

Unclassified

ENV/JM/MONO(2017)6

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

05-Apr-2017

English - Or. English

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

GUIDANCE DOCUMENT ON BOTANICAL ACTIVE SUBSTANCES USED IN PLANT PROTECTION
PRODUCTS

Series on Pesticides
No. 90

JT03412077

Complete document available on OLIS in its original format

This document and any map included herein are without prejudice to the status of or sovereignty over any territory, to the delimitation of international frontiers and boundaries and to the name of any territory, city or area.



ENV/JM/MONO(2017)6
Unclassified

English - Or. English

OECD Environment, Health and Safety Publications
Series on Pesticides
No. 90

**GUIDANCE DOCUMENT
ON BOTANICAL ACTIVE SUBSTANCES USED IN PLANT PROTECTION PRODUCTS**

IOMC

INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS

A cooperative agreement among **FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD**

Environment Directorate
ORGANISATION FOR ECONOMIC COOPERATION AND DEVELOPMENT
Paris 2017

About the OECD

The Organisation for Economic Co-operation and Development (OECD) is an intergovernmental organisation in which representatives of 34 industrialised countries in North and South America, Europe and the Asia and Pacific region, as well as the European Commission, meet to co-ordinate and harmonise policies, discuss issues of mutual concern, and work together to respond to international problems. Most of the OECD's work is carried out by more than 200 specialised committees and working groups composed of member country delegates. Observers from several countries with special status at the OECD, and from interested international organisations, attend many of the OECD's workshops and other meetings. Committees and working groups are served by the OECD Secretariat, located in Paris, France, which is organised into directorates and divisions.

The Environment, Health and Safety Division publishes free-of-charge documents in eleven different series: **Testing and Assessment; Good Laboratory Practice and Compliance Monitoring; Pesticides; Biocides; Risk Management; Harmonisation of Regulatory Oversight in Biotechnology; Safety of Novel Foods and Feeds; Chemical Accidents; Pollutant Release and Transfer Registers; Emission Scenario Documents;** and **Safety of Manufactured Nanomaterials.** More information about the Environment, Health and Safety Programme and EHS publications is available on the OECD's World Wide Web site (www.oecd.org/chemicalsafety/).

This publication was developed in the IOMC context. The contents do not necessarily reflect the views or stated policies of individual IOMC Participating Organizations.

The Inter-Organisation Programme for the Sound Management of Chemicals (IOMC) was established in 1995 following recommendations made by the 1992 UN Conference on Environment and Development to strengthen co-operation and increase international co-ordination in the field of chemical safety. The Participating Organisations are FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD. The purpose of the IOMC is to promote co-ordination of the policies and activities pursued by the Participating Organisations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

This publication is available electronically, at no charge.

Also published in the Series on Pesticides [link](#)

**For this and many other Environment,
Health and Safety publications, consult the OECD's
World Wide Web site (www.oecd.org/chemicalsafety/)**

or contact:

**OECD Environment Directorate,
Environment, Health and Safety Division
2 rue André-Pascal
75775 Paris Cedex 16
France**

Fax: (33-1) 44 30 61 80

E-mail: ehscont@oecd.org

© OECD 2017

Applications for permission to reproduce or translate all or part of this material should be made to: Head of Publications Service, RIGHTS@oecd.org, OECD, 2 rue André-Pascal, 75775 Paris Cedex 16, France

FOREWORD

This document provides guidance to both industry and regulatory authorities on how procedures and data requirements can be applied to facilitate the submission of a complete data package/dossier for botanical active substances used in plant protection products, and the subsequent evaluation of this data package/dossier by the regulatory authorities. (In this Guidance Document, 'botanical active substances' refers to active substances obtained from plant material.)

The document provides a summary of the legal frameworks and registration procedures for botanical active substances in several OECD member countries. It also describes various information elements concerning the specification of botanical active substances that are considered necessary for assessing the safety of these substances. Based on the taxonomy and/or current knowledge of the botanical source, several groups can be distinguished leading to different requirements.

The document has been developed within the framework of the OECD BioPesticides Steering Group (BPSG), 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 European Union (EU) served as the initial author of the guidance document which has been reviewed and further developed by the BPSG. The BPSG includes representatives from OECD member countries and the regulated industry.

The present guidance document received final approval of the OECD BPSG in June 2016 and of the OECD WGP by written procedure in October 2016.

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.

TABLE OF CONTENTS

Introduction.....	8
Background on Botanical Active Substances	8
Scope.....	9
Definitions	9
Registration of botanical active substances and legal frameworks	10
Documented uses and exposure	18
Identification, characterisation and analyses	20
Methods of manufacture	25
Technical equivalence.....	26
Mammalian toxicology	27
Residues	29
Fate and behaviour.....	30
Effects on non-target species	31
Efficacy.....	32
References.....	35

Introduction

1. In 2011, the OECD BioPesticides Steering Group (BPSG) held a seminar on the "Characterisation and Analyses of Botanicals for the Use in Plant Protection Products", to, among other things, identify key issues and challenges in the area of "botanicals", discuss options for further steps for OECD countries and others to address these issues, and recommend possible further steps for OECD (OECD, 2012). One of the recommendations emanating from that seminar was that there would be value in updating the EU *Draft Working Document Concerning the Data Requirements for Active Substances of Plant Protection Products made from Plants or Plant Extracts* SANCO/10472/2003, and including information from guidance documents already developed in Canada and the US and from work in the EU biocides area. As the EU Working Document only covered water and ethanol extracts and a limited number of plant parts, an updated document could also cover other extraction methods, as probably less than half of the plant extracts are indeed extracted with water or ethanol. Active substances from plant material can also be obtained by other extraction methods and physical processes such as pressing, milling and crushing.

2. On 20 March, 2014, the EU published a *Guidance Document on Botanical Active Substances Used in Plant Protection Products* (SANCO/11470/2012-rev8). In most jurisdictions, it is acknowledged that for some of the data requirements for plant extracts a different approach may be taken if adequately justified. Therefore, the EU Guidance Document aimed to provide practical solutions on how procedures and data requirements can be applied to facilitate the approval of these kinds of substances at the EU-level and the authorisation of plant protection products containing botanical active substances at Member State-level. In the development of the Guidance Document, information from non-EU countries, the European Chemicals Agency work on biocides, and the European Food Safety Authority were taken into account.

3. Following publication of the EU Guidance Document, the BPSG embarked on the development of this OECD Guidance Document which is based largely on the EU document, but revised to more broadly reflect the practices across OECD countries, such as the legal frameworks and registration procedures in OECD countries that concern botanical active substances.

Background on Botanical Active Substances

4. Botanical active substances for plant production products differ from synthesised chemical active substances in the way they are derived. Synthesised chemicals are produced by chemical reactions, whereas botanical active substances are obtained by processing material of biological origin.

5. To defend themselves against herbivores (including insects) and pathogens, plants produce a variety of components (also called 'secondary plant compounds'), including volatiles such as various alcohols, terpenes and aromatic compounds. These secondary plant compounds can enable plants to resist pathogens, deter insects or other herbivores from feeding, and have non-toxic or direct toxic effects on pests or they may be involved in drawing in predators and parasitoids in response to feeding damage. They may also be used by plants to attract pollinators or they may be involved in interplant communication. As these properties have been known and observed for a very long time, it is a logical progression that some of these compounds have been identified as candidates for crop protection use.

6. The composition of a botanical active substance depends on the material of biological origin and the manufacturing process(es) and may depend on further processing and purification. Therefore, botanical active substances may have a larger variation in the qualitative and quantitative composition than synthesised chemicals.

7. The production of substances of biological origin is influenced by the geographical areas and climatic conditions (e.g., duration/intensity of sunshine, rain, soil type, etc.) where the plant is grown, and thus the production may differ from year-to-year. Therefore, the nature and concentrations of substances vary naturally and affect the quantitative and qualitative composition of the botanical active substance.

8. In addition, the way in which botanical active substance are processed has an impact on the composition of the extracted material which varies depending on the technique applied (e.g., cold-pressing, water-steam-distillation, extraction with (organic) solvents or a combination of several steps) often resulting in a complex mixture of several components. As a result, a botanical active substance of the same biological origin could have different compositions. Therefore, certain physical parameters related to the processing method are important for characterising a botanical active substance.

Scope

9. The term 'botanical active substance' covers an extremely heterogeneous group of substances ranging from simple plant powders to unprocessed and processed plant extracts. Furthermore, plant extracts may be highly refined (i.e. one single active substance) or represent a complex mixture of components of which all or only some are biologically active.

10. For the purpose of this Guidance Document, 'botanical active substance' refers to active substances obtained from plant material. Therefore, substances referred to as analogues, mimics, natural-identical synthesised molecules and biosimilars are not covered by this Guidance Document.

11. Furthermore botanical active substances derived from Genetically Modified Organisms (GMO's), safeners, synergists, adjuvants and co-formulants are also outside the scope of this Guidance Document.

Definitions

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

13. A 'botanical active substance' consists of one or more components found in plants and obtained by subjecting plants or parts of plants of the same species to a process such as pressing, milling, crushing, distillation and/or extractions. The process may include further concentration, purification and/or blending, provided that the chemical nature of the components is not intentionally modified/alterd by chemical and/or microbial processes.

14. The 'technical grade' produced from the defined source(s) and by the described manufacturing processes, is equivalent to the 'active substance'.

15. A 'component of concern' means any component which has an inherent capacity to cause an adverse effect on humans, animals or the environment and is present or is produced in a plant protection product in sufficient concentration to present risk of such an effect.

16. The term 'pure active substance' does not typically apply to most botanical active substances because of their complex nature.

17. For botanical active substances, the technical grade will be in most cases a mixture of components from the plant and in addition all components that result from the cultivation, harvest, post-harvest storage and primary processing and manufacturing. It may be difficult to identify and characterise all individual components. Some of these components may be considered as components of concern which may be considered in the same way as 'relevant impurities'.

18. A 'chemical fingerprint' of a botanical active substance is a spectroscopic and/or chromatographic profile that is matched qualitatively and quantitatively against that of a reference sample or standard to ensure the identity and quality of a sample and consistency from sample to sample.

19. In studies performed with the technical grade, it may be required to use one or more component(s) as analytical lead substances, named 'lead component' concept. There can be different 'lead components' used for different sections of the risk assessment (e.g., metabolism, residues, environmental fate). The lead component(s) that is/are used should be justified in terms of its/their properties and quantities in particular with regard to representativeness of biological activity.

20. Lead components may be the most frequently occurring substances as demonstrated from the 'chemical fingerprint'. Alternatively, they may be substances which have been identified (e.g., from literature or in-house analysis) to be the source of potential effects. If the lead component approach is required, validated analytical methods should be made available in the dossier, as applicable.

21. A 'plant' (adapted from biology-online) is any organism that belongs to Kingdom *Plantae*, which is characterised by the following fundamental features:

- ability to make its own food by photosynthesis, i.e. capable of capturing energy via the green pigment (chlorophyll) inside the chloroplast, and of using carbon dioxide and water to produce sugars as food and oxygen as by-product;
- foods are stored in forms of sugars and starch;
- presence of rigid cell walls apart from the cell membrane;
- eukaryotic cells, i.e. the presence of a distinct nucleus surrounded by a membrane
- is mostly multicellular, i.e. made up of many cells organized to perform a specific function as a unit;
- unlimited growth at meristems (when present);
- organs are specialized for anchorage, support, and photosynthesis (e.g., roots, stems, leaves, etc.);
- response to stimuli is rather slow due to the absence of sensory organs and nervous systems, as do animals;
- limited movements due to a lack of organs for mobility, as do animals; and
- life cycle that involves both sporophytic and gametophytic phases (alternation of generation).

22. Plants are the major producers in an ecosystem, and in this context they include flowering plants, trees, herbs, bushes, grasses, vines, ferns, mosses, and algae. Fungi, lichen, mushrooms and yeast are excluded.

Registration of botanical active substances and legal frameworks

23. Botanical active substances' are regulated slightly differently in different global regulatory zones. This chapter provides an overview of the regulatory frameworks in Australia, Canada, the EU, Japan, New Zealand and the United States.

Australia

24. The Australian Pesticides and Veterinary Medicines Authority (APVMA) assess and registers agricultural and veterinary chemical products. A number of products of biological origin fall within the [Australian Government, Agricultural and Veterinary Chemicals Code Act 1994 \(the Agvet Code\)](#) definition of an agricultural chemical product and therefore must be registered by the APVMA. The definition of an agricultural chemical product includes not only plant protection products, but also biocides and other products. The APVMA's guidelines refer to these products by the term 'biological agricultural product'. APVMA define four major categories¹ of biological chemical products:

- Category 1: biological chemicals (e.g., pheromones, hormones, growth regulators, enzymes and vitamins)
- Category 2: plant and other extracts (e.g., plant extracts, oils)
- Category 3: microbial agents (e.g., bacteria, fungi, viruses, protozoa)
- Category 4: other living organisms (e.g., microscopic insects, plants and animals plus some organisms that have been genetically modified).

25. As the Australian regulator, the APVMA recognises the need for flexibility in determining the data requirements for biological products, and the APVMA's 'Guideline for the regulation of biological agricultural products' (<http://apvma.gov.au/node/11196>) allows for these products to be evaluated on a case-by-case basis as well as providing specific guidance for when reduced information requirements apply.

Canada

26. At the federal level in Canada, pesticides are regulated under the [Pest Control Products Act \(PCPA\)](#). All products, organisms and substances that are within the definition of "pest control product" as described in the Act must be registered before they are imported, manufactured or used in the country. The registration requirement does not apply to pesticides that are exempt by regulation (e.g., pesticide devices that do not pose unacceptable risks to people or the environment). For non-conventional pesticides, [Regulatory Directive DIR2012-01: Guidelines for the Registration of Non-Conventional Pest Control Agents](#) offers special guidance to prospective applicants and registrants. This directive recognises that non-conventional products may not fit well into a registration framework that was developed for conventional chemical pesticides with well-defined chemistries and molecular structures. The varied nature of these types of products can make it challenging to define a specific mode of action, to identify the active components of a mixture or to delineate a specific level of efficacy/value. This directive outlines a regulatory approach for non-conventional products that allows for innovation and flexibility in assessing whether they have value and pose any unacceptable risks to human health or the environment, while recognising that, even though a non-conventional product is perceived as different from a traditional chemical, its risks and value must meet the same acceptability standard under the PCPA legislation before it can be approved for registration.

27. Products eligible for consideration under this directive must have some, but not necessarily all, of the following characteristics: i) low inherent toxicity to humans and other non-target organisms (N.B. substances with chronic toxicity, genotoxicity, carcinogenicity, neurotoxicity or immunotoxicity, cause

¹ Although in the original text 'group' is mentioned, this has been replaced by 'category' to avoid any confusion with the 3 groups as defined in paragraph 86.

reproductive or developmental effects, metabolise into compounds of toxicological concern or are anticipated to bioaccumulate are not eligible for review under this directive); ii) low potential for their use to result in significant human or environmental exposure; iii) not persistent in the environment; iv) already widely available to the public for other uses, with a history of safe use under conditions posing equivalent potential for exposure to humans and the environment; v) pesticidal action that is not the result of toxicity to the target organism, for example, products that work by attracting, repelling, desiccating or smothering pests; or v) unlikely to select for pest resistance.

28. Substances eligible for review under this directive could include, but are not limited to: i) food items, extracts, preservatives or additives (for example, crushed garlic, garlic powder, table salt, citric acid); ii) plant extracts and oils (for example, vegetable or mineral oils); iii) commodity chemicals that have a range of non-pesticidal uses (for example, acetic acid); iv) fertilizer or other plant growth supplements, commonly used in the agricultural sector (for example, mineral salts, such as sodium, and potassium salts of phosphorus acid); or v) inert materials (for example, diatomaceous earth).

29. Health Canada's Pest Management Regulatory Agency (PMRA) assesses the eligibility of products for review under Regulatory Directive DIR2012-01 on the basis of all available lines of evidence. Applicants must submit a detailed rationale explaining why they believe their product is eligible for review under this directive. This rationale would include details of the proposed use pattern and label claims, and as much scientific evidence as possible on the characterisation of the components, toxicity, exposure and environmental fate of the product. The PMRA supports a tiered and flexible approach to information requirements and recognises that the information needed to make a regulatory decision should be commensurate with the level of anticipated risks. Applicants are encouraged to make use of the pre-submission consultation process to help determine what information is needed in support of registration. Relevant data could be related to either pesticidal or other uses, and could include published literature or original studies. Where they exist, submission of regulatory reviews conducted in other countries is encouraged. In some cases, data requirements may be waived on the basis of a scientifically valid rationale. For example, a long history of exposure to humans or the environment could form the basis of a request to waive some data requirements, especially if the historical routes and levels of exposure are similar to what would result from the proposed uses of the product. Detailed guidance on waiver requests is provided in Regulatory Directive DIR2012-01.

30. Prior to initiating any original testing, applicants are encouraged to consult the PMRA on proposed protocols, particularly those that may deviate from internationally recognised test guidelines.

31. At any point during the PMRA registration review, additional information may be requested if the submitted information is inadequate or if potential risks are identified.

EU

32. Botanical active substances have to be approved under [Regulation \(EC\) No 1107/2009](#) and a dossier has to be compiled according to the data requirements as laid down in [Regulation \(EU\) No 283/2013 \(active substance\)](#) and [Regulation \(EU\) No 284/2013 \(plant protection product\)](#). The legal framework will also be the basis for the peer review and decision making process and therefore the data requirements and the protection goals as laid down in [Regulation \(EU\) No 546/2011](#) -as regards uniform principles for evaluation and authorisation of plant protection products- have to be respected.

33. Although it is acknowledged that in the data requirements (Regulations (EU) No 283/2013)² the term 'plant extracts' is used, 'botanical active substances' is the preferred term to be used. Therefore, this

² To be read in conjunction with Commission Communications 2013/C 95/01.

guidance refers to botanical active substances and it is understood to be applicable when providing information in agreement with those provisions in the regulation that refer to "plant extracts".

34. For all 'botanical active substances' it should be made clear that the plant material has been produced with sustainable, reproducible methods and that the Nagoya Protocol on *Access to genetic resources and fair and equitable sharing of benefits*, adopted by the Conference of the parties to the Convention on Biological Diversity (2010 in Nagoya), has been respected.

Pre-submission meeting

35. Applicants are encouraged to request a pre-submission consultation with one of EU Member States' competent authority, particularly if they are not familiar with the regulatory system. The main objective of pre-submission meetings is to discuss the information requirements and regulatory approach. Although the data requirements are laid down in legislative documents applicants may need some guidance how to interpret these data requirements and whether studies, published literature and/or a reasoned approach can be accepted. It is up to the applicant to submit the relevant information.

36. It is recommended that applicants include the following information:

- The standard GAP (good agricultural practices) table for active substances (see Appendix I) and a draft label;
- The specification of the 'botanical active substance' (see chapter on Identification, characterisation and analyses);
- The composition of the product listing all the ingredients and their proportions or amounts;
- A brief description of manufacturing information (specific details on how the product is made; see chapter on Methods of manufacture); and
- A summary on the health, environmental and efficacy data and related risk assessments.

37. It should be noted that the EU Member States' competent authorities cannot be definitive on data/information requirements which are ultimately dependent on the full evaluation and peer review.

38. Information that normally should be considered confidential is listed in Article 63 of Regulation (EC) No 1107/2009.

39. If applicable and when available, the information should also include:

- International regulatory status;
- Other relevant information, such as summaries of other available evidence on the health, environmental and efficacy data and related risk assessments;
- Historical use information including other established uses of the proposed botanical active substance (e.g., in food or medicines) (see chapter on Documented uses and exposure);
- Natural background levels in plants and the environment (e.g., in crop or animal food items, in soil).

- Safety Data Sheets (SDS).

Dossier preparation

40. All information necessary for hazard identification and exposure assessment should be provided.

41. In general, data requirements can be fulfilled by submitting studies, a reasoned approach and/or relevant literature. If applicants submit relevant literature they should make clear reference to the specific data requirements which are considered to be addressed by this literature. Where scientific literature is provided it should have been searched and selected without bias and determined as 'reliable'. In this respect the EFSA guidance on submission of scientific peer reviewed open literature applies (EFSA 2011; see also Article 8(5) of Regulation (EC) No 1107/2009).

42. When providing technical reports/studies on the properties or safety on the botanical active substance with respect to human or animal health or the environment, the tests and analyses shall be conducted in accordance with the principles of Good Laboratory Practice (GLP). When providing technical reports/studies on the efficacy, the tests and analyses shall be conducted in accordance with the principles of Good Experimental Practice (GEP). However, the GLP- and GEP-requirement does not apply to studies reported in literature.

43. It should be noted that the test methods should be those specified in Commission Communications 2013/C 95/01 and 2013/C 95/02. Any other methods used or deviations from the methods should be justified. Where the identity of the test substance or material has not been adequately specified, or its stability in dosing vehicles or solvents used is questionable, the impact on the validity/reliability and usefulness of the test or study has to be assessed.

44. In the introduction to the Annex to the data requirements (Regulation (EU) No 283/2013) it is indicated that:

"The information shall include a full and unbiased report of the studies conducted as well as a full description of them. Such information shall not be required, where one of the following conditions is fulfilled:

(a) it is not necessary owing to the nature of the product or its proposed uses, or it is not scientifically necessary;

(b) it is technically not possible to supply.

In such a case a justification shall be provided."

45. For a number of botanical active substances these conditions may be particularly relevant.

46. If argumentation (i.e. a scientific rationale) is based on historical - and documented - use, a comparison should be provided of the exposure for the intended use compared to the documented use. The chemical composition of the botanical active substance should be comparable to those historically used taking into consideration natural variation.

47. For botanical active substances lacking a substantially reported history of use or for botanical active substances whose intended use levels will significantly exceed historical use or background exposure levels the assessment has to rely on basically the same set of data as for synthesised chemical active substances in plant protection products (default approach) with options for scientifically justified deviations from data requirements.

48. Studies shall usually be conducted with the technical grade although use of single components where more appropriate for a study can also be considered. Studies conducted with single components of concern could be useful for supporting the evaluation to predict how the botanical active substance might behave.

49. Extrapolating from one botanical active substance to another with respect to the same or similar component(s) of (eco)toxicological concern (read-across) can only be considered when accompanied by evidence of their composition with respect to the particular substance of concern.

50. Application of non-testing methods (e.g., the use of validated (Q)SAR models and TTC models) could also be taken into account when doing the assessment.

51. Since it is often not possible to radiolabel complex botanical active substances it may not be technically feasible to perform studies based on radioactive detection.

52. This document provides guidance on options on how to address data requirements when completing a dossier for a botanical active substance which is explained in more detail in the following chapters of this guidance document.

53. Under the following points in the data requirements (Regulation (EU) No 283/2013) it is stated that "*For plant extracts, a different approach may be taken if adequately justified:*

1.7: The molecular formula, molar mass and structural formula of the active substance, and where relevant, the structural formula of each isomer present in the active substance, shall be provided (see chapter on Methods of manufacture).

1.9 The minimum content in g/kg of pure active substance in the manufactured material used for production of plant protection products, shall be reported (see chapter on Methods of manufacture).

1.10 The minimum and maximum content in g/kg of each additive shall be provided. The maximum content in g/kg of each further component other than additives (1.10.2 - significant impurities and 1.10.3 - relevant impurities) shall also be provided (see chapter on Methods of manufacture)."

54. In addition, under point 1.11 it is stated that at least *five representative batches from recent and current industrial scale production* of the active substance shall be analysed for content of pure active substance, impurities, additives and each further component other than additives, as appropriate. *For plant extracts and semiochemicals (such as pheromones), justified exemptions can be made.*

55. In the framework of this document the term *batches* is replaced by "samples" to take into account situations, when the production process does not allow sampling of distinct batches (e.g., continuous production).

56. Also regarding point 6.2 (metabolism, distribution and expression of residues) *for plant extracts, a different approach may be taken if adequately justified.* In general, metabolism or processing studies are only considered necessary if high uncertainties remain on the nature and/or magnitude of the residues (see chapter on Residues).

Japan

57. For all 'botanical active substances' it should be made clear that the plant material has been produced with sustainable, reproducible methods and that the Nagoya Protocol on Access to genetic resources and fair and equitable sharing of benefits, adopted by the Conference of the parties to the Convention on Biological Diversity (2010 in Nagoya), has been respected.

58. Japan has no specific regulations and guidelines for the approval of botanical active substances. Therefore, in principle, for the evaluation and registration of botanical active substances, a complete set of data which is the same with that required for chemical substances under [Notification No.12- Nousan 8147](#) would be required. This Notification provides information about whether data requirements can be exempted when certain criteria are met (e.g., if there is enough information on the health effect of the active ingredients due to long history of safe consumption as food, certain data requirements can be waived).

New Zealand

59. The two main pieces of legislation covering the regulation of pesticides in New Zealand are:

- Agricultural Compounds and Veterinary Medicines (ACVM) Act 1997 administered by Ministry for Primary Industries (<http://www.mpi.govt.nz/importing/agricultural-compounds-and-veterinary-medicines>); and
- Hazardous Substances and New Organisms (HSNO) Act 1996 administered by the NZ Environmental Protection Authority (<http://www.epa.govt.nz/Pages/default.aspx>).

60. The ACVM Act authorises agricultural compounds (which includes agricultural chemicals, biological, botanical and chemical), veterinary medicines, animal feeds, fertilisers etc. either by registration of trade name products, or exempting product groups from the requirement of registration. The HSNO Act approves hazardous substances (which includes agricultural chemicals), and the approval can cover one or more trade name products.

United States

61. All pesticides are regulated within the United States (US) under the Federal Insecticide, Fungicide, and Rodenticide Act. The regulatory approaches proposed by OECD in this Guidance Document are similar to those conducted by the US Environmental Protection Agency (US EPA). There are two major exceptions. First, this Guidance focuses solely on bioactive substances obtained from botanical sources, whereas the US EPA addresses bioactive pesticidal substances obtained from any natural source (plant, animal, or geological). Secondly, the US EPA makes a distinction between natural substances that have a toxic mode of action and those substance that do not have a toxic mode of action. If a natural substance has a toxic mode of action against a target pest, the US EPA considers it to be a Conventional Chemical pesticide and is assessed for safety to human health and the environment as any synthetic chemical.

62. Naturally-occurring substances that have a non-toxic mode of action may be considered to be reviewed and assessed under a reduced data set, when compared to Conventional Chemicals, and considered to be Biochemical pesticides if they meet the following three statutory criteria, as described in 40 CFR 158.2000(a) (<https://www.gpo.gov/fdsys/granule/CFR-2012-title40-vol25/CFR-2012-title40-vol25-sec158-2000>):

- (i) It is a naturally-occurring substance, or if not naturally-occurring, is structurally-similar and functionally identical to a substance that occurs in nature;
- (ii) It has a history of exposure to humans and the environment with minimal toxicity;
- (iii) It has a non-toxic mode of action against the target pest.

63. It is noted here that the US EPA makes a further distinction between toxicity and lethality; many Biochemical pesticides can have a lethal mode of action against the target pest without being toxic. For example, some plant oils may act via a suffocating mode of action, or via a physico-chemical mode of action, such as membrane disruption or desiccation.

64. A 12-member Biochemical Classification Committee reviews all new active ingredients that are proposed to the US EPA as Biochemical pesticides to determine whether they meet the three statutory criteria described above.

65. Other similarities in this OECD Guidance Document to current practice at the US EPA relate to (i) reducing some of the data requirements, via the submission of historical data in the open technical literature (e.g., scientific journal articles) in lieu of guideline studies, (ii) comparison of application rates of the active substances vs. background levels already present in the environment, (iii) bridging of existing toxicological information from similar substances, and (iv) current exposures to humans and the environment via other uses of botanical active substances.

66. This Guidance Document also proposes a tiered approach (see below) to hazard assessment similar to that already in practice at the US EPA for both Biochemical and Microbial pesticides.

67. “Based on the taxonomy and/or current knowledge of the botanical source the following categories³ can be distinguished leading to different requirements especially for analytical methods and regulatory approaches:

Category 1

Botanical active substances that are -with current knowledge- known to have no unacceptable effects on humans, animals and the environment and are based on materials with known specifications e.g., food grade.

Category 2

Botanical active substances based on a material with an established specification and for which the taxonomy and current knowledge indicates that the botanical active substance may contain components of possible concern for humans, animals and/or the environment. In this case these components should be identified and quantified.

Category 3

Botanical active substances that are not based on a material with an established specification. In this case complete identification and characterisation is in principle needed.”

³ Although in the original text ‘group’ is mentioned, this has been replaced by ‘category’ to avoid any confusion with the 3 groups as defined in paragraph 86.

68. This OECD Guidance Document goes further into details of product chemistry data requirements, hazard assessments for mammalian toxicology and non-targets, residues, fate and behaviour in the environment, endocrine disruption and risk assessments, all of which are very similar to currently conducted practice in the Agency.

69. To be registered as a Biochemical pesticide, the natural substance:

- (i) must be a substance that meets all three Biochemical Classification criteria (described above);
- (ii) must contain only approved inerts; and,
- (iii) cannot contain a Conventional Chemical active ingredient.

70. Biochemical pesticide data requirements are as follows (see <http://www.ecfr.gov/>):

[40 CFR 158.2030](#) Product Chemistry

[40 CFR 158.2050](#) Human Health

[40 CFR 158.2060](#) Non-target Organism & Environmental Fate

71. OCSPP Harmonized Guideline study protocols (see <http://www.epa.gov/test-guidelines-pesticides-and-toxic-substances/final-test-guidelines-pesticides-and-toxic>):

[Series 830](#) Product Chemistry

[Series 870](#) Human Health

[Series 850](#) Non-target Organism & Environmental Fate

Documented uses and exposure

72. For thousands of years, agricultural practices relied heavily on crop rotation or mixed crop planting to optimise natural pest control (such as predation, parasitism, and competition). Therefore, the concept of 'natural plant protection' arose early in the development of agriculture. Greek and Roman scholars published treaties on agricultural practices to minimize the negative effects of pests on crops. Methods such as use of plant oils for pest control were mentioned. An early survey in China (25–220 A.D.) showed that 267 plant species were known to have pesticidal activity (Dayan *et al.* 2009).

73. A recent review on the diversity of organic chemical functionality confirms that there are 143 basic structural groups. Studies on the complementarity between synthetic and natural plant derived compounds highlighted that natural products generally have a high structural diversity, possessing more chiral centres, sp³-hybridized carbons, and rings than synthetic pesticides. Few natural products contain halogens (Cl, F, and Br), which are often added to synthesised molecules to modify physical-chemical or biological properties. This diversity of natural compounds may serve as a source for new botanical-based pesticides (Dayan *et al.* 2009).

74. Current trends for developing botanicals for plant protection include 'rediscovery' of traditional uses, screening of substance libraries to identify novel substances, refining of formulations to improve efficacy and systematic development of mixtures of active substances. As well as being efficacious in their own right, botanical active substances may have a number of potential benefits for plant protection such as

in resistance management, sustainable farming with Integrated Pest Management (IPM), low or no residues systems and organic crop production.

75. Variation in efficacy of botanical active substances when used as plant protection products may be more than expected for a synthesised chemical pesticide. Variation may occur for a number of reasons such as biological activity, UV instability, rain fastness, limited uptake by plants and/or pests.

76. This variation may also lead to more complexity in the risk assessment. Natural occurrence as such does not imply the use of these substances is always without risk.

77. Plants produce a variety of components (also called 'secondary plant compounds'), including volatiles such as various alcohols, terpenes and aromatic compounds. The specificity of these secondary plant compounds is critical to determining their ecological role and it is known that combinations of secondary plant compounds may have a desired or undesired synergistic effect.

78. As these secondary plant compounds are common in nature, human and environmental exposure to many of them is frequent in the natural environment. Quantification of this exposure may be complex. However, there are some substances for which there are well documented exposure assessments.

79. To consider what levels of exposure are common for humans and the environment the following types of questions should be addressed:

- What is the nature and the level of 'common background exposure'?
- Is there a history of safe use, and, if so, for what use and how is it documented?
- Are there reported incidence of adverse effects from the use of botanicals and, if so, what was the nature and level of exposures associated with that incidence?
- Which part of the plants was used and in which way it was processed?

80. If the history of the use of a botanical for plant protection or for other purposes is documented, it should be adequately considered. This includes the use of information from the 'peer reviewed' open literature and from other reliable public sources. Account should be taken for comparability of parts of plants used and manufacturing process. If these are not similar, a justification should be made to explain why an extrapolation is reasonable. Details of exposure from natural and other background levels such as the concentration and duration of exposure have to be considered (e.g., environmental, cosmetic and nutritional uses). Bridging of information from similar botanicals should be encouraged, but the relevance must be justified by the applicant in each case. Reference to natural or historical exposures may need to take into account the source or specification of the material to consider possible differences in the nature of the proposed botanical material and the material which has a natural (or other form of background) exposure. Reasoned cases should be based on comparability of exposure related to dose, natural concentrations (e.g., in food), background levels, and application pattern. Which data requirements can be fulfilled by such data should be discussed in a pre-submission meeting with evaluators of a competent authority.

81. The following provides an indication of how information from existing use could be considered in a risk assessment:

- Documented use in *human nutrition* (food or food additives⁴ e.g., spices or flavours, lecithin, rape seed oil) at similar concentrations may provide justifications to replace some or all oral toxicity and residue studies.
- Documented use in *animal feeding* at similar concentrations may provide justifications to replace some or all oral toxicity and residue studies.
- Documented use in *cosmetics* may provide justifications to replace some or all dermal irritation/sensitization and oral toxicity studies.
- Documented use as a *fertiliser*⁵ may provide justifications to replace some or all ecotoxicology and environmental fate studies, but this needs to be verified on a case-by-case basis.
- Documented use in *pharmacopoeia* (called 'original use' in this context) may provide justifications to replace studies on a case-by-case basis.
- Documented use as a *biocide* may provide justifications to replace studies on a case-by-case basis.
- Documented *technical use* (e.g., oils) may provide justifications to replace studies on a case-by-case basis.
- Documented use in *traditional gardening and agriculture* may provide justifications to replace some or all residues, ecotoxicology and environmental fate studies, but these need to be verified on a case-by-case basis.

Identification, characterisation and analyses

Identification of botanical source material

82. For identification (taxonomy) of the botanical source and botanical preparation, it is recommended that practitioners follow as much as possible the nomenclature of the European Pharmacopoeia. Additional nomenclature sources are as follows: World Checklist of Selected Plant Families (Royal Botanic Gardens, Kew); books by Peter Hanelt [e.g., Mansfeld's encyclopedia of agricultural and horticultural crops (except ornamentals), Hanelt et al., 2001] also available on the Internet as Mansfeld's World Database of Agricultural and Horticultural Crops; and the database by United States Department of Agriculture. If a scientific name is not found in any of the above-named references, its existence may be checked in The International Plant Names Index (<http://www.ipni.org>).

83. Since there have been many instances where species have been reclassified or renamed, the same species may be known by different scientific names which should be quoted. Common (vernacular) names may also be provided, but it should be noted that a common name used in one region to refer to a particular plant may be used elsewhere to refer to another quite unrelated species. Hence, common names may not uniquely identify a species and are not as reliable as the scientific names.

84. The following summarises the requirements for the description of the identity of the botanical:

⁴ The "Codex General Standard for Food Additives" adopted and updated by the FAO/WHO Codex Alimentarius Commission lists food additives which are recognised as suitable for use in food.

⁵ 'Fertiliser' means material, the main function of which is to provide nutrients for plants.' Defined in EU Regulation (EC) No 2003/2003 (see <http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1476178748121&uri=CELEX:32003R2003>).

- Scientific name: full systematic species name including botanical family, genus, species, author's name⁶ and, where relevant, variety, subspecies and chemotype.
- Synonyms: botanical name(s) that may be used interchangeably with the preferred scientific name.
- Common names: vernacular name(s).
- Biogeography: region(s), country(ies), area/site(s) of cultivation, natural habitat(s).
- Part of plant used: e.g., root, leaf, seed, fruit,
- Growth stage(es) of plant used.

85. Identification (taxonomy) of the botanical source and botanical preparation may in some cases be complicated. Taxonomic confirmation of species may need to be made by an independent botanical expert.

86. Based on the taxonomy and/or current knowledge of the botanical source the following groups can be distinguished leading to different requirements especially for analytical methods and regulatory approaches:

Group 1

Botanical active substances that are - with current knowledge - known to have no unacceptable effects on humans, animals and the environment and are based on materials with known specifications e.g., food grade⁷ (see chapter on Residues).

Group 2

Botanical active substances based on a material with an established specification and for which the taxonomy and current knowledge indicates that the botanical active substance may contain components of possible concern⁸ for humans, animals and/or the environment. In this case these components should be identified and quantified.

Group 3

Botanical active substances that are not based on a material with an established specification. In this case complete identification and characterisation is in principle needed.

Source of botanical material

87. It is common knowledge that plant quality varies from crop-to-crop. Therefore, sample to sample conformity of technical grade is required. If production of technical grade materials leads to variation in

⁶ In botanical nomenclature, author citation refers to citing the person (or group of people) who validly published a botanical name, i.e. who first published the name while fulfilling the formal requirements as specified by the International Code of Botanical Nomenclature (ICBN).

⁷ JECFA evaluations: <http://www.who.int/foodsafety/chem/jecfa/publications/en/index.html> and Food Chemicals Codex (<http://www.usp.org/food-ingredients/food-chemicals-codex>)

⁸ Compendium of botanicals reported to contain naturally occurring substances of possible concern for human health when used in food and food supplements; EFSA Journal 2012

the material produced, then this variation should be adequately characterised. Such variation can be reasonably expected and some degrees of variation can be accepted during evaluation. However, a general aim of minimising variability arising from production is considered good practice in order to ensure that a consistent, good quality botanical material is produced.

88. Sufficient information on agronomic practices should be provided.

89. The botanical raw material may be from more than one source to allow blending to manage the variability of the raw material. In that case, the sources should all be adequately described, including geographical origin(s) of material used, region(s), country(ies), area/site(s) of cultivation, and natural habitat(s). The sources may also be from secondary or waste material where such information may not be available. In such cases, the applicant should provide additional information on the methods used to guarantee consistent quality and composition of the final product.

90. The following information should be provided concerning the source of the botanical material.

91. Cultivation:

- wild harvest or cultivated, and if cultivated, seed and cultivation material should be specified,
- ecology/habitat or cultivation practices,
- usual agronomic conditions,
- where relevant, plant protection measures (including use of plant protection products used during cultivation of the botanical source).

92. Harvest:

- time of year of harvest,
- part of plant used: e.g., root, leaf, seed, fruit,
- growth stage at harvest,
- method of harvest and time to storage (e.g., including any drying in the field).

93. Post-harvest storage:

- storage conditions prior to any primary processing (e.g., time, humidity, drying, temperature) of the material from harvest to processing. Details should be provided indicating how storage conditions will avoid growth of micro-organisms (e.g., the humidity has not exceeded a maximal tolerance limit for moisture in stored plant material).

94. Primary processing:

- for plant material from more than one (cultivation) source: where relevant, sources of material will need to be described for their cultivation, harvest and storage (as above),
- preparation of material prior to any extraction (e.g., removal of seed pods, crushing, milling, etc.),

- conditions (e.g., time, humidity, temperature) of storage of the botanical material prior to manufacturing process.

Manufacturing process

95. Information that should be provided concerning the manufacturing processes is described in Chapter on Methods of manufacture. It constitutes part of the active substance specification.

Composition of the botanical material

96. Botanical material may be expected to be variable in composition and to be a more or less a complex mixture of naturally occurring components. Any combination of these components could be responsible for the biological activity of a botanical plant protection product.

97. To assure consistent quality and to define the botanical active substance, the technical grade should be defined by a justified suitable method such as chromatographic techniques in combination with spectroscopic techniques using a suitable reference sample or standard⁹, and the purity of these should be stated. New analytical methodology and modifications to existing methodology should be used when they are considered to offer additional quality. This characteristic profile is then the chemical fingerprint of the technical grade. If required, an applicant will need to provide reference samples and analytical standards used for the botanical active substance identification to a reference laboratory.

98. Depending on the group to which the botanical material belongs (Group 1, 2, 3) data on the chemical composition of the botanical active substance should be provided with emphasis on the concentrations of components of relevance for the safety assessment, such as:

- components that should be classified according to their chemical structure (e.g., flavonoids, terpenoids, alkaloids, etc.). Levels at which the components are present in the respective part of the technical grade or botanical preparation should be given where available.
- components that characterise the quality, chemical fingerprint, production process and/or biological activity of the preparation (lead components).
- components that provide reasons for concern due to their chemical, physiological or (eco)toxicological properties.

99. In some cases, it may be difficult to identify the component(s) responsible for an adverse effect. In such cases, the weight of evidence that supports a particular component being of concern should also be given.

100. The requirements regarding the specification for the different groups are detailed below.

Group 1

101. *Botanical active substances that are - based on current knowledge - known to have no unacceptable effects on humans, animals and the environment and are based on materials with known specifications e.g., food grade.*

⁹ Working Document SANCO/3030/99 - rev.4

102. It is not necessary to identify each component but to demonstrate that each sample of botanical active substance is similar in its composition and comparable to the specification, with variation within defined acceptable margins. However, if known, the components from the specification should be identified and declared. Validated analytical methods should be used, if appropriate. In the EU, five samples should be assessed following EU data requirements for batch analyses of active substances and acceptable ranges for the profile of components quantitatively provided. The acceptable variability between samples may be different for different botanicals or chemical classes. This will need to be assessed on a case-by-case basis. Where the proposed specifications are identical to those of a substance already approved for another use in the EU, the corresponding recent European or other internationally accepted specifications [e.g., ISO/TC54 Essential oils, pharmacopoeia or the guidelines of the EMA Committee on Herbal Medicinal Products (HMPC)] may be used, but only in addition to the manufacturing process (see chapter Methods of manufacture).

103. The technical grade considered as the active substance can be described by its 'chemical fingerprint' ensuring a standardised measure of the quality (and variability) of the material is available. The use of the technical grade/chemical fingerprint should be fully justified and demonstrate that safety tests were conducted using suitable material.

Group 2

104. *Botanical active substances based on a material with an established specification and for which taxonomy and current knowledge indicates that the botanical active substance may contain components of possible concern for humans, animals and/or the environment.*

105. Then these components should be identified and quantified in the sample analysis using validated analytical methods, if appropriate. This is in addition to the requirements as indicated under Group 1.¹⁰

Group 3

106. *Botanical active substances that are not based on a material with an established specification.* In this case, complete identification and characterisation is in principle needed.

107. For identified components (e.g., sugars, chlorophyll) known to be of no concern, further validation of the analytical methods is not considered necessary.

108. For identified components of possible concern for humans, animals and/or the environment these components should be quantified in the sample analysis using validated analytical methods, if appropriate.

109. For other components in the technical grade, another threshold for 'significance' (according to data requirements ≥ 1 g/kg) could be taken if adequately justified. Any component $\geq 10\%$ of the peak area of the main component and/or any component with a threshold of 10 g/kg and all components in total account for at least 80% of the total mass, need to be identified and quantified, but not necessarily using formally validated analytical methods.

110. This pragmatic approach should be taken as no international agreed standards are currently available for these types of active substances.

Groups 1, 2 and 3

¹⁰ Often botanical active substances are not produced in batches as referred to in Regulation (EU) No 283/2013. In such cases the term 'batches' is not appropriate and should be replaced by samples.

111. Where necessary, and depending on the cultivation, storage and processing conditions (see source of botanical material in this chapter and the chapter on manufacturing process), information on maximum levels for possible components of concern (including e.g., heavy metals, mycotoxins, pesticide residues, solvents, enzymes and other substances introduced during the manufacturing process) should be provided.

112. If the technical grade is variable and beyond the ranges given by the specification, this constitutes a new source for the botanical active substance which must be assessed for technical equivalence (see chapter on technical equivalence).

Methods of manufacture

113. The detailed manufacturing process will form part of the botanical active substance specification so the following information is considered necessary for assessing the safety of botanicals, including detailing quality assurance principles that are followed such as Hazard and Critical Control Points (HACCP):

- Information on the method(s) of manufacture [e.g., the process by which the raw material is converted into a technical grade, such as physical processes, extraction or other procedure(s)].
- Information on substances entering the manufacturing process, (e.g., identity of any extraction solvent, enzymes, stabilisers such as antioxidants), and any special precautions such as control of light, humidity and temperature.
- Details of any purification processes.
- Standardization criteria [e.g., ISO/TC54 Essential oils, pharmacopoeia or the guidelines of the EMA Committee on Herbal Medicinal Products (HMPC)].

114. It is recognised that some of the information regarding manufacturing processes could be commercially sensitive, so such information should be provided in the confidential sections of the dossiers. The detailed information remains confidential. A summary is provided in the non-confidential part of the dossier.

115. For physical processes (e.g., cold pressing, crushing, milling), the nature (mechanical, thermal or both combined) and method can greatly influence the final composition of the botanical active substance. For example, increasing temperature may considerably increase the proportion of less volatile components or alter the original components. Therefore, details of temperatures used during manufacturing should be provided.

116. In the case of extraction, the ability of the solvent to extract substances (polarity and capacity of dissolving the different components) is relevant. It is considered good practice to select solvent(s) for extraction that maximise the botanical substances required and minimise harmful components.

117. The solvent (or mixture of solvents) used for the extraction, will affect the contents of components in the technical grade. Any change may lead to a different composition. Therefore, the method and solvents used should be clearly described.

118. Any repeated extraction of the natural source may lead to a significant increase in components which were not fully extracted in the previous extraction step. Therefore, the number of extractions, as well as the mass relation of natural source to extraction solvent in each step, has to be clearly described.

119. Further processing (e.g., concentrating or purifying) also influences the composition of the botanical active substance and must be clearly described.

Technical equivalence

120. This chapter covers the following cases:

- When technical material comes from a new/different manufacturer other than the applicant of the reference specification.
- When the production is switched from a pilot scale to an industrial scale commercial production, the latter is regarded as a different source.
- When there is a change of the manufacturing location, and/or the addition of one or more alternative manufacturing locations (production sites).

121. As the method of manufacture (e.g., process or quality of starting materials) is part of the technical grade specification (see chapter on Definitions) a change in the method of manufacturing is considered a new specification.

122. As a general principle for the same botanical active substance the level of hazard posed to health and the environment must be comparable for different sources of technical material.

123. For the new source, if the hazard is considered different from the reference source, then an appropriate risk assessment should be conducted for the new source to determine whether plant protection products containing the new technical material will fulfil the safety requirements laid down in the relevant legislation.

124. The purpose is to apply harmonised hazard assessment criteria to a certain technical material which was not completely tested for toxicological and/or ecotoxicological effects according to the relevant legislation. By comparing the specification(s) of the reference source(s), which have been agreed, with the corresponding specifications for new sources or changes to those already assessed, technical materials can be considered as equivalent or not equivalent regarding their hazard potential, or certain data gaps can be identified where further toxicological and ecotoxicological testing is needed.

Definitions

Equivalence

125. If the botanical active substance from the new source has the same or less harmful effects compared to the reference specification, and it is manufactured by essentially the same process, then the new source can be considered (eco)toxicologically equivalent to the reference specification.

Reference specification

126. This is the specification on which the risk assessment in the Draft Assessment Report was based and for which a regulatory decision has been taken.

Evaluation of equivalence of technical materials (Tier I)

Evaluation process

127. For the evaluation of equivalence of different sources against the reference specification, the following criteria should be considered in the Tier I approach.

128. The new source is deemed to be equivalent to the reference specification if:

- no new components are present, and
- the variability is within the reference specification.

Decision-making – Tier I

129. On the basis of the above criteria, possible conclusions include:

- The new source is equivalent to the reference specification, therefore no further consideration is needed.
- Equivalence of the new source to the reference specification cannot be established based on the Tier I criteria alone, and therefore a Tier II evaluation is required.
- The new source is not equivalent to the reference specification. In this case, an appropriate risk assessment must be conducted for the new specification to determine whether plant protection products containing the technical material will fulfil the safety requirements laid down in relevant legislation.

Evaluation of equivalence of technical materials (Tier II)

130. If some new components have been identified where further toxicological and ecotoxicological testing is needed, this can be fulfilled by submitting studies, a reasoned approach and/or literature. In the first instance this should be based on information that is already available, bridging information based on a similar botanical, expert judgement, or on a case-by-case basis. The strategies as described in the chapter on mammalian toxicology and on effects on non-target species should be followed.

Decision-making – Tier II

131. In taking a decision the options available are:

- The new source presents no greater hazard hence is equivalent to the reference source.
- The new source is not equivalent to the reference specification because it presents a greater hazard.

132. Although the "*Guidance Document on the assessment of the equivalence of technical materials of substances regulated under Regulation (EC) No 1107/2009 (SANCO/10597/2003 – rev. 10.1, 13 July 2012)*" currently excludes most botanical active substances, some of the principles laid out in this document still may be applicable.

Mammalian toxicology

133. The aim of the human health risk assessment is to ensure that botanical active substances for use in plant protection products do not have any harmful effects on the health of consumers (via residues),

operators, workers, bystanders or residents. Botanical active substances are not *per se* non-toxic and often risk mitigation measures may be necessary to avoid risk for human health.

134. The application of this guidance to specific cases will depend on the nature of the botanical active substance, its intended uses, exposure levels and whether there is information on the botanical active substance from documented use (e.g., as a plant protection product, biocide, in food or medicine), which may be relevant for the exposure and effect assessment. The aim is to identify areas of potential adverse effect on human health or whether the exposure levels do not result in harmful effects under the proposed conditions of use.

Hazard identification

Data Requirements and read-across

135. It may be possible to use data derived from biocidal use, medical use or epidemiological studies, or any other data on possible adverse health effects, either anecdotal or on the basis of case reports of poisoning e.g., data related to toxicity on livestock animals). Reference values and good quality assessments from other regulatory frameworks may be taken into account if the basis for the derivation of these thresholds can be assessed.

136. Limitations regarding the use of human data apply in most jurisdictions. In general, no tests and studies involving the deliberate administration of the active substance or the plant protection product to humans with the purpose of determining a human ‘no observed effect level’ of an active substance should be contained in the dossier. However, this should not prevent the use of available data from e.g., clinical studies if the botanical active substance is used in human medicine.

137. Extrapolating from one botanical active substance to another with respect to the same component(s) of toxicological concern (read-across) can only be considered when accompanied by evidence of their composition with respect to the particular components of concern. In this respect, application of non-testing methods [e.g., the use of reliable (Q)SAR models] could also be taken into account.

Hazard assessment based on documented uses and exposure

138. Depending on the botanical active substance and its uses, where there is sufficient documented knowledge this should be used to avoid unnecessary animal testing. This would be the case when available data show that similar exposures to known levels of the botanical active substance by the same routes have occurred in large population groups for many years without adverse effects being reported e.g., in epidemiological studies. However, it is advised to discuss this approach at an early stage with the regulatory authority.

139. When adverse effects are sufficiently characterised (e.g., if a substance is known to be skin sensitising in humans) no animal testing is required.

Components of concern

140. In cases where components or components of concern with known toxic properties are present in the technical grade under evaluation the significance of overall exposure should be assessed and compared with existing health-based guidance values such as the acceptable/tolerable daily intake (ADI/TDI).

141. Consideration of exposure to the component(s) of concern in relation to the Threshold of Toxicological Concern (TTC) values may also be helpful. Guidance on the applicability of the TTC

concept can be found in the EFSA Document "Scientific Opinion on Exploring options for providing advice about possible human health risks based on the concept of Threshold of Toxicological Concern (TTC)" EFSA Journal 2012, 10 (7):2750, as well as in EFSA updates on its work on the Threshold of Toxicological Concern (TTC).

142. If components of concern have been identified and toxicological data in addition to those for the technical grade are deemed necessary, hazard identification should focus on these specific components. This will be the case for group 2. If components of concern have not been identified (group 3) and toxicological data in addition to those for the technical grade are deemed necessary, complete identification and characterisation is in principle needed.

143. It is recognised that it may be difficult to identify the active component(s) responsible for an adverse effect. However, the information submitted is required to be sufficient to assess if the botanical active substance fulfils the approval criteria as set out in relevant legislation.

Exposure assessment

144. The exposure assessment for operators, workers, bystanders and residents is always necessary. An assessment of potential occupational and bystander exposure during and following application of a product will be based on the proposed use pattern. The information required includes: i) description of typical practices for individuals applying the product, such as the amount of active substance handled and the site, timing, and method of mixing/loading and application; ii) description of the type, frequency and duration of any activities where post-application exposure could occur; and iii) description of the potential for exposure to bystanders, particularly in nearby residential communities, schools or recreational areas.

145. In principle, the standard approaches outlined in the relevant regulations should be followed (see chapter on registration of botanical active substances and legal frameworks).

Residues

146. It is acknowledged that if the proposed botanical active substance is considered to be the same material that is reasonably expected to be a, or to become a component of, food, this provides considerable reassurance for consumer exposure. Food grade material is difficult to define however, and therefore the applicant is asked to provide a reasoned case/evidence to the way the material complies with relevant food legislation, confirming that technical material is the same as that which is supplied to the food industry, and explaining the extent to which the material is used in food. The same approach applies to 'feed'.

147. For many botanical active substances residue data may not be required if it has been determined that detectable residues on the consumable commodity are unlikely to occur, or that residue levels are unlikely to exceed natural exposure and that the residues are not of toxicological concern. This can be demonstrated by a scientific rationale.

a) Food or feed

148. In case of botanical active substances listed as food and feed in the relevant regulatory framework, information on the nature and magnitude of residues is usually not necessary. For those botanical active substances, normally no MRLs are set (see e.g., EU Guidance document on criteria for inclusion of active substances in Annex IV of regulation (EC) No 396/2005).

b) *Not food or feed*

149. Though occurring naturally, for botanical active substances at a minimum, information on the nature and magnitude of residues in plants and processed products is needed for the consumer risk assessment. Further information (e.g., concerning the nature and magnitude of residues in livestock or in succeeding crops) may often be addressed by a reasoned case.

150. If it is necessary and technically feasible with reasonable efforts to synthesize and radiolabel the active component(s) and/or known components of toxicological concern, then the standard data requirements on metabolism apply. If components of toxicological concern are present in the technical grade, information should be provided and if necessary field residue studies should be performed using formally validated analytical methods, as appropriate. If required, an applicant will need to provide reference samples and analytical standards used for the botanical active substance identification to a reference laboratory.

151. If high uncertainties remain on the nature and/or magnitude of the residues because of the lack of plant metabolism studies or processing studies, it might be necessary to account for these in the risk assessment (e.g., applying a higher safety factor, using available knowledge on metabolic pathways).

152. If MRLs are in place or needed, residue data will be needed to show compliance with these MRLs. It is advised to discuss this approach at an early stage with the regulatory authority.

Exposure assessment

153. When residues on food or feed cannot be excluded, an exposure assessment for consumers will be required.

154. Where natural or documented exposures are being considered to address consumer exposure, the registrant should present in detail a consumer risk assessment that compares anticipated exposures from the intended use to the 'background' exposures.

155. In principle the standard approaches outlined in relevant legislation should be followed.

Fate and behaviour

156. The aim of the environmental risk assessment is to ensure that botanical active substances for use in plant protection products do not have any unacceptable effects on the environment. Botanical active substances are not *per se* non-toxic and often risk mitigation measures may be necessary to avoid risk for the environment.

157. The application of this guidance to specific cases will depend on the nature of the botanical active substance, its intended uses, exposure levels and whether there is information on the botanical active substance from documented use (e.g., as a plant protection product, biocide, in food or medicine) which may be relevant for the exposure and effect assessment. The aim is to identify areas of potential unacceptable effect on the environment or whether the exposure levels do not result in unacceptable effects under the proposed conditions of use.

158. In principle the standard approaches outlined in the relevant regulations should be followed (see chapter on registration of botanical active substances and legal frameworks).

159. Where these approaches are not appropriate or technically feasible the following aspects could be considered.

160. "Natural" exposure refers to levels of substances present in the environment taking into account in what way exposure levels have been altered (e.g., agriculture), and in situations relevant for the respective environmental compartment.

161. Arguments relating to natural exposure should be used and considered carefully. For example, whilst the plant from which the botanical active substance is derived may occur in the terrestrial environment, it may not occur in the aquatic environment. However, due to the use of the plant protection products, other environmental compartments may be exposed and this is likely to result in further information being required.

162. Taking into account good agricultural practice, estimated exposures of the (components of the) botanical active substance should be compared to the natural exposure situations in different relevant environmental compartments (water, soil, air). The risk can be considered acceptable when estimated exposures are lower or similar to the natural exposure situations and no unacceptable effects occur on relevant non-target organisms. If any estimated exposure(s) is higher than natural exposure situations, more information should be submitted to assess the relevant exposure levels addressing the persistence, transformation and mobility in the environment. The information to be submitted must be sufficient to address the concern identified and might be reduced to the relevant environmental compartment. The nature of the compound and its behaviour can also be taken into account. For example, for highly volatile compounds such as essential oils, a calculation based on the substance's volatility may be used to replace the need for certain studies/requirements, e.g., by providing estimates of rapidity and likely extent of volatilisation losses and gains by re-deposition.

163. In general, botanical active substances are complex mixtures comprising a number of components and therefore the whole technical grade is regarded as the active substance. However, there might be components with different properties. Therefore, studies conducted with single active components may provide more reliable information on fate and behaviour properties, however, single active components may also behave differently than the botanical active substance and provide mainly supporting information. If it is necessary and technically feasible with reasonable efforts to synthesize and radiolabel the active component(s) and/or known components of ecotoxicological concern, then the standard data requirements apply.

164. Components from botanical active substances occur in plants and it is to be anticipated that there will be common pathways for their breakdown and decomposition in plants and the environment. Relevant literature should be submitted and taken into account.

Effects on non-target species

165. The aim of the ecotoxicological risk assessment is to ensure that botanical active substances for use in plant protection products do not have any acute or long-term unacceptable effects on the non-target species, including beneficial organisms and bees. Botanical active substances are not *per se* non-toxic to non-target organisms, therefore risk mitigation measures may be necessary.

166. The application of this guidance to specific cases will depend on the nature of the botanical active substance, its intended uses, exposure levels and whether there is information on the botanical active substance from documented use (e.g., as a plant protection product, biocide, in food or medicine) which may be relevant for ecotoxicological assessment. The aim is to identify areas of potential unacceptable effect on the non-target species or whether the exposure levels do not result in unacceptable effects under the proposed conditions of use.

167. In principle, the standard approaches outlined in the relevant regulations should be followed (see chapter on registration of botanical active substances and legal frameworks).

168. Where these approaches are not appropriate or technically feasible the following aspects could be considered.

169. The risk can be considered acceptable when estimated exposures are lower or similar to the natural exposure situations and no unacceptable effects occur in relevant non-target organisms. If any estimated exposure(s) is higher than natural exposure situations more information shall be submitted to assess the possible effect on exposed non-target organisms. The information to be submitted must be sufficient to address the relevant data requirement(s).

170. The activity, the mode of action and the exposure route of the botanical active substance should be taken into account in order to focus on non-target organisms expected to be the most at risk, and to avoid animal testing when unnecessary. Due to the diversity and complexity of botanical active substances the non-target organisms potentially affected vary substantially and therefore a general testing strategy cannot be provided in this guidance. The applicant should propose a relevant testing strategy in line with the proposed use(s) and the relevant exposure situations. Available ecotoxicological information, including studies and publications, should be analysed and considered. Good quality assessments from other regulatory frameworks may be taken into account.

171. If components of concern have been identified and ecotoxicological data in addition to those for the technical grade are deemed necessary the ecotoxicological assessment should focus on these specific components. This will be the case for substances falling in group 2. If components of concern have not been identified (group 3) and ecotoxicological data in addition to those for the technical grade are deemed necessary, identification and further testing (ecotoxicology and/or fate) is in principle needed.

172. It is recognised that it may be difficult to identify the active principle responsible for an unacceptable effect. However, the information submitted needs to be sufficient to assess if the botanical active substance fulfils the approval criteria as set out in relevant legislation.

Exposure assessment

173. When exposure of non-target organisms cannot be excluded, an exposure assessment will be required.

174. Where natural or documented exposures are being considered to address exposure of non-target organisms, the registrant should present detailed non-target organisms risk assessments that compare anticipated exposures from the intended use to the 'background' exposures.

175. In principle the standard approaches outlined in the relevant regulations should be followed (see chapter on registration of botanical active substances and legal frameworks).

Efficacy

176. Different jurisdictions have different approaches and requirements as regards efficacy. In general, it is required that a plant protection product shall be sufficiently effective and it shall not have any unacceptable effects on the plants or plant products. In general, these approaches or requirements also state that an active substance alone or associated with a safener or synergist shall only be approved where this has been established for one or more representative uses for the associated plant protection product(s). This should be evaluated in accordance with the relevant legislation.

177. The efficacy of a product determines the good agriculture practice (GAP).

178. For botanical products it is necessary to demonstrate that a botanical product is sufficiently effective to justify the corresponding claims. This should be based on addressing the data requirements as specified in relevant guidelines. It should be noted that although there are various areas to be addressed, for some areas such as non-target plant effects, in practice it may be possible to use information in lieu of actual data for some of these areas. In doing so reference may be made to any relevant information.

179. The principle of acceptable efficacy is that because of the 'risk' attached to the use of plant protection products it is thus necessary to decide if the benefits from the use of the plant protection product outweigh any disadvantages. The net result of the positive and negative effects should be a sufficient overall agricultural benefit in order to justify the use of the plant protection product.

180. Efficacy data should be obtained in good quality independent trials. This should be done according to the principles of good experimental practice (GEP) and performed by official or officially recognised organizations. In deciding on the usefulness of trials to support the registration of a botanical product the following efficacy issues should be considered:

- pest/weed/disease control to support the label claims (minimum effective dose, efficacy with label recommended dose),
- safety to the treated crops,
- safety to succeeding and adjacent crops,
- yield, yield quality and processing will not be adversely affected,
- consideration of the likelihood of resistance or cross-resistance to the active substance developing,
- biological compatibility (lack of antagonism) if tank mix is recommended,
- no unacceptable adverse effects on beneficial organisms usefulness as components of IPM.

181. It should be recognised that botanical plant protection products may provide full control, partial control or contribute to control. They may also have more variable performance than would be expected for a conventional chemical plant protection product. Reduced performance should not in itself be grounds for refusal of authorisation, if the applicant reasons why the demonstrated efficacy might be "sufficient". Such reasons might be offering an alternative mode of action (relevant to resistance management), valuable uses, resistance management, chemical residue management or specific compatibility in for example IPM systems. At a minimum there must always be a statistically significant improvement, at an acceptable level of probability, of an appropriate measure of either pest control or crop yield, of sufficient magnitude to be worthwhile from an agronomic perspective.

182. In such cases, applicants and evaluating officials should concentrate on ensuring that users can be provided with accurate information on the likely performance of the botanical product and advice on how best to use the product so that it will perform as effectively and consistently as possible.

183. Efficacy data should be generated in field/glasshouse trials on the target crops and pests, performed to appropriate (EPPO) standards by official or officially recognised organisations. It is recognised, however, that deviations from the guidance may be required in some cases to account for the

specific properties of botanical plant protection products. Where this is the case, detailed descriptions and explanations for the methodologies used should be provided. The explanation may require relating the methodology to the mode of action and potential factors affecting its effectiveness under field conditions.

184. All trials should include an untreated control. In most trials an appropriately justified reference product should also be included. Because of the variability of the conditions under which plant protection products are used, the inclusion of a reference treatment is necessary in order to allow a meaningful evaluation of efficacy under the conditions of the trial and to permit comparison between different trials in a series. However, it is not required that acceptable efficacy must be relative to the standard but compared to the untreated controls where available.

185. Experimental designs must take account of relevant guidelines (e.g., the guidance in EPPO standard PP1/152) on design and analysis of efficacy evaluation trials.

186. In general, data from good quality and representative field trials will be required. Data from carefully designed small scale laboratory and growth chamber studies may form a component of the overall data package provided to registration authorities and the number of field/glasshouse trials can therefore be reduced.

References

- Access to genetic resources and fair and equitable sharing of benefits, adopted by the Conference of the parties to the Convention on Biological Diversity (2010 in Nagoya)
- Biology-online: http://www.biology-online.org/dictionary/Main_Page
- Commission Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC (OJ L 70, 16.3.2005, p. 1)
- Commission Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC (OJ L 309, 24.11.2009, p. 1)
- Commission Regulation (EU) No 546/2011 of 10 June 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards uniform principles for evaluation and authorisation of plant protection products (OJ L 155, 11.6.2011, p. 127)
- Commission Regulation (EU) No 283/2013 of 1 March 2013 setting out the data requirements for active substances, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market (OJ L 93, 3.4.2013, p. 1)
- Commission Regulation (EU) No 284/2013 of 1 March 2013 setting out the data requirements for plant protection products, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market (OJ L 93, 3.4.2013, p. 85)
- Dayan, F.E., Cantrell C.L., Duke S.O. (2009) Natural product in crop protection. *Bioorganic and Medicinal Chemistry* 17, 4022-4034
- Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances (OJ L 50, 20.2.2004, p. 44)
- Directive 2009/128/EC of the European Parliament and of the Council of 21 October 2009 establishing a framework for Community action to achieve the sustainable use of pesticides (OJ L 309, 24.11.2009, p. 71)
- Draft guidance document on the Efficacy composition of Core Dossier and National Addenda submitted to support the authorization of plant protection products under Regulation (EC) No 1107/2009 of the EU Parliament and Council on placing of plant protection products on the market (SANCO/10055/2013)
- Draft working document Concerning the Data Requirements for Active Substances of Plant protection Products made from Plants or Plant Extracts (SANCO/10472/2003 – rev. 5; 6.7.2004)
- EFSA Scientific Committee; Guidance on safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements, on request of EFSA. *EFSA Journal* 2009;

7(9):1249. [19 pp.]. doi:10.2903/j.efsa.2009.1249.
<http://www.efsa.europa.eu/en/efsajournal/pub/1249.htm>

EFSA Scientific Committee; Scientific Opinion on Exploring options for providing advice about possible human health risks based on the concept of Threshold of Toxicological Concern (TTC). EFSA Journal 2012;10(7):2750 [103 pp.] doi:10.2903/j.efsa.2012.2750.
<http://www.efsa.europa.eu/en/press/news/120221.htm>

EFSA; Compendium of botanicals reported to contain naturally occurring substances of possible concern for human health when used in food and food supplements. EFSA Journal 2012;10(5):2663. [60 pp.] doi:10.2903/j.efsa.2012.2663. <http://www.efsa.europa.eu/en/efsajournal/pub/2663.htm>

EFSA. Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (OJ L 309, 24.11.2009, p. 1-50). EFSA Journal 2011;9(2):2092. [49 pp.]. doi:10.2903/j.efsa.2011.2092.
<http://www.efsa.europa.eu/en/efsajournal/doc/2092.pdf>

EPA rule on Data Requirements for Biochemical and Microbial Pesticides:
<http://www.gpo.gov/fdsys/pkg/FR-2007-10-26/pdf/E7-20828.pdf>

Guidance document on criteria for inclusion of active substances in Annex IV of Regulation (EC) No 396/2005 (SANCO/11188/2013)

Guidance document on Data requirements on efficacy for the dossier to be submitted for the approval of new active substances contained in plant protection products (SANCO/10054/2013)

Guidance document on botanical active substances used in plant protection products (SANCO/11470/2012– rev. 8, 20 March 2014)

Guidelines for the Registration of Non-Conventional Pest Control Products, Regulatory Directive DIR2012-01, Health Canada, 27 February 2012; http://www.hc-sc.gc.ca/cps-spc/alt_formats/pdf/pubs/pest/pol-guide/dir2012-01/dir2012-01-eng.pdf

How to deal with extracts and oils of plant or animal origin? Document regarding the implementation of Directive 98/8/EC concerning the placing of biocidal products on the market

OECD (2008) Working Document on the Evaluation of Microbials for Pest Control. *Series on Pesticides*, No. 43.

OECD (2012) Report of the Third OECD BioPesticides Steering Group Seminar on Characterisation and Analyses of Botanicals for the Use in Plant Protection Products. *Series on Pesticides* No. 72. ENV/JM/MONO(2012)36

REBECA Deliverable 16: Improved regulatory procedures for botanicals and semiochemicals and list of knowledge gaps <http://www.rebeca-net.de/downloads/report/deliverable%2016.pdf> (accessed 15 September 2016).

REBECA Deliverable 17: SWOT analysis on improved regulatory road map based on case studies for botanicals and semiochemicals <http://www.rebeca-net.de/downloads/report/deliverable%2017.pdf> (accessed 15 September 2016).

REBECA Deliverable 18: Positive list of "low risk" candidate botanicals and semiochemicals.

<http://www.rebeca-net.de/downloads/report/deliverable%2018.pdf> (accessed 15 September 2016).

Regulatory Proposal, Value Guidance – Benefit Information and Use History, Regulatory Proposal PRO2010-07, Health Canada, 17 November 2010; [http://www.hc-sc.gc.ca/contact/order-pub-commande-eng.php?title=PMRA\(PRO2010-07\)](http://www.hc-sc.gc.ca/contact/order-pub-commande-eng.php?title=PMRA(PRO2010-07))

Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under regulation (EC) No 1107/2009. EFSA journal 2011; 9(2):2092 .

<http://www.efsa.europa.eu/it/efsajournal/pub/2092.htm>

United States Environmental Protection Agency: Product Properties, Test Guidelines, OPPTS 830.1750, Certified Limits

Working Document on the procedure for application of basic substances to be approved in compliance with Article 23 of Regulation (EC) No 1107/2009 (SANCO/10363/2012 rev.8; 25 June 2013)

Working Document - Technical Material and Preparations: Guidance for generating and reporting methods of analysis in support of pre- and post-registration data requirements for Annex II (part A, Section 4) and Annex III (part A, Section 5) of Directive 91/414 (SANCO/3030/99-rev.4)

Appendix I

Summary of representative uses evaluated (*active substance*)

(a)	Member State or Country	Product name	F, G or I (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks: (m)
					Type (d-f)	Conc. of as (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	kg as/hL min max	water L/ha min max	kg as/ha min max		

- Remarks**
- (a) For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (*eg.* fumigation of a structure)
 - (b) Outdoor or field use (F), glasshouse application (G) or indoor application (I)
 - (c) *eg.* biting and sucking insects, soil born insects, foliar fungi, weeds
 - (d) *eg.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
 - (e) GCPF Codes - CropLife Technical Monograph n°2, 6th Edition, Revised May 2008, Catalogue of pesticide formulation types and international coding system
 - (f) All abbreviations used must be explained
 - (g) Method, *eg.* high volume spraying, low volume spraying, spreading, dusting, drench
 - (h) Kind, *eg.* overall, broadcast, aerial spraying, row, individual plant, between the plants - type of equipment used must be indicated
 - (i) g/kg or g/l
 - (j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
 - (k) The minimum and maximum number of application possible under practical conditions of use must be provided
 - (l) PHI - minimum pre-harvest interval
 - (m) Remarks may include: Extent of use/economic importance/restrictions