

Unclassified

ENV/JM/MONO(2018)8

Organisation de Coopération et de Développement Économiques
Organisation for Economic Co-operation and Development

22-May-2018

English - Or. English

**ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY**

Cancels & replaces the same document of 16 May 2018

**GUIDANCE DOCUMENT FOR THE ASSESSMENT OF THE EQUIVALENCE OF TECHNICAL
GRADE ACTIVE INGREDIENTS FOR IDENTICAL MICROBIAL STRAINS AND ISOLATES**

**Series on Pesticides
No. 96**

JT03432182

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OECD Environment, Health and Safety Publications

Series on Pesticides

No. 96

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EQUIVALENCE OF TECHNICAL GRADE ACTIVE INGREDIENTS FOR
IDENTICAL MICROBIAL STRAINS AND ISOLATES

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Paris 2018

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FOREWORD

This document dealing with microbial pesticides is intended to provide guidance to both industry and regulatory authorities, in the context of the assessment of technical equivalence of micro-organisms used in plant protection products. This document has been developed in the framework of the OECD Expert Group on BioPesticides (EGBP), a sub-group of the OECD Working Group on Pesticides (WGP) that helps member countries to harmonise the methods and approaches used to assess biological pesticides and to improve the efficiency of control procedures.

The EU served as the lead in the preparation of this Guidance Document. This Guidance Document is based on EU 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 (SANCO/12823/2012) that was approved by the EU Standing Committee on Plants, Animals, Food and Feed on 12 December 2014 and has been modified to address OECD member countries' needs. The purpose of this document is to provide guidance for the assessment of technical equivalence of micro-organisms used in plant protection products and might also be helpful for dossier preparation.

The present Guidance Document received final approval of the OECD EGBP on 27 June 2017 and of the OECD WGP by written procedure on 9 October 2017.

This document is being published under the responsibility of the Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology, which has agreed that it be declassified and made available to the public.

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INTRODUCTION

1. Micro-organisms are usually approved at strain level. As a general principle, for the same microbial strain or isolate, the level of hazard posed for health and environmental protection must be comparable for different sources of technical material. This document is intended to provide guidance to both industry and regulatory authorities, in the context of the assessment of technical equivalence of micro-organisms used in plant protection products. This Guidance Document is applicable for changes to the same strain only in the framework of application for authorisations for plant protection products, where the strain already has been approved. 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 always needs to be demonstrated. The evaluation should compare two sources of technical active ingredient of the same strain of a micro-organism for several parameters, aiming to ensure that the new source is equivalent to the approved source.

BACKGROUND

2. Within most OECD Member Countries, micro-organisms used as plant protection products are approved at strain level and the current practice is to consider each new strain or isolate on its own merits for registration. For every new strain or isolate, a reference source for the technical material should be approved. For changes to the same strain technical equivalence with the approved (reference) source always needs to be demonstrated. In all cases the data requirements should be fulfilled at strain level. Also, the methodology for identification at strain level and for taxonomic classification may need to be reconfirmed by the applicant because methods are evolving very fast.

3. This Guidance Document is applicable for changes to the same strain only in the framework of application for authorisations for plant protection products. 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 or additional manufacturing plant,
- Scale up of fermentation vessel¹,
- Change of manufacturing process, like change of production equipment or propagation conditions (e.g. temperature or ingredients).

4. 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 of 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:

¹ Data requirements, OECD IIM point 1.4.3.2 'Content of the micro-organism': In general, where the information provided relates to a pilot plant production system, the information required must again be provided to the regulatory authority once industrial scale production methods and procedures have stabilised, if production changes result in a changed specification of purity.

- 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.

5. The new source is considered as technically equivalent when the 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
- 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 referred limits in the Working Document on microbial contamination limits for microbial pest control products².

6. In case the above criteria are fulfilled the source is considered as technically equivalent in Tier I and therefore no Tier II assessment is required. For Tier I and Tier II, reference is made to the Annex to this Guidance Document. 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 are still fulfilled. The onus is on the applicant to justify the acceptability of the altered levels.

7. A five batch analysis should be conducted either 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.

8. For all levels of evaluation, there will be value in preparing an evaluation report using the template provided in the Annex to this guidance document.

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

² *Issue Paper on Microbial Contaminant Limits for Microbial Pest Control Products*" (OECD Series on Pesticides No. 65, 2011)

PROCEDURE FOR THE ASSESSMENT OF THE EQUIVALENCE OF NEW SOURCES OF TECHNICAL MATERIALS

10. On receipt of the application for equivalence the reporting country should prepare the evaluation report on equivalence according to the template in the Annex. Timelines and procedures can differ per country. In general, a draft version of the evaluation report will be circulated for commenting. This commenting round should preferably also include the applicant. After having received and evaluated the comments, the report can be finalised, under the condition that for the assessment the principles and guidance in place at the regulatory jurisdiction have been used.

11. To facilitate the evaluation process the applicant may already submit a prefilled report according to template provided for in the Annex. However, it is the responsibility of the reporting country to prepare the final evaluation report.

12. In all cases confidentiality and of business and trade secrets must be respected in cases where the applicant under consideration is different to the one of the reference source.

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.

ANNEX: EVALUATION REPORT - TEMPLATE

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

XXXXXXXXXXXX

date

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Name of microorganism:
Applicant:
Date:

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

The reporting member country must indicate in the table below which case has been examined

Change of location of manufacturing plant or additional 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.

Name of microorganism:

Applicant:

Date:

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:

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Name of microorganism:
Applicant:
Date:

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 reporting member country.

Name of microorganism:

Applicant:

Date:

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/mL, 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 reporting member country.

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

Table A.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)											
Add here discussion on observed differences.											

* 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 reporting member country.

Name of microorganism:

Applicant:

Date:

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 A.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/mL)											
<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 reporting member country.

Name of microorganism:
 Applicant:
 Date:

MATERIAL FOR PRODUCTION

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

Table A.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 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 reporting member country.

Name of microorganism:

Applicant:

Date:

CONTAMINATING MICRO-ORGANISMS

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

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

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 TGAI 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 reporting member country.

Name of microorganism:

Applicant:

Date:

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 A.8.1, A.9.1, A.9.2 and A.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		

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 reference source”, “content of relevant metabolites lower in new source than reference 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