic substances that are currently approved in the EU. Most of these substances have a fungicidal activity (calcium hydroxide, chitosan, chitosan hydrochloride, *Equisetum arvense* L., hydrogen peroxide, lecithins, cow milk, mustard seed powder, *Salix* spp., sunflower oil, sodium chloride, sodium hydrogen carbonate, *Urtica* spp., vinegar, and whey). Considering the increasing requests from consumers of fruits and vegetables for high quality produce with no or a reduced amount of pesticide residues, basic substances can complement and, at times, replace the application of synthetic pesticides. As there is a need for application protocols, large-scale trials are important to design the best dosage and strategies for the application of basic substances against pathogens and pests in different growing environments and contexts.

The Ctgb approved 23 basic substances. The approval of five potential basic substances is pending (sodium hypochlorite, caffeine, ozone, willow bark and stem extract). Unapproved applications were often justified by a risk assessment for toxicology and ecotoxicology that was not comprehensive enough which left doubts (Romanazzi, Orçonneau et al., 2022). For instance, black soap and calcium propionate impurities (additives, preservatives for black soap, lead, mercury and arsenic for calcium) could lead to risks which were not included in the applicants' dossiers. Human exposure was also a concern for calcium propionate.

[10] "For the purposes of this Regulation, "food" (or "foodstuff") means any substance or product, whether processed, partially processed or unprocessed, intended to be, or reasonably expected to be ingested by humans" (extract of Article 2, No 178/2002). Further details https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32002R0178&from=EN (last accessed 04/12/2023).

[11] A preharvest interval is the minimum amount of time between the last application of a pesticide and when the crop can be harvested.

[12] European Commission. Approval of Active Substance. URL: https://food.ec.europa.eu/plants/pesticides/approval-active-substances_en#basic-substances (last accessed: 29/11/2023).

2.2.4 Market for basic substances

Basic substances are approved indefinitely and thus do not need a renewal of the approval.

While the approval of a basic substance is done based on definitions provided by Regulation (EC) No 1107/2009, a product consisting of one or more basic substances must not be placed on the market as a plant protection product, with the following nuances (European Commission 2021b):

- The label on the product may indicate that the basic substance it contains is approved under Article 23 of the Regulation (EC) No 1107/2009.
- Whenever the producer will add a reference to Article 23, it is recommended to add also any information related to conditions of approval of the basic substances of which the product consists of.

The guidance from the EC mentions that "it is recognized that the producer of such product may choose not to add such reference to the label", for instance when the producer is the applicant for the approval as a basic substance. In relation to this limitation concerning marketing as a plant protection product, there is also no record kept of the quantities of basic substances used as active substance in agriculture (Costantini and La Torre 2022).

The cost for registering a botanical as a basic substance is about €50,000. However, as a basic substance cannot be placed on the market as a plant protection product, marketing is not attractive and the possibilities to create a market are limited. This impedes the development of the use of, and knowledge relative to, basic substances which have no residue concerns, per definition. While it is possible to re-apply after non-approval, a majority of non-approved applications were abandoned due to financial reasons (costs of dossier preparation and registration process) (Robin and Marchand 2019).

As marketing is less attractive, the guidance for basic substances underlines that "the Commission as well as Member States will have to put measures into place to inform the public of basic substance approvals and their respective conditions." (European Commission 2021b).

2.3 Use of Low-risk substances in Integrated Pest Management strategies and organic farming

2.3.1 Integrated Pest Management in the Netherlands

In the policy document, Healthy Growth, Sustainable Harvest (Ministerie van Economische Zaken - Ministry of Economic Affairs 2013), the Dutch Government presented its crop protection policy for the 2013–2023 period. In its future plans, the Dutch government developed a roadmap for the future crop protection (https://www.toekomstvisiegewasbescherming2030.nl/) where in 2030 the current agriculture and horticulture will consist of a sustainable production with resilient plants and crops. The government's ambition is to make crop protection practice more sustainable and to comply with international standards for the environment, food safety and working conditions by 2030. The policy aims to achieve these targets by means of Integrated Pest Management (IPM). This involves crop management in which chemical crop protection is kept to a minimum and crop production remains economically viable. Preventive measures, such as the use of resilient crops, form the basis for such a cultivation system. When pests and diseases need to be controlled, non-chemical methods are preferred, such as biological pest control. This policy document also contains interim targets for 2018. These targets were evaluated in a survey that was conducted as part of an interim assessment (Netherlands Environmental Assessment Agency [PBL] 2019). The authors found that while most of the farmers used IPM steps and measures to prevent and control diseases and pests, not all possibilities were used yet. Moreover, there were major differences between different types of cultivation in terms of the extent to which farmers had switched to a system of IPM. Strengthening the application of IPM is a key component of the Dutch Implementation Programme 2022 – 2025[5]. The aim is to have a sustainable production with resilient plants and crops by means of Integrated Pest Management and where the use of low-risk substances is part of it. In this context the Board for the Authorization of Plant Protection Products and Biocides in The Netherlands (Ctgb) has opened a separate 'Sustainability Desk'. Applications for crop protection products that contribute to sustainable agriculture are processed with priority through this desk.

This means that a broader package of crop protection products that meets the criteria for sustainability will become available to Dutch growers more quickly. With this measure, the Ctgb is responding to calls from politics and society to actively facilitate more sustainable agriculture.

2.3.2 Organic farming

Organic farming allows a limited range of pesticides which are mainly made of naturally occurring substances such as microorganisms, plant extracts and pheromones (European Commission 2021a). The use of chemical plant protection products is significantly restricted (European Commission 2021a). Preference should be given to techniques which do not involve the use of plant protection products, such as crop rotation, natural enemies, the choice of species, varieties and heterogeneous material, cultivation techniques and thermal processes (European Commission 2018b). If such techniques do not provide adequate protection, the use of certain plant protection products is allowed, but only if those plant protection products have been authorized in accordance with Regulation (EC) No 1107/2009. They must be assessed and found to be compatible with the objectives and principles of organic production.

The use of biological alternatives for chemical pesticides plays a key role in organic farming and in Integrated Pest Management[13]. Farmers must give preference to preventive actions, monitoring and biological plant protection alternatives (including microorganism-based products), before using chemical plant protection products. Note that pesticides authorized in organic agriculture generally belong to the group of the registered pesticides that have a relatively low-risk profile.

Because of their potential lower or targeted efficiency, low-risk substances might be used in combination or rotation with traditional pesticides, or with other low-risk pesticides. While delaying pest resistance, it can be counterproductive when, for instance, a living organism is sensitive to the other pesticide. Positive synergies were also observed (Glare, Caradus et al., 2012).

[13] "Integrated pest management means careful consideration of all available plant protection methods and subsequent integration of appropriate measures that discourage the development of populations of harmful organisms and keep the use of plant protection products and other forms of intervention to levels that are economically and ecologically justified and reduce or minimise risks to human health and the environment. "Integrated pest management" emphasises the growth of a healthy crop with the least possible disruption to agro-ecosystems and encourages natural pest control mechanisms." (URL: https://food.ec.europa.eu/plants/pesticides/sustainable-use-pesticides/integrated-pest-management-ipm_en, accessed 28-02-2023)

3 Plant Biostimulants

3.1 Introduction

Biostimulants comprise a variety of products including substances, mixtures and microorganisms. They are not inputs of nutrients, but rather, they stimulate the natural nutrition processes of plants (European Commission 2019) independently of the product's nutrient content with the sole aim of improving one or more of the following characteristics of the plant or the plant rhizosphere: nutrient-use efficiency, toleration of abiotic stress (i.e. difficult growing conditions like extreme temperatures, drought or water logging, among others), and crop quality[14]. Biostimulants are regulated in the new EU Fertilising Products Regulation (FPR) 2019/1009 that went into force in July 2019 (European Commission 2019). Farmer interest in biostimulants is growing.

The FPR provides a common definition of plant biostimulants and offers access to a single European market. It started in July 2022 when the first CE-marked EU fertilising products were placed on the market. This European regulation will co-exist alongside national laws, but it has also promoted alignment on definitions and approaches to placing products on national markets.

Europe decided to define biostimulants by a functional approach with four kinds of functions/claims. These include increasing the plants' nutrient-use efficiency, increasing their tolerance to abiotic stress, increasing their quality traits and increasing the availability of confined nutrients in the soil or rhizosphere. By nature of these aims, they are more similar to fertilising products than to most categories of plant protection products. They act in addition to fertilisers, with the aim of optimising the efficiency of those fertilisers and reducing the nutrient application rates (European Commission 2019). Therefore, these products are excluded from the scope of Regulation (EC) No 1107/2009 of the European Parliament and of the Council. If products have one or more functions, of which one is covered by the scope of Regulation (EC) No 1107/2009 (plant protection product), these products will fall within the scope of Regulation (EC) No 1107/2009 and are excluded from the FPR regulation.

3.2 Summary of current guidance

Biostimulants are regulated under the EU Fertilising Products Regulation (FPR) that went into force in July 2019 (European Commission 2019). In total, the FPR recognizes seven different Product Function Categories (PFCs), with plant biostimulants being PFC 6. They may also be found in PFC 7 blends. The FPR provides a common definition of plant biostimulants. This European regulation co-exists alongside national laws but has promoted alignment on definitions and approaches to placing products on national markets. Biostimulants can be categorized into microbial plant stimulants and non-microbial plant stimulants. The regulation FPR also defines which component material can be used (and only these) to produce biostimulants (e.g. "plants, plant parts or plant extracts" or "microorganisms"). These categories of materials are called Component Material Categories (CMCs). There are 11 CMCs defined in the regulation. Some amendments are on-going for new inclusions of raw materials[15].

Microorganisms currently must be inscribed on an approved list (CMC 7 in Annex II of Regulation [EC] No 1107/2009).

[14] European biostimulants industry council. EU Regulation Ensures that Biostimulants Are Safe and Effective. URL: https://biostimulants.eu/highlights/eu-regulation-ensures-that-biostimulants-are-safe-and-effective/# (last accessed: 29/11/2023).

[15] European biostimulants industry council. EU Regulation Ensures that Biostimulants Are Safe and Effective. URL: https://biostimulants.eu/highlights/eu-regulation-ensures-that-biostimulants-are-safe-and-effective/# (last accessed: 29/11/2023).

A microbial plant stimulant needs to meet several criteria. It must consist of a microorganism or a consortium of microorganisms referred to in CMC 7 in Part II of Annex II of Regulation (EC) No 1107/2009. Pathogens must not exceed maximum limits set out in the regulation. Also certain limit values for a number of metals need to be adhered to (European Commission 2019). The label must contain the following phrase: "Microorganisms may have the potential to provoke sensitizing reactions." Plant biostimulants must have a pH optimal for contained microorganisms and for plants. For microbial plant stimulants all intentionally added microorganisms must be indicated. Where the microorganism has several strains, the intentionally added strains must be listed. Their concentration must be expressed as the number of active units per volume or weight, or in any other manner that is relevant to the microorganism, e.g. colony forming units per gram (cfu/g). For Microorganisms (CMC 7), only four are listed in the regulation: *Azotobacter* spp., Mycorrhizal fungi, *Rhizobium* spp. and *Azospirillum* spp.

The FPR does not include a list of toxicology and ecotoxicology data points. For the substances covered by Europe's chemical legislation, these questions fall under the REACH registration. Materials derived from animal by-products must have an endpoint relative to the Animal By-Products Regulation.

To obtain the CE mark, which allows for sale in the European Union, a biostimulant must be evaluated by an independent notified body by applying a relevant module of conformity. Whatever the module of conformity, a dossier is required and must contain manufacturing process, recipes, analyses, label, technical data sheet, safety data sheet, and efficiency trials.

Member States must implement EU Regulation 2019/1009 (Fertilising Products Regulation [FPR]) in order to make EU fertilising products available on the market.

3.3 Considerations and research questions biostimulants

Biostimulants improve plant resistance to diseases and can therefore be efficient against pests. The use of biostimulants could therefore be a lever in the Green Deal Farm to Fork strategy. However, the use and regulation of biostimulants raise some research questions:

- How can biostimulants be integrated into a crop approach with low-risk pesticides?
- How is the risk assessment for biostimulants being performed compared to low-risk pesticides under the pesticide directive?
- What are specific requirements and criteria for biostimulants to obtain the CE mark?

4 Microbial pesticides

4.1 Introduction

Microbial pesticides or Microbial Pest Control Agents (MPCAs) are agents based on living organisms and used for the control of plant diseases and pests. These organisms include bacteria, fungi, viruses, yeasts, protozoa and microsporidia among others and are also named microorganisms. MPCAs are natural enemies of phytophagous invertebrates, plant diseases or weeds. OECD (2012) defines a MPCA (Microbial Pest Control Agents) as a microorganism (e.g. bacterium, fungus, protozoan, virus, viroid, mycoplasma, algae) and any associated biological compounds/toxins, fermentation residues as manufactured, to which the effect of the pest control is attributed.

The term microorganism, as defined in Article 3 of Regulation (EC) No 1107/2009 (European Commission 2017), applies to, but is not limited to, bacteria, fungi, protozoa, viruses and viroids. This regulation defines microorganisms as any microbiological entity, including lower fungi and viruses, cellular or non-cellular, capable of replication or of transferring genetic material. In ECHA (2017) microorganisms are defined as any microbiological entity cellular or non-cellular, capable of replication or of transferring genetic material, including lower fungi, viruses, bacteria, yeasts, moulds, algae, protozoa and microscopic parasitic helminths. For all microorganisms that are subject to application, all available relevant knowledge and information in literature should be provided. The most important information is obtained by the characterization and identification of a microorganism. Such information should include identity, biological properties and any further information which form the basis for an assessment of human health and environmental effects. Newly generated data from conventional toxicological and/or pathological experiments on laboratory animals are normally required unless the applicant can justify, based on the previous information, that the use of the microorganism under the proposed conditions of use does not have any harmful effects on human and animal health or on groundwater or any unacceptable influence on the environment. The content of all fermentation residues in the growth media is an integral part of microbial pesticides. This means that, in addition to the living microorganism, any other metabolites are part of the microbial pesticide product.

Microbial pesticides can control many different kinds of pests, although each separate active ingredient is relatively specific for its target pest(s) (Leahy, Mendelsohn et al., 2014). Therefore, microbial pesticides can exhibit a range of Modes of Action. This is listed based on OECD classification (OECD 2012) in Table 1.

Table 1 *Modes of Action of Microbial pesticides (OECD 2012).*

Nr	Mode of Action	Explanation
1	Antibiosis	the antagonism resulting from the toxicity of secondary metabolites produced by one microorganism for other microorganisms, e.g. production of toxins, fungal bioactives (metabolites), production of cell-wall degrading enzymes.
2	Toxicity	toxins are included in the action of antibiosis.
3	Pathogenicity: mortality or sub-lethal effects	usually manifests in effects like mortality or obvious sublethal effects; dose-effect relation may however remain unclear because a microorganism will multiply in the target organism.
4	Induction of resistance in plants	as a result of interference with the virulence of a pathogenic target organism.
5	Interference with infectious organisms	infectious organisms include pathogenic bacteria, viruses, parasites or fungi.
6	Endophytic growth	any microorganism that inhabits internal tissues of plants.
7	Root colonisation	the proliferation of microorganisms in, on, or around roots of plants.
8	Competition for the ecological niche	e.g. competition for nutrients or habitats.
9	Parasite invasion	parasites invading other organisms and benefiting at the other's expense.

4.2 Summary of current guidance

4.2.1 Microorganisms as active substances

Microbial pesticides are regulated by Regulation (EC) No 1107/2009. In microbial pesticides the active ingredient is not a chemical molecule but rather living organisms. The risk assessment, therefore, does not fit well in a risk assessment for chemicals. Up to now, these pesticides have faced a major hurdle on unclear data providing guidelines to facilitate the registration process for the European Union.

At the European level a working group (EU WG) on biopesticides including several Member States has worked on proposals for the revision of the data requirements and the uniform principles for microbial pesticides. The Dutch working group on microbial pesticides, consisting of representatives of WUR, RIVM, NIOO, UU and the Ctgb and chaired by WUR (WENR), has contributed to this process by discussing topics and questions from the EU WG in the form of informal advice and memos which were brought into the discussions of the EU WG by the Ctgb. In the Dutch working group, topics that were discussed specifically included: antimicrobial compounds and antimicrobial resistance; secondary metabolites; endophytic versus epiphytic lifestyle; environmental fate and behaviour; effects on non-target microorganisms; invasiveness; indigenous nature of microorganisms; and other topics related to the data requirements and uniform principles.

The new uniform principles and data requirements were accepted by the European Commission and came into force on 21 November 2022[16]. The new rules are intended to facilitate the approval of microorganisms for use as active substances in plant protection products and the authorisation of products containing them. The purpose is for farmers across the European Union to have better access to biological alternatives to chemical pesticides.

The new data requirements for microorganisms used as active ingredients in microbial pesticides include a separate part of the Annex to Commission Regulation (EU) No 283/2013 that is dedicated to these type of pesticides (Part A: Chemical active substances, part B: Microorganisms including viruses). This is the part of the regulatory risk assessment that has been adapted and made more fit-for-purpose for microbial pesticides.

The new uniform principles and data requirements are based on the biology and ecology of each microorganism. In addition to being more focused on the relevant characteristics of each genus/strain of microorganism, the regulatory requirements are also made more flexible, i.e., only focusing on the relevant data. Overall, a microorganism can only enter the approval process for use if it has been proven that it does not cause diseases in humans and animals. In addition:

a. viruses shall only be approved if, based on the assessment carried out on the information provided in accordance with the data requirements, it is concluded that the isolate of the virus is not infective to humans;
b. strains of bacteria shall only be approved if, on the basis of the assessment carried out on the information provided in accordance with the data requirements, it is concluded that they do not have any known, functional and transferable gene coding for resistance to relevant antimicrobial agents as defined in accordance with the data requirements.

Of course, resistance to relevant antimicrobial agents (genes that are resistant against antibiotics) is of concern and needs to be assessed in the risk assessment.

For each microbial strain the data requirements request a full dataset to be delivered "from scratch", without acknowledging the fact that strains belong to higher groups (species) for which often a body of knowledge is already available. This includes knowledge on potential pathogenicity, the production of known harmful metabolites and the potential for cytotoxicity.

[16] European commission. Microorganisms used in plant protection products. URL: https://food.ec.europa.eu/plants/pesticides/micro-organisms_en (last accessed: 29/11/2023).

The Dutch working group on microbial pesticides concluded that the new uniform principles and data requirements are not expected to lead to a quicker access of microbial pesticides on the market. The working group has the opinion that the QPS (Qualified presumption of safety) principle for microbial pesticides, similar to the application of this principle in the Food and Feed risk assessment performed by EFSA[17] (Herman et al., 2019) is a better way forward. The QPS concept was developed in 2003 to provide a harmonised, generic safety pre-appraisal of microorganisms used in the food and feed chain (European Commission 2003). Well-defined biological taxonomic units (TUs) are assessed for their taxonomic identification, body of knowledge, safety (possible pathogenicity) and end use. If the TU does not raise safety concerns or if any safety concerns can be defined and excluded (the qualification), the TU can be granted QPS status. Thereafter, any strain of microorganism whose identity can be unambiguously established and assigned to a TU with QPS status is freed from the need for further assessment other than satisfying any qualification specified.

Lists of microorganisms that qualify for the QPS approach are public and are regularly updated[18]. The Dutch working group has argued that the QPS approach should be extended to microbial pesticides, thereby creating a more harmonized approach in the safety assessment of all microbial products in the EU and over the different policy areas. Moreover the use of the QPS approach for all microbial products is in line with the "one substance, one assessment" strategy that is embedded in the Green Deal (van Dijk, Gustavsson et al., 2021).

Microorganisms not considered suitable for a QPS status would remain subject to a full safety assessment (Herman, Chemaly et al., 2019). Strains belonging to TUs having QPS status may benefit from a fast-track evaluation. The lowest level of TU for which the QPS status is granted is the species level for bacteria and yeasts and the family level for viruses. Based on the current body of knowledge and the ambiguous taxonomic position, some TUs (e.g. filamentous fungi, bacteriophages, *Enterococcus faecium*, *Escherichia coli*, *Streptomyces* spp. and Oomycetes) are not considered eligible for QPS status (Herman, Chemaly et al., 2019). There is an opening for change; three virus families used as plant protection products (plant viruses Alphaflexiviridae and Potyviridae; insect viruses Baculoviridae [EFSA 2017]) are included on the QPS list of 2016, while the QPS principle is not accepted and included in the revised uniform principles and data requirements of Regulation (EC) No 1107/2009.

All microorganisms applying for acceptance in regulated products (like pesticides) are screened by the BIOHAZ Panel of EFSA to determine if they meet the QPS criteria. If it meets the QPS criteria, it can follow a fast-track procedure for the safety assessment. This route can only be followed if the fast-track procedure is laid down in regulation. Until now the EC has decided that the QPS principle is not applicable to microbial pesticides. The rationale for this decision is that the focus of QPS is on food and feed safety, so the environmental risks might not be addressed sufficiently.

Currently, the BIOHAZ Panel is taking action to foster the application of the QPS principle in the assessment of microbial pesticides. The BIOHAZ Panel takes care of the QPS qualifications and criteria.

The new uniform principles and data requirements include many conditional data requirements. Although this conditionality ensures more flexibility and a case-specific approach in safety assessment, the downside may be a difference in interpretation by competent national authorities and EFSA regarding whether these data are needed or not. To come to a harmonized approach within the EU, clear guidance is needed to specify when a specific data requirement is considered relevant or not.

[17] EFSA (02/10/2023). Qualified presumption of safety (QPS). URL: https://www.efsa.europa.eu/en/topics/topic/qualified-presumption-safety-qps (last accessed: 29/11/2023).

[18] EFSA (07/07/2021). Update of the list of QPS-recommended biological agents intentionally added to food or feed as notified to EFSA 14: suitability of taxonomic units notified to EFSA until March 2021. URL: https://www.efsa.europa.eu/en/efsajournal/pub/6689 (last accessed: 29/11/2023).

At the end of 2020, two guidance documents for microorganisms were accepted and published by the European commission:

- EC, 2020. Guidance on the approval and low-risk criteria linked to "Antimicrobial resistance" applicable to microorganisms used for plant protection in accordance with Regulation (EC) No 1107/2009. SANTE/2020/12260. 14 pp.
- EC, 2020. Guidance on the risk assessment of metabolites produced by microorganisms used as plant protection active substances in accordance with Article 77 of Regulation (EC) No 1107/2009. 42 pp.

These two guidance documents are not legally binding.

4.2.2 Summary of new microbial pesticide data requirements

The new uniform principles and data requirements accepted by the European Commission that came into force on 21 November 2022 have taken the approach of a hazard assessment.

The specific Part B of data requirements[19] is focused on active substances that are microorganisms. In this section a brief summary of the data requirements focusing on the fate and effects of microbial pesticides is presented.

The data requirements for active substances take the principles from the 2020 guidance documents on antimicrobial resistance and metabolites. The data requirements adopt the terminology of (potential) metabolites of concern and apply these to secondary metabolites (i.e. metabolites not involved in primary processes). The metabolites of concern apply to both metabolites in the products and those produced in situ, unless otherwise indicated.

Within the risk assessment, it is required that an assessment be made of the exposure of humans and non-target organisms to the active substance and, where relevant, to metabolites of concern. In case metabolites which are hazardous to humans or non-target organisms are present in the microbial pesticides as manufactured, the predicted environmental concentration of the metabolites in the relevant environmental compartment (i.e. soil, surface water, groundwater or air) must be provided. No predicted environmental concentration calculations are needed for metabolites for which a hazard to human health or non-target organisms was identified that are produced in situ but are not present in the microbial pesticides as manufactured. This requirement was lifted as making metabolites in-situ is a biological property of microorganisms. For those metabolites for which a hazard to non-target organisms is identified, an estimation of exposure of the relevant non-target organisms must be provided. This latter requirement was not lifted.

Another requirement that was not lifted is as follows. If a potential risk is identified for humans or non-target organisms or information is not sufficient to make a conclusion, the population density of the microorganism must be determined in relevant environmental compartments (e.g. soil, water, plant surfaces).

If a hazard to non-target organisms is identified, information on toxicity to the non-target organisms is required. Effects on non-target species include the evaluation of short- and long-term risks for populations, communities, and processes, as appropriate. A summary on potential infectivity and pathogenicity of the microorganism to non-target arthropods other than bees, as well as on non-target soil meso- and macro-organisms, non-target terrestrial plants and non-target microorganisms is also required. If studies are necessary, they must be performed on two non-target meso- and macro-organism species chosen based on the biological properties of the microorganism under evaluation, where possible, for which agreed testing protocols are available.

The new data requirements need guidance for further implementation. OECD has taken up this task. The NL working group considers it as its task to discuss draft guidance documents and comment on them.

[19] European commission. Micro-organisms used in plant protection products. URL: https://food.ec.europa.eu/plants/pesticides/micro-organisms_en (last accessed: 29/11/2023).

4.3 Considerations and research questions microbial pesticides

The revised data requirements for microbial pesticides benefit from a clear distinction of these requirements in a separate part B. The hazard approach, whereby further risks are assessed only if a hazard is identified, is also an improvement. Some requirements are still included in the new regulation which were discussed by the Dutch working group on microbial pesticides and identified as not necessarily based on scientific knowledge, e.g. in-soil risk assessment for other microbes.

One topic is the question of whether microorganisms are endophytic. Many microorganisms are optionally endophytic[20]. Therefore, the working group concluded that this criterium is not adequate, given the transient presence of endophytic biocontrol microorganisms and the overall low concentrations in which they occur. This conclusion was underpinned by a literature research (Scheepmaker 2021).

Actions to foster the application of the QPS principle in the assessment of microbial pesticides would be a big step forward. Although the new uniform principles and data requirements are based on the biology and ecology of each microorganism, and a hazard approach was adopted, the data requirements are still very demanding and therefore expensive (see also Sundh and Eilenberg 2021). Relevance and weight of evidence are a part of the data requirements and the industry (mostly small and medium-sized enterprises) needs to make a case for their product. To lower the effort, a problem formulation approach could be followed in which the biological properties and the use of the microorganisms are included in a scenario. This would lead to a more targeted risk assessment.

Test methodologies could also be approved and could be made more targeted, considering the routes of exposure. A follow-up action for the Dutch working group is to write a paper about the application of the QPS approach to microbial pesticides which is in line with the "one substance, one assessment" strategy that is embedded in the Green Deal.

Sundh and Eilenberg (2021) investigated the reason that the authorization of microbial pest control agents is lengthier under regulatory frameworks of the European Union (EU) than in comparable jurisdictions. A main conclusion is that although the EU's regulatory processes have strong scientific foundations, the most appropriate scientific concepts, knowledge and expertise have not been applied in the safety assessment of microorganisms and biological control. Tradition and conceptual legacies from assessments of conventional chemical pesticides have likely contributed to this by steering the evaluations of microorganisms in less appropriate directions. In conclusion, more expertise is needed at regulatory bodies.

[20] An endophyte is any microbe (typically fungal or bacterial) that enters and inhabits internal tissues of plants.

5 Botanicals

5.1 Introduction

Plants synthesize molecules that are able to repel or kill insects as part of their intrinsic defensive mechanism. Those chemicals are referred to as "secondary plant products". Extract from such plants have been used historically as insecticides and repellents, but their field of application has been extended to bactericides, fungicides, herbicides and nematicides (Acheuk, Basiouni et al., 2022).

For the EU, "botanical active substances" are defined as consisting of one or more components found in plants and obtained by subjecting plants[21] or parts of plants of the same species to a process such as pressing, milling, crushing, distillation and/or extractions. The process may include further concentration, purification and/or blending, provided that the chemical nature of the components is not intentionally modified/altered by chemical and/or microbial processes. This is an extension of a prior regulation that only considered plant extracts obtained with water and alcohol, both solvents that are easily accessible.

Botanical active substances differ from synthesized chemicals in their origin. Synthesized chemicals are produced by chemical reactions whereas botanical active substances are obtained by processing material of biological origin. If botanical molecules are obtained through synthesis they will not fall under the definition of botanicals for regulatory purposes.

Of the different natural substances, botanicals are the only group for which an approval guidance is available at the European level (European Commission 2014). The possible explanation is that only few natural substances of animal/microbial or mineral origin are candidates. Currently, natural substances represent 50% of the 216 biocontrol active substances registered (Robin, Merlet et al., 2022). A guidance is also available from the OECD (OECD 2017).

The following summarizes the requirements for describing the identity of the botanical (European Commission 2014):

- Scientific name: full systematic species name including botanical family, genus, species, author's name and where relevant variety, subspecies and chemotype. Synonyms: botanical name(s) that may be used interchangeably with the preferred scientific name.
- Common names: vernacular name(s).
- Biogeography: regions, countries, area/sites of cultivation, natural habitats.
- Part of plant used: e.g. root, leaf, seed, fruit.
- Growth stage(es) of plant used.

As plant material might vary from plant to plant as a result of natural variability and as a result of the mode of extraction, some variability of the produced material might occur (Villaverde, Sevilla-Morán et al., 2014). This variability is accounted for in the definition of the technical grade. The technical grade produced from the defined sources and by the described manufacturing processes is the active substance in the sense of Regulation (EC) No 1107/2009. Therefore, the sources of the material and the methods of manufacture are also part of the active substance specification. The technical grade should be defined by a justified suitable method, such as chromatographic techniques in combination with spectroscopic techniques using a suitable reference sample or standard, and the purity of these should be stated.

The sourcing of the plant is relevant in the approval process (European Commission 2014). "For all 'botanical active substances' it should be made clear that the plant material has been produced with sustainable, reproducible methods and that the Nagoya Protocol on Access to genetic resources and fair and equitable

[21] Note that as the term plant, as used in this guidance, includes any organism belonging to Kingdom Plantae. As a consequence, this term includes flowering plants, trees, herbs, bushes, grasses, vines, ferns, mosses, and algae. Fungi, lichens, mushrooms and yeast are excluded. As a consequence, botanicals do not include extract from fungi, lichens, mushrooms or yeast.

sharing of benefits, adopted by the Conference of the parties to the Convention on Biological Diversity (2010 in Nagoya), has been respected."

Some plant extracts act as semiochemicals. However, they are treated differently in the regulation (see section 2.2.1, Article 5.1.3 of the Annex II point 5 of the substances Regulation (EC) No 1107/2009).

Botanicals can act as insecticides, herbicides and fungicides. Their mode of action might cause repellent, antifeedant, toxic and growth regulation effects (Figure 3) (Acheuk, Basiouni et al., 2022).

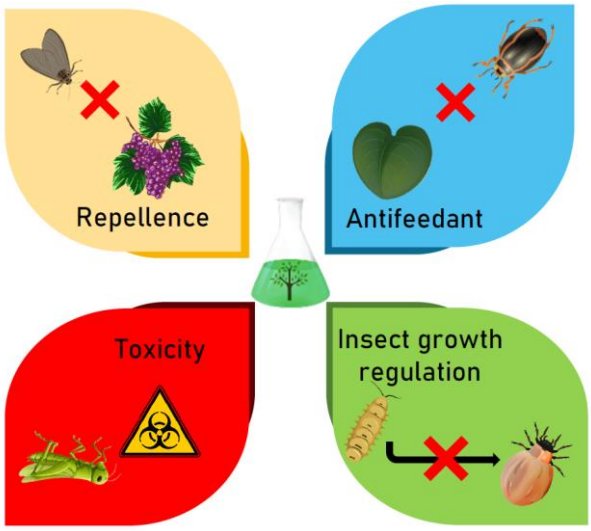

Figure 3 *Different modes of action of botanicals which protect plants from insects (Acheuk, Basiouni et al., 2022).*

Botanicals can belong to different chemical families. This information is important to know as it might relate to the Mode of Action of the botanical:

- Alkaloids (any of a class of naturally occurring organic nitrogen-containing bases)
- Phenolics (secondary metabolites widely spread throughout the plant kingdom with around 8,000 different phenolic structures)
- Essential oils (distilled essence of various aromatic plants)
- Limonoids (a prominent group of secondary metabolites in citrus fruit)
- Pyrethrins (also known as pyrethrum, is a compound extracted from the chrysanthemum flower; it has insecticidal mode of action)
- Polyketides (produced in bacteria, fungi, plants, and certain marine organisms)
- Fatty acids (components of glycerol-containing lipids or glycerolipids)

5.2 Summary of current guidance

5.2.1 Botanicals as active substances

As presented in the introduction, botanicals fall under the regulation for active substances Regulation (EC) No 1107/2009 (European Commission 2009). Considering the potential toxic effects of some botanicals, they are not automatically considered as potentially low-risk (Smith and Perfetti 2020). As a result, the same procedure as for chemical PPP is required. A botanical of lower-risk might then be registered as a low-risk product or basic substance.

General considerations for plant extracts are described by the Guidance Document on botanical active substances used in plant protection products (European Commission 2014). This guidance takes into consideration the natural origin of the product and aims to provide practical solutions on how procedures and data requirements can be applied to facilitate the approval of botanical active substances at the EU level.

Botanicals are more or less complex mixtures of naturally occurring components. Each component could be involved in the efficiency of the material, while the share of each component in this efficiency might be unknown. The guidance stipulates that the degree of required characterisation (concentration, number of chemicals to characterise, method used) of the chemical composition is a result of:

- The state of knowledge of the botanical concerning its safe use, or possible adverse or toxic effects of the material itself. The level of required detail will then differ (see paragraph below);
- The type of chemical which is required to characterise. An emphasis will be made on the components of relevance for the safety assessment.

Based on the taxonomy and/or current knowledge of the botanical source, the following groups can be distinguished. This leads to different requirements, especially for analytical methods and regulatory approaches (European Commission 2014):

Group 1
Botanical active substances that are currently known to have no unacceptable effects on humans, animals and the environment and are based on materials with known specifications, e.g. food grade[22].

Group 2
Botanical active substances based on a material with an established specification and for which the taxonomy and current knowledge indicates that the botanical active substance may contain components of possible concern (EFSA 2012) for humans, animals and/or the environment. In this case these components should be identified and quantified.

Group 3
Botanical active substances that are not based on a material with an established specification. In this case, complete identification and characterization is needed.

The list of botanicals not approved as active substances (and therefore not able to access the status of low-risk substance) contains the following (Vekemans and Marchand 2020):

- Citrus extract
- Grapefruit seed extract
- Conifer needle powder
- Extract from Menta piperita
- Garlic pulp
- Marigold extract
- Onion extract
- Mustard powder
- Marjoram oil
- Coconut oil
- Soybean extract
- Wheat gluten
- *Reynoutria sachalinensis* extract

5.2.2 Low-risk botanical active substances

Specific modifications were made to Regulation (EC) No 1107/2009 to facilitate the approval of naturally occurring substances as low-risk. This was done by removing the criteria for persistence and bioconcentration if the criteria for toxicity are satisfied (see point 5.1.2 of the Annex II, as presented in Section 2.2.1).

In 2018 a list of approved active substances which were potential low-risk substances was created. None of the botanical substances on the list were approved as low-risk, and two were not approved as active substance under Regulation (EC) No 1107/2009 at all. To compare with the other natural substances (non-botanicals) of the list, three natural substances were approved (Robin and Marchand 2022).

[22] The guidance refers to the use of JEFCA evaluations and of the Food Chemicals Codex.

The list of approved active substances with low-risk (date 23 May 2023) is provided in Annex 2.

5.2.3 Botanical active substances registered as basic substances

Despite the facilitated processes, 13 botanicals proposed as basic substances were not approved:
1. Grape (*Vitis vinifera*) cane tannins,
2. propolis (water-soluble extract),
3. *Saponaria officinalis* (root extract),
4. *Artemisia absinthium L.*,
5. *Origanum vulgare L.* essential oil,
6. *Satureja montana L.* essential oil,
7. *Arctium lappa L.* (aerial parts),
8. *Tanacetum vulgare L.*,
9. *Artemisia vulgaris L.*,
10. paprika extract (capsanthin, capsorubin E 160 c),
11. *Achillea millefolium L.*,
12. *Rheum officinale* root extract, and
13. citrus pulp.

The motivations for refusal referred to an insufficient risk assessment. This left doubts for about 20 of the botanicals (Romanazzi, Orçonneau et al., 2022).

Seven substances were withdrawn:
1. extract of the wood of *Quassia amara L.*,
2. rhododendron honey,
3. *Castanea* tannins,
4. *Schinopsis* tannins,
5. fermented extract from leaves of *Symphytum officinale L.* (comfrey),
6. extract from Rhododendron, and
7. Valerian extract (Vekemans and Marchand 2020).

Of the 24 approved basic substances, seven are botanicals:
1. garlic extract,
2. onion oil,
3. sunflower oil,
4. *Equisetum arvense* L.,
5. *Salix* spp.,
6. mustard seeds powder, and
7. *Urtica* spp.

The list of approved basic substances is provided in Annex 3.

5.3 Considerations and research questions botanicals

Plant extracts can represent a risk for humans and non-target organisms. The corresponding risk should be addressed accordingly. If the studied botanicals are ranked in categories based on either the known toxicity or the level of knowledge concerning the toxicity, the guidance can then use these categories for assessing the risk. Based on their level of risk, botanicals can be registered as active substances, low-risk active substances or basic substances. Recommendations for facilitating registrations under those different status would help.

Natural extracts represent a large share of existing active substances. However, a study shows that botanicals can face difficulties in obtaining approval as an active (regular or low-risk) substance even though they might present a similar risk as chemical products which are already approved (Vekemans and Marchand

2020). Botanicals also seem to meet rejections for their approval as basic substances from EFSA (Vekemans and Marchand 2020).

In the framework of IPM, understanding and tackling the difficulties specific to botanicals in being registered should be a priority to increase the number of approved plant-based PPPs.

The current approval process for PPPs is cumbersome and costly. The most protective regulation in the world also hinders the arrival to the market of botanical substances, as pointed out by Vekemans and Marchand (2020). The limiting points for botanicals' acceptance as active or basic substances are (Vekemans and Marchand 2020, Romanazzi, Orçonneau et al., 2022):

- Supposed toxicity (in the case of grape cane tannins, despite its status as a basic substance and its use as a feed additive for mammals)
- Supplementary data requests for impact on the environment, birds and aquatic species
- Toxicity of one ingredient (ex: rotenone, nicotine)

Suggested changes which would give botanicals better access to the status of active substance are (Romanazzi 2022):

- Accelerating the acquirement of toxicological data for promising botanicals
- Precisely stating the degree to which the composition of the botanical needs to be determined and how much a batch can differ

Difficulties for risk assessment might relate to tests which were tailored for chemical pesticides with high potency at low dose. Botanicals can present different physical-chemical characteristics, which are not compatible with those tests. Therefore focusing on the requirements and developing techniques which contractor labs could easily apply for such compounds would help.

Given the fact that botanicals suffer from uncertainty in the data requirements which hampers the availability of these substances on the market, botanicals would benefit from research focusing on the data requirements relevant to this group of substances. An important research question could be formulated as: What should the data requirements and a regulatory framework for botanicals look like?

6 Semiochemical active substances

6.1 Introduction

The EC (2016) presents a definition of semiochemicals: Semiochemicals are substances or mixtures of substances emitted by plants, animals, and other organisms that evoke a behavioural or physiological response in individuals of the same or other species.

Different types of semiochemicals are:

- *Allelochemicals*, produced by individuals of one species that modify the behaviour of individuals of a different species (i.e. an interspecific effect). They include allomones (emitting species benefits), kairomones (receptor species benefits) and synomones (both species benefit).
- *Pheromones*, produced by individuals of a species that modify the behaviour of other individuals of the same species (i.e. an intraspecific effect).
- *Straight-chained lepidopteran pheromones* (SCLPs), a specific class of pheromones consisting of unbranched aliphatics which have a chain of nine to eighteen carbons, containing up to three double bonds, ending in an alcohol, acetate or aldehyde functional group. This structural definition encompasses most known pheromones produced by insects in the order Lepidoptera, which includes butterflies and moths.

Semiochemical active substances must be approved under Regulation (EC) No 1107/2009, and a dossier must be compiled according to the data requirements as laid down in Part A to Regulation (EU) No 283/2013 (active substance) and Part A to Regulation (EU) No 284/2013 (plant protection product) (European Commission 2016). The legal framework will also be the basis for the peer review and decision-making process, which means the data requirements and the protection goals, as laid down in the Uniform Principles Part I (Regulation (EU) No 546/2011), must be respected. The European Guidance document on semiochemical active substances and plant protection products (SANTE/12815/2014 rev. 5.2) was published and came into force per 1 January 2017.

The OECD Working Group on Pesticides (WGP) has developed guidance and rationales for the specific registration requirements for semiochemicals (European Commission 2016). However, guidance is not legally binding.

The use of pheromones has a large potential (Witzgall, Kirsch et al., 2010, European Commission 2016). Hundreds of pheromones and other semiochemicals have been discovered that are used to monitor the presence and abundance of insects and to protect plants and animals against insects (Witzgall, Kirsch et al., 2010). Pheromones may be used to mass trap insects in order to reduce population levels, or applied as a mating disruption method to control populations of insect pests (Reddy, Sharma et al., 2020). Semiochemicals may also be used as part of weed control measures (Gaffke, Alborn et al., 2021). In developing a regulatory approach for semiochemicals, their specific properties should be considered. They are often target-specific and act by modifying behaviour, may be used at concentrations close to those present in nature, and may dissipate and/or degrade rapidly. Up to now efficacy, environmental and health studies have demonstrated that such substances may provide effective pest control at low volumes, and at minimal risk (European Commission 2016).

6.2 Summary of current guidance

In the updated data requirements of Regulation (EC) No 1107/2009 from November 2022, semiochemical active substances are considered chemicals and included in part A of the data requirements. Semiochemicals need to follow the regulation for chemical pesticides, but in this process they can make use of justified

exemptions. No specific data requirements focusing on semiochemicals are currently distinguished from chemical pesticides.

Guidance exists for Waiving of Data Requirements for Pheromones for Inclusion in Annex I/IA of Directive 98/8/EC (Directorate-General ENV 2005). The OECD has also provided guidance (OECD 2003, recently updated in SANTE/12815/2014 rev. 5.2 [European Commission 2016]).

Key information for the assessment of semiochemicals includes information on the biology of the target organism(s) and the specificity of the communication between organisms and the resulting lack of effects on non-target organisms. Information is needed to demonstrate this can be collected from efficacy trials or fundamental investigations on emitting and receiving species. Data requirements for human health and environmental risk assessment also depend on the type of plant protection product and on its realistic conditions of use. In this context, SANTE/12815/2014 differentiates between different types of application techniques, e.g. different types of dispensers, granular products, and seed treatment products. These different application techniques all require different approaches to the exposure assessment and hazard identification. It may also be possible to use effects data derived from dossiers provided for other uses such as biocidal use, medical and veterinary use, cosmetic use, food and feed additives (European Commission 2016). The aim is to identify either areas of potential unacceptable effects on the non-target species or whether the exposure levels do not result in unacceptable effects under the proposed conditions of use.

The guidance SANTE/12815/2014 stresses that semiochemicals are active substances in plant protection products with a non-toxic, target specific mode of action and with a natural occurrence. The release of a semiochemical should be compared to natural exposure levels of the semiochemical or a group of related semiochemicals when justified.

6.3 Considerations and research questions semiochemicals

Despite their advantages, progress with practical implementation and commercial exploitation of semiochemicals has been slow. There is limited uptake of using them in pest control, but there is a high potential for them to become part of integrated pest management (IPM) (Sharma, Sandhi et al., 2019).

Historical separation of agriculture and pure biology at most universities has prevented the implementation of ecological principles in agriculture. This has contributed to a slow adoption of new technologies in agriculture (Witzgall, Kirsch et al., 2010). It is the role of science to link these fields of expertise and make knowledge more applicable in agriculture.

Given the fact that semiochemicals suffer from uncertainty in the data requirements and that this hampers the availability of these substances on the market, they would benefit from research focusing on the data requirements relevant for this group of substances. A main research question is: what should the data requirements and a regulatory framework for semiochemicals look like?

Another research question is: which semiochemicals, that are not already approved, are promising for registration? (Already approved ones include ones against grapevine and codling moths [a few countries in Europe], Isomate CLR, Checkmate, and Isonet [the Netherlands].)

7 Natural substances other than botanicals

7.1 Introduction

Natural substances are covered by the regulation for active substances Regulation (EC) No 1107/2009 (European Commission 2009). "Natural substances" is a term that is not defined in this regulation. The term covers substances of plant origin (also called "botanicals", subject treated in Section 5), but also substances from mineral and animal origin. Therefore, natural substances are a diverse group (IBMA 2022). This diversity is also reflected in the different definitions that are used. Some definitions are based on Mode of Action, some on origin, some on risk, and some on a mixtures of parameters (IBMA 2022). Natural substances are considered to have a more favourable safety profile, a specific mode of action and a faster biodegradability compared to conventional synthetic pesticides (IBMA 2022).

In 2022, the natural substances approved as low-risk, other than botanicals were (Robin and Marchand 2022):

- Three mineral extracts: ferric pyrophosphate, sodium hydrogen carbonate, calcium carbonate;
- One extract from an algae type: Laminarin;
- One mix plant/animal extract: COS-OGA;
- One extract from yeast: ABE-IT 56.

The list of approved active substances with low-risk (accessed date 23 May 2023) is provided in Annex 2, and the list of approved basic substances (accessed date 23 May 2023) is provided in Annex 3.

Since 2018, with the publication of the list of potentially low-risk active substances, three natural substances were added: blood meal, calcium carbonate and potassium hydrogen carbonate. These additions make a total of 11 natural substances in the low-risk group. Despite them being included on the list of potentially low-risk substances, three natural substances (other than botanicals) were not renewed as active substances (Robin et al., 2022). Non-renewal of the approval was either due to the mode of action not covered by Regulation (EC) No 1107/2009 (attractant, physical barrier, biostimulant) or due to the absence of a new submitted application supporting the renewal of the substance.

For instance, sea-algae extract was approved as a low-risk substance in 2008. The substance AGRI-40, which is based on sea-algae extract, was accepted with the claim that it created a physical barrier which would suffocate the insect. In the meantime, sea-algae extract is now on the market as a biostimulant. In 2019, when the approval of sea-algae extract should have been renewed, no new dossier was submitted that supported a re-approval as an active substance, and therefore sea-algae extract is not on the list of low-risk substances any more.

The EU is characterized by a reduced number of registered natural substances and ranks high in the uncertainty level on the data requirements.

7.2 Summary of current guidance

The EU does not have a specific regulatory framework for natural substances (IBMA 2022). They are regulated under Regulation (EC) No 1107/2009. Natural substances can be approved as either active or basic substances. There is no specific guidance for substances of mineral or animal origin. Regulation (EC) No 1107/2009 mentions that "justified exemptions can be made" or "a different approach may be taken if adequately justified".

Recent changes (2017) in the criteria for approval of low-risk substances (see details in section 2.2.1) regarding the persistence in the environment and bioconcentrations might be favourable for the acceptance of some natural substances.

7.3 Considerations and research questions natural substances other than botanicals

Given the fact that natural substances form a heterogenous group and uncertainty in the data requirements hampers their availability on the market, they would benefit from research focusing on the relevant data requirements. An important research question is therefore: How should the data requirements and a regulatory framework for natural substances look?

Natural substances having a physical action are facing not being renewed as low-risk, while they might be effective for the treatment of a pest. Natural substances falling out of Regulation (EC) No 1107/2009 enter a grey zone while they can still have a use for pest management. The Member States should accompany these substances in order to help the development of appropriate doses and ensure that their use on fields is sustainable.

8 Recommendations and conclusions

8.1 Regulation of lower-risk pesticides and access to the European market

Active substances used in plant protection formulations are approved within the context of Regulation (EC) No 1107/2009. These substances might show different levels of risk. This is now partially captured by the definition of low-risk substances and basic substances within this regulation.

To be approved as a low-risk substance, an active substance must meet both the regular approval criteria for active substances and the low-risk criteria defined in Regulation (EC) No 1107/2009. For a substance to get the status of basic substance they should already be on the market, for instance as foodstuff, feed or cosmetics. The marketing of a basic substance as a pesticide is not allowed. The status of low-risk can be indicated on the active as well as on the final product.

Low-risk substances and basic substances are heterogeneous groups of active substances, which include naturally occurring substances (called here biopesticides) as for instance botanicals, semiochemicals and microorganisms. Note that while no synthetic chemical active substance currently obtained the status of low-risk or basic substances according to Regulation (EC) No 1107/2009 (see the data collected in Annex 2 and 3 in the context of this research) biopesticides are not exempt of risks and should be evaluated before being allowed on the market.

The prominence of biopesticides in the lower risk pesticides make them promising for reaching the Farm to Fork objectives of harmful pesticide reduction. However, Regulation (EC) No 1107/2009 was developed for chemical pesticides, and biopesticides present physical, chemical or biological specificities which are not easily taken into account in the approval process. Consequently, Regulation (EC) No 1107/2009 was recently adapted for microorganisms (Part B of the regulation) and, to some extent, to semiochemicals. However, for other biopesticides there are no specific considerations and a targeted framework is missing. At the moment, only non-binding guidance documents are available for botanicals and semiochemicals. Other approaches could be considered. For instance the USA, Brazil and Australia have set a dedicated regulation for natural substances, while Europe has not prepared a separate track for their approval (IBMA 2022). Arche (2018) concludes that the current regulation for pesticides is not sufficiently adapted to substances of natural origin.

Additionally, fees for registration of low-risk substances with a nontoxic mode of action were reported to be much higher in Europe compared to the US, with shorter timelines in the US than in Europe (IBMA 2022). Other drawbacks of the European regulations are that criteria for low-risk are hazard-based and not risk-based. Hazard is the potential of something to cause harm, while risk is the likelihood of harm occurring[23]. The regulations do not distinguish a prioritization path or fast-tracks for active substances with a low-risk profile. Low-risk active substances are bound to renewal times of 15 years. A rolling review for low-risk substances could be beneficial in this context (Tamm 2022). Once an active substance has been approved, the approval as a product can follow a fast-track.

Most low-risk pesticides are developed for and used in niche markets. With a demanding and expensive registration procedure in Europe and companies willing to engage in the development of low-risk pesticides often being small and medium-sized enterprises (Robin and Marchand 2022), the current approval system will not lead to a quick change to an increased use of these types of pesticides in agriculture.

[23] EFSA. Hazard vs. risk. URL: https://www.efsa.europa.eu/en/campaigns/hazard-vs-risk#:~:text=A%20Hazard%20is%20something%20that,of%20a%20hazard%20causing%20harm (last accessed 04/12/2023).

Finally, as no marketing can be done for basic substances regarding their properties for fighting pests, there is not economical interest in bringing a basic substance to the market, as well as developing knowledge about appropriate doses or combined (crop) approach using a basic substance.

The USA system allows for identification of substances of natural origin early in the process, which are then subject to a different set of data requirements, evaluation process, timelines and fee structure, all designed to facilitate an appropriate level of regulatory compliance for these types of compounds. The EU system, beyond microbial requirements, does not (Frederiks and Wesseler 2019; IBMA 2022).

A recent publication demonstrated that only drastic pesticide-use reduction, such as allowing only lower hazard substances, would result in the targeted 50% use and risk reductions (Silva, Yang et al., 2022). In this simulation, seven different scenarios inspired by the Farm to Fork use reduction were compared. In this study, the lower hazard pesticides did not correspond to the low-risk category defined in Regulation (EC) No 1107/2009, but were based on a hazard score defined for the EU authorized active substances listed in the Pesticide Property Database (PPDB) (Lewis and Green 2011). The PPDB includes only synthetic pesticides, excludes biopesticides, and comprises authorized active substances, including candidates for substitution. For each pesticide, two cumulative hazard scores were calculated: for humans, and for ecosystems. The lower-risk scenario consisted in evaluating the change in overall risk in which the pesticides with the highest hazard scores would not be used anymore, still allowing on the market 136 out of the initial 230 molecules. While this scenario was not the most performant of the seven tested scenarios regarding risk reduction, it would successfully reduce by 50% the risk to ecosystems and to humans if applied. This is an encouraging message for the strategy consisting in developing low-risk pesticides and reducing the use of higher-risk pesticides.

8.2 Recommendations from literature

8.2.1 Existing recommendations within the EU considering low-risk substances

The EU investigated the implementation of the PPP regulation relative to the low-risk substances. Their recent recommendations concern all stakeholders in the PPP regulations. Targeted actions were therefore recommended to Member States. Some of this work has already led to implementations by the Member States, and some of it is on-going and should be supported. The following reports are available:

- Progress report on the implementation plan to increase the availability of low-risk plant protection products and accelerate implementation of integrated pest management in Member States—2019 10278/19 (Council of the European Union 2019).

The above progress report concerns the implementation of the following report:

- (Council of the European Union 2016) Acceleration of sustainable plant production – outcome of the work carried out by the expert group – 2016 – 10041/16 (Council of the European Union 2016).
- Sustainable use of plant protection products: limited progress in measuring and reducing risks – European court of auditors – 2020 (section "Non-chemical methods are evolving, but the number of low-risk PPPs is low") (European court of auditors 2020).
- Report from the commission to the European parliament and the council: Evaluation of Regulation (EC) No 1107/2009 on the placing of plant protection products on the market and of Regulation (EC) No 396/2005 on maximum residue levels of pesticides. 2020 COM (2020) 208 final (European Commission 2020).
- Working document on the procedure for application of basic substances to be approved in compliance with Article 23 of Regulation (EC) No 1107/2009 (European Commission 2021b).

Those recommendations concern the general functioning of the approval process, and how Member States can help, for instance, with financial incentives, providing training and information, recruiting of specialists, faster approval track, and research projects.

8.2.2 Recommendations from other EU legislations

While it was not specifically addressed in previous chapters, EU pesticide regulation and the EU pesticides approval process can learn from other regulations within the EU (Arche, 2018):

- Within the Food and Feed regulations three streams of data requirements are distinguished: chemical, botanical and microbial. This is a way forward to make regulations more fit-for-purpose;
- The Biocides regulation 528/2012 includes a simplified authorisation procedure. Annex I includes the active substances: plant extracts, pheromones, oils, viruses and food additives. An active substance or product can become listed in Annex I. After incorporation in Annex I, a simplified procedure is applicable. In that case the efficacy and stability of the product needs to be demonstrated, however, no risk assessment is required. The fast-track can only be followed if certain criteria are met. However, not all biocidal products containing substances of biological origin can apply for this simplified procedure (e.g. pyrethrins);
- The REACH regulation distinguishes UVCB substances (unknown or variable composition, complex reaction products or biological materials). A UVCB has many different constituents, some of them may be unknown. The composition can be variable or difficult to predict. UVCB substances are often not fully identifiable and therefore you need to provide a description of the manufacturing process and other types of information. Active substances in biological plant protection products can often be considered as UVCBs or multi-constituents, e.g. botanicals. Examples registered under REACH are essential oil of spearmint and a UVBC containing yeast, carbohydrates, minerals and salts.

Twenty-nine substances (reference year 2022) with potential low-risk still have to wait for their renewal to be approved as low-risk (Robin and Marchand 2022). Here, a fast-track procedure is apparently missing.

8.2.3 Approval of low-risk substances

While low-risk products are approved with shorter time frames than their non-low risk counterparts, their approval seems to remain at a slow pace (European court of auditors 2020).

After modification of the criteria for an active substance to be low-risk in 2017, a list of potential low-risk substances within the already registered active substances was constructed in 2018 (European Commission 2018a). This list had no influence on the status of the substances, however, as there is no direct granting of low-risk status. Eventually substances on this list were even refused as low-risk during their renewal. The transfer operation only takes place during the renewal of the active substance. For some of these substances, this renewal will be due only in a decade (Vekemans and Marchand 2020).

The following recommendations were provided:

1. Automatically grant the status of low-risk to the active substances which were listed in 2018 as potential low-risk (Robin and Marchand 2022). This suggestion is supported by the conclusion of the report EC (2016), which suggests that the following ways be explored (Council of the European Union 2016):
   a. grant low-risk status earlier and faster,
   b. prevent reopening the dossier in each Member State, and
   c. consider removing the need for renewal of the low-risk status while offering the possibility to review the status if information relative to risk becomes available, as for basic substances.
2. Harmonize the concepts of specific mitigation measures. Example of gloves: the recommendation to wear gloves prevented the approval as low-risk for some substances in the Netherlands. In other countries it was not considered as a specific risk mitigation measure and the status of low-risk was approved (Vekemans and Marchand 2020).
3. Provide clear regulatory definitions and processes to classify natural substances (IBMA 2022), botanicals and semiochemicals.

The fast-track of approval for low-risk substances can be compared with vaccine approval during COVID. "Registration for covid vaccines went through a fast-track, with rapid scientific advice, rolling review, accelerated assessment and extension of indication and marketing authorization (Tamm 2022)." Such a rolling review for approval could be considered for low-risk substances. A fast-track procedure does exist in the EU for *products* if the *active substance* has been given a low-risk status.

8.2.4 Basic substances

The development of the use of basic substances relates to the relatively poor information about the effectiveness of basic substances as compared to synthetic pesticides and biological PPPs. Several recommendations are provided (Romanazzi, Orçonneau et al., 2022):

1. Higher testing and validation of the use of basic substances as a phytosanitary measure;
2. Defining the most effective dosage of the basic substance (which is a critical question for phytosanitary consultants, growers, stakeholder, and companies);
3. A defined timeline for approval is basilar to have the chance to increase the number of basic substances available for growers, the scientific community, and the whole agricultural sector, with final benefits for the consumers.

With the limited requirements in the approval process for basic substances, there is a lack of data for establishing doses applicable in the field. Current recommended doses might lack underpinning by field experiments. "For this reason, flexibility might be required in the suggested dosage of basic substances approved to ensure good maintenance of the quality and quantity of production, which is one of the keys of the Farm to Fork Strategy of the European Green Deal."(Romanazzi, Orçonneau et al., 2022).

Costantini and La Torre (2022) recommend that shared and updated resources be created concerning the use of basic substances (notably doses and time of use). Existing published reviews can help in the constructing of these resources. They also recommend that farmers and technicians be trained for the use of these products. Basic substances should be used in accordance with the specific conditions included in the conclusions of their respective reports (Costantini and La Torre 2022). Finally, as marketing is not possible, the guidance for basic substances underlines that "the Commission as well as Member States will have to put measures into place to inform the public of basic substance approvals and their respective conditions." (European Commission 2021b).

8.2.5 General recommendations

While "low-risk" and "biocontrol" are not necessarily equivalent, facilitating access of low-risk pesticides to the market is in line with the transition to a lesser chemical pressure on the environment. Considering this, "An effective first step towards a better consideration of biocontrol would be to include a clear definition of 'biocontrol' in plant protection regulation at least (European Commission 2009), or even to create a specific category within the regulation to ease understanding" (Robin, Merlet et al., 2022).

Favouring low-risk and biocontrol solutions can take place at different stages:

- Prioritizing applications of low-risk or potentially low-risk substances; this is, in principle, part of an IPM approach;
- Favouring derogation to substances which have been on the list of low-risk or potentially low-risk substances where the uses exist over derogation to older chemistry;
- Facilitating extension for the use of low-risk or potentially low-risk substances in all crops;
- Installing market-based policy instruments, such as taxes, that can integrate the external costs and trade-off into decisions made by farmers, the food industry, and consumers.

For biopesticides, a recommendation is to distinguish between toxicity (due to a poisonous substance) and lethality (causing death without being poisonous, e.g. causing a physical barrier thereby prohibiting invertebrates to breath).

Outside of the box:
The market of biopesticides is larger than agricultural products. "Supporting the development of biopesticides for insects, the vector of human diseases can also facilitate the acceptance of biopesticides as safe, cheap, sustainable by consumers and retailers" (Glare, Caradus et al., 2012), as well as make their effectiveness recognized in society.

8.3 Recommendations for the research agenda

International research programs do exist already, e.g. within the Horizon Europe program of the European Commission. These are expected to add to a more targeted risk assessment for low-risk substances in future. National research programs are also running, e.g. BO-43-102.01 A2 Risk Assessment for Low-risk Pesticides. In addition, based on the current study, research for the following topics is recommended:

1. Develop scientific approaches to accelerate the approval process, e.g. by adopting a problem formulation approach and a more targeted approach for the risk assessment (RA);
2. Develop focused data requirements, including scientific underpinning for the RA of biopesticides;
3. For botanicals:
   a. many areas are open, e.g. collect toxicological and fate data, develop toxicity tests, develop analytical tools and develop QSAR approaches for the botanical mixtures;
   b. Accelerating the acquirement of toxicological data for promising botanicals (Romanazzi, Orçonneau et al., 2022).
4. For microbials:
   a. Develop a concrete list of simplifications that are possible in the data requirements (action could be performed by the NL working group) including scientific underpinning of the data requirements;
   b. Develop the qualified presumption of safety (QPS) approach, including how it could be applied for microbial pesticides and for which aspects of the RA;
   c. Write a paper on the QPS approach and how it could be applied (NL WG) and for which aspects of the RA?
5. For semiochemicals:
   a. Evaluate the current use of semiochemicals in crops and explore how the use can be extended to other crops.
6. For other natural substances:
   a. Adapt the risk assessment and tools for paraffin oil, rapeseed oil and others to make them more fit-for-purpose for these compounds.
7. For basic substances:
   a. Study and prescribe doses for basic substances, flexibility over the doses and rates of application (Romanazzi, Orçonneau et al., 2022);
   b. Study the effects of a combination of low-risk active substances, i.e. if synergies do exist and/or antagonistic effects (Pavela 2016, van Oudenhove, Cazier et al., 2023). Field trials are often missing, which might lead to a use of botanicals in doses that undermine their efficacy in open fields, e.g. if they are antagonistic. As a result, farmers might find those products inadequate and stop using them. Such field trials seem particularly important as some botanicals might require that they be used in combination with other compounds to reach a satisfying result;
   c. Budgeting research for basic substances, appropriate formulations and improved application recommendations (Romanazzi, Orçonneau et al., 2022).

8.4 Conclusions

1. Switching to lower-risk substances is one of the possible solutions to reach the goals from the Farm to Fork strategy.
2. Active substances regulated under Regulation (EC) No 1107/2009 are only categorized as low-risk if they meet specific additional criteria. Currently, no synthetic chemical active substance is classified as low-risk.
3. For microorganisms, additional criteria apply for persistence, bioconcentration and multiple resistance to anti-microbials used in human or veterinary medicine to be classified as low-risk.
4. Naturally occurring active substances and semiochemicals meeting the low-risk criteria are classified as low-risk even if they do not meet the additional criteria for persistence and bioconcentration.
5. Baculoviruses must not have demonstrated adverse effects on non-target insects to be classified as low-risk.

6. Currently, already registered and potential low-risk products have limited usage and functions, and they are not widely applied in crops nor are they widely included in an Integrated Pest Management (IPM) approach. The 2009 directive on sustainable use of pesticides introduced the IPM approach. Low-risk substances have a clear position in IPM, overlapping with non-chemical and chemical methods. IPM should be implemented and stimulated in Member States.
7. Although the new uniform principles and data requirements are based on the biology and ecology of each microorganism, and a hazard approach was adopted, the data requirements are still very demanding and therefore expensive.
8. Low-risk pesticides and basic substances might be used in combination or rotation with other active substances.
9. The status of basic substance forbids their marketing as plant protection products. However, some of them are increasingly being used in pest management (IPM) programs as excipient or in a rotation programme, e.g. paraffin (petroleum) oils.
10. Regulation (EC) No 1107/2009 is not sufficiently adapted to substances of biological or natural origin. It has recently been adapted for microorganisms (Part B of the regulation); however, this has not been done for other potentially low-risk substances. These are all regulated under Part A of the regulation.
11. Regulation (EC) No 1107/2009 can learn from other EU regulations how low-risk substances can be supported in the renewal and approval process.
12. Harmonisation of requirements is very important for facilitating the research, development, commercialisation, and use of low-risk chemicals for plant protection. Using similar registration requirements for products in different countries would make it easier for applicants to submit applications to different countries and make it possible for regulatory agencies to benefit from each other's reviews.
13. Although the EU's regulatory processes have strong scientific foundations, the most appropriate scientific concepts, knowledge and expertise have not been applied in the safety assessment of microorganisms, botanicals, semiochemicals and other potential low-risk chemicals. Given the time-consuming procedures for admitting low-risk chemicals on the European market, these chemicals would benefit from more fit-for purpose regulations, separated from the regulations for synthesized chemical molecules.

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Annex 1 Glossary

Basic substances refer to active substances that are not on the market as PPP but for other product classes, for instance as foodstuff, feed, or cosmetics. Their safe use is easy to prove. One example is vinegar, used as fungicide, herbicide or pH modifier, but available on the market as foodstuff or cleaning agent.

Biopesticides comprise living organisms as well substances from biological or natural origin used as plant protection product in agriculture.

Biostimulant are natural products which influence the growth of plants without releasing fertilizers.

Botanical active substances are defined as consisting of one or more components found in plants and obtained by subjecting plants or parts of plants of the same species to a process such as pressing, milling, crushing, distillation and/or extractions. The process may include further concentration, purification and/or blending, provided that the chemical nature of the components is not intentionally modified/altered by chemical and/or microbial processes.

Green pesticides are not defined in regulations but in the context of the Green Deal refers to products of natural origin or identical products of synthetic nature, with a supposedly lower risk to man, animal, the environment and non-target organisms.

Low-risk pesticides are active substances that meet both the regular approval criteria and the low-risk criteria following Annex II, point 5 of Regulation (EC) 1107/2009.

Microbial pesticides or Microbial Pest Control Agents (MPCAs) are agents that contain microorganisms (and their metabolites) as their active substances instead of chemicals; they are used for the control of plant diseases and pests. These organisms include bacteria, fungi, viruses, yeasts, protozoa and microsporidia among others and are also named microorganisms.

Natural substances are substances of plant origin (also called 'botanicals') and substances from mineral and animal origin.

Regulation (EC) No 1107/2009 is an EU-wide regulation concerning the placing of plant protection products (active substances and products) on the market.

Semiochemicals are substances or mixtures of substances emitted by plants, animals, and other organisms that evoke a behavioural or physiological response in individuals of the same or other species.

Annex 2 Low risk substances approved by EU (by 23 May 2023)

Active Substance ID	Substance	Status under Reg. (EC) No 1107/2009	Date of approval	Expiration of approval
357	(E)-11-Tetradecen-1-yl acetate	Approved		
1330	(E)-5-Decen-1-yl acetate	Approved	01/09/2022	30/08/2037
361	(E)-8-Dodecen-1-yl acetate	Approved	01/09/2022	30/08/2037
352	(E,E)-7,9-Dodecadien-1-yl acetate	Approved	01/09/2022	30/08/2037
355	(E,E)-8,10-Dodecadien-1-yl acetate	Approved	01/09/2022	30/08/2037
349	(E,Z)-2,13-Octadecadien-1-yl acetate	Approved		
1499	(E,Z)-3,13-Octadecadien-1-yl acetate	Approved	01/09/2022	30/08/2037
1241	(E,Z)-3,8-Tetradecadien-1-yl acetate	Approved		
1328	(E,Z)-7,9-Dodecadien-1-yl acetate	Approved		
1240	(E,Z,Z)-3,8,11-Tetradecatrien-1-yl acetate	Approved	01/09/2022	30/08/2037
367	(Z)-11-Hexadecen-1-yl acetate	Approved		
368	(Z)-11-Tetradecen-1-yl acetate	Approved		
1496	(Z)-7-dodecen-1-yl acetate	Approved	01/09/2022	30/08/2037
374	(Z)-8-Dodecen-1-yl acetate	Approved	01/09/2022	30/08/2037
1246	(Z)-8-Tetradecen-1-yl acetate	Approved	01/09/2022	30/08/2037
375	(Z)-9-Dodecen-1-yl acetate	Approved	01/09/2022	30/08/2037
377	(Z)-9-Tetradecen-1-yl acetate	Approved	01/09/2022	30/08/2037
353	(Z,E)-7,11-Hexadecadien-1-yl acetate	Approved		
1226	(Z,E)-9,11-tetradecadien-1-yl-acetate	Approved		
356	(Z,E)-9,12-Tetradecadien-1-yl acetate	Approved		
1500	(Z,Z)-3,13-Octadecadien-1-yl acetate	Approved	01/09/2022	30/08/2037
354	(Z,Z)-7,11-Hexadecadien-1-yl acetate	Approved	01/09/2022	30/08/2037
1337	24-Epibrassinolide	Approved	31/03/2021	31/03/2036
1307	ABE-IT 56	Approved	20/05/2019	20/05/2034
265	*Akanthomyces muscarius* Ve6 (formerly *Lecanicillium muscarium* strain Ve6)	Approved	01/03/2021	29/02/2036
345	*Ampelomyces quisqualis* strain AQ10	Approved	01/08/2018	01/08/2033
1260	Aqueous extract from the germinated seeds of sweet Lupinus albus	Approved	27/04/2021	27/04/2036
1257	*Bacillus amyloliquefaciens* AH2	Approved	27/09/2021	27/09/2036
1333	*Bacillus amyloliquefaciens* IT-45	Approved	27/02/2022	27/02/2037
1197	*Bacillus amyloliquefaciens* strain FZB24	Approved	01/06/2017	01/06/2032
1278	*Bacillus subtilis* strain IAB/BS03	Approved	20/10/2019	20/10/2034
468	Blood meal	Approved	01/04/2021	31/03/2036
1185	COS-OGA	Approved	22/04/2015	22/04/2030
495	Calcium carbonate	Approved	01/11/2021	31/10/2036
1065	Cerevisane	Approved	23/04/2015	23/04/2030
766	*Clonostachys rosea* strain J1446 (*Gliocladium catenulatum* strain J1446)	Approved	01/04/2019	31/03/2034
569	*Coniothyrium minitans* Strain CON/M/91-08 (DSM 9660)	Approved	01/08/2017	31/07/2032
837	Dodecyl acetate	Approved	01/09/2022	30/08/2037
23	Ferric phosphate	Approved	01/01/2016	31/12/2030
1310	Ferric pyrophosphate	Approved	03/08/2020	03/08/2035
772	Heptamaloxyloglucan	Approved	01/03/2023	28/02/2038
1498	Hexadecyl acetate	Approved		
938	*Isaria fumosorosea* Apopka strain 97 (formerly *Paecilomyces fumosoroseus*)	Approved	01/01/2016	31/12/2030
260	Laminarin	Approved	01/03/2018	28/02/2033
1223	*Lavandulyl senecioate*	Approved	03/06/2020	03/06/2035

Active Substance ID	Substance	Status under Reg. (EC) No 1107/2009	Date of approval	Expiration of approval
1319	*Metarhizium brunneum* Strain Ma 43 (formerly *Metarhizium anisopliae* var *anisopliae*)	Approved	01/05/2022	30/04/2037
1287	Mild Pepino Mosaic Virus isolate VC 1	Approved	29/03/2017	29/03/2032
1288	Mild Pepino Mosaic Virus isolate VX 1	Approved	29/03/2017	29/03/2032
1309	*Pasteuria nishizawae* Pn1	Approved	14/10/2018	14/10/2033
1334	Pepino mosaic virus (PepMV) Chilean (CH2) strain, mild isolate Abp2 (PEPMVO)	Approved	28/06/2021	28/06/2036
1335	Pepino mosaic virus (PepMV) European (EU) strain, mild isolate Abp1 (PEPMVO)	Approved	28/06/2021	28/06/2036
1187	Pepino mosaic virus strain CH2 isolate 1906	Approved	07/08/2015	07/08/2030
1294	*Phlebiopsis gigantea* strain FOC PG 410.3	Approved	01/09/2020	31/08/2035
1295	*Phlebiopsis gigantea* strain VRA 1835	Approved	01/09/2020	31/08/2035
1296	*Phlebiopsis gigantea* strain VRA 1984	Approved	01/09/2020	31/08/2035
51	Potassium hydrogen carbonate	Approved	01/11/2021	31/10/2036
1285	*Purpureocillium lilacinum* PL 11	Approved	25/01/2022	24/01/2037
856	Repellents by smell of animal or plant origin/ fish oil	Approved	01/03/2023	28/02/2038
1196	*Saccharomyces cerevisiae* strain LAS02	Approved	06/07/2016	06/07/2031
1235	Sodium hydrogen carbonate (low risk active substance)	Approved	01/10/2020	01/10/2035
1423	Spodoptera exigua multicapsid nucleopolyhedrovirus (SeMNPV), isolate BV-0004	Approved	18/04/2022	18/04/2037
1205	*Trichoderma atroviride* strain SC1	Approved	06/07/2016	06/07/2031
192	*Verticillium albo-atrum* (formerly *Verticillium dahliae*) strain WCS850	Approved	01/11/2019	31/10/2034

Annex 3 Basic substances approved by EU (by 23 May 2023)

Active Substance ID	Substance	Status under Reg. (EC) No 1107/2009
1424	Allium cepa L. bulb extract	Approved
1415	Beer	Approved
497	Calcium hydroxide	Approved
1490	Chitosan	Approved
1193	Chitosan hydrochloride	Approved
1225	Clayed charcoal	Approved
1255	Cow Milk	Approved
611	Diammonium phosphate	Approved
106	*Equisetum arvense* L.	Approved
1400	Fructose	Approved
131	Hydrogen peroxide	Approved
1291	L-cysteine	Approved
1208	Lecithins	Approved
1416	Mustard seeds powder	Approved
1304	Onion oil	Approved
874	Salix spp. cortex	Approved
1141	Sodium chloride	Approved
1148	Sodium hydrogen carbonate (basic substance)	Approved
1206	Sucrose	Approved
45	Sunflower oil	Approved
1419	Talc E553B	Approved
1224	Urtica spp.	Approved
1207	Vinegar	Approved
1399	Whey	Approved

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