STATEMENT

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Update of the list of QPS-recommended biological agents intentionally added to food or feed as notified to EFSA 9: suitability of taxonomic units notified to EFSA until September 2018

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Abstract

The qualified presumption of safety (QPS) procedure was developed to provide a harmonised generic pre-evaluation to support safety risk assessments of biological agents performed by EFSA's Scientific Panels. The taxonomic identity, body of knowledge, safety concerns and antimicrobial resistance were assessed. Safety concerns identified for a taxonomic unit are, where possible and reasonable in number, reflected by 'qualifications' which should be assessed at the strain level by the EFSA's Scientific Panels. During the current assessment, no new information was found that would change the previously recommended QPS taxonomic units and their qualifications. Between April and September 2018, the QPS notification list was updated with 48 microorganisms from applications for market authorisation. Of these, 30 biological agents already had QPS status, 15 were excluded from the QPS exercise by the previous QPS mandate (five filamentous fungi) or from further evaluations within the current mandate (two notifications of *Enterococcus faecium*, one of *Streptomyces* spp. and seven of *Escherichia coli*). One taxonomic unit was (re)evaluated: *Pseudomonas fluorescens* had been previously evaluated in 2016, and was now re-evaluated within this mandate. The revision of the literature supports the previously identified safety concerns (e.g. production of biocompounds with antimicrobial activity and virulence features), preventing the inclusion of *P. fluorescens* in the QPS list. *Mycobacterium setense* and *Komagataeibacter sucrofermentans* were evaluated for the first time. *M. setense* cannot be considered for the QPS assessment because there are significant safety concerns. *K. sucrofermentans* (*Acetobacter xylinus* subsp. *sucrofermentans*) can be proposed for the QPS list but only for production purposes. The QPS status of *Corynebacterium glutamicum* is confirmed with the qualification extended to other production purposes.

Keywords: safety, QPS, bacteria, yeast, *Pseudomonas fluorescens*, *Mycobacterium setense*, *Komagataeibacter sucrofermentans*, *Corynebacterium glutamicum*

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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) biological agents intentionally added to food or feed. The request included three specific tasks as mentioned in the Terms of Reference (ToR).

The QPS process was developed to provide a harmonised generic pre-evaluation procedure to support safety risk assessments of biological agents performed by EFSA's scientific Panels and Units. The taxonomic identity, body of knowledge and safety of biological agents are assessed. Safety concerns identified for a taxonomic unit (TU) are, where possible and reasonable in number, reflected as 'qualifications' that should be assessed at the strain level by the 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).[3]

The evaluation is undertaken every 3 years in a scientific Opinion of the BIOHAZ Panel. Meanwhile, the list of microorganisms is maintained and re-evaluated approximately every 6 months in a Panel Statement. If new information is retrieved from extended literature searches that would change the QPS status of a microbial species or its qualifications, this is published in the Panel Statement. The Panel Statement also includes the evaluation of microbiological agents notified to EFSA within the 6-month period for an assessment for use as feed additives, food enzymes, food additives and flavourings, novel foods or plant protection products (PPP). The main results of the assessments completed from 2017 will be included in the scientific Opinion of the BIOHAZ Panel to be published by the end of the current mandate in December 2019. In the interim, as a result of each Panel Statement, the '2016 updated list of QPS status recommended biological agents for safety risk assessments carried out by EFSA scientific Panels and Units' is extended by the inclusion of new recommendations for QPS status, and appended to the Opinion adopted in December 2016 (Appendix E).

The *first ToR* requires ongoing updates of the list of biological agents notified to EFSA, in the context of a technical dossier, for intentional use in food and/or feed or as sources of food and feed additives, enzymes and PPP for safety assessment. The list was updated with the notifications received since the latest review in March 2018. Within this period, 48 notifications were received by EFSA, of which 41 were for feed additives, three for food enzymes, food additives and flavourings, four for novel foods and none for PPP. The new notifications, received between April and September 2018, are included in a table appended to the current Statement (Appendix F).

The *second ToR* concerns the revision of the TUs previously recommended for the QPS list and their qualifications when new information has become available, and the updating of the information provided in the previous Opinion adopted in December 2016. According to the articles retrieved through an extensive literature search (ELS), for articles published from January to June 2018 no new information was found that would affect the QPS status of those TUs and their qualifications.

The *third ToR* requires a (re)assessment of TUs notified to EFSA, but not present in the current QPS list, for their suitability for inclusion in the updated list. The current Statement focuses on the assessments of the TUs that were notified to EFSA between April 2018 and September 2018. Of the 48 notifications received, 30 biological agents already had QPS status and did not require further evaluation in this Statement and 15 were not included because: five were notifications of filamentous fungi that were excluded from the QPS exercise; two were notifications of *Enterococcus faecium*, one of *Streptomyces* spp. and seven of *Escherichia coli* that were excluded from further QPS evaluations within the current QPS mandate. Three new TUs were considered for the QPS assessment within this Statement: *Pseudomonas fluorescens*, already evaluated in 2016 (EFSA BIOHAZ Panel, 2017a), and was re-evaluated within this mandate and *Mycobacterium setense* and *Komagataeibacter sucrofermentans*, which were evaluated for the first time.

The revision of the literature supports the previous identified safety concerns (e.g. production of biocompounds with antimicrobial activity and virulence features), preventing the inclusion of *P. fluorescens* in the QPS list. *M. setense* cannot be considered for the QPS assessment because there are significant safety concerns. *K. sucrofermentans* (*Acetobacter xylinus* subsp. *sucrofermentans*) can be proposed for the QPS list but only for production purposes.

In parallel to the standard procedure for assessing a TU for a possible QPS status, in relation to *Corynebacterium glutamicum*, and in response to a request from an EFSA unit, it was decided to run a complementary reassessment for another specific end-use as the QPS qualification 'only applies when the species is used for amino acid production'. The QPS status of *C. glutamicum* is confirmed with the qualification extended to other production purposes.

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1. Introduction

The qualified presumption of safety (QPS) approach was developed by the EFSA Scientific Committee to provide a generic concept to prioritise and to harmonise risk assessment within the European Food Safety Authority (EFSA) of microorganisms intentionally introduced into the food chain, in support of the respective Scientific Panels and Units in the frame of market authorisations (EFSA, 2007a). The list, first established in 2007, has been continuously revised and updated. The publication of the overall assessment of the taxonomic units (TUs) previously recommended for the QPS list is to be evaluated every 3 years through a scientific Opinion by the Panel on Biological Hazards (BIOHAZ). Intermediate deliverables in the form of a Panel Statement are produced and published for periods of around 6 months, should an assessment for a QPS classification of a microbiological agent notified to EFSA be requested by the Units dealing with feed additives, food enzymes, food additives and flavourings, novel foods, or plant protection products. These Panel Statements also include the results of the assessment of the relevant new papers related to the TUs with QPS status.

1.1. Background and Terms of Reference as provided by EFSA

1.1.1. Background as provided by EFSA

A wide variety of microorganisms are intentionally added at different stages into the food and feed chain. In the context of applications for market authorisation of these biological agents, used either directly or as sources of food and feed additives, food enzymes and plant protection products, EFSA is requested to assess their safety.

Several taxonomic units (usually species for bacteria and yeasts, families for viruses) have been included in the qualified presumption of safety (QPS) list either following notifications to EFSA or proposals made initially by stakeholders during a public consultation in 2005, even if they were not yet notified to EFSA (EFSA, 2005).[1] The EFSA Scientific Committee reviewed the range and numbers of microorganisms likely to be the subject of an EFSA Opinion and published in 2007 a list of microorganisms recommended for the QPS list.[2]

In 2007, the Scientific Committee recommended that a QPS approach should provide a generic concept to prioritise and to harmonise safety risk assessment of microorganisms intentionally introduced into the food chain, in support of the respective Scientific Panels and EFSA Units in the frame of the market authorisations. The same Committee recognised that there would have to be continuing provision for reviewing and modifying the QPS list and in line with this recommendation, the EFSA Scientific Panel on Biological Hazards (BIOHAZ) took the prime responsibility for this and started reviewing annually the existing QPS list. The first annual QPS update[3] was published in 2008 and EFSA's initial experience in applying the QPS approach was included. The potential application of the QPS approach to microbial plant protection products was discussed in the 2009 update.[4] Also in 2009, bacteriophages were assessed and were not considered appropriate for the QPS list. After consecutive years of reviewing the existing scientific information, the filamentous fungi (2008 to 2013 updates) and enterococci (2010 to 2013 updates) were not recommended for the QPS list. The 2013 update[5] of the recommended QPS list included 53 species of Gram-positive non-spore-forming bacteria, 13 Gram-positive spore forming bacteria (*Bacillus* species), one Gram-negative bacterium (*Gluconobacter oxydans*), 13 yeast species, and three virus families.

In 2014 the BIOHAZ Panel, in consultation with the Scientific Committee, decided to change the revision procedure: the overall assessment of the taxonomic units previously recommended for the QPS list is no longer carried out annually but over 3-year periods. From 2017, the search and revision of the possible safety concerns linked to those taxonomic units start to be done every 6 months

[1] Opinion of the Scientific Committee on a request from EFSA related to a generic approach to the safety assessment by EFSA of microorganisms used in food/feed and the production of food/feed additives. EFSA Journal 2005;226, 1–12.

[2] Introduction of a Qualified Presumption of Safety (QPS) approach for assessment of selected microorganisms referred to EFSA - Opinion of the Scientific Committee. EFSA Journal 2007;293, 1–85.

[3] Scientific Opinion of the Panel on Biological Hazards on a request from EFSA on the maintenance of the list of QPS microorganisms intentionally added to food or feed. EFSA Journal 2008;923, 1–48.

[4] Scientific Opinion of the Panel on Biological Hazards (BIOHAZ) on the maintenance of the list of QPS microorganisms intentionally added to food or feed (2009 update). EFSA Journal 2009;7(12):1431, 92 pp. https://doi.org/10.2903/j.efsa.2009.1431

[5] EFSA BIOHAZ Panel (EFSA Panel on Biological Hazards), 2013. Scientific Opinion on the maintenance of the list of QPS biological agents intentionally added to food and feed (2013 update). EFSA Journal 2013;11(11):3449, 107 pp. https://doi.org/10.2903/j.efsa.2013.3449

period. The update of the 2013 QPS list version (EFSA BIOHAZ Panel, 2013) was done in 2016 (EFSA BIOHAZ Panel, 2017a) and the next update will be published in a scientific Opinion of the BIOHAZ Panel after its adoption in December 2019.[6] The QPS list of microorganisms has been maintained and frequently checked, based on the evaluation of extensive literature searches. In the meantime and every 6 months, a Panel Statement, compiling the assessments for a QPS status of the microbiological agents notified to EFSA requested by the Feed Unit, the Food Ingredients and Packaging (FIP) Unit, the Nutrition Unit or by the Pesticides Unit, has been produced and published. In the follow up of the 2013 update[5] the Scientific Committee agreed to exclude some biological groups (filamentous fungi, bacteriophages and *Enterococcus faecium*[7]) notified to EFSA from the QPS assessment because it was considered unlikely that any taxonomical units within these groups would be granted QPS status in the foreseeable future. Thus, the assessment of members of these biological groups needs to be done at a strain level, on a case-by-case basis, by the relevant EFSA Unit.

The QPS provides a generic safety pre-assessment approach for use within EFSA that covers risks for human, animals and the environment. In the QPS concept a safety assessment of a defined taxonomic unit is considered independently of any particular specific notification in the course of an authorisation process. The QPS concept does not address hazards linked to the formulation or other processing of the products containing the microbial agents and added into the food or feed chain. Although general human safety is part of the evaluation, specific issues connected to type and level of exposure of users handling the product (e.g. dermal, inhalation, ingestion) are not addressed. In the case Genetically Modified Microorganisms (GMM) for which the species of the recipient strain qualifies for the QPS status, and for which the genetically modified state does not give rise to safety concerns, the QPS approach can be extended to genetically modified production strains (EFSA BIOHAZ Panel, 2018a).[8] Assessment of potential allergenicity to microbial residual components is beyond the QPS remit; if there is however, science-based evidence for some microbial species it is reported. Where applicable these aspects are assessed, separately by the EFSA Panel responsible for assessing the notification. Antimicrobial resistance was introduced as a possible safety concern for the assessment of the inclusion of bacterial species in the QPS list published in 2008 QPS Opinion (EFSA, 2008)[3]. In the 2009 QPS Opinion (EFSA BIOHAZ Panel, 2009)[4] a qualification regarding the absence of antimycotic resistance for yeasts was introduced.

1.1.2. Terms of Reference as provided by EFSA

The Terms of Reference, as provided by EFSA are as follows:

ToR 1: Keep updated the list of biological agents being notified in the context of a technical dossier to EFSA Units such as Feed, Pesticides, Food Ingredients and Packaging (FIP) and Nutrition, for intentional use directly or as sources of food and feed additives, food enzymes and plant protection products for safety assessment.

ToR 2: Review taxonomic units previously recommended for the QPS list and their qualifications when new information has become available. The latter is based on a review of the updated literature aiming at verifying if any new safety concern has arisen that could require the removal of the taxonomic unit from the list, and to verify if the qualifications still efficiently exclude safety concerns.

ToR 3: (Re) assess the suitability of new taxonomic units notified to EFSA for their inclusion in the QPS list. These microbiological agents are notified to EFSA and requested by the Feed Unit, the FIP Unit, the Nutrition Unit or by the Pesticides Unit.

1.2. Interpretation of the Terms of Reference

The absence of acquired genes conferring resistance to clinically relevant antimicrobials is a qualification[9] applied to all QPS bacterial TUs. The verification of such qualification is under the remit of the Unit conducting the safety assessment of the organism notified to EFSA for market authorisation, therefore is done at strain level (EFSA BIOHAZ Panel, 2017a).

[6] References updated from the original self-task mandate.
[7] The taxonomic unit was corrected from the original mandate: 'enterococci'. It is only referred to *Enterococcus faecium*, the only species which was evaluated for a possible QSP status.
[8] Sentence included, correcting the previous sentence from the original self-task mandate: 'Genetically modified microorganisms are similarly not taken into account'.
[9] Identified safety concerns, including acquired antimicrobial resistance genes, for a certain TU can be, where reasonable in number and not universally present, reflected as 'qualifications'.

In June of 2017 (EFSA BIOHAZ Panel, 2017b), the BIOHAZ Panel has agreed to exclude *Escherichia coli* and any species of the genus *Streptomyces* from QPS evaluation within this mandate.

In June of 2018 (EFSA BIOHAZ Panel, 2018b), the BIOHAZ Panel clarified that the qualification 'for production purpose only' implies the absence of viable cells of the production organism in the final product and can also be applied for food and feed products based on microbial biomass.

2. Data and methodologies

2.1. Data

Only valid TUs covered by the relevant international committees on the nomenclature for microorganisms are considered for the QPS assessment.

In reply to ToR 3, (re)assessment of the suitability of TUs notified within the time period covered by this Statement (from April to September 2018) is carried out. The literature review considered the identification, the body of knowledge, the potential safety concerns, and the knowledge on acquired antimicrobial resistance (AMR). Relevant databases, such as PubMed, Web of Science, Cases Database, CAB Abstracts or Food Science Technology Abstracts (FSTA) and Scopus, were searched. More details on the search strategy, search keys, and approach are described in Appendix A.

In reply to ToR 2, concerning the revision of the TUs previously recommended for the QPS list and their qualifications, an extensive literature search (ELS) was conducted as described in Appendices B and C.

2.2. Methodologies

2.2.1. Evaluation of a QPS recommendation for Taxonomic Units notified to EFSA

In response to ToR 1, the EFSA Units were asked to update the list of biological agents being notified to EFSA. A total of 48 notifications were received between April and September 2018, of which 41 were for a feed additive, three for food enzymes, food additives and flavourings, four for novel foods and none for plant protection products (Table 1).

In response to ToR 3, out of the 48 notifications, 30 were related to TUs that already had QPS status and did not require further evaluation. Of the remaining 18 notifications, 15 were related to TUs not evaluated for a QPS status for the following reasons:

- Five notifications related to filamentous fungi, which were excluded from QPS evaluations in the follow up of a recommendation of the QPS 2013 and 2016 updates (EFSA BIOHAZ Panel, 2013, 2014, 2016),
- Seven notification related to *E. coli*, one to *Streptomyces* spp. and two of *Enterococcus faecium*, which were recently excluded from the current mandate by the BIOHAZ Panel.

The TUs corresponding to the remaining three notifications were now evaluated (or re-evaluated if they had been evaluated prior to 2016) for possible QPS recommendation:

- *Pseudomonas fluorescens* already evaluated in 2016 and not granted QPS status (EFSA BIOHAZ Panel, 2017a),
- *Mycobacterium setense* and *Komagataeibacter sucrofermentans*, both evaluated for the first time.

In parallel to the standard procedure for assessing a TU for a possible QPS status, and in response to a request from an EFSA unit, in relation to *Corynebacterium glutamicum,* it was decided to run a complementary reassessment for another specific end-use as the QPS qualification 'only applies when the species is used for amino acid production', considering that some time passed by since 2016 and that new data may have been published.

The notifications received by EFSA, per risk assessment area, by biological group from April to September 2018 are presented in Table 1.

Table 1: Notifications received by EFSA, per risk assessment area and by biological group, from April to September 2018

Risk assessment area / Biological group	Not evaluated in this statement		Evaluated in this statement	Total
	Already QPS	Excluded in QPS[(a)]		
Feed additives	**28**	**12**	**1**	**41**
Bacteria	22	8	1	31
Filamentous fungi	0	4	0	4
Yeasts	6	0	0	6
Novel foods	**1**	**1**	**2**	**4**
Bacteria	1	1	2	4
Plant protection products	**0**	**0**	**0**	**0**
Food enzymes, food additives and flavourings	**1**	**2**	**0**	**3**
Bacteria	1	1	0	2
Filamentous fungi	0	1	0	1
Total	**30**	**15**	**3**	**48**

QPS: qualified presumption of safety.
(a): The number includes filamentous fungi or enterococci excluded from QPS evaluation in the 2013 QPS Opinion, other bacterial species (seven notifications of *E. coli*, one of *Streptomyces* spp. and two of *Enterococcus faecium*) already excluded in the Panel Statement adopted in December 2016 (EFSA BIOHAZ Panel, 2017a).

2.2.2. Monitoring of new safety concerns related to the QPS list

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 since the previous QPS review (i.e. publications from January to June 2018). For a detailed protocol of the process and search strategies, refer to Appendices B and C.

After removal of duplicates, 3,034 records were submitted to the *title screening* step, which led to the exclusion of 2,918 of them. The remaining 116 records were found eligible for the *Title and abstract screening* step, which led to the exclusion of 58 of these. Of the 58 articles that finally reached the *Article evaluation step* (full text), 35 were considered to be relevant for the QPS project.

The flow of records from their identification by the different search strategies (as reported in Appendix C) to their consideration potentially relevant papers for QPS, is shown in Table 2.

Table 2: Flow of records by search strategy

Species	No. papers			
	Title screening step****	Title/ abstract screening step****	Article evaluation step (screening for potential relevance)	Article evaluation step (identification of potential safety concerns)
Bacteria	**1,750**	**57**	**23**	**14**
Bacillus spp.	537	3	2	1
Bifidobacterium spp.	168	17	6	1
Carnobacterium divergens			0	
Corynebacterium glutamicum	47	0	0	0
Gluconobacter oxydans	132	2	0	0
Xanthomonas campestris			1	0
Lactobacillus spp.	426	13	7	7
Lactococcus lactis	152	9	4	4
Leuconostoc spp.	44	9	3	1
Microbacterium imperiale			0	0

Species	No. papers			
	Title screening step****	Title/ abstract screening step****	Article evaluation step (screening for potential relevance)	Article evaluation step (identification of potential safety concerns)
Oenococcus oeni	43	0	0	0
Pasteuria nishizawae			0	0
Pediococcus spp.	126	1	0	0
Propionibacterium spp.	30	1	0	0
Streptococcus thermophilus	45	2	0	0
Viruses	**74**	**1**	**0**	**0**
Alphaflexiviridae	26	0	0	0
Baculoviridae	48	1	0	0
Yeasts	**1,210**	**58**	**35****	**21*, **, *****
Candida famata (teleomorph = *Debaryomyces hansenii*)	1210	58	35	5
Candida kefyr (teleomorph = *Kluyveromyces marxianus*)				13
Candida pelliculosa				2
Hanseniaspora uvarum				1
Saccharomyces cerevisiae including *Saccharomyces boulardii*				5
Total	**3,034**	**116**	**58**	**35**
Excluded	**2,918**	**58**	**23**	

*: 21 relevant articles with 26 studies as some articles describe possible safety concerns linked to more than one TU.
**: More details can be found in Table D.1 in Appendix D.
***: For the other yeast species with QPS status, no relevant studies were identified through the ELS.
****: For practical reasons, some TUs were grouped for the screening steps.

3. Assessment

3.1. Taxonomic Units evaluated during the previous QPS mandate and re-evaluated in the current Statement

3.1.1. *Pseudomonas fluorescens*

P. fluorescens has been previously evaluated and was not included in the QPS list (EFSA BIOHAZ Panel, 2017a).

3.1.1.1. Identity

Since the last update on the QPS status (EFSA BIOHAZ Panel, 2016) no new information on the taxonomy of *P. fluorescens* has been published.

3.1.1.2. Body of knowledge

P. fluorescens is a ubiquitous bacterium commonly encountered in aquatic, aerial, and soil matrices, as well as on rhizospheres and surfaces of plants, and also colonises mammalian hosts (Bergsma-Vlami et al., 2005; Dickson et al., 2014).

This metabolically versatile species produces a large number of secondary metabolites enabling it to succeed in competing with other microorganisms, and also making it of interest for biotechnology applications, namely, for use as a plant-growth promoter. Rhizosphere-inhabiting *P. fluorescens* produces compounds with antimicrobial activities (e.g. pyrrolnitrin) (Ramette et al., 2003; Mavrodi et al., 2006), which might contribute to natural plant protection from phytopathogens. Moreover, the production of mupirocin, used for prevention of methicillin-resistant *Staphylococcus aureus* infections, is also attributed to *P. fluorescens* (Sutherland et al., 1985; Villiger et al., 1986; Umio et al., 1987; Ligon et al., 2000).

3.1.1.3. Safety concerns

In humans, *P. fluorescens* has long been considered to be an opportunistic pathogen, involved in acute nosocomial infections. Most of those infections are iatrogenic, affect the bloodstream, and are attributable to the use of contaminated equipment used for intravenous infusion (Oba et al., 2017). In fact, it is considered as a platelet transfusion-relevant microorganism by WHO (Spindler-Raffel et al., 2017).

While significantly less virulent than *P. aeruginosa*, different features of *P. fluorescens* have been associated with the ability to cause disease in humans (e.g. production of haemolysins, siderophores, type III secretion system and the ability to form biofilms) (Scales et al., 2014; Mazurier et al., 2015).

3.1.1.4. Antimicrobial resistance aspects

P. fluorescens can present antimicrobial resistance due to intrinsic and acquired antimicrobial resistance mechanisms (EFSA, 2007a). No new relevant information on AMR has been described.

3.1.1.5. Conclusions on a recommendation for the QPS list

The revision of the literature supports the previous identified safety concerns (e.g. production of biocompounds with antimicrobial activity and virulence features), preventing the inclusion of *P. fluorescens* in the QPS list.

3.2. Taxonomic Units to be evaluated for the first time

3.2.1. *Mycobacterium setense*

3.2.1.1. Identity

M. setense is a member of the *Mycobacterium fortuitum* complex, being more closely related, based on the sequence of the 16S rRNA gene, to *Mycobacterium houstonense* and *Mycobacterium senegalense* and on the sequence of the *rpoB* gene, to *Mycobacterium conceptionense.*

3.2.1.2. Body of knowledge

It is recognised that non-tuberculous mycobacteria are ubiquitously distributed in the environment, where they can be isolated from water and soil (Tortoli, 2014). Nevertheless, there is a paucity of data regarding this species' habitat. Recently, a strain from this species (strain Manresensis) that was isolated from river water was claimed to delay tubercle bacilli colonisation into open tuberculosis in laboratory animals when used after heat-inactivation (Cardona et al., 2015; Tukvadze et al., 2016). A trial on human healthy volunteers seemed to indicate that its oral administration was safe in the short term (Montané et al., 2017).

3.2.1.3. Safety concerns

M. setense is part of the *M. fortuitum* complex, which is well known for its ability to cause skin, bone and joint infections (Yu et al., 2013) and mycolic acids of mycobacteria are recognised to induce granulomatous lesions (Fujita et al., 2007).

3.2.1.4. Antimicrobial resistance aspects

No information is available in the scientific literature.

3.2.1.5. Conclusions on a recommendation for the QPS list

M. setense cannot be considered a suitable microorganism species for the QPS status because there are significant safety concerns.

3.2.2. *Komagataeibacter sucrofermentans*

3.2.2.1. Identity

The bacterial species, *K. sucrofermentans* (Validation List nr. 149, IJSM 2013, 63, 1-5) was previously named *Acetobacter xylinus* subsp. *sucrofermentans* (Toyosaki et al., 1996) and *Gluconacetobacter sucrofermentans* (Cleenwerck et al., 2010). The species is clearly described based on a polyphasic approach (Cleenwerck et al., 2010).

3.2.2.2. Body of knowledge

K. sucrofermentans strains are characterised by their ability to produce large amounts of cellulose from sucrose in agitated cultures (Cleenwerck et al., 2010). Searching PubMed database for this species delivered 11 hits, all concerning the cellulose production capacity. In Asia, cellulose has traditionally been produced from the fermentation of coconut waste-water by *K. sucrofermentans* and used in food.

3.2.2.3. Safety concerns

No safety concerns were reported by using *K. sucrofermentans*.

3.2.2.4. Antimicrobial resistance aspects

No information is available.

3.2.2.5. Conclusions on a recommendation for the QPS list

K. sucrofermentans (A. xylinus subsp. *sucrofermentans)* can be proposed for the QPS list but only for production purposes.

3.2.3. Extension of qualification of *Corynebacterium glutamicum*

C. glutamicum has been recommended for the QPS status but the qualification has only been applied when the species is used for aminoacid production. In the meantime, notifications arrived to EFSA for other production purposes and it was requested from EFSA units to extend the qualification to other uses.

C. glutamicum does not produce known toxic compounds. Consequently, there is no hazard related to the presence of toxic metabolites in the fermentation broth.

The QPS status of *C. glutamicum* is confirmed with the qualification extended to other production purposes.

3.3. Monitoring of new safety concerns related to organisms on the QPS list

The summaries of the evaluation of the possible safety concerns for humans, animals or the environment caused by QPS organisms described and published since the previous evaluation (i.e. ELS search run between January and June 2018, as described in Appendices B and C) are presented below. The references selected as potentially relevant for the QPS exercise are included in Appendix D for each of the TUs or groups of TUs that are part of the QPS list (Appendix E). As already explained in 2.2.2, for practical reasons, some TUs were grouped for the screening steps.

3.3.1. Gram-positive non-sporulating bacteria

3.3.1.1. *Bifidobacterium* spp.

Search of papers potentially relevant for the QPS consideration of *Bifidobacterium* spp. and *Carnobacterium divergens* provided 168 references. The analysis of their titles left 17 articles for consideration; the rest were discarded because they did not deal with safety concerns. Six articles were found relevant for the QPS consideration of *Bifidobacterium* spp. at the level of title and abstract screening (de Andres et al., 2018; Downes et al., 2018; Kim et al., 2018a; Kumar et al., 2018; Martínez et al., 2018). After screening the entire papers, five of them were finally discarded because they did not deal with safety concerns. The paper of Martínez et al. (2018) was kept because the authors identified and characterised a novel gene, homolog to rRNA methylases, which confers erythromycin and clindamycin resistance that can be found in some strains of *Bifidobacterium* spp.

Based on the available evidence as described above, the QPS status of *Bifidobacterium* spp. is not changed.

3.3.1.2. *Carnobacterium divergens*

Search of papers potentially relevant for the QPS consideration of *Bifidobacterium* spp. and *Carnobacterium divergens* provided 168 references. The analysis of their titles left 17 articles for consideration; the rest were discarded because they did not deal with safety concerns. No article arrived to the final stage for this TU. Consequently, the QPS status of *C. divergens* is not changed.

3.3.1.3. *Corynebacterium glutamicum*

Search of papers potentially relevant for the QPS consideration of *Corynebacterium glutamicum* provided 47 references. No paper reached the final selection phase, so no new safety concern was found.

In parallel to the standard procedure for assessing a TU for a possible QPS status and to the maintenance of a QPS status, it was decided to run a complementary reassessment for another specific end-use of this TU as the QPS qualification 'only applies when the species is used for amino acid production'. The QPS status of *Corynebacterium glutamicum* is confirmed with the qualification extended to other production purposes.

3.3.1.4. *Lactobacillus* spp.

Search of papers potentially relevant for the QPS consideration of any of the 35 *Lactobacillus* species included in the list, provided 426 references. Analysis of their titles left 13 articles for consideration; the rest were discarded because they did not deal with safety concerns. Analysis of the abstracts of these allowed the selection of seven papers that raised safety concerns (Biesiada et al., 2018; Boumis et al., 2018; García Carretero et al., 2018; Harding-Theobald and Maraj, 2018; Kane et al., 2018; Koyama et al., 2018; de Seynes et al., 2018). Single papers dealt with infections by *L. casei* (de Seynes et al., 2018), *L. plantarum* (Biesiada et al., 2018), *L. paracasei* (Harding-Theobald and Maraj, 2018), *L. salivarius* (García Carretero et al., 2018) and there were three on *L. rhamnosus* (Boumis et al., 2018; Kane et al., 2018; Koyama et al., 2018).

There were methodological shortcomings on the *L. casei* and *L. plantarum* identifications (both were done by just phenotypical methods) (Biesiada et al., 2018; de Seynes et al., 2018). All articles involved single cases of infection of patients that suffered from predisposing illnesses such as metastatic lung cancer (Biesiada et al., 2018), haemorrhagic telangiectasia (Boumis et al., 2018), alcoholic cirrhosis (Harding-Theobald and Maraj, 2018), anastomotic leak from a bariatric surgery (García Carretero et al., 2018), osteoarthritis (de Seynes et al., 2018) or were immunocompromised after having received a bone marrow transplant (Koyama et al., 2018).

Based on the available evidence as described above, the QPS status of the lactobacilli involved in the reported cases and, by extension, of all others included in the QPS list is not changed.

3.3.1.5. *Lactococcus lactis*

Search of papers potentially relevant for the QPS consideration of *Lactococcus lactis* provided 152 references. Analysis of their titles left nine articles for consideration; the rest were discarded because they did not deal with safety concerns. Analysis of the abstracts allowed selection of four papers that raised safety concerns (Georgountzos et al., 2018; Mussano et al., 2018; Tato Rodríguez et al., 2018; Wünnemann et al., 2018). Three of them described cases of human endocarditis (Georgountzos et al., 2018; Tato Rodríguez et al., 2018) and oral lesions (Mussano et al., 2018) while the fourth described infection of the fish *Alosa alosa*.

However, there was no indication on how the identification of the causal organism was done in the case described by Georgountzos et al. (2018), and the paper by Mussano et al. (2018) reported a polymicrobial infection from which more than 25 bacterial species were identified, including well known pathogens, which makes the lactococcal aetiology of the lesions doubtful. The endocarditis case presented by Tato Rodríguez et al. (2018) affected an 80-year-old man that presented predisposing conditions; namely, previous valve replacement and aortocoronary bypass. Finally, the fish studied by Wünnemann et al. (2018) had been recently captured from the wild and kept in an overpopulated tank under very low oxygen concentrations, conditions described by the authors as very stressful.

Based on the available evidence as described above, the QPS status of *Lactococcus lactis* is not changed.

3.3.1.6. *Leuconostoc* spp.

Search of papers potentially relevant for the QPS consideration of *Leuconostoc* and *Microbacterium imperial* provided 44 references. The analysis of their titles left nine articles for consideration; the rest were discarded because they did not deal with safety concerns. Most of these nine papers lacked information on the identification procedures used to identify the infectious agents. Three papers arrived to the full text phase. Two were immediately excluded as they were not dealing with these TUs. One paper, Lin et al. (2018) arrived to the final stage of the evaluation. This study describes a case of hemophagocytic lymphohistiocytosis with *Leuconostoc pseudomesenteroides* bacteraemia in a

33-year-old man with a previous medical history including unexplained anaemia and splenomegaly. The identification of *L. pseudomesenteroides* from the blood cultures was achieved by phenotypic testing. The infections reported were extremely rare and the affected patients already suffered from debilitating illnesses.

Based on the available evidence as described above, there is no need to change the QPS recommendation of *L. pseudomesenteroides* and of other *Leuconostoc* species included in the QPS list.

3.3.1.7. *Microbacterium imperiale*

Search of papers potentially relevant for the QPS consideration of *Leuconostoc* and *Microbacterium imperial* provided 44 references. The analysis of their titles left nine articles for consideration; the rest were discarded because they did not deal with safety concerns. Most of these nine papers lacked information on the identification procedures used to identify the infectious agents. Three papers arrived to the full text phase but were immediately excluded as they were not dealing with this TU. Consequently, the QPS status of *M. imperiale* is not changed.

3.3.1.8. *Oenococcus oeni*

Search of papers potentially relevant for the QPS consideration of *Oenococcus oeni* and *Pasteuria nishizawae* provided 43 references. The analysis of their titles did not leave any articles for consideration. As no paper reached the final selection phase, no new safety concern was found. Consequently, the QPS status of *O. oeni* is not changed.

3.3.1.9. *Pasteuria nishizawae*

Search of papers potentially relevant for the QPS consideration of *Oenococcus oeni* and *Pasteuria nishizawae* provided 43 references. The analysis of their titles did not leave any articles for consideration. As no paper reached the final selection phase, no new safety concern was found. Consequently, the QPS status of *P. nishizawae* is not changed.

3.3.1.10. *Pediococcus* spp.

Search of papers potentially relevant for the QPS consideration of *Pediococcus* spp. provided 126 references. The analysis of their titles left one single article for consideration that did not reach the final selection phase; so, no new safety concern was found. Consequently, the QPS status of *Pediococcus* spp. is not changed.

3.3.1.11. *Propionibacterium* spp.

Search of papers potentially relevant for the QPS consideration of *Propionibacterium* spp. provided 30 references. The analysis of their titles left one single article for consideration that did not reach the final selection phase; so, no new safety concern was found. Consequently, the QPS status of *Propionibacterium* spp. is not changed.

3.3.1.12. *Streptococcus thermophilus*

Search of papers potentially relevant for the QPS consideration of *Streptococcus thermophilus* provided 45 references. The analysis of their titles left two articles for consideration that did not reach the final selection phase; so, no new safety concern was found. Therefore, the QPS status of *S. thermophilus* is not changed.

3.3.2. Gram-positive spore-forming bacteria

3.3.2.1. *Bacillus* spp.

Search of papers potentially relevant for the QPS consideration of *Bacillus* spp. and *Geobacillus stearothermophilus* provided 537 references. The analysis of their titles left three articles for consideration; the rest were discarded because they did not deal with safety concerns.

Two papers concerning *Bacillus* spp. reached the final selection phase and were analysed in-depth (Kim et al., 2018b; Tran et al., 2018). Tran et al. (2018) paper was excluded because there was not enough information (conference proceedings). The work of Kim et al. (2018b), describing a case of a pyometra in an immunosuppressed dog, presented several methodological shortcomings and therefore the data presented were not included in the current assessment.

The ELS did not come up with any information that would change the status of the *Bacillus* species included in the QPS list.

3.3.2.2. *Geobacillus stearothermophilus*

Search of papers potentially relevant for the QPS consideration of *Bacillus* spp. and *Geobacillus stearothermophilus* provided 537 references. The analysis of their titles left three articles for consideration; none of them were related to this TU. Consequently, the QPS status *Geobacillus stearothermophilus* is not changed.

3.3.3. Gram-negative bacteria

3.3.3.1. *Gluconobacter oxydans*

Search of papers potentially relevant for the QPS consideration of *Gluconobacter oxidans* and *Xanthomonas campestris* provided 132 references. The analysis of their titles left two articles for consideration; the rest were discarded because they did not deal with safety concerns. No paper reached the final selection phase for this TU. Consequently, the QPS status of *G. oxydans* is not changed.

3.3.3.2. *Xanthomonas campestris*

Search of papers potentially relevant for the QPS consideration of *Gluconobacter oxidans* and *Xanthomonas campestris* provided 132 references. The analysis of their titles left two articles for consideration; the rest were discarded because they did not deal with safety concerns. One paper (Sundin and Wang, 2018) reached the final selection phase. It was excluded because it does not deal with safety concerns. Consequently, the QPS status of *X. campestris* is not changed.

3.3.4. Yeasts

Search of papers potentially relevant for the QPS consideration of the yeasts' species included in the QPS list provided 1,210 references.

Thirty-five papers reached the final step of the ELS. Fourteen of these were immediately excluded because they were not in English or because they were not dealing with safety concerns. Thus, the ELS identified 21 articles relevant for the different yeast species with QPS status (please refer to Appendix D for the complete list of references).

For 6 (Kumari et al., 2018; Mohamed et al., 2018; Rajkowska and Kunicka-Styczyńska, 2018; Vieira et al., 2018; Yang and Mao, 2018; Yenisehirli et al., 2018) of these 21 references, the value of the results and conclusions presented were very limited due to a weaknesses in the methodology used for identity confirmation of the microorganism in all references, to a lack of information regarding the source attribution in three of them (Rajkowska and Kunicka-Styczyńska, 2018; Yenisehirli et al., 2018) or to predisposing factors in the exposed subject (Yang and Mao, 2018).

From the remaining 15 references that describe a safety concern, 13 were related to human health (Al-Tekreeti et al., 2018; Aslani et al., 2018; Charsizadeh et al., 2018a,b,c; Jahanshiri et al., 2018; Nejat et al., 2018; Ortiz et al., 2018; Sav et al., 2018; Scapaticci et al., 2018; Siavoshi et al., 2018; Taverna et al., 2018; Wasilewska and Wroblewska, 2018); one to animal health (Dangarembizi et al., 2018) and four to antimicrobial resistance (Sav et al., 2018; Scapaticci et al., 2018; Sekyere and Asante, 2018; Taverna et al., 2018).

Out of these 15 papers describing a safety concern for one or several QPS yeast species, 10 referred to *Candida kefyr* (teleomorph = *Kluyveromyces marxianus*) (Al-Tekreeti et al., 2018; Aslani et al., 2018; Charsizadeh et al., 2018a,b,c; Jahanshiri et al., 2018; Nejat et al., 2018; Ortiz et al., 2018; Sav et al., 2018; Scapaticci et al., 2018)), five to *Saccharomyces cerevisiae* of which one was identified as *Saccharomyces boulardii* (Aslani et al., 2018; Dangarembizi et al., 2018; Scapaticci et al., 2018; Sekyere and Asante, 2018; Wasilewska and Wroblewska, 2018)), five to *Candida famata* (teleomorph = *Debaryomyces hansenii*) (Kumari et al. (2018); (Mohamed et al., 2018; Rajkowska and Kunicka-Styczyńska, 2018; Taverna et al., 2018; Vieira et al., 2018) and one to *Hanseniaspora uvarum* (Siavoshi et al., 2018).

S. cerevisiae/*S. boulardii*, *C. famata* and *H. uvarum* were reported to be very occasionally (up to four studies) associated with fungal and nosocomial infections in immunocompromised or post-surgery patients. However, 10 studies referred to *C. kefyr*/*K. marxianus*. The last one has received increased attention in recent years, but reports where it has been unambiguously shown to be causative agent of infectious disease in otherwise healthy individuals are very rare. There is reason to closely follow whether there is a tendency for *C. kefyr*/*K. marxianus* to become more common in this kind of infection.

For the other yeast species with QPS status, no relevant studies were identified through the ELS.

In short, the ELS did not identify with any information that would change the status for the yeast species included in the QPS list.

3.3.5. Viruses used for plant protection

The ELS did not come up with any information that would change the current QPS status of any of the virus families.

3.3.5.1. Alphaflexiviridae

Search of papers potentially relevant for the QPS consideration of Alphaflexiviridae provided 26 references. No paper reached the final selection phase, so no new safety concern was found.

3.3.5.2. Baculoviridae

Search of papers potentially relevant for the QPS consideration of Baculoviridae provided 48 references. The analysis of their titles left one single article for consideration that did not reach the final selection phase, so no new safety concern was found.

4. Conclusions

ToR 1: *Keep updated the list of biological agents being notified, in the context of a technical dossier to EFSA Units (such as Feed, Food Ingredients and Packaging (FIP), Nutrition Unit and Pesticides Unit), for intentional use in feed and/or food or as sources of food and feed additives, enzymes and plant protection products for safety assessment*:

- Between April and September 2018, the list was updated with 48 notifications that were received by EFSA, of which 41 were for feed additives, three for food enzymes, food additives and flavourings, four for novel foods and none for plant protection products.

ToR 2: *Review taxonomic units previously recommended for the QPS list and their qualifications when new information has become available*:

- In relation to the results of the monitoring of possible new safety concerns related to the QPS list, there were no results that justify removal of any TU from the QPS list or changes in their respective qualifications.

ToR 3: *(Re)assess the suitability of taxonomic units notified to EFSA not present in the current QPS list for their inclusion in that list*:

- The TUs corresponding to 30 out of the 48 notifications received, already had a QPS status.
- The TUs corresponding to 15 out of the 18 notifications without a QPS status were: five notifications related to filamentous fungi which were excluded from QPS activities in the follow-up of a recommendation of the QPS 2013 update (EFSA BIOHAZ Panel, 2013, 2014, 2016), seven notification related to *E. coli*, one to *Streptomyces* spp. and two to *Enterococcus faecium*, which were recently excluded from the current mandate by the BIOHAZ Panel (EFSA BIOHAZ Panel, 2018a).
- Three TUs, corresponding to the other three out of those 18 notifications, were evaluated for potential QPS recommendation: *Pseudomonas fluorescens* already evaluated in 2016 and not granted QPS status (EFSA BIOHAZ Panel, 2017a) was now re-evaluated within this mandate, *Mycobacterium setense* and *Komagataeibacter sucrofermentans*, both evaluated here for the first time.

5. Recommendations

- The revision of the literature supports the previous identified safety concerns (e.g. production of biocompounds with antimicrobial activity and virulence features), preventing the inclusion of *P. fluorescens* in the QPS list.
- *M. setense* cannot be considered for the QPS assessment because there are significant safety concerns.
- *K. sucrofermentans* (*A. xylinus* subsp. *sucrofermentans*) can be proposed for the QPS list but only for production purposes.
- The QPS status of *Corynebacterium glutamicum* is confirmed with the qualification extended to other production purposes.

This new QPS recommendation will be included as an addition to the list of QPS status recommended biological agents (EFSA BIOHAZ Panel, 2016), published both as an update to the Scientific Opinion (EFSA BIOHAZ Panel, 2016) and as supporting information available on the Knowledge Junction at https://doi.org/10.5281/zenodo.1146566.

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Glossary and Abbreviations

AMR	antimicrobial resistance
BIOHAZ	EFSA Panel on Biological Hazards
ELS	extensive literature search
FIP	EFSA Food ingredients and packaging Unit
FSTA	Food Science Technology Abstracts
GMM	genetically modified microorganisms
QPS	qualified presumption of safety
PPP	plant protection product
ToR	Term of Reference
TU	taxonomic unit
WG	Working Group

Appendix A – Search strategy followed for the (re)assessment of the suitability of TUs notified to EFSA not present in the current QPS list for their inclusion in the updated list (reply to ToR 3)

Pseudomonas fluorescens

A literature search was performed in PubMed database, using the search terms "Pseudomonas fluorescens" AND ("infection" OR "risk"), from 2016: 41 hits were identified and screened. Another search was done in Web of Science using the search terms "Pseudomonas fluorescens" AND "infection": 94 hits were identified and screened.

Mycobacterium setense

A literature search was performed in the Web of Science, using the search term "Mycobacterium setense", from 2016: three hits were identified and screened.

Komagataeibacter sucrofermentans

A literature search was performed in PubMed database, using the search term "Komagataeibacter sucrofermentans" from 2010*: 11 hits were identified, all concerning the cellulose production capacity.

*Keywords: "Acetobacter xylinus subsp. Sucrofermentans" (seven hits), "Gluconacetobacter sucrofermentans" (nine hits, including those seven found with "Acetobacter xylinus subsp. Sucrofermentans"), "Komagataibacter sucrofermentans" (two hits).

Another search was performed in Google: "Komagataeibacter sucrofermentans" and "taxonomy": three references were found.

Appendix B – Protocol for Extensive literature search (ELS), relevance screening, and article evaluation for the maintenance and update of list of QPS-recommended biological agents (reply to ToR 2)

The following protocol for extensive literature search (ELS) will be used in the context of the EFSA self-task mandate on the list of QPS-recommended biological agents intentionally added to the food or feed (EFSA-Q-2016-00684).

B.1. Description of the process

An ELS of studies related to safety concerns for humans, animals, plants and/or the environment of microorganisms recommended for the Qualified Presumption of Safety (QPS) 2019 list will be performed.

The process will be performed according to the following main steps:

- ELS for potentially relevant citations;
- Relevance screening to select the citations identified by the literature search, based on titles and abstract and then full-text;
- Evaluation of articles according to pre-specified categories of possible safety concerns;
- Discussion between experts to come to collective expert evaluation of the outcome, reflected in the QPS Opinion and Panel Statements.

Considering the purpose of the QPS approach, a broad search will be performed.

The review questions will be broken down into key elements using the PECO conceptual model:

- Population of interest (P);
- Exposure of interest (E);
- Comparator (C);
- Outcomes of interest (O).

B.1.1. Objective

The aim is to identify any publicly available studies reporting on safety concerns for humans, animals or the environment caused by microorganisms on the QPS recommended list (see Appendix E).

B.1.2. Target population

The populations of interest are humans, animals, plants and the environment.

B.1.3. Exposure

Citations must report on at least one species included in one of the five groups of named species specified in the EFSA QPS recommended list of the QPS 2016 update (see Table A1 in Appendix A to (EFSA BIOHAZ Panel, 2017a)):

a) Gram-positive non-spore-forming bacteria;
b) Gram-positive spore-forming bacteria;
c) Gram-negative bacteria;
d) Viruses used for plant protection;
e) Yeasts.

In more detail:

a) Gram-positive non-spore forming bacteria:

Bifidobacterium adolescentis, Bifidobacterium animalis, Bifidobacterium bifidum, Bifidobacterium breve, Bifidobacterium longum, Carnobacterium divergens, Corynebacterium glutamicum, Lactobacillus acidophilus, Lactobacillus amylolyticus, Lactobacillus animalis, Lactobacillus amylovorus, Lactobacillus alimentarius, Lactobacillus aviaries, Lactobacillus brevis, Lactobacillus buchneri, Lactobacillus casei, Lactobacillus cellobiosus, Lactobacillus collinoides, Lactobacillus coryniformis, Lactobacillus crispatus, Lactobacillus curvatus, Lactobacillus delbrueckii, Lactobacillus diolivorans Lactobacillus farciminis, Lactobacillus fermentum, Lactobacillus gallinarum, Lactobacillus gasseri, Lactobacillus helveticus,

Lactobacillus hilgardii, Lactobacillus johnsonii, Lactobacillus kefiranofaciens, Lactobacillus kefiri, Lactobacillus mucosae, Lactobacillus panis, Lactobacillus paracasei, Lactobacillus paraplantarum, Lactobacillus pentosus, Lactobacillus plantarum, Lactobacillus pontis, Lactobacillus reuteri, Lactobacillus rhamnosus, Lactobacillus sakei, Lactobacillus salivarius, Lactobacillus sanfranciscensis, Lactococcus lactis, Leuconostoc citreum, Leuconostoc lactis, Leuconostoc mesenteroides, Leuconostoc pseudomesenteroides, Microbacterium imperiale, Oenococcus oeni, Pasteuria nishizawae, Pediococcus acidilactici, Pediococcus dextrinicus, Pediococcus parvulus, Pediococcus pentosaceus, Propionibacterium freudenreichii, Propionibacterium acidopropionici, Streptococcus thermophilus;

b) Gram-positive spore-forming bacteria:

Bacillus amyloliquefaciens, Bacillus atrophaeus, Bacillus clausii, Bacillus coagulans, Bacillus flexus, Bacillus fusiformis, Bacillus lentus, Bacillus licheniformis, Bacillus megaterium, Bacillus mojavensis, Bacillus pumilus, Bacillus smithii, Bacillus subtilis, Bacillus vallismortis, Geobacillus stearothermophilus;

c) Gram-negative bacteria:

Gluconobacter oxydans; *Xanthomonas campestris*

d) Viruses used for plant protection:

Plant viruses (Family): Alphaflexiviridae, Potyviridae
Insect viruses (Family): Baculoviridae

e) Yeasts:

Candida cylindracea, Debaryomyces hansenii, Hanseniaspora uvarum, Kluyveromyces lactis, Kluyveromyces marxianus, Komagataella pastoris, Lindnera jadinii, Ogataea angusta, Saccharomyces bayanus, Saccharomyces cerevisiae, Saccharomyces pastorianus, Schizosaccharomyces pombe, Wickerhamomyces anomalus, Xanthophyllomyces dendrorhous.

For the yeast species, as previously, the name of the teleomorphic form is used in the list of QPS species, when available. Important synonyms and older names were also included in the searches. For instance, names of the anamorphic growth forms were included, when such a form is known:

- *Debaryomyces hansenii*: anamorph *Candida famata*;
- *Hanseniaspora uvarum*: anamorph *Kloeckera apiculata*;
- *Kluyveromyces lactis*: anamorph *Candida spherica*;
- *Kluyveromyces marxianus*: anamorph *Candida kefyr*;
- *Komagataella pastoris*: synonym *Pichia pastoris*;
- *Lindnera jadinii*: synonyms *Pichia jadinii*, *Hansenula jadinii*, *Torulopsis utilis*, anamorph *Candida utilis*;
- *Ogataea angusta*: synonym *Pichia angusta*;
- *Saccharomyces cerevisiae*: synonym *Saccharomyces boulardii*;
- *Saccharomyces pastorianus*: synonym *Saccharomyces carlsbergensis*;
- *Wickerhamomyces anomalus*: synonyms *Hansenula anomala*, *Pichia anomala*, *Saccharomyces anomalus*, anamorph *Candida pelliculosa*;
- *Xanthophyllomyces dendrorhous*: anamorph *Phaffia rhodozyma*.

B.1.4. Comparator

It is expected that the prevalent study designs will be case reports or case series and studies based on surveys or isolate collections. The remaining study designs may include: studies using laboratory isolates; randomised controlled trials, field trials, or experimental designs in the laboratory; experimental designs in live animals with a deliberate disease challenge; observational study designs; animal or insect models; investigations to identify or to understand the causes of safety concerns (e.g. identification, characterisation of toxic factors, virulence mechanisms); studies to demonstrate beneficial effects but with reporting of unwanted side-effects.

Since it is expected that in the majority of the study designs relevant for the review question, the comparator will not be available, the latter will not be included as a key element in the search strategy.

B.1.5. Outcomes of interest

The outcomes of interest to this ELS are:
Question 1:

- potential harms;
- safety issues;
- virulence or infectivity;
- intoxication.

Question 2:

- (acquired/intrinsic) antimicrobial resistance (AMR) covering phenotypic and genotypic aspects.

The QPS concept does not address hazards linked to the formulation or processing of the products based on biological agents added into the food or feed chain. Neither the safety of users handling the product nor the genetic modifications are taken into account.

B.1.6. Identification of the review questions

The following research questions will be addressed:

- Is there evidence of any safety concerns, including virulence features and toxin production, for humans, animals, plants and/or the environment associated with microbial species currently recommended for the QPS list since the previous QPS review (i.e. published from June 2016 until June 2019)?
- Is there evidence related to the presence or absence of antimicrobial resistance or antimicrobial resistance genes for the same microbial species published during the same time period?

B.2. Eligibility criteria for study selection

The selection of studies relevant to questions 1 and 2 will be performed applying the eligibility criteria described in Table B.1 below.

Table B.1: Eligibility criteria for questions 1 and 2

	Criteria
Study design	No specific type of study design will be used to include/exclude relevant studies, although it is expected that the prevalent study designs will be case reports or case series and studies based on surveys or isolate collections
Study characteristics:	No exclusion will be based on study characteristics
Population	Humans, animals, plants, environment
Exposure	Studies must report on at least one TU as identified in Section B.1.3
Outcome of interest	Outcomes as listed in Section B.1.5
Language	English
Time	From June 2016 until end June 2019
Publication type	Primary research studies and secondary studies reporting previously unpublished primary studies

B.3. Literature searches

Searches will be conducted in a range of relevant information sources to identify any evidence of safety concerns and AMR regarding the target microbial species.

Considering the results of the previous QPS exercise, to handle the high number of studies identified in each group, 20 search strategies were prepared: three for yeasts, one for insect viruses, one for plant viruses, 13 for Gram-positive bacteria and two for Gram-negative bacteria according to named species specified by EFSA in the QPS recommended list of the QPS 2016 update (see Table A1 in Appendix A to (EFSA BIOHAZ Panel, 2017a)).

The 20 subgroups of target microbial species will be searched separately.

Each search strategy will comprise two elements: the search terms (Section B.3.1) and the information sources (Section B.3.2) to be searched.

B.3.1. Search terms

The search strategies used to identify studies are given in Appendix C.
Each strategy will comprise two key elements:

- Target microbial species as described in Section B.1.3 ('Exposure');
- Safety issues as described in Section B.1.5 ('Outcomes').

In order to maximise the sensitivity of the search for the species for which the number of overall publications in the relevant time period is expected to be low, the search strategy will not include outcome-related terms.

The population of interest (humans, animals, plants or the environment) will not be included as a key element in the search strategies, as it is often not explicitly described within a title or abstract. It would also have been difficult to describe adequately such a broad population using title/abstract words and/or subject headings. Population information will be captured at the time of evaluating the articles (see Section B.1 above).

Search terms for safety issues were identified in close collaboration with the information specialist; example of such terms, are the following: 'toxin*', 'disease*', 'infection*', 'clinical*', 'virulen*', 'antimicrobial resistan*', 'endocarditis'.

The 20 subgroups of target microbial species will be entered on separate search lines. The search line for each group will be combined with the safety terms individually.

The searches will not be limited by language or study design.

The review period will be from June 2016 to June 2019.

B.3.2. Information sources searched

The same information sources used for the previous QPS exercise (EFSA BIOHAZ Panel, 2017a) will be searched for studies reporting safety concerns regarding the target microbial species (see Table B.2 below).

Table B.2: Information sources to be searched to identify relevant studies

Information source	Interface
Web of Science Core Collection	Web of Science, Thomson Reuters 2018
CAB Abstracts	Web of Science, Thomson Reuters 2018
BIOSIS Citation Index	Web of Science, Thomson Reuters 2018
MEDLINE	Web of Science, Thomson Reuters 2018
Food Science Technology Abstracts (FSTA)	Web of Science, Thomson Reuters 2018

Search results will be downloaded from the information sources and imported into EndNote® X8 bibliographic management software. For each of the 20 species groups, within-group removal of duplicate entries will be done in EndNote® X8. Following uploading of the species groups into the DistillerSR[10] online software, removal of duplicates will again be undertaken, using the Duplicate Detection feature.

B.4. Study selection and article evaluation

To identify potentially relevant studies to be included in the review the studies will be selected by a three -step procedure using the DistillerSR online software.

The results of the different phases of the study selection process will be reported in a flowchart as recommended in the PRISMA statement on preferred reporting items for systematic reviews and meta-analyses (Moher et al., 2009).

B.4.1. Screening for potential relevance at title level

Articles will initially be screened at title level in parallel by two Working Group (WG) expert reviewers and, if needed, EFSA staff.

[10] DistillerSR, Evidence Partners, Ottawa, Canada. https://www.evidencepartners.com/products/distillersr-systematic-review-software/

If the information in the title is not relevant for the research objectives, the article will not proceed to the next step (Section B.4.2).

Articles that will be excluded during screening at this step will be stored in Distiller SR.

In case of doubts or divergences between the reviewers, the paper will proceed to step 2.

B.4.2. Screening for potential relevance at title and abstract level

The articles passing the first step will undergo a screening at abstract level in parallel by two experts.

If the information in title and abstract is not relevant for the research objectives, the article will not proceed to the next step (Section B.4.3).

Articles that will be excluded during screening at this step will be stored in Distiller SR.

In case of doubts or divergences between the reviewers, the paper will proceed to step 3.

B.4.3. Article evaluation

The aim of this step will be to confirm that the article is relevant for the QPS project and, in case it is, to evaluate it. It will be carried out at full text level.

The articles passing the second step will undergo a validation procedure carried out by two experts. One reviewer will initially be tasked with the evaluation of a paper. The evaluation will be then forwarded to another reviewer for the validation of the appraisal received.

In case of disagreement with the initial appraisal, the second reviewer will write down their comments. The reviewers will initially try to solve the disagreement. In case this will not be possible, the conflicting information will be presented for collective expert evaluation of the ELS outcome (see Section B.5).

If the information contained in the article is not relevant for the research objectives, the article will not be evaluated. Articles that will not be considered relevant will be stored in Distiller SR.

B.4.3.1. Questions for study selection and article evaluation

STEP 1 (Screening for potential relevance):

Question 1: Is the full-text available, in English and dealing with safety concerns?

- Yes: Include and continue to Article evaluation form;
- Full text not available: Exclude;
- Full text not in English: Exclude;
- Full text in English but not dealing with safety concerns: Exclude.

STEP 2 (Article evaluation):

Question 2: Identification of the microorganisms

- The article will be characterised in terms of the microorganisms involved
  Single choice question: the Experts will identify the microorganism/s described in the article. In case more than one microorganism is described in the paper, the form will be repeated for each microorganism.

Question 3: Is there any "methodological" problem identified in the paper under consideration?

- No problems identified;
- Yes some problems were identified.

Question 4: Which "methodological" problems were identified in the paper under consideration? (this question will appear in case in question 3 the option "Yes some problems were identified" will be selected)

- Methodology used for identity confirmation of the microorganism;
- Reliability of the source attribution;
- Misuse of the microorganism (e.g. parenteral exposure);
- Predisposing factors in the exposed subjects;
- Others.

When one of the above options will be selected a dedicated free text box will appear to describe the problem identified.

Question 5: Is there any safety concern identified? (this question will appear in case in question 3 the option "No problems identified" will be selected)

- No safety concerns identified;
- Yes some safety concerns were identified.

Question 6: Which safety concerns were identified? (this question will appear in case in question 5 the option "Yes some safety concerns were identified" will be selected)

- On human health;
- On animal health;
- On the environment;
- On the environment;
- On AMR;
- On other aspects.

When one of the above options will be selected a dedicated free text box will appear to describe the safety concern identified.

Question 7: Overall, is there any information that could potentially lead to a change in the QPS status of the microorganism? (this question will appear in case in question 5 the option "Yes some safety concerns were identified" will be selected)

- No;
- Yes.

In case the option "Yes" will be selected a dedicated free text box will appear to describe the information that could potentially lead to a change in the QPS status of the microorganism.

B.5. Collective expert evaluation of the ELS outcome and presentation in the QPS opinion

The overall results of the searches and evaluations of individual articles will be presented in tabular format for each group/sub-group and species. These results will be further evaluated collectively by the working group and the outcome will be reflected in the QPS opinion.

B.6. Update of the process

The literature search, study selection and collective expert evaluation will be repeated every 6 months.

References

EFSA BIOHAZ Panel (EFSA Panel on Biological Hazards), 2017. Scientific Opinion on the update of the list of QPS-recommended biological agents intentionally added to food or feed as notified to EFSA. EFSA Journal 2017;15(1):4664, 177 pp. https://doi.org/10.2903/j.efsa.2017.4664

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Appendix C – Search strategies for the maintenance and update of list of QPS-recommended biological agents (reply to ToR 2)

Gram-Positive Non-Spore-forming Bacteria

Bifidobacterium spp.

String for species	
"Bifidobacterium adolescentis" OR "Bifidobacterium animalis" OR "Bifidobacterium bifidum" OR "Bifidobacterium breve" OR "Bifidobacterium longum" OR "B adolescentis" OR "B animalis" OR "B bifidum" OR "B breve" OR "B longum"	
OUTCOME	**String**
1. Antimicrobial/Antibiotic/Antimycotic	"antimicrobial resistan*" OR "antibiotic resistan*" OR "antimicrobial susceptibil*"
2. Infection/Bacteremia/Fungemia/Sepsis	infection* OR abscess* OR sepsis* or septic* OR bacteremia OR bacteraemia OR toxin*
3. Type of disease	endocarditis OR abscess OR meningitis
4. Mortality/Morbidity	clinical* OR death* OR morbidit* OR mortalit* OR disease* OR illness*
5. Disease Risk	opportunistic OR virulen*

Carnobacterium divergens

String for species	
"Carnobacterium divergens" OR "C divergens"	
OUTCOME	**String**
6. Antimicrobial/Antibiotic/Antimycotic	*Not applied*
7. Infection/Bacteremia/Fungemia/Sepsis	*Not applied*
8. Type of disease	*Not applied*
9. Mortality/Morbidity	*Not applied*
10. Disease Risk	*Not applied*

Corynebacterium glutamicum

String for species	
"Corynebacterium glutamicum" OR "C glutamicum" OR "Brevibacterium lactofermentum" OR "B lactofermentum"	
OUTCOME	**String**
1. Antimicrobial/Antibiotic/Antimycotic	"antimicrobial resistan*" OR "antibiotic resistan*" OR "antimicrobial susceptibil*"
2. Infection/Bacteremia/Fungemia/Sepsis	infection* OR abscess* OR sepsis* or septic* OR bacteremia OR bacteraemia OR toxin* OR "pathogen*"
3. Type of disease	*Not applied*
4. Mortality/Morbidity	clinical* OR death* OR morbidit* OR mortalit* OR disease* OR illness*
5. Disease Risk	opportunistic OR virulen*

Lactobacillus spp.

String for species	
"Lactobacillus acidophilus" OR "Lactobacillus amylolyticus" OR "Lactobacillus amylovorus" OR "Lactobacillus alimentarius" OR "Lactobacillus animalis" OR "Lactobacillus aviaries" OR "Lactobacillus brevis" OR "Lactobacillus buchneri" OR "Lactobacillus casei" OR "Lactobacillus zeae" OR "Lactobacillus cellobiosus" OR "Lactobacillus coryniformis" OR "Lactobacillus crispatus" OR "Lactobacillus curvatus" OR "Lactobacillus delbrueckii" OR "Lactobacillus diolivorans" OR "Lactobacillus farciminis" OR "Lactobacillus fermentum" OR "Lactobacillus gallinarum" OR "Lactobacillus gasseri" OR "Lactobacillus helveticus" OR "Lactobacillus hilgardii" OR "Lactobacillus johnsonii" OR "Lactobacillus kefiranofaciens" OR "Lactobacillus kefiri" OR "Lactobacillus mucosae" OR "Lactobacillus panis" OR "Lactobacillus collinoides" OR "Lactobacillus paracasei" OR "Lactobacillus paraplantarum" OR "Lactobacillus pentosus" OR "Lactobacillus plantarum" OR "Lactobacillus pontis" OR "Lactobacillus reuteri" OR "Lactobacillus rhamnosus" OR "Lactobacillus sakei" OR "Lactobacillus salivarius" OR "Lactobacillus sanfranciscensis" OR "L acidophilus" OR "L amylolyticus" OR "L amylovorus" OR "L alimentarius" OR "L animalis" OR "L aviaries" OR "L brevis" OR "L buchneri" OR "L casei" OR "L zeae" OR "L cellobiosus" OR "L coryniformis" OR "L crispatus" OR "L curvatus" OR "L delbrueckii" OR "L diolivorans" OR "L farciminis" OR "L fermentum" OR "L gallinarum" OR "L gasseri" OR "L helveticus" OR "L hilgardii" OR "L johnsonii" OR "L kefiranofaciens" OR "L kefiri" OR "L mucosae" OR "L panis" OR "L collinoides" OR "L paracasei" OR "L paraplantarum" OR "L pentosus" OR "L plantarum" OR "L pontis" OR "L reuteri" OR "L rhamnosus" OR "L sakei" OR "L salivarius" OR "L sanfranciscensis"	
OUTCOME	**String**
1. Antimicrobial/Antibiotic/Antimycotic	"antimicrobial resistan*" OR "antibiotic resistan*" OR "antimicrobial susceptibil*"
2. Infection/Bacteremia/Fungemia/Sepsis	infection* OR abscess* OR sepsis* or septic* OR bacteremia OR bacteraemia OR toxin*
3. Type of disease	endocarditis OR abscess OR meningitis
4. Mortality/Morbidity	*Not applied*
5. Disease Risk	opportunistic OR virulen*

Lactococcus lactis

String for species	
"Lactococcus lactis" OR "L lactis"	
OUTCOME	**String**
1. Antimicrobial/Antibiotic/Antimycotic	"antimicrobial resistan*" OR "antibiotic resistan*" OR "antimicrobial susceptibil*"
2. Infection/Bacteremia/Fungemia/Sepsis	infection* OR abscess* OR sepsis* or septic* OR bacteremia OR bacteraemia OR toxin*
3. Type of disease	endocarditis OR abscess OR meningitis
4. Mortality/Morbidity	clinical* OR death* OR morbidit* OR mortalit* OR disease* OR illness*
5. Disease Risk	opportunistic OR virulen*

Leuconostoc spp.

String for species	
"Leuconostoc mesenteroides" OR "Leuconostoc lactis" OR "Leuconostoc pseudomesenteroides" OR "Leuconostoc citreum" OR "L mesenteroides" OR "L lactis" OR "L pseudomesenteroides" OR "L citreum"	
OUTCOME	**String**
1. Antimicrobial/Antibiotic/Antimycotic	"antimicrobial resistan*" OR "antibiotic resistan*" OR "antimicrobial susceptibil*"
2. Infection/Bacteremia/Fungemia/Sepsis	infection* OR abscess* OR sepsis* or septic* OR bacteremia OR bacteraemia OR toxin*
3. Type of disease	*Not applied*
4. Mortality/Morbidity	clinical* OR death* OR morbidit* OR mortalit* OR disease* OR illness*
5. Disease Risk	opportunistic OR virulen*

Microbacterium imperiale

String for species	
"Microbacterium imperiale" OR "M imperiale"	
OUTCOME	**String**
6. Antimicrobial/Antibiotic/Antimycotic	*Not applied*
7. Infection/Bacteremia/Fungemia/Sepsis	*Not applied*
8. Type of disease	*Not applied*
9. Mortality/Morbidity	*Not applied*
10. Disease Risk	*Not applied*

Oenococcus spp.

String for species	
"Oenococcus oeni" OR "O oeni"	
OUTCOME	**String**
1. Antimicrobial/Antibiotic/Antimycotic	*Not applied*
2. Infection/Bacteremia/Fungemia/Sepsis	*Not applied*
3. Type of disease	*Not applied*
4. Mortality/Morbidity	*Not applied*
5. Disease Risk	*Not applied*

Pasteuria nishizawae

String for species	
"Pasteuria nishizawae" OR "P nishizawae"	
OUTCOME	**String**
11. Antimicrobial/Antibiotic/Antimycotic	*Not applied*
12. Infection/Bacteremia/Fungemia/Sepsis	*Not applied*
13. Type of disease	*Not applied*
14. Mortality/Morbidity	*Not applied*
15. Disease Risk	*Not applied*

Pediococcus spp.

String for species	
"Pediococcus pentosaceus" OR "Pediococcus dextrinicus" OR "Pediococcus acidilactici" OR "Pediococcus parvulus" OR "P pentosaceus" OR "P dextrinicus" OR "P acidilactici" OR "P parvulus"	
OUTCOME	**String**
1. Antimicrobial/Antibiotic/Antimycotic	*Not applied*
2. Infection/Bacteremia/Fungemia/Sepsis	*Not applied*
3. Type of disease	*Not applied*
4. Mortality/Morbidity	*Not applied*
5. Disease Risk	*Not applied*

Propionibacterium spp.

String for species	Number papers retrieved and notes
"Propionibacterium acidipropionici" OR "Propionibacterium freudenreichii" OR "P acidipropionici" OR "P freudenreichii"	**176**
OUTCOME	**String**
1. Antimicrobial/Antibiotic/Antimycotic	*Not applied*
2. Infection/Bacteremia/Fungemia/Sepsis	*Not applied*
3. Type of disease	*Not applied*
4. Mortality/Morbidity	*Not applied*
5. Disease Risk	*Not applied*

Streptococcus thermophilus

String for species	
"Streptococcus thermophilus" OR "S thermophilus" "Streptococcus thermophilus" OR "S thermophilus"	
OUTCOME	**String**
1. Antimicrobial/Antibiotic/Antimycotic	"antimicrobial resistan*" OR "antibiotic resistan*" OR "antimicrobial susceptibil*"
2. Infection/Bacteremia/Fungemia/Sepsis	infection* OR abscess* OR sepsis* or septic* OR bacteremia OR bacteraemia OR toxin*
3. Type of disease	*Not applied*
4. Mortality/Morbidity	clinical* OR death* OR morbidit* OR mortalit* OR disease* OR illness*
5. Disease Risk	opportunistic OR virulen*

Gram-Positive Spore-forming Bacteria

Bacillus spp.

String for species	
"Bacillus amyloliquefaciens" OR "Bacillus coagulans" OR "Bacillus clausii" OR "Bacillus atrophaeus" OR "Bacillus flexus" OR "Bacillus fusiformis" OR "Lysinibacillus fusiformis" OR "Bacillus licheniformis" OR "Bacillus lentus" OR "Bacillus mojavensis" OR "Bacillus megaterium" OR "Bacillus vallismortis" OR "Bacillus smithii" OR "Bacillus subtilis" OR "Bacillus pumilus" OR "Geobacillus stearothermophilus" OR "B amyloliquefaciens" OR "B coagulans" OR "B clausii" OR "B atrophaeus" OR "B flexus" OR "B fusiformis" OR "L fusiformis" OR "B licheniformis" OR "B lentus" OR "B mojavensis" OR "B megaterium" OR "B vallismortis" OR "B smithii" OR "B subtilis" OR "B pumilus" OR "G stearothermophilus"	
OUTCOME	**String**
1. Antimicrobial/Antibiotic/Antimycotic	"antimicrobial resistan*" OR "antibiotic resistan*" OR "antimicrobial susceptibil*"
2. Infection/Bacteremia/Fungemia/Sepsis	infection* OR abscess* OR sepsis* or septic* OR bacteremia OR bacteraemia OR toxin*
3. Type of disease	endocarditis OR abscess OR meningitis
4. Mortality/Morbidity	*Not applied*
5. Disease Risk	opportunistic OR virulen*

Gram-negative bacteria

Gluconobacter oxydans

String for species	
"Gluconobacter oxydans" OR "G oxydans"	
OUTCOME	**String**
1. Antimicrobial/Antibiotic/Antimycotic	*Not applied*
2. Infection/Bacteremia/Fungemia/Sepsis	*Not applied*
3. Type of disease	*Not applied*
4. Mortality/Morbidity	*Not applied*
5. Disease Risk	*Not applied*

Xanthomonas campestris

String for species	
"Xanthomonas campestris" OR "X campestris"	
OUTCOME	**String**
1. Antimicrobial/Antibiotic/Antimycotic	*Not applied*
2. Infection/Bacteremia/Fungemia/Sepsis	*Not applied*
3. Type of disease	*Not applied*
4. Mortality/Morbidity	*Not applied*
5. Disease Risk	*Not applied*

Yeasts

TUs without keywords for OUTCOME

String for species	
"Candida cylindracea" OR "Debaryomyces hansenii" OR "Candida famata" OR "Hanseniaspora uvarum" OR "Kloeckera apiculata" OR "Ogataea angusta" OR "Pichia angusta" OR "Saccharomyces bayanus" OR "Saccharomyces pastorianus" OR "Saccharomyces carlsbergensis" OR "Wickerhamomyces anomalus" OR "Hansenula anomala" OR "Pichia anomala" OR "Saccharomyces anomalus" OR "Candida pelliculosa" OR "Xanthophyllomyces dendrorhous" OR "Phaffia rhodozyma" OR "C cylindracea" OR "D hansenii" OR "C famata" OR "H uvarum" OR "K apiculata" OR "O angusta" OR "P angusta" OR "S bayanus" OR "S pastorianus" OR "S carlsbergensis" OR "W anomalus" OR "H anomala" OR "P anomala" OR "S anomalus" OR "C pelliculosa" OR "X dendrorhous" OR "P rhodozyma"	
OUTCOME	**String**
1. Antimicrobial/Antibiotic/Antimycotic	*Not applied*
2. Infection/Bacteremia/Fungemia/Sepsis	*Not applied*
3. Type of disease	*Not applied*
4. Mortality/Morbidity	*Not applied*
5. Disease Risk	*Not applied*

TUs with keywords for OUTCOME except for type of disease and morbility/mortality

String for species	
"Kluyveromyces lactis" OR "Candida spherica" OR "Kluyveromyces marxianus" OR "Candida kefyr" OR "Komagataella pastoris" OR "Pichia pastoris" OR "Lindnera jadinii" OR "Pichia jadinii" OR "Hansenula jadinii" OR "Torulopsis utilis" OR "Candida utilis" OR "Schizosaccharomyces pombe" OR "K lactis" OR "C spherica" OR "K marxianus" OR "C kefyr" OR "K pastoris" OR "P pastoris" OR "L jadinii" OR "P jadinii" OR "H jadinii" OR "T utilis" OR "C utilis" OR "S pombe"	
OUTCOME	**String**
1. Antimicrobial/Antibiotic/Antimycotic	"antimicrobial resistan*" OR "antimycotic resistan*" OR "antimicrobial susceptibil*"
2. Infection/Bacteremia/Fungemia/Sepsis	infection* OR abscess* OR sepsis* or septic* OR fungemia OR fungaemia OR mycos*
3. Type of disease	*Not applied*
4. Mortality/Morbidity	*Not applied*
5. Disease Risk	opportunistic OR virulen*

TUs with keywords for OUTCOME except for type of disease

String for species	
"saccharomyces cerevisiae" OR "saccharomyces boulardii" OR "s cerevisiae" OR "s boulardii"	
OUTCOME	**String**
1. Antimicrobial/Antibiotic/Antimycotic	"antimicrobial resistan*" OR "antimycotic resistan*" OR "antimicrobial susceptibil*"
2. Infection/Bacteremia/Fungemia/Sepsis	infection* OR abscess* OR sepsis* or septic* OR fungemia OR fungaemia OR mycos*
3. Type of disease	*Not applied*
4. Mortality/Morbidity	clinical* OR death* OR morbidit* OR mortalit* OR disease* OR illness*
5. Disease Risk	opportunistic OR virulen*

Viruses used for plant protection

Alphaflexiviridae

String for species	
Alphaflexiviridae OR Potyviridae	
OUTCOME	**String**
1. Antimicrobial/Antibiotic/Antimycotic	*Not applied*
2. Infection/Bacteremia/Fungemia/Sepsis	necros*
3. Type of disease	*Not applied*
4. Mortality/Morbidity	mortalit* OR "safety concern*" OR "health hazard"
5. Disease Risk	virulen*

Baculoviridae

String for species	
"Nuclear polyhedrosis virus" OR granulovirus OR baculoviridae	
OUTCOME	**String**
1. Antimicrobial/Antibiotic/Antimycotic	*Not applied*
2. Infection/Bacteremia/Fungemia/Sepsis	*Not applied*
3. Type of disease	"nuclear polyhedrosis" OR granulosis
4. Mortality/Morbidity	mortalit* OR "safety concern*" OR "health hazard"
5. Disease Risk	*Not applied*

Appendix D – References selected from the ELS exercise as relevant for the QPS for searches from January to June 2018 (reply to ToR 2)

Gram-Positive Non-Sporulating Bacteria

Bifidobacterium spp.

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Kim MJ, Ku S, Kim SY, Lee HH, Jin H, Kang S, Li R, Johnston TV, Park MS and Ji GE, 2018. Safety Evaluations of *Bifidobacterium bifidum* BGN4 and *Bifidobacterium longum* BORI. International Journal of Molecular Sciences, 19.

Kumar K, Saadi M, Ramsey FV, Schey R and Parkman HP, 2018. Effect of *Bifidobacterium infantis* 35624 (Align) on the lactulose breath test for small intestinal bacterial overgrowth. Digestive Diseases and Sciences, 63, 989–995.

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Downes KL, Ravel JG, Pawel E and Michal A, 2018. Specific microbes present in the early third trimester in the cervicovaginal space are associated with spontaneous labor at term. American Journal of Obstetrics and Gynecology, 218, S239–S240.

Carnobacterium divergens

None.

Corynebacterium glutamicum

None.

Lactobacilli spp.

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Koyama S, Fujita H, Shimosato T, Kamijo A, Ishiyama Y, Yamamoto E, Ishii Y, Hattori Y, Hagihara M, Yamazaki E, Tomita N, Nakajima H and Yokohama Cooperative Study Group for, Hematology, 2018. Septicemia from *Lactobacillus rhamnosus* GG, from a Probiotic Enriched Yogurt, in a Patient with Autologous Stem Cell Transplantation. Probiotics and Antimicrobial Proteins.

Lactococcus lactis

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Wunnemann H, Eskens U, Prenger-Berninghoff E, Ewers C and Lierz M, 2018. *Lactococcus lactis*, causative agent of an endocarditis valvularis and parietalis thromboticans in the allis shad, *Alosa alosa* (L.). Journal of Fish Diseases.

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Leuconostoc spp.

Mussano F, Ferrocino I, Gavrilova N, Genova T, Dell'Acqua A, Cocolin L and Carossa S, 2018. Apical periodontitis: preliminary assessment of microbiota by 16S rRNA high throughput amplicon target sequencing. BMC Oral Health, 18.

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Lin X, Jiang Q, Liu J, Zhao F and Chen W, 2018. *Leuconostoc pseudomesenteroides*-associated hemophagocytic syndrome: a case report. Experimental and Therapeutic Medicine, 15, 1199–1202.

Microbacterium imperiale

None.

Oenococcus oeni

None.

Pasteuria nishizawae

None.

Pediococcus spp.

None.

Propionibacterium spp.

None.

Streptococcus thermophilus

None.

Gram-Positive Spore-forming Bacteria

Bacillus spp.

Kim MK, Yoon HY, Lee MH and Kim JH, 2018. Canine pyometra associated with *Bacillus* species: a case report. Veterinarni Medicina, 63, 143–149.

Tran TT, Varghese M and Baer S, 2018. Polymicrobial endocarditis caused by abiotrophia defectiva, *Bacillus cereus*, *Bacillus subtilis* and *Bacillus megaterium* in the setting of injection drug use. Journal of Investigative Medicine, 66, 473–473.

Geobacillus stearothermophilus

None.

Gram-negative bacteria

Gluconobacter oxydans

None.

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Jahanshiri Z, Manifar S, Moosa H, Asghari-Paskiabi F, Mahmoodzadeh H, Shams-Ghahfarokhi M and Razzaghi-Abyaneh M, 2018. Oropharyngeal candidiasis in head and neck cancer patients in Iran: Species identification, antifungal susceptibility and pathogenic characterization. Journal de Mycologie Medicale, 28, 361–366.

Kumari S, Dey S, Sena A, Kumar D and Akhter K, 2018. Characterisation and antifungal susceptibility testing of *Candida* species isolated from clinical samples of patients attending Katihar Medical College, Katihar. BIHAR Journal of Evolution of Medical and Dental Sciences-Jemds, 7, 662–666.

Li M-C, Chang TC, Chen H-M, Wu C-J, Su S-L, Lee SSJ, Chen P-L, Lee N-Y, Lee C-C, Li C-W, Syue L-S and Ko W-C, 2018. Oligonucleotide Array and VITEK Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry in Species Identification of Blood Yeast Isolates. Frontiers in Microbiology, 9.

Ortiz B, Perez-Aleman E, Galo C and Fontecha G, 2018. Molecular identification of *Candida* species from urinary infections in Honduras. Revista Iberoamericana De Micologia, 35, 73–77.

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Viruses used for plant protection

Alphaflexiviridae

None.

Baculoviridae

None.

Table D.1: Articles that arrived to the article evaluation phase for the QPS status yeasts group

Thirty-five articles reached the article evaluation phase (final step of the ELS) for the QPS status yeasts group.[(a),(b)]

Not relevant for the QPS exercise	Articles not in English, no full text or not describing safety concerns	14 ref.	Denis et al. (2018), Gaisne et al. (2018), Li et al. (2018), Mount et al. (2018), Musatti et al. (2018), Mixao and Gabaldon (2018), Robledo-Leal et al. (2018), Rosenberg et al. (2018), Scott et al. (2018), Steenkamp et al. (2018), Steenkamp et al. (2018), Phadke et al. (2018), Sivamaruthi (2018), Wayakanon et al. (2018)							
Relevant to the QPS exercise	Articles dealing with safety concerns	21 ref.	Aslani et al. (2018), Al-Tekreeti et al. (2018), Charsizadeh c) et al. (2018), Dangarembizi et al. (2018), Charsizadeh (b) et al. (2018), Charsizadeh (a) et al. (2018), Jahanshiri et al. (2018), Kumari et al. (2018), Ortiz et al. (2018), Mohamed et al. (2018), Nejat et al. (2018), Rajkowska et al. (2018), Scapaticci et al. (2018), Sav et al. (2018), Siavoshi et al. (2018), Sekyere et al. (2018), Vieira et al. (2018), Taverna et al. (2018), Wasilewska et al. (2018), Yenisehirli et al. (2018), Yang and Mao (2018)	**Any methodological problem identified?**	*Yes*	6 ref.	**Article(s) not considered because of:**	*Methodology used for identity confirmation of the microorganism*	6 ref.	Kumari et al. (2018), Mohamed et al. (2018), Rajkowska et al. (2018), Vieira et al. (2018), Yenisehirli et al. (2018), Yang and Mao (2018)
								Reliability of the source attribution	3 ref.	Rajkowska et al. (2018), Vieira et al. (2018), Yenisehirli et al. (2018)
								Misuse of the microorganism	0 ref.	
								Predisposing factors in the exposed subjects	1 ref.	Yang and Mao (2018)
								Other reasons	0 ref.	
				No	15 ref.	**Articles describing any safety concern on:**	*Human health*	13 ref.	Aslani et al. (2018), Al-Tekreeti et al. (2018), Charsizadeh c) et al. (2018), Charsizadeh (b) et al. (2018), Charsizadeh (a) et al. (2018), Jahanshiri et al. (2018), Ortiz et al. (2018), Nejat et al. (2018), Scapaticci et al. (2018), Sav

										et al. (2018), Siavoshi et al. (2018), Taverna et al. (2018), Wasilewska et al. (2018)
									Animal health	1 ref. Dangarembizi et al. (2018)
									Environment	0 ref.
									AMR	4 ref. Scapaticci et al. (2018), Sav et al. (2018), Sekyere et al. (2018), Taverna et al. (2018)
									Other aspects	0 ref. 0

(a): Please refer to Appendix D for the complete list of references.
(b): Number of references (ref.) indicated for each step.

Appendix E – The 2016 updated list of QPS Status recommended biological agents in support of EFSA risk assessments

The list of QPS status recommended biological agents (EFSA BIOHAZ Panel, 2016) is being maintained in accordance with the self-task mandate of the BIOHAZ Panel (2017–2019). Possible additions to this list are included around every 6 months, with the first Panel Statement adopted in June 2017 and the last Panel Statement planned for adoption in December 2019. These additions are published as updates to the Scientific Opinion (EFSA BIOHAZ Panel, 2016); the latest update is available at https://doi.org/10.2903/j.efsa.2017.4664 and, as of January 2018, also as supporting information linked to every Panel Statement available on the Knowledge Junction at https://doi.org/10.5281/zenodo.1146566.

Appendix F – Microbial species as notified to EFSA, received between April and September 2018 (reply to ToR 1)

EFSA risk assessment area	Microorganism species/ strain	Intended use	EFSA Question number[a] and EFSA webpage link[b]	Additional information provided by the EFSA Scientific Unit	Previous QPS status?[c]	To be evaluated? yes or no[d]
Bacteria						
Feed additives	*Bacillus amyloliquefaciens* DSM 25840	Zootechnical additive	EFSA-Q-2018-00678	Gut flora stabilisers	Yes	No
Feed additives	*Bacillus licheniformis* DSM 5749 and *Bacillus subtilis* DSM 5750	Zootechnical additive	EFSA-Q-2018-00668	Gut flora stabilisers	Yes	No
Feed additives	*Bacillus licheniformis* ENV01/ DSM 32457	Technological additive	EFSA-Q-2018-00690	Silage additives	Yes	No
Feed additives	*Bacillus subtilis* C-3102, DSM 15544	Zootechnical additive	EFSA-Q-2018-00677	Gut flora stabilisers	Yes	No
Feed additives	*Bacillus subtilis* DSM 25841	Zootechnical additive	EFSA-Q-2018-00679	Gut flora stabilisers	Yes	No
Feed additives	*Bacillus subtilis* DSM 28343	Zootechnical additive Production of L-arginine	EFSA-Q-2018-00584	Gut flora stabilisers	Yes	No
Feed additives	*Bacillus subtilis* LMG S-27588	Zootechnical additive Production of endo-1,4-beta-xylanase	EFSA-Q-2018-00669	Digestibility enhancers	Yes	No
Feed additives	*Corynebacterium glutamicum**	Nutritional additive Production of lysine	EFSA-Q-2018-00427	Amino acids	Yes	No
Feed additives	*Corynebacterium glutamicum**	Nutritional additive Production of L-lysine monohydrochloride and concentrated liquid L-lysine (base)	EFSA-Q-2018-00507	Amino acids	Yes	No
Food enzymes, food additives and flavourings	*Corynebacterium glutamicum** (strain FIS002)	Production of food enzyme D-psicose 3-epimerase	EFSA-Q-2018-00115		Yes	No
Novel Food	*Corynebacterium glutamicum** (strain FIS002)	Novel Food Production of allulose which involves the epimerisation of fructose at the C-3 position, in a reaction catalysed by D-psicose 3-epimerase, which is contained within a non-viable, immobilised *Corynebacterium glutamicum* FIS002	EFSA-Q-2018-00472	Summary of application: https://ec.europa.eu/food/sites/food/files/safety/docs/novel-food_sum_ongoing-app_allulose.pdf	Yes	No

EFSA risk assessment area	Microorganism species/ strain	Intended use	EFSA Question number[(a)] and EFSA webpage link[(b)]	Additional information provided by the EFSA Scientific Unit	Previous QPS status?[(c)]	To be evaluated? yes or no[(d)]
Feed additives	*Corynebacterium glutamicum** KCCM 10227	Nutritional additive Production by fermentation of L-lysine of monohydrochloride and concentrated liquid lysine	EFSA-Q-2018-00442	Amino acids	Yes	No
Feed additives	*Corynebacterium glutamicum** KCCM 80117	Nutritional additive Production by fermentation of L-threonine	EFSA-Q-2018-00506	Amino acids	Yes	No
Feed additives	*Corynebacterium glutamicum** KCCM 80172	Nutritional additive Production of histidine	EFSA-Q-2018-00438	Amino acids	Yes	No
Feed additives	*Corynebacterium glutamicum** KCCM 80176	Nutritional additive Production of tryptophane	EFSA-Q-2018-00451	Amino acids	Yes	No
Feed additives	*Corynebacterium glutamicum** KCCM 80178	Nutritional additive Production of L-threonine	EFSA-Q-2018-00627	Amino acids	Yes	No
Feed additives	*Corynebacterium glutamicum** KCCM 80179	Nutritional additive/Sensory additive Production by fermentation of L-histidine monohydrochloride monohydrate	EFSA-Q-2018-00547	Amino acids/Flavouring compounds	Yes	No
Feed additives	*Corynebacterium glutamicum** KCCM 80182	Nutritional additive/Sensory additive Production of L-arginine	EFSA-Q-2018-00612	Amino acids/Flavouring compounds	Yes	No
Feed additives	*Corynebacterium glutamicum** NITE BP-02524	Nutritional additive/Sensory additive Production of L-glutamine	EFSA-Q-2018-00693	Amino acids/Flavouring compounds	Yes	No
Feed additives	*Enterococcus faecium* DSM 7134	Zootechnical additive	EFSA-Q-2018-00419	Gut flora stabilisers	No	No
Feed additives	*Enterococcus faecium* DSM 7134	Zootechnical additive	EFSA-Q-2018-00647	Gut flora stabilisers	No	No
Feed additives	*Escherichia coli* CGMCC 11473	Nutritional additive Production of L-threonine	EFSA-Q-2018-00695	Amino acids	No	No
Novel foods	*Escherichia coli* commercial strain BL21 (DE3) Expression strain	Novel Food Production of a recombinant protein	EFSA-Q-2018-00316	Summary of this application: https://ec.europa.eu/food/sites/food/files/safety/docs/novel-food_sum_ongoing-app_apoaequorin.pdf	No	No

EFSA risk assessment area	Microorganism species/ strain	Intended use	EFSA Question number[(a)] and EFSA webpage link[(b)]	Additional information provided by the EFSA Scientific Unit	Previous QPS status?[(c)]	To be evaluated? yes or no[(d)]
Feed additives	*Escherichia coli* K12 KCCM 80159	Nutritional additive Production by fermentation of L-valine	EFSA-Q-2018-00712	Amino acids	No	No
Feed additives	*Escherichia coli* KCCM 10534	Nutritional additive Production by fermentation of L-tryptophan	EFSA-Q-2018-00545	Amino acids	No	No
Feed additives	*Escherichia coli* KCCM 80180 and *Escherichia coli* KCCM 80181	Sensory additive Production by fermentation of L-cysteine monohydrochloride monohydrate	EFSA-Q-2018-00552	Flavouring compounds	No	No
Feed additives	*Escherichia coli* NITE BP-02351	Nutritional additive/Sensory additive Production of L-leucine	EFSA-Q-2018-00548	Amino acids/Flavouring compounds	No	No
Feed additives	*Escherichia coli* NITE SD 00268	Nutritional additive Production of L-histidine monohydrochloride monohydrate	EFSA-Q-2018-00546	Amino acids	No	No
Novel foods	*Komagataeibacter sucrofermentans*	Novel Food	EFSA-Q-2018-00294	Summary of this application: https://ec.europa.eu/food/sites/food/files/safety/docs/novel-food_sum_ongoing-app_bacterial-cellulose.pdf	No	Yes
Feed additives	*Lactobacillus farciminis* CNCM I-3699	Zootechnical additive	EFSA-Q-2018-00422	Other zootechnical additives	Yes	No
Feed additives	*Lactobacillus hilgardii* CNCM I-4785 and *Lactobacillus buchneri* CNCM I-4323	Technological additive	EFSA-Q-2018-00287	Silage additive	Yes	No
Feed additives	*Lactobacillus rhamnosus* CNCM I-3698	Zootechnical additive	EFSA-Q-2018-00422	Other zootechnical additives	Yes	No

EFSA risk assessment area	Microorganism species/ strain	Intended use	EFSA Question number[a] and EFSA webpage link[b]	Additional information provided by the EFSA Scientific Unit	Previous QPS status?[c]	To be evaluated? yes or no[d]
Novel foods	*Mycobacterium setense* strain Manresensis	Novel Food	EFSA-Q-2018-00278	Summary of this application: https://ec.europa.eu/food/sites/food/files/safety/docs/novel-food_sum_ongoing-app_heat-killed-mycobacterium.pdf	No	Yes
Feed additives	*Pediococcus acidilactici* CNCM MA 18/5M	Zootechnical additive	EFSA-Q-2018-00632	Other zootechnical additives	Yes	No
Feed additives	*Pediococcus acidilactici* CNCM MA 18/5M	Zootechnical additive	EFSA-Q-2018-00641	Gut flora stabilisers	Yes	No
Feed additives	*Pseudomonas fluorescens* BD50104	Zootechnical additive Production of 6-phytase	EFSA-Q-2018-00421	Digestibility enhancers	No	Yes
Food enzymes, food additives and flavourings	*Streptomyces mobaraensis* (strain DSM40587)	Production of food enzyme transglutaminase	EFSA-Q-2017-00615		No	No
Filamentous fungi						
Feed additives	*Aspergillus niger* CBS DSM 25770	Zootechnical additive Production of 6-phytase	EFSA-Q-2018-00623	Digestibility enhancers GMM	No	No
Feed additives	*Aspergillus niger* (CBS 109.713 and DSM 18404)	Zootechnical additive Production of endo-1,4-beta-xylanase and endo-1,4-beta-glucanase	EFSA-Q-2018-00417	Digestibility enhancers GMM	No	No
Food enzymes, food additives and flavourings	*Aspergillus niger* (NZYM-BF)	Production of food enzyme glucoamylase	EFSA-Q-2018-00265		No	No
Feed additives	*Aspergillus oryzae* DSM 10287	Zootechnical additive Production of endo-1,4-beta-xylanase	EFSA-Q-2018-00622	Digestibility enhancers GMM	No	No
Feed additives	*Trichoderma citrivirinode* IMI SD142	Zootechnical additive Production of endo-1,4-beta-xylanase	EFSA-Q-2018-00420	Digestibility enhancers	No	No
Yeasts						
Feed additives	*Komagataella pastoris* CGMCC 12056	Zootechnical additive Production of 6-phytase	EFSA-Q-2018-00478	Digestibility enhancers GMM	Yes	No

EFSA risk assessment area	Microorganism species/ strain	Intended use	EFSA Question number[(a)] and EFSA webpage link[(b)]	Additional information provided by the EFSA Scientific Unit	Previous QPS status?[(c)]	To be evaluated? yes or no[(d)]
Feed additives	*Saccharomyces cerevisiae* CNCM I-1077	Zootechnical additive	EFSA-Q-2018-00630	Digestibility enhancers and Gut flora stabilisers	Yes	No
Feed additives	*Saccharomyces cerevisiae* CNCM I-1079	Zootechnical additive	EFSA-Q-2018-00473	Gut flora stabilisers	Yes	No
Feed additives	*Saccharomyces cerevisiae* CNCM I-1079	Zootechnical additive	EFSA-Q-2018-00631	Other zootechnical additives	Yes	No
Feed additives	*Saccharomyces cerevisiae* MUCL 39885	Zootechnical additive	EFSA-Q-2018-00474	Gut flora stabilisers	Yes	No
Feed additives	*Schizosaccharomyces pombe* (ATCC SD 5233)	Zootechnical additive Production of 6-phytase	EFSA-Q-2018-00516	Digestibility enhancers GMM	Yes	No

*: Qualification that QPS only applies when the species is used for amino acid production is extended to other production purposes uses in this Panel Statement.
(a): To find more details on specific applications please access the EFSA website - Register of Questions: http://registerofquestions.efsa.europa.eu/roqFrontend/ListOfQuestionsNoLogin?0&panel=ALL
(b): Where no link is given this means that the risk assessment has not yet been published.
(c): Included in the QPS list as adopted in December 2016 (EFSA BIOHAZ Panel, 2017a,b) and respective updates which include new additions (latest: EFSA BIOHAZ Panel, 2018a,b).
(d): In the current Panel Statement.