EXTERNAL SCIENTIFIC REPORT

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Database on the taxonomical characterisation and potential toxigenic capacities of microorganisms used for the industrial production of food enzymes and feed additives, which do not have a recommendation for Qualified Presumption of Safety

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Abstract

The present work constitutes the external scientific report of the EFSA open call OC/EFSA/FEED/2015/01. The aim of the call was to provide EFSA with a database from a review on the taxonomical description and potential toxigenic capacities of microorganisms used for the industrial production of feed additives and food enzymes. The review includes microorganisms used as source of feed additives and food enzymes for which EFSA has received or can potentially receive applications for safety assessment, and which have not been recommended for Qualified Presumption of Safety status. The database also comprises the molecular taxonomical identifiers and biosynthetic pathways involved in the production of toxic compounds and the responsible genes. The main result of the project is shown as a database developed according to the EFSA data structure. The methodological aspects and the queries used in the systematic search, as well as the procedure applied for the screening of scientific documents retrieved are described in this report. Details are available in supplementary appendices.

In total, 22970 scientific documents were screened in the literature search, from which 411 were initially selected for providing pertinent data for the scope of the project. From the review of the selected articles, 474 bioactive secondary metabolites were recorded and 59 compounds were further studied in order to obtain data on their toxicology and the conditions in which they are produced by the microorganisms used in industrial fermentations. The database generated in this project comprises details that characterise, when available, the production conditions, genes involved and toxicity of these 59 compounds. This provides information that can be used to establish safety measures when using potentially toxigenic microorganisms in industrial fermentations

Key words: Systematic review, literature search, safety, QPS, risk assessment, data collection

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Summary

The use of microorganisms in industrial fermentations for the production of food and feed additives (enzymes, vitamins, antimicrobial substances, etc.) with beneficial effects for agriculture, farming and primary food production is in continuous development. However, the production of secondary metabolites by these microorganisms should be studied and the safety of the products obtained during fermentation should be assessed properly before its commercialization.

In order to define appropriate endpoints for the safety assessment of microbial fermentation products, it is necessary to identify the production microorganisms and the range of toxic compounds which can be produced by them. In addition, further information on the molecular and genetic basis of the production of such metabolites helps to evaluate and compare the efficiency of any genetic manipulation that could be designed and performed to avoid their synthesis. Thus, obtaining a database from a review on the appropriate taxonomical identifiers and potential toxigenic capacities of these microorganisms provides information that can be used to establish safety measures when using potentially toxigenic microorganisms in industrial fermentations.

Regulation (EC) No 1831/2003 establishes the rules for the authorisation of feed additives in the European Union (EU) according to the principles in Regulation (EC) No 429/2008. In addition, Regulation (EC) No 1332/2008 on food enzymes constitutes the legal basis for the authorisation and use of food enzymes in the European Union (EU). The procedural aspects concerning the authorisation and the evaluation procedure of food enzymes are laid down in Regulation (EC) No 1331/2008, which establishes a common authorisation procedure for food additives, food enzymes and food flavourings.

This report is the external scientific report of the European Food Safety Authority (EFSA) contract OC/EFSA/FEED/2015/01, and describes the methodology and results of a project aiming to provide EFSA with a database from a review on the correct taxonomical description and potential toxigenic capacities of microorganisms used for the industrial production of feed additives and food enzymes. Data collection is an important task of EFSA and a fundamental component of risk assessment (Articles 22 and 23 of Regulation (EC) No 178/2002). The extraction of the scientific information was retrieved in a database, which structure of the data model and its terminology was established according to EFSA standard coding systems.

The methodology applied in this project consisted in the following steps: systematic search by the application of a well-defined searching strategy, the study of the information obtained and extraction methods and the integration procedure to store the relevant information.

The database contains detailed information on (1) taxonomical descriptions and potential toxigenic capacities of microorganisms used for the industrial production of feed additives and food enzymes; (2) the type of toxic compounds that can be produced; (3) the physiological conditions in which each identified toxic compound is produced; (4) the biosynthetic pathways and corresponding genes leading to the production of the toxic compound; and (5) the mechanism of toxic action of the identified toxic compound and the dose under which harmful effects are observed in humans and animals.

The systematic search has been done with the aid of an *ad hoc* searching platform (iWatch) to perform automatic searching that supports the data searching, extraction and management of the workflow. This automatic searching tool was set up to access eight searching engines as well as 45 web sites and provides a way for organising the data in a temporary local database that could be then exported to be integrated in the final database.

In total, 22970 scientific documents have been retrieved with the searching platform and manual search, classified by microorganism and reviewed, to obtain pertinent data. A total of 411 scientific documents were selected that contain data on 474 secondary metabolites with bioactivity. A selection

of 59 toxic or potentially toxic compounds identified in these documents was further examined for retrieving information on toxicity doses, biosynthesis and conditions under which they are produced. All suitable data extracted from the relevant articles was introduced in the database developed in this project.

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1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

The aim of the contract was the preparation of a database from the results of a systematic search set to establish potential toxicological profile of microorganisms for which EFSA has received or can potentially receive applications for safety assessment, and which have not been recommended for Qualified Presumption of Safety (QPS) status, excluding the microorganisms for which EFSA has already established a guidance for the assessment of their potential toxicity. The prokaryotic and eukaryotic microorganisms that should be considered as minimum are alphabetically listed as follows:

Actinomadura yumaensis, Actinomadura roseorufa, Arthrobacter ramosus, Aspergillus aculeatus, Aspergillus japonicus, Aspergillus melleus, Aspergillus niger, Aspergillus oryzae, Aspergillus sojae, Candida cylindracea, Candida lipolytica, Candida rugosa, Cellulosimicrobium cellulans, Chaetomium erraticum, Chaetomium gracile, Chryseobacterium proteolyticum, Corynebacterium glutamicum, Cryphonectria parasitica, Disporotrichum dimorphosporum, Escherichia coli, Fusarium venenatum, Geobacillus stearothermophilus, Geobacillus caldoproteolyticus, Geobacillus pallidus, Hansenula polymorpha, Humicola insolens, Klebsiella planticola, Klebsiella pneumoniae, Leptographium procerum, Leuconostoc citreum, Microbacterium imperiale, Micrococcus luteus, Mucor javanicus, Paenibacillus alginolyticus, Paenibacillus lentus, Paenibacillus macerans, Penicillium camemberti, Penicillium chrysogenum, Penicillium citrinum, Penicillium decumbens, Penicillium funiculosum, Penicillium multicolor, Penicillium lilacinum, Penicillium roqueforti, Pseudomonas aeruginosa, Pseudomonas amyloderamosa, Pullulanibacillus naganoensis, Rhizomucor miehei, Rhizopus niveus, Rhizopus oryzae, Sphingobacterium multivorum, Sporobolomyces singularis, Streptomyces albus, Streptomyces aureofaciens, Streptomyces chrestomyceticus, Streptomyces chromofuscus, Streptomyces cinnamonensis, Streptomyces cinnamoneus, Streptomyces lasaliensis, Streptomyces lividans, Streptomyces mobaraensis, Streptomyces murinus, Streptomyces netropsis, Streptomyces olivochromogenes, Streptomyces rubiginosus, Streptomyces violaceoruber, Streptoverticillium mobaraense, Trametes hirsuta, Talaromyces emersonii, Talaromyces cellulolyticus, Talaromyces versatilis, Trametes versicolor, Trichoderma citrinoviride, Trichoderma harzianum, Trichoderma koningii, Trichoderma longibranchiatum , Trichoderma reesei, Trichoderma viride.

The particular objectives of this project were:

- To perform a systematic search and to collect all relevant scientific information with respect to the characterization of microorganisms used to produce food enzymes and feed additives, with the following requisites:
    a) To include as a minimum the microorganisms listed above.
    b) To cover a time span of the last 20 years, only reduced in cases that the amount of literature references retrieved for a given species was higher than 500.
- To extract pertinent scientific information retrieved in an Excel database, with the following requisites:
    a) A structure of the data model and its terminology in agreement with EFSA and including the use of EFSA standard coding systems for the items when possible.
    b) The contents of the database with the following information for each considered microbial species:
    - Valid scientific name, scientific synonyms (when appropriate) and the existing methods for its taxonomical identification.
    - Toxic compounds or secondary metabolites potentially toxic for humans or animals and harmful doses.

  - Physiological conditions of the microorganism for the production (or potential production) of toxic compounds or relevant substances.
  - Biosynthetic pathways and genes implicated in the production of toxic compound and relevant substances.

- To prepare a collection of module maps containing graphical representations of the biosynthetic pathways leading to the integrated synthesis of the different toxic compounds included in the database, including the list of genes and/or clusters involved in such synthesis, highlighting matching genes between pathways.
- To prepare an external scientific report to support the preparation of Guidance Documents on the subject, with the following requisites:

  a) Protocol for the search and data integration.

  b) Inclusion and exclusion criteria for selecting references.

  c) Summary of the literature review and data collection and main findings.

  d) Complete list with the relevant sequences and literature references, per species.

  e) A proposal to keep the databases updated in an efficient manner

This contract/grant was awarded by EFSA to:
AINIA, centro tecnológico. Parque Tecnológico de Valencia, Paterna, Valencia, Spain.
Beneficiaries: AINIA, Universidad de Navarra
Contract/Grant title: Database on the taxonomical identification and potential toxigenic capacities of microorganisms used for the industrial production of food and feed additives, which do not have a qualified presumption of safety
Contract/Grant number: OC/EFSA/FEED/2015/01.

2. Methodology

The principles of Systematic Review methodology (EFSA, 2010) have been applied to the literature search protocol (Figure 1). This involves the following steps:

- defining the review objectives and developing the eligibility criteria for studies;
- searching for research studies;
- selecting studies for inclusion or exclusion in the review;
- assessing validity and quality of included studies;
- collecting data from the included studies and creating evidence tables;
- synthesising data from included studies;
- presenting data and results.

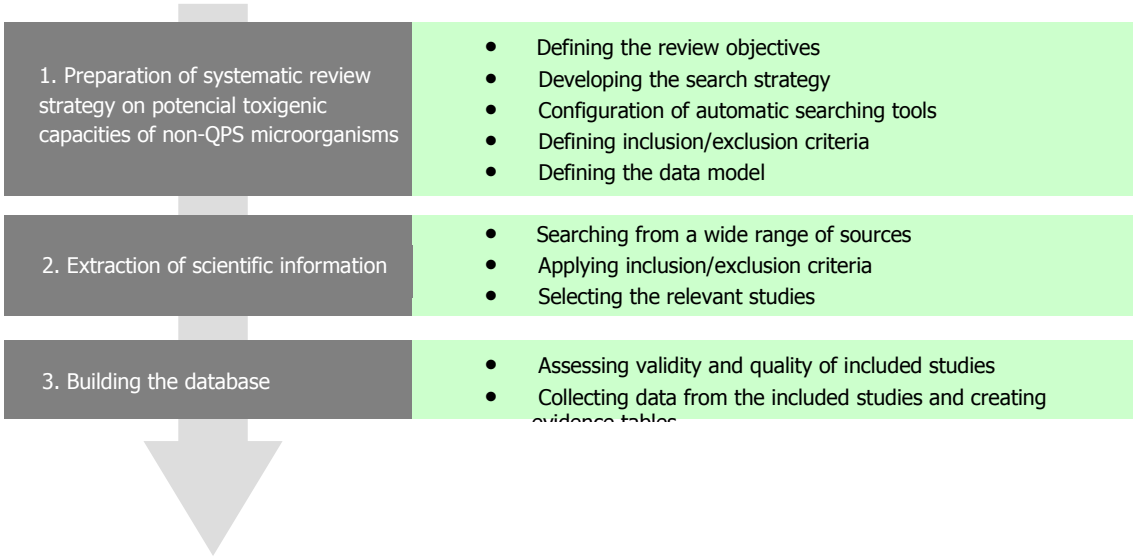

Figure 1: Methodology workflow for the literature search and data collection.

2.1. Defining the review objectives

The first step of the literature review process consisted of the analysis of the five review objectives in order to identify the key elements and to clarify their scopes.

REVIEW OBJECTIVE 1: Description of the current valid scientific name, taxon assignation, synonyms and the existing methods for the taxonomical description of microorganisms used to produce food enzymes and feed additives, which have not been recommended for Qualified Presumption of Safety (QPS) status.

Key aspects:

- To collect updated and relevant scientific information about the identification, classification and nomenclature of the microorganisms used to produce food enzymes and feed additives.

REVIEW OBJECTIVE 2: Identification of toxins or potentially toxic secondary metabolites/substances produced by the microorganisms used to produce food enzymes and feed additives.

Key aspects:

- To identify and characterise substances with toxic or other undesirable properties that are synthesised by the microorganisms used in biotechnological processes (some of them may be produced during the fermentative processes for obtaining food enzymes & feed additives). This review objective focuses on the safety assessment of unintentionally produced substances, therefore the review does not consider the safety of the food enzyme or feed additive itself.

- Some of the species of microorganisms used for the production of substances of interest have many different strains, within them could be present pathogenic strains. This review does not include the production of well-defined toxins or undesirable substances by recognised pathogenic strains.

REVIEW OBJECTIVE 3: Identification of the conditions under which the microorganism can produce the toxic compound.

Key aspects:

- Identification of culture conditions (life cycle and physiological conditions) as well as external factors (temperature, aeration, etc.) in which the identified toxic compounds are produced.

REVIEW OBJECTIVE 4: Toxicity characterisation of toxic compounds produced by the microorganism.

Key aspects:

- To identify the adverse effects of each identified toxic compound and the dose under which harmful effects are observed in humans and animals.

REVIEW OBJECTIVE 5: Biosynthetic pathway and genetic characterisation of the toxic compounds produced by the microorganism.

Key aspects:

- Acquisition of knowledge on the genetic basis of the production of toxic metabolites to assess the efficiency of any genetic manipulation performed in the microorganisms used in fermentative processes, in order to prevent the synthesis of these undesirable products.

2.2. Developing the searching strategy

The methodology applied is summarised in Figure 2.

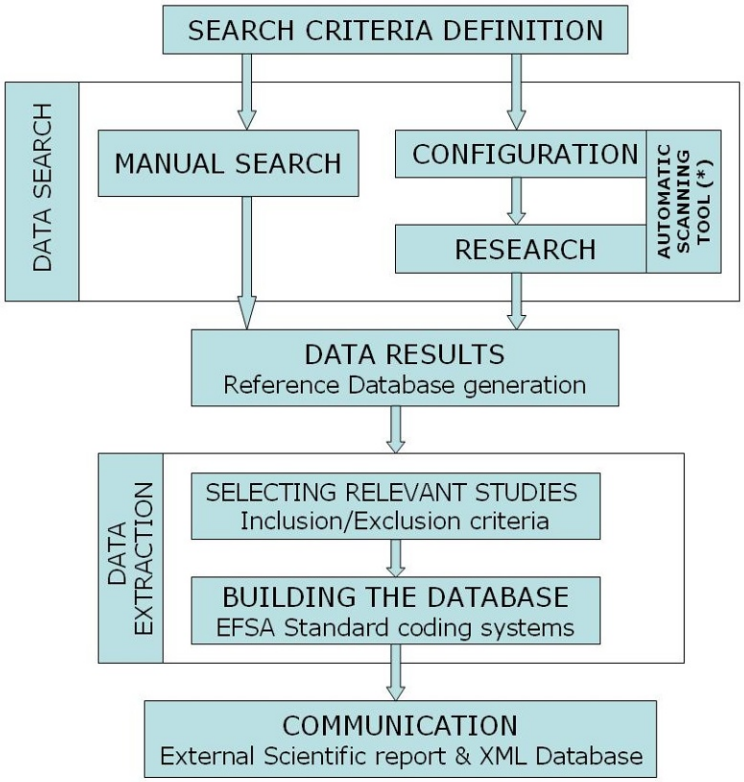

Figure 2: Workflow for the search strategy and data extraction.

As shown in Figure 2, after defining search criteria according to the required information and validated by EFSA, the systematic data search (A) was performed by two ways, either by manual searching or by the automatic scanning tool of the iWatch platform (Web Crawler, marked with an asterisk), which was used in all the cases where structured data sources allowed data scrapping. The scanning tool was configured with the information sources (scientific searching engines as well as scientific web pages) that were accessible to the crawling tool designed as well as with the keywords defined in the searching strategy. This system allowed for rapid data collection from multiple sources and easy

access to the information. Searches in engines or other information sources which did not allow automatic crawling were done manually.

To allow the management of all references (both automatic and manual searches) iWatch Platform provided a user interface as a collaborative environment for the users. On one side, the platform facilitated the integration of all results and their analysis after its configuration with the working methodology based on the inclusion/exclusion criteria. On the other side, the system permitted users to add information by filling formularies configured to include the required information for the data base.

2.2.1. Outline of the searching strategy and definition of the keywords

The searching strategy was defined after a preliminary study in which,general information about the fermentative process involving the microorganisms within the scope was obtained. This allowed to identify possible problems that can arise when retrieving data from this heterogeneous group of microorganisms, for instance, the large amount of literature associated to some of the microorganisms of the scope of this review (*Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Aspergillus niger*), and that is not relevant to the subject of the project, as well as the limited number of data available in the case of other microorganisms.

In this previous preliminary study performed to prepare the searching strategy, a review of the entries obtained by each species in the searching engine PubMed was done. This preliminary work helped to identify useful terms for the search as well as which microorganisms are more or less reported in the scientific documents.

According to these findings, several groups of species and groups of keywords were established to perform the searching strategy. The groups of keywords are the following:

- Keywords group 1: Terms related to toxin production and hazards
- Keywords group 2: Terms related to feed additives and food enzymes
- Keywords group 3: Terms related to fermentative processes
- Keywords group 4: Terms related to toxicology
- Keywords group 5: Terms related to biosynthetic pathways

The names of the species of **microorganisms** considered for the scientific search are listed in Section 1.1 of this document, as well as synonyms found for some of these species (see Appendix A), and the following considerations were taken into account:

The species *Corynebacterium glutamicum* and *Leuconostoc citreum* originally included in the list of microorganisms considered for this procurement, have been excluded as they are classified and confirmed as QPS in the latest revision 2016 (EFSA BIOHAZ Panel, 2013c). On the contrary, in the preliminary study the species *Penicillium salamii* (Perrone *et al*. 2015) has been identified as a new species to be included and has been added to the list. Regarding the species *Escherichia coli*, the term *K12* was used to exclude documents related to the pathogenic nature of many of the serogroups and strains of *E. coli*.

The microbial species have been divided into 3 groups, Species I, Species II, and Species III, according to the preliminary outcome in PubMed search:

The microorganisms that belong to **Species I**: Microorganisms that produced ≤ 200 entries when searched by just their scientific name. This group is integrated by the following microorganisms: *Actinomadura yumaensis, Actinomadura roseorufa, Arthrobacter ramosus, Aspergillus japonicus, Aspergillus melleus, Aspergillus sojae, Cellulosimicrobium cellulans, Chaetomium erraticum, Chaetomium gracile, Chryseobacterium proteolyticum, Disporotrichum dimorphosporum, Fusarium*

venenatum, Geobacillus caldoproteolyticus, Geobacillus pallidus, Humicola insolens, Klebsiella planticola, Leptographium procerum, Microbacterium imperiale, Mucor javanicus, Paenibacillus alginolyticus, Paenibacillus lentus, Paenibacillus macerans, Penicillium camemberti, Penicillium decumbens, Penicillium funiculosumm, Penicillium multicolour, Penicillium lilacinum, Penicillium salamii, Pseudomonas amyloderamosa, Pullulanibacillus naganoensis, Rhizopus niveus, Sphingobacterium multivorum, Sporobolomyces singularis, Streptomyces chrestomyceticus, Streptomyces chromofuscus, Streptomyces cinnamonensis, Streptomyces cinnamoneus, Streptomyces lasaliensis, Streptomyces mobaraensis, Streptomyces murinus, Streptomyces netropsis, Streptomyces olivochromogenes, Streptomyces rubiginosus, Streptomyces violaceoruber, Trametes hirsuta, Talaromyces cellulolyticus, Talaromyces emersonii, Talaromyces cellulolyticus, Talaromyces versatilis, Trichoderma citrinoviride, Trichoderma koningii, Trichoderma longibranchiatum.

The microorganisms that belong to **Species II**: Microorganisms that produced > 200 but ≤ 500 entries when searched by scientific name and keywords from group 1. This group is integrated by the following microorganisms: *Aspergillus aculeatus, Aspergillus oryzae, Candida lipolytica, Candida rugosa, Cryphonectria parasitica, Geobacillus stearothermophilus, Hansenula polymorpha, Penicillium chrysogenum, Penicillium citrinum, Penicillium roqueforti, Rhizomucor miehei, Rhizopus oryzae, Streptomyces albus, Streptomyces aureofaciens, Streptomyces lividans, Trametes versicolor, Trichoderma harzianum, Trichoderma reesei, Trichoderma viride.*

The microorganisms that belong to **Species III**: Microorganisms that produced > 500 entries when searched by scientific name and keywords from group 1. This group is integrated by the following microorganisms: *Aspergillus niger, Escherichia coli K12, Klebsiella pneumoniae, Micrococcus luteus* and *Pseudomonas aeruginosa*.

With the considerations of the preliminary work and in order to retrieve information in the most effective way, a stepwise search was proposed. Figure 3 shows a flowchart of the search.

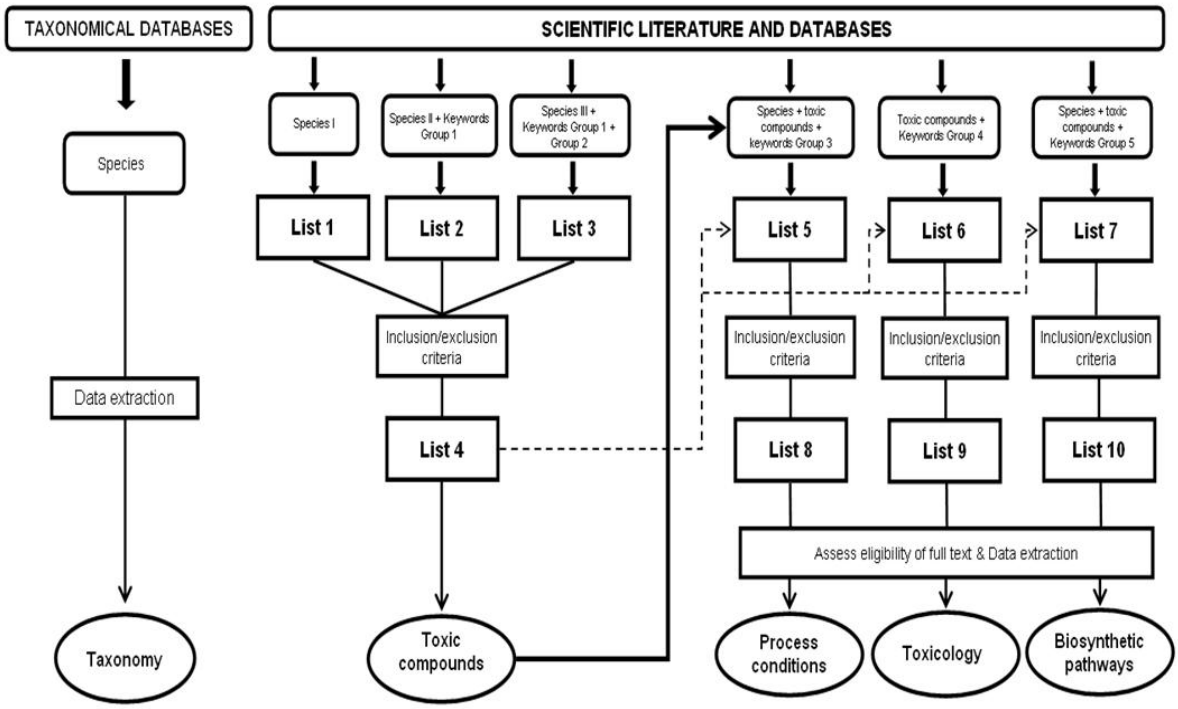

Figure 3: Searching strategy. Oval shape figures represent the main outcome descriptors containing endpoints.

For the purpose of the present review, a specific search to obtain taxonomical data was performed in databases specific for taxonomy (see Section 2.2.3) by searching each of the names of the species considered in the scope of the review. The information obtained by this search provided data for the review objective 1.

For the rest of the review objectives, the search was carried out using the different groups of keywords described above, that cover a range of searching terms in relation to toxins, additives, fermentative processes, biosynthetic pathways and toxicology.

A combination of the name of the species and the different groups of keywords allowed to obtain several lists of documents that were further screened by applying the inclusion and exclusion criteria (Section 2.3).

For the group **Species I**, the lists of documents were obtained by searching only the name of microorganism (**List 1**). For **Species II**, the **List 2** was obtained by searching the name of the microorganism AND keywords group 1. For **Species III**, the **List 3** was obtained by searching the microorganism name AND keywords group 1 AND keywords group 2. Once obtained these three lists, the inclusion/exclusion criteria defined for this first screening (see Table 2 in section 2.3.1) were applied to obtain the **List 4**. The documents from this **List 4** give information of the toxins or potentially toxic compounds that can be produced by the microorganism. They could be directly included in the **Lists 5, 6** or **7**, depending on the type of information provided. The toxic compounds retrieved from these documents were used as keywords for three new searches:

- **List 5**: toxic compounds combined with keywords group 3 (process conditions) and the name of the species. The documents resulting from this search were subjected to the corresponding inclusion/exclusion criteria ensuring that they cover conditions of production of the toxic substance when produced by the microorganisms within the scope of the project. This fed **List 8** that went for data extraction.
- **List 6**: toxic compounds combined with keywords group 4 (toxicology). The documents resulting from this search were subjected to the corresponding inclusion/exclusion criteria to feed **List 9** that went for data extraction.
- **List 7**: toxic compounds combined with keywords group 5 (biosynthetic pathways) and the name of the species. The documents resulting from this search were subjected to the corresponding inclusion/exclusion criteria ensuring that they covered genes and pathways for the production of the toxic substance by the microorganisms within the scope of the project. This fed **List 10** that went for data extraction.

The documents included in List 8, 9 and 10 were full-text screened for quality and adequacy before data extraction.

The search keywords used in relation to toxic compounds, food & feed additives, fermentation conditions and toxicology, are listed below.

- For toxic compounds relation (Keywords Group 1: TOXINS & BIOHAZARD):

adverse effect OR aflatoxin OR allerg* OR allergy OR bacteremi* OR biogenic amine* OR biohazard OR candidaemia OR carcinogen* OR coccidios*OR colitis OR co-ocurrence of toxin* OR cytotox* OR death OR developmental toxicity OR disease* OR emerging OR endocrine disruption OR endotoxin OR*

enterotoxin OR fungemia OR genotox OR health OR hepatotox* OR hypersensitivity OR immune OR immunotox* OR infection* OR morbid* OR mortal* OR mutagen* OR mycosis OR mycotoxin OR necro* OR nephrotox* OR neurotox* OR ochratoxin OR opportunistic OR pathogen* OR poison* OR qualified presumption of safety OR reprotox* OR risk* OR safety OR safety assessment OR sepsis OR septicaemia OR toxic peptid* OR toxic* OR toxicokinetic* OR toxigenic potential OR toxigenic OR toxin OR undesirable co-product* OR undesirable substance* OR virulence.*

- For food and feed relation (Keywords Group 2: ADDITIVES):

additive OR amino acid* OR aminopeptidase OR amylase OR antibiotic* OR arginine OR cellulose OR enzyme* OR galactosidase OR glucanase OR glucosidase OR hydrolase OR inulinase OR laccase* OR lasalocid OR lipase* OR lipopolysaccharide OR lysine OR mannanase OR metabol* OR methionine OR monensin OR mutant* OR narasin OR paromomycin OR pectinase OR penicillin OR phytase OR polygalacturonase OR proline OR protease* OR salinomycin OR threonine OR transglutaminase OR tryptophan OR valine OR vitamin* OR xylanase OR carbapenemase OR semduramicin OR salinomycin OR glutaminase OR pullulanase OR phospholipase OR phosphodiesterase OR glucoamylase OR nuclease OR asparaginase OR trypsin OR urease OR biosynthesis OR bioprod* OR fermentation.*

- For fermentative process relation (Keywords Group 3: FERMENTATIVE PROCESS):

aerobic OR aerobiosis OR anaerobic* OR anaerobiosis OR aeration OR bioprocess OR bioprod* OR bioreact* OR biosynthesis OR by-product OR culture conditions OR culture media OR culture medium OR downstream OR end product OR engineer* OR feed OR fermentation OR food OR food industry OR immobil* OR life cycle OR life stage OR metabol* OR performance* OR pH OR physicochemical OR processing OR productivity OR purif* OR raw material* OR recover* OR semisolid OR solid state fermentation OR spore OR sporulat* OR submerged OR synthe* OR temperature OR worker exposure OR yield.*

- For toxicology relation (Keywords Group 4: TOXICOLOGY):

abiotic OR absorbed dose OR absorption OR action OR action level OR activation OR active ingredient OR active metabolite OR acute toxicity OR administration OR allergen OR allergy OR antago OR antidote OR carcinogen* OR chronic toxicity OR concentration OR critical effect OR cumulative effect OR adverse effect* OR harmful effects OR cytotoxicity OR dose OR dose-response OR epidemiology OR genotoxicity OR reprotoxic OR hepatotox* OR immunotox* OR nephrotox* OR neurotox* OR incidence OR ingestion OR inhalation OR intake OR intestinal immunity OR morbidity OR mortality OR mutagen* OR worker exposure OR prevalence OR sensitization OR source of contamination OR sub-chronic toxicity OR susceptibility OR reproductive toxicity OR tolerance OR toxicolog* OR toxicity OR toxicity assay OR toxicity testing OR toxicological profile OR toxicokinetic* OR toxigenic OR toxigenic potential OR risk assessment OR safety OR safety assessment OR developmental toxicity OR hypersensitivity.*

- For biosynthetic pathways (Keywords Group 5: BIOSYNTHETIC PATHWAYS):

precursor OR enzyme OR synthesis OR gene OR expression OR structure OR pathway OR molecular OR biosynthesis OR promoter OR sequence* OR DNA OR cloning OR encode* OR biosynthetic OR route OR regulation OR biochemical OR biogenesis OR coenzyme OR molecule OR cofactor.*

2.2.2. Automatic searching tool – Web Crawler

The web crawler is integrated in an "ad hoc" platform called iWatch that allows the automatic search of scientific data on structured web sources by providing a tool for web scrapping (Web Crawler), parameterized with the search strategy explained in the previous section. For this purpose, the tool was configured in order to allow searching from the proposed databases and web sources (see Appendix B) applying a matching algorithm that filters and classifies the articles within the different lists. To this end, as required by the strategy, the algorithm checks title and abstract looking for any of the keywords depending on the microorganism type.

For all the articles searched (which included at least one of the microorganisms or synonyms considered for this tender), the Web Crawler searched on title or abstract the required keywords depending on its group. The following figure displays the Web Crawler architecture where experts specified both the keywords and the search strategy:

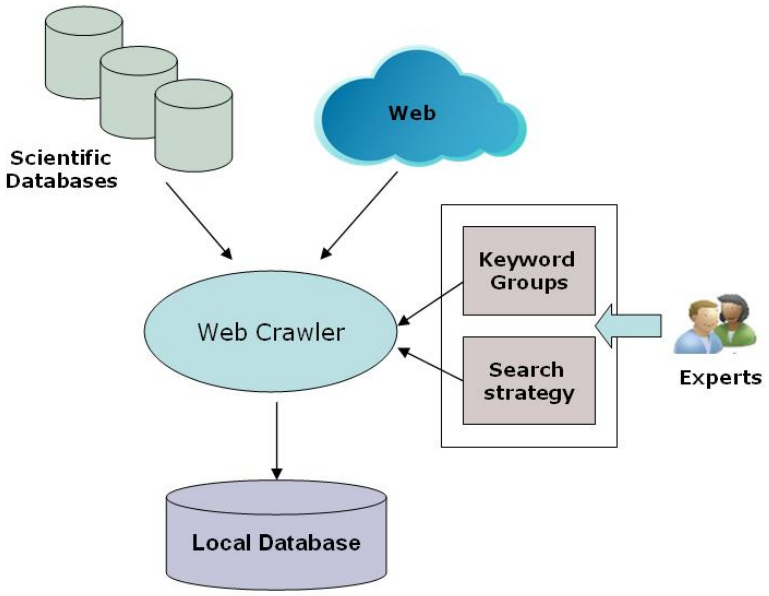

Figure 4: Automatic data collection architecture.

The result of the automatic search was stored in the iWatch database as a list of articles tagged by the microorganism and classified by the matched keywords, and was accessible using the iWatch user interface

In order to avoid double counting of studies, the scientific documents were compared for title, author names and publication area in which the study was conducted. The duplicates were discarded. This was done automatically by iWatch.

In addition to the review undertaken by the Web Crawler tool, a complementary manual literature search was carried out using the methodology explained above to search the sources that do not allow automatic searching

2.2.3. Searching sources

The search was conducted through a comprehensive list of searching engines, scientific web pages and other sources containing technical data.

For the taxonomic search (providing data for the review objective 1), an extensive search on the current taxonomy and nomenclature of microorganisms was done by using several websites and documents (Lapage *et al.*, 1992; Parker *et al.*, 2015). In the case of bacteria, a comprehensive and up-to-date presentation of the current taxonomy and nomenclature was obtained from LPSN (List of Prokaryotic names with Standing in Nomenclature, formerly List of Bacterial names with Standing in Nomenclature (LBSN)) (http://www.bacterio.net) and the list of validated prokaryotic names (IJSEM validated lists; http://www.dsmz.de/bacterial-diversity/prokaryotic-nomenclature-up-to-date.html) which contains the validly published names of bacteria complied until September 2016. For fungi, the current taxonomic status and synonymy was obtained by using the online fungal nomenclature database Mycobank (http://www.mycobank.org) (Robert *et al.* 2013) and the International Code of Nomenclature for algae, fungi, and plants (ICN) (http://www.iapt-taxon.org) (Mcneill *et al.* 2011). In both cases, to search for conserved genes, National Center of Biotechnology Information (NCBI) was used and complemented by a literature search using the terms "housekeeping" or "conserved genes" and the name of the microorganisms.

For the rest of the review objectives, the Table 1 shows the different categories of sources that have been used in the project. Additionally to this table, Appendix B includes the details of web sites that are configured in Web Crawler. The sources that do not allow data crawling have been searched manually.

In the case of the review objective 5, the databases KEGG (http://www.genome.jp) and MetaCyc (https://metacyc.org) containing metabolic pathways have been used to provide graphical representations.

Table 1: Searching engines and web sites that have been used as searching sources in the review. The web sites marked with an asterisk are automatically searched by iWatch.

Searching Engines and sites for Scientific documents and reports
Web of Science*, Scopus*, PubMed*, ScienceDirect*, Embase, EspaceNet*, Medline, WorldWideScience, SpringerLink, Directory of Open Access Journals*, BASE: Bielefeld Academic Search Engine, SciELO, Science.gov High wire; Agencia EFE*; Agrodigital*; Agromeat-Agronews*; Albeitar*; Baden-Wuerttemberg*; CIDRAP*; ClubDarwin *; CODEX Alimentarius*; EDIPORC*; EFEAgro*; Food Business Review*; Harvard School Public Health*; Natural News*; New Scientist*; Nutraceutical Business Review* ;Nutraingredients*; RSSL Food & News*; Science Insider*; Sience Daily*; SINC; UNILEVER*;WIPO*.
Competent authorities, Food policy makers, Government databases, Food safety agencies, EU and Internationals Scientific Committees for Food Safety
European Commission*, FoodSafety (USA)*; FSA (UK)*; Health and Safety executive (UK)*; Health Protection Agency (UK)*; AHVLA (UK)*; ECDC, CDC (USA)* USDA(USA)*; USEPA(USA)*; SCIRI-AESAN (Spain); Health Canada*, AGES (Austria); AFSCA (Belgium); Ministry of Food, Agriculture & Fisheries (Denmark); National Food Agency Finland; ANSES (France)*; Bundesministerium für Ernährung, Landwirtschaft und Verbraucherschutz (Germany); Hellenic Food Authority (Greece); FSAI (Ireland)*; Livsmedelsverket (Sweden); VWA (The Netherlands); Norwegian Scientific Committee for Food Safety; CFIA Canadian Food Inspection*; FAO*; Risk Experts (AESA; FDA*; SICURA Net), CSPINET (Center for Science in the Public interest), RASFF, FSANZ (Food Standard Australia New Zealand)*; BFR*.
Medical and Veterinary Databases
Environmental Health News *; Environmental Health Perspectives*; Infection Control Horizon Scanning*; OIE*; PigProgress*; WHO*; CABI (CAB Abstracts); EBSCOHost Databases with consultation of Food Science Source and Agricola database (National Agricultural Library); Clinical Evidence by BMJ; BMJ Learning; The New England Journal of Medicine; American Society of Microbiology (ASM); BioMedCentral; CAB Abstracts, FishBase (WorldFish Center).
Food industries information, food industry associations, trade organizations and Consultative Platform
Food Navigator (USA)*; Food quality news*; European Food Institutes (EFI), Spanish Agency for Consumer Affairs, Food Safety and Nutrition (AECOSAN); Spanish Agency of Medicines and Medical Devices (AEMPS), Bureau Européen des Unions de Consommateurs (BEUC); European Liaison Committee for Agricultural and Agri-Food Trade (CELCAA); Confederation of the Food and Drink Industries in the EU (CIAA); European Farmers - European Agri-Cooperatives (COPA-COGECA); European Federation of the Food,; European Public Health Alliance (EPHA); European Food Information Council (EUFIC); Eurogroup for animals; EuropaBIO; European Feed Manufacturers Federation (FEFAC); EU Association of Speciality Feed Ingredients and their Mixtures (FEFANA); Freshfel Europe.
Specific database on chemicals toxicity
Data bases on carcinogenic hazard characterization from the IARC*, International Agency for Research on Cancer (classification and monographs) or the NTP, U.S. National Toxicology Program (Studies and Report on Carcinogens); Developmental and Reproductive Toxicology Database (DART) and Hazardous Substances Data Base (HSDB) from TOXNET*, the U.S. National Library of Medicine Toxicology Data Network; JECFA* and EFSA scientific reports and monographs on chemical risks; Chemical watch*.

Grey literature
Including theses and dissertations (University websites and research non-published reports), conference proceedings, newsletters, reports, informal communications, translations, census data, technical reports, standards, patents (e.g. European Patent Office, US Patent and Trademark Office).
Scientific opinions, scientific reports, statements and guidance documents from EFSA

As specified by the open call, the search has covered a time span of at least the last 20 years, only reduced to the last 10 years in case that the amount of literature references retrieved for a given species was ≥500. In addition, extra information on toxicity of compounds produced by microorganisms has been retrieved manually from a cluster of Toxnet databases: HSDB (Hazardous Substances Data Bank) and ChemIDplus for general toxicity data information; CTD (Comparative Toxicogenomics Database) for data describing relationships between chemicals, genes and human diseases; Haz-Map for occupational information; CCRIS (Chemical Carcinogenesis Research Information System), CPDB (Carcinogenic Potency Database) and GENE-TOX (Genetic Toxicology Data Bank) for genotoxicity and carcinogenicity tests. No date filter was applied for this manual search. The information obtained with this search complemented the findings of the searching strategy and is summarised in Appendix C.

2.3. Selection of studies

The selection of the scientific documents recovered in the search was done following the criteria explained below.

The relevant studies selected were:

- referring to the microorganism of interest as a producer of a secondary metabolite/toxic compound
- providing data on its taxonomical identifiers and potential toxigenic capacities. Studies providing data on toxicity of compounds that have already been assessed by EFSA have been included in the database but extraction of data from the toxicological point of view has been considered not necessary.

The selection and extraction process has been conducted in two stages: Level 1 and Level 2.

Level 1: Screening of titles and abstracts: Inclusion/exclusion criteria were applied after reading either in the title or abstract of the documents retrieved at each stage of the searching (List 1-List 3 and List 5-List 7). Examination of title and abstracts of documents included in list 4 permitted the identification of the secondary metabolites produced by the microorganisms that might have a potential toxic effect. Some documents from List 4 were also included directly in Lists 5, 6 or 7, depending on the type of information provided. After having identified the potentially toxic metabolites from List 4, a second search was carried out with the corresponding keywords (see Figure 3), to obtain documents for Lists 5, 6 and 7. The title and abstract of these documents were read and the corresponding inclusion/exclusion criteria (see Table 2) applied to select the documents for Lists 8, 9 and 10, respectively.

Level 2: Full examination of documents: The full text of reports from Lists 8, 9 and 10 were examined at Level 2. Inclusion/exclusion criteria (see Table 3) were also applied at this stage, in order to select the documents that met all the conditions to extract the information for the database. The examination of the complete documents allowed in many cases to discard documents that passed the screening at Level 1, but that after a further examination were concluded as not containing relevant data. Documents containing any relevant information to provide data for the review objectives were used to extract information for the database. The quality of the information was assessed by the application of the inclusion/exclusion criteria.

For both levels, the lists of documents were evaluated by two independent reviewers (parallel review) from each area of specialization (microbiology, molecular biology and toxicology). In the case of disagreements between them, the scientific document was discussed to reach a consensus before proceeding to the next step of the screening process.

1.1.1. Screening of titles and abstracts for the relevance of the study questions: Level 1

The inclusion/exclusion criteria used to select relevant documents at title and abstract level are described in the following table (Table 2).

Table 2: Inclusion/Exclusion Criteria.

To be selected for **List4**	**INCLUSION**	Is the main aim of the document directly related to the microorganisms within the scope of the review? (Yes/No)
		Is there a metabolite/substance produced by the microorganism regarded as toxic/causing adverse effect? (Yes/No/Unknown)
	EXCLUSION	Is the metabolite/substance produced by the microorganism included in the list of food enzymes & feed additives (Appendix D)[1]? (Yes/No)
		Is the document related to the production of toxins or adverse effects outside the scope of the systematic search (antimicrobial, antifungal, responsible for the pathogenicity of the species)?
To be selected for **List 8**	**INCLUSION**	Is the toxic metabolite/substance produced under specific conditions (process conditions detailed) described? (Yes/No/Unknown)
	EXCLUSION	Is the fermentation process not linked to the microorganism within the scope of the review? (Yes/No)
To be selected for **List 9**	**INCLUSION**	Is the toxin/ secondary metabolite/substance evaluated from a toxicological point of view? (Yes/No)
	EXCLUSION	Is the toxicological study focused on ecotoxicology? (Yes/No)
		Is the compound evaluated an undesirable substance in animal feed (Dir 2002/32/EC)? (Appendix E) (Yes/No)
		Has the substance already been evaluated by IARC (Monographs on the Evaluation of Carcinogenic Risks to humans), NTP (Report on Carcinogens) or EFSA (Appendix E)? (Yes/No)
To be selected for **List 10**	**INCLUSION**	Does the document deal with the biochemistry or biosynthetic pathway of the toxic compound? (Yes/No/Unknown)
	EXCLUSION	Is the biosynthesis of the toxic compound not linked to the microorganism within the scope of the review? (Yes/No)

[1]List of food enzymes & feed additives provided in Appendix D is used as exclusion criteria. If the substance regarded as toxic is included in the list, the document is considered ineligible, because the scope of the review does not include an assessment of the toxicological aspects of the food enzyme or additive itself but other not intentionally produced substances that could occur during the fermentation.

The screening consisted of several steps corresponding to four lists of questions (Table 2). It is defined that if any inclusion criteria was not fulfilled (answered NO) it was not necessary to proceed with the screening and the document was considered ineligible (all inclusion criteria must be answered YES or UNKNOWN to be included in study). On the other hand, if any exclusion criteria was answered YES the document was also discarded (exclusion criteria must be answered NO or UNKNOWN to be included in the study).

In the majority of the cases, the screening did not identify precise information concerning specific eligibility criteria regarding the toxicity of the compound; therefore the answer was inconclusive (UNKNOWN) that led to the inclusion of the document. The document was selected and the secondary compounds mentioned in these scientific documents recorded in a form "ITEM ENTRY" (see Section 2.4.). From all the compounds initially recorded, the ones selected for the second search had to comply with at least one of these conditions:

1) The compound is referred as a toxin in the scientific document or is a known toxin or mycotoxin or is involved in the biosynthetic route of one toxin.
2) The compound has been found to be produced by more than one species.
3) More than one reference has been found indicating the production of the compound by one species.

2.3.1. Eligibility criteria for full text documents: Level 2

Documents that potentially met eligibility criteria at the abstract and title screening stage were retrieved (Lists 8-10) and the full text documents were reviewed for eligibility. The criteria for inclusion or rejection of full text documents are recorded in the following table (Table 3**)**.

Table 3: Inclusion/Exclusion Criteria.

INCLUSION	Is the toxin compound produced well identified/defined? (Yes/No)
	Are the experimental designs/protocols/material and methods reported? (Yes/No)
EXCLUSION	Does the document not report the designated outcomes: process conditions or toxicology or metabolic pathway of the toxic compound? (Yes/No)
	Is the document a preliminary toxicological assessment /toxicity is not clear or related to potential medical properties of the substance? (Yes/No)
	Is the occurrence of the toxic compound doubtful or anecdotic? (Yes/No)

The reasons for rejection of full text articles are justified and recorded in Appendix F of the report, together with their references.

Compounds of potential concern but with no standard toxicity information to be included in the final database (*e.g.* a very preliminary toxicity assessment, study of interaction with a molecular target, etc) are reported in Appendix G**.** They were found at the first level of the reviewing process, to obtain the name of the secondary metabolites potentially toxic that might be produced by the different species. They were identified whether in the abstract or when reviewing the complete document at level 2.

2.3.2. Collecting data from the included studies and creating evidence tables

As explained before, all retrieved articles in Lists 8, 9 and 10 were submitted to the Level 2 review, conducted by examining the full-text of the articles. At this point, the quality of the paper was assessed by applying the inclusion/exclusion criteria (Table 3).

The assessment of full-text documents was carried out also by 2 different reviewers. Data extracted from each document was verified by a second person (sequential method). In case of disagreement, the document was discussed between the different reviewers involved in the screening to reach a

consensus. In every case possible the extraction of the data was aided by the collaboration platform iWatch as explained below.

Collaboration platform - iWatch

The interface provided by the iWatch Web platform eases the work of filtering, reviewing and extracting the data required by the tender as specified in the methodology. The platform provides the functionality required to manage the outcomes of the search strategy, allowing for the storage of the manual search results and the management of the automatic search results.

Regarding the collaboration tasks, the tool has allowed the following functionalities:

- Filtering of documents by the keywords groups used in the searching strategy, allowing for the distribution of the work within the experts groups.
- Creation of classifying folders in order to facilitate the reviewing cycle (experts should be able to review documents two times).
- Executing batch actions with a group of entries to allow selecting a group of entries and executing the same action with all of them.
- Searching documents by words within a defined list to facilitate the application of inclusion/exclusion criteria (batch actions allow removing or adding tags to identify them).
- Addition of tags to identify documents within a topic.
- Discard non useful documents or addition of documents found by manual search.
- Inclusion of comments into each entry to save important information found.

Also, **iWatch** tool was configured to facilitate the work of data extraction by allowing entering data through different forms. These forms were designed after the information required for the data model which included text and numerical fields and drop-down lists when required to select options for EFSA collections. Finally, the submissions sent by the users were also stored at the platform database.

The following forms for data registration were created:

- ***Item Entry***: internal entry form that allows introducing and collecting possible toxic compounds of interest extracted from List 4. It includes information about the source, the microorganism and toxic compound. This information was used to obtain Appendix G.
- ***Fact Entry***: entry form to include information extracted from selected articles of interest from Lists 8, 9 and 10, which will be included into the database. It includes information about the source, the microorganism, biosynthetic pathways, process conditions and toxicology.

To extract the data submitted by users, iWatch export module was configured in order to allow the processing of all entries and its storage in a Data Schema created for this project as defined in section 2.6. For each entry, the module processes all fields converting to the format required for the data base specifications when required (see Appendix H) and stores the result in the schema. Once stored, the Data Base Management System allowed the data extraction in the XLM format required by EFSA.

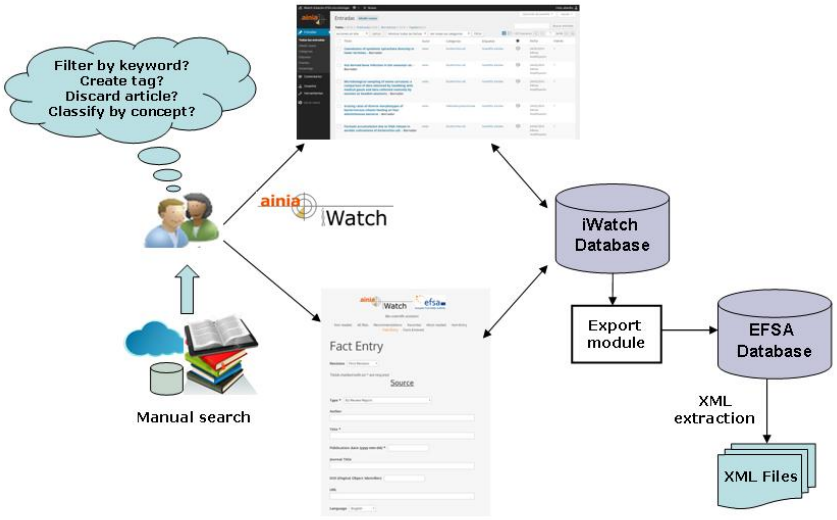

Figure 5: Collaboration Platform Architecture.

2.4. Assessing the validity and quality of the included studies

The overall development of this review was carried out under a framework of quality assurance system and under the supervision of a Quality Assurance Unit.

The main feature to control the quality of the review and the data extracted was a double check review done by two experts for each area of knowledge (microbiology, molecular biology and toxicology).

Moreover, and specifically for this project, a number of control mechanisms at the data entry level were implemented to guarantee high quality of deliverables and reduce unintended errors:

- Sharing the preliminary results with the requestor in order to obtain an external validation of the work that has already been done.
- Expert groups meetings to review the methodologies and conclusions.
- Furthermore, an external quality check was implemented by:
    - Automatic verification of data quality at the data entry level.
    - Manual revision of the collected data to be submitted.

Automatic verification entails the definition and implementation of rules aiming to minimise errors during data entry, thus maximizing data quality. In the data entry phase, errors that can be detected automatically are: type mismatches, missing values for mandatory fields, wrong format (e.g., dates), and length exceeding the maximum allowed size.

For these structural errors the nature itself of a Database Management System (DBMS) engine such as MySQL can prevent to store wrong data. In fact, at the database creation phase, it was specified for each fields its type, length, and format and if it is a mandatory field. In this way the DBMS will not allow storage of data that is not compliant with the corresponding field definition. In addition, more complex rules can be specified to the database engine using the SQL language, such as foreign keys. For catalogue fields, namely fields that can assume only a value chosen within a predefined list, it is possible to define catalogue tables and refer to them in the proper fields through the creation of foreign keys. A web-interface guides and supports the operator in the data entry phase.

2.5. Data model

A relational database (Appendix H) was designed to store the extracted information, following a relational methodology based in an iterative process, in which EFSA provided a framework and advice for the database structure. The database shares the same structure and some catalogues already built for other EFSA's databases, in particular the *Chemical hazards database* created to hold a summary hazard data from EFSA's chemical risk assessments in food and feed. This data collection covers the opinions and statements adopted by EFSA panels including FEEDAP Panel (Additives and Products or Substances used in Animal Feed), CEF Panel (Food Contact Materials, Enzymes, Flavourings and Processing Aids), ANS Panel (Food Additives and Nutrient Sources Added to Food) and NDA Panel (Dietetic Products, Nutrition and Allergies). The catalogues used to include some of the data in the database are available in EFSA's Data Collection Framework. All the suitable new terms encountered in this review that were not included in the catalogues have been introduced by sending the pertinent information to the EFSA DCF Data Manager.

The starting point for this database is the harmful substance or toxin produced by the microorganism as a secondary metabolite during the fermentative process. This substance is always going to be associated to the **PARAM substance definition** as provided in the standard sample description (EFSA, 2013). If a substance was not included in the EFSA PARAM catalogue, such substance was intriduced as explained previously. The information to be provided to the EFSA DCF Data Manager for these substances is included in Appendix I and contains the following:

CAS Number: The Chemical Abstract Service registration number of the substance. The CAS number can be retrieved from publicly available databases such as: PubChem, ChemIDPlus, etc.

Molecular formula: The molecular formula is reported. The molecular formula can be retrieved from publicly available databases in particular PubChem (Bolton, 2008).

SMILES notation: The SMILES (Simplified Molecular Input Line Entry Specification) for the substance. The coded structure can be retrieved from publicly available databases such as: PubChem, ChemIDPlus. The structure code can be also obtained by manually drawing the structure in popular chemical drawing programs that allow for the SMILES generation such as ChemSpider. When this option is used, verification of the structures codified will be done. Together with the SMILES, the source of this notation will be also included.

Figure 6 shows the logical map that represents the intrinsic properties of the data to be structured in the database as extracted from this scientific review and describes the following tables of keywords:

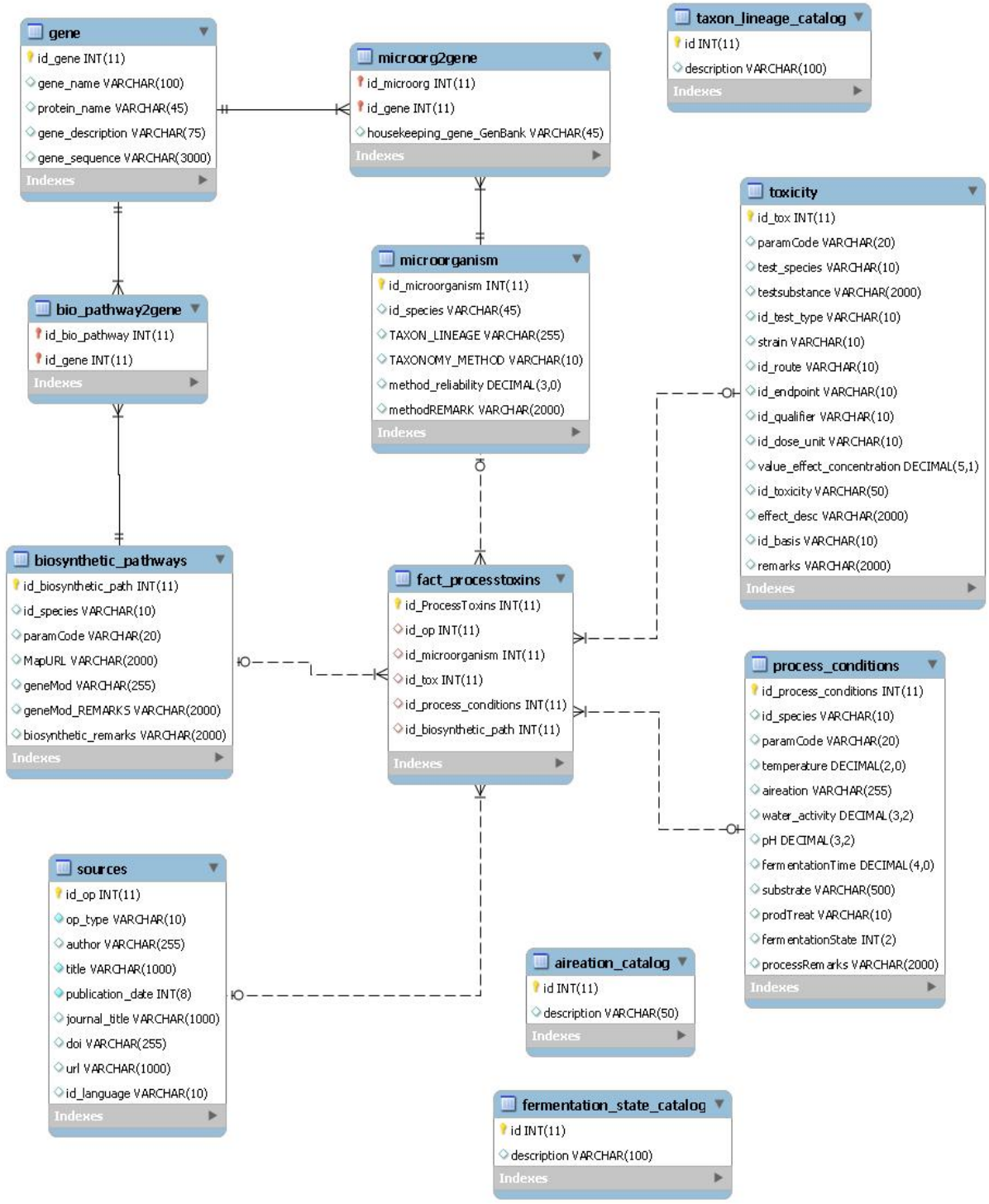

Figure 6: Data model for the review.

FACT_ PROCESSTOXIN: Codification of each fact that is described in the database.

MICROORGANISM: Descriptors of the microorganism associated to the facts, normally one of the microbial species considered in the scope of this review.

BIOSYNTHETIC PATHWAYS: Descriptors of the metabolic route used by the microorganism for the synthesis of the toxic compounds associated to the facts.

PROCESSING CONDITIONS: Descriptors of the processing conditions in which the microorganism is able to synthesize the toxic compounds associated to the facts.

TOXICOLOGY: Descriptors of the toxicological parameters of the toxic compounds associated to the facts.

SOURCES: Descriptors of the document from which the information for the facts is obtained.

2.5.1. The sections of the data model – Description and general information

The descriptors chosen for each of the features (tables) forming the data model were the following (see also **Appendix H**; Excel file of the Data Model):

FACT_ PROCESSTOXIN

- **id_ProcessToxins:** Unique ID for fact_processtoxin table.
- **id_op (FK):** Foreign key (FK) with a unique ID from the source table.
- **id_microorganism (FK):** Foreign key with a unique ID from the microorganism table.
- **id_tox (FK):** Foreign key with the unique ID from the toxicology data.
- **id_process conditions (FK):** Foreign key with a the unique ID from the process conditions table.
- **id_biosynthetic path (FK):** Foreign key with a the unique ID from the biosynthetic pathway table.

MICROORGANISM

- **id_microorganism (PK):** Primary key (PK) with a unique ID for the microorganism table.
- **id_species:** Microorganism used in the biotechnological process. The data type is a code from the **MTX** catalogue. MTX catalogue is filled with new entries of the microorganisms of this review that are not included yet. Data to be provided is:
    - a complete identification kingdom-order-family
    - the more recent recognized name
    - possible synonyms
- **TAXON_LINEAGE:** (picklist) General classification of the microorganism (filamentous fungi, yeast or bacteria) which provide information useful for the safety assessment.
- **TAXONOMY_METHOD:** Acceptable scientific methodologies and techniques for the identification of microorganisms. This data type is a code from the **ANLYMD** catalogue.
- **method_reliability:** (number) Measure of the consistency of the taxonomic method (% Homology/Closenest given in the molecular studies).
- **methodREMARKS:** (free text) Include the reference organism for the comparison and the homology threshold considered.

SOURCES

- **id_op (PK):** Unique ID for fact processtoxin table.

- **op_TYPE:** Type of document (picklist): whether the document is an scientific article, report, book, thesis, EFSA opinion or statement etc. This field will be using one of the terms in the EFSA's REF-TYPE catalogue.
- **Author:** (free text) Author(s) of the journal article.
- **TITLE:** Title of the journal article or document (title, free text): the title of the document as reported in the published document (PDF file) is reported.
- **PUBLICATION_DATE:** (number) Date of the publication the publication. The format is yyyy-mm-dd.
- **JOURNAL_TITLE:** (free text) Title of the journal where has been published the scientific article.
- **DOI:** (free text) Digital Object Identifier of the journal article.
- **URL:** (free text) The journal link (internet address) or publisher.
- **id_LANGUAGE:** (picklist) Language used to fill in the free text fields (ISO-639-1) and **LANG** catalogue.

BIOSYNTHETIC PATHWAY

- **id_biosynthetic path:** Identification of the synthesis pathway of the metabolite.
- **id_species:** Microorganism used in the biotechnological process. The data type is a code from the **MTX** catalogue.
- **paramCode:** Toxic compound described according to the Substance Code from **PARAM** catalogue.
- **MapURL:** Link to the diagram where the route of synthesis of the substance is represented.
- **geneMod:** (picklist) Genetic modification, where the gen has been genetically modified or not.
- **geneMod_REMARKS:** (free text) Genetic modification (information of genes inserted or deleted). It can be used to comment on the result of gene modification.
- **Biosynthetic_REMARKS:** (free text) Details of the biosynthetic pathway (promotors, etc).

PROCESS CONDITIONS

- **id_process conditions:** The data elements belonging to this section describe information related to the process conditions.
- **id_species:** Microorganism used in the biotechnological process. The data type is a code from the **MTX** catalogue.
- **temperature: (number)** Temperature in degrees centigrade.
- **aireation: (picklist)** Oxygen requirements for the microorganism during the fermentative process (*Aerobic*: ≥ 20% oxygen; *Anaerobic*: < 5% oxygen; *Microaerophilic*: 20% > oxygen ≥ 5%)
- **WaterActivity: (number)** Water activity, as it is expressed with numerical number from the range (0-1).
- **Substrate: (free text)** Type of substrate used in the biotechnological process. It makes reference to the substrate used in the fermentative process (Main protein source (yeast extract), polysaccharides (molasses), etc.)

- **pH: (number)** pH during the fermentative process, as it is expressed with numerical number from the range (0-14).
- **Fermentation time (h):** Time in hours of the fermentative process.
- **prodTreat:** Used to characterise a food product based on the treatment or processes applied to the product. This data will be obtained from the **PRODTR catalogue** catalogue.
- **fermentationState: (picklist)** Types of fermentative processes: *solid state* (microbial growth and product formation occur at the surface of solid substrates); *semi-solid* (this type of fermentation is a sort of SSF in which the free liquid content has been increased in order to facilitate nutrient availability and fermentation control), *submerged batch* (closed culture system which contains limited amount of nutrient medium); *submerged fed-batch* (batch culture to which is added new fresh nutrient medium without removing the growing microbial culture), *submerged continuous* (a culture in which nutrients are supplied and end products are continuously removed), *immobilized cell bioreactors* (bioreactors based on immobilized cells), *immobilized enzyme bioreactors* (continuous flow reactors based on immobilized enzymes).
- **paramCode: (free text)** Its data type is a code from the **PARAM** catalogue. It is used to describe the toxic substance aim of the study.
- **processRemarks: (free text)** Additional remarks on process conditions. Its data type is free text of up to 2000 characters. It can be used to comment on the process analysed.

TOXICITY

- **id_tox:** The data elements belonging to this section describe information related to toxicology.
- **paramCode: (free text)** Its data type is a code from the **PARAM** catalogue. It is used to describe the toxic substance aim of the study.
- **test_species:** Species of the organism/cell culture used as the test organism in the toxicological study
- **testsubstance:** Description of test material used in the toxicological study.
- **id_test_type:** Type of toxicological test. Its data type is a code from the **TEST_TYPE** catalogue.
- **Strain:** Identification of the strain used as the test organism.
- **id_route:** Indicator how the substance is administered to the organism (human/animals). Its data type is a code from the **ROUTE_EXP** catalogue.
- **id_endpoint:** Endpoint reported in the study to describe the reported values (e.g. dose level). The reference point is described in the EFSA documents and used to derive health-based guidance values, margin of exposure values for human health, margin of safety values for human or animal health. The opinion may also discuss a reference point or toxicity values for animal health. This data type is a code from the **ENDPOINT_HGV** catalogue.
- **id_qualifier:** Qualifier for the reported endpoint values (e.g. =, <=, >=). Its data type is a code from the **QUALIFIER** catalogue.
- **id_dose-unit:** Enumeration of group units for group assessment. Its data type is a code from the **UNIT** catalogue.
- **Value_ effect_concentration**: Effect concentration.

- **id_toxicity:** This field refers to classification of critical effect according to toxicity target (Owens 2002) and the data type is a code from the **TOXICITY** catalogue.
- **Effect_desc:** (Free text) Description of the effects observed in the toxicological study.
- **id_basis:** Characterisation of the measures toxicological outcome measure. Its data type is a code from the **BASIC_EFFECT** catalogue.
- **Remarks:** Additional remarks on toxicological study

GENE

- **id_gene:** The data elements belonging to this section describe information related to the gene.
- **Gene_name:** Gene name involved in the synthesis of the substance.
- **Protein_name:** Name of protein synthesised from the gene.
- **Gene_decription:** (Free text) Description of the gene function.
- **Gene_sequence:** Sequence of the involved in the synthesis route.

BIO_PATHWAY2GENE

- **id_bio_pathway:** The data elements belonging to this section describe information related to the identification of the biosynthetic pathway.
- **id_gene:** The data elements belonging to this section describe information related to the genes involved in the biosynthesis of the compound.

MICROORG2GENE

- **id_microorg:** The data elements belonging to this section describe information related to the taxonomy of the microorganism.
- **id_gene:** The data elements belonging to this section describe information related to the genes involved in the microorganism identification.
- **housekeeping_gene_GenBank: GenBank ID for the housekeeping gene**

3. Results

3.1. Taxonomic characterisation

A literature search was carried out for each microorganism included in the scope of the project with the purpose of assessing the available scientific information on the taxonomical characterisation (see section 2.2.3.). A list of microorganisms including information about its valid current name and the taxonomic ranks (kingdom, order, family), as well as other scientific names and synonyms, was prepared and sent to EFSA for the inclusion in the MTX catalogue.

The literature search on taxonomy data produced 123 references with the methods for its relevant and accurate taxonomical identifiers, genomes sequenced and housekeeping genes (see Appendix J, and Appendix K).

Bacterial taxonomy determination is mainly based on several molecular techniques, each one for retrieving the information at different levels (proteins, fatty acids, DNA) and the obtained results are combined and analysed to reach the correct taxonomic identification of the microorganism.

The taxonomy of fungi is currently very complex. There is still an ongoing need of unique identifiers harmonisation, in this regards, big data tools contribute to harmonise approaches (three official

registries are approved: MycoBank, Index Fungorum, Fungal Names). However, debate on species concepts in the mycological society results in a lack of a universally accepted fungal taxonomy.

Several studies have been dedicated to explore high-throughput expression profiles, in order to identify candidate housekeeping genes. The 16S ribosomal RNA (16S rRNA) gene sequence to study bacterial phylogeny and taxonomy has been universally accepted as the common housekeeping genetic marker. A commonly used reference gene for fungi is the 18S ribosomal RNA (18S rRNA). The accession numbers to the Genbank database for the sequences of the conserved genes found in the search is reported in Appendix J (Appendix J Bacteria, Appendix J Fungi). The appendix also includes the links to the available ID genome annotations for the type species of the microorganism when available. Those links allow downloading sequence and annotations for current versions of genome assemblies from the NCBI genomes FTP site.

The results of the taxonomic review were integrated into the database, and synonyms were also included as new keywords for the searching strategy.

3.2. Retrieval of relevant documents

According to the searching strategy explained in Section 2.2, IWatch tool was set up and configured for the retrieval of scientific documents that match with the different sets of keywords and non-searchable databases were manually searched in order to complement the search. The total number of scientific documents retrieved for the first level was 22970. The references were distributed into several groups using the microorganism name as a keyword.
The election of the articles for the revision by the two reviewers was also done by the IWatch tool that displayed the abstract and allowed direct access to the URL of the document. The reviewers labeled the articles as "first" or "second" revision and as "included" or "excluded" which facilitated the management of the review.
After having examined the titles and abstracts of Lists 1, 2 and 3 (22970 documents in total) and applying the inclusion/exclusion criteria, 411 documents (List 4) were selected. The revision of the articles allowed the identification of 474 bioactive secondary metabolites synthesised by the different microorganisms of the scope that were subjectd to a further selection according to the criteria explained in section 2.3.1. Figure 7 shows the outcome of each searching and screening stage conducted in this project.

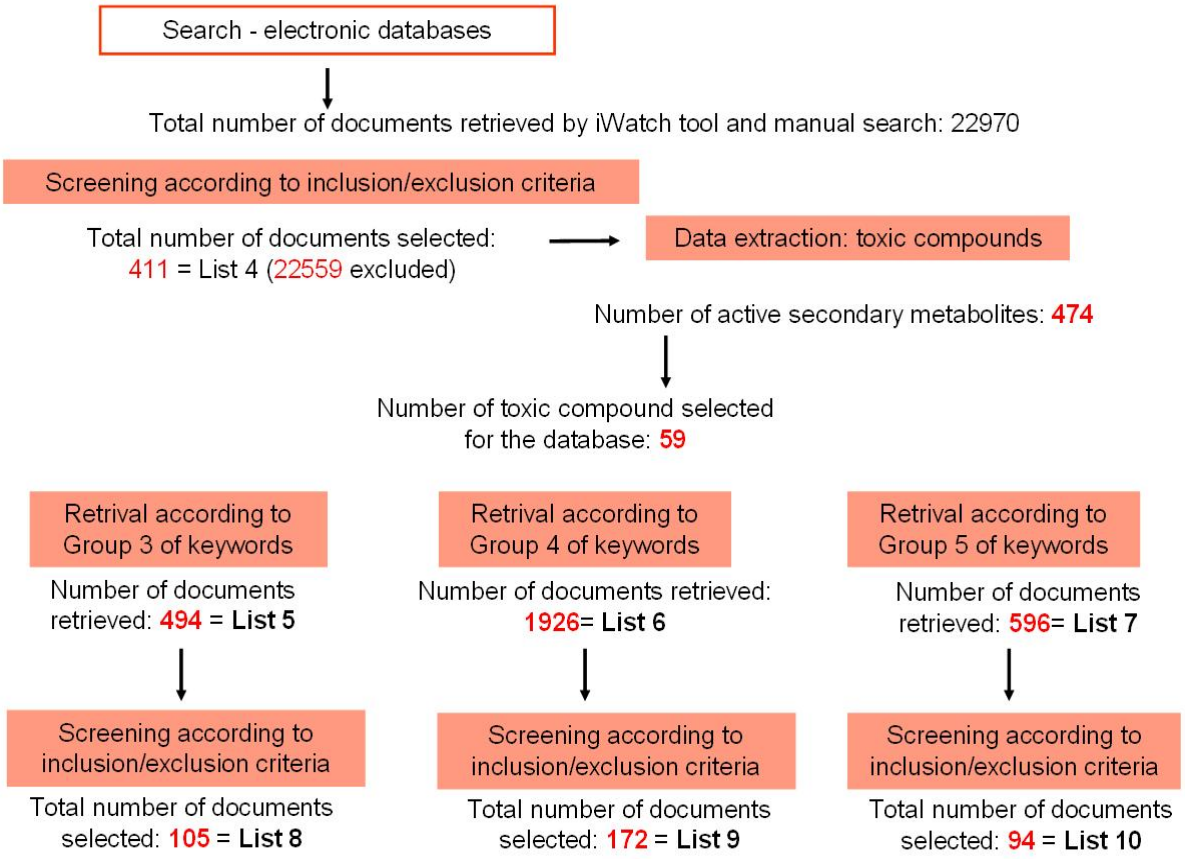

Figure 7: Flow-chart summarising results of the literature search and retrieval of relevant documents.

For the second search, aimed to obtain pertinent information about the toxicity characteristics of the compounds, biosynthetic pathways and fermentation conditions, 59 compounds (see below) were selected from the total number of bioactive metabolites identified, based on the data available about the toxicity or potential toxicity of these compounds or the role they may have on the biosynthetic routes, as explained in section 2.3.1. From these 59 compounds selected, 18 were mycotoxins or groups of mycotoxins that have already been characterised for their toxicological impact. Those toxins are (Appendix E):

> Aflatoxin B1, Aflatoxin B2, Beauvericin, Citrinin, Deoxynivalenol, Enniatins, Ergot alkaloids, Fumonisin B1, Fumonisin B2, Fumonisin B4, Fusarin C, Ochratoxin A, Patulin, Penicillic acid, Sterigmatocystin, T-2 toxin, Trichothecenes, Zearalenone.

Another 41 compounds were toxins not yet fully characterised from the toxicological point of view:

> 1-Hydroxyphenazine, 3-Nitropropionic acid, Andrastin A, Aristolochene, Asperparaline A, Citreoviridin, Culmorin, Cyclopenol, Cyclopiazonic acid, Cytolysin A, Diacetoxyscirpenol, Endophenazine A, Festuclavine, Isofumigaclavine A, Isofumigaclavine B, Isotrichodermin, Isotricodermol, Kojic acid, LPS endotoxin, Malformin(s), Maltoryzine, Marcfortine(s), Mitorubrinic acid, Mycophenolic acid, Naphto-gamma-pyrones, Neoxaline, Nigerazines, Nigragillin, Orlandin, Oxalic acid, Perinadine A, Phenazine-1-carboxylic acid, Phenazines, PR-toxin, Pyocianin, Roquefortin, Sambucinol, Secalonic acid, Trichodermin, Trichorzin, Xanthomegnin.

In the second search to obtain List 5 and List 7, each of the 59 compounds were used as keywords, combined with the name of the microorganism(s) that produced the compound and the keywords

groups 3 and 5 to obtain the List 5 and List 7. List 6 was obtained for the compounds not included in Appendix E, as mentioned in Section 2.2.

Additional information regarding the molecular characterisation of these compounds (Molecular formula, CAS number, SMILES, INCHI and IUPAC) was also obtained for those compounds not included in the EFSA catalogues (Appendix I).

The URL with the toxicological information retrieved for each compound (as explained in section 2.2.3) was provided as supplementary data (Appendix C)[1].

3.3. Production of toxic secondary metabolites by microorganisms used in industrial fermentations

In this review, it has been found that many of the species of microorganisms studied produce a wide range of secondary metabolites, in addition to the substances that are intentionally produced for industrial purposes. Several of these secondary metabolites have been described as toxic to humans and animals.

In many cases, the metabolic role of these compounds is unknown and/or not well defined; however, biotechnological of biopharmaceutical interest in these compounds is considerable, as many of these substances have been studied for application in medical, industrial and/or agricultural areas. The benefits of these compounds as natural sources for pesticides, pigments, plant growth regulators, biocontrol agents, antitumor or antimicrobial products are in continuous research. There are still not enough concluding data about the possible adverse effects that these compounds could pose to mammals or humans, when unintentionally exposed to them through the diet or the environment. However, the unintentional presence of these substances in feed or food a contaminants from the fermentation product could raise safety concerns. The absence of toxicological information does not mean absence of toxicity, and thus more research will be needed for the toxicological characterization of these compounds.

On the other hand, some of the substances found to be produced by fungi such as *Aspergillus niger*, *A oryzae* or *Fusarium venenatum* are well recognised mycotoxins, some of them already present in the current legislative frameworks. In these cases it is essential to obtain data about the genes involved in the biosynthetic pathways of these substances, as well as the culture conditions in which they are produced, in order to select the adequate strain and fermentation conditions that impair the production of these toxins. In this sense, it is common that industrial strains are genetically modified to avoid the expression of the genes responsible for the biosynthesis of mycotoxins.

A list of the 474 bioactive secondary metabolites produced by the microorganisms within the scope of this project that have been found during the literature search is presented in Appendix G. The 59 compounds selected for further searching are marked in bold.

3.3.1. Toxic secondary metabolites produced by fungi

In the present review, several mycotoxins and other toxic compounds have been found associated to the fungal species within the scope of this work. The most important and relevant facts in relation to the production of these substances are described below.

3.3.1.1. Substances produced by fungi not characterised in depth from a toxicological point of view

Several secondary substances produced by species of fungi used in industrial fermentations have been reported as toxic or potentially toxic substances, but still are not officially recognized as toxins and

[1] The databases CCRIS, CPDB and GENE-TOX are no longer updated

fwe information about their biosynthesis, production and toxicological data on humans and animals is available. Some characteristics of these compounds are summarised below:

3-Nitropropionic acid

3-nitropropionic acid is a mycotoxin that inactivates succinate dehydrogenase thus inhibiting mitocondrial respiration. It is a neurotoxin that induces rat striatal degeneration; systemic intoxication by 3-nitropropionic acid induces selective lesions of the striatum in most species. It can be used as an experimental pharmacological model of Huntington disease in rodents. Thus, many articles related to the mechanism of action underlying striatal lesions have been found.

In this project, 3-nitropropionic acid has been identified as a secondary metabolite of *A. oryzae*. Acute and subacute effects (5-days) were investigated in adult male Wistar rats after receiving 3-nitropropionic acid doses by i. p. route (Szabó *et al.*, 2005). Several neurological alterations and a significant decrease of the thymus weight were observed in the treated rats.

In another study, 3-nitropropionic acid was given by i.p. route to C57Bl/6 adult male mice in two different dose regimes: a low-dose (total dose of 340 mg/kg in 7 days) or a high-dose (total dose of 560 mg/kg in 7 days) (Fernagut *et al.*, 2002). The main objective of the study was to carefully characterise the motor disorder, its time course and the histopathological correlations. The low-dose regimen was not lethal but the high-dose regimen produced 37.5% of lethality to mice.

The effects of 3-nitropropionic acid were evaluated in males of four different mouse strains: BALB/c, C57BL/6, FVB/n and 129SVEMS mice (Gabrielson *et al.*, 2001). It was found that 3-nitropropionic acid induced brain and heart lesions and that cardiac pathology had a different degree depending on the strains; the follow up investigation on the biochemical mechanisms of cardiac toxicity suggested that the inhibition of the succinate dehydrogenase in heart mitochondria was also the cause.

Finally, acute intoxication of male and female adult Wistar rats was induced by the subcutaneous injection of 3-nitropropionic acid (20 mg/kg) once a day for 2 or 3 days (Nishino *et al.*, 1997). Intoxication produced motor symptoms and striatum-specific lesions; it also irreversibly increased astrocytic [Ca2+]i. The possible mechanisms conducting to astrocyte destruction are discussed in the article.

Andrastin A

Andrastin A is a farnesyltransferase inhibitor isolate from *Penicillium* species including *P. roqueforti* (Rasmussen *et al.*, 2011). Andrastin A inhibits the activity of the ras protein farnesyltransferase, and therefore these meroterpenoids are promising leads for anticancer drugs, since the farnesylation of the ras oncogene protein is essential for its function (Uchida *et al.*, 1996).

The first identification of the biosynthetic gene cluster for andrastins is based on genome database of *P. chrysogenum*. The cluster contains eleven genes, and nine of them are likely to be directly involved in the biosynthesis of andrastin A, the most complex andrastin molecule (Uchida *et al.*, 1996).

The industrial strains of *P. roqueforti* showed high levels of aspartylprotease AspA, whereas the culture collection strain showed barely detectable levels of this enzyme, as shown by proteolysis tests and by immunodetection with anti-AspA antibodies. The lipolytic activity was similar in the strains isolated from the three types of local blue cheeses (Fernández-Bodega *et al.*, 2009).

Andrastin A was produced by all strains analysed at different levels. *P. roqueforti* CECT 2905 showed high ability to synthesize this compound. Andrastin A was present in all industrial and local varieties of blue cheese.

A

ORF, Pc22g22XXX	Amino acids (base pairs)	Closest protein homologue	Similarity/identity (%)	Proposed function
820 (*adrA*)	512 (1744)	BDBG_03859 (*Ajellomyces dermatitidis*)	77/58	Cytochrome P450
830 (*adrB*)	213 (1162)	–	–	Hypothetical protein
840 (*adrC*)	1442 (4613)	ANI_1_1494064 (*Aspergillus niger*)	73/58	ABC transporter
850 (*adrD*)	2496 (7930)	AusA (*Aspergillus nidulans*)	69/54	Polyketide synthase
860 (*adrE*)	336 (1280)	PMAA_102060 (*Talaromyces marneffei*)	64/48	Ketoreductase
870 (*adrF*)	255 (949)	Trt9 (*Aspergillus terreus*)	81/67	Short chain dehydrogenase
880 (*adrG*)	325 (1073)	AusN (*Aspergillus nidulans*)	74/56	Prenyltransferase
890 (*adrH*)	451 (1643)	AusM (*Aspergillus nidulans*)	68/55	FAD-dependent monooxygenase
900 (*adrI*)	248 (803)	Trt1 (*Aspergillus terreus*)	66/45	Terpene cyclase
910 (*adrJ*)	498 (1556)	AOR_1_310024 (*Aspergillus oryzae*)	60/42	Acetyltransferase
920 (*adrK*)	277 (1060)	AusD (*Aspergillus nidulans*)	80/67	Methyltransferase

B

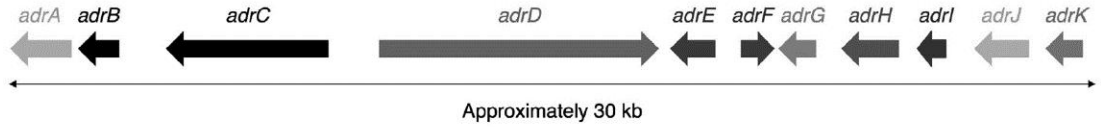

Figure 8: (A) Annotation of each protein in the *adr* gene cluster. Deduced function of each open reading fram (ORF) and amino acid sequence similarity/identity, compared with the closest homologues found by BLAST search at NCBI. (B) Schematic representation of the cluster. The direction of the arrow indicates the direction from the start to the stop codon (Matsuda *et al.*, 2013).

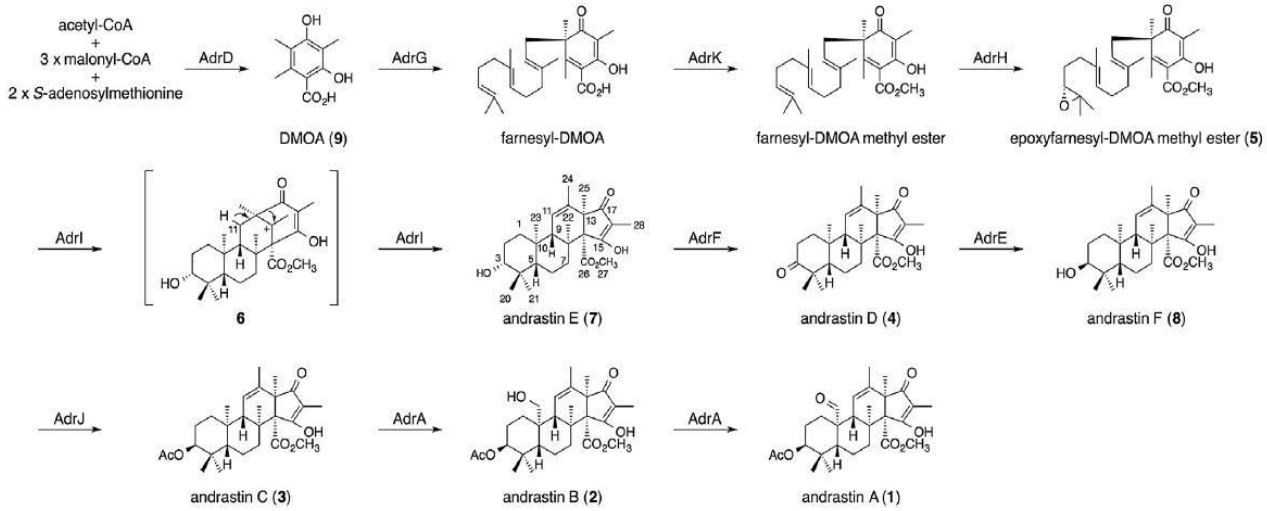

Figure 9: Proposed biosynthetic pathway of andrastin A (Matsuda *et al.*, 2013).

Aristolochene

Aristolochene is a sesquiterpene biosynthesized from farnesyl pyrophosphate by aristolochene synthase and is the precursor of a range of sesquiterpenoid toxins produced by filamentous fungi (Hohn *et al.*, 1991), including PR-toxin produced by *P. roqueforti*.

Asperparalines

Asperparalines A, B and C, were isolated from okara (the insoluble residue of whole soybean) that had been fermented with *A. japonicus* JV-23, and they were shown to have paralytic activities in silk worms (Hayashi *et al.*, 1997 and 2000). More recently, it has been demonstrated that asperparaline A selectively blocks insect nicotinic acetylcholine receptors (Hirata *et al.*, 2011).

No standard toxicity studies have been found in this review.

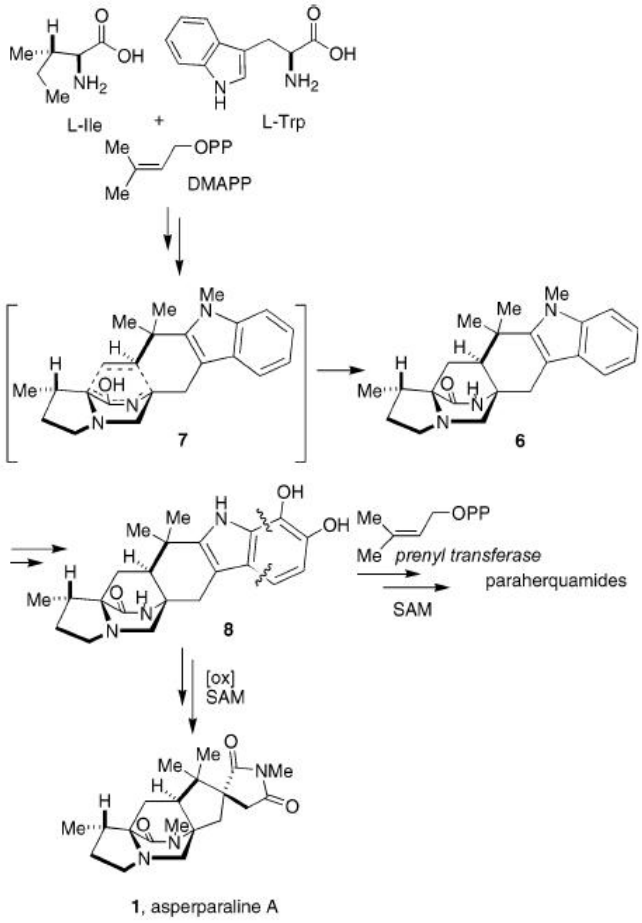

Figure 10: Studies on the biosynthesis of Asperparaline A: Origin of the Spirosuccinimde Ring System (from Gray *et al.*, 2003).

Citreoviridin

Citreoviridin A is a mycotoxin found in cereal and bread grains. It exhibits pro-oxidative, anticancer chemotherapeutic, antibacterial, antifungal, and antiviral activities. *In vitro*, citreoviridin A increases ROS levels and decreases glutathione, inducing oxidative stress, destabilizing the lysosome and mitochondria and causing DNA damage.

It is a neurotoxin, acutely toxic to mice, with intraperitoneal and oral LD_{50} of 7.5 mg/kg and 20 mg/kg respectively (Ueno and Ueno, 1972).

Culmorin

The sesquiterpene culmorin was first isolated by Ashley*et al.* (1937) from *Fusarium culmorum*. It has been shown to be produced also by *F. venenatum* (Greenhalgh *et al.*, 1984; Lauren *et al.*, 1992; Miller and MacKenzie, 2000). This compound has been detected in cereals.

Strongman *et al.* (1987) showed the antifungal activity of culmorin against a variety of marine and medically relevant fungi. The only reported study on the toxicity of culmorin in mammals was published by Rotter *et al.* (1992). Culmorin has a low toxicity in several biological assays (Pedersen and Miller, 1999) but a synergistic effect with deoxynivalenol has been demonstrated (Dowd *et al.*, 1989)

Cyclopenol

Cyclopenol is a benzodiazepine metabolite produced in several species of *Penicillium*. It displays antimicrobial and phytotoxic properties.

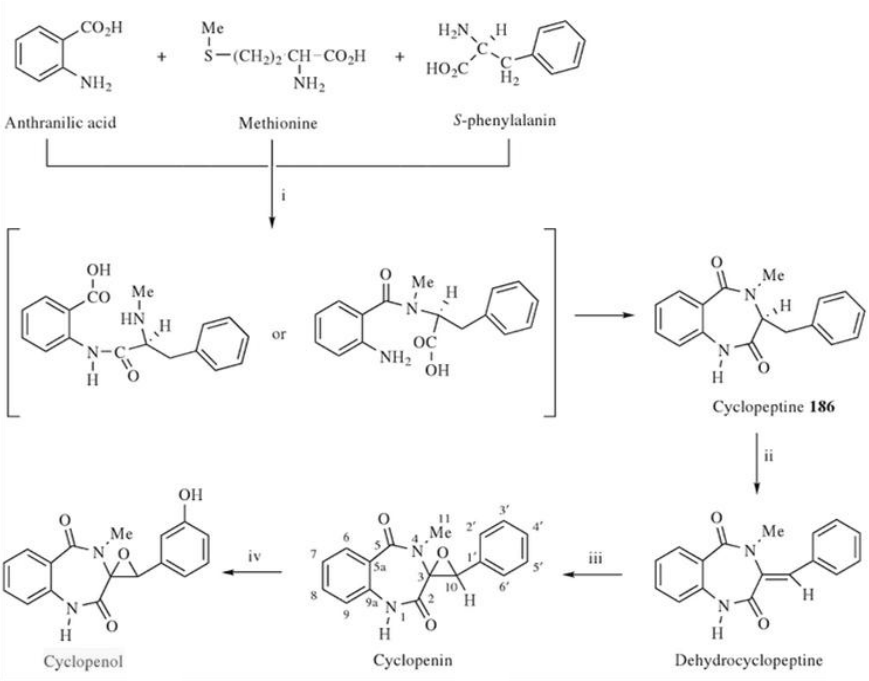

Figure 11: Biosynthetic pathway to cyclopenin and cyclopenol (modified from Diana P and Cirrincione G. Biosynthesis of Heterocycles: From Isolation to Gene Cluster. Wiley, 2015)

Cyclopiazonic Acid (α-cyclopiazonic acid)

Cyclopiazonic acid (CPA) is a mycotoxin produced by the genera *Aspergillus* and *Penicillium* whic has been shown to be toxic in several animal species including swine, chickens, turkeys, guinea pigs, rats, and dogs.

CPA may be produced by the same species that produce aflatoxins. No standard toxicity studies have been found in this revision, apart from some in vitro cytotoxicity studies in porcine lymphocytes or human cells. A discussion on the article regarding safety assesssment of the CPA that had been published by Burdock and Flamm in 2000 has been found (De Waal, 2002).

Cyclopiazonic acid is an indole-tetramic acid mycotoxin and it has been reported to be produced by *A. oryzae* and *P. camembertii*, both species used in food fermentation (Bockelmann *et al.*, 1999; Chang *et al.*, 2009; Shimada *et al.*, 2000)

There have been identified three clustered biosynthetic genes in *A. flavus* and closely related *A. oryzae* (Chang *et al.*, 2009; Tokuoka *et al.*, 2008)

The toxicity of CPA is attributed to its ability to alter normal intracellular calcium flux through the specific inhibition of sarcoplasmic or endoplasmic reticulum calcium-dependent ATPase (SERCA) essential for calcium uptake as in the muscle contraction-relaxation cycle, which results in increased muscle contraction.

Regarding the biosynthesis, it has been reported that the gen cluster involved in CPA biosynthesis is adjacent to the aflatoxin gene cluster (Chang *et al.*, 2009) and that the dimethylallyl-cycloacetoacetyl-L-tryptophan synthase (DCAT-S) gene from an *A. oryzae* is involved in the CPA production, as disruption of this gene resulted in the loss of production of this toxin.

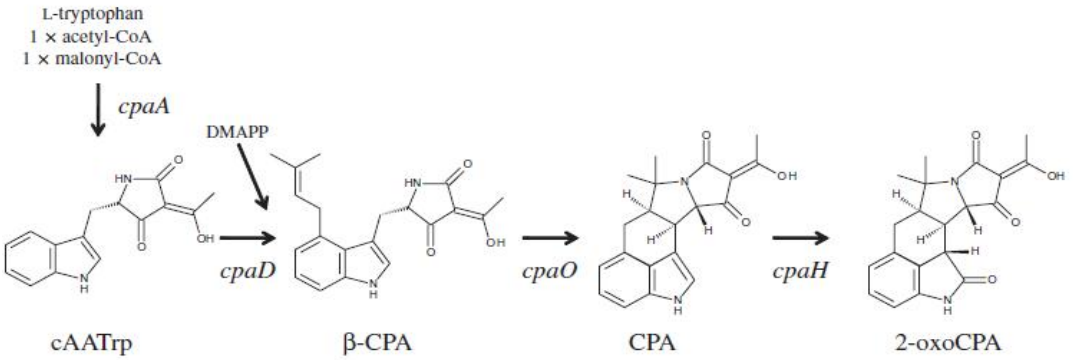

Figure 12: Cyclopiazonic Acid Biosynthesis Gene Cluster in *A. oryzae*. Structures of the intermediates in the biosynthetic pathway of 2-oxocyclopiazonic acid (2-oxoCPA) in *A. oryzae*. Genes in CPA cluster corresponding to each pathway are described beside arrows. Abbreviations: cAATrp, cyclo-acetoacetyl-L-tryophan; B-CPA, B-cyclopiazonic acid; CPA, cyclopiazonic acid; 2-oxoCPA, 2-oxocyclopiazonic acid; DMAPP, dimethylallyl diphosphate) (from Shinohara *et al.*, 2011)

These authors reported that the co-localization of the two gene clusters explains why strains of *A. flavus* and *A. oryzae* have different abilities to produce aflatoxin and CPA. This understanding has significant health implications. The genetic diversity of *A. flavus* and *A. oryzae* in the region adjoining the CPA gene cluster suggests a divergence of *A. flavus* from *A. oryzae*. The conclusion is that *A. oryzae* most likely descended from an ancestor that was the precursor of the *Aspergillus* SBG variant, while *A. flavus* descended from a precursor of *A. parasiticus* (Chang *et al.*, 2009).

Regarding *A. niger*, it has been reported that it can be modified by mutagenesis, resulting in the deletion of gene clusters required for the synthesis of this mycotoxin (EFSA Journal 2014b).

Isotrichodermin/Isotricodermol

These compounds belong to the class of organic compounds known as trichothecenes. These are sesquiterpene mycotoxins structurally characterized by the presence of an epoxide ring and a benzopyran derivative with a variant number of hydroxyl, acetyl, or other substituents. The most important structural features causing the biological activities of trichothecenes are the 12,13-epoxy ring, the presence of hydroxyl or acetyl groups at appropriate positions on the trichothecene nucleus and the structure and position of the side-chain.

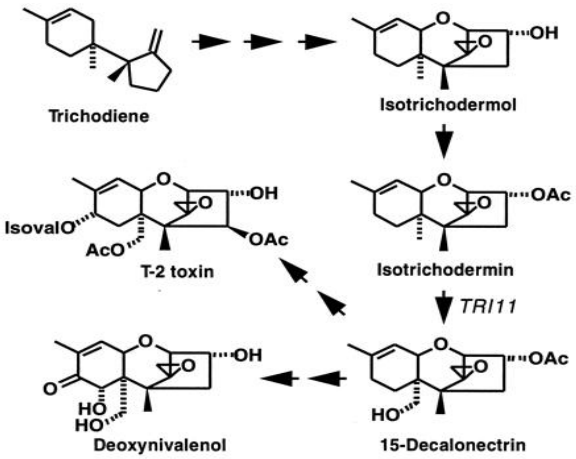

Figure 13: Trichothecene pathway (from Alexander NJ *et al.*, 1998)

Kojic acid

Kojic acid is produced by several *Aspergillus* and *Penicillium* species. It is a tyrosinase inhibitor thus inhibiting the production of pigments in animals and vegetables. Among other applications, it is used as a food additive to avoid browning of vegetables and crustaceans, and as a cosmetic ingredient for skin lightening. It was evaluated by the IARC and classified in the Group 3 *not classifiable as to its carcinogenicity to humans,* due to inadequate evidence in humans and limited evidence in experimental animals (IARC, 2001).

In this project, kojic acid has been identified as a secondary metabolite of *A. oryzae* (Chaves *et al.*, 2012) and three reports giving information on toxic effects of this compound have been retrieved.

In a 55-week chronic toxicity study performed on male F344/DuCrj rats, kojic acid was given at 0 (control group), 0.5% and 2% in the diet (Ota *et al.*, 2009). Dose-dependent toxic effects were observed in liver, kidney, thyroids and adrenals, with very significant differences at the highest dose. A no observed adverse effect level (NOAEL) below 0.5%, which is equivalent to 227 mg/kg body weight/day in male rats, was determined.

In a 26-week chronic toxicity study performed on male heterozygous p53-deficient CBA [p53(+/–)] mice and wild-type [p53(+/+)] mice, kojic acid was given at 0 (control group), 1,5% and 3% in the diet, and the tumorigenic potential in the thyroids and the liver was determined (Takizawa *et al.*, 2003). It was observed that kojic acid induced diffuse hypertrophy and hyperplasia of thyroid follicular epithelial cells with decreased serum thyroxine levels in both p53 (+/-) and p53 (+/+) mice, but caused no thyroid tumors. In the liver, the incidence of altered hepatocellular foci and hepatocellular adenomas was significantly increased, and the heterozygous p53 (+/-) mice appeared to be more susceptible in terms of the tumorigenic dose of kojic acid, with a greater prevalence of hepatic proliferative lesions. Thus, the contribution of genotoxicity on hepatocellular tumor development could not be ruled out.

Finally, a thorough investigation, under Good Laboratory Practice (GLP) conditions, of the genotoxicity and general toxicity of kojic acid, has been performed in order to estimate a margin of safety for topical exposure in humans to this compound (Nohynek *et al.*, 2004). The authors concluded that the genotoxic risk for humans using kojic acid as a skin lightening agent is negligible, and is in any case much less than from exposure to kojic acid from fermented foods. They also pointed out that the data obtained also suggested that consumer exposure from fermented foods does not pose a significant risk to human health.

Malformins

Malformins are a group of secondary metabolites originally discovered and isolated from culture filtrate of the fungus *A. niger* (Blumenthal, 2004).

No standard toxicity studies have been found in this review. The only *in vivo* study in which some toxicological endpoints were evaluated (Wang *et al.*, 2015) in BDF1 mice concluded that malformin C has potent cell growth inhibition activity, but the therapeutic index is too low to be an anti-cancer drug.

Some of the compiled articles evaluated malformins for their potential therapeutic properties (anti-cancer, fibrinolytic, anti-HIV and antimicrobial activities). Three different types of malformins (A, C and E) have been studied.

An LD_{50} (3.1 mg/kg, i.p, mouse) (from 1975) has been found in ChemIDplus database.

Maltoryzine

This compound was first isolated from the culture broth of a strain of *A. oryzae* (Blumenthal, 2004). No standard toxicity studies have been found in this review. The only original document reporting toxic effects found is a study from 1962 (Iizuka *et al.*, 1962).

An LD_{50} (> 3mg/kg, i.p, mouse) (from 1969) has been found in ChemIDplus database.

Mycophenolic acid

Mycophenolic acid (MPA) is a toxic metabolite produced by many *Penicillium* species such as *P. stoloniferum*, *P. viridicatum*, *P. brevicompactum*, *P. carneum*, *P. raciborskii* and some strains of *P. roqueforti*. Mycophenolic acid (MPA) is an approved therapeutic drug used as an immunosuppressant and numerous articles devoted to its therapeutic effects have been found. Its main mechanism of action is related to a reversible inhibition of inosine monophosphate dehydrogenase. More toxicological data can be obtained from its preclinical and clinical assessment, mainly from mycophenolate mofetil, which is its prodrug.

In this review, it has been found two reports on developmental defects in zebrafish embryos have been retrieved. Morphological defects including tail curvature and severe pericardial edema in zebrafish embryos were found in a dose-dependent manner (3.7-11.1 µmol/L). The teratogenic index (25% lethal concentration value (LC25)/no observed adverse effect level ratio) was 16, which indicated mycophenolic acid as a teratogen (Jiang *et al.*, 2016). In a second study (Schmidt *et al.*, 2013) in which MPA was evaluated at concentrations of 0.1; 0.25; 0.5; 0.75 mg/ L (0.31; 0.78; 1.56; 2.34 µM), all zebrafish embryos showed dysmorphic changes at 0.75 mg MPA/ L medium. Embryos exposed to 0.25 mg MPA/ L medium showed impaired development of nerves, and at 0.1 mg/ L, no effects were detectable.

Other report with preliminary toxicity assessments, such as cytotoxicity in zebrafish, mechanistic information related to damage of insulin-secreting cells of MPA or gastrointestinal tract toxic effects in rats have been found. A recent review providing an update of the literature on the pharmacology and toxicology of the prodrug of MPA, mycophenolate, in organ transplant recipients has been found (Staatz and Tett, 2014).

Some information (updated in 1995) related to its genotoxic effects can be found in CCRIS and GENE-TOX databases (see Appendix C). No conclusions were obtained from an Ames test from 1978, and negative results have been found in an Ames test (from 1983) performed with TA98 and TA100 *Salmonella typhimurium* strains in presence of metabolic activation. Negative results were obtained in Rec-assay (from 1981), while positive results were obtained in a chromosome aberrations test performed in vitro (from 1981).

Various LD_{50} (all previous to 1983) in different animal species and with different routes of exposures are collected in ChemIDplus database (see Appendix C).

In this review, reports have been found on the production of MPA in blue-veined cheeses due to the fact that *P. roqueforti* (a producer of MPA) is used in the production of this type of cheeses (Malekinejad *et al.*, 2015).

Naphtho-γ-pyrones

These compounds have been associated with *A. niger* and are defined as a group of aromatic compounds able to cause central nervous system signs in albino mice and rats leading to death when dosed intaperitonially (Blumenthal, 2004).

No standard toxicity studies have been found in this review. It is a generic name of naturally-occurring structurally-related compounds.

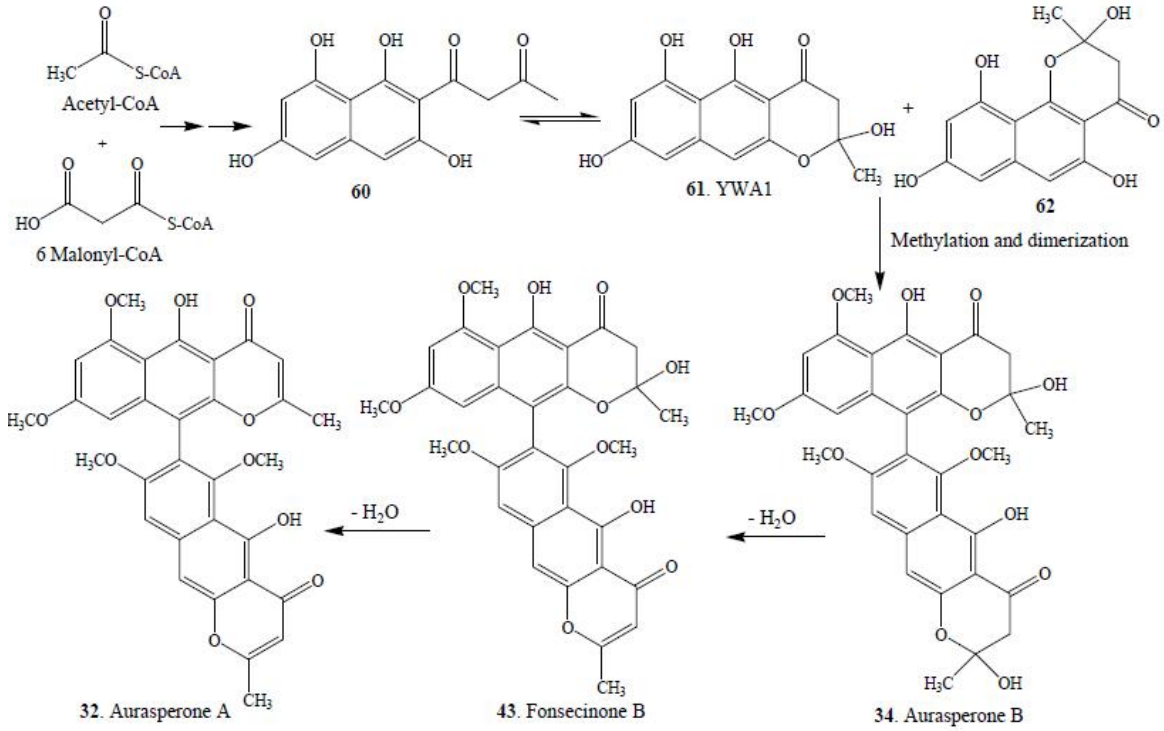

Figure 14: Proposed biosynthetic pathway of asperpyrone-type bis-naphtho-γ-pyrones in *A. niger*. (from Lu *et al.*, 2014)

Neoxaline

This compound has been described as an alkaloid produced by *A. japonicus* (Hirano *et al.*, 1969). No standard toxicity studies have been found in this review. An LD_{50} (> 200 mg/kg, i.p, mouse) (from 1979) has been found in ChemIDplus database.

Neoxaline has been reported to have antiproliferative activity (in an MTT assay) and arrest the cell cycle at the G2/M phase in Jurkat cells (Koizumi *et al.*, 2004)

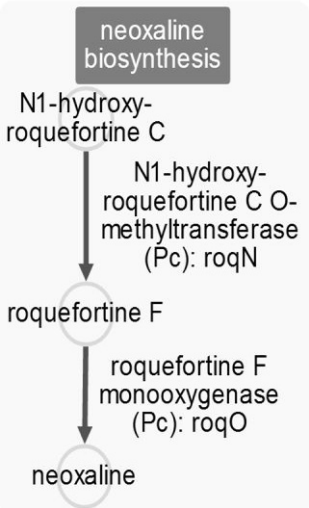

Figure 15: Biosynthetic pathway of neoxaline. From Caspi *et al.*, 2014, "The MetaCyc database of metabolic pathways and enzymes and the BioCyc collection of Pathway/Genome Databases, "*Nucleic Acids Research* 42:D459-D471.

Nigerazines

Nigerazines were first isolated by Iwamoto *et al.* (1983, 1985) from *A. niger* and found to inhibit root growth of lettuce seedlings. Nigerazines can be extracted from the mycelia of *A. niger* (Iwamoto *et al.*, 1983). Acute toxicity (LD_{LO}) in mice was determined to be 75 ~ 150 mg/kg.

Nigragillin

This toxin was obtained in 1969 by Caesar *et al.* as a fungal alkaloid from the *A. niger* group. It can be extracted from culture filtrate and was demonstrated to be toxic to silkworm larvae (Isogai *et al.*, 1975). The compound was also found to be produced by *A. phoenicis* which is a species of Aspergilli Section Nigri (Cole and Cox, 1981).

Orlandin

This compound has been identified as a secondary metabolite produced by *A. niger* together with other toxins, such as fumonisin B 2 (Sørensen *et al.*, 2009). No standard toxicity studies have been found in this review, an LD_{50} (> 125 mg/kg, oral, chicken) (from 1979) has been found in ChemIDplus database.

Oxalic acid

Oxalic acid is a toxic organic compound found in certain plants and natural sources. Although there have been reports of oxalic acid poisoning involving the consumption of food, toxicological effects in humans are relatively uncommon but include gastrointestinal effects, hypocalcemia secondary to calcium oxalate crystal formation and renal toxicity. *A. niger* is associated with pulmonary oxalosis consisting of calcium oxalate crystals, which generate local oxidants that cause cell injury (Blumenthal, 2004).

In this review, no standard toxicity studies have been found. Some information related to its genotoxic effects can be found in CCRIS (updated for this compound in 2006). Three different Ames tests (from 1987, 1988 and 1997) were negative with and without metabolic activation using different bacteria strains (*S. typhimurium*: TA 97, TA 98, TA 100, TA 102, TA 104, TA 1535, TA 1537, *E.coli*: WP2 UVRA,

WP2 UVRA/PKM101). A previous study from 1983 cited by the National Toxicology Program (NTP) also reported negative results for the Ames test.

Another study from the NTP (1985) in which the effects of oxalic acid on reproduction and fertility were assessed in CD-1 mice via drinking water concluded that oxalic acid is a reproductive toxicant in Swiss mice at concentrations that reduce parental water consumption, but that cause few other somatic effects.

Various LD_{50} (previous to 1990) in different animal species and with different routes of exposures are collected in ChemIDplus database (**see Appendix C**). The LD_{50} ranged from 112 mg/kg in cats (subcutaneous administration) to 7500 mg/kg in rats (oral administration). In humans, a lethal dose of 600 mg/kg was reported in 1980 (females).

Several occupational limit values have been established by different occupational safety organizations (information in HAZ-MAP database).

The production of oxalic acid in *A. niger* involves the enzyme oxaloacetate acetylhydrolase (Ruijter *et al.*, 1999), but a second pathway that has been elucidated demonstrates the production of oxalate from pentoses via glycolate and glyoxylate as intermediates. There are several reports that provide the optimised parameters for transformation of different substrates, including wastes containing free glucose or sugars to oxalic acid by *A. niger* strains (Mandal and Banerjee, 2005; Cameselle *et al.*, 1998)

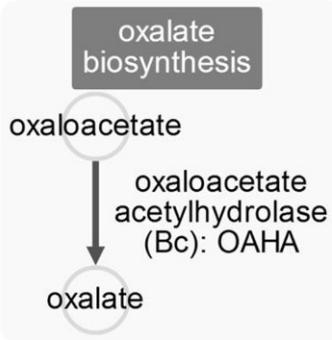

Figure 16: Biosynthetic pathway of oxalic acid (oxalate). From Caspi *et al.*, 2014, "The MetaCyc database of metabolic pathways and enzymes and the BioCyc collection of Pathway/Genome Databases, "*Nucleic Acids Research* 42:D459-D471.

Perinadine A

Perinadine A is an alkaloid isolated from *P. citrinum* in 2006 (Sasaki M *et al.*, 2005). No standard toxicity studies have been found. No data were available for this compound in any of the databases consulted.

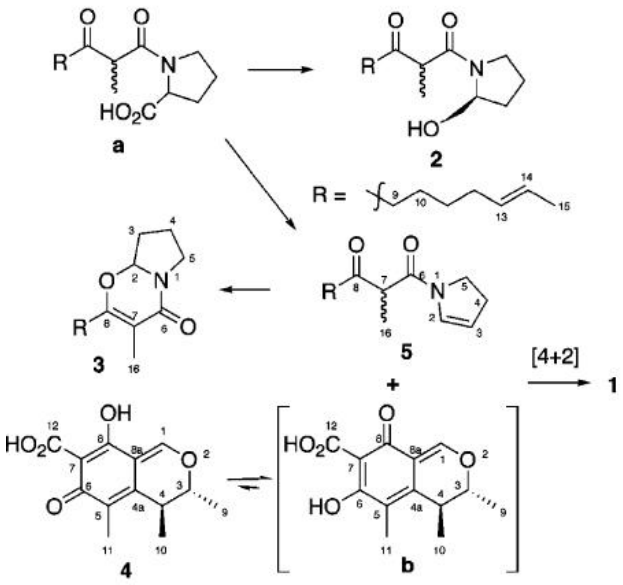

Figure 17: Synthesis of perinadine A. Perinadine A (1) may be derived from a known pyrrolidine alkaloid (5) isolated from *P. brevicompactum* and citrinin (4), a well-known mycotoxin. An intermediate a, which may be derived from glutamic acid or proline and a pentaketide, are considered to be converted into 5 by decarboxylation at C-16. Intermolecular cyclization between 5 and an intermediate b equal to citrinin (4) may give perinadine A (1). On the other hand, scalusamide A (2) may be generated from a through reduction of the carboxyl Group at C-16, while pyrrolo[2,1-*b*]oxazines (3) is likely to be converted from 5 through Michael-type cyclization between C-2 and a carbonyl oxygen at C-8 (from Sasaki *et al.*, 2005).

PR-toxin

This compound produced by *P. roqueforti* is a sesquiterpenoid mycotoxin. PR-toxin produced acute toxic effects in animals via an increase of capillary permeability and direct damage to lungs, heart, liver and kidneys.

In this review no standard toxicity studies have been found. Some studies evaluating the effects on health status and animal performance found that PR-toxin did not affect rumen fermentation pattern (Gallo *et al.*, 2015; Gallo *et al.*, 2015b)

PR-toxin selectively exhibited cytotoxic activity towards certain cancer cell lines (Darsih *et al.*, 2015) and Caco-2 cells (Rasmussen *et al.*, 2011). Some information related to its genotoxic effects can be found in CCRIS (updated in 1994) and GENE-TOX (updated in 1998) databases. PR-toxin gave positive Ames tests with TA 98 and TA100 strains. Positive results were also obtained in Rec-assay in *Bacillus subtilis* and gene conversions assays in *Saccharomyces cerevisiae* and *Neurospora crassa*.

Various LD_{50} (previous to 1990) in rodents and with different routes of exposures are collected in ChemIDplus database. The LD_{50} ranged in mice from 2 mg/kg (intravenous and intraperitoneal administration) to 72 mg/kg in after oral administration. In rats, LD_{50} ranged from 8.2 mg/kg (intravenous) to 11.6 mg/kg (intraperitoneal). A LD_{LO} of 115mg/kg has been reported in rats.

There have been reported the conditions of PR-toxin production, which only happens in stationary cultures, within the pH range of 4.5-9.0 and temperature range of 10º-30ºC with the optimum temperature at 24ºC. In the database it is also included the PR-toxin biosynthetic pathway by *P.roqueforti*, through the action of aristolochene synthase.

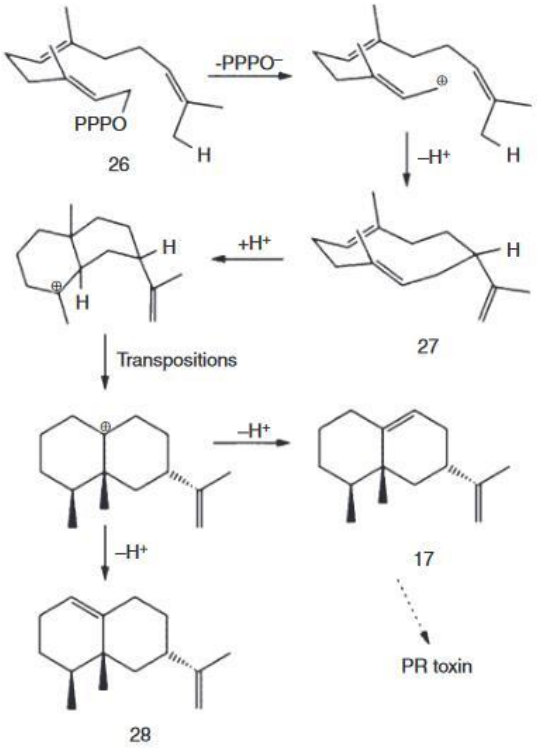

Figure 18: Biogenesis of volatile sesquiterpenes involved in the pathway of PR-toxin in toxic strains of P. roqueforti. [farne-syl pyrophosphate (26); aristolochene (17); AS enzyme with germacrene A (27), valencene (28)] (from Mioso et al., 2015)

Roquefortine C

Roquefortine C is a neurotoxic mycotoxin derived from the diketopiperazine cyclo (Trp-dehydro-His) that causes a paralytic syndrome. Its mechanism of action is unknown but it can interact with cytochrome P450 and other haemoproteins (Aninat *et al.*, 2001). It can also activate P-glicoprotein transport system (Aninat *et al.*, 2005).

Roquefortine-type alkaloids are produced by several *Penicillium* species including species of industrial applications such as *P. roqueforti* (Sumarah *et al.*, 2005) and *P. chrysogenum* (Bringmann *et al.*, 2005).

P. roqueforti roquefortine cluster contains only four genes (rds, rdh, rpt, and gmt) encoding the roquefortine dipeptide synthetase, roquefortine D dehydrogenase, roquefortine prenyltransferase, and a methyltransferase, respectively.

Silencing of the *rds* or *rpt* genes by the RNAi strategy reduced roquefortine C production by 50%, confirming the involvement of these two key genes in roquefortine biosynthesis.

P. roqueforti lacks the genes that encode the enzymes for the conversion of roquefortine C to roquefortine L (or glandicoline A) and meleagrin, a difference between other *Penicillium* species with the same gene cluster as *P. chrysogenum.*

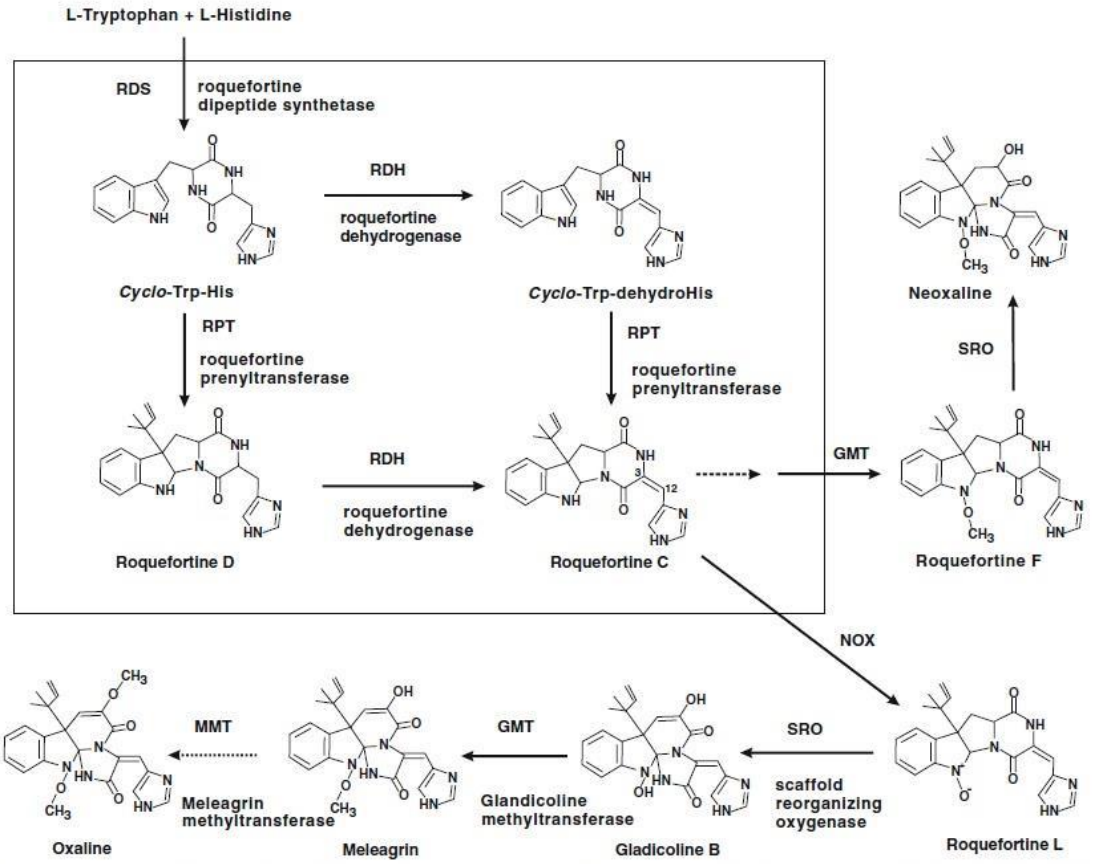

Figure 19: Biosynthetic pathways of roquefortine C. The meleagrin pathway (from roquefortine C) is shown below and the neoxaline branch on the right side. The putative conversion of meleagrin into oxaline is indicated by a dashed arrow at the left side below the box. This conversion is catalyzed by a second methyltransferase (MMT, meleagrin methyl transferase) (from Martín *et al.*, 2016)

Derivatives of roquefortine

- **Isofumigaclavine A** and **B**: Isofumigaclavine A is another alkaloid produced by *P.roqueforti*. This toxin and the product of its hydrolysis, isofumigaclavine B, are identical with roquefortines A and B, respectively.
- **Festuclavine** and **Marcfortine A**: Festuclavine is an intermediate metabolite for the synthesis of ergot alkaloids and Marcfortine A is clavine alkaloid toxins produced by *P. roqueforti.* No standard toxicity studies have been found in this review; however, Marcfortine has been reported to have a potent antihelmintic activity.
- The mitorubrins are a unique subclass of azaphilones (Marsini *et al.*, 2006) isolated from a variety of fungal species. In this review, **mitorubrinic acid** has been identified in the fermentation broth of *P. funiculosum*, together with other bioactive metabolites (Lesová *et al.*, 2001). No standard toxicity studies have been found in this review. It is a polyketide and has been considered, together with mitorubrinol, as virulence factors of *P. marneffei* (Marsini *et al.*, 2006). A recent review was done by Tam EW *et al.*, 2015.

Sambucinol

This is a trichothecene metabolite produced by several species of *Fusarium* such as *F. venenatum*. The metabolic route of this compound has been studied and postulated that 2a-hydroxytrichodiene is the first oxygenated step in its biosynthesis (Zamir et al. 1999).

Secalonic acid D

Secalonic acid D (SAD), a metabolite of *P. oxalicum*, although it has been reported that can be produced by *A. aculeatus* (Gao *et al.*, 2014).

In this review, no standard toxicity studies have been found. However, some mechanistically-relevant articles and reviews have been retrieved from the systematic search. Secalonic acids, mainly secalonic D, have been evaluated for potential anticancer activity in vitro (antiangiogenic activity, cytotoxicity, ABCG2 downregulation, cell signaling disruption, DNA topoisomerase I inhibitor, apoptosis, cell cycle arrest at G1). In vivo, a preliminar preclinical validation and mechanistic definition of the antiangiogenic activity of secalonic acid D with potential application as a cancer-selective therapeutic agent was carried out. Treatment of SAD at all experimental doses was nontoxic in solid tumor model animals (mice) as no mortality (0/7) occurred during the course of the experiment (Guru *et al.*, 2015).

Secalonic A has shown to antagonize the cytotoxicity of colchicine in the rat cortical neurons through inhibition of phosphorylation of JNK and p38 MAPKs, calcium influx, and the activation of caspase-3.

Another set of articles found focused on unraveling the mechanism of teratogenesis (cleft palate induction) of SAD in mice.

Some information related to genotoxic effects of secalonic acid D can be found in CCRIS (updated in 1993) and GENE-TOX (updated in 1995) databases: negative results with and without metabolic activation were obtained in an Ames test (TA 100) (study from 1992). No conclusions were drawn from a previous study performed in 1978.

An LD_{LO} (15.6 mg/kg, mouse, intraperitoneal) (from 1952) has been found in ChemIDplus database.

Trichordermin

As mentioned in the previous section, Trichodermin is a trichothecene (4β-acetoxy-12, 13-epoxy-Δ9-trichothecene). A review of the understanding of the relationship between structure and known function of these compounds has been found (Alexander NJ *et al.*, 1998). No standard toxicity studies have been found in this review. Some reports evaluated trichordermin for its potential therapeutic effects as antifungal or antitumoral.

An LD_{50} (500 mg/kg, mouse, intraperitoneal and subcutaneous) (from 1986) have been found in ChemIDplus database.

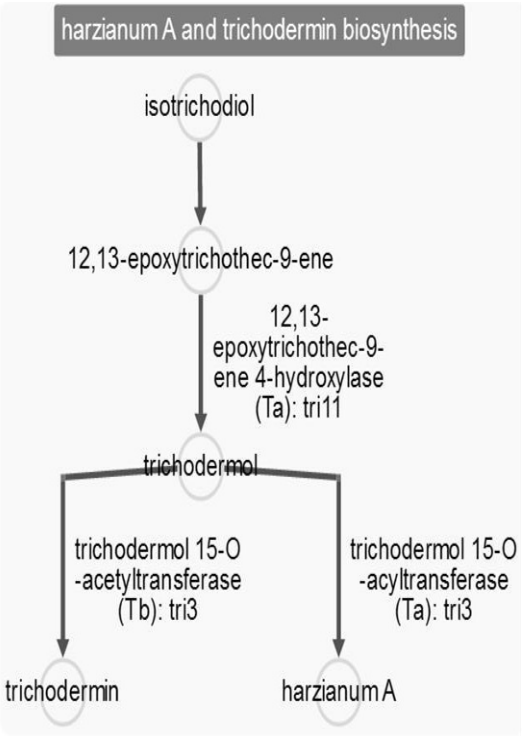

Figure 20: Biosynthetic pathway of trichodermin. From Caspi *et al.*, 2014, "The MetaCyc database of metabolic pathways and enzymes and the BioCyc collection of Pathway/Genome Databases, "*Nucleic Acids Research* 42:D459-D471.

Trichorzin

This substance reported as a mycotoxin by Bisht *et al.* 2011, belongs to a peptaibol family and has been studied for different functionalities as calcitonin (CT) agonist (Katayama et al. 2001) and antibiotic activity against phytopathogenic fungi as well as several bacteria (Bisht et al. 2011).

Xanthomegnin

This compound has been identified as a secondary metabolite of *A. melleus* (Neidig *et al.*, 2013).

Xanthomegnin has shown to have potent inhibitory activity in the inducible nitric oxide synthase (iNOS) assay (Alvi *et al.*, 2000). No standard toxicity studies have been found in this review.

This compound has been studied in the past. No teratogenic effects were observed in ICR mice (Bolin *et al.*, 1991) and it has been proposed has a potential genotoxic (Carlton *et al.*, 1976; Mori *et al.*, 1983). Some hepatic alterations alterations produced in mice by xanthomegnin were evaluated in 1976 (Carlton *et al.*, 1976)

3.3.1.2. Toxic substances produced by fungi fully characterised from the toxicological point of view (Appendix E)

There are several recognised toxic compounds, some of them legislated under European regulations for food and feed and that have been reported to be produced by species of fungi used in industrial fermentations. Some of their characteristics and biosynthesis are described below.

Aflatoxins

Aflatoxins are one of the main mycotoxins, produced by some species of *Aspergillus* Section Flavi.

Aflatoxin B1 is the most common in food and widely studied mycotoxin. It is produced primarily by the two species: *A. flavus* and *A. parasiticus,* which are especially found in areas with hot and humid climates. *A. flavus* is ubiquitous, favouring the aerial parts of plants (leaves, flowers) and produces B aflatoxins. *A. parasiticus* produces both B and G aflatoxins. Aflatoxins are classified by the International Agency for Research on Cancer in the Group 1 "carcinogenic to human", producing liver cancer (IARC, 2012). Aflatoxins are also considered as "known to be human carcinogens" by the NTP (2016).

Based on the existing evidence related to the toxicological effects of these mycotoxins, The European Regulation (EC) 1881/2006 and its modifications have established maximum permitted levels in certain foodstuffs, such peanuts, pistachios, tree nuts, cereals, maize, rice and milk.

The section Flavi of genus *Aspergillus* also includes *A. oryzae* and *A. sojae*, which are used for the production of various industrial enzymes and fermented foods in eastern Asia. Although is generally recognized by the scientific community that *Aspergillus oryzae* and *A. sojae* do not produce aflatoxins, some controversy has arisen in the past from reports by some authors (Atalla *et al*., 2003). These fungi are taxonomically similar to aflatoxin-producing species; therefore, it is necessary to determine whether these strains have the potential to make toxins.

Amadi and Adeniyi (2009) reported the production of aflatoxin B1 from *A. oryzae* isolated from stored grains (rice, maize and millet), that was determined by thin layer chromatography (TLC).

In this review, it has been found several reports (Matsushima *et al*., 2001; Kim *et al*., 2014) that described the natural mutations in the *afl*R gene (main transcriptional regulator of aflatoxin biosynthesis) that many strains of *A. oryzae* and *A. sojae* have and that prevents theses microorganisms from producing aflatoxins.

The main conclusion from this data is that *afl*R gene could be examined to assess possible aflatoxin production by industrial strains within the group *Aspergillus* section Flavi.

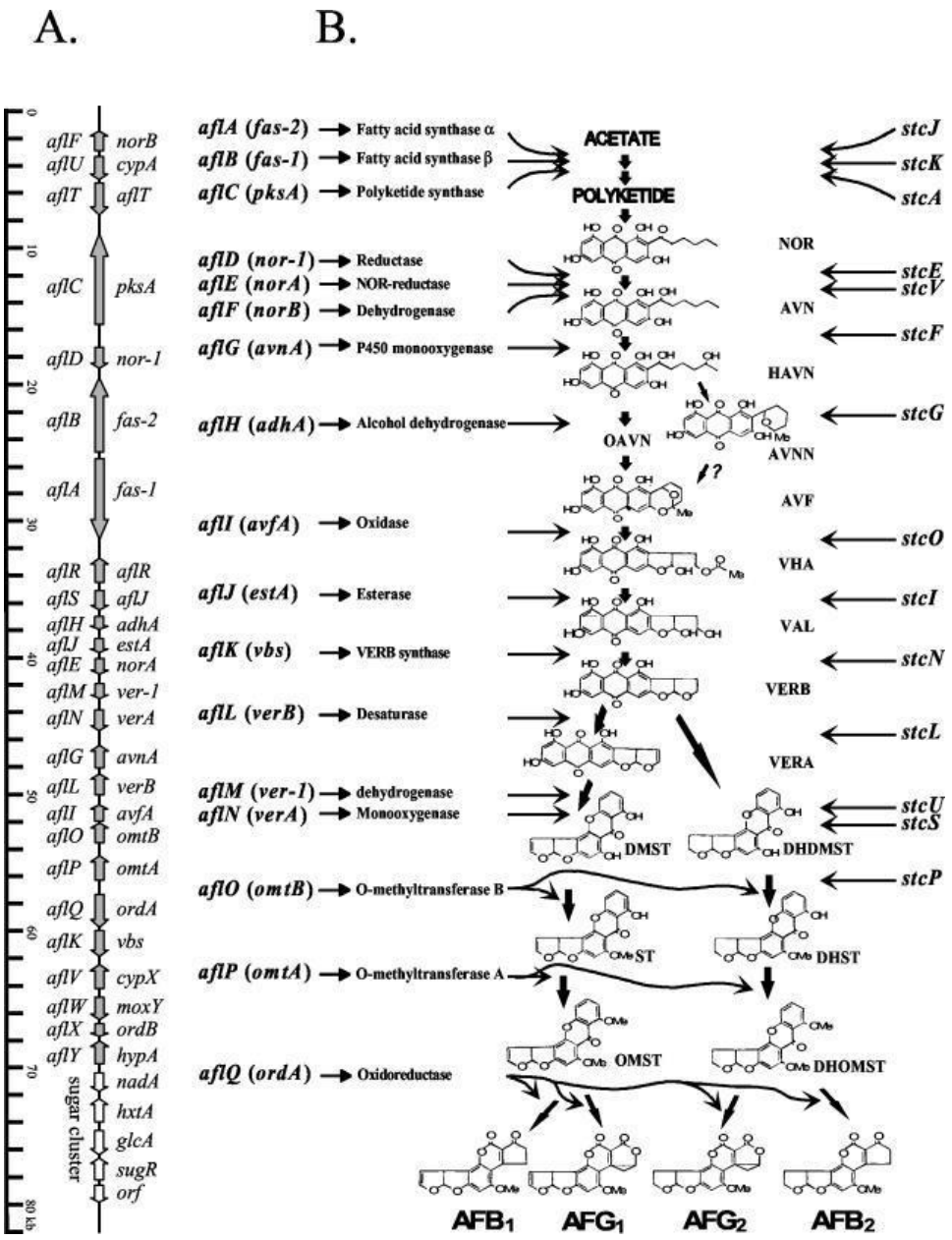

Figure 21: Clustered genes (A) and the aflatoxin biosynthetic pathway (B). The generally accepted pathway for aflatoxin and ST biosynthesis is presented in panel B. The corresponding genes and their enzymes involved in each bioconversion step are shown in panel A. The vertical line represents the 82-kb aflatoxin biosynthetic pathway gene cluster and sugar utilization gene cluster in *A. parasiticus* and *A. flavus*. The new gene names are given on the left of the vertical line and the old gene names are given on the right. Arrows along the vertical line indicate the direction of gene transcription. The ruler at far left indicates the relative sizes of these genes in kilobases. The ST biosynthetic pathway genes in *A. nidulans* are indicated at the right of panel B. Arrows in panel B indicate the connections from the genes to the enzymes they encode, from the enzymes to the bioconversion steps they are involved in, and from the intermediates to the products in the aflatoxin bioconversion steps. Abbreviations: NOR, norsolorinic acid; AVN, averantin; HAVN, 5′-hydroxyaverantin; OAVN, oxoaverantin; AVNN, averufanin; AVF, averufin; VHA, versiconal hemiacetal acetate; VAL, versiconal; VERB, versicolorin B; VERA, versicolorin A; DMST, demethylsterigmatocystin; DHDMST, dihydrodemethylsterigmatocystin; ST, sterigmatocystin; DHST, dihydrosterigmatocystin; OMST, O-methylsterigmatocystin; DHOMST, dihydro-O-methylsterigmatocystin; AFB1, aflatoxin B1; AFB2, aflatoxin B2; AFG1, aflatoxin G1; AFG2, aflatoxin G2 (from Yu *et al.*, 2004)

Beauvericin and Enniatins

These secondary metabolites are produced by *Fusarium* species, typical mycotoxin producing fungi. They are predominantly found in cereal grains and their products.

Beauvericin and enniatins possess a wide range of biological activities. These substances are known as ionophores, antimicrobial and antibiotic compounds, enzyme inhibitors, and as compounds inducing oxidative stress. They also have cytotoxic activity towards different cell types inducing apoptosis.

There are no reports on mycotoxicoses associated with these toxins, although different toxic actions are known *in vitro* for enniatins and beauvericin, probably related to their ionophoric properties. For beauvericin, the LD_{50} for acute toxicity was 100 mg/kg b.w. upon oral administration to mice. An LD_{50} of 350 mg/kg b.w. was reported for fusafungine (a mixture of enniatins) in mice upon oral administration. A sub-acute toxicity study on enniatin A with some limitations showed no adverse effects. Beauvericin is a strong insecticidal product (EFSA Journal 2014c).

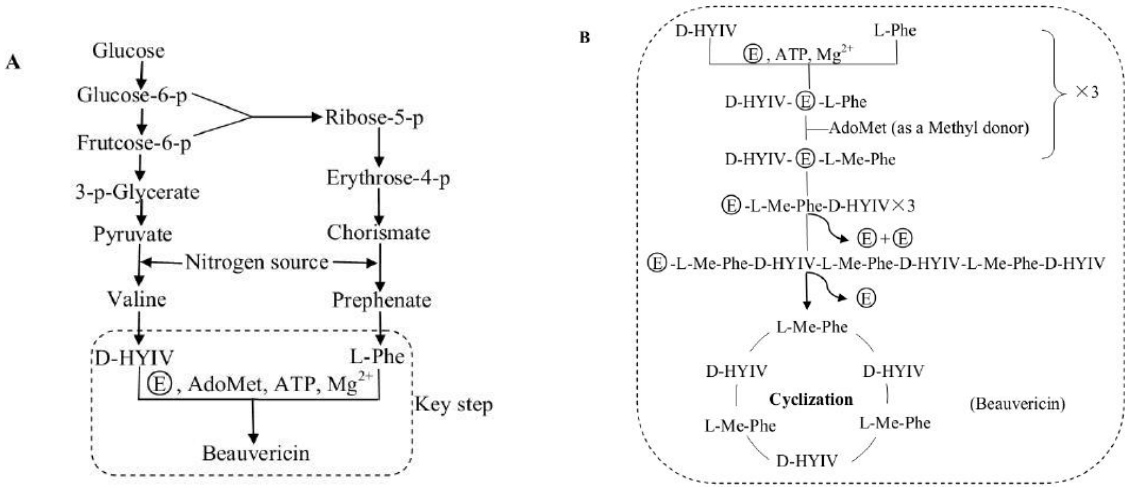

Figure 22: Beauvericin biosynthesis pathway; B, The specific substeps of the key step (E represents the beauvericin synthetase; the dashed frame indicates the key step of beauvericin synthesis); C, The possible structure of the beauvericin synthetase (E1 is the D-HYIV module; E2 is the L-Phe module; SH1,2,3 are the 4'-phosphopantetheine residues corresponding to D-HYIV, L-Phe, and the linear hexadepsipeptide acceptor; M is the N-methyltransferase domain; Cy is the cyclization cavity). Adapted from Wang Q and Xu L, 2012.

Citrinin

Citrinin is a nephrotoxic mycotoxin produced by several species of the genera *Aspergillus*, *Penicillium* and *Monascus*. It has been implicated in porcine nephropathy and has been found as a natural contaminant of corn, rice, wheat, rye, barley, and oats. Citrinin was classified as group 3 (not classifiable as to its carcinogenicity to humans) by IARC (IARC, 1987) and was more recently evaluated by EFSA (EFSA Journal 2012b).

Maximum levels of citrinin in food supplements based on rice fermented with red yeast Monascus purpureus have been laid down in the EU Commission regulation 212/2014 (amending Regulation (EC) No 1881/2006).

Citrinin is a polyketide that has been reported to be produced by the two fungal species *P. citrinum*, *P. chrysogenum,* but besides citrinin, a large number of citrinin derivatives have been isolated from different fungal species, citrinin decomposes during heat treatment to form other complex compounds, such as citrinin H1 and citrinin H2, respectively with higher and weaker cytotoxicity than the original citrinin.

There are some reports on the biosynthesis of citrinin by *P. citrinum* and the effect of several process conditions on the production of this mycotoxin by microorganisms used in industrial fermentations (Reddy *et al.*, 2010; Prabha *et al.*, 2009; Pimentel *et al.*, 1996; Panda *et al.*, 2015).

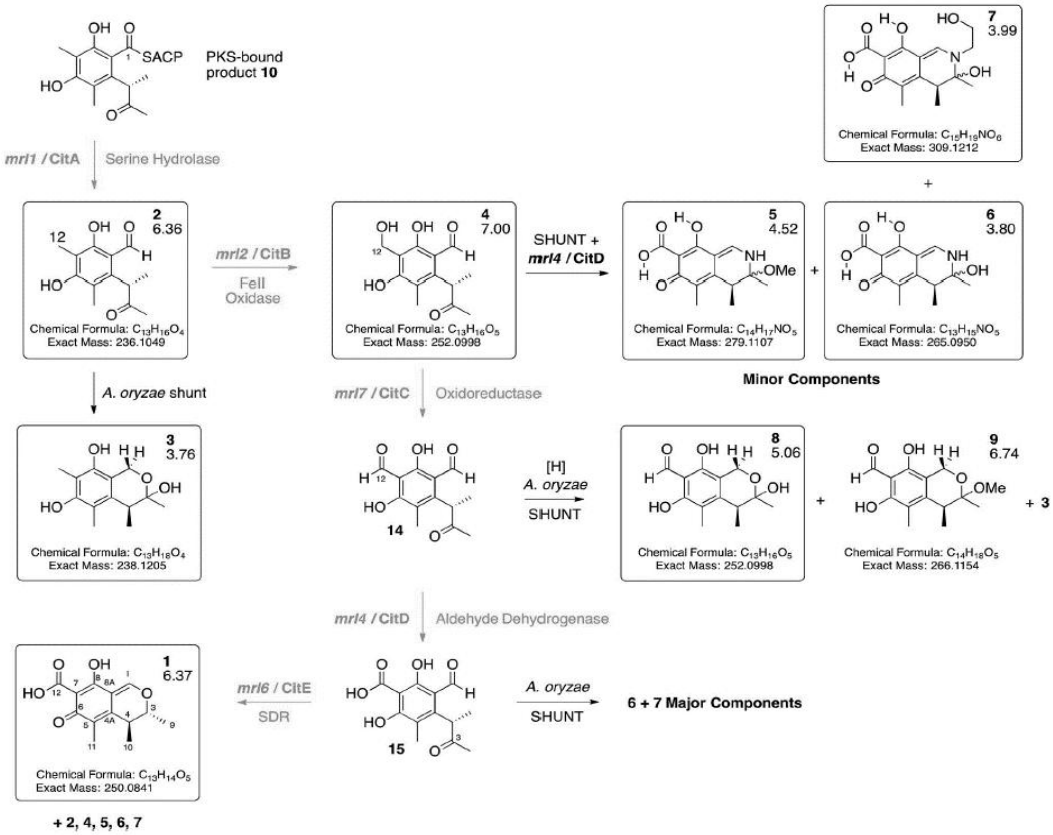

Figure 23: Deduced biosynthetic pathway to citrinin 1 (red steps). Boxed compounds purified and characterised. Black steps represent shunts branching from the main pathway. Figures below compound numbers re LCMS-Rt values. Unboxed compounds structure inferred (from He and Cox, 2016).

Ergot alkaloids

Ergot alkaloids (EA) belong to a diverse group of mycotoxins with neurological effect on humans, but also with a range of biological activities that have important applications in medicine and agriculture. EAs are produced by a variety of plant associated fungi, mainly of the genera *Claviceps* and *Aspergillus.* In this review it has been found to be produced by *A. japonicus* (Nielsen *et al.*, 2014) and *P. roqueforti* (Mioso *et al.*, 2015)

Ergot alkaloids in food and feed have been assessed by EFSA (EFSA Journal 2012a). EAs are not listed in Directive 2002/32/EC, however, the Directive sets a maximum content for rye ergot (*Claviceps purpurea*) of 1000 mg/kg in all feed containing unground cereals. The maximum content relates to a feed with a moisture content of 12%.

The production of ergot alkaloids has been linked to biosynthetic gene clusters found in several species, containing eight genes, seven of which (*dmaW*, *easF*, *easE*, *easC*, *easD*, *easA*, *easG*) are homologous to genes previously implicated in the biosynthesis of festuclavine or agroclavine in other filamentous fungi (Jakubczyk *et al.*, 2014).

All ergot alkaloids are derived from the common biosynthetic intermediate chanoclavine-I, and the structural diversity within the ergot alkaloids results from the elaborate chemical derivatization of this intermediate. Cycloclavine has been observed in only one species of filamentous fungus, *A. japonicus*. Inspection of the *A. japonicus* genome revealed a 16.8-kb biosynthetic cluster containing eight genes.

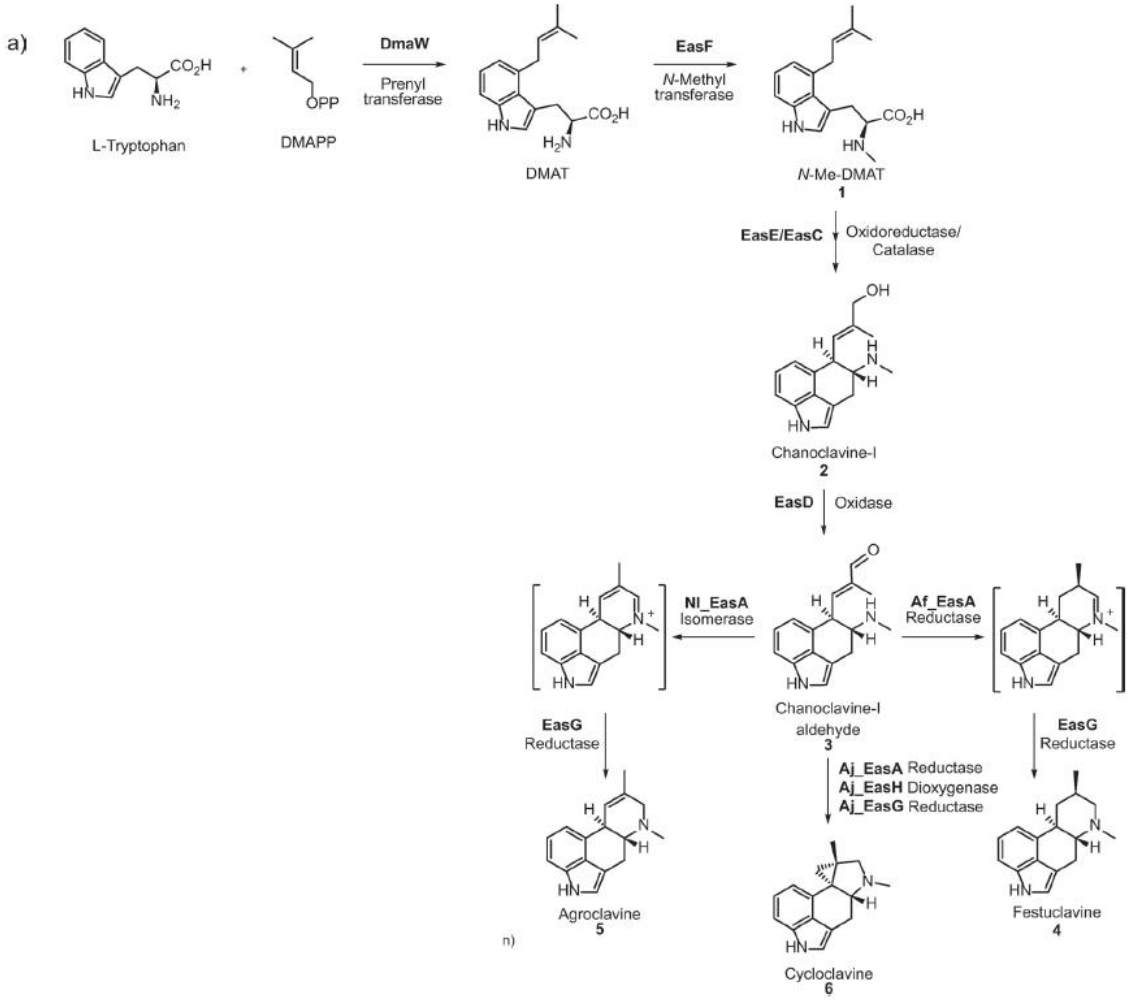

Figure 24: Ergot alkaloid biosynthetic pathway. A) Biosynthesis of festuclavine (4), agroclavine(5), and cycloclavine (6) from L-trytopahn and dimethylallyl pyrophosphate (DMAPP) (from Jakubczyk *et al.*, 2015).

Fumonisins

Fumonisins are formed mainly by *F. verticillioides* (syn. *F. moniliforme*) and *F. proliferatum*. At least 12 fumonisin analogues are known, the most important being the B series (fumonisins B1, B2 and B3). The most significant crop, in which fumonisins occur, is maize, particularly when grown in warmer regions. Fumonisin B1, B2 and fusarin C were classified by IARC as group 2B (possibly carcinogenic to humans) (IARC, 1993). This classification was maintained for fumonisin B1 in 2002 (IARC, 2002).

Fumonisins have been evaluated by EFSA in an Opinion of the Scientific Panel on contaminants in the food chain CONTAM) related to fumonisins as undesirable substances in animal feed (EFSA Journal 2014a). EU legislation has set maximum levels for fumonisins in foodstuffs and more in particular for the sum of fumonisin B1 and B2, in maize and maize-based foods (EC 1881/2006 and its

modifications). Recently a scientific statement on the increase of risk for public health related to a possible temporary derogation from the maximum level fumonisins in maize and maize products has been published (EFSA Journal 2014a).

Some guidance values for the sum of fumonisin B1 and 2 in feed materials have been proposed in an EU Commission Recommendation (2006/576/EC).

It has been reported that *A. niger* strains produce fumonisins B2, B4, and B6 but not B1 (Frisvad *et al.*, 2011) (Pel *et al.*, 2007; Fanelli *et al.*, 2012; Sørensen *et al.*, 2009). In this revision papers relating *A. niger* strains and fumonisin B1 production have not been found. Mogensen *et al.* (2009) found that *A. niger* had the highest production of FB2 was at 25-30°C in PDA agar and the addtition of 2.5-5% NaCl, or 10-20% sucrose increased the production of the toxin but glycerol has an opposite effect.

It has been reported that some of the most frequently used strains in industry, *A. niger* NRRL 337, 3112 and 3122 produced fumonisins and several strains used for citric acid production were among the highest producers of fumonisins in pure agar culture. Most strains used for other biotechnological processes also produced fumonisins. These mycotoxins can be produced under conditions of citric acid fermentation so it is recommended to use strains of *A. niger* with inactive or inactivated gene clusters for fumonisins and ochratoxins (Frisvad *et al.*, 2011).

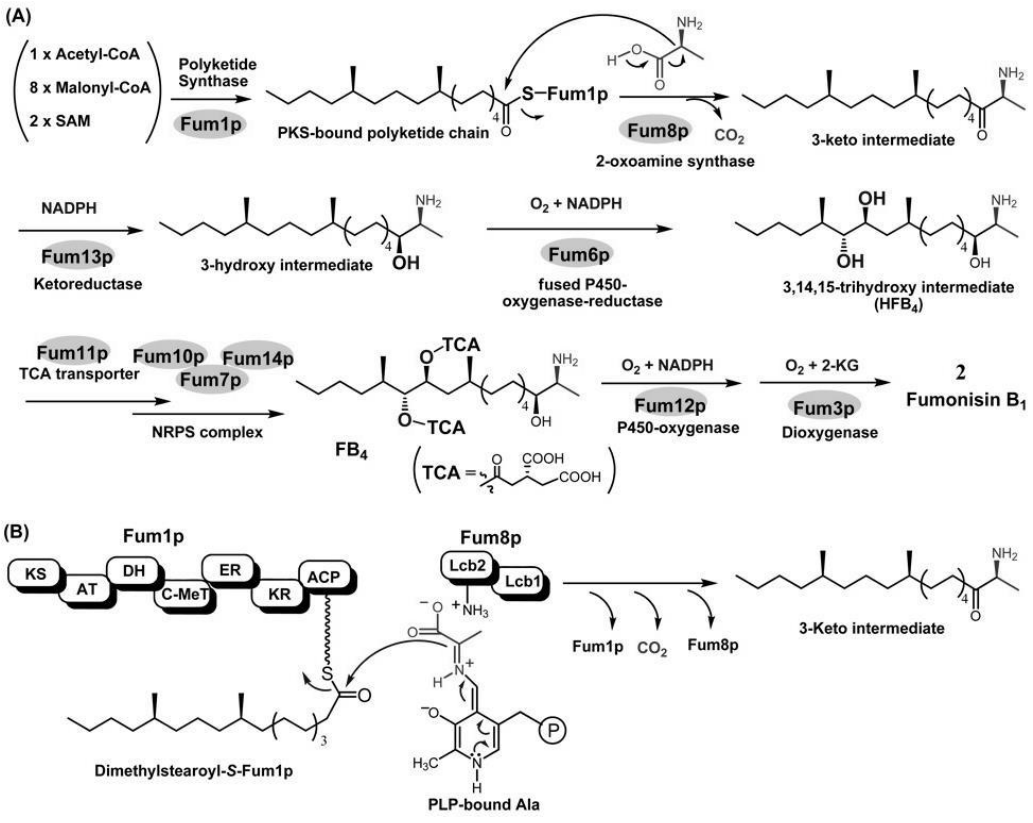

Figure 25: Biosynthetic mechanism for fumonisins. A, the biosynthetic pathway for FB1; B, the PLP-dependent polyketide chain-releasing mechanism in fumonisin biosynthesis (from Huffman J *et al.*, 2010)

Fusarin C

Fusarin C is a mycotoxin produced by several *Fusarium* species. Fusarin C, like other mycotoxins produced by *F. moniliforme* was classified as possible carcinogenic to humans (Group 2B) by the IARC

(1996). It gave positive results in several genotoxicity assays and was able to induce induced papilloma and carcinoma of the oesophagus and forestomach in mice and rats (IARC, 1996). The biosynthesis of fusarin C has been partially resolved and is performed by a polyketide synthase/nonribosomal peptide synthetase system.

In this review, it has been found a report elucidating the biosynthesis of Fusarin C by the species *F. venenatum*. A homologous gene of *fus*A in *F. moniliforme* is responsible for the early stages of fusarin biosynthesis in *F. venenatum* (Song *et al.*, 2004).

Ochratoxin A

Ochratoxin A (OTA) is a nephrotoxic mycotoxin, potentially carcinogenic, hepatotoxic, and teratogenic toxin with immunosuppressive activities. It is produced by several fungal species in the *Penicillium* and *Aspergillus* genera, primarily *P. verrucosum*, *A. ochraceus* and Aspergilli of the section Nigri, including *A. niger.*

OTA is classified by the International Agency for Research on Cancer (IARC) as possibly carcinogenic to humans (group 2B), based on sufficient evidence for carcinogenicity in animal studies and has been considered as reasonably anticipated to be a human carcinogen by the NTP (National Toxicology Program, 2016). It has been evaluated by EFSA in 2004 and 2006 (EFSA Journal 2004; EFSA Journal 2006).

The European Regulation (EC) 1881/2006 and its modifications, sets the maximum levels for OTA in cereals, vine fruit, coffee, and certain spices. Some guidance values have been proposed for products intended for animal feeding (EU Commission Regulation 2006/576/EC and its modifications).

Expression of the *pks* gene appears to be correlated with OTA production in *A. niger*; therefore this finding provides data to find a route for avoiding the production of OTA in industrial strains. The genome sequencing of *A. niger* strain CBS 513.88 revealed the presence of a *pks* gene An15g07920 that has a strong similarity to the *pks* gene of *A. ochraceus* involved in OTA biosynthesis. It has been reported that a fragment of this gene is specific for ochratoxigenic strains of *A. niger* and therefore deletion of this fragment should be sought for avoiding OTA in industrial processes (Shinohara *et al.*, 2011).

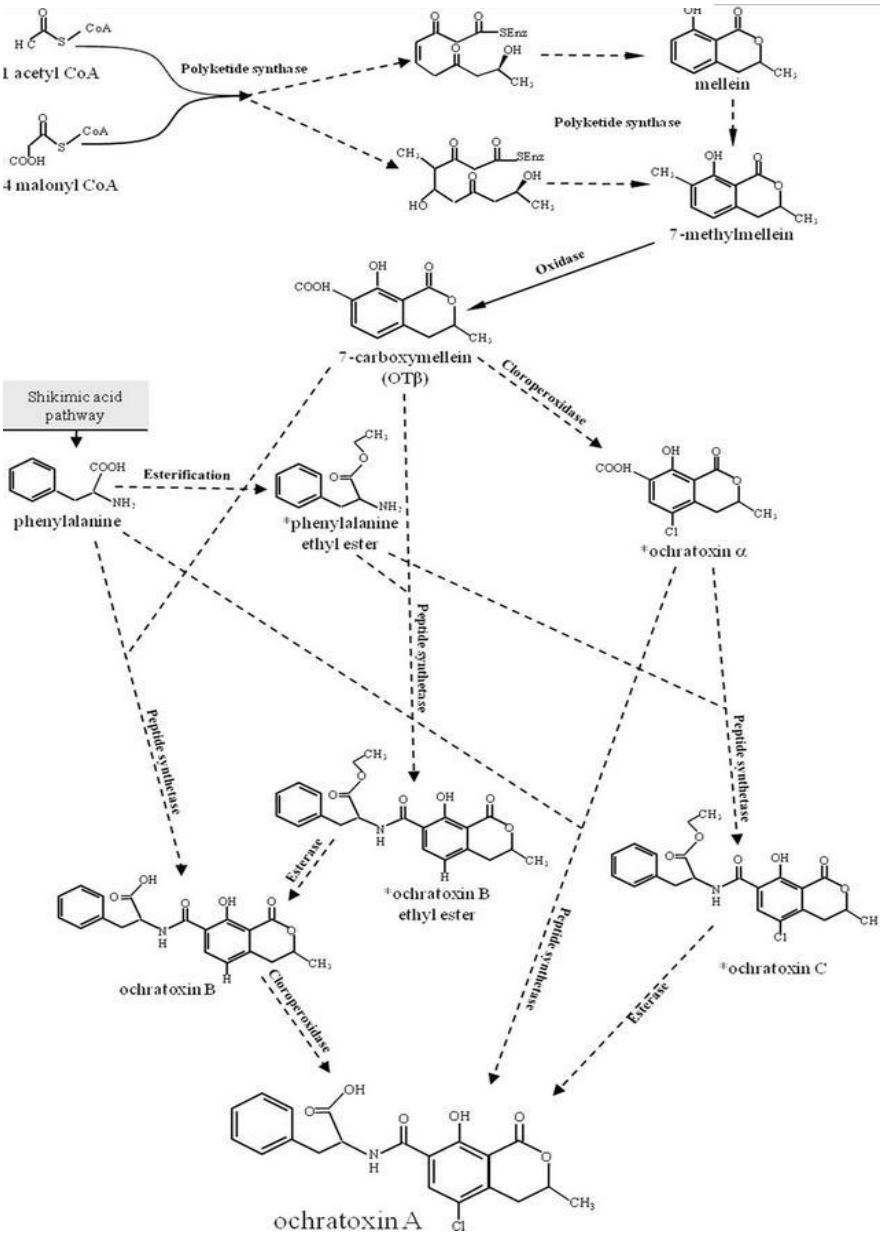

Figure 26: Scheme showing all the different hypotheses of the OTA biosynthesis pathway according to the literature data available, hypothetical intermediary compounds (Gallo *et al.*, 2012)

Regarding the production of OTA by *P. nordicum*, there is a study that shows the effect of sodium chloride on the regulation of ochratoxin A biosynthesis in *Penicillium* species. High amounts of ochratoxin A are produced by *P. nordicum* over a wide concentration range of NaCl (5 to 100 g/L), with an optimum at about 20 g/L on YES medium (Schmidt-Heydt and Geisen, 2007).

Patulin

Patulin is a toxic chemical contaminant produced by several species of mold, especially within *Aspergillus* and *Penicillium*. It is the most common mycotoxin found in apples and apple-derived products such as juice, cider, compotes and other food intended for young children. Exposure to this

mycotoxin is associated with immunological, neurological and gastrointestinal outcomes (Puel *et al.*, 2010).

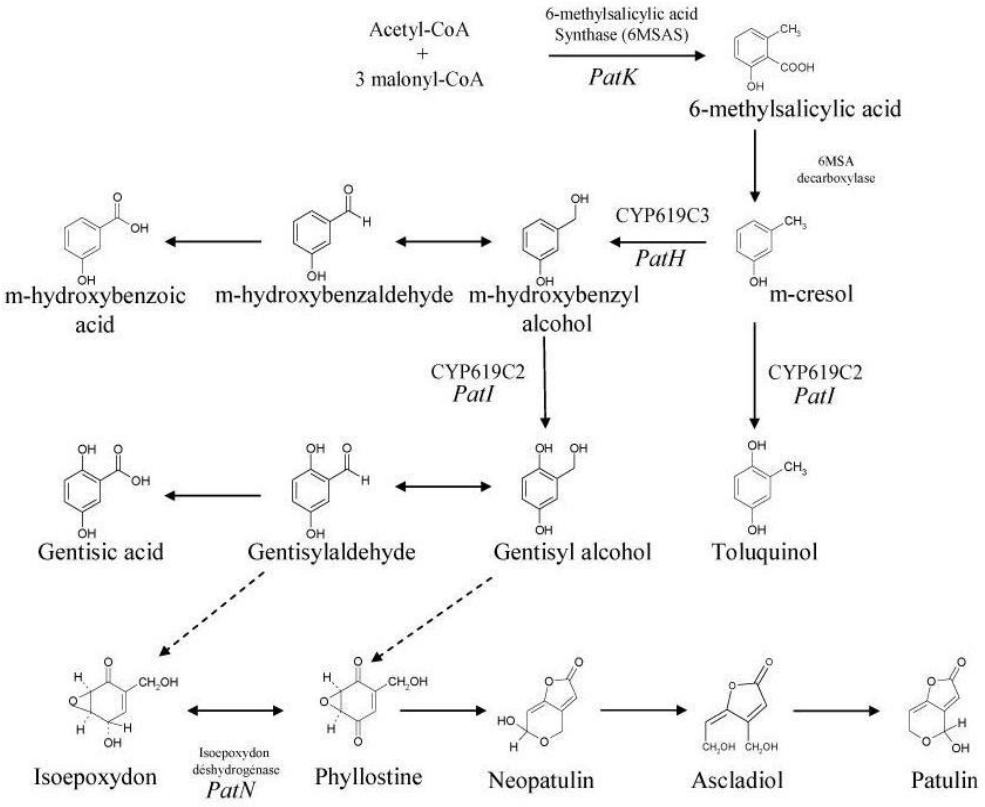

Figure 27: Scheme of patulin biosynthetic pathways. From Puel O *et al.*, 2010.

Penicillic acid

Penicillic acid (PA) is a polyketide mycotoxin produced by several species of *Aspergillus* and *Penicillium*. This mycotoxin is toxic in experimental animals and has also been reported to be carcinogenic. It can cause generalized hepatic necrosis in the mouse and cytotoxicity in cultured cells, including hepatocytes.

The cytotoxicity of penicillic acid was studied in rat alveolar macrophages (AM) in vitro Sorenson *et al.*, 1986). The data demonstrate that penicillic acid is toxic to rat alveolar macrophages in vitro and suggest the possibility of a respiratory hazard to agricultural workers exposed to contaminated grain. This mycotoxin was also evaluated for its toxicity in broiler chickens (Huff *et al.*, 1980). The data suggest that penicillic acid by itself has little toxicity in chickens (less than 1% compared with aflatoxin).

Sterigmatocystin

Sterigmatocystin is a mycotoxin produced mainly by *Aspergillus* fungi, and is an intermediate in the biosynthesis of aflatoxin B1. Major producing microbes include *A. versicolor* and *A. nidulans*

The structure and the bioactivity of sterigmatocystin are similar to those of aflatoxin, but its toxicity is weaker than aflatoxin and is observed in the liver and the lung. Its toxicity is said to be 1/125 and the carcinogenicity to be 1/250 of aflatoxin B1, and its acute toxicity is low (The Pharmaceutical Society of Japan: Methods of Analysis in Health Science, 2010). Carcinogenicity is reported in animal studies.

Sterigmatocystin has been detected in feed materials including maize, wheat, barley, milo, cassava, corn gluten feed, corn gluten meal, bran, and soybean meal.

Sterigmatocystin is classified as Group 2B with possible carcinogenicity in humans by the International Agency for Research on Cancer (IARC: Summaries & Evaluations, 10 (1987)). Effects of the toxin on human health are not well known. It has been reported that it causes apoptosis in human peripheral lymphocytes (Sun *et al.*, 2002).

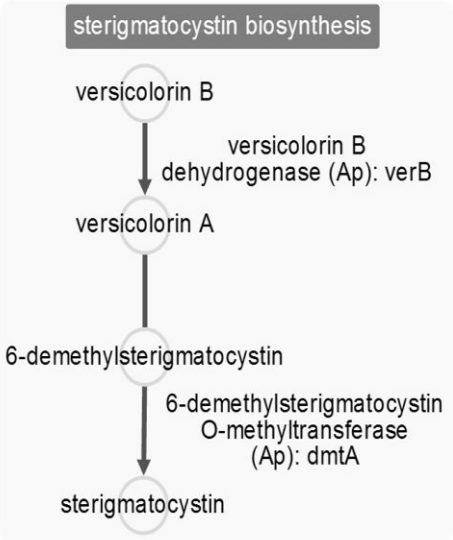

Figure 28: Biosynthetic pathway of sterigmatocystin. From Caspi *et al.*, 2014, "The MetaCyc database of metabolic pathways and enzymes and the BioCyc collection of Pathway/Genome Databases, "*Nucleic Acids Research* 42:D459-D471.

Trichothecenes

Trichothecenes are one of the major classes of mycotoxins, produced by several fungi genera including *Fusarium, Myrothecium, Spicellum, Stachybotrys, Cephalosporium, Trichoderma, and Trichothecium* and are potent inhibitors of eukaryotic protein synthesis.

Trichothecenes are a family of over 200 toxins with a common tricyclic 12,13-epoxytrichothec-9-ene (EPT) core structure that have been classified into four groups (Types A, B, C, and D).

Type A trichothecenes include **T-2 toxin**, neosolaniol, **trichodermin**, **diacetoxyscirpenol (DAS)**, and harzianum A. In this review, several reports on the production of these toxins by the microorganisms within the scope of the review, such as *F. venenatum* (DAS) (Miller and Mackenzie, 2000); *T. viride* (DAS and T-2 toxin) and *T. harzium* and *T. reesei* (Trichodermin) (Mohamed *et al.*, 2006; Blumenthal, 2004)

Type B trichothecenes include nivalenol, **deoxynivalenol (DON)**, that can be produced by *A. oryzae* (Atalla *et al.*, 2003), and trichothecin.

Type C trichothecenes include crotocin.

Type D trichothecenes include roridin A, verrucarin A, satratoxin H.

Some of these compounds have been evaluated by IARC as "toxins derived from *Fusarium*" and have been classified as group 3 (not classifiable as to its carcinogenicity to humans) (IARC, 1993).

The European Regulation (EC) 1881/2006 and its modifications, sets the maximum levels for certain types of trichothecenes, such DON, ZEA and T-2 and HT-2.

Zearalenone

Zearalenone (ZEA) is a mycotoxin produced mainly by fungi belonging to the genus *Fusarium* in foods and feeds. It is frequently implicated in reproductive disorders of farm animals and occasionally in hyperoestrogenic syndromes in humans. There is evidence that ZEA and its metabolites possess oestrogenic activity in pigs, cattle and sheep. However, ZEA is of a relatively low acute toxicity after oral or interperitoneal administration in mice, rat and pig. Although ZEA is toxic, it globally presents a potential danger for animal and human health only when it is absorbed in high amounts or over a long time of exposure (Zinedine *et al.*, 2007)

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) 2016 established a provisional maximum tolerable daily intake (PMTDI) for ZEA of 0.5 µg/kg of body weight.

3.3.2. Toxic Secondary metabolites produced by bacteria

Potentially toxic substances produced by bacteria that have not been fully evaluated from the toxicological point of view have been identified in this review. The majority are associated with virulence factors, such as signaling molecules (that are only elicit in the presence of competitors), or adhesion proteins that allow bacteria the attachment, favoring the formation of biofilms and therefore, providing more resistance to external aggression. Moreover, information on possible effects of the LPS (lipopolysacharide endotoxins), released by the microorganism species of the scope of the project, would need to be taken into account as relevant information.

A short description of the most relevant compounds synthesized by bacteria within the scope of this project is given below.

Cytolysin A

Cytolysin A (ClyA) is a hemolytic protein of *Escherichia coli* K-12, they damage host cells by forming holes in the cytoplasmic membrane, which may result in cell death and osmotic cell lysis. It has been reported that this pore-forming cytotoxic protein encoded by the *clyA* gene protein, is not expressed under normal laboratory conditions. Genetic analysis suggested that *clyA* is silenced by the nucleoid protein H-NS. Purified H-NS protein showed preferential binding to *clyA* sequences in the promoter region.

In this review, it has been found a study that test the purified cytotoxic of ClyA and a ClyA-expressing *E. coli* strain to both human and murine macrophages, showing the induction of a massive amount of

apoptosis and host cell DNA fragmentation (Enow *et al.*, 2014; Ludwig *et al.*, 2010; Oscarsson *et al.*, 1999)

Lipopolysaccharide endotoxins

Endotoxin refers to the lipopolysaccharide (LPS) that constitutes the outer leaflet of the outer membrane of most Gram-negative bacteria. The biological activity of endotoxin is associated with the LPS. Toxicity is associated with the lipid component (Lipid A) and immunogenicity is associated with the polysaccharide components. Both Lipid A (the toxic component of LPS) and the polysaccharide side chains (the nontoxic but immunogenic portion of LPS) act as determinants of virulence in Gram-negative bacteria (Table 4).

Table 4: Characteristics of bacterial endotoxins.

PROPERTY	ENDOTOXIN
CHEMICAL NATURE	Lipopolysaccharide
RELATIONSHIP TO CELL	Part of outer membrane
DENATURED BY BOILING	No
ANTIGENIC	Yes
FORM TOXOID	No
POTENCY	Relatively low (>100ug)
SPECIFICITY	Low degree
ENZYMATIC ACTIVITY	No
PYROGENICITY	Yes

Most enzymes and genes related to the biosynthesis and export of lipopolysaccharide have been identified in *E. coli*, and they are shared by most Gram-negative bacteria based on available genetic information. However, the detailed structure of lipopolysaccharide differs from one bacterium to another, suggesting that additional enzymes that can modify the basic structure of lipopolysaccharide exist in bacteria, especially some pathogens. These structural modifications of lipopolysaccharide are sometimes tightly regulated. They are not required for survival but closely related to the virulence of bacteria.

Table 5: Information on nine enzymes required for the biosynthesis of Lipid A in *E. coli* (from Wang and Quinn, 2010).

ENZYME	GENE	FUNCTION
LpxA	*lpxA*	Acyltransferase
LpxC	*lpxC*	Deacetylase
LpxD	*lpxD*	Acyltransferase
LpxH	*lpxH*	Pyrophasphatase
LpxB	*lpxB*	Disaccharide synthase
LpxK	*lpxK*	4′-Kinase
KdtA	*kdtA*	Kdo transferase
LpxL	*lpxL*	Acyltransferase
LpxM	*lpxM*	Acyltransferase

The first three enzymes LpxA, LpxC and LpxD of the LPS biosynthetic pathway have been purified, and their structures have been characterised by X-ray diffraction and NMR methods. Based on the structural information from these proteins, research into developing new antibiotics is being carried out.

LPS from well-known species can cause diseases such as septic shock, multiple organ dysfunction and failure. Understanding the biochemistry of LPS modifications and their impact on pathogenesis could lead to novel treatment options for these diseases.

Phenazines

Phenazines are pigmented, redox-active, heterocyclic, nitrogen containing molecules secreted by a considerable number of .*Streptomyces*, (Sarmin *et al.*, 2013) and multiple fluorescent *Pseudomonas* (Cezairliyan *et al.*, 2013). Several derives have been found in this review, such as **1-Hydroxyphenazine** , **Phenazine-1-carboxylic acid** and **Endophenazine A.**

Phenazines display a broad spectrum of (toxic) activity toward prokaryotic and eukaryotic organisms, varying according to the nature and position of the substituent on the heterocyclic ring. They are considered as virulent factor pf *P. aeruginosa* (Ballok and O'Toole, 2013), but no standard toxicity data have been found in this report for these substances. Phenazines are considered redox-active compounds as well as a cytotoxic pigment. Pyocyanin, (1-hydroxy-5-methylphenazine) is the best-studied natural phenazine.

In this review it has been found that several of the articles related to virulence of *P. aeruginosa*, do not include toxicological evaluation. Others are related with cystic fibrosis lung (patients are specially affected by *P. aeruginosa* infection).

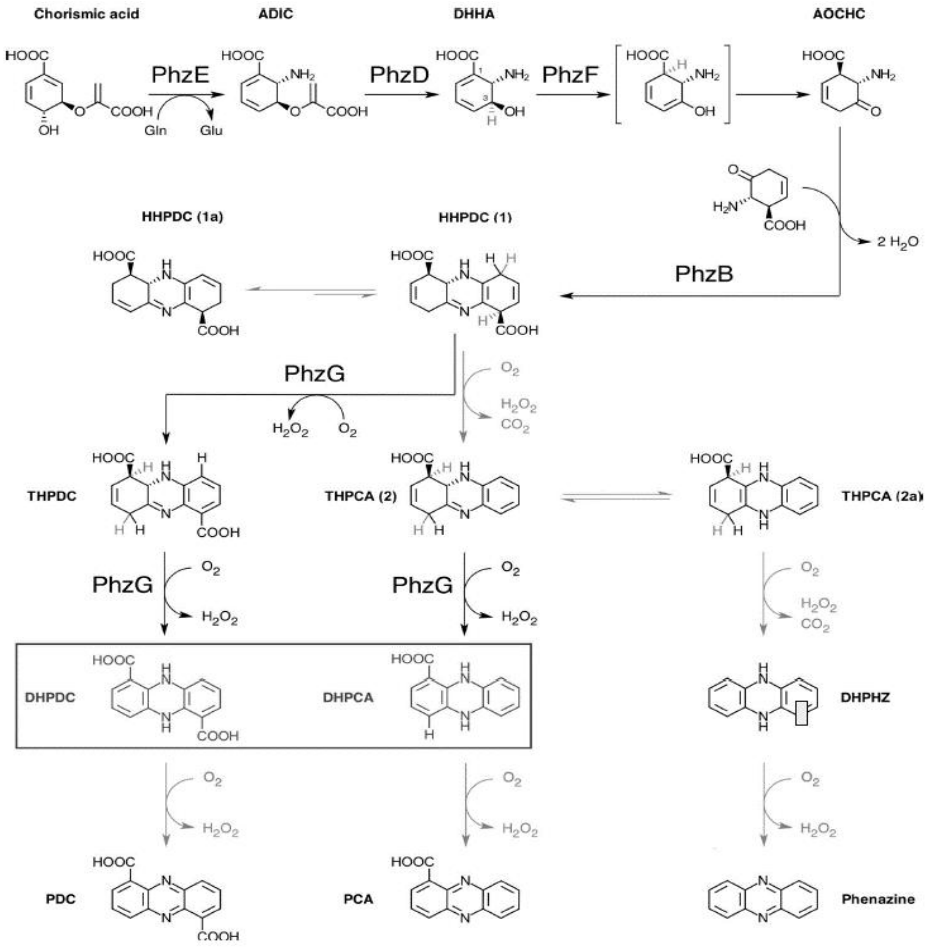

Figure 29: Enazine biosynthesis. Abstracted or shifted hydrogens are shown in red, grey arrows indicate uncatalyzed steps. 5,10-Dihydro-PCA and 5,10-dihydro-PDC are the final products of the pathway (green) (from Blankenfeldt and Parsons, 2014)

Pyocyanin

Pyocianin (5-*N*-methyl-1-hydroxyphenazine), the first and most-studied member of the phenazine family,. Phenazines are low-molecular-weight secondary metabolites including nitrogen-containing heterocyclic pigments. Almost all phenazines exhibit broad spectrum activity against plant pathogenic bacteria and fungi.

Pyocianin is produced only by *P. aeruginosa* and 90 to 95% of *P. aeruginosa strains* produce pyocyanin. This specificity that has been useful in the rapid diagnosis of this opportunistic pathogen.

Pyocianin produced in the rhizosphere of plants plays an important role in the biological control activity of *P. aeruginosa* against *Fusarium* wilt of chickpea and *Pythium* damping off of bean.

This blue phenazine is one of the major virulence factors in this pathogen, contributing to both acute and chronic infections. It suppresses lymphocyte proliferation, damages epithelial cells as a consequence of hydroxyl radical formation, inactivates protease inhibitors (consequently causing tissue damage by endogenous proteases), and targets multiple cellular functions.

The redox-active pyocianin (PCN) secreted by the respiratory pathogen *P. aeruginosa* generates reactive oxygen species (ROS) and causes oxidative stress to pulmonary epithelial cells.

Pyocianin is able to produce oxidative stress damage in mammalian tissues. Several toxicological endpoints were dectected in mechanisitic studies (related mainly with sepsis and bacteria pathogenicity/virulence): neurotoxicity, haemotoxicity, inhibition of ATPase and immunotoxicity (neutrophil extracellular traps promotion).

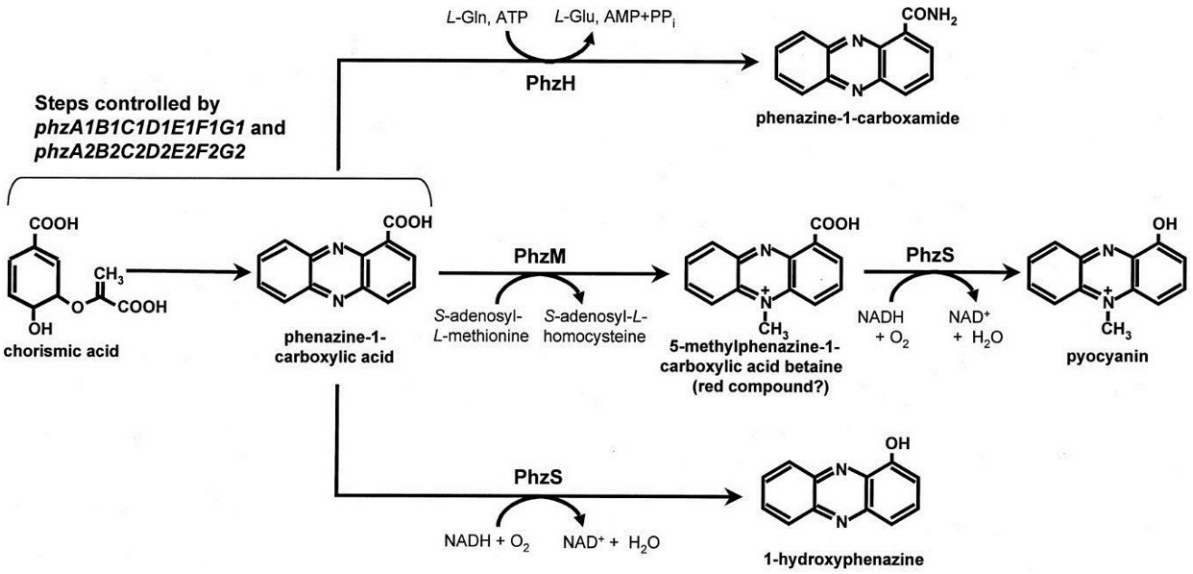

Figure 30: Proposed mechanism for the synthesis of pyocyanin, 1-OH-PHZ, and PCN in *P. aeruginosa* PAO1 (from Mavrodi *et al.*, 2001).

4. Proposal for the sustainability of the database

As a result of this project, different methodologies, studies and technologies have been developed and integrated, as described below:

a. A well-defined searching strategy proved to be suitable for the purpose of this project that included sets of suitable keywords identified in the areas of toxicology, industrial

fermentation as well as biosynthetic pathways, which can help to retrieve useful information in future searches.

b. A customized technology based on a collaboration platform (iWatch) capable of extracting information from different web databases. This platform provides two tools: a crawler tool implemented and configured to collect and classify all documents as required by the search strategy and a user interface parameterized to implement the working methodology. Both allow continuing with extraction of information efficiently.

c. A working methodology based on inclusion/exclusion criteria to allow experts the review, the analysis and classification of all extracted documents. This can be useful to continue efficiently with the same workflow in future searches.

d. A validated Database to store all data extracted by experts regarding taxonomy, process conditions, biosynthetic pathways and toxicology on non-QPS microorganisms. Also a tool to extract, convert and store the information retrieved in collaboration with the platform (iWatch) integrated into the database. All can be useful to continue efficiently updating the database with new information included by the experts.

e. A report on more than 400 bioactive secondary metabolites produced by industrial microorganisms have been identified and recorded. Most of these compounds have been reported in relation to some metabolic aspects and studies related to their toxicity were not found, and therefore only a small part of the identified compounds are included in the database, however, new information could be gathered in the future and the name of this compounds could be used as new keywords for future searches.

Considering the above aspects, the sustainability of the database can be ensured by updating it periodically (every year) maintaining the same structure.

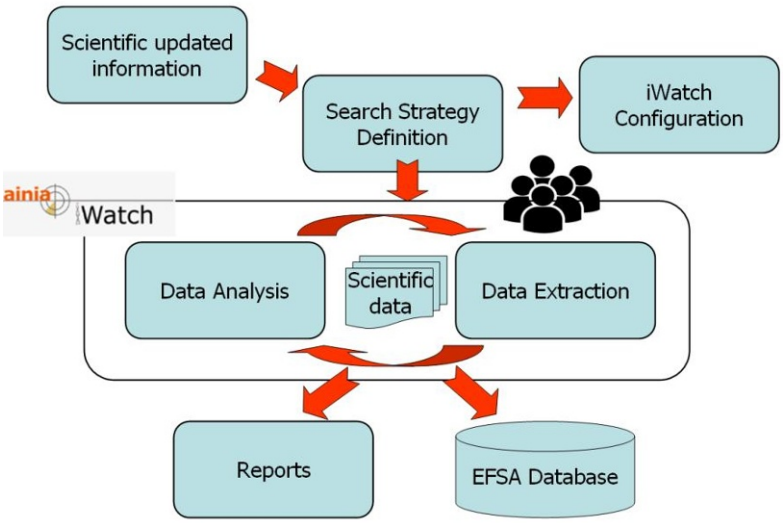

Figure 31: Sustainability of the EFSA Database.

5. Conclusions

In the present project, it has been developed an integrative and useful database for supporting safety assessment that includes relevant and accurate information about taxonomical characterisation and potential toxigenic capacities of microorganisms used for the industrial production of feed additives and food enzymes. The structure of the data model and its terminology includes the use of EFSA standard coding system.

The data model has been aimed to include the following information:

- Description of microbial species used to produce food enzymes and feed additives which have not been recommended for Qualified Presumption of Safety (QPS) status, with its main identifiers: the current scientific name, taxon assignation, synonyms, existing methods for the taxonomical characterisation and accession numbers for housekeeping genes.
- Identification of toxins or potentially toxic secondary metabolites/substances produced by the microorganisms used to produce food enzymes and feed additives
- Identification of the conditions under which the microorganisms can produced the toxic compound/s.
- Biosynthetic pathway and genetic characterization of the toxic compounds produced by the microorganism.

The contents of the database have been retrieved by the performance of a systematic search that has been aided by the use of an "ad hoc" automatic tool.

For the microbial taxonomic review, a total of 123 scientific documents have been obtained to extract the relevant information for the database. For the identification of secondary metabolites, 22970 scientific documents have been recovered combining the searching platform and manual searching, classified by microorganism species names and systematically revised, to obtain pertinent data. A total of 411 scientific documents were selected that contain relevant data on potentially toxic secondary metabolites.

A total of 474 bioactive secondary metabolites were found to be produced by the microbial species within the scope of this project, from which 59 were selected for further searches for data on their toxicity and biosynthesis. Fungal species are the most predominant group to produce toxic metabolites, including well known mycotoxins. However, in the majority of the cases, industrial strains contain a natural or artificially induced safeward mutation or genetic modification which prevents the production of the toxin under defined fermentation conditions.

The majority of secondary metabolites produced by fungi found in this review are studied for their biotechnological and biopharmaceutical potential due to their properties such as antimicrobial, antinematode, antitumor, etc.

Reports on secondary metabolites produced by bacterial species within the scope of this project were less common and in most of the cases those metabolites are identified as virulent factors, expressed only under certain conditions

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Abbreviations

AEMPS	Spanish Agency of Medicines and Medical Devices
AESAN	Agencia española de Consumo, Seguridad alimentaria y Nutrición. (Spanish Agency for Consumer Affairs, Food Safety and Nutrition)
AFSCA	Federal Agency for the safety of the food chain
AGES	Austrian Agency for Health and Food Safety
AHVLA	Animal Health and Veterinary Laboratories Agency
AINIA	Asociación Investigación Industria Agroalimentaria (Food Industry Research Association)
ANSES	French Agency for Food, Environmental and Occupational Health & Safety
BEUC	Bureau Européen des Unions de Consommateurs (The European Consumer Organisation)
BFR	The Federal Institute for Risk Assessment
CAS	(Number) Chemical Abstract Service
CCRIS	Chemical Carcinogenesis Research Information System
CDC	Centers for Disease Control and Prevention
CELCAA	European Liaison Committee for Agricultural and Agri-Food Trade
CFIA	Canadian Food Inspection
CIAA	Confederation of the Food and Drink Industries in the EU
ClyA	Cytolysin A
COPA-COGECA	European Farmers - European Agri-Cooperatives
CSPINET	Center for Science in the Public interest
DART	Developmental and Reproductive Toxicology Database
DAS	Diacetoxyscirpenol
DBMS	Database Management System
DCF	Data Collection Framework (EFSA)
DNA	Deoxyribonucleic acid
DON	Deoxynivalenol
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
EFI	European Food Institutes
EFSA	European Food Safety Authority
EPHA	European Public Health Alliance

EU	European Union
EUFIC	European Food Information Council
FAO	Food and Agriculture Organization of the United Nations
FDA	U S Food and Drug Administration
FEEDAP	Panel on Additives and Products or Substances used in Animal Feed
FEFAC	European Feed Manufacturers Federation
FEFANA	EU Association of Speciality Feed Ingredients and their Mixtures
FK	Foreign key
FSA	Food Standards Agency (UK)
FSAI	Food Safety Authority of Ireland
FSANZ	Food Standard Australia New Zealand
HPA	Hydroxypropionaldehyde
HSDB	Hazardous Substances Data Base
ICAR	International Agency for research on Cancer
ID	Identification
iNOS	Nitric oxide synthase
ISO	International Organization for Standardization
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LBSN	List of Bacterial names with Standing in Nomenclature
LPS	Lipopolysaccharide
NTP	National Toxicology Program
OTA	Ochratoxin A
PSK	polysaccharide-K
QMS	Quality Management System
QPS	Qualified Presumption of safety
RASFF	Food and Feed Safety Alerts - European Commission
SICURA	Spanish Network for Food Security
SQL	Structured Query Language
TOXNET	TOXicology Data NETwork
URL	Uniform Resource Locator
USDA	U.S. Department of Agriculture
USEPA	US Environmental Protection Agency
VWA	The Netherlands Food and Consumer Product Safety Authority

Appendices

Appendix A – Search in Iwatch: number of entries per microorganism (annexed)

Appendix B – Websites and Databases list for authomatic search by IWatch (annexed)

Appendix C – Additional toxicological information databases (annexed)

Appendix D – List of food and feed additives (annexed)

Appendix E – List of toxins evaluated by EFSA, IARC or NTP or included in Directive 2002/32/EC

Appendix F – List of excluded articles. Level 2 (annexed)

Appendix G – Summary of secondary metabolites with bioactivity (annexed)

Appendix H – Relational database (annexed)

Appendix I – Attributes for Param Catalogue (annexed)

Appendix J – Microorganism taxonomical identifiers (annexed)

Appendix K – Taxonomy references (annexed)

Appendix A – Search in IWatch: number of entries per microorganism

MICROORGANISMS CLASSIFICATION							
SEARCH KEYWORDS							
Species I: scientific name of the microorganism Species II: scientific name of the microorganism AND (keywords group 1) Species III: scientific name of the microorganism AND (keywords group 1) AND (keywords group 2)							
MICROORGANISMS	**SEARCH**			**MICROORGANISMS**	**SEARCH**		
	Species I	**Species II**	**Species III**		**Species I**	**Species II**	**Species III**
Actinomadura roseorufa	0	-	-	*Penicillium chrysogenum*	-	446	-
Actinomadura yumaensis	5	-	-	*Penicillium citrinum*	-	236	-
Aeribacillus pallidus (Syn. *Geobacillus pallidus*)	17	-	-	*Penicillium decumbens*	145	-	-
Arthrobacter ramosus	12	-	-	*Penicillium funiculosum*	313	-	-
Aspergillus aculeatus	-	31	-	*Penicillium lilacinum*	16	-	-
Aspergillus japonicus	173	-	-	*Penicillium multicolor*	32	-	-
Aspergillus melleus	57	-	-	*Penicillium notatum*	-	118	-
Aspergillus niger	-	-	1186	*Penicillium roqueforti*	-	112	-
Aspergillus oryzae	-	523	-	*Penicillium salamii*	3	-	-
Aspergillus sojae	156	-	-	*Pseudomonas aeruginosa*	-	-	9426
Bacillus macerans	237	-	-	*Pseudomonas amyloderamosa*	14	-	-
Bacillus naganoensis	12	-	-	*Pullulanibacillus naganoensis*	6	-	-
Bacillus soli (syn. *Paenibacillus macerans*)	8	-	-	*Rhizomucor miehei*	-	38	-
Bullera singularis (syn. *Sporobolomyces singularis*)	6	-	-	*Rhizopus niveus*	92	-	-
Candida cylindracea (syn. *Candida rugosa*)	-	274	-	*Rhizopus oryzae*	-	330	-
Candida lipolytica	-	39	-	*Sphingobacterium multivorum*	58	-	-
Candida paralipolytica (syn. *Candida lipolytica*)	-	1	-	*Sporobolomyces singularis*	11	-	-
Candida rugosa	-	135	-	*Sporotrichum dimorphosporum*	1	-	-
Cellulosimicrobium cellulans	77	-	-	*Streptomyces albus*	-	41	-
Chaetomium erraticum	8	-	-	*Streptomyces aureofaciens*	-	24	-
Chaetomium gracile	9	-	-	*Streptomyces chrestomyceticus*	3	-	-
Chryseobacterium proteolyticum	8	-	-	*Streptomyces chromofuscus*	85	-	-
Cryphonectria parasitica	-	370	-	*Streptomyces cinnamonensis*	43	-	-
Disporotrichum dimorphosporum	1	-	-	*Streptomyces cinnamoneus*	14	-	-
Endothia parasitica (syn. *Cryphonectria parasitica*)	-	21	-	*Streptomyces lasaliensis*	8	-	-
Escherichia coli	-	-	778	*Streptomyces lividans*	-	89	-
Flavobacterium multivorum	9	-	-	*Streptomyces mobaraensis*	70	-	-
Fusarium venenatum	56	-	-	*Streptomyces murinus*	13	-	-
Geobacillus caldoproteolyticus	2	-	-	*Streptomyces netropsis*	10	-	-
Geobacillus pallidus	26	-	-	*Streptomyces olivochromogenes*	17	-	-
Geobacillus stearothermophilus	-	173	-	*Streptomyces rubiginosus*	35	-	-
Hansenula polymorpha	-	132	-	*Streptomyces violaceoruber*	40	-	-
Humicola insolens	254	-	-	*Streptoverticillium cinnamoneum (syn. Streptomyces cinnamoneus)*	77	-	-
Klebsiella planticola	76	-	-	*Streptoverticillium mobaraense* (syn. *Streptomyces mobaraensis*)	57	-	-
Klebsiella pneumoniae	-	-	3436	*Talaromyces cellulolyticus*	16	-	-
Leptographium procerum	44	-	-	*Talaromyces emersonii*	89	-	-
Microbacterium imperiale	20	-	-	*Talaromyces versatilis*	6	-	-
Micrococcus luteus	-	-	290	*Trametes hirsuta*	291	-	-
Mucor circinelloides	107	-	-	*Trametes versicolor*	-	232	-
Mucor javanicus	97	-	-	*Trichoderma citrinoviride*	43	-	-
Ogataea polymorpha (syn. *Hansenula polymorpha*)	-	9	-	*Trichoderma harzianum*	-	950	-
Paecilomyces lilacinus (syn. *Penicillium lilacinum*)	275	-	-	*Trichoderma koningii*	213	-	-
Paenibacillus alginolyticus	8	-	-	*Trichoderma longibrachiatum*	285	-	-
Paenibacillus lentus	1	-	-	*Trichoderma reesei*	-	196	-
Paenibacillus macerans	107	-	-	*Trichoderma viride*	-	435	-
Penicillium camemberti	73	-	-	*Yarrowia lipolytica*	-	205	-

Appendix B – Websites and Databases list for authomatic search by Iwatch

NAME	URL	DESCRIPTION
EFE	http://www.efe.com/efe/noticias/english/4	EFE Agency
Agrodigital	www.agrodigital.com	Agrodigital
Agromeat - Agronews	http://www.agromeat.com	Agromeat - Agronews website
AHVLA	http://www.defra.gov.uk/ahvla-en	Animal Health and Veterinary Laboratories Agency
Albeitar	http://albeitar.portalveterinaria.com/	Veterinary website
ANSES FRANCE	https://www.anses.fr/en	National Food Agency France
Baden-Wuerttemberg	http://www.cvuas.de/pub/default.asp?subid=1&lang=EN	Investigative office for food control and animal health
BFR	http://www.bfr.bund.de/en/home.html	The Federal Institute for Risk Assessment
CDC (USA)	http://www.cdc.gov/niosh/nioshtic-2/20023037.html	Center of Diseace Control (USA)
CFIA	http://www.inspection.gc.ca/about-the-cfia/newsroom	Canadian Food Inspection Agency
Chemical Watch	http://chemicalwatch.com	Chemical Watch
CIDRAP	http://www.cidrap.umn.edu/cidrap/index.html	Center for Infectious Disease Research and Policy
ClubDarwin	http://www.clubdarwin.net/	ClubDarwin
CODEX Alimentarius	http://www.codexalimentarius.org/	Codex Alimentarius Reports
EDIPORC	http://www.ediporcguia.com/	Technical Farming Editions
EFEAgro	http://www.efeagro.com/	Agrofood news
EFSA	http://www.efsa.europa.eu/en/newsletters/highlights.htm	European Food Safety Agency reports
EHN	http://www.environmentalhealthnews.org	Environmental Health News
EHP	http://ehp.niehs.nih.gov/	Environmental Health Perspectives
Espacenet	https://worldwide.espacenet.com/	European Patent Office
Eurekalert	http://www.eurekalert.org/rss.php	Online, global news service operated by AAAS
European Comission	http://ec.europa.eu/	European commision news alert
EPHA	http://www.epha.org/	European Public Health Alliance
FAO	http://www.fao.org	Food and Agriculture Organization of the United Nations
FDA	http://www.fda.gov/Safety/Recalls/default.htm	Recalls, Market Withdrawals, & Safety Alerts
Food Business Review	http://www.food-business-review.com/	Food Business Review
Food Navigator	http://www.foodnavigator.com/	Food Navigator
FoodNavigator	http://www.foodnavigator.com/	Daily online news service
FoodQuality	http://www.foodqualitynews.com/	Food Quality
FoodSafety	http://www.foodsafety.gov/recalls/recent/index.html	FoodSafety.gov
FSA	http://www.food.gov.uk/enforcement/alerts/	Food Standards Agency UK
FSAI	http://www.fsai.ie/news_centre/food_alerts.html	Food Safety Authority of Ireland
FSANZ	http://www.foodstandards.gov.au	Food Standards Australia New Zealand
GlobalMeatNews	http://www.globalmeatnews.com	Global Meat News
Harvard School Public Health	www.hsph.harvard.edu	Harvard School Public Health
HSE UK	http://www.hse.gov.uk/index.htm	Health and Safety Executive UK
Health Canada	http://www.hc-sc.gc.ca/	Health Canada
HPA	http://www.hpa.org.uk/Topics/ InfectiousDiseases/InfectionsAZ	Health Protection Agency
IARC	http://www.iarc.fr/en/feeds/index.php	International Agency For Research on Cancer.
Infection Control Horizon Scanning	http://infectioncontrolnwpctl.wordpress.com/	Infection Control
JECFA	http://www.fao.org/fao-who-codexalimentarius/codex-home/en/	International Food Standards
Natural News	http://www.naturalnews.como	Natural News
New Scientist	http://www.newscientist.com/	New Scientist
Nutraceutical Business Review	http://www.nutraceuticalbusinessreview.com	Nutraceutical Business Review
Nutraingredients	http://www.nutraingredients.com	Breaking News on Supplements & Nutrition - Europe
OIE	http://www.oie.int/wahis_2/public	Animal Health Information
PigProgress	http://www.pigprogress.net	PigProgress
Pubmed	http://www.ncbi.nlm.nih.gov/pubmed	Searching Engine
RSSL Food e News	http://www.rssl.com/services/food/foode-news	RSSL Food e News
ScienceDirect	http://www.sciencedirect.com/	Searching Engine
Science Insider	http://news.sciencemag.org/	Science Insider
Scopus	www.scopus.com	Searching Engine
Sience Daily	http://www.sciencedaily.com	Science Daily
SINC	htttp://www.agenciasinc.es	Sinc Science
Toxnet	http://toxnet.nlm.nih.gov/	Toxicology data network
Unilever	http://www.unilever.com/	Unilever Resources
USDA	http://www.fsis.usda.gov/Fsis_Recalls/index.asp	Food Safety and Inspection Service (FSIS)
USEPA	http://www.epa.gov/	U.S Environmental Protection Agency
Web of science	https://apps.webofknowledge.com	Searching Engine
WHO	http://www.who.int/csr/don/ 2013_06_02_ncov/en/index.html	Global Alert and response GAR
WIPO	http://www.wipo.int/portal/en/index.html	World Intellectual Property Organization

Appendix C – Additional toxicological information databases

Compound	Title	Source. *Last update*	Information	URL
1-hydroxyphenazine	1-HYDROXYPHENAZINE CASRN: 528-71-2	ChemIDplus (TOXNET)	acute toxicity	https://chem.nlm.nih.gov/chemidplus/rn/528-71-2
		CTD (TOXNET)	genomics	http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ctd:@term+@DOCNO+CTD/C050093
3-nitropropionic acid	3-NITROPROPIONIC ACID CASRN: 504-88-1	HSDB (TOXNET). *Updated 2003*	--	http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+4147
		CCRIS (TOXNET). *Updated 2003*	carcinogenicity /genotoxicity	http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ccris:@term+@DOCNO+454
		GENE-TOX (TOXNET). *Updated 1992*	genotoxicity	http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+genetox:@term+@DOCNO+1519
		ChemIDplus (TOXNET)	acute toxicity	https://chem.nlm.nih.gov/chemidplus/rn/504-88-1
		CPDB (TOXNET)	carcinogenicity / genotoxicity	https://toxnet.nlm.nih.gov/cpdb/chempages/3-NITROPROPIONIC%20ACID.html
		CTD (TOXNET)	genomics	http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ctd:@term+@DOCNO+CTD/C015392
		HAZ-MAP (TOXNET)	occupational	https://hazmap.nlm.nih.gov/category-details?table=copytblagents&id=3470
	Bioassay of 3-nitropropionic acid for possible carcinogenicity (CAS No. 504-88-1)	NTP	carcinogenicity	http://ntp.niehs.nih.gov/results/pubs/longterm/reports/longterm/abstracts99/tr052/index.html
	NTP Assessments 3-Nitropropionic acid - 10620-G.	NTP	general toxicity / genotoxicity / carcinogenicity	http://ntp.niehs.nih.gov/testing/status/agents/ts-10620-g.html
	Target Organs and Levels of Evidence for TR-052	NTP	carcinogenicity	http://ntp.niehs.nih.gov/results/summaries/chronicstudies/tr0099/bydate/tr052levels/index.html
andrastin A	--	--	--	--
aristolochene	ARISTOLOCHENE CASRN: 26620-71-3	ChemIDplus (TOXNET)	--	https://chem.nlm.nih.gov/chemidplus/rn/26620-71-3

Compound	Title	Source. *Last update*	Information	URL
asperparaline(s)	--	--	--	--
citreoviridin	CITREOVIRIDIN CASRN: 25425-12-1	GENE-TOX (TOXNET). *Updated 1991*	genotoxicity	http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+genetox:@term+@DOCNO+3451
		ChemIDplus (TOXNET)	acute toxicity	https://chem.nlm.nih.gov/chemidplus/rn/25425-12-1
culmorin	CULMORIN CASRN: 18374-83-9	ChemIDplus (TOXNET)	--	https://chem.nlm.nih.gov/chemidplus/rn/18374-83-9
cyclopenol	CYCLOPENOL CASRN: 20007-85-6	ChemIDplus (TOXNET)	--	https://chem.nlm.nih.gov/chemidplus/rn/20007-85-6
cyclopiazonic acid	CYCLOPIAZONIC ACID CASRN: 18172-33-3	HSDB (TOXNET). *Updated 2005*	--	http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+7248
		CCRIS (TOXNET). *Updated 1993*	genotoxicity	http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ccris:@term+@DOCNO+4942
		GENE-TOX (TOXNET). *Updated 1995*	genotoxicity	http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+genetox:@term+@DOCNO+3284
		ChemIDplus (TOXNET)	acute toxicity	https://chem.nlm.nih.gov/chemidplus/rn/18172-33-3
		CTD (TOXNET)	genomics	http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ctd:@term+@DOCNO+CTD/C000543
		HAZ-MAP (TOXNET)	occupational	https://hazmap.nlm.nih.gov/category-details?table=copytblagents&id=4609
cytolysin A	--	--	--	--
endophenazine A	--	--	--	--
festuclavine	FESTUCLAVINE CASRN: 569-26-6	ChemIDplus (TOXNET)	acute toxicity	https://chem.nlm.nih.gov/chemidplus/rn/569-26-6
		CCRIS (TOXNET). *Updated 1995*	genotoxicity	http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ccris:@term+@DOCNO+6640
isofumigaclavine	ISOFUMIGACLAVINE CASRN: 72626-13-2	ChemIDplus (TOXNET)	--	https://chem.nlm.nih.gov/chemidplus/rn/72626-13-2
	ISOFUMIGACLAVINE B CASRN: 58800-20-7	ChemIDplus (TOXNET)	--	https://chem.nlm.nih.gov/chemidplus/rn/58800-20-7

Compound	Title	Source. *Last update*	Information	URL
isotrichodermin	ISOTRICHODERMIN CASRN: 91423-90-4	ChemIDplus (TOXNET)	--	https://chem.nlm.nih.gov/chemidplus/rn/91423-90-4
isotrichodermol	ISOTRICHODERMOL CASRN: 104155-10-4	ChemIDplus (TOXNET)	--	https://chem.nlm.nih.gov/chemidplus/rn/104155-10-4
kojic acid	KOJIC ACID CASRN: 501-30-4	HSDB (TOXNET). *Updated 2009*	--	http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+7664
		CCRIS (TOXNET). *Updated 2009*	carcinogenicity / genotoxicity	http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ccris:@term+@DOCNO+4131
		GENE-TOX (TOXNET). *Updated 1995*	genotoxicity	http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+genetox:@term+@DOCNO+1514
		ChemIDplus (TOXNET)	acute toxicity	https://chem.nlm.nih.gov/chemidplus/rn/501-30-4
		CPDB (TOXNET)	carcinogenicity / genotoxicity	https://toxnet.nlm.nih.gov/cpdb/chempages/KOJIC%20ACID.html
		CTD (TOXNET)	genomics	http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ctd:@term+@DOCNO+CTD/C011890
	Volume 79. Some Thyrotropic Agents	IARC monographs. *Updated 2001*	carcinogenicity	http://monographs.iarc.fr/ENG/Monographs/vol79/index.php
LPS endotoxin	ENDOTOXINS CASRN: 11034-88-1	ChemIDplus (TOXNET)	--	https://chem.nlm.nih.gov/chemidplus/rn/11034-88-1
		HAZ-MAP (TOXNET)	occupational	https://hazmap.nlm.nih.gov/category-details?table=copytblagents&id=1358
	ENDOTOXINS NO CASRN	CTD (TOXNET)	genomics	http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ctd:@term+@DOCNO+CTD/D004731
malformin(s)	MALFORMINS CASRN: 3022-92-2	ChemIDplus (TOXNET)	acute toxicity	https://chem.nlm.nih.gov/chemidplus/rn/3022-92-2
maltoryzine	MALTORYZINE CASRN: 6826-42-2	ChemIDplus (TOXNET)	acute toxicity	https://chem.nlm.nih.gov/chemidplus/rn/6826-42-2
marcfortine	MARCFORTINE A CASRN: 75731-43-0	ChemIDplus (TOXNET)	--	https://chem.nlm.nih.gov/chemidplus/rn/75731-43-0
mitorubrinic acid	--	--	--	--

Compound	Title	Source. *Last update*	Information	URL
mycophenolic acid	MYCOPHENOLIC ACID CASRN: 24280-93-1	CCRIS (TOXNET). *Updated 1994*	genotoxicity	http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ccris:@term+@DOCNO+5565
		GENE-TOX (TOXNET). *Updated 1995*	genotoxicity	http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+genetox:@term+@DOCNO+3414
		ChemIDplus (TOXNET)	acute toxicity	https://chem.nlm.nih.gov/chemidplus/rn/24280-93-1
		CTD (TOXNET)	genomics	http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ctd:@term+@DOCNO+CTD/D009173
naphtho-pyrones	--	--	--	--
neoxaline	NEOXALINE CASRN: 71812-10-7	ChemIDplus (TOXNET)	acute toxicity	https://chem.nlm.nih.gov/chemidplus/rn/71812-10-7
nigerazine	B: N-Methyl-trans-2,5-dimethyl-N'-cinnamoylpiperazine CASRN	ChemIDplus (TOXNET)	acute toxicity	https://chem.nlm.nih.gov/chemidplus/rn/85982-75-8
nigragillin	NIGRAGILLIN(E) CASRN: 24779-38-2	ChemIDplus (TOXNET)	--	https://chem.nlm.nih.gov/chemidplus/rn/24779-38-2
orlandin	ORLANDIN CASRN: 69975-77-5	ChemIDplus (TOXNET)	acute toxicity	https://chem.nlm.nih.gov/chemidplus/rn/69975-77-5
oxalic acid	OXALIC ACID CASRN: 144-62-7	HSDB (TOXNET). *Updated 2009*	--	http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+1100
		CCRIS (TOXNET). *Updated 2006*	genotoxicity	http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ccris:@term+@DOCNO+1454
		ChemIDplus (TOXNET)	acute toxicity	https://chem.nlm.nih.gov/chemidplus/rn/144-62-7
		CTD (TOXNET)	genomics	http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ctd:@term+@DOCNO+CTD/D019815
		HAZ-MAP (TOXNET)	occupational	https://hazmap.nlm.nih.gov/category-details?table=copytblagents&id=582
	NTP Assessments Oxalic acid - 10049-C	NTP	genotoxicity / reproductive toxicity	http://ntp.niehs.nih.gov/testing/status/agents/ts-10049-c.html
	Oxalic Acid (CAS #144-62-7): Reproduction and Fertility Assessment in CD-1 Mice When Ad	NTP	reproductive toxicology	http://ntp.niehs.nih.gov/testing/types/repro/abstracts/racb84064/index-32.html
	Oxalic acid ICSC: 0529	ICSC (Inchem). *Updated 2009*	safety card	http://www.inchem.org/documents/icsc/icsc/eics0529.htm

Compound	Title	Source. *Last update*	Information	URL
perinadine A	--	--	--	--
phenazine-1-carboxylic ac	--	--	--	--
phenazines	PHENAZINE CASRN: 92-82-00	HAZ-MAP (TOXNET)	occupational	https://hazmap.nlm.nih.gov/category-details?table=copytblagents&id=16513
PR toxin	PR-TOXIN CASRN: 56299-00-4	HSDB (TOXNET). *Updated 2014*		http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+7247
		CCRIS (TOXNET). *Updated 1994*	genotoxicity	http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ccris:@term+@DOCNO+4938
		GENE-TOX (TOXNET). *Updated 1998*	genotoxicity	http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+genetox:@term+@DOCNO+3920
		ChemIDplus (TOXNET)	acute toxicity	https://chem.nlm.nih.gov/chemidplus/rn/56299-00-4
		HAZ-MAP (TOXNET)	occupational	https://hazmap.nlm.nih.gov/category-details?table=copytblagents&id=6825
pyocianin	--	--	--	--
roquefortine	ROQUEFORTINE CASRN: 58735-64-1	ChemIDplus (TOXNET)	acute toxicity	https://chem.nlm.nih.gov/chemidplus/rn/58735-64-1
		HAZ-MAP (TOXNET)	occupational	https://hazmap.nlm.nih.gov/category-details?table=copytblagents&id=6976
sambucinol	SAMBUCINOL CASRN: 90044-33-0	ChemIDplus (TOXNET)	--	https://chem.nlm.nih.gov/chemidplus/rn/90044-33-0
secalonic acid	SECALONIC ACID D CASRN: 35287-69-5	CCRIS (TOXNET). *Updated 1993*	genotoxicity	http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ccris:@term+@DOCNO+4937
		GENE-TOX (TOXNET). *Updated 1995*	genotoxicity	http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+genetox:@term+@DOCNO+3636
	SECALONIC ACID CASRN: 56283-72-8	ChemIDplus (TOXNET)	acute toxicity	https://chem.nlm.nih.gov/chemidplus/rn/56283-72-8
trichodermin	TRICHODERMIN CASRN: 4682-50-2	ChemIDplus (TOXNET)	acute toxicity	https://chem.nlm.nih.gov/chemidplus/rn/4682-50-2
	International Programme on Chemical safety. Environmental Health Criteria 105. Selected mycotoxins: ochratoxins, tricothecenes, ergot	IPCS (Inchem)	--	http://www.inchem.org/documents/ehc/ehc/ehc105.htm

Compound	Title	Source. *Last update*	Information	URL
xanthomegnin	XANTOMEGNIN CASRN: 1685-91-2	ChemIDplus (TOXNET)	--	https://chem.nlm.nih.gov/chemidplus/rn/1685-91-2

Appendix D. List of food enzymes & feed additives used as exclusion criteria.

Product
(1→4)-α-D-glucan 1-α-D-glucosylmutase
1,4-alpha-Glucan branching enzyme
3-Phytase
4-alpha-glucanotransferase
4-Phytase
6-phytase
Acetolactate decarboxylase
Acetylhexosaminidase (beta-L-N)
Acid prolyl endopeptidase
Acylglycerol lipase
Alginate lyase
Alpha-trehalase
Alpha-amylase
Alpha-galactosidase
Alpha-glucosidase
Alpha-L-arabinofuranosidase
Alpha-L-rhamnosidase
Alternansucrase
Aminoacylase
Aminopeptidase
AMP deaminase
Aqualysin 1
Arabinanase
Arabinofuranosidase
Arginine
Asparaginase
Asparaginase
Aspergillopepsin I
Aspergillus nuclease S1
Bacillolysin
Beta-amylase
Beta-galactosidase (lactase)
Beta-glucanase
Beta-Glucosidase
Beta-mannanase
Bromelain
Carboxypeptidase (serine-type)
Carboxypeptidase C
Catalase
Cellobiose dehydrogenase
Cellulase
Chitinase
Chymosin
Chymotrypsin
Cyclomaltodextrin glucanotransferase
Dextranase
D-Fructose 4-Epimerase
D-psicose 3-epimerase
Endo-1,3(4)-β-glucanase
Endo-1,4-beta-xylanase
Endothiapepsin
Ferulic acid esterase
Ficin
Food enzyme consisting of Aspergillopepsin I and Aspergillopepsin II

Product
Food enzyme consisting of cellulase as a main activity and cellulose 1,4-β-cellobiosidase and β-glucosidase as subsidiary activities)
Food enzyme consisting of Cellulase, Endo-1,3(4)-β-glucanase, and Xylanase
Food enzyme consisting of Cellulase, Glucanase and Hemicellulase covering Xylanase and Mannanase
Food enzyme consisting of Pectinase, Polygalacturonase, Pectinesterase, Pectin Lyase and Arabanase
Food enzyme consisting of Protease, Leucyl aminopeptidase, Oryzin and Aspergillopepsin I
Food enzyme consisting of Trypsin and Chymotrypsin
Food enzyme consisting of Trypsin, Chymotrypsin, Elastase and Carboxypeptidase
Food enzyme consisting of Xylanase, Endo-1,3(4)-β-glucanase and Glucan 1,3-β-glucosidase
Glucan 1,4-alpha-glucosidase
Glucan 1,4-alpha-maltotetraohydrolase
Glucan 1,4-α-maltohydrolase
Glucanase
Glucoamylase
Glucose isomerase
Glucose oxidase
Glucosidase (alpha)
Glucosidase (beta)
Glucosyltransferase or Transglucosidase
Glutaminase
Hemicellulase
Hexose oxidase
Inulase
Inulinase
Invertase
Isoamylase
Isomaltulose synthase
Laccase
Lactase or Galactosidase (beta)
Lactoperoxidase
lasalocid sodium
L-ascorbate oxidase
Leucyl aminopeptidase
Lipase
Lipase monoacylglycerol
Lipase triacylglycerol
Lipoxygenase
Lysine
Lysophospholipase
Lysozyme
Maduramicin
Maltogenic amylase
Mannanase (endo-1.4-beta)
Membrane alanyl aminopeptidase
Methionine
Microbial collagenase
Monensin
Mucorpepsin
Narasin
Organophosphate esterase
Oryzin
Pancreatin
Papain
Paromomycin
Pectate lyase

Product
Pectin lyase
Pectin methylesterase or Pectinesterase
Pectinase
Penicillin amidase
Pentosanase
Peroxidase
Phosphodiesterase
Phospholipase A
Phospholipase B
Phospholipase C
Phospholipase D
Plant coagulant (Phytepsin)
Polygalacturonase
Protease
Protein glutaminase
Pullulanase
Rennet
Rhizopuspepsin
Ribonuclease P
Salinomicyn
Semduramicin
Subtilisin
Tannase
Thermolysin
Threonine
Thrombin
Transglutaminase
Trypsin
Tryptophan
Urease
Valine
Xaa-Pro dipeptidase
Xylanase
Xylose isomerase

Appendix E – List of toxins evaluated by EFSA, IARC or NTP or included in Directive 2002/32/EC

Table 1E. List of toxins evaluated by IARC (Monographs on the Evaluation of Carcinogenic Risks to humans), NTP (Report on Carcinogens) or EFSA, or included in the Directive 2002/32/EC

TOXINS	CAS NUMBER	Agency (year)	Evaluation title/classification
Aflatoxin B1[1]	1162-65-8		
Aflatoxins	1402-68-2	IARC (2012)	Group 1[4]
		NTP (2016)	Known to be human carcinogens
		EFSA (2006)	Opinion of the scientific panel on contaminants in the food chain [CONTAM] related to the potential increase of consumer health risk by a possible increase of the existing maximum levels for aflatoxins in almonds, hazelnuts and pistachios and derived products
		EFSA (2004)	Opinion of the Scientific Panel on contaminants in the food chain [CONTAM] related to Aflatoxin B1 as undesirable substance in animal feed
Beauvericin	26048-05-5	EFSA (2014)	Scientific Opinion on the risks to human and animal health related to the presence of beauvericin and enniatins in food and feed
Citrinin	518-75-2	IARC (1987)	Group 3[5]
		EFSA (2012)	Scientific Opinion on the risks for public and animal health related to the presence of citrinin in food and feed
Deoxynivalenol	51481-10-8	IARC (1993)[2]	Group 3
		EFSA (2007)	Opinion of the Scientific Panel on Contaminants in the Food Chain on a request from the Commission related to Deoxynivalenol (DON) as undesirable substance in animal feed
Enniatin A, A1, B, B1	2503-13-1; 4530-21-6; 917-13-5; 19914-20-6	EFSA (2014)	Scientific Opinion on the risks to human and animal health related to the presence of beauvericin and enniatins in food and feed
Ergot alkaloids[1]		EFSA (2011)	Scientific Opinion on Ergot alkaloids in food and feed
Fumonisin B1	116355-83-0	IARC (1993[3], 2002)	Group 2B[6]
Fumonisin B2	116355-84-1	IARC (1993)[3]	Group 2B
Fumonisins		IARC (1993)[3]	Group 2B
		EFSA (2005)	Opinion of the Scientific Panel on contaminants in the food chain [CONTAM] related to fumonisins as undesirable substances in animal feed
Fusarenone X		IARC (1993)[2]	Group 3
Fusarin C	116355-84-1	IARC (1993)[3]	Group 2B
Nivalenol	23282-20-4	IARC (1993)[2]	Group 3
		EFSA (2013)	Scientific Opinion on risks for animal and public health related to the presence of nivalenol in food and feed
Ochratoxin A	303-47-9	IARC (1993)	Group 2B
		NTP	Reasonably anticipated to be HC

		EFSA (2006)	Opinion of the Scientific Panel on contaminants in the food chain [CONTAM] related to ochratoxin A in food
TOXINS	**CAS NUMBER**	**Agency (year)**	**Evaluation title/classification**
		EFSA (2004)	Opinion of the Scientific Panel on contaminants in the food chain [CONTAM] related to ochratoxin A (OTA) as undesirable substance in animal feed.
Patulin	149-29-1	IARC (1987)	Group 3
Penicillic acid	90-65-3	IARC (1987)	Group 3
Phomopsin A	64925-80-0	EFSA (2012)	Scientific Opinion on the risks for animal and public health related to the presence of phomopsins in feed and food
Sterigmatocystin	10048-13-2	IARC (1987)	Group 2B
T2 and HT-2 toxins	21259-20-1; 26934-87-2	EFSA (2011)	Scientific Opinion on the risks for animal and public health related to the presence of T-2 and HT-2 toxin in food and feed
T2-toxin	21259-20-1	IARC (1993)	Group 3
Zearalenone	17924-92-4	IARC (1993)[2]	Group 3
		EFSA (2011)	Scientific Opinion on the risks for public health related to the presence of zearalenone in food
		EFSA (2004)	Opinion of the Scientific Panel on contaminants in the food chain [CONTAM]related to Zearalenone as undesirable substance in animal feed.

[1]Included in Directive 2002/32/EC
[2]IARC agent "Fusarium graminearum, F. culmorum, and F. crookwellense, toxins derived from (zearalenone, deoxynivalenol, nivalenol, and fusarenone X)"
[3]IARC agent "Fusarium moniliforme, toxins derived from (fumonisin B1, fumonisin B2, and fusarin C)"
[4]Carcinogenic to humans
[5]Not classifiable as to its carcinogenicity to humans
[6]Possibly carcinogenic to humans

Appendix F – List of excluded articles. Level 2

Table F1: List of articles excluded according to the criteria established for phase 2 of the revision, and reasons of exclusion

CITATION	REASON OF EXCLUSION
Abbas, 2015.	Document does not report designated outcomes
Albillos, *et al.*, 2011.	Data not well defined/reported for inclusion in the DB
Alvi *et al.*, 2000	Document does not report designated outcomes
Aninat *et al.*, 2005	Document does not report designated outcomes
Bai *et al.*, 2015	Data not well defined/reported for inclusion in the DB
Ballok *et al.*, 2013	Document does not report designated outcomes
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Dantasa *et al.*, 2013	Data not well defined/reported for inclusion in the DB

CITATION	REASON OF EXCLUSION
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Dhulipala, 2005	Data not well defined/reported for inclusion in the DB
Dhulipala *et al.*, 2004a	Data not well defined/reported for inclusion in the DB
Dhulipala *et al.*, 2004b	Data not well defined/reported for inclusion in the DB
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Liao *et al.*, 2010.	Data not well defined/reported for inclusion in the DB
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Massi *et al.*, 2016b	Data not well defined/reported for inclusion in the DB
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CITATION	REASON OF EXCLUSION
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Reddy, 2005	Document does not report designated outcomes
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Shipkova *et al.*, 2005	Document does not report designated outcomes
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Sio *et al.*, 2006	Document does not report designated outcomes
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Stern *et al.*, 2007	Data not well defined/reported for inclusion in the DB
Su *et al.*, 2013.	Data not well defined/reported for inclusion in the DB
Susca *et al.*, 2014	Data not well defined/reported for inclusion in the DB
Takahashi *et al.*, 2002	Document does not report designated outcomes
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CITATION	REASON OF EXCLUSION
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Zhang *et al.*, 2014	Data not well defined/reported for inclusion in the DB
Zheng *et al.*, 2007	Document does not report designated outcomes
Zizzo *et al.*, 2010	Data not well defined/reported for inclusion in the DB

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Appendix G – Summary of secondary metabolites with bioactivity

Microorganism	Secondary Metabolites	Comments	Ref.
Actinomadura roseorufa	reports not found		
Actinomadura yumaensis	reports not found		
Aeribacillus pallidus Syn. *Geobacillus pallidus*	reports not found		
Arthrobacter ramosus	reports not found		
Aspergillus aculeatus	(5aS,6S,7S)-3,7-dihydroxy-6-methoxy-1,4,6,9-tetramethyl-6,7-dihydro-5aHdibenzo[b,e][1,4]dioxepine-8,11-dione	bioactive compound	[1]
	15a hydroxy 22E, 24R ergosta 3, 5, 8 14, 22 tetraen 7 one 1	bioactive compound	[2]
	2,5-dimethyl-1,3-benzenediol	bioactive compound	[1]
	3,8-dihydroxy-1,4,6,9-tetramethyldibenzo[b,e][1,4]dioxepin-11-one	bioactive compound	[1]
	4-O-demethylbarbatic acid	bioactive compound	[1]
	aculeatusquinones A-D	bioactive compound	[1]
	aculenes A-D (sesquiterpenoid)	bioactive compound	[3]
	asperaculane A (sesquiterpenoid)	bioactive compound	[3]
	asperaculane B (sesquiterpenoid)	bioactive compound	[3]
	atraric acid	bioactive compound	[1]
	nordaucane one (sesquiterpenoid)	bioactive compound	[3]
	okaramines H and I	insecticidal activity	[4]
	secalonic acid D	mycotoxin	[3]

Microorganism	Secondary Metabolites	Comments	Ref.
Aspergillus japonicus	**asperparalines**	bioactive compound	[5, 6, 7]
	chanoclavine-I	ergot alkaloids intermediate	[8]
	cycloclavin	ergot alkaloid	[9]
	ergot alkaloids	mycotoxin	[8]
	festuclavine	ergot alkaloid	[9]
	neoxaline	alkaloid	[10, 11]
	ochratoxin A	mycotoxin	[12]
	preparaherquamide	alkaloid	[13]
	secalonic acid F	mycotoxin	[14, 15]
	sterigmatocystin	mycotoxin	[16]
Aspergillus melleus	aspyrone	nematicidal activity	[17]
	mellamide	insecticidal activity	[18]
	ochratoxin A	mycotoxin	[18]
	viomellin	bioactive compound	[18]
	xanthomegnin	bioactive compound	[18]
Aspergillus niger	anthraquinones	bioactive compound	[19]
	asperenone	bioactive compound	[20]
	aspernigerin	bioactive compound	[21]
	aspernigrins	bioactive compound	[22]

Microorganism	Secondary Metabolites	Comments	Ref.
	aurasperone B ;F; G	naphtho-gamma-pyrone	[23, 24]
	campyrone A;B;C	bioactive compound	[25]
	coprogen B	iron chelator	[26]
	desmethylkotanin	bioactive compound	[23]
	ferrichrome	iron chelator	[26]
	fonsecin	bioactive compound	[22]
Aspergillus niger	**fumonisin; B2; B4**	mycotoxin	[23, 27-37]
	funalenone	collagenase inhibitor	[31]
	hexylitaconic acid	plant growth regulator	[38]
	kotanin	bioactive compound	[23, 31, 34]
	malformin A; C	cause malformations in plants	[22, 23, 31, 34]
	maltoryzine	mycotoxin	[39]
	naphtho-gamma-pyrones	toxic aromatic compounds	[31, 34, 40]
	nigerasperone A;B;C	naphtho-gamma-pyrones	[41]
	nigerazine B	plant growth inhibitor	[42]
	nigragillin	alkaloid	[40, 42]
	ochratoxin A;alpha	mycotoxin	[23, 24, 29, 31, 33, 34, 43-53]
	orlandin	bioactive compound	[23, 40]
	oxalates and oxalic acid	toxic organic compound	[54-57]

Microorganism	Secondary Metabolites	Comments	Ref.
	pyranonigrin A	antioxidative activity	[23, 31]
Aspergillus niger	rubrofusarins	bioactive compound	[22]
	saponins	foaming glucoside	[19]
	tensidol B	antimicrobial compound	[23, 31]
	tensyuic acids	antibiotic	[38]
	yanuthone K;L;M;X2	antifungal compound	[58]
Aspergillus oryzae	13-desoxypaxilline	intermediate metabolite	[59]
	2-oxocyclopiazonic acid	less toxic analogue of CPA	[60]
	3-nitropropionic acid	mycotoxin	[42]
	aflatoxins B1 and B2	mycotoxin	[61, 62]
	aspergillomarasmine	phytotoxins	[42]
	aspirochlorine	inhibitor of fungal protein synthesis	[63]
	astellolides A; B; C-E; F-I	sesquiterpenoids	[64]
	bisdethio(bismethylthio)gliotoxin	bioactive compound	[65]
	cyclo-(Pro,Val)	bioactive compound	[65]
	cyclo-(Tryp,Tyr)	bioactive compound	[65]
	cyclopiazonic acid	mycotoxin	[42, 60, 65- 69]
	deoxynivalenol (DON)	mycotoxin	[62]
	ditryptophenaline	alkaloid	[65]

Microorganism	Secondary Metabolites	Comments	Ref.
	kojic acid	tyrosinase inhibitor	[42, 65, 66, 70]
Aspergillus oryzae	**maltoryzine**	cause food poisoining in cows	[42]
	oryzaeins	bioactive compound	[71]
	parasiticolide A	secondary metabolite	[59]
	pseurotin A	bioactive compound	[65]
	speradines B -H	bioactive compounds	[72, 73]
	T-2 toxin	mycotoxin	[62]
	uridine	bioactive compound	[65]
	violacetin	bioactive compound	[42]
	zearalenone	mycotoxin	[62]
Aspergillus sojae	**aflatoxin**	mycotoxin	[74]
	glyceollins	isoflavone bioactive compound	[75, 76]
Bacillus macerans	reports not found		
Syn. *Paenibacillus macerans*			
Bacillus naganoensis	reports not found		
Syn. *Pullulanibacillus naganoensis*			
Bacillus soli	reports not found		
Syn. *Paenibacillus macerans*			

Microorganism	Secondary Metabolites	Comments	Ref.
Bullera singularis	reports not found		
Syn. *Sporobolomyces singularis*			
Candida cylindracea	reports not found		
Syn. *Candida rugosa*			
Candida lipolytica	tryptanthrin	agonists of the dioxin receptor	[77, 78]
Syn. *Mycotorula lipolytica*			
Candida paralipolytica	reports not found		
Syn. Candida lipolytica			
Candida rugosa	reports not found		
Cellulosimicrobium cellulans	antharanilic acid	bioactive compound	[79]
	cyclo-(dehydroala-l-Leu)	bioactive compound	[79]
	cyclo-(l-Pro-l-Leu)	bioactive compound	[79]
	cyclo-(l-Pro-l-Tyr)	bioactive compound	[79]
Cellulosimicrobium cellulans	cyclo-(l-Pro-l-Val)	bioactive compound	[79]
	L-phenylalanine	bioactive compound	[79]
Chaetomium erraticum	reports not found		
Chaetomium gracile	22E,24R)-ergosta-7,22-diene-3β,5alfa,6beta-triol	antimicrobial substance	[80]
	adenosine	antimicrobial substance	[80]
	chaetochromin A	antimicrobial substance	[80]

Microorganism	Secondary Metabolites	Comments	Ref.
	chaetoquadrin	antimicrobial substance	[80]
	ergosterol	antimicrobial substance	[80]
	eugenitol	antimicrobial substance	[80]
	glycerol monopalmitate	antimicrobial substance	[80]
	indole-3-carboxylic acid	antimicrobial substance	[80]
	p-hydroxylbenzaldehyde	antimicrobial substance	[80]
Cryphonectria parasitica	A (1 --> 3)-beta-D-glucan	immunostimulant	[81]
Syn. *Endothia parasitica*	cryparin	hydrophobin protein	[82, 83]
	cryphonectric acid	phytotoxin	[84]
	diaporthin	produce canker in leaves	[84]
Cryphonectria parasitica	L- p-hydroxyphenyllactic acid (HOPLA)	phytotoxin	[84]
	orthosporin	produce canker in leaves	[84]
	phleichrome	pigment (quinone)	[85]
Chryseobacterium proteolyticum	endotoxin	(virulence factor), low production	[86]
Disporotrichum dimorphosporum	reports not found		
Endothia parasitica	reports not found		
Syn. *Cryphonectria parasitica*			
Escherichia coli K-12	curli proteins	adhesion protein	[87]
	cytolysin A (ClyA)	cytotoxin	[88, 89]

Microorganism	Secondary Metabolites	Comments	Ref.
	lipopolysaccharide (LPS) or endotoxin	endotoxin	[90]
	SheA hemolysin	cytotoxin	[91]
	Tsh protein	hemagglutinin (virulence factor)	[92]
Flavobacterium multivorum	reports not found		
Fusarium venenatum	apotrichothecene	mycotoxin (trichothecenes)	[93]
	beauvericin	mycotoxin	[94]
	butenedioic acid	bioactive compound	[95]
	culmorin	sesquiterpene	[93]
	culmorone	sesquiterpene	[93]
	diacetoxyscirpenol	mycotoxin (trichothecenes)	[93, 95, 96]
	enniatin B	sesquiterpene	[93]
	fusarin C	mycotoxin	[97]
	hexadecane	bioactive compound	[95]
	hexadecanoc acid	bioactive compound	[95]
Fusarium venenatum	imidazole	bioactive compound	[95]
	isotrichodermin	mycotoxin (trichothecenes)	[93]
	isotrichodermol	mycotoxin (trichothecenes)	[93]
	phenol, 2,5-bis (1,1- dimethylethyl)	bioactive compound	[95]
	phthalic acid	bioactive compound	[95]

Microorganism	Secondary Metabolites	Comments	Ref.
	sambucinol	mycotoxin (trichothecenes)	[93]
	tetradecanoic acid	bioactive compound	[95]
Geobacillus caldoproteolyticus	reports not found		
Geobacillus palidus	antimicrobial polipeptide	antimicrobial	[98]
Geobacillus stearothermophilus	reports not found		
Hansenula polymorpha	reports not found		
Humicola insolens	reports not found		
Klebsiella planticola	indole-3-acetic acid (IAA)	auxin (plant hormone)	[99]
klebsiella pneumoniae	3-hydroxypropionaldehyde (HPA)	antimicrobial	[100]
	capsule polysaccharide	virulence factor	[101]
	lipopolysaccharide (LPS)	virulence factor	[101]
Leptographium procerum	reports not found		
Microbacterium imperiale	reports not found		
Micrococcus luteus	reports not found		
Mucor circinelloides Syn. *Mucor javanicus*	**3-nitropropionic acid**	mycotoxin	[102]
Mucor javanicus Syn. *Mucor circinelloides*	reports not found		

Microorganism	Secondary Metabolites	Comments	Ref.
Mycotorula lipolytica Syn. *Candida lipolytica*	reports not found		
Ogataea polymorpha Syn. *Hansenula polymorpha*	reports not found		
Paecilomyces lilacinus Syn. *Penicillium lilacinum*	leucinostatins	bioactive compounds	[103, 104]
Paenibacillus alginolyticus	reports not found		
Paenibacillus lentus	reports not found		
Paenibacillus macerans	anti-phytopathogenic compounds		[105]
	nematicidal compounds		[106]
Penicillium camemberti	**cyclopiazonic acid**	mycotoxin	[107]
Penicillium chrysogenum	(3R, 4R)-3,4,8-trihydroxy-3,4-dihydronaphthalen-1 (2H)-one	bioactive compound	[108]
	(9Z,12Z)-2,3-dihydroxypropyl octadeca-9,12-dienoate	neuroprotective effect	[109]
	(E)-N-(4-hydroxystyryl) formamide	bioactive compound	[108]
	(Z)-N-(4-hydroxy styryl) formamide	bioactive compound	[108]
	1,2,4 dihydroxy 6 methylbenzoyl glycerol	antifungal compound	[110]
	11 bromoroquefortine C	bioactive compound	[111]
	2,2,4 dihydroxy 6 methylbenzoyl glycerol	antifungal compound	[110]
	2-(4-hydroxyphenyl)acetamides	bioactive compound	[112]

Microorganism	Secondary Metabolites	Comments	Ref.
	2-(4-hydroxyphenyl) acetonitrile	bioactive compound	[108]
	2,3-dihydrosorbicillin	neuroprotective effect	[109]
	2-[(2-hydroxypropionyl) amino] benzamide	neuroprotective effect	[109]
	24 epicyclocitrinol 9	steroid	[113]
	2S,3R oxaline	bioactive compound	[108]
	4-(2-hydroxyethyl) benzene-1,2-diol	bioactive compound	[108]
	bisvertinolone	bioactive compound	[114]
	BMS 182123	TNF-alpha inhibitor	[115]
	chrysogenamide A	neuroprotective effect	[109]
	chrysotriazoles A and B	bioactive compound	[112]
	circumdatin G	neuroprotective effect	[109]
Penicillium chrysogenum	**citrinin**	mycotoxin	[116-118]
	conidiogenones	diterpenes	[119]
	conidogenol	diterpenes	[119]
	cyclocitrinol	steroid	[113]
	emodin	bioactive compound	[108, 120]
	ergosterol endoperoxide	bioactive compound	[121]
	erythro 11 hydroxyneocyclocitrinol	steroid	[113]
	linolenic acid	bioactive compound	[121]

Microorganism	Secondary Metabolites	Comments	Ref.
	lovastatin	bioactive compound	[122]
	meleagrin	bioactive compound	[120, 123]
	methyl 2-(4-hydroxyphenyl) acetate	bioactive compound	[108]
	N 4 hydroxystyryl formamides	bioactive compound	[112]
	neocyclocitrinols A-D	steroid	[113]
	norcyclocitrinol A	steroid	[113]
	ochratoxin A	mycotoxin	[124, 125]
	oxosorbicillinol	bioactive compound	[114]
	penicillin G	antibiotic	[123]
	penicimonoterpene	antifungal compound	[110]
	penicisteroid A, B	cytotoxic polyoxygenated steroids	[126]
Penicillium chrysogenum	penicitide A, B	cytotoxic and antimicrobial	[110]
	penicitols A and C	citrinin analogues	[127]
	penimethavone A	flavone	[128]
	penixanacid A	xanthone derivative	[127]
	pesudocyclocitrinol A	cytotoxic polyoxygenated steroids	[113]
	phenoxyacetic acid	antifungal compound	[129]
	phenylacetic acid	citrinin analogues	[129]
	PR toxin	sesquiterpenoid mycotoxin	[130]

Microorganism	Secondary Metabolites	Comments	Ref.
	quinazolinones	bioactive compound	[112]
	roquefortine C	mycotoxin	[114, 120, 123, 131-133]
	rugulosin	bioactive compound	[134]
	secalonic acid	mycotoxin	[120, 135]
	skyrin	bioactive compound	[134]
Penicillium chrysogenum	sorbicillactones A and B	bioactive compound	[114]
	sorbicillin	bioactive compound	[114]
	sorbicillinol	bioactive compound	[114]
	sorbivinetone	bioactive compound	[114]
	xanthocillin X	bioactive compound	[123]
Penicilium citrinum	(3S)-4,6-dihydro-8-mehoxy-3,5-dimethyl-6-oxo-3H-2-benzopyran	bioactive compound	[136]
	(3S)-6-hydroxy-8-methoxy-3,5-dimethylisochroman	bioactive compound	[136]
	1,2,3,11b-tetrahydroquinolactacide	bioactive compound	[136]
	2-(hept-5-enyl)-3-methyl-4-oxo-6,7,8,8a-tetrahydro-4H-pyrrolo[2,1-b]-1,3-oxazine	bioactive compound	[137]
	2,4,5-trimethylbenzene-1,3-diol	bioactive compound	[137]
	2,4-dihydroxy-3, 5,6-trimethylbenzoic acid	bioactive compound	[137]
	3-methoxy-2-methyl-4H-pyran-4-one	bioactive compound	[137]
	4-hydroxyquinolin-2(1H)-one	bioactive compound	[136]
	5-methyl alternariol ether	bioactive compound	[137]

Microorganism	Secondary Metabolites	Comments	Ref.
	6-methylcurvulinic acid	bioactive compound	[136]
	8-methoxy-3,5-dimethylisoquinolin-6-ol	bioactive compound	[136]
	ω-hydroxyemodin	bioactive compound	[137]
	alternariol	bioactive compound	[137]
	arohynapene D	bioactive compound	[136]
	citrinamide	bioactive compound	[136]
	citrinin, H1, H2	**mycotoxin**	[137-147]
	citriquinochroman	citrinin derivative	[136]
Penicilium citrinum	conioxanthone A	bioactive compound	[137]
	decarboxycitrinin	citrinin derivative	[137, 142]
	decarboxydihydrocitrinone	citrinin derivative	[145]
	dicitrinin	citrinin derivative	[142]
	dicitrinol A and B	citrinin derivative	[142]
	ergot alkaloids	mycotoxin	[148]
	indole acetic acid methyl ester	bioactive compound	[136]
	methyl 8-hydroxy-6-methyl-9-oxo-9H-xanthene-1-carboxylate	bioactive compound	[137]
	methylpenicinoline	bioactive compound	[136]
	mevastatine	statins	[149]
	Pen c 1, 2, 3, 13, n18, 22, 24, 30, 32	allergen	[150-157]

Microorganism	Secondary Metabolites	Comments	Ref.
	penicinoline	bioactive compound	[136]
	penicitrinol B, C, D, E13, G, L	cytotoxic compound	[142, 145, 158]
	penicitrinone A	cytotoxic compound	[158]
	penidicitrinin B	cytotoxic compound	[158]
	perinadine A	alkaloid	[137, 159]
	phenol A, phenol A acid	bioactive compound	[142]
Penicilium citrinum	quinolactacide	TNF inhibitor	[136, 160]
	quinolactacin A	TNF inhibitor	[137]
	redoxcitrinin	citrinin derivative	[137]
	sclerotinin A, B	bioactive compound	[137]
	sydowinin B	bioactive compound	[137]
	tanzawaic acid A, B, F, G, H	anti-inflammatory activity	[136, 147]
	trichodermamide	bioactive compound	[136]
	tricitrinol A, B	bioactive compound	[142]
	vanillic acid	bioactive compound	[136]
Penicillium decumbens	(16R)-16-hydroxy-24-epi-cyclocitrinol	bioactive compound	[161]
Syn. *Penicillium indicum*	12R-hydroxycyclocitrinol	bioactive compound	[161]
	20-O-methyl-24-cyclocitrinol	bioactive compound	[161]
	20-O-methyl-24-epi-cyclocitrinol	bioactive compound	[161]

Microorganism	Secondary Metabolites	Comments	Ref.
	22-acetylisocyclocitrinol A	bioactive compound	[161]
	24-epi-cyclocitrinol	bioactive compound	[161]
	cyclocitrinol	bioactive compound	[161]
Penicillium decumbens	cyclopenicillone	bioactive compound	[161, 162]
	decumbenones A and B	fungal inhibitor	[163]
	isocyclocitrinol A, B	bioactive steroid	[161]
	neocyclocitrinol A, B, C, D	bioactive steroid	[161]
	OH-15 derivative of 24-epi-cyclocitrinol	bioactive compound	[161]
	versiol	fungal inhibitor	[163]
Penicillium funiculosum	2,3,4 trihydroxybutanamide	antimicrobial compound	[164]
Syn. *Talaromyces funiculosum*	chrodrimanins I and J	bioactive compound	[165]
	citreoviridin	mycotoxin	[166]
	gibberellins (diterpenoid acids)	plant growth promoter	[167]
	mitorubrinic acid	derivative of roquefortine	[168, 169]
	OR 1	a mixture of esters of glyceric acid	[169, 170]
	patulin	mycotoxin	[171]
	prenyleudesmane diterpenoids 1 and 2	terpenoid	[172]
	siderophores	iron chelator	[173]
Penicillium funiculosum	wortmannin	cytotoxic steroid	[174]

Microorganism	Secondary Metabolites	Comments	Ref.
Penicillium lilacinum	leucinostatins, A	statin	[103, 104, 175]
Syn. *Purpureocillium lilacinum* Syn. *Paecylomices lilalicinus*	phytotoxins	agonist to nematodes	[176]
Penicillium multicolor	(S)-6-((1S,2S)-1,2-dihydroxypentyl)-4-methoxy-5,6-dihydro-2H-pyran-2-one	antitumor	[177]
	5 bromoochrephilone	bioactive compound	[178]
	5-hydroxy-4-methoxy-5,6-dihydro-2H-pyran-2-one	bioactive compound	[177]
	8-O-methylsclerotiorinamine	bioactive compound	[179]
	dechloroisochromophilone II- IV (azaphilone)	bioactive compound	[177, 178]
	epi-isochromophilone III (azaphilone)	bioactive compound	[177]
	ergosterol	bioactive compound	[177]
	ergosterol peroxide	bioactive compound	[177]
	isochromophilone I–IV, VI, VIII (azaphilone)	bioactive compound	[177, 178, 180]
	Isorotiorin (azaphilone)	bioactive compound	[178]
	Ochrephilone (azaphilone)	bioactive compound	[177]
	sclerotioramine (azaphilone)	bioactive compound	[177]
Penicillium multicolor	sclerotiorin (azaphilone)	bioactive compound	[177, 180]
Penicillium nordicum	**ochratoxin A**	mycotoxin	[181-191]

Microorganism	Secondary Metabolites	Comments	Ref.
Penicillium notatum	reports not found		
Syn. Penicillium chrysogenum			
Penicillium roqueforti	1-hydroxyeremophil-7(11),9(10)-dien-8-one		[192]
	andrastins A-D	bioactive compounds	[192-195]
	aristolochene	in the biosynthetic route of PR toxin	[130, 196]
	eremofortines A-E	alkaloid	[197]
	festuclavine	ergot alkaloid	[197-199]
	isofumigaclavines A and B	ergot alkaloids	[197, 198]
	marcfortines	derivatives of roquefortine	[195, 200]
	mycophenolic acid	mycotoxin	[192, 200-208]
	patulin	mycotoxin	[204, 205, 208]
	penicillic acid	mycotoxin	[204, 205, 208]
	PR toxin	mycotoxin	[130, 192, 193, 196, 198, 200, 205, 209-212]
	roquefortine A, C, D	mycotoxin	[192, 193, 195, 197, 198, 200, 204, 206-209, 212-219]
Penicillium salamii	reports not found		
Penicillium sclerotiorum	**cyclopenol**	benzodiazepine alkaloid	[220]
Syn. Penicillium multicolor	ergosterol	bioactive alkaloid	[220]
	ergosterol peroxide	bioactive alkaloid	[220]

Microorganism	Secondary Metabolites	Comments	Ref.
	isochromophilone VI	antimicrobial substance	[221]
	pencolide	antimicrobial substance	[221]
	sclerotiorin	aldose reductase inhibitor	[221, 222]
	verrucosidin	bioactive alkaloid	[220]
	viridicatin	bioactive alkaloid	[220]
	viridicatol	bioactive alkaloid	[220]
Pichia angusta *Syn. Hansenula polymorpha*	reports not found		
Pseudomonas aeruginosa	2-aminoacetophenone	virulence factor	[223]
	alkylquinoline	signaling molecule	[224]
	CFTR inhibitory factor	virulence factor	[225, 226]
	elastase		[227]
	ETA		[228]
	ExoS	virulence factor	[228-231]
	ExoT	virulence factor	[228, 229]
	Exotoxin A	virulence factor	[227, 232]
	ExoU	virulence factor	[233-237]
	L-2-amino-4-methoxy-3-butenoic acid		[238]
	lipopolysaccharide (LPS)	endotoxin	[239, 240]

Microorganism	Secondary Metabolites	Comments	Ref.
	lipotoxin		[241]
	metallo-β-Lactamase	antimicrobial resistance factor	[242]
	PcrV (type III secretion system)	virulence factor	[243]
	phenazine and derivates	virulence factor	[244-246]
Pseudomonas aeruginosa	pseudoverdine	virulence factor	[247]
	pyochelin (siderophore)	virulence factor	[248]
	pyocyanin (phenazide)	virulence factor	[223, 249-262]
	pyoluteorin		[263]
	pyoverdine	virulence factor	[227, 264-266]
	rhamnolipids	bacterial surfactants	[227, 267]
	Tse2	virulence factor	[268]
	TypA	virulence factor	[269]
	Type II secretion system	virulence factor	[270]
	Type III secretion system	virulence factor	[271-274]
Pseudomonas amyloderamosa	reports not found		
Pullulanibacillus naganoensis	reports not found		
Purpureocillium lilacinum *Syn. Penicillium lilacinum* *Syn. Paecylomices*	reports not found		

Microorganism	Secondary Metabolites	Comments	Ref.
Raoultella planticola	reports not found		
Syn. Klebsiella planticola			
Rhizomucor miehei	reports not found		
Rhizopus niveus	reports not found		
Rhizopus oryzae	gamma-linolenic acid methyl ester (methyl GLA)	antiapoptotic effect	[275]
	linoleic acid	cytotoxic and antiinflamatory	[276]
Rhizopus oryzae	linolenic acid methyl ester	cytotoxic and antiinflamatory	[276]
	palmitic acid	cytotoxic and antiinflamatory	[276]
	palmitic acid methyl ester	cytotoxic and antiinflamatory	[276]
	Rhi o 1	allergen	[277]
Sphingobacterium multivorum	reports not found		
Sporobolomyces singularis	reports not found		
Streptomyces albus	bacteriocin	antibacterial compound	[278]
	pyranones	antitumor	[279]
	rebeccamycin (indolocarbazole alkaloids)	antitumor	[280]
	siderophore	iron chelant	[278]
	terpene	bioactive compound	[278]
Streptomyces aureofaciens	reports not found		

Microorganism	Secondary Metabolites	Comments	Ref.
Streptomyces chrestomyceticus	albofungin	antibiotic	[281]
	chloroalbofungin	antibiotic	[281]
	chrestoxanthones A-C	antifungal	[281]
Streptomyces chromofuscus	carazostatin	carbazole alkaloids	[282]
Streptomyces chromofuscus	herboxidiene	bioactive compound	[283]
Streptomyces cinnamonensis	2-demethylmonensihs A, B	minor congeners of monensins	[284]
	arcyriaflavin E	indolocarbazole alkaloid	[285]
	endophenazine A	antimicrobial compound	[286, 287]
	furanonaphthoquinone I (FNQ I)	bioactive compound	[286, 287]
Streptomyces cinnamoneus	reports not found		
Streptomyces lasaliensis	manumycin A and lycorine	antimicrobial substance	[288]
Streptomyces lividans	colabomycin E	anti inflammatory agent	[289]
Streptomyces mobaraensis	bleomycin	anticancer substance	[290]
Streptomyces murinus	reports not found		
Streptomyces netropsis	congocidine analogs (pyrrolamide compounds)	antibiotics	[291]
	congocidine (pyrrolamide compound)	antibiotic	[292]
	disgocidine (pyrrolamide compound)	antibiotic	[292]
	distamycin (pyrrolamide compound)	antibiotic	[291, 292]
Streptomyces olivochromogenes	reports not found		

Microorganism	Secondary Metabolites	Comments	Ref.
Streptomyces rubiginosus	reports not found		
Streptomyces violaceoruber	granaticin A, C	bioactive polyketide	[293, 294]
Streptomyces violaceoruber	granatomycin E	bioactive polyketide	[293]
	kendomycin	bioactive polyketide	[295]
	metenaticin A, B and C	bioactive polyketide	[293]
Streptoverticillium cinnamoneum	antibiotic HA 94	antimicrobial substance	[296]
Streptoverticillium mobaraense	reports not found		
Talaromyces cellulolyticus	reports not found		
Talaromyces emersonii	reports not found		
Syn. *Rasamsonia emersonii*			
Talaromyces versatilis	reports not found		
Torula lypolitica	reports not found		
Trametes hirsuta	1-phenyl-3-methylpyrazolones	oxidoreductase mediators	[297]
	aryl tetral226in lignans	bioactive compounds	[298]
	podophyllotoxin	bioactive compounds	[298]
Trametes versicolor	funatrol D	bioactive compound	[299]
	isodrimenediol	sesquiterpenes (anticancer)	[299]
	tramspiroins	sesquiterpenes (anticancer)	[299]
	triterpenes	bioactive compounds	[300]

Microorganism	Secondary Metabolites	Comments	Ref.
	rosenonolactone 15,16-acetonide	sesquiterpenes (anticancer)	[299]
Trichoderma citrinoviride	24-methylenecycloartanol		[301]
	5-hydroxy-2,3-dimethyl-7-methoxychromone		[301]
	bislongiquinolide	insecticide activity	[302]
	citrantifidiene	insecticide activity	[303]
	citrantifidiol	insecticide activity	[303]
	citrinoviric acid	cytotoxic metabolite	[304]
	citrostadienol	antimicrobial activity	[301]
	cyclo Leu Pro, cyclo Ile Pro, cyclo Phe Pro		[304]
	dihydrotrichodimerol	insecticide activity	[302]
	lignoren		[304]
Trichoderma citrinoviride	nafuredin	antimicrobial activity	[301]
	penicillenol B1; B2, D	cytotoxic metabolite	[304]
	peptaibols	bioactive compounds	[305, 306]
	trichocitrin	antimicrobial activity	[301]
	trichoderiol A, C		[304]
	trichodimerol	insecticide activity	[302]
Trichoderma harzianum	1,8-dihydroxy-3-methyl-anthraquinone	antifungal	[307-309]
	1-hydroxy-3-methylanthraquinone	antifungal	[307-309]

Microorganism	Secondary Metabolites	Comments	Ref.
	2(5H)-furanone	antifungal	[308]
	2,4-di-tert-butylphenol	bioactive compound	[310]
	2,6,10-trimethylundeca-5,9-dienal	bioactive compound	[310]
	2-phenylethanol	bioactive compound	[311]
	6-pentyl-alpha-pyrone	bioactive compound	[312, 313]
	6-methyl-1,3,8-trihydroxyanthraquinone	antifungal	[308]
	6-n-pentyl-a-pyrone	bioactive compound	[311]
	6-pentyl-2H-pyran-2-one	antifungal	[308]
	alpha-cubebene	bioactive compound	[310]
	alpha-curcumene	bioactive compound	[310]
	anthraquinones	antifungal	[314]
	azaphilone	antifungal	[307, 309]
	b-bisabolene	bioactive compound	[310]
	biformen (6CI)	bioactive compound	[310]
	butenolide	antifungal	[307, 309]
	chrysophanol	antifungal	[314, 315]
	cytochalasin analogs	cytotoxic compound	[316]
Trichoderma harzianum	decanolactone	antifungal	[308]
	emodin	antifungal	[314]

Microorganism	Secondary Metabolites	Comments	Ref.
	ergosterol	antifungal	[308, 311, 317]
	fleephilone	bioactive compound	[318]
	gliotoxin	bioactive compound	[319]
	gliovirin	bioactive compound	[319, 320]
	harzianic acid	siderophore	[321]
	harzianolide	anti-phytopathogen	[307, 309, 322]
	harzianopyridone	anti-phytopathogen	[307-309]
	harziphilone	bioactive compound	[318]
	hexahydrofarnesol	bioactive compound	[310]
	indol acetic acid	anti-phytopathogen	[323-325]
	lignocerane	bioactive compound	[310]
	nerolidol	bioactive compound	[310]
	pachybasin, hydroxypachybasin	anti-phytopathogen	[314, 315]
	pentadecane	bioactive compound	[310]
	peptaibols	bioactive compounds	[326, 327]
	pristane	bioactive compound	[310]
Trichoderma harzianum	sitosterol	antifungal	[308]
	sorbicillin	bioactive compound	[311]
	stigmasterol	antifungal	[308]

Microorganism	Secondary Metabolites	Comments	Ref.
	tandyukisins B-D (decalin derivative)	cytotoxic	[328]
	trichodenone A, B, C	cytotoxic	[329]
	trichodermin	trichotecene toxin	[319, 330]
	trichodermol (detected in hydrolysed crude extracts)	trichotecene toxin	[331]
	trichorzin	peptaibol	[332]
	tyrosol	bioactive compound	[311]
	verticillol	bioactive compound	[310]
	viridiofungin A	anti-phytopathogen	[333]
Trichoderma koningii	6, 4-oxopentyl-2H-pyran-2-one	antifungal	[334]
	6-pentyl-pyranone	antifungal	[334]
	7-O-methylkoninginin D (polyketide derivative)	antimicrobial	[335]
	alpha-aminoisobutyric acid		[336]
	amino alcohol (peptaibols)		[336]
	decanolactone	antifungal	[334]
	koninginins A, D, E, F, L, M	phospholipase A 2 inhibitors	[335, 337, 338]
	stigmasterol	antifungal	[334]
	trichodermaketones A-D (polyketide derivatives)	antimicrobial	[335, 337]
	trichokonins (peptaibols)	antimicrobial	[339-341]
Trichoderma longibranchiatum	longibranchins (LGA I-V and LGB II-III) (peptaibols)	biooactive compounds	[342-345]

Microorganism	Secondary Metabolites	Comments	Ref.
	trichobrachin A, C (peptaibols)	biactive compounds	[346]
	trichogin GA IV (peptaiboils)	bioactive compound	[347]
	trilongins BI-BIV (peptaibols)	mitochondriotoxic	[348]
Trichoderma reesei	fusarinine	siderophore	[349]
	kojic acid	antibacterial activity	[350]
	trichoderide A (cyclotetrapeotide)	bioactive compound	[351]
	trichodermatide A-D	bioactive compound	[352]
	trichodermin (trichothecene)	mycotoxin	[42]
Trichoderma viride	**diacetoxyscirpenol**	mycotoxin	[353]
	kojic acid	antibacterial activity	[350]
	lovastatin	bioactive compound	[122]
	trichovirins II (peptaibols)	antimicrobial	[354]
	T2-toxin	mycotoxin	[124]
Yarrowia lipolytica Syn. *Candida lipolytica*	Y-decolactone		[355]

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Appendix H – Relational database

Entity	Name	description	dataType	catalogueCode	isNullable	precision	scale	maxLength
SOURCES	id_op (PK)	Primary key for the source	VARCHAR2		FALSE			20
SOURCES	op_type	Type of document	VARCHAR2	REF_TYPE	FALSE			400
SOURCES	author	Author of the journal article	VARCHAR2		TRUE			255
SOURCES	TITLE	Title of the journal article	VARCHAR2		FALSE			1000
SOURCES	PUBLICATION_DATE	Date of the publication (yyyymmdd)	NUMBER		FALSE	8	0	
SOURCES	JOURNAL_TITLE	Title of the journal where has been published the article	VARCHAR2		TRUE			1000
SOURCES	DOI	Digital Object Identifier of the journal article	VARCHAR2		TRUE			255
SOURCES	URL	the jornal link (internet address) or publisher	VARCHAR2		TRUE			1000
SOURCES	id_language	Language used to fill in the free text fields (ISO-639-1) from LANG catalogue	CATALOGUE	LANG	TRUE			400
MICROORGANISM	id_microorganism (PK)	Primary key for the identification of the microorganism	NUMBER		FALSE			20
MICROORGANISM	id_species	microorganism used in the biotechnological process	CATALOGUE	MTX	FALSE			
MICROORGANISM	TAXON_LINEAGE	Contains a general classification of the microorganism (molds/yeast/bacteria)	VARCHAR2		FALSE			255
MICROORGANISM	TAXONOMY_METHOD	Acceptable scientific methodologies and techniques for the identification of microorganisms	CATALOGUE	ANLYMD	TRUE			
MICROORGANISM	method_reliability	Measure of the consistency of the taxonomic method (% Homology/Closenest)	NUMBER		TRUE	3	10	
MICROORGANISM	methodREMARK	Additional remarks on taxonomy study	VARCHAR2		TRUE			2000
TOXICITY	id_tox (PK)	Primary key for the identification of the toxicology data	NUMBER		FALSE			20
TOXICITY	paramCode	Toxic compound described according to the Substance Code from PARAM catalogue	CATALOGUE	PARAM	FALSE			400
TOXICITY	test_species	Organism/cell culture used in the toxicological study	CATALOGUE	MTX	TRUE			

Entity	Name	description	dataType	catalogueCode	isNullable	precision	scale	maxLength
TOXICITY	testsubstance	Description of test material used in the toxicological study	VARCHAR2		TRUE			2000
TOXICITY	id_test_type	Type of toxicological test	CATALOGUE	TEST_TYPE	FALSE			400
TOXICITY	strain	The strain of the organism tested	CATALOGUE	STRAIN	TRUE			
TOXICITY	id_route	Indicator how the substance is administered to the organism (human/animals)	CATALOGUE	ROUTE_EXP	TRUE			
TOXICITY	id_endpoint	Endpoint reported in the study to describe the reported values (e.g. NOAEL, dose level)	CATALOGUE	ENDPOINT_HGV	FALSE			400
TOXICITY	id_qualifier	Qualifier for the reported endpoint values (e.g. =, <=, >=)	CATALOGUE	QUALIFIER	TRUE			400
TOXICITY	id_dose_unit	Enumeration of group units for group assessment	CATALOGUE	UNIT	TRUE			
TOXICITY	value_effect_concentration	Effect concentration	NUMBER		TRUE	5	1	
TOXICITY	id_toxicity	Classification of critical effect according to toxicity target (Owens 2002)	CATALOGUE	TOXICITY	TRUE			
TOXICITY	effect_desc	Free text to describe effects observed in the toxicological study	VARCHAR2		TRUE			2000
TOXICITY	id_basis	Characterisation of the measures toxicological outcome measure	CATALOGUE	BASIC_EFFECT	FALSE			400
TOXICITY	remarks	Additional remarks on toxicological study. Free text on hazard assessment including (if necessary): 1) short explanation on how the study has been carried on; 2) any conclusions on the hazard identication	VARCHAR2		TRUE			2000
PROCESS CONDITIONS	id_process conditions (PK)	Primary key for the identification of the process conditions	NUMBER		FALSE			20
PROCESS CONDITIONS	id_species	microorganism used in the biotechnological process	CATALOGUE	MTX	FALSE			
PROCESS CONDITIONS	temperature	Temperature in degrees centigrade	NUMBER		TRUE	2	10	

Entity	Name	description	dataType	catalogueCode	isNullable	precision	scale	maxLength
PROCESS CONDITIONS	aeration	Aerobic/Anaerobic/Microaerophilic conditions	VARCHAR2		TRUE			255
PROCESS CONDITIONS	waterActivity	Water activity	NUMBER		TRUE	1	10	
PROCESS CONDITIONS	substrate	Type of substrate used in the biotechnological process	VARCHAR2		TRUE			300
PROCESS CONDITIONS	pH	pH during the fermentation process	NUMBER		TRUE	2	10	
PROCESS CONDITIONS	FermentationTime	Time in hours of the fermentation process	NUMBER		TRUE	20	10	
PROCESS CONDITIONS	prodTreat	Used to characterise a food product based on the treatment or processes applied to the product or any indexed ingredient from PRODTR catalogue	CATALOGUE	PRODTR catalogue	TRUE			
PROCESS CONDITIONS	fermentationState	Types of fermentation: solid State, semi-solid, submerged batch, submerged fed-batch, submerged continuous, immobilized cell bioreactors, immobilized enzyme bioreactors	NUMBER		TRUE	1	0	
PROCESS CONDITIONS	paramCode	Toxic compound described according to the Substance Code from PARAM catalogue	CATALOGUE	PARAM	FALSE			
PROCESS CONDITIONS	processRemarks	Additional remarks on process conditions. Free text	VARCHAR2		TRUE			2000
BIOSYNTHETIC PATHWAYS	id_biosysthetic path (PK)	Primary key for the identification of the synthesis pathway of the metabolite	NUMBER		FALSE			20
BIOSYNTHETIC PATHWAYS	id_species	microorganism used in the biotechnological process	CATALOGUE	MTX	FALSE			
BIOSYNTHETIC PATHWAYS	paramCode	Toxic compound described according to the Substance Code from PARAM catalogue	CATALOGUE	PARAM	FALSE			
BIOSYNTHETIC PATHWAYS	MapURL	link to the diagram where the route of synthesis of the substance is represented	VARCHAR2		TRUE			2000
BIOSYNTHETIC PATHWAYS	geneMod	Genetic modification (YES/NO)	VARCHAR2		TRUE			255

Entity	Name	description	dataType	catalogueCode	isNullable	precision	scale	maxLength
BIOSYNTHETIC PATHWAYS	geneMod_REMARKS	Genetic modification (information of genes inserted or deleted)	VARCHAR2		TRUE			2000
BIOSYNTHETIC PATHWAYS	biosynthetic_remarks	Additional remarks on biosynthetic pathways. Free text	VARCHAR3		TRUE			2000
FACT_PROCESSTOXINS	id_ProcessToxins (PK)	Unique ID for fact table	NUMBER		FALSE			20
FACT_PROCESSTOXINS	id_op (FK)	Foreing key for the source	NUMBER		FALSE			20
FACT_PROCESSTOXINS	id_microorganism (FK)	Foreing key for the identification of the microorganism	NUMBER		TRUE			20
FACT_PROCESSTOXINS	id_tox (FK)	Foreing key for the identification of the toxicology data	NUMBER		TRUE			20
FACT_PROCESSTOXINS	id_process conditions (FK)	Foreing key for the identification of the process conditions	NUMBER		TRUE			20
FACT_PROCESSTOXINS	id_biosysthetic path (FK)	Foreing key for the identification of the synthesis pathway of the metabolite	NUMBER		TRUE			20
GENE	id_gene (PK)	Primary key for the identification of the gene	NUMBER		FALSE			20
GENE	gene_name	Gene name involved in the synthesis of the substance	VARCHAR2		FALSE			100
GENE	protein_name	Name of protein synthesised from the gene	VARCHAR2		TRUE			45
GENE	gene_description	Free text to describe the function of the gene	VARCHAR2		TRUE			75
GENE	gene_sequence	sequence of the involved in the synthesis route	VARCHAR2		TRUE			3000
BIO_PATHWAY2GENE	id_bio_pathway (PK & FK)	Foreign key for the identification of the biosynthetic pathway and Primary key in the relationship	NUMBER		FALSE			20
BIO_PATHWAY2GENE	id_gene (PK & FK)	Foreing key for the identification of the gene and Primary key in the relationship	NUMBER		FALSE			20
MICROORG2GENE	id_microorg (PK & FK)	Foreing key for the identification of the microorganism taxonomy and Primary key in the relationship	NUMBER		FALSE			20
MICROORG2GENE	id_gene (PK & FK)	Foreing key for the identification of the gene and Primary key in the relationship	NUMBER		FALSE			20
MICROORG2GENE	housekeeping_gene_GenBank	GenBank ID for the housekeeping gene	VARCHAR2		TRUE			45

Appendix I – Attributes for Param Catalogue

code	extendedName	shortName	reportable	IUPAC	CAS	MOLECULAR_FORMULA	SMILES_NOTATION	INCHI
RF-00004558-PAR	**1-Hydroxyphenazine**	(1-HP)	Yes	5H-phenazin-1-one	CAS 528-71-2	C12H8N2O	C1=CC=C2C(=C1)NC3=CC=CC(=O)C3=N2	NAD
RF-00004547-PAR	**Andrastin A**	-	Yes	(3S,5R,8S,9R,10S,13R,14R)-methyl 3-acetoxy-10-formyl-4,4,8,12,13,16-hexamethyl-15,17-dioxo-2,3,4,5,6,7,8,9,10,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthrene-14-carboxylate	CAS 174232-42-9	C28H38O7	CC1C([C@]2(C)C(C)=C[C@]3([H])[C@@](CC[C@@]4([H])[C@@]3(C=O)CC[C@H](OC(C)=O)C4(C)C)(C)[C@]2(C(OC)=O)C1=O)=O	InChI=1S/C28H38O7/c1-15-13-19-25(6,28(23(33)34-8)22(32)16(2)21(31)26(15,28)7)11-9-18-24(4,5)20(35-17(3)30)10-12-27(18,19)14-29/h13-14,16,18-20H,9-12H2,1-8H3/t16?,18-,19-,20+,25+,26+,27+,28-/m1/s1
RF-00004573-PAR	**Aristolochene**	-	Yes	(4S,4aR,6S)-4,4a-dimethyl-6-prop-1-en-2-yl-2,3,4,5,6,7-hexahydro-1H-naphthalene	NAD	C15H24	C[C@H]1CCCC2=CC[C@@H](C[C@]12C)C(=C)C	InChI=1S/C15H24/c1-11(2)13-8-9-14-7-5-6-12(3)15(14,4)10-13/h9,12-13H,1,5-8,10H2,2-4H3/t12-,13-,15+/m0/s1
RF-00004548-PAR	**Asperparaline A**	-	Yes	(1*R*,5a*R*,7*R*,8a*R*,9a*S*)-1,1',8,8,11-pentamethyltetrahydro-1*H*,2'*H*,5'*H*,8*H*,10*H*-spiro[5a,9a-(epiminomethano)cyclopenta[*f*]indolizine-7,3'-pyrrolidine]-2',5',10-trione	CAS 195966-93-9	C20H29N3O3	C[C@@H]1CCN2C[C@@]34C[C@@]5(CC(=O)N(C)C5=O)C(C)(C)[C@H]3C[C@@]12C(=O)N4C	InChI=1S/C20H29N3O3/c1-12-6-7-23-11-19-10-18(9-14(24)21(4)15(18)25)17(2,3)13(19)8-20(12,23)16(26)22(19)5/h12-13H,6-11H2,1-5H3/t12-,13-,18-,19+,20+/m0/s1
RF-00004572-PAR	**Citreoviridin**	-	Yes	6-[(1E,3E,5E,7E)-8-[(2S,3R,4R,5R)-3,4-dihydroxy-2,4,5-trimethyloxolan-2-yl]-7-methylocta-1,3,5,7-tetraenyl]-4-methoxy-5-methylpyran-2-one	NAD	C23H30O6	C[C@@H]1[C@](C[C@H]([C@](O1)(C)/C=C(\C)/C=C/C=C/C=C/C2=C(C(=CC(=O)O2)OC)C)O)(C)O	InChI=1S/C23H30O6/c1-15(14-22(4)21(25)23(5,26)17(3)29-22)11-9-7-8-10-12-18-16(2)19(27-6)13-20(24)28-18/h7-14,17,21,25-26H,1-6H3/b8-7+,11-9+,12-10+,15-14+/t17-,21+,22+,23+/m1/s1
RF-00004574-PAR	**Culmorin**	-	Yes	NAD	NAD	C15H26O2	CC1(CCCC2(C3C1C(C2(CC3O)C)O)O)C)C	InChI=1S/C15H26O2/c1-13(2)6-5-7-14(3)10-9(16)8-15(14,4)12(17)11(10)13/h9-12,16-17H,5-8H2,1-4H3
RF-00004579-PAR	**Cyclopenol**	-	Yes	3'-(3-hydroxyphenyl)-4-methylspiro[1H-1,4-benzodiazepine-3,2'-oxirane]-2,5-dione	NAD	C17H14N2O4	CN1C(=O)C2=CC=CC=C2NC(=O)C13C(O3)C4=CC(=CC=C4)O	InChI=1S/C17H14N2O4/c1-19-15(21)12-7-2-3-8-13(12)18-16(22)17(19)14(23-17)10-5-4-6-11(20)9-10/h2-9,14,20H,1H3,(H,18,22)
RF-00004562-PAR	**Cyclopiazonic acid**	CPA	Yes	(6a*R*,11a*S*,11b*R*)-10-Acetyl-11-hydroxy-7,7-dimethyl-2,6,6a,7,11a,11b-hexahydro-9*H*-pyrrolo[1',2':2,3]isoindolo[4,5,6-*cd*]indol-9-one	CAS 18172-33-3	C20H20N2O3	CC(=O)/C1=C(\O)[C@H]5N(C1=O)[C@@](C)(C)[C@@H]4Cc2cccc3ncc(c23)[C@@H]45	NAD
RF-00004559-PAR	**Cytolysin A**	ClyA	Yes	NAD	NAD	NAD	NAD	NAD
RF-00004560-PAR	**Endophenazine A**	-	Yes	9-(3-Methyl-2-buten-1-yl)-1-phenazinecarboxylic acid	CAS 86125-71-5	C18H16N2O2	CC(=CCC1=C2C(=CC=C1)N=C3C=CC=C(C3=N2)C(=O)O)C	NAD
RF-00004549-PAR	**Fusarin C**	-	Yes	methyl (2E,3E,5E,7E,9E)-2-ethylidene-11-[(1R,4S,5R)-4-hydroxy-4-(2-hydroxyethyl)-2-oxo-6-oxa-3-azabicyclo[3.1.0]hexan-1-yl]-4,6,10-trimethyl-11-oxoundeca-3,5,7,9-tetraenoate	NAD	C23H29NO7	C/C=C(\C=C(/C)\C=C(/C)\C=C\C=C(/C)\C(=O)[C@@]12[C@@H](O1)[C@](NC2=O)(CCO)O)/C(=O)OC	InChI=1S/C23H29NO7/c1-6-17(19(27)30-5)13-15(3)12-14(2)8-7-9-16(4)18(26)23-20(31-23)22(29,10-11-25)24-21(23)28/h6-9,12-13,20,25,29H,10-11H2,1-5H3,(H,24,28)/b8-7+,14-12+,15-13+,16-9+,17-6+/t20-,22-,23-/m0/s1
RF-00004575-PAR	**Isofumigaclavine A**	-	Yes	[(6aR,9S,10R)-7,9-dimethyl-6,6a,8,9,10,10a-hexahydro-4H-indolo[4,3-fg]quinoline-10-yl] acetate	NAD	C18H22N2O2	C[C@H]1CN([C@@H]2CC3=CNC4=CC=CC(=C34)C2[C@@H]1OC(=O)C)C	InChI=1S/C18H22N2O2/c1-10-9-20(3)15-7-12-8-19-14-6-4-5-13(16(12)14)17(15)18(10)22-11(2)21/h4-6,8,10,15,17-19H,7,9H2,1-3H3/t10-,15+,17?,18+/m0/s1

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code	extendedName	shortName	reportable	IUPAC	CAS	MOLECULAR_FORMULA	SMILES_NOTATION	INCHI
RF-00004576-PAR	**Isofumigaclavine B**	-	Yes	(6aR,9S,10R,10aR)-7,9-dimethyl-6,6a,8,9,10,10a-hexahydro-4H-indolo[4,3-fg]quinoline-10-ol	NAD	C16H20N2O	C[C@H]1CN([C@@H]2CC3=CNC4=CC=CC(=C34)[C@H]2[C@@H]1O)C	InChI=1S/C16H20N2O/c1-9-8-18(2)13-6-10-7-17-12-5-3-4-11(14(10)12)15(13)16(9)19/h3-5,7,9,13,15-17,19H,6,8H2,1-2H3/t9-,13+,15+,16+/m0/s1
RF-00004577-PAR	**Isotrichodermin**	-	Yes	NAD	NAD	C17H24O4	CC1=C[C@@H]2[C@](CC1)(C3(C[C@H]([C@H](C34CO4)O2)OC(=O)C)C)C	InChI=1S/C17H24O4/c1-10-5-6-15(3)13(7-10)21-14-12(20-11(2)18)8-16(15,4)17(14)9-19-17/h7,12-14H,5-6,8-9H2,1-4H3/t12-,13-,14-,15+,16?,17?/m1/s1
RF-00004578-PAR	**Isotricodermol**	-	Yes	NAD	NAD	C15H22O3	CC1=C[C@@H]2[C@](CC1)([C@]3(C[C@H]([C@H](C34CO4)O2)O)C)C	InChI=1S/C15H22O3/c1-9-4-5-13(2)11(6-9)18-12-10(16)7-14(13,3)15(12)8-17-15/h6,10-12,16H,4-5,7-8H2,1-3H3/t10-,11-,12-,13+,14-,15?/m1/s1
RF-00004561-PAR	**Kojic acid**	-	Yes	5-Hydroxy-2-(hydroxymethyl)-4H-pyran-4-one	CAS 501-30-4	C6H6O4	O=C1/C=C(\O/C=C1/O)CO	NAD
RF-00004563-PAR	**Malformins**	-	Yes	10-butan-2-yl-7-(2-methylpropyl)-4-propan-2-yl-15,16-dithia-3,6,9,12,18-pentazabicyclo[11.4.2]nonadecane-2,5,8,11,19-pentone	CAS 3022-92-2	C23H39N5O5S2	CCC(C)C1C(=O)NC2CSSCC(C(=O)NC(C(=O)NC(C(=O)N1)CC(C)C)C(C)C)NC2=O	NAD
RF-00004564-PAR	**Maltoryzine**	-	Yes	1-(2,3,6-trihydroxyphenyl)pent-3-en-1-one	CAS 6826-42-2	C11H12O4	OC1=C(O)C=CC(O)=C1C(/C=C/CC)=O	NAD
RF-00004580-PAR	**Marcfortines**	-	Yes		CAS 75731-43-0	C28H35N3O4	NAD	NAD
RF-00004550-PAR	**Mitorubrinic acid**	-	Yes	(2E)-3-{7-[(2,4-Dihydroxy-6-methylbenzoyl)oxy]-7-methyl-6,8-dioxo-7,8-dihydro-6H-isochromen-3-yl}acrylic acid	CAS 58958-07-9	C21H16O9	Cc1cc(cc(c1C(=O)OC2(C(=O)C=C3C=C(OC=C3C2=O)/C=C/C(=O)O)C)O)O	InChI=1S/C21H16O9/c1-10-5-12(22)8-15(23)18(10)20(28)30-21(2)16(24)7-11-6-13(3-4-17(25)26)29-9-14(11)19(21)27/h3-9,22-23H,1-2H3,(H,25,26)/b4-3+
RF-00004565-PAR	**Naphtho-γ-pyrones**	-	Yes	1H-Benzo[f]chromen-1-one	NAD	C13H8O	O=C3/C=C\Oc2ccc1ccccc1c23	NAD
RF-00004551-PAR	**Neoxaline**	-	Yes	(14E)-11-HYDROXY-14-[(1H-IMIDAZOL-5-YL)METHYLIDENE]-2-METHOXY-9-(2-METHYLBUT-3-EN-2-YL)-2,13,16-TRIAZATETRACYCLO[7.7.0.0¹,¹³.0³,⁸]HEXADECA-3,5,7-TRIENE-12,15-DIONE	CAS 71812-10-7	C23H25N5O4	CC(C)(C=C)C12CC(C(=O)N\3C1(NC(=O)/C3=C\C4=CN=CN4)N(C5=CC=CC=C25)OC)O	InChI=1S/C23H25N5O4/c1-5-21(2,3)22-11-18(29)20(31)27-17(10-14-12-24-13-25-14)19(30)26-23(22,27)28(32-4)16-9-7-6-8-15(16)22/h5-10,12-13,18,29H,1,11H2,2-4H3,(H,24,25)(H,26,30)/b17-10+
RF-00004566-PAR	**Nigerazines**	-	Yes	(E)-3-phenyl-1-[(2S,5R)-2,4,5-trimethylpiperazin-1-yl]prop-2-en-1-one	NAD	C16H22N2O	C[C@H]1CN([C@@H](CN1C(=O)/C=C/C2=CC=CC=C2)C)C	InChI=1S/C16H22N2O/c1-13-12-18(14(2)11-17(13)3)16(19)10-9-15-7-5-4-6-8-15/h4-10,13-14H,11-12H2,1-3H3/b10-9+/t13-,14+/m1/s1
RF-00004567-PAR	**Nigragillin**	-	Yes	(2E,4E)-1-[(2R,5S)-2,4,5-trimethylpiperazin-1-yl]hexa-2,4-dien-1-one	CAS 24779-38-2	C13H22N2O	C/C=C/C=C/C(=O)N1C[C@@H](N(C[C@H]1C)C)C	InChI=1S/C13H22N2O/c1-5-6-7-8-13(16)15-10-11(2)14(4)9-12(15)3/h5-8,11-12H,9-10H2,1-4H3/b6-5+,8-7+/t11-,12+/m0/s1
RF-00004583-PAR	**Orlandin**	-	Yes	7-hydroxy-8-(7-hydroxy-4-methoxy-5-methyl-2-oxochromen-8-yl)-4-methoxy-5-methylchromen-2-one	NAD	C22H18O8	CC1=CC(=C(C2=C1C(=CC(=O)O2)OC)C3=C(C=C(C4=C3OC(=O)C=C4OC)C)O)O	InChI=1S/C22H18O8/c1-9-5-11(23)19(21-17(9)13(27-3)7-15(25)29-21)20-12(24)6-10(2)18-14(28-4)8-16(26)30-22(18)20/h5-8,23-24H,1-4H3
RF-00004552-PAR	**Penicillic acid**	-	Yes	(2Z)-3-methoxy-5-methyl-4-oxohexa-2,5-dienoic acid	CAS 90-65-3	C8H10O4	CC(=C)C(=O)/C(=C/C(=O)O)/OC	InChI=1S/C8H10O4/c1-5(2)8(11)6(12-3)4-7(9)10/h4H,1H2,2-3H3,(H,9,10)/b6-4-

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code	extendedName	shortName	reportable	IUPAC	CAS	MOLECULAR_FORMULA	SMILES_NOTATION	INCHI
RF-00004571-PAR	**Perinadine A**	-	Yes	NAD	NAD	C28H37NO7	[C@H]12[C@H]3[C@H](N(CC3)C(=O)C(C(=O)CCCC/C=C/C)C)Oc3c1c([C@@H]([C@H](O2)C)C)c(c(c3C(=O)O)O)C	InChI=1S/C28H37NO7/c1-6-7-8-9-10-11-19(30)15(3)26(32)29-13-12-18-24-21-20(14(2)17(5)35-24)16(4)23(31)22(28(33)34)25(21)36-27(18)29/h6-7,14-15,17-18,24,27,31H,8-13H2,1-5H3,(H,33,34)/b7-6+/t14-,15?,17-,18+,24+,27-/m1/s1
RF-00004557-PAR	**Phenazine-1-carboxylic acid**	PCA	Yes	phenazine-1-carboxylic acid	CAS 2538-68-3	C13H8N2O2	C1=CC=C2C(=C1)N=C3C=CC=C(C3=N2)C(=O)O	NAD
RF-00004556-PAR	**Phenazines**	-	Yes	Phenazine	CAS 92-82-0	C12H8N2	n1c3c(nc2c1cccc2)cccc3	NAD
RF-00004553-PAR	**PR toxin**	-	Yes	[(1aR,3R,3'S,3aR,5R,7bS)-3'-formyl-3,3',3a-trimethyl-6-oxospiro[2,3,4,7b-tetrahydro-1aH-naphtho[1,2-b]oxirene-5,2'-oxirane]-2-yl] acetate	CAS 56299-00-4	C17H20O6	C[C@H]1C([C@@H]2[C@@H](O2)C3=CC(=O)[C@@]4(C[C@]13C)[C@@](O4)(C)C=O)OC(=O)C	InChI=1S/C17H20O6/c1-8-12(21-9(2)19)14-13(22-14)10-5-11(20)17(6-15(8,10)3)16(4,7-18)23-17/h5,7-8,12-14H,6H2,1-4H3/t8-,12+,13-,14+,15+,16+,17-/m0/s1
RF-00004555-PAR	**Pyocyanin**	PYO	Yes	5-Methylphenazin-1-one	CAS 85-66-5	C13H10N2O	CN1C2=CC=CC=C2N=C3C1=CC=CC3=O	NAD
RF-00004569-PAR	**Roquefortine C**	-	Yes	NAD	CAS 58735-64-1	C22H23N5O3	CC(C)(C=C)C12CC3C(=O)N/C(=C/C4=CN=CN4)/C(=O)N3C1N(C5=CC=CC=C25)O	InChI=1S/C22H23N5O3/c1-4-21(2,3)22-10-17-18(28)25-15(9-13-11-23-12-24-13)19(29)26(17)20(22)27(30)16-8-6-5-7-14(16)22/h4-9,11-12,17,20,30H,1,10H2,2-3H3,(H,23,24)(H,25,28)/b15-9+
RF-00004582-PAR	**Sambucinol**	-	Yes	NAD	NAD	C15H22O4	CC1=C[C@]23[C@](CC1)([C@]4(C[C@@H]([C@H]([C@]4(O2)CO)O3)O)C)C	InChI=1S/C15H22O4/c1-9-4-5-12(2)13(3)7-10(17)11-14(13,8-16)19-15(12,6-9)18-11/h6,10-11,16-17H,4-5,7-8H2,1-3H3/t10-,11+,12+,13+,14+,15+/m0/s1
RF-00004554-PAR	**Secalonic acid**	-	Yes	methyl (3R,4S,4aS)-7-[(5S,6R,10aS)-1,5,9-trihydroxy-10a-methoxycarbonyl-6-methyl-8-oxo-6,7-dihydro-5H-xanthen-2-yl]-4,8,9-trihydroxy-3-methyl-1-oxo-3,4-dihydro-2H-xanthene-4a-carboxylate	CAS 35287-69-5	C32H30O14	C[C@@H]1CC(=O)C2=C(C3=C(C=CC(=C3O)C4=C(C5=C(C=C4)O[C@@]6([C@H]([C@@H](CC(=O)C6=C5O)C)O)C(=O)OC)O)O[C@@]2([C@H]1O)C(=O)OC)O	InChI=1S/C32H30O14/c1-11-9-15(33)21-25(37)19-17(45-31(21,27(11)39)29(41)43-3)7-5-13(23(19)35)14-6-8-18-20(24(14)36)26(38)22-16(34)10-12(2)28(40)32(22,46-18)30(42)44-4/h5-8,11-12,27-28,35-40H,9-10H2,1-4H3/t11-,12-,27+,28+,31+,32+/m1/s1
RF-00004568-PAR	**Trichodermin**	-	Yes	(4β,12*R*)-12,13-epoxytrichothec-9-en-4-yl acetate	CAS 4682-50-2	C17H24O4	CC1=C[C@@H]2[C@](CC1)([C@]3([C@@H](C[C@H]([C@@]34CO4)O2)OC(=O)C)C)C	NAD
RF-00004570-PAR	**Xanthomegnin**	-	Yes	(3R,3'R)-10,10'-Dihydroxy-7,7'-dimethoxy-3,3'-dimethyl-3,3',4,4'-tetrahydro-1H,1'H-8,8'-bibenzo[g]isochromene-1,1',6,6',9,9'-hexone	CAS 1685-91-2	C30H22O12	C[C@@H]1Cc2cc3c(c(c2C(=O)O1)O)C(=O)C(=C(C3=O)OC)C4=C(C(=O)c5cc6c(c(c5C4=O)O)C(=O)O[C@@H](C6)C)OC	InChI=1S/C30H22O12/c1-9-5-11-7-13-17(23(33)15(11)29(37)41-9)25(35)19(27(39-3)21(13)31)20-26(36)18-14(22(32)28(20)40-4)8-12-6-10(2)42-30(38)16(12)24(18)34/h7-10,33-34H,5-6H2,1-4H3/t9-,10-/m1/s1

NAD: Non-available data

Appendix J - Microorganism taxonomical identifiers

Table J1. BACTERIA

MICROORGANISMS NAME BY PROCUREMENT/ CURRENT NAME	SYNOMYM NAMES	TAXONOMY KINGDOM PHYLUM/ORDER/FAMILY	TAXONOMY REFERENCES	METHODS SUMMARY	HOUSEKEEPING GENES SEQUENCE ID GENBANK	HOUSEKEEPING GENES	REFERENCES HOUSEKEEPING GENES**	GENOME ID	CONCLUSION
Actinomadura yumaensis	*Actinomadura yumaense*	BACTERIA/Actinobacteria/ Actinomycetales/ Thermomonosporaceae	[1]	Scanning electron microscopy, cell chemistry, physiological tests	AF163122.1	16S rRNA gene	[85]	NAD	Current taxonomy valid update *Actinomadura yumaensis* 35:335*
Actinomadura roseorufa	NAD	-	[2]	Information from a Patent	NAD	NAD	NAD	NAD	No Taxonomy data available/ Not validated name
Arthrobacter ramosus	NAD	BACTERIA/Actinobacteria/ Actinomycetales/ Micrococcaceae	[3]	16S rRNA gene for the type strain: AM039435.	AM039435	16S rRNA gene	[86]	NAD	Current taxonomy valid update *Arthrobacter ramosus* 30:254 (AL)
Cellulosimicrobium cellulans	*Brevibacterium fermentans Brevibacterium lyticum*	BACTERIA/Actinobacteria/ Actinomycetales/ Promicromonosporaceae	[4]	16S rRNA sequence analyses	X83809	16S rRNA gene	[80]	https://www.ncbi.nlm.nih.gov/genome/genomes/15565	Current taxonomy valid update *Brevibacterium lyticum* 30:269 (AL) = *Cellulosimicrobium cellulans*
Chryseobacterium proteolyticum	NAD	BACTERIA/Bacteroidetes/ Flavobacteriales/ Flavobacteriaceae	[5]	Physiological and biochemical characteristics, 16S rRNA gene sequence analysis	AB039830	16S rRNA gene	[5]	NAD	Not validated name
Escherichia coli	NAD	BACTERIA/Proteobacteria/ Enterobacteriales/ Enterobacteriaceae	[6]	Comparative analysis of 5S and 16S rRNA sequences	X80725	16S rRNA gene	[79]	https://www.ncbi.nlm.nih.gov/genome/genomes/167	Current taxonomy valid update *Escherichia coli* 30:296 (AL)
					KJ858767.1	*adk* (adenylate kinase)	[57; 83]		
					KJ868320.1	*fumC* (fumarate hydratase)	[57]		
					DQ447149.1	*gyrB* (DNA gyrase)	[57]		
					KJ868480.1	*icd* (isocitrate/isopropylmalate dehydrogenase)	[57]		
					KJ868560.1	*mdh* (malate dehydrogenase	[57]		
					KJ868640.1	*purA* (adenylosuccinate dehydrogenase	[57]		
					JQ907532.1	*recA* (ATP/GTP binding motif)	[57]		
Geobacillus stearothermophilus	*Bacillus stearothermophilus*	BACTERIA/Firmicutes/ Bacillales/Bacillaceae	[7]	Phenotypic characterization, Chemotaxonomic characterization (fatty acid methyl ester analysis), Genotypic characterization (16S rRNA gene sequencing)	FN428694	16S rRNA gene	[78]	https://www.ncbi.nlm.nih.gov/genome/genomes/673	Current taxonomy valid update *Geobacillus stearothermophilus* 51:443*
					-	genes of carbohydrate metabolism	[58; 59]		
Geobacillus caldoproteolyticus	*Anoxybacillus caldiproteolyticus*	BACTERIA/Firmicutes/ Bacillales/Bacillaceae	[119; 7]	16S rRNA gene sequence analysis; and rpoB sequencing	FN428698	16S rRNA gene	[7]	NAD	Current taxonomy valid update *Anoxybacillus caldiproteolyticus* 62:1483*
					DQ642082.1	rpoB gene	[58; 59; 120]		
Geobacillus pallidus	*Aeribacillus pallidus*	BACTERIA/Firmicutes/ Bacillales/Bacillaceae	[7]	16S rRNA sequence analyses	Z26930	16S rRNA gene	[69]	https://www.ncbi.nlm.nih.gov/genome/genomes/14084	Current taxonomy valid update *Geobacillus pallidus* 54:2200 ≡ *Aeribacillus pallidus*
					DQ642059.1	rpoB gene	[58; 59; 120]		

MICROORGANISMS NAME BY PROCUREMENT/ CURRENT NAME	SYNOMYM NAMES	TAXONOMY KINGDOM PHYLUM/ORDER/FAMILY	TAXONOMY REFERENCES	METHODS SUMMARY	HOUSEKEEPING GENES SEQUENCE ID GENBANK	HOUSEKEEPING GENES	REFERENCES HOUSEKEEPING GENES**	GENOME ID	CONCLUSION
Klebsiella planticola	*Raoultella planticola*	BACTERIA/Proteobacteria/ Enterobacteriales/ Enterobacteriaceae	[8]	Biochemical tests, 16S rRNA and rpoB sequencing.	AF129443.1	16S rRNA gene	[8]	https://www.ncbi.nlm.nih.gov/genome/genomes/11487	Current taxonomy valid update *Klebsiella planticola* 32:266 ≡ *Raoultella planticola*
Klebsiella pneumoniae	NAD	BACTERIA/Proteobacteria/ Enterobacteriales/ Enterobacteriaceae	[8]	Biochemical tests, 16S rRNA and rpoB sequencing; MLSA.	X87276	16S rRNA gene	[77]	https://www.ncbi.nlm.nih.gov/genome/genomes/815	Current taxonomy valid update *Klebsiella pneumoniae* 34:355
					-	*folA* (dihydrofolate reductase)	[60; 61; 62]		
					AF146532.1	*waa* gene cluster	[60; 61; 62]		
					FJ769969.1	*gnd* (6-phosphogluconate dehydrogenase)	[60; 61; 62]		
					-	*ugd* (UDP-glucose 6-dehydrogenase)	[60; 61; 62]		
Microbacterium imperiale	*Brevibacterium imperiale*	BACTERIA/Actinobacteria/ Actinomycetales/ MicroBACTERIA/ceae	[9]	sequence comparison of gyrB, rpoB, recA and ppk and 16S rRNA genes	X77442	16S rRNA gene	[76]	NAD	Current taxonomy valid update *Brevibacterium imperiale* 30:269 (AL) ≡ *Microbacterium imperiale*
Micrococcus luteus	*Micrococcus lysodeikticus*	BACTERIA/Actinobacteria/ Actinomycetales/ Micrococcaceae	[10]	morphological, cultural, and biochemical studies	AJ536198	16S rRNA gene *Type strain	Swiderski J. Unpublished (2003)	https://www.ncbi.nlm.nih.gov/genome/genomes/888	Current taxonomy valid update / *Micrococcus luteus* 30:320 (AL)
Paenibacillus alginolyticus	*Bacillus alginolyticus*	BACTERIA/Firmicutes/Bacillales Paenibacillaceae	[11]	16S rRNA gene sequence and cellular fatty acid composition analyses	AB073362	16S rRNA gene	[75]	https://www.ncbi.nlm.nih.gov/genome/14779	Current taxonomy valid update/ *Paenibacillus alginolyticus* 47:295*
Paenibacillus lentus	NAD	BACTERIA/Firmicutes/Bacillales/ Paenibacillaceae	[12]	16S rRNA gene sequence analysis	KC800716	16S rRNA gene	[12]	NAD	Current taxonomy valid update / *Paenibacillus lentus* 64:1171*
Paenibacillus macerans	*Bacillus macerans, Aerobacillus macerans, Zymobacillus macerans, Bactrillum macerans, Bacillus acetoethylicum, Bacillus betanigrificans, Bacillus soli, Aerobacillus schuylkilliensis, Bacillus vagans*	BACTERIA/Firmicutes/Bacillales/ Paenibacillaceae	[23]	sequence analysis of the rplK, sequence analysis of the 26 N-terminal amino acid residues of ribosomal L30 proteins	AB073196.1	16S rRNA gene	[75]	https://www.ncbi.nlm.nih.gov/genome/genomes/33271	Current taxonomy valid update / *Paenibacillus macerans* 45:197
Pseudomonas aeruginosa	NAD	BACTERIA/Proteobacteria/ Pseudomonadales/ Pseudomonadaceae	[13; 122]	16S rRNA sequence analyses; Housekeeping genes: rpoD; gyrB MLSA.	HE978271 /NR_026078.1	16S rRNA *gene*	Swiderski J. Unpublished (2012)/ [121]	https://www.ncbi.nlm.nih.gov/genome/genomes/187	Current taxonomy valid update / *Pseudomonas aeruginosa* 30:349 (AL)
					-	phzA1-G1	[63]		
					-	phzA2-G2	[63]		
					KR824168.1	phzM	[63]		
					AF116283.1	mexG	[63]		
					U89892.1	vfr	[63]		
					FJ649224.1	algU	[63]		
					U27988.1	gacA	[63]		
					JN868722.1	phoP	[63]		
					AY280952.1	mvaT	[63]		
					-	algR	[63]		
					-	phoB	[63]		

MICROORGANISMS NAME BY PROCUREMENT/ CURRENT NAME	SYNOMYM NAMES	TAXONOMY KINGDOM PHYLUM/ORDER/FAMILY	TAXONOMY REFERENCES	METHODS SUMMARY	HOUSEKEEPING GENES SEQUENCE ID GENBANK	HOUSEKEEPING GENES	REFERENCES HOUSEKEEPING GENES**	GENOME ID	CONCLUSION
Pseudomonas amyloderamosa	NAD	BACTERIA/ Proteobacteria/ Pseudomonadales/ Pseudomonadaceae	[13]	16S rRNA sequence analyses: Housekeeping genes and MLSA.	NAD	NAD	NAD	NAD	No Taxonomy data available/ Not validated name
Pullulanibacillus naganoensis	*Bacillus naganoensis*	BACTERIA/Firmicutes/ Bacillales/Bacillaceae	[14]	16S rRNA sequence analyses	AB021193/ NR_024694.1	16S rRNA gene	[74]	NAD	Current taxonomy valid update / *Pullulanibacillus naganoensis* 56:2550*
Sphingobacterium multivorum	*Flavobacterium multivorum*	BACTERIA/Bacteroidetes/ Sphingobacteriales/ Sphingobacteriaceae	[15; 16]	phenotypic characters, DNA-DNA hybridization	AB100738	16S rRNA gene	[87]	https://img.jgi.doe.gov/cgi-bin/m/main.cgi?section=ANI&page=cliqueDetails&clique_id=8537	Current taxonomy valid update / *Flavobacterium multivorum* 31:33* ≡ *Sphingobacterium multivorum*
Streptomyces albus	NAD	BACTERIA/Actinobacteria/ Actinomycetales/ Streptomycetaceae	[17; 18]	Chemotaxonomic methods, DNA–DNA hybridization, LFRFA, RAPD-PCR assays, 16S rRNA, 23S rRNA, 5S rRNA genes, RFLPs of rRNA	AJ621602	16S rRNA gene	Swiderski J. Direct Submission (2004)	https://www.ncbi.nlm.nih.gov/genome/genomes/1821	Current taxonomy valid update / *Streptomyces albus* 30:371 (AL)
Streptomyces aureofaciens	NAD	BACTERIA/Actinobacteria/ Actinomycetales/ Streptomycetaceae	[17]	Chemotaxonomic methods, DNA–DNA hybridizations, LFRFA, RAPD-PCR assays, 16S rRNA, 23S rRNA, 5S rRNA genes, RFLPs of rRNA	AY207608	16S rRNA gene	Song J, Lee S-C, Kang J-W and Suh J-W. Direct Submission (2002)	https://www.ncbi.nlm.nih.gov/genome/genomes/32330	Current taxonomy valid update / *Streptomyces aureofaciens* 30:373 (AL)
Streptomyces chrestomyceticus	NAD	BACTERIA/Actinobacteria/ Actinomycetales/ Streptomycetaceae	[17]	Chemotaxonomic methods, DNA–DNA hybridizations, LFRFA, RAPD-PCR assays, 16S rRNA, 23S rRNA, 5S rRNA genes, RFLPs of rRNA	AJ621609	16S rRNA gene	Swiderski, J. Direct Submission (2004)	https://www.ncbi.nlm.nih.gov/genome/genomes/40695	Current taxonomy valid update / *Streptomyces chrestomyceticus* 30:376 (AL)
Streptomyces chromofuscus	NAD	BACTERIA/Actinobacteria/ Actinomycetales/ Streptomycetaceae	[17]	Chemotaxonomic methods, DNA–DNA hybridizations, LFRFA, RAPD-PCR assays, 16S rRNA, 23S rRNA, 5S rRNA genes, RFLPs of rRNA	AB184194	16S rRNA gene	[88]	NAD	Current taxonomy valid update / *Streptomyces chromofuscus* 30:376 (AL)
Streptomyces cinnamonensis	NAD	BACTERIA/Actinobacteria/ Actinomycetales/ Streptomycetaceae	[17]	Chemotaxonomic methods, DNA–DNA hybridizations, LFRFA, RAPD-PCR assays, 16S rRNA, 23S rRNA, 5S rRNA genes, RFLPs of rRNA	AB184707	16S rRNA gene	[88]	NAD	Current taxonomy valid update / *Streptomyces cinnamonensis* 30:377 (AL)
Streptomyces cinnamoneus	*Streptomyces cinnamoneum*	BACTERIA/Actinobacteria/ Actinomycetales/ Streptomycetaceae	[19]	phenotypes, DNA-DNA hybridization data and partial sequences of gyrB	AB184850	16S rRNA gene	[88]	https://www.ncbi.nlm.nih.gov/genome/genomes/50490	Current taxonomy valid update / *Streptomyces cinnamoneus* 41:456
Streptomyces lasaliensis	NAD	BACTERIA/Actinobacteria/ Actinomycetales/ Streptomycetaceae	[65]	16S rRNA sequence analyses	HQ537060	16S rRNA gene	[68]	NAD	Not validated name
Streptomyces lividans	*Actinomyces lividans*	BACTERIA/Actinobacteria/ Actinomycetales/ Streptomycetaceae	[17]	Chemotaxonomic methods, DNA–DNA hybridizations, LFRFA, RAPD-PCR assays, 16S rRNA, 23S rRNA, 5S rRNA genes, RFLPs of rRNA	EU790486.1	16S rRNA gene	[89]	https://www.ncbi.nlm.nih.gov/genome/genomes/1888	Not validated name
Streptomyces mobaraensis	*Streptoverticillium mobaraense*	BACTERIA/Actinobacteria/ Actinomycetales/ Streptomycetaceae	[19]	phenotypes, DNA-DNA hybridization data and partial sequences of gyrB	DQ442528	16S rRNA gene	[90]	https://www.ncbi.nlm.nih.gov/genome/genomes/14887	Current taxonomy valid update / *Streptomyces mobaraensis* 41:456
Streptomyces murinus	NAD	BACTERIA/Actinobacteria/ Actinomycetales/ Streptomycetaceae	[21]	16S rRNA sequence analyses	AB184155	16S rRNA gene	[88]	NAD	Current taxonomy valid update / *Streptomyces murinus* 30:393 (AL)

MICROORGANISMS NAME BY PROCUREMENT/ CURRENT NAME	SYNOMYM NAMES	TAXONOMY KINGDOM PHYLUM/ORDER/FAMILY	TAXONOMY REFERENCES	METHODS SUMMARY	HOUSEKEEPING GENES SEQUENCE ID GENBANK	HOUSEKEEPING GENES	REFERENCES HOUSEKEEPING GENES**	GENOME ID	CONCLUSION
Streptomyces netropsis	NAD	BACTERIA/Actinobacteria/ Actinomycetales/ Streptomycetaceae	[19]	phenotypes, DNA-DNA hybridization data and partial sequences of gyrB	EF178671	16S rRNA gene	[90]	NAD	Current taxonomy valid update / *Streptomyces netropsis* 41:456
Streptomyces olivochromogenes	*Actinomyces olivochromogenus*	BACTERIA/Actinobacteria/ Actinomycetales/ Streptomycetaceae	[20]	DNA–DNA hybridization, partial sequences of the gyrB gene, 16S rRNA fragment	AY094370	16S rRNA gene	[91]	https://www.ncbi.nlm.nih.gov/genome/genomes/42751	Current taxonomy valid update / *Streptomyces olivochromogenes* 30:395 (AL)
Streptomyces rubiginosus	*Actinomyces rubiginosus*	BACTERIA/Actinobacteria/ Actinomycetales/ Streptomycetaceae	[21]	16S rRNA sequence analyses	AB122724.1	16S rRNA gene	[115]	NAD	Current taxonomy valid update / *Streptomyces rubiginosus* 30:400 (AL)
Streptomyces violaceoruber	*Actinomyces violaceus-ruber*	BACTERIA/Actinobacteria/ Actinomycetales/ Streptomycetaceae	[22]	16S rRNA sequence analyses	AF503492	16S rRNA gene	[92]	https://www.ncbi.nlm.nih.gov/genome/genomes/16431	Current taxonomy valid update / *Streptomyces violaceoruber* 30:404 (AL)

Methods Summary highlights molecular methodology that complements basic phenotypic and classical characterisation
NAD: Non-available data/ No relevant data
NAD*: Non-available data/ No Teleomorph synonyms needed
Not validated name: According to International Code of Nomenclature, IJSEM validated list
AL: Included in the Approved Lists (Skerman et. al. (1980), (1989); Euzéby, J.P. (1997))
***: Original publication in IJSB or IJSEM Volume:page**
(≡) homotypic (formerly: objective) synonym; the original name is indicated as a basonym. International Code of Nomenclature of Bacteria (1990 revision); Tindall, B.J. (1999).
(=) heterotypic (formerly:subjective) synonym; the name published first has priority over. International Code of Nomenclature of Bacteria (1990 revision); Tindall, B.J. (1999).
****: Direct submissions to the GenBank Database.** Not cited in articles.

Appendix J - Microorganism taxonomical identifiers

Table J2. FUNGI

MICROORGANISMS NAME BY PROCUREMENT/ CURRENT NAME	SYNOMYM NAMES	TAXONOMY KINGDOM PHYLUM/ORDER/FAMILY	TAXONOMY REFERENCES	METHODS SUMMARY	HOUSEKEEPING GENES SEQUENCE ID GENBANK	HOUSEKEEPING GENES	REFERENCES HOUSEKEEPING GENES**	GENOME ID	CONCLUSION
Aspergillus aculeatus	*Aspergillus japonicus* var. *aculeatus*	FUNGI/Ascomycota/Eurotiales/ Trichocomaceae	[24; 26]	ITS and 5.8S rRNA gene	EU714394.1	18S rRNA; ITS1; 5.8S rRNA gene; ITS2; 28S rRNA gene	[55; 56; 114]	https://www.ncbi.nlm.nih.gov/genome/genomes/12515	Current/Legitimate name: *Aspergillus aculeatus*
Aspergillus japonicus	NAD*	FUNGI/Ascomycota/Eurotiales/ Trichocomaceae	[25; 26]	ITS1-5.8S rRNA gene-18S rRNA gene-ITS2 region, RFLPs of nuclear DNA, and secondary-metabolite profiles	AJ279993	18S rRNA gene; 5.8S rRNA gene; ITS1; ITS2	[55; 56; 25]	NAD	Current/Legitimate name: *Aspergillus japonicus*
Aspergillus melleus	NAD*	FUNGI/Ascomycota/Eurotiales/ Trichocomaceae	[26]	nuc rRNA internal transcribed spacer rRNA region (ITS1-5.8S-ITS2), calmodulin (CaM), β-tubulin (BenA), RNA polymerase II second largest subunit (RPB2)	AF203796	18S rRNA; ITS1; 5.8S rRNA gene; ITS2; 28S rRNA gene	[73]	NAD	Current/Legitimate name: *Aspergillus melleus*
Aspergillus niger	NAD*	FUNGI/Ascomycota/Eurotiales/ Trichocomaceae	[26; 27]	RFLP analysis; 18S rRNA	JN587346 -	18S rRNA gene -	[72] [54; 55; 56]	https://www.ncbi.nlm.nih.gov/genome/genomes/429	Current/Legitimate name: *Aspergillus niger*
Aspergillus oryzae	*Aspergillus flavus* var. *oryzae*	FUNGI/Ascomycota/Eurotiales/ Trichocomaceae	[28]	nuc rRNA internal transcribed spacer rRNA region (ITS1-5.8S-ITS2), calmodulin (CaM), β-tubulin (BenA), RNA polymerase II second largest subunit (RPB2)	DQ155287.1	18S rRNA; ITS1; 5.8S rRNA gene	[52; 113]	https://www.ncbi.nlm.nih.gov/genome/genomes/526	Current/Legitimate name: *Aspergillus flavus var. oryzae*
Aspergillus sojae	NAD*	FUNGI/Ascomycota/Eurotiales/ Trichocomaceae	[29]	scanning electron micrograph (morphological characteristics) and physiological characteristics	AB008419.1	18S rRNA gene	[52]	https://www.ncbi.nlm.nih.gov/genome/genomes/10858	Current/Legitimate name: *Aspergillus sojae*
Candida cylindracea	NAD*	FUNGI/ Ascomycota/ Saccharomycetales/ Saccharomycetaceae	[30]	SSU rRNA sequence, 18S rRNA sequence, 5S rRNA sequences, CUG codon	X64703.1 X64704.1 X66006.1 X66007.1 X66008.1	*lip1* *lip2* *lip3* *lip4* *lip5*	[71; 116] [71; 116] [71; 116] [71; 116] [71; 116]	NAD	Current/Legitimate name: *Candida cylindracea*
Candida lipolytica	*Yarrowia lipolytica, Torula lipolytica, Mycotorula lipolytica, Candida paralipolytica, Candida oleae*	FUNGI/ Ascomycota/ Saccharomycetales/ Saccharomycetaceae	[31]	ITS-PCR	AJ250347.1	*act1*	[93]	https://www.ncbi.nlm.nih.gov/genome/genomes/194	Current/Legitimate name: *Candida deformans*
Chaetomium erraticum	*Chaetomium gracile, Chaetomium arcuatum Chaetomium virescens* var. *thielavioideum*	FUNGI/Ascomycota/ Sordariales/Chaetomiaceae	[32]	-	-	-	-	NAD	Current/Legitimate name: *Chaetomium virescens var. thielavioideum*
Chaetomium gracile	*Chaetomium erraticum, Chaetomium virescens* var. *Thielavioideum*	FUNGI/Ascomycota/ Sordariales/ Chaetomiaceae	[33]	-	JX536280.1	18S rRNA; ITS1; 5.8S rRNA gene; ITS2; 28S rRNA gene	[94]	NAD	Current/Legitimate name: *Chaetomium virescens var. thielavioideum*

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MICROORGANISMS NAME BY PROCUREMENT/ CURRENT NAME	SYNOMYM NAMES	TAXONOMY KINGDOM PHYLUM/ORDER/FAMILY	TAXONOMY REFERENCES	METHODS SUMMARY	HOUSEKEEPING GENES SEQUENCE ID GENBANK	HOUSEKEEPING GENES	REFERENCES HOUSEKEEPING GENES**	GENOME ID	CONCLUSION
Cryphonectria parasitica	*Endothia parasitica, Diaporthe parasitica, Endothia gyrosa var. Parasitica, Valsonectria parasitica*	FUNGI/Ascomycota/ Diaporthales/Valsaceae	[34]	Ribosomal RNA (ITS1, 5.8S, ITS2) and b-tubulin gene sequencing. Morphological studies	L42441.1	18S rRNA gene	[95]	Mitocondrial Plasmid only available: AF218210	Current/Legitimate name: *Cryphonectria parasitica*
Disporotrichum dimorphosporum	*Sporotrichum dimorphosporum*	FUNGI/Basidiomycota/ Agaricales/ Incertae sedis	[35]	-	NAD	NAD	NAD	NAD	No Taxonomy data available
Fusarium venenatum	NAD*	FUNGI/Ascomycota/ Hypocreales/ Nectriaceae	[36]	RAPDs/PCR using species-specific primers	GQ915554.1	*tri*5	[52; 53; 67; 117]	NAD	Current Legitimate name: *Fusarium venenatum*
Hansenula polymorpha	*Pichia angusta; Ogataea polymorpha*	FUNGI/Ascomycota/ Saccharomycetales/ Saccharomycetaceae	[37]	18S rRNA gene/26S rRNA gene	FJ914915	18S rRNA gene	[37]	https://www.ncbi.nlm.nih.gov/genome/genomes/14402	Current/Legitimate name: *Ogataea polymorpha*
Humicola insolens	NAD*	FUNGI/Ascomycota/ Sordariales/Chaetomiaceae	[38]	-	HQ850154.1	18S rRNA gene	[81]	NAD	Current/Legitimate name: *Humicola insolens*
Leptographium procerum	NAD*	FUNGI/Ascomycota/ Ophiostomatales/ Ophiostomataceae	[39]	Phylogenetic analyses of seven gene regions (ITS2-LSU, actin, β-tubulin, calmodulin, translation elongation factor 1-α, and the mating type genes *MAT1-1-3* and *MAT1-2-1*	JF440600.1	18S rRNA; ITS1; 5.8S rRNA; ITS2; 28S rRNA	[96]	https://www.ncbi.nlm.nih.gov/genome/genomes/35500	Current/Legitimate name: *Leptographium procerum*
Mucor javanicus	*Mucor circinelloides* *heterotypic synonyms	FUNGI/Zygomycota/ Mucorales/Mucoraceae	[40]	LSU, SSU, ITS1, ITS2, 5.8S rRNA, actin (act) and translation elongation factor 1-alpha (tef)	HM234130.1	18S rRNA; ITS1; 5.8S rRNA; ITS2; 28S rRNA	[123]	https://www.ncbi.nlm.nih.gov/genome/genomes/2804	Current/Legitimate name: *Mucor circinelloides f. circinelloides*
Penicillium camemberti	NAD*	FUNGI/Ascomycota/Eurotiales/ Trichocomaceae	[41]	Macromorphology, Micromorphology, Internal transcribed spacer (ITS), β-tubulin (BenA), calmodulin (CaM) or the RNA polymerase II second largest subunit (RPB2) genes	AB479314	18S rRNA; ITS1; 5.8S rRNA; ITS2; 28S rRNA	[64; 70]	https://www.ncbi.nlm.nih.gov/genome/genomes/30945	Current/Legitimate name: *Penicillium camemberti*
Penicillium chrysogenum	NAD*	FUNGI/Ascomycota/Eurotiales/ Trichocomaceae	[41]	Macromorphology, Micromorphology, Internal transcribed spacer (ITS), β-tubulin (BenA), calmodulin (CaM) or the RNA polymerase II second largest subunit (RPB2) genes	L76153.1	18S rRNA gene	[64; 118]	https://www.ncbi.nlm.nih.gov/genome/genomes/10820	Current/Legitimate name: *Penicillium chrysogenum*
Penicillium citrinum	NAD*	FUNGI/Ascomycota/Eurotiales/ Trichocomaceae	[41; 82]	ITS regions, β-tubulin and calmodulin sequence analysis	LN835269	18S rRNA; ITS1; 5.8S rRNA; ITS2; 28S rRNA	[64; 112]	https://www.ncbi.nlm.nih.gov/genome/genomes/40785	Current/Legitimate name: *Penicillium citrinum*

MICROORGANISMS NAME BY PROCUREMENT/ CURRENT NAME	SYNOMYM NAMES	TAXONOMY KINGDOM PHYLUM/ORDER/FAMILY	TAXONOMY REFERENCES	METHODS SUMMARY	HOUSEKEEPING GENES SEQUENCE ID GENBANK	HOUSEKEEPING GENES	REFERENCES HOUSEKEEPING GENES**	GENOME ID	CONCLUSION
Penicillium decumbens	NAD*	FUNGI/Ascomycota/Eurotiales/ Trichocomaceae	[41]	Macromorphology, Micromorphology, Internal transcribed spacer (ITS), β-tubulin (BenA), calmodulin (CaM) or the RNA polymerase II second largest subunit (RPB2) genes	KF284158.1	18S rRNA gene	[64; 111]	NAD	Legitimate name: *Penicillium decumbens*
Penicillium funiculosum	*Talaromyces funiculosum*	FUNGI/Ascomycota/Eurotiales/ Trichocomaceae	[42]	sequencing, RAPD, AFLP	KC013273.1	18S rRNA; ITS1; 5.8S rRNA; ITS2; 28S rRNA	[64; 110]	NAD	Current/Legitimate name: *Penicillium funiculosum*
Penicillium multicolor	*Penicillium implicatum var. aureomarginatum, Penicillium sclerotiorum*	FUNGI/Ascomycota/Eurotiales/ Trichocomaceae	[41]	Macromorphology, Micromorphology, Internal transcribed spacer rRNA area (ITS), β-tubulin (BenA), calmodulin (CaM) or the RNA polymerase II second largest subunit (RPB2) genes	KC790402.1	18S rRNA; ITS1; 5.8S rRNA; ITS2; 28S rRNA	[64; 109]	NAD	No Current/Legitimate name
Penicillium lilacinum	*Purpureocillium lilacinum; Paecilomyces lilacinus*	FUNGI/Ascomycota/Eurotiales/ Trichocomaceae	[43]	18S rRNA gene, internal transcribed spacer (ITS) and partial translation elongation factor 1-a (TEF) sequences	HQ842812	18S rRNA gene	[43; 64]	https://www.ncbi.nlm.nih.gov/genome/genomes/42115	Current/Legitimate name: *Purpureocillium lilacinum* ; *Paecilomyces lilacinus*
Penicillium roqueforti	NAD*	FUNGI/Ascomycota/Eurotiales/ Trichocomaceae	[41]	Macromorphology, Micromorphology, Internal transcribed spacer rDNA area (ITS), β-tubulin (BenA), calmodulin (CaM) or the RNA polymerase II second largest subunit (RPB2) genes	DQ119124.1	18S rRNA gene	[64; 108]	https://www.ncbi.nlm.nih.gov/genome/genomes/24568	Current/Legitimate name: *Penicillium roqueforti*
Penicillium salamii	NAD*	FUNGI/Ascomycota/Eurotiales/ Trichocomaceae	[44]	calmodulin, β tubulin and ITS sequences, phenotypic characters and extrolite patterns			[64]	NAD	No Current Legitimate name
Penicillium nordicum	NAD*	FUNGI/Ascomycota/Eurotiales/ Trichocomaceae	[41]	Macromorphology, Micromorphology, Internal transcribed spacer rDNA area (ITS), β-tubulin (BenA), calmodulin (CaM) or the RNA polymerase II second largest subunit (RPB2) genes	KJ834513.1	18S rRNA; ITS1; 5.8S rRNA; ITS2; 28S rRNA	[41; 64]	https://www.ncbi.nlm.nih.gov/genome/genomes/32546	Current/Legitimate name: *Penicillium nordicum*
Rhizomucor miehei	*Mucor miehei*	FUNGI/Zygomycota/ Mucorales/Mucoraceae	[45]	18S and 28S rRNA sequences	AJ278360	18S rRNA; ITS1; 5.8S rRNA; ITS2; 28S rRNA	[97]	https://www.ncbi.nlm.nih.gov/genome/genomes/11518	Current/Legitimate name: *Rhizomucor miehei*

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MICROORGANISMS NAME BY PROCUREMENT/ CURRENT NAME	SYNOMYM NAMES	TAXONOMY KINGDOM PHYLUM/ORDER/FAMILY	TAXONOMY REFERENCES	METHODS SUMMARY	HOUSEKEEPING GENES SEQUENCE ID GENBANK	HOUSEKEEPING GENES	REFERENCES HOUSEKEEPING GENES**	GENOME ID	CONCLUSION
Rhizopus niveus	NAD*	FUNGI/Zygomycota/ Mucorales/Mucoraceae	[46]	rRNA gene (ITS), actin, translation elongation factor 1 (EF-1)	DQ641284.1	18S rRNA; ITS1; 5.8S rRNA; ITS2; 28S rRNA	[107]	NAD	Current/Legitimate name: *Rhizopus niveus*
Rhizopus oryzae	NAD*	FUNGI/Zygomycota/ Mucorales/Mucoraceae	[46]	18S rRNA nucleotide sequences	AF113440.1	18S rRNA gene	[106]	https://www.ncbi.nlm.nih.gov/genome/genomes/322	Current/Legitimate name: *Rhizopus oryzae*
Sporobolomyces singularis	*Bullera singularis, Hamamotoa singularis*	FUNGI/Basidiomycota/ Sporidiobolales/ Sporidiobolaceae	[47]	18S rRNA nucleotide sequences	AB021690	18S rRNA gene	[47]	NAD	Current/Legitimate name: *Hamamotoa singularis' (MB 813188)*
Talaromyces emersonii	*Rasamsonia emersonii*	FUNGI/Ascomycota/Eurotiales/ Trichocomaceae	[49; 99]	Morphological analysis, TS, BenA and RPB2 multigene phylogeny; phenotypic characters, extrolite patterns, ITS and partial calmodulin and β-tubulin sequences	D88321.2	18S rRNA gene	[104]	https://www.ncbi.nlm.nih.gov/genome/genomes/36802	Current/Legitimate name: *Rasamsonia emersonii*
Talaromyces cellulolyticus	*Acremonium cellulolyticus*	FUNGI/Ascomycota/Eurotiales/ Trichocomaceae	[49; 84]	Morphological analysis, TS, BenA and RPB2 multigene phylogeny	KF811039.1	18S rRNA; ITS1; 5.8S rRNA gene; ITS2; 28S rRNA gene	[105]	https://www.ncbi.nlm.nih.gov/genome/genomes/35980	*Current/Legitimate name: Talaromyces cellulolyticus*
Talaromyces versatilis	NAD*	FUNGI/Ascomycota/Eurotiales/ Trichocomaceae	[49]	Morphological analysis, TS, BenA and RPB2 multigene phylogeny	KC962113.1	18S rRNA; ITS1; 5.8S rRNA gene; ITS2; 28S rRNA gene	[103]	NAD	Current/Legitimate name: *Talaromyces versatilis*
Trametes hirsuta	NAD*	FUNGI/Basidiomycota/ Polyporales/Polyporaceae	[48]	18S rRNA nucleotide sequences	EU771080.1	18S rRNA; ITS1; 5.8S rRNA gene; ITS2; 28S rRNA gene	Deng X, Song R and Sun H. Direct Submission (2008)	https://www.ncbi.nlm.nih.gov/genome/genomes/40253	Current/Legitimate name: *Trametes hirsuta*
Trametes versicolor	NAD*	FUNGI/Basidiomycota/ Polyporales/ Polyporaceae	[48]	ITS and mt SSU rDNA	KF638522.1	rRNA genes, ITS1 and ITS2 DNA	[102]	https://www.ncbi.nlm.nih.gov/genome/genomes/3260	Current/Legitimate name: *Trametes versicolor*
Trichoderma citrinoviride	NAD*	FUNGI/Ascomycota/ Hypocreales/Hypocreaceae	[50]	rRNA ITS, actin, EF-1α	JF745094.1	18S rRNA; ITS1; 5.8S rRNA gene; ITS2; 28S rRNA gene	[101]	NAD	Current/Legitimate name: *Trichoderma citrinoviride*
Trichoderma harzianum	NAD*	FUNGI/Ascomycota/ Hypocreales/Hypocreaceae	[51]	rRNA ITS, actin, EF-1α	AF508862.1	18S rRNA; ITS1; 5.8S rRNA; ITS2	Kim S-J. Direct Submission (2002)	https://www.ncbi.nlm.nih.gov/genome/genomes/2441	Current/Legitimate name: *Trichoderma harzianum*
Trichoderma koningii	NAD*	FUNGI/Ascomycota/ Hypocreales/Hypocreaceae	[51]	rRNA ITS, actin, EF-1α	KU314996.1	18S rRNA; ITS1; 5.8S rRNA; ITS2	Garzoli L and Varese GC. Direct Submission (2015)	https://www.ncbi.nlm.nih.gov/genome/genomes/51821	Current/Legitimate name: *Trichoderma koningii*
Trichoderma longibrachiatum	NAD*	FUNGI/Ascomycota/ Hypocreales/Hypocreaceae	[51]	rRNA ITS, actin, EF-1α	Z31019.1	rRNA genes, ITS1 and ITS2 DNA	[98]	https://www.ncbi.nlm.nih.gov/genome/genomes/18220	Current/Legitimate name: *Trichoderma longibrachiatum*
Trichoderma reesei	NAD*	FUNGI/Ascomycota/ Hypocreales/Hypocreaceae	[50]	rRNA ITS, actin, EF-1α	JX841312.1	*lae1*	[66]	https://www.ncbi.nlm.nih.gov/genome/genomes/323	Current/Legitimate name: *Trichoderma reesei*
Trichoderma viride	NAD*	FUNGI/Ascomycota/ Hypocreales/Hypocreaceae	[51]	rRNA ITS, actin, EF-1α	KF765423.1	18S rRNA; ITS1; 5.8S rRNA; ITS2	[100]	NAD	Current/Legitimate name: *Trichoderma viride*

Methods Summary highlights molecular methodology that complements basic phenotypic and classical characterisation
NAD: Non-available data/ No relevant data
NAD*: Non-available data/ No Teleomorph synonyms needed
Not validated name: According to International Code of Nomenclature, IJSEM validated list
AL: Included in the Approved Lists (Skerman et. al. (1980), (1989); Euzéby, J.P. (1997))
***: Original publication in IJSB or IJSEM Volume:page**
(≡) homotypic (formerly: objective) synonym; the original name is indicated as a basonym. International Code of Nomenclature of Bacteria (1990 revision); Tindall, B.J. (1999).
(=) heterotypic (formerly:subjective) synonym; the name published first has priority over. International Code of Nomenclature of Bacteria (1990 revision); Tindall, B.J. (1999).
****: Direct submissions to the GenBank Database.** Not cited in articles.

Appendix K – Taxonomy references

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