



EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Safety of the Food Chain
Chemicals, contaminants, pesticides

SANCO/12823/2012 –rev. 4
12 December 2014

**GUIDANCE DOCUMENT FOR THE ASSESSMENT OF THE
EQUIVALENCE OF TECHNICAL GRADE ACTIVE INGREDIENTS FOR
IDENTICAL MICROBIAL STRAINS OR ISOLATES APPROVED UNDER
REGULATION (EC) No 1107/2009**

This document has been conceived as a guidance document of the Commission Services. It does not represent the official position of the Commission. It does not intend to produce legally binding effects. Only the European Court of Justice has jurisdiction to give preliminary rulings concerning the validity and interpretation of acts of the institutions of the EU pursuant to Article 267 of the Treaty.

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Background

Within the EU micro-organisms are approved at strain level¹ and the current practice is to consider each new strain or isolate on its own merits for registration. Where justified (e.g. baculoviruses) another approach can be taken. The methodology for identification and for taxonomic classification may need to be reconfirmed by the applicant because methods are evolving very fast. The data requirements as described in Commission Regulations (EU) No 283/2013 and No 284/2013 (for micro-organisms identical to the data requirements listed in Commission Directive 2001/36/EC) should be fulfilled at strain level.

This Guidance Document is applicable for changes to the same strain only in the framework of application for authorisations for plant protection products at Member State level. The purpose of this document is to provide guidance for the assessment of technical equivalence of micro-organisms used in plant protection products and may also be helpful for dossier preparation. It is acknowledged that flexibility of manufacturing is key for industry to meet demand for a product. However, technical equivalence with the approved (reference) source needs to be demonstrated in one or more of the following cases:

- Change of location of manufacturing plant,
- Scale up of fermentation vessel²,
- Change of manufacturing process, like change of production equipment or propagation conditions (e.g. temperature or ingredients).

These changes can alter the properties of the technical grade active ingredient (micro-organism as manufactured), including the phenotype of the microorganism. Also visual changes e.g. in the morphology may occur. This may be relevant for all areas of the assessment. The evaluation compares two sources of technical active ingredient the same strain of a micro-organism. The aim is to ensure that the new source is equivalent to the approved source for the following parameters:

- Identity of the micro-organism;
- Content of the active micro-organism (determined in relevant units e.g. CFU);
- Content of relevant metabolites/toxins
- Composition of material for production (e.g. inoculum, culture media);
- Content of microbial contaminants.

The new source is considered as technically equivalent in Tier I –and therefore no Tier II assessment is required- when strain or isolate is established as identical and the following criteria are fulfilled:

- Content of the active micro-organism (determined in relevant units e.g. CFU) is higher than/equal to (within the minimum-maximum range) the reference source, and
- Content of relevant metabolites/toxins is lower/equal than in the reference source, and
- Composition of material for production is the same, and

¹ Guideline developed within the Standing Committee on the Food Chain and Animal Health on the taxonomic level of micro-organisms to be included in Annex I to Directive 91/414/EEC (SANCO/10754/2005 rev. 5; 15 April 2005)

² Regulation (EU) No 283/2013, point 1.4.1 'Content of the micro-organism':

"Where the information provided relates to a pilot plant production system, the information required must again be provided to the Commission and the Member States once industrial scale production methods and procedures have stabilised, if production changes result in a changed specification of purity."

- Content of microbial contaminants is lower than,/equal to the reference source. However, higher levels can be accepted as long as the content of microbial contaminants in the product is within the limits of the Working Document on microbial contamination limits for microbial pest control products³.

In the case the above criteria are not fulfilled the technical grade active ingredient can be considered under a TIER II assessment to determine if the changes in composition (chemical and/or microbiological) are without increased risk to human health and the environment. For every change of method of manufacture or changes in the manufacturing process it has to be established that the safety requirements laid down in Article 4 of Regulation (EC) No 1107/2009 are still fulfilled. The onus is on the applicant to justify the acceptability of the altered levels.

A five batch analysis should be conducted on the technical grade active ingredient or in the case of continuous production or non-stable technical active substances, on the formulated product, as appropriate.

For all levels of evaluation an equivalence report should be prepared using the template provided in the Annex to this guidance document.

This guidance document has been prepared as the guidance document for the equivalence of technical materials of chemical substances⁴ is not applicable to micro-organisms. However, the procedure for the assessment of the equivalence of new sources of technical materials according to Article 38 of Regulation (EC) No 1107/2009 is considered the same for chemicals as for micro-organisms.

For all micro-organisms it should be made clear that the material has been produced with sustainable and reproducible methods.

Implementation schedule

This document has been finalised in the Standing Committee on Plants, Animals, Food and Feed on 12 December 2014. It will apply to applications submitted from 1 April 2015 onwards.

³ Working document on microbial contaminants limits for microbial pest control products (SANCO/12116/2012 rev. 0; September 2012)

⁴ SANCO/10597/2003 rev. 10.1 Guidance document on the assessment of equivalence of technical materials of substances regulated under Regulation (EC) No 1107/2009

Definitions

In the framework of this Guidance Document the following definitions apply.

Contaminant

A contaminant is an unintentional microbial ingredient that occurs during manufacturing.

Isolate

An isolate is a pure culture derived from a heterogeneous, wild population of a microorganism. In the context of this document it is used when identification at strain level is inappropriate e.g. (baculo)viruses.

Material for production

Material for production is considered to be all ingredients used for the manufacturing of the technical grade active ingredient.

Metabolite

A metabolite is any metabolite or a degradation product of a micro-organism, formed either in organisms or in the environment.

Reference source

The reference source is the approved source on which the risk assessment in the Assessment Report was based and for which a regulatory decision has been taken.

Relevant metabolite

A relevant metabolite is any metabolite that is of concern for human or animal health and/or the environment. In this way, some toxins can be considered relevant metabolites.

Strain

A strain is a population of an organism that descends from a single cell or a pure culture isolate. Typically, it is the result of a succession of cultures ultimately deriving from an initial single colony. For the purpose of this document 'strain' refers to a culture that is specifically linked to a collection number.

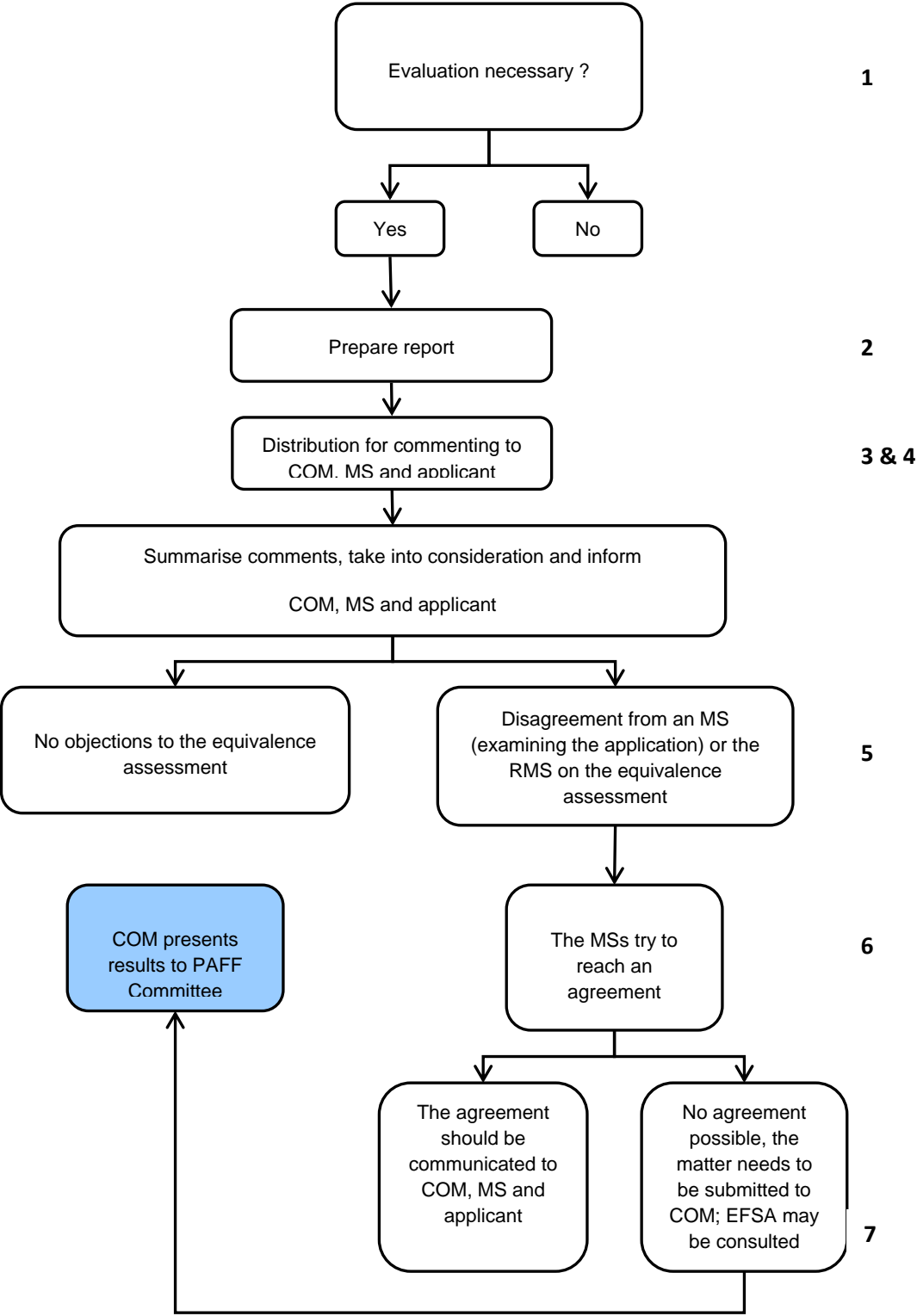
Technical grade active ingredient (TGAI)

A micro-organism (e.g. bacterium, fungus, protozoan, virus, viroid, mycoplasma, algae) and any associated metabolites/toxins, fermentation residues and contaminants as manufactured.

Toxin

A toxin is any substance that is able to injure or cause damage in a host.

Flow chart and time table on the procedure for the assessment of the equivalence of new sources of technical materials according to Article 38 Regulation (EC) No 1107/2009 (The numbering corresponds to the explanation given on the next pages).



1. Immediately on receipt of the application for equivalence, it should be confirmed whether an assessment is necessary.. It is crucial that the intention of a MS to conduct the equivalence assessment of a specific source appears in the table of '*equivalent sources and compliance checks*' on CIRCABC. Therefore, as soon as a MS (Rapporteur Member State (RMS) or Designated Member State (DMS)) agrees to conduct an equivalence assessment, this should be communicated to the responsible contact point⁵ and COM (in copy) by e-mail together with a 'completed row' (Excel file template) containing the relevant information on the application, in order to enable an update of the table. An up-to-date template can be found on CIRCABC

https://circabc.europa.eu/faces/jsp/extension/wai/navigation/container.jsp?FormPrincipal:_idcl=FormPrincipal:_id3&FormPrincipal_SUBMIT=1&id=9fe32f90-02ed-4233-aedd-e836120f7a76&javax.faces.ViewState=rO0ABXVyABNbTGphdmEubGFuZy5PYmplY3Q7kM5YnxBzKWwCAAB4cAAAAAN0AAIxNHBOACsvanNwL2V4dGVuc2lvbi93YWkvbmF2aWdhdGlubi9jb250YWluZXIuanNw).

2. The RMS/DMS has to prepare the report on equivalence within 60 days from receiving the application (This should include the possibility for the applicant to submit comments).
3. The report has to be communicated to the COM, the other Member States and the applicant. The report is placed on CIRCABC. Relevant contact points are informed by e-mail together with the deadline for comments. However, the confidentiality of business and trade secrets must be respected in cases where the applicant under consideration is different to the one of the references source.
4. Within 30 days the COM, the MS and the applicant should send their comments to the DMS/RMS.
- 5.1 In the case of a positive conclusion on equivalence and where no objection to this conclusion has been raised, the conclusion should be communicated within 10 days after the deadline (for commenting) to the COM and the Member States. If required, the initial report on CIRCABC is replaced by a revised version that takes into account the comments received. For the report the following naming convention should be used when uploading on CIRCABC: "*active substance equivalence Notifier Source (City) MS Date "draft" resp. "final"*".

A reporting table that summarizes all comments on the equivalence report should be uploaded on CIRCABC (in the same folder as the equivalence report). Each comment should be addressed by the RMS/DMS and non-adoption of comments should be fully justified.

⁵ The e-mail should be sent to equivalence@health.belgium.be. Please be sure to use the proper template (see CIRCABC).

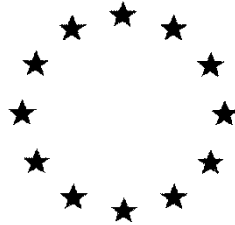
The outcome of the peer-reviewed equivalence assessment should be communicated to the relevant contact points and the table of 'equivalent sources and compliance checks' on CIRCABC should be updated accordingly.

- 5.2 Where an MS examining the application does not agree with the conclusion of the rapporteur MS or vice versa, the RMS/DMS shall inform the applicant, the other MS and the Commission stating its reasons. A reporting table that summarizes all comments on the equivalence report should be uploaded on CIRCABC (in the same folder as the equivalence report). Each comment should be addressed by the RMS/DMS and non-adoption of comments should be fully justified.

[It should be noted that disagreement on the assessment by another MS than the RMS or the MS examining the application does not necessarily lead to step 6. For the sake of feasibility though, all MS should express their concerns in step 4 and the DMS/RMS should take them into consideration even if this is not required according to Art. 38, paragraph 3.]

6. The MS concerned shall try to reach agreement on the assessment. They shall provide the applicant with an opportunity to submit comments. Where the MSs concerned do not reach agreement within 45 days, the MS assessing equivalence shall submit the matter to the COM. The COM shall present the results to the Standing Committee on Plants, Animals, Food and Feed.
7. Before the COM adopts a decision according to the regulatory procedure referred to in Article 79, paragraph 3, the COM may ask the EFSA for an opinion, or for scientific or technical assistance.

European Commission



*Evaluation report on the equivalence
of technical grade active ingredient
of micro-organism*

XXXXXXXXXXXXXX

*RMS
date*

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1. STATEMENT OF SUBJECT MATTER AND PURPOSE FOR WHICH THE REPORT WAS PREPARED

The rapporteur must indicate in the table below which case has been examined

Change of location of manufacturing plant

Scale up of fermentation vessel

Change of manufacturing process, like change of production equipment or propagation conditions

2. SUMMARY, EVALUATION AND ASSESSMENT OF DATA (Dossier Documents J, K-II and L-II)

SECTION A: IDENTITY OF THE MICRO-ORGANISM (OECD IIM 1)

A.1 NAME AND ADDRESS OF APPLICANT(S) (OECD IIM 1.1)

Name of the person responsible for the submission of the application:

Contact:

Telephone:

E-mail:

A.2 TAXONOMIC NAME, STRAIN /ISOLATE DESIGNATION (OECD IIM 1.3)

Information on current and previous taxonomic names as well as current strain/isolate designation and synonyms has to be provided on the new source.

A.3 MANUFACTURER'S DEVELOPMENT CODE NUMBER (OECD IIM 1.3.5)

Information has to be provided on the new source.

A.4 CULTURE COLLECTION AND CIPAC NUMBERS (OECD IIM 1.3.2 AND IIM 3.5.2.3)

CULTURE COLLECTION No:

CIPAC No: *(if available)*

Information has to be provided on the new source.

A.5 STRAIN CHARACTERISATION (OECD IIM 1.3.1)

Information has to be provided on the new source. It has to be ensured that the new source is the same strain as the reference source. Also information on the seed stock has to be provided.

A.6 MANUFACTURER OR MANUFACTURERS OF THE MICRO-ORGANISM (OECD IIM 1.2)

Manufacturer name:

Contact point:

Telephone:

E-mail:

Location of the plant for the micro-organism:

A.7 METHOD OR METHODS OF MANUFACTURE (OECD IIM 1.4.3)

Production scheme and, where relevant, a detailed description of the manufacturing process for the new source and where possible a comparison with the reference source should be provided. When not possible for the applicant it should be provided by the rapporteur.

A.8 CONTENT OF MICRO-ORGANISM (OECD IIM 1.4.3.2)

Minimum and maximum content of the micro-organism used for manufacturing of the formulated product (CFU/g, CFU/L, or other appropriate units) both, where possible, for the new source and the reference source. When not possible for the applicant it should be provided by the rapporteur.

Preferably the requested information should be presented in the following overview table:

Table 8.1 - Minimum and maximum content of the micro-organism used for manufacturing of the formulated product for reference source and new source of XXXXXXX.

Source	Reference source					New source					Company limits
Material tested*											
Batch number/manufacturing date											
Minimum and maximum content of the micro-organism (CFU/g, CFU/mL or other appropriate units)											
<i>Add here discussion on observed differences.</i>											

* Material tested: Please specify production stage of TGA1 or formulated product. Add or delete columns as appropriate.

When it is not possible for the applicant to provide information for the reference source it should be provided by the rapporteur.

A.9 IDENTITY OF RELEVANT METABOLITES/TOXINS, MATERIAL FOR PRODUCTION AND CONTAMINANTS (OECD IIM 1.4.1, 1.4.2 AND 1.4.2.3)

RELEVANT METABOLITES/TOXINS

Preferably the requested information should be presented in the following overview table:

Table 9.1 - Result of relevant metabolites/toxins analyses for reference source and new source of XXXXXXXX.

Source	Reference source					New source					Company limits
Material tested*											
Batch number/ manufacturing date											
Relevant metabolites/toxins (g/kg or g/L)											
<i>Add here discussion on observed differences.</i>											

* Material tested: Please specify production stage of TGAI or formulated product. Add or delete columns as appropriate.

When it is not possible for the applicant to provide information for the reference source it should be provided by the rapporteur.

MATERIAL FOR PRODUCTION

Preferably the requested information should be presented in the following overview table:

Table 9.2 - Material for production (list of all components of media (with their origin and quantity, g/kg or g/L) for reference source and new source of XXXXXXXX.

Ingredients /	Reference source	New source
<i>Add here discussion on observed differences.</i>		

* Material tested: Please specify production stage of TGA1 or formulated product. Add or delete columns as appropriate.

When it is not possible for the applicant to provide information for the reference source it should be provided by the rapporteur.

CONTAMINATING MICRO-ORGANISMS

Preferably the requested information should be presented in the following overview table:

Table 9.3 - Result of contaminant analyses for reference source and new source of XXXXXXX.

Source	Reference source					New source					OECD or company limits**
Material tested*											
Batch number/ manufacturing date											
Contaminating micro-organisms (CFU/g, CFU/mL or other appropriate units)											
<i>Add here discussion on observed differences.</i>											

* Material tested: Please specify production stage of TGA1 or formulated product. Add or delete columns as appropriate.

** OECD or company limits: Please delete as appropriate or add one more column if OECD and company limits are not the same.

When it is not possible for the applicant to provide information for the reference source it should be provided by the rapporteur.

A.10 ANALYTICAL PROFILE OF BATCHES (OECD IIM 1.4.4)

Add here overall discussion on observed differences in identity of relevant metabolites/toxins, material for production and contaminants.

SECTION B: ANALYTICAL METHODS

B.1 ANALYTICAL METHODS FOR THE IDENTIFICATION AND QUANTIFICATION OF CONTENT OF MICRO-ORGANISM IN THE TECHNICAL GRADE ACTIVE INGREDIENT (OECD IIM 4.3)

B.1.1 Analytical methods for the identification of micro-organism in the technical grade active ingredient (OECD IIM 4.3.1)

Description of method.

B.1.2 Analytical methods for the quantification of content of micro-organism in the technical grade active ingredient (OECD IIM 4.3.4)

Description of method.

B.2 ANALYTICAL METHODS FOR THE DETERMINATION OF RELEVANT METABOLITES/TOXINS AND CONTAMINANTS IN THE TECHNICAL GRADE ACTIVE INGREDIENT (OECD IIM 4.3.5)

B.2.1 Analytical methods for the determination of relevant metabolites/toxins in the technical grade active ingredient (OECD IIM 4.3.5)

Description of method.

B.2.2 Analytical methods for the determination of microbial contaminants in the technical grade active ingredient (OECD IIM 4.3.5 AND 4.3.6)

Description of method.

Analytical methods for the determination of microbial contaminants should be those that are internationally approved (e.g. for feed/food).

3. TIER I: EVALUATION OF MICROBIOLOGICAL EQUIVALENCE

1. ASSESSMENT OF MICROBIOLOGICAL EQUIVALENCE

Summary of the conclusions of the information in Tables 8.1, 9.1, 9.2 and 9.3.

	Equivalent Y/N	Justification
Identity of the micro-organism		
Content of the micro-organism		
Content of relevant metabolites/toxins		
Composition of material for production		
Content of microbial		

contaminants		
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It should be stated whether the assessment made above shows equivalence or not (in Tier I) for the listed parameters, and an explanation added (e.g. “content of micro-organism is higher in new source than ref source”, “content of relevant metabolites lower in new source than ref source”, “composition of material for production is identical” etc, and specify/justify differences identified).

2. CONCLUSIONS AND RECOMMENDATIONS

Conclusions on Tier I assessment addressing the following points:

- Identity of the micro-organism;
- Content of the micro-organism (determined in relevant units e.g. CFU);
- Content of relevant metabolites/toxins
- Composition of material for production (e.g. inoculum, culture media);
- Content of microbial contaminants.

Recommendation including consideration of need for Tier II assessment

4 TIER II: HUMAN HEALTH & ENVIRONMENTAL EFFECTS

1. ASSESSMENT OF EQUIVALENCE

In Tier II possible effects on human health and the environment due to the changes identified in Tier I are assessed. No additional information over and above that already submitted and considered for the reference source should be requested.

2. CONCLUSIONS AND RECOMMENDATIONS

5. OVERALL CONCLUSION ON EQUIVALENCE

Give summary of TIER I and TIER II assessment

Technical material equivalent following Tier I assessment?

Technical material equivalent following Tier II assessment?

6. REFERENCES RELIED ON

A. IDENTITY (OECD IIM 1.1-1.5)

Data point	Author(s)	Year	Title Source (where different from company), Report No GLP or GEP status (where relevant) Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner

B. METHODS OF ANALYSIS (OECD IIM 4.1 - 4.3.6)

Data point	Author(s)	Year	Title Source (where different from company), Report No GLP or GEP status (where relevant) Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner

4.1. HUMAN HEALTH EFFECTS (OECD IIM, Point 5)

Data point	Author(s)	Year	Title Source (where different from company), Report No GLP or GEP status (where relevant) Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner

4.2. ENVIRONMENTAL EFFECTS (OECD IIM, Point 8)

Data point	Author(s)	Year	Title Source (where different from company), Report No GLP or GEP status (where relevant) Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner

SUMMARY OF THE EQUIVALENCE OF TECHNICAL GRADE ACTIVE INGREDIENT

The compilation of the evaluated sources and the results of the assessment provide useful information for the Member States. In order to facilitate the data input in the existing table on CIRCABC ("Equivalent sources and compliance checks"), the respective data should be provided in the Excel file template

(<https://circabc.europa.eu/faces/jsp/extension/wai/navigation/container.jsp?FormPrincipal: idcl=FormPrincipal: id3&FormPrincipal SUBMIT=1&id=9fe32f90-02ed-4233-aedd-e836120f7a76&javax.faces.ViewState=rO0ABXVyABNbTGphdmEubGFuZy5PYmplY3Q7kM5YnxBzKWwCAAB4cAAAAAN0AAIxNHB0ACsvanNwL2V4dGVuc2lvbi93YWkvbmF2aWdhdGlvbi9jb250YWluZXluaXNw>).