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## Update of the list of qualified presumption of safety (QPS) recommended microorganisms intentionally added to food or feed as notified to EFSA

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### Abstract

The qualified presumption of safety (QPS) provides a generic pre-assessment of the safety of microorganisms intended for use in the food or feed chains, to support the work of EFSA's Scientific Panels. QPS assessment allows a fast track evaluation of strains belonging to QPS taxonomic units (TUs): species for bacteria, yeast, fungi, protists/microalgae and families for viruses. QPS TUs are assessed for their body of knowledge and safety. Safety concerns related to a QPS TU are reflected, when possible, as 'qualifications', which should be tested at strain and/or product level. Based on the possession of potentially harmful traits by some strains, filamentous fungi, bacteriophages, oomycetes, streptomycetes, *Enterococcus faecium*, *Escherichia coli* and *Clostridium butyricum* are excluded from the QPS assessment. Between October 2019 and September 2022, 323 notifications of TUs were received, 217 related to feed additives, 54 to food enzymes, food additives and flavourings, 14 to plant protection products and 38 to novel foods. The list of QPS-recommended TUs is reviewed every 6 months following an extensive literature search strategy. Only sporadic infections with a few QPS status TUs in immunosuppressed individuals were identified and the assessment did not change the QPS status of these TUs. The QPS list has been updated in relation to the most recent taxonomic insights and the qualifications were revised and streamlined. The qualification 'absence of aminoglycoside production ability' was withdrawn for *Bacillus velezensis*. Six new TUs received the QPS status: *Bacillus paralicheniformis* with the qualification 'absence of toxigenic activity' and 'absence of bacitracin production ability'; *Bacillus circulans* with the qualifications for 'production purposes only' and 'absence of cytotoxic activity'; *Haematococcus lacustris* (synonym *Haematococcus pluvialis*) and *Ogataea polymorpha*, both with the qualification 'for production purposes only'; *Lactiplantibacillus argentoratensis*; *Geobacillus thermodenitrificans* with the qualification 'absence of toxigenic activity'.

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## Summary

The European Food Safety Authority (EFSA) asked the Panel on Biological Hazards (BIOHAZ) to deliver a Scientific Opinion on the maintenance of the list of qualified presumption of safety (QPS) taxonomic units (TUs). The list of QPS TUs contains microorganisms, intentionally added to food and feed, which have received QPS status.

QPS provides a generic safety pre-assessment approach for use within EFSA that covers safety concerns for humans, animals and the environment. In the QPS concept, a safety assessment of a defined TU is performed independently of the legal framework under which the application is made in the course of a market authorisation process. Strains belonging to QPS TUs still require an assessment based on a specific data package by the relevant EFSA Scientific Panel, but the QPS status facilitates a fast track evaluation. For genetically modified microorganisms (GMMs) for which the species of the recipient strain qualifies for the QPS status, and for which the genetic modification does not give rise to safety concerns, the QPS approach can be extended to genetically modified production strains (EFSA BIOHAZ Panel, 2018).

Although general human safety is part of the QPS evaluation, specific issues connected to the type and level of exposure of users handling the product (e.g. dermal contact, inhalation, ingestion) are not addressed. The assessment of potential allergenicity to residual microbial components is beyond the QPS remit; however, it is reported for some microbial species if science-based evidence is available. These aspects are separately assessed, where applicable, by the EFSA Panel responsible for assessing the application.

Safety concerns for a TU are, where possible, reflected as 'qualifications', which should be assessed at strain and/or product level by EFSA's Scientific Panels. A generic qualification for all QPS bacterial TUs applies in relation to the absence of acquired genes conferring resistance to clinically relevant antimicrobials (EFSA, 2008).

The lowest TU for which the QPS status is granted is the species level for bacteria, yeasts and protists/algae, and family for viruses. Filamentous fungi, bacteriophages, streptomycetes, oomycetes, *Enterococcus faecium*, *Escherichia coli*, *Clostridium butyricum* (EFSA BIOHAZ Panel, 2020b) are excluded from the QPS assessments based on the potential presence of harmful traits in strains of the TU. The assessment of members of the excluded microbiological groups needs to be carried out at the strain level, by the relevant EFSA Unit and Scientific Panel. The exclusion of bacteriophages from the QPS assessment was re-evaluated and their exclusion was confirmed because the new phylogenetic classification is still not universally accepted and because the distinction between temperate/virulent and the mode of nucleic acid packaging, essential to judge the safety risks of phages, cannot be linked to particular TUs.

The BIOHAZ Panel was requested to address three specific tasks as mentioned in the three Terms of Reference (ToR). The tasks have been covered by each of the six Panel Statements adopted between July 2020 and December 2022. The current Opinion summarises the results of those six Panel Statements.

The first ToR requires ongoing updates of the list of microorganisms notified to EFSA, in the context of a technical dossier for safety assessment. The overall list (<https://doi.org/10.5281/zenodo.3607183>) has been updated with the notifications received since the previous Opinion (EFSA BIOHAZ Panel, 2020a). Between October 2019 and September 2022, 323 notifications were received and analysed. From these, 217 were for microorganisms used for the production of feed additives, 54 for the production of food enzymes, food additives and flavourings, 14 as plant protection products (PPPs) and 38 for novel foods; 214 were bacteria, 57 were filamentous fungi/oomycetes, 38 were yeasts, 12 were protists/algae and 2 were viruses.

The second ToR concerns the revision of the TUs previously recommended for the QPS list and their qualifications. The updated list of QPS-recommended microbiological agents for safety risk assessments carried out by EFSA ('2022 QPS list') is available at the Knowledge Junction in Zenodo (<https://doi.org/10.5281/zenodo.1146566>). For this revision, articles published from July 2019 were assessed. The articles were retrieved and assessed through an extensive literature search (ELS) protocol available at the Knowledge Junction in Zenodo (see <https://doi.org/10.5281/zenodo.3607188>) and the search strategies (see <https://doi.org/10.5281/zenodo.3607192>). Relevant information from the ELS includes case reports of human diseases. Several of the QPS TUs have been sporadically reported as causing infections in individuals with recognised predisposing conditions for the acquisition of opportunistic infections. In some of these cases, previous use of microorganisms as food supplements for humans, which does not fall under the remit of the QPS assessment, was reported.

The QPS status of these TUs has not been withdrawn because of the extremely low incidence of infections when compared with the exposure level, the predisposing circumstances of the patient that facilitate these opportunistic infections, the lack of evidence of transmission through food/feed sources and the functional characterisation of genes discovered in the available genome sequences indicating no documented virulence factor determinants. The qualification ‘absence of aminoglycoside production ability’ was removed for *Bacillus velezensis* based on recent information, which did not support possible aminoglycoside production, thereby contradicting the original data.

The QPS list has been updated in relation to the most recent taxonomic insights in the genera *Bacillus* and *Lactobacillus*. TUs belonging to a previously designated species in these genera were transferred to the new species and both the previous and new names are included in the QPS list. The qualifications associated with the QPS status TUs were streamlined within this 3-year period (EFSA BIOHAZ Panel, 2020b, 2022a).

The third ToR requires a (re)assessment of new TUs notified to EFSA in the context of a technical dossier for safety assessment, for their suitability for inclusion in the updated list of QPS TUs at the Knowledge Junction in Zenodo (<https://doi.org/10.5281/zenodo.1146566>). Six new TUs received the QPS status between October 2019 and September 2022:

- 1) *Bacillus circulans* was recommended for QPS status with the qualifications ‘for production purposes only’ and ‘absence of cytotoxic activity’;
- 2) *Bacillus paralicheniformis*, with the qualification ‘absence of toxigenic activity’ and ‘absence of bacitracin production ability’;
- 3) *Haematococcus lacustris* (synonym *Haematococcus pluvialis*) with the qualification ‘for production purposes only’;
- 4) *Geobacillus thermodenitrificans* with the qualification ‘absence of toxigenic activity’;
- 5) *Lactiplantibacillus argentoratensis* (previously *Lactobacillus plantarum* subs. *argentoratensis*);
- 6) *Ogataea polymorpha* with the qualification ‘for production purposes only’.

For future QPS developments, the following recommendations can be considered:

- to include more detailed guidance to facilitate the interpretation of phenotypic and genotypic antimicrobial resistance data;
- to include in future QPS assessments, the analysis of the publicly available whole genome sequencing (WGS) of microorganisms.

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## 1. Background as provided by EFSA

A wide variety of microorganisms is intentionally added at different stages into the food and feed chain. In the context of applications for market authorisation, EFSA is requested to assess the safety of microorganisms used as production organisms for food and feed additives, as food enzymes, as plant protection products (PPPs), as novel food or as genetically modified microorganism (GMM).

EFSA's work on qualified presumption of safety (QPS) activities started in 2004 when the Scientific Committee issued a Scientific Opinion in continuation of the 2003 working document 'On a generic approach to the safety assessment of microorganisms used in feed/food and feed/food production' prepared by a Working Group (WG) consisting of members of the former Scientific Committee on Animal Nutrition, the Scientific Committee on Food and the Scientific Committee on Plants of the European Commission.<sup>1</sup> The document, made available for public consultation, proposed the introduction of the concept of QPS, to be applied to selected groups of microorganisms. Microorganisms not considered suitable for the QPS status would remain subject to a full safety assessment. EFSA management asked its Scientific Committee to consider whether the QPS approach could be applied to the safety assessment of microorganisms across the various EFSA Scientific Panels. In doing so, the Committee was required to take into account the response of stakeholders to the QPS approach. In its 2005 Opinion (EFSA, 2005), the Scientific Committee concluded that the QPS approach could provide a generic assessment system that could be applied to all requests received by EFSA for the safety assessments of microorganisms deliberately introduced into the food and feed chain. Its introduction was intended to make the process more transparent and aid in the consistency of approaches across the EFSA Scientific Panels. Applications involving a taxonomic unit (TU) belonging to a species/family that falls within the QPS consideration do not require a full safety assessment.

Several TUs (usually species for bacteria, yeasts, fungi, protists/algae and families for viruses) have been assessed for the QPS list by proposals made initially by stakeholders during a public consultation in 2005 (EFSA, 2005) and later on by notification to EFSA through an application for market authorisation.

The EFSA Scientific Committee reviewed the range and numbers of microorganisms likely to be the subject of an EFSA Opinion and, in 2007, published a list of microorganisms recommended for the QPS list. In their 2007 Opinion (EFSA, 2007), the Scientific Committee recommended that the QPS approach should provide a generic concept to prioritise and to harmonise the safety assessment of microorganisms intentionally introduced into the food chain, in support of the respective EFSA Scientific Panels and Units in the context of market authorisations. The same Committee recognised that the provision for reviewing and modifying the QPS list would have to be continued and, in line with this recommendation, the EFSA Scientific Panel on Biological Hazards (EFSA BIOHAZ Panel) took the prime responsibility for this and started reviewing the existing QPS list annually. In 2008, the first annual QPS update was published (EFSA, 2008).

In 2014, the EFSA BIOHAZ Panel, in consultation with the Scientific Committee, decided to change the revision procedure; the overall assessment of the TUs previously recommended for the QPS list (EFSA BIOHAZ Panel, 2013) was no longer carried out annually as done from 2007, but over a 3-year period. From 2017, the search and revision of the possible safety concerns linked to the QPS TUs started to be carried out every 6 months through Extensive Literature Searches (ELS). The update of the 2013 QPS list (EFSA BIOHAZ Panel, 2013) was done in 2016 (EFSA BIOHAZ Panel, 2017). From 2016 onwards, the QPS list (<https://doi.org/10.5281/zenodo.1146566>) and the list of notifications to EFSA (<https://doi.org/10.5281/zenodo.3607183>) have been continuously updated, independently of the publication of the QPS Opinion, and are available at the Knowledge Junction in Zenodo. The previous QPS Opinion (EFSA BIOHAZ Panel, 2020a) summarised the main results of the previous 3-year ELS (2017–2019) on the QPS TUs. Over that period, updates on the process for granting the QPS status were published as Panel Statements every 6 months. These compiled the assessments for the QPS status of the microorganisms notified to EFSA in the context of a technical dossier as requested by the Feed and Contaminants (FEEDCO) Unit, the Food Ingredients and Packaging (FIP) Unit, the Nutrition and Food Innovation (NIF) Unit and the Pesticides Peer Review (PREV) Unit,<sup>2</sup> as well as a summary of each 6-monthly ELS exercise. Each QPS Panel Statement contains the evaluations of the new notifications for microorganisms submitted for ascription of the QPS status and the result of an ELS, performed every 6 months, on possible new safety concerns related to the TUs already included

<sup>1</sup> [https://ec.europa.eu/food/sites/food/files/safety/docs/sci-com\\_scf\\_out178\\_en.pdf](https://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_scf_out178_en.pdf)

<sup>2</sup> Units as in December 2022.

in the QPS list. The data identified are used to decide whether any TU may or may not remain in the QPS list, and whether any qualification needs revision.

The establishment of the QPS status is based on four pillars: the taxonomic grouping for which the QPS is sought (*'taxonomic identification'*); whether sufficient information is available about the proposed group of microorganisms to conclude on human/animal exposure by food/feed (*'body of knowledge'*); whether the grouping proposed contains known pathogens or can be related to safety concerns (*'safety'*) and, finally, the safety for the environment. If a hazard related to a TU is identified, which can be tested at the strain or product level, a *'qualification'* to exclude that hazard may be established. The subject of these qualifications for the microbial strain under investigation is evaluated by the EFSA Scientific Panel to which the application dossier has been allocated. The absence of acquired genes coding for resistance to antimicrobials relevant for humans and animals is a generic qualification for all bacterial TUs; the absence of antimycotic resistance should be proved if viable yeasts are to be used in the food or feed chains. The qualification *'for production purposes only'* implies the absence of viable cells of the production microorganism in the final product and can also be applied to food and feed products based on microbial biomass (EFSA BIOHAZ Panel, 2020a).

Because the QPS evaluation is, after its initial creation, only triggered through an application dossier notified to EFSA for safety assessment, the QPS list is not exhaustive.

In summary, the QPS provides a generic safety pre-assessment approach for use within EFSA that covers safety concerns for humans, animals and the environment. In the QPS concept, a safety assessment of a defined TU is performed independently of the legal framework under which the application is made in the course of an authorisation process. Although general human safety is part of the evaluation, specific issues connected to the type and level of exposure of users handling the product (e.g. dermal contact, inhalation, ingestion) are not addressed. For GMMs for which the species of the recipient strain qualifies for the QPS status, and for which the genetic modification does not give rise to safety concerns, the QPS approach can be extended to genetically modified production strains (EFSA BIOHAZ Panel, 2018). The assessment of potential allergenicity to microbial residual components is beyond the QPS remit; however, it is reported for some microbial species if science-based evidence is available. These aspects are separately assessed, when applicable, by the EFSA Panel responsible for assessing the application.

Filamentous fungi, bacteriophages, streptomycetes, oomycetes, *Enterococcus faecium*, *Escherichia coli*, *Clostridium butyricum* (excluded in EFSA BIOHAZ Panel, 2020b) are excluded from the QPS assessments based on an ambiguous taxonomic position or the possession of potentially harmful traits making it unlikely that any TUs within these groups would be granted the QPS status in the foreseeable future. Thus, the assessment of members of these microbiological groups needs to be carried out at a strain level, on a case-by-case basis, by the relevant EFSA Scientific Panel.

The Terms of Reference (ToR) are as follows:

ToR 1: Keep updated the list of microorganisms being notified in the context of a technical dossier for safety assessment to EFSA Units such as FEEDCO, PREV, FIP and NIF,<sup>3</sup> for intentional use directly or as sources of food and feed additives, food enzymes and PPPs and GMMs for safety assessment.

ToR 2: Review TUs previously recommended for the QPS list and their qualifications when new information becomes available. The latter is based on an update of the ELS aimed at verifying if any new safety concern has arisen that could require the removal of the TU from the list, and to verify if the qualifications remain efficient to exclude safety concerns.

ToR 3: (Re)assess the suitability of new TUs notified to EFSA in the context of a technical dossier for safety assessment, for their inclusion in the QPS list. These microorganisms are notified to EFSA in the context of technical dossiers for safety assessment and trigger a QPS assessment.<sup>4</sup>

## 1.1. Additional information

### 1.1.1. Introduction of microorganisms in the QPS list

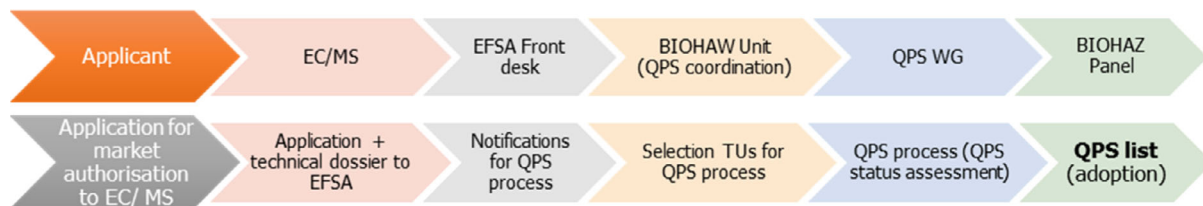
The first QPS list was established in 2007 and was based on notifications to EFSA collected by a public consultation. After this initial QPS list, the introduction of new microorganisms in the QPS list is only triggered by an application for market authorisation as a part of regulated products requiring a

<sup>3</sup> Units as in December 2022: Feed and Contaminants (FEEDCO), Pesticides Peer Review (PREV), Food Ingredients and Packaging (FIP) and the Nutrition and Food Innovation (NIF).

<sup>4</sup> Previous text: 'These microorganisms are notified to EFSA and requested by the Feed Unit, the FIP Unit, the Nutrition Unit or by the Pesticides Unit'.

safety assessment by EFSA (Figure 1). Consequently, the QPS list is not an exhaustive list of microbial TUs. As some microbial applications in the agri-food chain do not require a safety assessment by EFSA (e.g. starter cultures for fermented products aimed for human consumption, which are not novel foods), it has not been possible for those microorganisms to be considered for QPS after the publication of the initial list. The regulated products concerned include:

- feed additives including animal 'probiotics' and silage starter cultures, food enzymes, additives and flavourings produced by microorganisms;
- microorganisms intended as novel foods or used in the production of novel foods;
- microorganisms used as PPPs;
- products containing GMMs.



**Figure 1:** Flow for microbial TUs to enter the QPS list

### 1.1.2. Simplified safety assessment by EFSA for QPS microorganisms

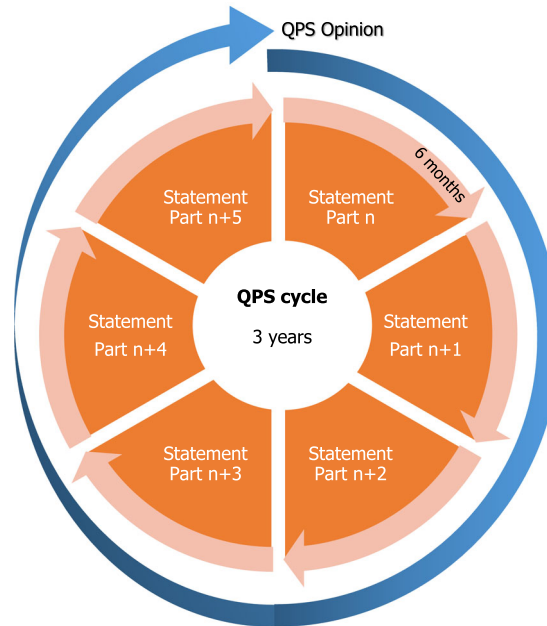
The QPS status of microbial TUs provides a simplified safety assessment of microbial strains belonging to the QPS TUs. Data on the safety of the target microorganism and toxicological tests related to the metabolites it could produce are not required.

Strains belonging to a QPS TU still require an assessment based on a specific data package as requested by the respective guidance documents for the different application areas of the requested product authorisation. Requirements may include, for example, data confirming the taxonomic identification of the requested microbiological strain as belonging to the QPS TU. If the QPS status of the TU to which the strain belongs is defined with some qualifications, data confirming the compliance with these qualifications are required, e.g. the generic qualification for all QPS bacterial TUs in relation to the absence of acquired genes conferring resistance to clinically relevant antimicrobials. For *Bacillus* spp., the lack of toxigenic potential needs to be confirmed. The qualification 'for production purposes only' needs to be met by submitting data excluding the presence of viable cells of the microorganism in the product under assessment in the concerned technical dossier. For GMMs, the safety of the genetic modification needs to be confirmed. EFSA guidance documents on how to assess the microbiological requirements to undertake the risk assessment approach based on QPS under the specific regulatory framework are available (EFSA FEEDAP Panel, 2018; EFSA, 2021; EFSA CEP Panel, 2021).

The following aspects of the EFSA risk assessment are not covered by the QPS status of the TUs and have to be separately assessed, when applicable, by the EFSA Scientific Panel responsible for assessing the application: (1) risk to users handling the product (e.g. dermal contact, inhalation, ingestion); (2) potential allergenicity of the microbe or its residual components or produced metabolites; (3) environmental hazards for PPPs; and (4) hazards linked to the formulation and/or the production and product purification process.

To address the ToR, an EFSA Panel Statement is published every 6 months. At the end of the 3-year cycle of the QPS mandate, a QPS Opinion is published with a more extended explanation of the QPS process and a reflection on the QPS Panel Statements published during the mandate (Figure 2).



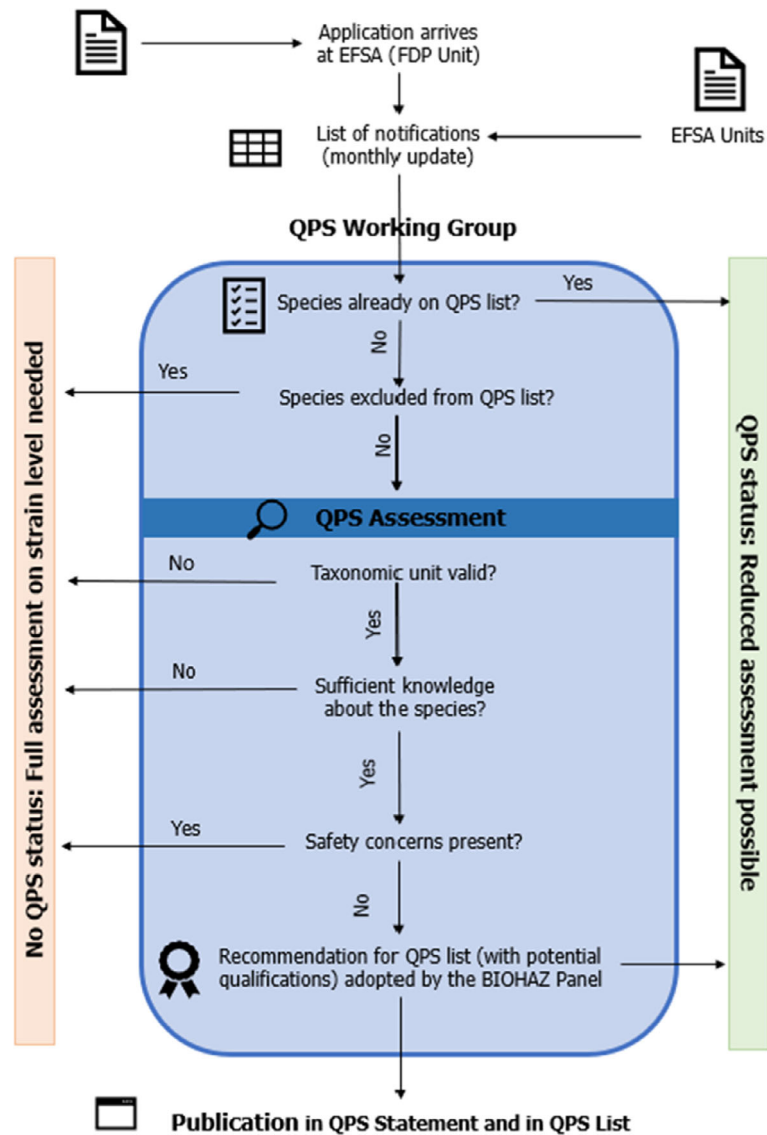


**Figure 2:** Overview of the timeline in a QPS cycle. An updated Opinion is published every 3 years. In between, Panel Statements of the BIOHAZ Panel are published every 6 months

## 2. Data and methodologies

### 2.1. ToR 1: update of EFSA notifications list

Applications sent to EFSA are first checked for completeness at the front desk and workforce planning (FDP) unit, before being distributed to the respective units. Simultaneously, a list with all notified applications that include a microorganism is prepared and shared monthly with the BIOHAZ Team. The list 'Microbiological agents as notified to EFSA' (<https://doi.org/10.5281/zenodo.3607183>) compiles all microorganisms notified to EFSA in the context of a technical dossier for safety assessment, from the beginning of the QPS exercise in 2007 (Figure 3).



**Figure 3:** Overview of the workflow from application of a regulated product to a potential inclusion in the QPS list of a microorganism

## 2.2. ToR 2: review of taxonomic units previously recommended for the QPS list and their qualifications

In reply to the ToR 2, on the revision of the TUs previously recommended for the QPS list and their qualifications, an ELS is conducted every 6 months. The protocol is available at the Knowledge Junction in Zenodo (<https://doi.org/10.5281/zenodo.3607188>), and the Search strategies as well (<https://doi.org/10.5281/zenodo.3607192>). Artificial intelligence (see ELS protocol) is used for prescreening papers on yeasts, *Bacillus* spp. and *Geobacillus stearothermophilus*, *Bifidobacterium* spp., *Carnobacterium divergens*, genera arising from the former *Lactobacillus* genus and *Lactococcus lactis*. The reports selected by the ELS approach are inspected by at least two experts in the field and, in case of any discrepancy or need for further clarification, submitted to the QPS WG. The updated literature is searched to verify if any new safety concern has arisen that could require a change in the QPS status of the TU; this could result in a withdrawal from the list or a change in the qualifications.

### 2.3. ToR 3: evaluation of a QPS recommendation for taxonomic units notified to EFSA

To address the ToR 3, (re)assessment of the suitability of TUs notified is carried out each 6-month period. These microorganisms are notified to EFSA in the context of a technical dossier for safety assessment and trigger a QPS assessment. Relevant databases, such as PubMed, Web of Science, CAB Abstracts, Food Science Technology Abstracts (FSTA) and Scopus, are searched in relation to the four pillars of the QPS assessment: (1) taxonomic identification; (2) body of knowledge; (3) safety concerns in relation to virulence/pathogenicity; and (4) safety for the environment. The searches performed are documented for each assessment.

To complete the assessment, an ELS-based approach was in some cases (whenever necessary due to some doubts on the safety of the TU based on the first literature findings), applied from Panel Statement Part 16 (EFSA BIOHAZ Panel, 2022b). When this has been required, the ELS followed the same methodology as used for monitoring new safety concerns related to species with QPS status.

#### 2.3.1. Taxonomic identification

The TU for which the QPS status is granted corresponds to the species for bacteria, yeasts and protists/algae and to the family for viruses.

Only unambiguously defined microbiological TUs are considered for inclusion in the QPS list. Microbial taxonomy is a very dynamic discipline, recently supported mainly by phylogenetic analysis of housekeeping genes and whole genome relatedness [e.g. digital DNA–DNA hybridisation (dDDH), average nucleotide identity (ANI), phylogenomics, etc.] (EFSA FEEDAP Panel, 2018; EFSA, 2021; EFSA CEP Panel, 2021). The resulting reclassifications of microorganisms have led to necessary adaptations in the QPS list, which is updated in successive QPS Panel Statements.

##### Bacterial taxonomy

Taxonomic identity is based on internationally accepted classification, overseen by the International Committee on Systematics of Prokaryotes. The nomenclature of bacteria and the nomenclatural changes, as cited in the Approved Lists of Bacterial Names or validly published in the International Journal of Systematic Bacteriology or in the International Journal of Systematic and Evolutionary Microbiology, are reported on the website: List of Prokaryotic Names with Standing in Nomenclature (LPSN)<sup>5</sup> (Parte, 2018).

##### Fungal taxonomy

The nomenclature and taxonomy of fungi, including yeasts, are covered by the International Code of Nomenclature for Algae, Fungi and Plants (ICN) (Turland et al., 2018). The most recent authoritative taxonomy of yeasts was published in 2011 (Kurtzman et al., 2011).

##### Viral taxonomy

The taxonomy and nomenclature of viruses are the responsibility of the International Committee on Taxonomy of Viruses (ICTV, online). Updates are made annually, based on proposals of study groups and after adoption by the Executive Committee. These updates from the 10th Report of the ICTV are available through the ICTV website (<https://ictv.global/taxonomy>). The most recent update is from 2021 (ICTV, online). Despite the introduction of higher taxa, there are no consequences for the currently approved taxa for QPS. Two families of plant viruses (*Alphaflexiviridae*, 65 species and *Potyviridae*, 237 species) and one insect virus family (*Baculoviridae*, 91 species) are included in the QPS list.

A species is the lowest taxon recognised by the ICTV and a strain is a genetic variant or subtype within a species with stable microbiological characteristics. In the case of baculoviruses, a species is based on a consensus sequence with >95% sequence homology (Wennmann et al., 2018).

##### Protists/algae taxonomy

Algae are a highly diverse group of organisms ranging from unicellular algae (microalgae) to multicellular algae (macroalgae). The group has been assigned into numerous families and genera but, to date, a general tool for identification is not available. With genomic tools and an increased knowledge of algal phylogeny, the taxonomic classification will continue to evolve.

<sup>5</sup> LPSN – List of Prokaryotic names with Standing in Nomenclature (bacterio.net). <https://www.bacterio.net/>

For protists/algae taxonomy, (algaeBase, online), Available online: <https://www.algaebase.org/>, and GenBank <https://www.ncbi.nlm.nih.gov/genbank/> (GenBank, online) can be used as the basis for the assessment.

### 2.3.2. Body of knowledge

The body of knowledge is mainly obtained through inspection of peer-reviewed papers published in journals and books that appear in scientific literature databases. To evaluate if the body of knowledge is sufficient to grant a TU QPS status, several aspects are taken into account, such as the robustness of available scientific evidence indicating a certain degree of exposure of humans and animals through food and feed use.

Aspects of the ecology of the microorganism are also taken into account. This includes the distribution of the TU in natural environments (e.g. as part of the human microbiota, of wild and farmed animals and in natural and cultivated plant ecosystems) and their colonisation ability and routes for dispersal. The body of knowledge also includes the history of the use of a TU in agricultural and food manufacturing systems and its related occurrence in the food and feed chains or in other sectors (e.g. biotechnological or medical applications). For this, information on the direct use of viable cells (e.g. as feed additives including those with 'probiotic' activity, food starter cultures, novel foods or PPPs), the use for production purposes (e.g. production of amino acids, biomass, enzymes, vitamins and polysaccharides) or its use in biotechnological or medical applications is examined. When detection in food or feed microbial communities is reported, its presence as a spontaneous contaminant versus its use as a main fermentative microorganism is considered.

### 2.3.3. Safety concerns in relation to pathogenicity and virulence

TUs assessed for the QPS list should not represent a hazard to human and animal health and to the environment when used in the food or feed chain.

Relevant information includes case reports of human diseases, particularly infections or intoxications linked to the TU under assessment. Additional important information considers the negative impacts affecting individuals with conditions favouring opportunistic infections, such as immunosuppression, and whether transmission occurred through food or other routes (e.g. medical devices). Studies indicating the presence of virulence factors (e.g. toxins and enzymes that might contribute to the pathogenicity of the microorganism) in the TU are also relevant for the identification of potential safety concerns. The knowledge on relevant acquired antimicrobial resistance (AMR) is also included. As WGS of microorganisms is becoming increasingly publicly available, their analysis searching for the possible presence of genetic determinants encoding genes of potential concern has been incorporated in this assessment. The WGS also offers the opportunity to check if a TU mentioned in QPS relevant papers is correctly identified based on, e.g. ANI or dDDH. It is foreseen that WGS analysis will be more systematically incorporated with the support, by the Microorganisms Pipelines Project (MoPS), which is currently under development and will provide relevant information from available genomes of the TU under scrutiny. Assessment of allergenicity of residual microbial components in microbial products (e.g. proteins, secondary metabolites, etc.) is beyond the QPS assessment remit; nevertheless, if there is science-based evidence for some microbial species related to well-defined clinical cases, this is taken into consideration. Although general human safety is part of the evaluation, specific issues connected to the exposure of users handling the product (e.g. dermal, inhalation) are not addressed.

Reports of infection, intoxication or other diseases caused by the assessed TU in livestock and wild animals are also relevant information for identifying potential safety concerns. As with safety concerns for humans, whether diseases are acquired through exposure via feed, or other routes (e.g. wounds, inhalation) are also relevant information.

The assessment of the safety of the environment considers the assessment of adverse effects on organisms present in the natural environment. The environmental risk assessment of PPPs is not included in the QPS assessment is carried out by the Member State competent authority and peer reviewed by EFSA's Units dealing with PPPs based on the information in the application dossier.

## 3. Assessment

### 3.1. ToR 1: update of EFSA notifications list

Between October 2019 and September 2022, 323 notifications were received and analysed. From these, 217 were for feed additives; 54 for food enzymes, food additives and flavourings; 14 for PPPs

and 38 for novel foods; 214 were bacteria, 57 filamentous fungi/ oomycetes, 38 yeasts, 12 protists/ algae and 2 viruses (Table 1). The notification list, which is updated every 6 months, is publicly available (<https://doi.org/10.5281/zenodo.3607183>).

**Table 1:** Notifications received by risk assessment area from October 2019 until September 2022, per type microorganism (from Panel Statements, Part 12 to Part 17)

	Algae	Bacteria	Filamentous fungi	Oomycetes	Viruses	Yeasts	Grand Total
Feed additives	4	164	24			25	217
Food enzymes, food additives and flavourings	1	26	17			10	54
Novel foods	7	20	8			3	38
Plant protection products		4	7	1	2		14
<b>Grand Total</b>	<b>12</b>	<b>214</b>	<b>56</b>	<b>1</b>	<b>2</b>	<b>38</b>	<b>323</b>

### 3.2. ToR 2: review of taxonomic units previously recommended for the QPS list and their qualifications

#### 3.2.1. Review of the taxonomic units by extensive literature search

The aim of the ELS carried out in response to ToR 2 (review of the recommendations for the QPS list and specific qualifications) was to identify any publicly available studies reporting on safety concerns for humans, animals or the environment caused by QPS organisms (Table 2).

Within the time frame of this Opinion, a total of six ELS exercises have been run, with searches made for the following periods of publication. The summary of the results obtained for the data retrieved was published every 6 months within the Panel Statements:

- From July 2019 to December 2019 (inclusive): Panel Statement Part 12;
- From January 2020 to June 2020 (inclusive): Panel Statement Part 13;
- From July 2020 to December 2020 (inclusive): Panel Statement Part 14;
- From January 2021 to June 2021 (inclusive): Panel Statement Part 15;
- From July 2021 to December 2021 (inclusive): Panel Statement Part 16;
- From January 2022 to June 2022 (inclusive): Panel Statement Part 17.

No safety concerns related to the TUs on the QPS list have been identified. The QPS list has been updated related to the most recent taxonomic insights and the qualifications were streamlined (EFSA, 2020b, 2022a).

The updated QPS list is available at the Knowledge Junction in Zenodo (<https://doi.org/10.5281/zenodo.1146566>).

The Artificial Intelligence (AI) function (DistillerSR) was used for prescreening of papers for *Bifidobacterium* spp., *Carnobacterium divergens*, lactobacilli, *Lactococcus lactis*, bacilli and yeasts, followed by a second screening of those articles retrieved by AI that was carried out by two experts (Tables 3 and 4).

In this 3-year period, 12,406 records were initially screened by AI and excluded from the ELS exercise.

**Table 2:** Flow of records for AI prescreening vs. ELS for the 3-year period (July 2019 until June 2022)

	Prescreened by AI and excluded	Title screening step
<b><i>Bacillus</i> spp.</b>	3,170	2,929
<b><i>Bifidobacterium</i> spp.</b>	1,169	991
<b><i>Carnobacterium</i></b>	133	32
<b>Lactobacilli</b>	2,735	2,544
<b><i>Lactococcus lactis</i></b>	732	589
<b>Yeasts</b>	4,467	3,468
<b>Total</b>	<b>12,406</b>	<b>10,553</b>

**Table 3:** Flow of records by search strategy step for the 3-year period (July 2019 until June 2022)

Species/family	Title screening step	Title/abstract screening step	Article evaluation step (screening for potential relevance)	Article evaluation step (identification of potential safety concerns)
	<b>Numbers of articles retrieved</b>			
<b>Bacteria (total)</b>	<b>11,446</b>	<b>514</b>	<b>250</b>	<b>74</b>
Bacilli	2,929	97	44	23
<i>Bifidobacterium</i>	991	122	70	7
<i>Carnobacterium divergens</i>	32	2	2	0
<i>Corynebacterium glutamicum</i>	197	6	1	0
Gram negatives <sup>(a)</sup>	1,423	13	3	0
Lactobacilli	2,544	122	70	28
<i>Lactococcus lactis</i>	589	44	24	7
Leuconostoc	489	40	22	8
<i>Microbacterium imperiale</i>	2	0	0	0
<i>Oenococcus</i>	223	3	1	0
<i>Pasteuria nishizawae</i>	3	0	0	0
Pediococci	1,151	27	6	1
<i>Propionibacterium</i>	194	3	0	0
<i>Streptococcus thermophilus</i>	679	35	7	0
<b>Viruses (total)</b>	<b>552</b>	<b>11</b>	<b>1</b>	<b>0</b>
Alphaflexiviridae/ Potyviridae	249	5	0	0
Baculoviridae	303	6	1	0
<b>Yeasts</b>	<b>3,468</b>	<b>427</b>	<b>211</b>	<b>112</b>
<b>Protist</b>	<b>364</b>	<b>63</b>	<b>17</b>	<b>4</b>
<b>Algae</b>	<b>703</b>	<b>47</b>	<b>8</b>	<b>0</b>
<b>Total</b>	<b>16,533</b>	<b>1,062</b>	<b>486</b>	<b>190</b>
Excluded	15,514	506	321	

(a): *Gluconobacter oxydans*/*Xanthomonas campestris*/*Cupriavidus*/*Komagataibacter*.

### 3.2.2. Review of new evidence in the published literature

The qualification 'absence of aminoglycoside production ability' was withdrawn for *Bacillus velezensis* based on recent information that did not support possible aminoglycoside production, thereby contradicting the original data on which the qualification was based (EFSA BIOHAZ Panel, 2023).

### 3.2.3. Microbial safety/opportunistic infections by QPS species

The pathogenicity potential of QPS species is investigated on a regular basis mainly by literature search analysis of:

- pathogenicity evidence from clinical cases and epidemiological data sources;
- functional characterisation of genes discovered in available genome sequences of TU with special attention to documented virulence factors and AMR determinants;
- experimental approaches using *in vitro* and *in vivo* model systems.

Opportunistic infections related to TUs mentioned on the QPS list are sporadically reported. Therefore, these were further investigated, leading to the following observations:

- The development of opportunistic infections is based both on the host factors and features of the microorganisms. These features are related to virulence potential and to exposure. The

concentration of microorganisms involved in the exposure and the severity of pre-existing host morbidity determine the probability of the occurrence of opportunistic infections. So, opportunistic infections would often result from the combination of these different aspects.

- In relation to the putative pathogens, the clinical reports frequently omit essential data on the isolation and identification of the associated microorganisms or describe procedures for identification that are not taxonomically appropriate. This results in uncertainty about the real identity of the claimed pathogens. Moreover, the co-detection of other microorganisms, including primary pathogens, is common. This suggests that in these cases, either colonisation or sample contamination by the claimed QPS organism may have occurred. This questions the causality relation between the QPS organism and the adverse effect, making it impossible to determine its pathogenic character.
- For patients, the literature usually describes the main features of the cases with an emphasis on the clinical characteristics of the patient, including any pre-existing conditions and the final outcome. In most cases, the infections associated with QPS species occur in individuals who suffer severe impairment of their immune response due to one or several of the following conditions: prematurity, metabolic illnesses such as diabetes, lymphoma and other tumours, AIDS, previous infection by primary pathogens that could not be controlled by antimicrobials, illnesses that generate life-threatening conditions, such as endocarditis, septicaemia, abdominal or thoracic organ malfunction, etc.
- Moreover, the incidence of the infections is extremely low, especially when compared with the level of exposure: most of the species involved are widespread and common components of the microbial communities of the food system. As such, they can occur in spontaneous food fermentations and are commonly used as starter cultures for food and feed processing and, in most cases, are ingested alive in large amounts with no harm to the consumers. This is the case for several QPS species of the family *Lactobacillaceae*, the genera *Bacillus* and *Bifidobacterium* and the species *Lactococcus lactis* and *Saccharomyces cerevisiae*. In addition, bifidobacteria and lactobacilli have functions being essential for the functioning of the digestive and urogenital tracts. Although the level of exposure to these microorganisms could potentially suggest a food or endogenous source for the infections, only very rarely can the putative aetiological pathogens be ascribed to components of the diet or to presence among the human microbiota, and such infections are almost invariably linked to consumption of high doses of organisms within probiotic food supplements administered to greatly weakened patients.
- The WGS data available do not reveal clear virulence determinants in the genomes of the QPS microorganisms most frequently found associated with opportunistic infections.

In conclusion, although infection ascription to some QPS species is occasionally reported, their QPS status has not been withdrawn due to the frequently incomplete description of the identification method, the lack of clear virulence determinants in their genomes, the extremely low incidence of infections when compared with the level of exposure to the concerned species, the frequent weakness of patients that predispose for opportunistic infections and the habitual lack of transmission evidence through food/feed sources.

### 3.3. ToR 3: evaluation of a QPS recommendation for taxonomic units notified to EFSA

#### 3.3.1. Evaluation of notified taxonomic units to EFSA

In response to ToR 3, the microorganisms notified to EFSA in the context of a technical dossier for safety assessment were (re)assessed for their suitability for inclusion in the QPS list. Of the 323 notifications received, 185 referred to bacterial species that already had the QPS status and, consequently, were not further evaluated; neither were the 57 filamentous fungi/oomycetes and 44 bacteria (9 *Enterococcus faecium* notifications, the 25 notifications of *E. coli*, 3 of *Clostridium butyricum* and the 7 of *Streptomyces* spp.) (Tables 4 and 5). The remaining 37 notifications were considered for assessment of the suitability of the respective TUs for inclusion in the QPS list. Of these, 27 were on bacteria, 4 on yeasts and 6 on algae (see Tables 5 and 6).

The assessments of the respective TUs were published in six Panel Statements, adopted every 6 months from July 2020 to December 2022 (see Table 6).

**Table 4:** Notifications received by type of risk assessment area and by microbiological group from October 2019 until September 2022 (included in one of six Panel Statements, from Part 12 to Part 17)

Risk assessment area	Not evaluated		Evaluated	Total
	Already QPS	Excluded in QPS		
<b>Microbiological group</b>				
<b>Feed additives</b>	<b>152</b>	<b>51</b>	<b>14</b>	<b>217</b>
Algae	4	0	0	4
Bacteria	124	27	13	164
Filamentous fungi	0	24	0	24
Yeasts	24	0	1	25
<b>Novel foods</b>	<b>5</b>	<b>20</b>	<b>13</b>	<b>38</b>
Algae	1	0	6	7
Bacteria	1	12	7	20
Filamentous fungi	0	8	0	8
Yeasts	3	0	0	3
<b>Plant protection products</b>	<b>4</b>	<b>8</b>	<b>2</b>	<b>14</b>
Bacteria	2	0	2	4
Filamentous fungi	0	7	0	7
Oomycetes		1		1
Viruses	2	0	0	2
<b>Food enzymes, food additives and flavourings</b>	<b>24</b>	<b>22</b>	<b>8</b>	<b>54</b>
Algae	1			1
Bacteria	16	5	5	26
Filamentous fungi	0	17	0	17
Yeasts	7	0	3	10
<b>Total</b>	<b>185</b>	<b>101</b>	<b>37</b>	<b>323</b>

**Table 5:** Notifications received by microbiological group from October 2019 until September 2022 (included in one of six Panel Statements, from Part 12 to Part 17)

Microbiological group	Not evaluated		Evaluated	Total
	Already QPS	Excluded in QPS		
Algae	6		6	12
Bacteria	143	44	27	214
Filamentous fungi	0	56	0	56
Oomycetes		1		1
Yeasts	34	0	4	38
Viruses	2	0	0	2
<b>Total</b>	<b>185</b>	<b>101</b>	<b>37</b>	<b>323</b>

**Table 6:** TUs assessed for a QPS status per Panel Statement (PS) from Part 12 to 17

	PS12	PS13	PS14	PS15	PS16	PS17	Grand Total
<b>Algae</b>	<b>1</b>			<b>4</b>			<b>6</b>
<i>Chlamydomonas reinhardtii</i>				1			1
<i>Galdieria sulphuraria</i>	1						1
<i>Haematococcus pluvialis</i>				1			1
<i>Schizochytrium aggregatum</i>				1			1
<i>Schizochytrium mangrovei</i>				1			1
<i>Schizochytrium</i> sp.			1				1



	PS12	PS13	PS14	PS15	PS16	PS17	Grand Total
<b>Bacteria</b>	<b>3</b>	<b>3</b>	<b>6</b>	<b>3</b>	<b>8</b>	<b>4</b>	<b>27</b>
<i>Akkermansia muciniphila</i>	1						1
<i>Anoxybacillus caldiproteolyticus</i>			1				1
<i>Bacillus circulans</i>		1					1
<i>Bacillus nakamurai</i>				1			1
<i>Bacillus paralicheniformis</i>			1				1
<i>Clostridium butyricum</i>	1						1
<i>Companilactobacillus formosensis</i>					3		3
<i>Corynebacterium stationis</i>			1				1
<i>Dyella</i> sp. ( <i>Pseudomonas amyloclavata</i> )			1				1
<i>Ensifer adhaerens</i>					1		1
<i>Enterobacter hormaechei</i>			1				1
<i>Enterococcus lactis</i>				1			1
<i>Geobacillus thermodenitrificans</i>						1	1
<i>Lactococcus garvieae</i>			1				1
<i>Methylobacterium extorquens</i>		1					1
<i>Microbacterium foliorum</i>					1		1
<i>Mycobacterium aurum</i>		1					1
<i>Paenibacillus lentus</i>				1			1
<i>Pseudomonas chlororaphis</i>	1						1
<i>Pseudomonas fluorescens</i>					1		1
<i>Pseudonocardia autotrophica</i>					1		1
<i>Streptococcus oralis</i>						1	1
<i>Streptococcus salivarius</i>					1		1
<i>Xanthobacter</i>						1	1
<i>Lactiplantibacillus argentoratensis</i>						1	1
<b>Yeasts</b>			<b>2</b>		<b>1</b>	<b>1</b>	<b>4</b>
<i>Eremothecium ashbyii</i>			1				1
<i>Kodamaea ohmeri</i>			1				1
<i>Ogataea polymorpha</i>						1	1
<i>Papiliotrema terrestris</i> ( <i>Cryptococcus laurentii</i> )					1		1
<b>Grand Total</b>	<b>4</b>	<b>3</b>	<b>9</b>	<b>7</b>	<b>9</b>	<b>5</b>	<b>37</b>

### 3.3.2. New QPS recommendations from October 2019 until September 2022

In four of the six Statements Parts 13, 14, 15 and 17 (EFSA BIOHAZ Panel, 2021a,b, 2022a, 2023) produced during this period, six new TUs were recommended for the QPS status. In Panel Statement Part 13 (EFSA BIOHAZ Panel, 2021a), *Bacillus circulans* was recommended for QPS status with the qualifications 'for production purposes only' and 'absence of cytotoxic activity'. In Panel Statement Part 14 (EFSA BIOHAZ Panel, 2021b), *Bacillus paralicheniformis* was recommended with the qualification 'absence of toxigenic activity' and 'absence of bacitracin production ability'. In Panel Statement Part 15 (EFSA BIOHAZ Panel, 2022a), *Haematococcus lacustris* synonym *Haematococcus pluvialis* (algae) was recommended for the QPS status with the qualification 'for production purposes only, which implies the absence of viable cells in the end product'. In Panel Statement 17 (EFSA BIOHAZ Panel, 2023), *Ogataea polymorpha* (synonyms: *Hansenula polymorpha*, *Candida thermophila*) was proposed for the QPS status with the qualification 'for production purposes only', *G. thermodenitrificans* was recommended for the QPS status with the qualification 'absence of toxigenic activity' and *Lactiplantibacillus argentoratensis* (*Lactobacillus plantarum* subsp. *argentoratensis*) was included in the QPS list (Table 7).

**Table 7:** QPS new recommendations per TU group and TU, for notifications received from October 2019 until September 2022

<b>Algae</b>	
<i>Haematococcus pluvialis</i> synonym <i>Haematococcus pluvialis</i>	<i>Haematococcus lacustris</i> is recommended for QPS status with the qualification 'for production purposes only'
<b>Bacteria</b>	
<i>Bacillus circulans</i>	<i>Bacillus circulans</i> was recommended for QPS status with the qualifications 'for production purposes only' and 'absence of cytotoxic activity'
<i>Bacillus paralicheniformis</i>	<i>Bacillus paralicheniformis</i> was recommended for the QPS status with the qualifications 'absence of toxigenic activity' and 'absence of bacitracin production ability'
<i>Geobacillus thermodenitrificans</i>	<i>Geobacillus thermodenitrificans</i> was recommended for the QPS status with the qualification 'absence of toxigenic activity' based on its inability to grow at animal and human physiological temperatures and the absence of safety concerns reported.
<i>Lactiplantibacillus argentoratensis</i>	<i>Lactiplantibacillus argentoratensis</i> (previously <i>Lactobacillus plantarum</i> subs. <i>argentoratensis</i> ) was recommended for the QPS status based on the absence of safety concerns and its former taxonomic position as a subspecies of <i>L. plantarum</i> which had the QPS status.
<b>Yeasts</b>	
<i>Ogataea polymorpha</i>	<i>Ogataea polymorpha</i> was recommended for the QPS status with the qualification 'for production purposes only' based on the absence of safety concerns and the body of knowledge related to its use as a production organism.

### 3.3.3. Suitability of bacteriophages for QPS assessment

Bacteriophages were excluded from the QPS assessment, as explained in the EFSA QPS Opinions 2009 (EFSA BIOHAZ Panel, 2009) and 2017 (EFSA BIOHAZ Panel, 2017), based on the impossibility of allocating them to precise TUs (genera and species). As a consequence, the lack of safety concerns, such as the ability of some to transduce bacterial DNA, which has to be deduced from their DNA-packaging characteristics, could not be related to a certain TU. Also, the discrimination between their temperate/virulent nature and the possible carriage of undesirable genes in their genomes requires strain-dependent DNA/RNA sequencing and analysis.

Over the last few years, whole genome and proteome analysis has been applied as a basis for new taxonomic insights that may lead to a phylogeny-based classification of phages (Chibani et al., 2019; Adriaenssens et al., 2020) and, potentially, of all viruses (Moreno-Gallego and Reyes, 2021). However, although these new insights may open new perspectives for the future classification of phages, the QPS WG concluded that the actual taxonomic situation is still unsettled and not generally accepted.

In the meantime, phages (and their endolysins) have been developed for use in applications requiring a safety assessment by EFSA before entering the EU market. Among them are the elimination of food-spoilage bacteria, use as biocides against plant and animal pests, food-ripening acceleration through early starter lysis, etc. (O'Sullivan et al., 2019; Chang, 2020; Gambino and Brøndsted, 2021). Some of these applications of phages have already been implemented in the food and feed chain, mainly outside Europe, apparently without any related health problems for the consumers (Żbikowska et al., 2020; Vikram et al., 2021).

However, there are still uncertainties that preclude the consideration of any phage as eligible for QPS assessment. Among them are the frequent presence of genes encoding proteins that do not have counterparts in the databases, which hinders the understanding of their precise role (Hammerl et al., 2012; Łobocka et al., 2012) and the possibility of recombination between phages that might allow gene-shuffling (Hammerl et al., 2012), which might lead to subsequent changes of host ranges and their virulent/lysogenic lifestyle (Vegge et al., 2006).

Based on the above, it is concluded that phages should be excluded from QPS assessment until the uncertainties discussed above are solved, and that their safety evaluation has to be conducted on a strain basis in relation to particular applications.

### 3.3.4. Synthetic microorganisms

Synthetic Biology (SynBio) is the engineering of biology that aims to develop new biological systems and impart new functions to viable cells. EFSA published two opinions on the evaluation of the existing EFSA assessment framework for the microbial characterisation and environmental risk assessment (EFSA Scientific Committee, 2020) and the food and feed safety assessment (EFSA Scientific Committee, 2022) of synthetic microorganisms. In these opinions, it is stated that no clear criteria to differentiate between a GMM and a synthetic microorganism could be identified and that synthetic microorganisms are the result of a continuous increase in the introduction of genetic modifications and other molecular techniques, being xenobionts, defined as new to nature organisms with new to nature components (e.g. nucleotides, amino acids), as examples of the most evolved ones.

As the QPS assessment is based on the unambiguous taxonomic identification of the microorganism and on its body of knowledge, including safety for humans, animals and the environment, the QPS concept, as such, is currently not applicable for the intensively engineered synthetic microorganisms (EFSA Scientific Committee, 2020, 2022). However, the QPS risk assessment concept is worthwhile for considering as a basis for the risk assessment of building blocks of SynBio microorganisms (e.g. chassis, metabolic building blocks) for which there is sufficient familiarity in literature with the QPS organism (EFSA Scientific Committee, 2020).

## 4. Conclusions

### Answer to the Terms of Reference (ToR)

*ToR 1: Keep updated the list of microorganisms being notified in the context of a technical dossier for safety assessment to EFSA Units (such as FEEDCO, PREV, FIP and NIF) for intentional use directly or as sources of food and feed additives, food enzymes and PPPs and GMMs for safety assessment.*

- The list 'Microbiological agents as notified to EFSA' (<https://doi.org/10.5281/zenodo.3607183>) comprises all microorganisms notified to EFSA in the context of a technical dossier for safety assessment, from the beginning of the QPS exercise in 2007. The list of microorganisms notified in the context of technical dossiers has been updated every 6 months with every Panel Statement.
- In total, 323 notifications were received between October 2019 and September 2022, of which 217 were of microorganisms used for the production of feed additives, 54 for the production of food enzymes, food additives and flavourings, 14 as PPPs and 38 for novel foods; 214 were bacteria, 57 filamentous fungi/oomycetes, 38 yeasts, 12 protists/algae and 2 viruses.

*ToR 2: Review TUs previously recommended for the QPS list and their qualifications when new information has become available. Update the information provided in the previous opinion when appropriate.*

- The list of QPS-recommended TUs is reviewed every 6 months, following an ELS strategy. The outcome of this task has been covered by each of the Panel Statements published from July 2020 onwards. The updated list of 'QPS-recommended Microbiological agents' for safety risk assessments carried out by EFSA ('2022 QPS list') is available at the Knowledge Junction in Zenodo (<https://doi.org/10.5281/zenodo.1146566>).
- Relevant information from the ELS includes case reports of human diseases. Several of the QPS-TUs are sporadically reported to cause infections in individuals with conditions recognised as predisposing to the acquisition of opportunistic infections. Previous use of the microorganisms as food supplements for humans, which does not fall under the remit of the QPS assessment, was reported in some of these cases. The QPS status of these TUs has not been withdrawn because of the extremely low incidence of infection when compared with the exposure level, the predisposing circumstances of the patient that facilitate these opportunistic infections, the lack of transmission evidence through food/feed sources and the identification of the function of the genes (e.g. virulence gene, AMR gene) discovered in the available genome sequences indicating no documented virulence factor determinants.
- The qualification '*absence of aminoglycoside production ability*' was withdrawn for *Bacillus velezensis* based on recent information that did not support possible aminoglycoside production contradicting the original data.
- The QPS list has been updated in relation to the most recent taxonomic insights in the genera *Bacillus* and *Lactobacillus*. TUs belonging to a previously designated species in these genera

were transferred to the new species and both the previous and new names are included in the QPS list.

- The qualifications of the TUs in the QPS list were streamlined within this 3-year period.

*ToR 3: (Re)assess the suitability of TUs notified to EFSA in the context of a technical dossier for safety assessment, for their inclusion in the QPS list.*

- Filamentous fungi, bacteriophages, streptomycetes, oomycetes, *Enterococcus faecium*, *Escherichia coli*, *Clostridium butyricum* (EFSA BIOHAZ Panel, 2020b) are excluded from the QPS assessments based on the possession of potentially harmful traits, and it is considered unlikely that any TUs within these groups would be granted QPS status in the foreseeable future. The assessment of members of the excluded biological groups needs to be carried out at strain level by the relevant EFSA Unit.
- The exclusion of bacteriophages from the QPS assessment was re-evaluated and their exclusion was reconfirmed because the new phylogenetic classification is still unsettled and because the distinction between temperate/virulent and the mode of nucleic acid packaging, which is essential to judge the safety risks of phages, cannot be linked to particular TUs.
- Six Panel Statements have been published periodically (approximately every 6 months) in order to assess the suitability of new TUs notified to EFSA in the context of a technical dossier for safety assessment and to update the list with those microorganisms that were recommended for the QPS list. Six new TUs received the QPS status between October 2019 and September 2022:
  - *Bacillus circulans* with the qualifications ‘for production purposes only’ and ‘absence of cytotoxic activity’;
  - *Bacillus paralicheniformis* with the qualification ‘absence of toxigenic activity’ and ‘absence of bacitracin production ability’;
  - *Haematococcus lacustris* (synonym *Haematococcus pluvialis*) with the qualification ‘for production purposes only’;
  - *Geobacillus thermodenitrificans* with the qualification ‘absence of toxigenic activity’;
  - *Lactiplantibacillus argentoratensis* (previously *Lactobacillus plantarum* subs. *argentoratensis*);
  - *Ogataea polymorpha* with the qualification ‘for production purposes only’.

## Recommendations

- In relation to the current qualification for all QPS status bacteria ‘the strains should not harbour any acquired AMR genes to clinically relevant antimicrobials’, it is recommended to include more detailed guidance to facilitate the interpretation of phenotypic and genotypic AMR data.
- It is recommended that in future QPS assessments, the analysis of the publicly available WGS of microorganisms is included whenever found necessary. This will allow the discovery of sequence information that might code for hazardous traits. It will also make it possible to check the taxonomic identity of microbial strains reported in the published literature. When data are available, this approach will be applied to establish possible links between the use of a strain in the food chain and possible safety issues.

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## Abbreviations

AI	artificial intelligence
AMR	antimicrobial resistance
ANI	average nucleotide identity
BIOHAZ Panel	EFSA Panel on Biological Hazards
CEF Panel	EFSA Panel of Food Contact Materials, Enzymes, Flavourings and Processing Aids
DG SANCO	Health and Food Safety Directorate-General
ELS	extensive literature search
FDP	front-desk and workforce planning
FEEDAP Panel	EFSA Panel on Additives and Products of Substances used in Animal Feed
FEEDCO	EFSA Feed and Contaminants Unit
FIP	EFSA Food Ingredients and Packaging Unit
FSTA	Food Science Technology Abstracts
GMM	genetically modified microorganisms
ICN	International Code of Nomenclature
ICTV	International Commission on the Taxonomy of Viruses
NIF	EFSA Nutrition and Food Innovation Unit
QPS	qualified presumption of safety
PPP	plant protection products
PREV	EFSA Pesticides Peer Review Unit
ToR	Term of Reference
TU	taxonomic unit
WGS	Whole genome sequencing