agriculture

Department:
Agriculture
REPUBLIC OF SOUTH AFRICA

GUIDELINES ON REQUIREMENTS FOR RESIDUES ARISING FROM THE USE OF BIOLOGICAL REMEDIES IN SOUTH AFRICA

Issued by the Registrar: Act No. 36 of 1947, Private Bag X343, Pretoria 0001

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DEFINITIONS

For the purposes of this document, the following terms are considered to mean:

Active ingredient(s)	The ingredients within a formulation which have general or specific action against harmful organisms or on plants, parts of plants or plant products.
ADI	Acceptable daily intake which refers to the amount of a substance that can be consumed without risk, on a daily basis for the average life expectancy of a consumer.
Allelochemicals	These are substances produced by individuals of one species that modify the behaviour of individuals of a different species (i.e. an interspecific effect). They include allomones (emitting species benefits), kairomones (receptor species benefits) and synomones (both species benefit).
Bacteria	Single-celled microorganisms that divide through binary fission and lack a nuclear membrane.
Biological Remedy	The active ingredient and/or associated metabolites, derived from natural materials such as animals, plants and microorganisms, together with its co-formulants, designed to render the remedy useful and effective for the purpose claimed and for the envisaged end use, in the form in which it is packaged and sold.
Dispenser	A device that is able to release semiochemicals at controlled release rates.
Fungi	Species of the Kingdom of Fungi which are spore-producing, eukaryotic organisms that are typically filamentous and lack chlorophyll. Fungi can be saprophytic, obtaining nutrients from dead organic matter, or parasitic, deriving nutrients from living hosts. Beneficial fungi contribute to nutrient cycling, soil health, and plant growth through symbiotic relationships.
Impurity	Any component other than the pure active substance and/or variant which is present in the technical material or formulated product (including components originating from the manufacturing process or from degradation during storage).
Inoculants	Agricultural amendments that use beneficial rhizospheric or endophytic bacteria or fungi to improve plant health by forming mutually beneficial symbiotic relationships with target crops such as legumes.
Maximum Residue Limit (MRL)	The maximum permitted concentration of an agricultural remedy, and it's metabolites, resulting from its use according to good agricultural practice directly or indirectly for the production and/or protection of the commodity for which the limit is recommended.
Micro-organism	Living or non-living structures which are made up of single or multiple cells that are smaller than 0.1mm in size e.g. virus, bacteria, protozoa, algae and fungi.
Macro-organism	Living, multi-celled structures which are larger than 0.1mm in size. In terms of biological control, these organisms typically belong to the classes of Insecta, Nematoda or Arachnida (e.g. mites).
Metabolite of concern	A breakdown/degradation product or substance produced by the organism/active ingredient under assessment, with known toxicity, which is present in the biological remedy at levels that may present a risk to human health, animal health or the environment, and/or for which it cannot be adequately justified that in-situ production of the metabolite is not relevant for the risk assessment.
Natural exposure level	The level of exposure that might occur in the environment by a high population of emitting organisms independently from the use of plant protection products, thus expected to be experienced by humans and other non-target organisms.

Other Arthropod Pheromones (OAPs)	A group of pheromones not directly, structurally related to SCLPs in definition, i.e. consisting of branched or unbranched aromatic or aliphatic (straight or cyclic) hydrocarbons and containing two to thirty carbons, zero to several unsaturated bonds and having zero to several functional alcohol, ester, aldehyde, ketone or epoxide groups. This structural definition encompasses the majority of known pheromones produced by and acting on a variety of organisms which encompasses different taxonomic orders assigned to Coleoptera, Diptera, Hymenoptera, Thysanoptera and Hemiptera.
Other Chained Arthropod Pheromones (OCAP)	A group of pheromones structurally similar to SCLPs in definition, i.e. consisting of acyclic, branched or unbranched aliphatics, containing five to thirty carbons, zero to three unsaturated bonds and having zero to several functional alcohol, ester, aldehyde, ketone or epoxide groups. This structural definition encompasses the majority of known pheromones produced by and acting on a variety of organisms which include also taxonomic orders beyond Lepidoptera (for instance Coleoptera, Diptera, Hemiptera, Acarida, Thysanoptera, Hymenoptera).
Pheromones	Substances produced by individuals of a species that modify the behaviour of other individuals of the same species (i.e. an intraspecific effect). Different types of pheromones include straight-chained lepidopteran pheromones, straight-chain arthropod pheromones, other chained arthropod pheromones and other arthropod pheromones.
Primary metabolites	Metabolites directly involved in general metabolism required for basic life processes, such as enzymes for example.
Secondary metabolites	Metabolites produced in response to specific survival functions of the microorganism, such as competition, parasitism or symbiosis and metal transport.
Semiochemicals	Substances or mixtures of substances emitted by plants, animals, and other organisms that evoke a behavioural or physiological response in individuals of the same or other species.
Straight Chain Arthropod Pheromones (SCAPs)	A group of pheromones structurally compliant with the SCLPs definition, except that triple bonds are possible i.e. consisting of unbranched aliphatics having a chain of nine to eighteen carbons, containing up to three unsaturated bonds, ending in an alcohol, acetate or aldehyde functional group. This structural definition encompasses the majority of known pheromones produced by and acting on a variety of organisms which also include taxonomic orders beyond Lepidoptera (for instance Coleoptera, Diptera, Hemiptera, Acarida, Hymenoptera, Thysanoptera).
Straight-Chained Lepidopteran Pheromones (SCLPs)	A group of pheromones consisting of unbranched, aliphatics having a chain of nine to eighteen carbons, containing up to three double bonds, ending in an alcohol, acetate or aldehyde functional group. This structural definition encompasses the majority of known pheromones produced by insects in the order Lepidoptera, which includes butterflies and moths.
Viruses	Infective agents only able to multiply within the living cells of a host and typically consist of a nucleic acid molecule covered in a protein coat. This includes baculoviruses and bacteriophages, which infect insects and bacteria, respectively.

INTRODUCTION

The purpose of this document is to outline the residue data and documentation required for the registration of biological remedies regulated under Act 36 of 1947. As part of risk/benefit assessment in the registration process of agricultural remedies, residue studies/data are required to ensure that food safety is not compromised. This is achieved mainly through quantifying the expected range of residues in crops after their treatment with registered agricultural remedies as well as through setting of Maximum Residue Limits (MRLs) on commodities. Furthermore, it is necessary to ensure compliance with international trade requirements regarding the acceptable levels of residues on food commodities. It is important that only data with a direct bearing on the registration application are presented. It should be noted that the Act makes provision for the Registrar to call for any further information in order to determine whether a remedy is acceptable in the context of public interest.

Biological remedies are typically regarded as being lower risk as they are derived from natural sources and not synthetically made. However, in some cases, these remedies may still be hazardous to consumption or may produce metabolites, or secondary components, that are toxic, hazardous or allergenic to humans, animals or the environment. **Refer to Figure 1** for guidance on the stages of evaluation required by the registrant to establish the risk metabolites of concern associated with the biological remedy. This figure is derived from the SANCO/2020/12258 European Commission Guidance document which should be referred to for more detailed guidance.

The requirement for residue data may differ within a category of biological remedies or with a specific biological remedy. In all cases, the registrant is recommended to consider available information, scientific literature or studies regarding the toxicity of the remedy. If the active ingredient is registered elsewhere, global MRLs should be referenced. As biological remedies are in principle, naturally derived, exposure to humans and the environment is typically frequent and quantification of this exposure may be complex. However, exposure assessments are well documented for certain substances.

For guidance on what levels of exposure are common for consumption, consider the following:

- The nature and level of ‘common background exposure’
- Is there documented evidence for the historical, safe use of the remedy
- Are there any incidences of adverse effects for the level of use proposed
- Is there a difference in processing between historically used substances and the proposed remedy

Refer to Annex 1 for guidance on the considerations for exemption of the requirement of residue data and guidance on the preparation of adequate rationale to support exemption.

Where residue data is required, this should be conducted in accordance with the latest version of the “Guidelines on Residue Study Requirements for Registration of Agricultural Remedies and Setting of Maximum Residue Limits (MRLs) in South Africa, as published on the NDA website https://www.nda.gov.za/index.php/publication/581-guidelines. Specific requirements, considerations and exemptions for the major types of biological remedies are summarised in sections 1 to 5 of this guideline.

For other data requirements pertaining to the registration of biological remedies, applicants are referred to the latest version of the Guideline on the Data required for Registration of Biological/Biopesticide remedies in South Africa. The current document should also be read in conjunction with other documents such as the residue and data requirements guidelines for agricultural remedies published by the office of the Registrar and are not intended to replace these. Consideration must be given to co-formulants/inert components and carriers for their toxicity profile and MRL requirement where relevant.

For toxicological data requirements, applicants are advised to read guidelines published by the National Department of Health - “Requirements: Toxicological Assessments of Agricultural and Stock Remedies. In accordance with these guidelines, as well as the guidelines referred to above, toxicological studies must be conducted following the relevant Organisation for Economic Cooperation and Development (OECD) guidelines.

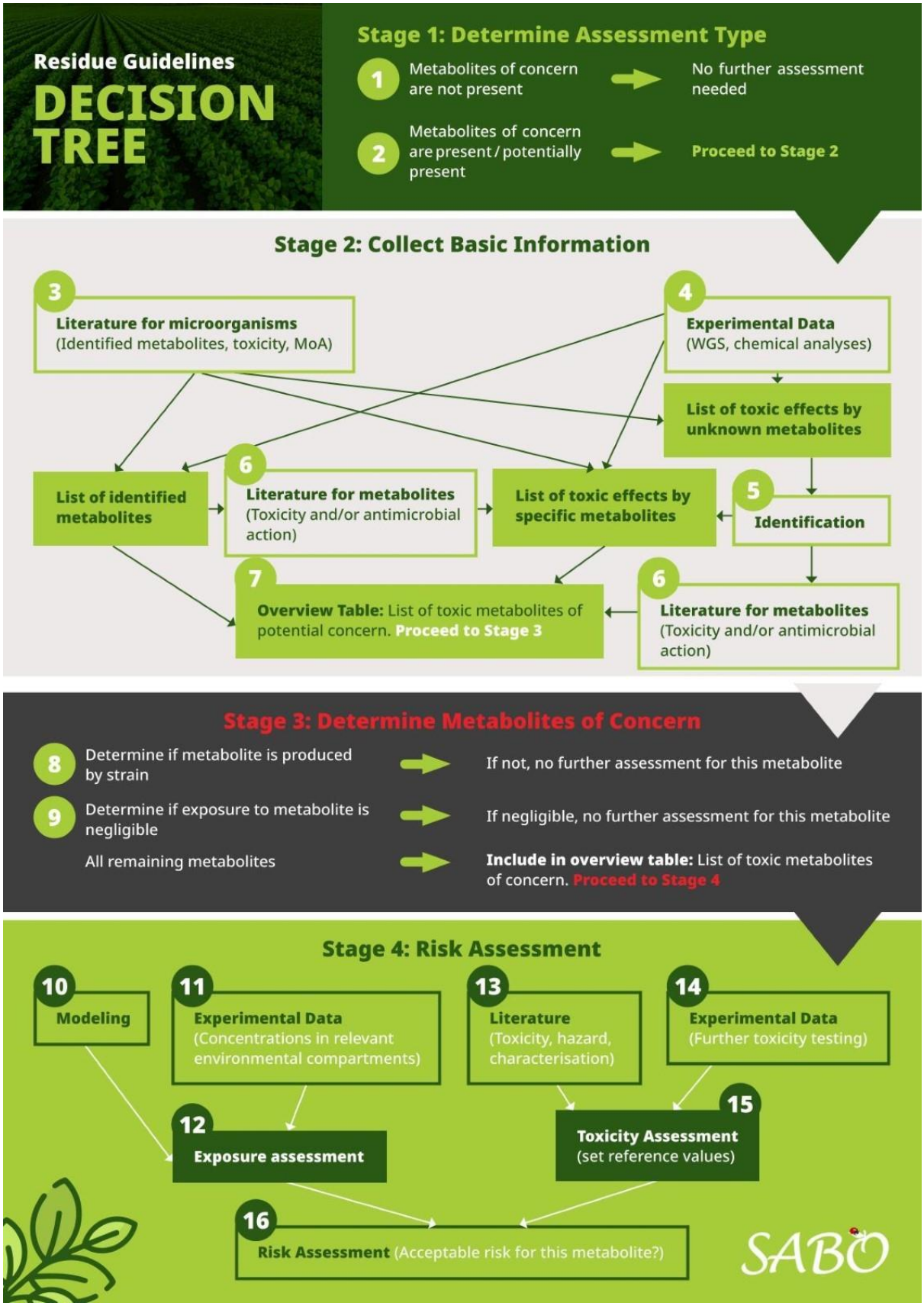

Figure 1 Decision tree for the risk assessment associated with residues and metabolites based on SANCO/2020/12258.

1. Micro-organisms

This section speaks to residue considerations for agricultural remedies that utilize viruses, bacteria, and fungi as active ingredients. These products require a different approach to that specified for breakdown products (metabolites) of chemical pesticides. Microorganisms have the potential to produce a range of primary and secondary metabolites, present or formed either in contact with target organisms, with non-target organisms or in the environment depending on biotic and/or abiotic factors (SANCO, 2020). Of these metabolites, only those of toxicological concern are of interest in a consideration of residues. Refer to **Figure 1** and **Annex 1** for guidance on the establishment of toxicity or preparation of a rationale to prove the absence of toxicity to humans and the environment.

The applicant can refer to the Microbial Pesticide Test Guidelines OPPTS 885.2000 and SANCO/2020/12258 for further information or guidance regarding the residue analysis of Microbial Pest control agents.

The residue considerations for each category of microorganism are detailed here:

1.1 Viruses

Viruses may only be used as the active ingredients of biological control products if they are highly specific to insects or plant disease causing agents and may not result in human disease.

Insect specific viruses (baculoviruses) have a long history of safe use and do not result in residues which may be harmful to human health. Thus, it will not be required to generate residue data on the condition that:

(i) The baculovirus is adequately identified (Guideline on the data required for registration of biological/biopesticides remedies in South Africa, June 2015, Point 3.4 or latest version);

(ii) The baculovirus mode of action is well demonstrated through supporting literature;

Viruses specific to plant disease-causing agents (bacteriophages) are a novel technology which generally do not result in residues by themselves which may be harmful to human health, and it will not be required to generate residue data on the condition that:

(i) The bacteriophage(s), and the bacteria in which it is produced are adequately identified (Guideline on the data required for registration of biological/biopesticides remedies in South Africa, June 2015, Point 3.4 or latest version);

(ii) The associated bacteria in which the bacteriophage is produced are not known to produce any metabolites of concern which could be of harm to human health (or animal health, were relevant) (Guideline on the data required for registration of biological/biopesticides remedies in South Africa, June 2015, Point 3.8 & 4.1.4 or latest version*);*

(iii) The bacteriophage mode of action is well demonstrated through supporting literature;

OR

If the associated bacteria in which the bacteriophage is produced are known to produce any metabolites of concern (Figure 1), the bacteria will be subjected to the residue data requirements for bacteria as described in section 1.2.

1.2 Bacteria and Fungi (including legume inoculants and other inoculants)

For microbial bioproducts utilizing bacteria and fungi as active ingredients, including legume inoculants and other inoculants, **no residue trial data is required** in the following cases:

(i) The active ingredient is not known to produce metabolites that are hazardous to human health (or animal health, where relevant) based on current scientific literature and taxonomy (Figure 1);
(ii) Genomic analysis of the active ingredient shows the absence of the gene(s) encoding the metabolite(s) of concern;
(iii) The metabolites of concern can be excluded or are not present in the product;
(iv) The estimation of consumer exposure to the metabolites of concern demonstrates the risk is low or acceptable for example through scientific literature or published ADI's (Acceptable Daily Intake levels);
(v) Based on a weight of evidence approach, it can be justified that possible metabolites of concern identified are not hazardous to humans as a result of the intended use;
(vi) The acute oral toxicity or pathogenicity data of the active ingredient indicates no risk to human health (or animal health, where relevant).
(vii) The active substance is listed in EFSA QPS list or FDA GRAS list or already registered as a low-risk active substance for PPPs at EU level.

However, **residue trial data is required** in the following cases and should be conducted in accordance with the latest Residue Guideline requirements in South Africa:

(i) Only conflicting or unreliable information is available on the active ingredient;
(ii) The current scientific literature and taxonomy of the active ingredient indicate that it does or may produce metabolites that are hazardous to human health (or animal health, where relevant);
(iii) Genomic analysis of the active ingredient shows the presence of the gene(s) encoding the metabolite(s) of concern;
(iv) The active ingredient is closely related to known mammalian pathogens;
(v) The estimation of consumer exposure to the metabolites of concern demonstrates the risk is high or unacceptable;
(vi) Data of the active ingredient indicates evidence of risk to human or animal consumption health (or animal health, where relevant);
(vii) The metabolites of concern are overexpressed or purposefully concentrated during production.

In all cases, a rationale should be submitted within the dossier to substantiate the need for, or exemption from, residue trial data. Refer to Annex 1 which provides guidance on the rationale to be drafted in support of exemption. This is derived from the guidance document "Guidance on the risk assessment of metabolites produced by microorganisms used as plant protection active substances" (SANCO/2020/12258) which can be utilized by both applicants and regulatory authorities as a practical stepwise approach to determining metabolites of concern and the risk assessment thereof.

2. Macro-organisms

It is generally accepted that macro-organisms used as biological control agents do not result in residues which may be harmful to human or environmental health, and it will not be required to generate residue data on the condition that:

(i) The mode of action (e.g. life cycle) is well demonstrated indicating NO substances which could result in residues, including primary/secondary metabolites (Annex 1).

OR

If there is any reason to suspect that residues may result from the intended use of the product for which the macro-organism is the active ingredient, then residue data will have to be generated and submitted (Figure 1 and Annex 1).

3. Biochemicals

3.1 Semio-chemicals

Semio-chemicals are biochemical substances or mixtures of substances that are derived from animals, plants or other organisms and function by altering the behaviour of a pest. This group is divided into allelochemicals (including allomones, kairomones and synomones) and pheromones (including SCLPs, SCAPs, OCAPs and OAPs).

3.1.1 Residue Data Requirements

Residue data are not required for semiochemical products or devices that do not come into direct contact with plant parts (e.g., leaves, stems, roots, flowers, fruits) and do not leave chemical residues on the plants. This includes products like pheromone traps or dispensers that work by attracting or repelling pests without depositing residues on plant material.

Furthermore, the Department of Health may grant an exemption from the residue data submission requirement for certain products, provided that the active ingredients used in the formulation do not pose a toxicological risk to human or environmental health. Refer to Annex 1 for guidance in the preparation of a rationale in support of exemption.

If the semiochemical product or device does come into direct contact with plant parts (e.g., leaves, stems, roots, flowers, fruit), **and** the active ingredients or any of their breakdown products or metabolites present a toxicological concern (Figure 1), residue data will be required in accordance with the latest Residue Guideline requirements in South Africa. If the semio-chemical only comes into contact with non-edible plant parts, and it can be demonstrated that the chemical is not systemic, no residue data will be required.

3.2 Hormones

Hormones are biochemical agents that are synthesised in one part of an organism and transported to another part of the same organism where they have controlling, behavioral or regulating effects. These hormones can be extracted, purified and applied to targets or to hosts to manipulate the natural hormonal balance and achieve a desired outcome. Biological hormones do not include synthetic hormones i.e. those that are manufactured outside of an organism. Biological hormones may be derived from a plant source, from an insect or from other organisms relevant to the final desired outcome. These have indirect toxicity and/or modifying behavior on the target.

3.2.1 Plant-derived hormones

Plant growth regulators or hormones intend to influence the life processes of plants, such as substances influencing their growth, other than as a nutrient fall under agricultural remedies regulations. Plant hormones include the natural plant regulators which are biochemicals produced by plants that have inhibitory, stimulatory or other modifying effects on the same or other species of plants.

Residue requirement

Residue studies are usually not required for plant-derived hormones. The applicant must request an exemption from the need for a maximum residue limit (MRL) and provide reasoned scientific argument for the exemption together with information on potential hazard and exposure where applicable. Refer to Annex 1 for guidance on preparation of a rationale for exemption. Scientific argument against the need for residue data and requests for exemption from the need for an MRL will be considered on a case-by-case basis. Situations where residues do not or should not occur in foods or animal feeds; or where the residues are identical to, or indistinguishable from, natural food components or are otherwise of no toxicological significance, are generally considered not to require MRLs. If the product is exempt overseas from the need for MRLs or tolerances, this information must be provided in the application. The information must include detail of the reasons for the exemption (Refer to Annex 1).

The requirement for Maximum Residue Limits (MRLs) for plant growth regulators (PGRs) can be influenced by whether the residues from naturally occurring and exogenously applied PGRs can be

differentiated. If a PGR is a naturally occurring substance in plants, such as certain hormones or compounds, and it is difficult to differentiate between residues from natural sources and those applied exogenously, MRLs may not be required. For substances that are inherently present in plants (like IAA, gibberellins, or ABA), the residues from these compounds are generally considered part of the plant's natural composition. Therefore, specific MRLs might not be necessary because the residues are part of the normal variation in plant biology. In all cases where exemption is required, scientific argument must be provided.

For guidance on the differentiation between synthetic and naturally occurring PGR's which fulfill the requirements of biological remedies, refer to Annex 2.

3.2.2 Non-plant derived hormones

These are hormones which are derived from sources other than botanical/plant sources. These exclude semio-chemicals, which are discussed further in section 3.1.

Insect growth regulators (IGRs) are substances derived from non-botanical organisms that have an impact on an insect's growth cycle e.g. inhibitory, stimulatory or other modifying effects (Masih *et al.* 2019). Exposure to the hormones leads to abnormalities which affect the insect's survival, typically through regulation of metamorphosis or interference with reproduction. Examples of IGRs include: precocenes, chitin synthesis inhibitors, juvenile hormones, juvenile hormone agonists, moulting hormones and moulting inhibitors.

It should be noted that these substances are different to synthetic insect growth regulators which have been synthesized outside of an organism. Synthetic IGR's must conform to the requirements listed for chemical agricultural remedies and are not covered by these guidelines.

Residue requirement

The requirement for studies to be conducted on remaining residues and metabolites after application of non-plant derived hormones is dependent on the toxicity profile of the biological remedy and the method of application (Refer to Figure 1 and Annex 1). Should the biological remedy come into contact with the plant and/or subsequent commodity, information on the potential hazard and exposure must be investigated and presented. The following conditions allow the absence of MRLs to be established for this group of remedies:

i) If residues of the parent compound and metabolites do not, or should not, occur in derived food or animal feed
ii) If residues are indistinguishable from natural levels of hormones;
iii) If the active does not have toxicological significance.

Residue analysis on treated commodities will therefore not be required if these conditions are met. However, proof of this should be included in the submitted dossier, in the form of scientific rationale, peer-reviewed scientific publications, proof of degradation pattern and/or is recognized as exemption by the following regulatory bodies OECD, EU, EPA, APVMA, Canada Japan or Brazil. Refer to Annex 1 for further guidance on preparation of rationale for exemption.

If any of the above conditions are not met, residue data should be generated in accordance with the guidelines for establishment of MRLs for agricultural remedies.

4. Enzymes

Enzymes are naturally occurring proteins (based on peptides and amino acids), which are produced by living cells to catalyze chemical reactions which are critical for physiological processes. Enzymes may also contain non-protein components such as carbohydrates, lipids, phosphate groups and metallic ions. All living organisms depend on enzymes to regulate energy releasing reactions, synthesize the building blocks of cells, gene expression and for regulation of virtually all other physiological processes. Enzymes, for the purposes of this document, do not include toxins (exo- or endo-toxins), which are also proteins that may be produced and used for pesticide control.

Residue Requirement

Because enzymes are readily biodegradable, and will breakdown into peptides which are naturally occurring, it is challenging to differentiate between natural levels of these peptides when enzyme-based products are applied as agricultural remedies. Their environmental release is thus, unlikely to cause a negative impact on the environment. To ensure human safety the microbial enzymes must be obtained from non-pathogenic and non-toxicogenic micro-organisms grown on raw materials that do not contain components that might be hazardous to human health. Residue analysis on treated commodities will therefore not be required if these conditions are met. However, proof of this should be included in the submitted dossier, in the form of scientific rationale, peer-reviewed scientific publications, proof of degradation pattern and/or the active or remedy is recognized as exempted by the following regulatory bodies OECD, EU, EPA, APVMA, Canada Japan or Brazil. Refer to Annex 1 for further guidance on preparation of rationale for exemption. If any of the above conditions are not met, e.g. if substrates for production have significant health hazards, residue data should be generated according to the guidelines for establishment of MRLs for agricultural remedies.

5. Extracts

Extracts are substances derived from naturally occurring plants, animals and other organisms that may be formulated and applied as an agricultural remedy for the purposes of pest control or host regulation. For semio-chemicals, hormones and enzymes that are extracted from organisms, refer to Sections 3 and 4 respectively.

5.1 Plant extracts

Remedies containing plant extracts consist of active substances with one or more components found in plants. They are a mixture of aromatic secondary metabolites such as phenols, phenolic acids, terpene, terpenoid, flavonoids, and sometimes fatty acids that are usually obtained by subjecting plants or parts of plants of the *same species* to a process such as pressing, milling, crushing, distillation and/or other methods of extraction. To be considered a biological remedy the chemical nature of the extract should not be altered by extraction processes. 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.

Plant extracts used as agricultural remedies differ from synthesised chemical active substances in the way they are derived or the origin. Synthesised chemicals are produced by chemical reactions, whereas plant extracts are obtained by processing material of biological origin. Therefore, substances referred to as analogues, mimics, natural-identical synthesised molecules and biosimilars are not covered by this Guidance Document. Furthermore, plant extracts derived from Genetically Modified Organisms (GMO's), safeners, synergists, adjuvants and co-formulants are also outside the scope of this Guidance Document.

5.1.1 Major groups of plant extracts:

5.1.1.1 Essential Oils

Essential oils are concentrated natural volatile compounds that are extracted from plants usually using hydro-distillation, steam distillation, and cold pressing. Essential oils are complex and contain several different components that vary in concentrations, some of these molecules will occur in large amounts while some in low amounts (Sharifi-Rad *et al.*, 2017). Furthermore, the essential oil of one plant species can vary due to chemotype, which means plants belonging to the same genus and species can differ in composition significantly (Maes et al., 2019). These include but are not limited to: Lavender oil, Tea tree Oil, Frankincense oil, peppermint oil, Eucalyptus oil, Lemon oil, Lemongrass oil, Orange oil, Rosemary oil Bergamot oil, Cedarwood oil.

5.1.1.2 Food or feed derived plant extract

For active ingredients or remedies that have documented use in human nutrition or animal feeding at similar concentrations as proposed for an agricultural remedy, residue study requirements are waived and no MRL's are typically set for these products. The applicant is required to provide evidence that the

active ingredient or remedy confirming that it is the same as that supplied to the food/feed industry, that it complies with any relevant food legislation and how it is used in feed/food products. If the biological remedy contains a known allergen, the significance of the overall exposure based on the proposed use pattern needs to be assessed with consideration of acceptable/tolerable daily intake (ADI/TDI) to determine whether warnings and residue decline studies are required.

Where concentrations are in excess of documented use (e.g. concentrated garlic or chilli extract), scientific rationale or bridging principles should be used to indicate the expected impact on risk for consumption.

5.2 Other Extracts

Other extracts, for example extracts from animals or organisms that are not used in food or feed that are applied as an agricultural remedy.

5.3 Residue requirements for Extracts

The data requirements for registration of extracts are similar to those required for chemical pesticides, with the adaptations recommended below. For Plant Extracts that lack a comprehensively reported history of use and those whose intended use levels will significantly exceed historical use or background exposure levels, the conventional chemical pesticide data requirements will apply, with options for scientifically justified deviations from certain data requirements (Annex 1). Based on the taxonomy and/or current knowledge of the botanical source, plant extracts can be classified/distinguished into different groups which have specific residue requirements:

For extracts that are used as active ingredients, **no residue trial data** is required in the following cases:

- MRLs are considered exempt for the extract locally and/or internationally
- Extracts are already known to have no unacceptable effects on humans, animals and the environment (including allergenic responses) and are based on materials with known specifications e.g. food grade (FAO/WHO, 2017; FFC, 2017). Refer to section 5.1.1.2 above for food derived active ingredients.
- The active ingredient is not known to produce secondary metabolites that are hazardous to human, animal, and environment based on current scientific literature and taxonomy;
- Metabolites of concern can be excluded or are not present in the product;
- The estimation of consumer exposure to the metabolites of concern demonstrates the risk is low or acceptable in relation to the established ADI;
- Based on a weight of evidence approach, it can be justified that possible metabolites of concern identified are not hazardous to humans as a result of the intended use
- The acute oral toxicity or pathogenicity data of the active ingredient indicates no risk to human or animal health and environment

Refer to Annex 1 for guidance on the preparation of rationale to support exemption of residue data.

However, **residue trial data is required** in the following cases and should be conducted in accordance with the latest Residue Guideline requirements in South Africa:

Scenario 1: extracts with an established specification and for which scientific literature and taxonomy of the active ingredient indicate that it does or may produce metabolites hazardous to humans, animals and/or the environment (EFSA, 2012a). Residue data for the components of concern will be required for registration and components of possible concern should be identified and quantified. This also includes extracts for which:

- The host organism from which the active was extracted shows the presence of the gene(s) encoding the metabolite(s) of concern;
- The estimation of consumer exposure to the metabolites of concern demonstrates the risk is high or unacceptable;
- The acute oral toxicity or pathogenicity data of the active ingredient indicates a risk to human, animal and/or the environment.
- The metabolites of concern are overexpressed or purposefully concentrated during production.

Scenario 2: extracts that do not have an established specification. In this case, complete identification and characterization of the technical grade is needed in principle with an exception for components such as sugars and chlorophyll for which residue analysis is not necessary. Unless scientific rationale can be provided that proves that these components will not persist on treated commodities, residue data for these components will be required for registration. This includes extracts for which:

- Only conflicting or unreliable information is available on the active ingredient;
- The risk of impact on the environment or consumption is unknown or cannot be extrapolated from current data

For identified components of possible toxic concern for humans, animals and/or the environment, these should be quantified, as no international agreed standards are currently available for these types of active substances.

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Annex 1

Guidance for creating rationale to support exemption from residue data for a biological remedy registration due to absence of risk to human or environmental health

The rationale should be based on details of the proposed use pattern and label claims, and as much scientific evidence as possible on the characterization of the components, mode of action, toxicity (including metabolites of concern where relevant), exposure and environmental fate (or cross references to other sections of the dossier). Where they exist, provide regulatory reviews from other countries. Summarise and present all the rationale support under the residue section following the guidance below:

For all biological products utilise the suggested rationale route (**Figure 1**) and provide explanations and relevant data.

For microbial actives where a risk assessment of exposure from the intended use to potentially hazardous secondary metabolites is required according to the decision tree in **Figure 1**, the following applies:

a) Determine whether there are secondary metabolites of concern based on information and toxicity studies on the microorganism at strain level. Consider the mode of action; the analysis of the fermentation culture medium after harvesting the microorganism and analysis of the active ingredient as manufactured and/or microbial remedy. Identify and quantify these substances and determine whether they are a hazard in terms of toxicity and/or antimicrobial action.

   NOTE: Metabolites are normally produced by the microorganism when specific physical and biological conditions are jointly in place. The capacity of an individual strain of microorganism to produce metabolites of concern depends on many environmental and genetic parameters relevant for the specific strain. The absence of production of undesirable compounds for one or more strains does not necessarily lead to hypothesize that the same occurs for all strains within the same species (or vice versa). If there is evidence that supports similarity/equivalence between the genetic capacity of strains for the absence metabolites of concern, this should also be presented.

b) Utilise the decision tree provided in **Figure 1** and use the results in your rationale.

Criteria for proving the absence of risk to human or environmental health

The absence of risk to human or environmental health must be proven through allocation of the remedy into one of the categories listed for (i) toxicology **AND** (ii) environmental toxicology below. In the case of all categories listed below, rationales should be supported by references. Cite references by number in brackets in order of mention in the text as if it were in a published technical journal article. Provide full references at the end.

(i) <u>Toxicology</u>

Category 1: Increased environmental exposure to the active ingredient, due to use of the end-use product, will be minimal:

Describe levels of naturally occurring substance in environment/use site. Address whether it is ubiquitous in nature and provide information on its geographical distribution and sources; from where it has been isolated (for example, soil, plants/crops/vegetables/fruits, insects, streams, ponds, lakes, etc.). Describe its environmental fate and/or degradation rate and/or formation of metabolites and metabolite fate/degradation. Discuss the extent to which the proposed use pattern will increase the active ingredient above background levels and estimate the time it will take to return to background levels.

Note: Consideration may need to be given to properties of the formulated product such as solubility, movement in water, persistence in the absence of host; persistence in water, effect on wastewater systems of greenhouse, movement in soil, entry to ground water.

Category 2: No evidence of toxicity and/or no adverse effects:

Conduct an extensive literature search of key databases (for example, TOXLINE7, Biological Abstracts, CHEMTOX7 [Hazardous and Regulated Chemicals Database]) on the active ingredient and its metabolites to ascertain whether there are any acute, short-term and chronic toxicity data available on humans and/or other mammals (for example, rodents). If little or no public data/information is available on the toxicity of the active ingredient to be registered, then data may be submitted on equivalent (chemically or genetically) or similar substances with an accompanying explanation why the surrogate data should be considered supportive of the toxicological effects expected of the active ingredient. Products with low inherent toxicity to humans would be expected to have minimal health risks even if exposure is extensive.

Note: Emphasise if the active is already widely available to the public for other uses, with a history of safe use under conditions posing equivalent potential for exposure to humans. For example, substances already approved in health industry or food industry, as colourants, flavourings etc.

Category 3: Proposed label uses mitigate/eliminate human exposure:

Discuss proposed label use sites (for example, outdoor food/non-food, greenhouses, etc.) and rate/timing of application, application methods (for example, spray, dip, soil incorporation, ground boom, aerial, foliar etc.) and their effects on limiting human exposure, if applicable. Address measures to minimize/eliminate direct exposure to humans (workers and bystanders), as well as whether timing of application precludes direct/indirect exposure to humans. When exposure is negligible, risks may be minimal even if the product has some inherent toxicity.

Category 4: Mode of action of pesticide/active mitigates/eliminates human exposure

Include for example specificity to host, not a human pathogen, growth temp range excludes human body temperature, role of metabolites, 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.

(ii) <u>Environmental Exposure/Environmental Toxicology</u>

Category 1: Toxicity to the non-target organism or environmental fate can be described by own and/or surrogate data

Surrogate data (for example, bridging information based on a similar active ingredient) or product-specific data that describes potential environmental toxicity or fate of the proposed pesticide, and a rationale supporting the validity of extrapolating from the surrogate data to the proposed pesticide. Products with low inherent toxicity to non-target organisms to non-target organisms would be expected to have minimal environmental risks even if exposure is extensive. Own data for example effect on non-target organisms, including those used for biocontrol (refer to US EPA guidance on Microbial Pesticide Test OPPTS 885.4340 Nontarget Insect Testing for list of suitable species to include), and pollinators.

Category 2: Increase in non-target organism exposure to the active will be negligible

Describe levels of the naturally occurring substance in environment/use site and relate to exposure by product application. Give geographical distribution and sources. Has it been isolated from soil, plants, crops, vegetables, fruits, insects, streams, ponds or lakes? Describe environmental fate/degradation rate including formation of metabolites and their fate/degradation, if applicable.

Category 3: There is no evidence of toxicity or adverse effects to the non-target organism at relevant exposure levels demonstrating a long history of safe exposure

For natural or existing substances that have a history of environmental exposure, a literature search demonstrating that there is no information indicating toxicity or adverse effects on the non-target organism can be submitted (Annex II for guidance on how to conduct a literature search). Indicate which databases were searched and the search terms (year range, active name, synonyms, metabolites, etc.)

The results or a summary of the results of the literature search should be submitted. Non-target organism exposure of natural/existing substance must also be estimated and compared to the proposed use. Note: Emphasise if already widely in use with a history of safe use under conditions posing equivalent potential for exposure to the environment.

Category 4: Proposed label uses mitigate or eliminate exposure

Describe how method of application minimizes direct exposure to the non-target organism. Describe how timing of application precludes direct or indirect exposure to the non-target organism. Discuss proposed label use sites and rate/timing of application, application methods and their effects on limiting drift/runoff, if applicable. Give degradation rates of active ingredient in days/weeks/months, if available. Would runoff or overspray result in effects not seen from natural exposure? Emphasise low potential for use to result in significant human or environmental exposure. If relevant include evidence that selection for pest resistance is unlikely.

Annex 2

Differentiating between synthetic and naturally occurring PGR's

When comparing synthetic and naturally occurring substances as plant growth regulators (PGRs), it's helpful to understand how their origins influence their properties and uses.

1. Origin

Synthetic Substances: Created through chemical synthesis in laboratories. These are often designed to mimic or modify natural growth processes but are not derived directly from living organisms. Examples include growth regulators like 2,4-D and paclobutrazol.

Naturally Occurring Substances: Derived from natural sources such as plants, fungi, or bacteria. They are either extracted in their natural form or slightly modified. Examples include auxins like indole-3-acetic acid (IAA) and gibberellins from plant tissues.

2. Development and Production

Synthetic Substances: Developed to have specific effects on plant growth. Their production involves chemical reactions and can be optimized for various attributes like stability, persistence, and efficacy.

Naturally Occurring Substances: Typically extracted from natural sources (e.g. *in vivo* or *in vitro)* or produced by organisms. Their development focuses on harvesting and purifying these substances. In some cases, they may be modified to enhance their effectiveness or stability but still remain of natural origin.

3. **Mode of Action**

Synthetic Substances: Designed to target specific growth processes or pathways. They can be highly selective and potent. For instance, synthetic auxins like 2,4-D can promote or inhibit plant growth depending on concentration and application.

Naturally Occurring Substances: Act through natural pathways. They often mimic or enhance the plant's own growth regulators. For example, gibberellins, which are naturally occurring, influence stem elongation, seed germination, and flowering.

4. Environmental Impact

Synthetic Substances: Can have varying environmental impacts, including potential residues in soil and water. They might also influence non-target plants and organisms. Concerns about persistence and resistance are common.

Naturally Occurring Substances: Generally considered to have a lower environmental impact due to their natural origin and tendency to break down more easily. They often pose less risk to non-target organisms, though this can vary.

5. Regulation and Approval

Synthetic Substances: Subject to stringent regulation and testing to ensure they are safe for use and effective. This includes evaluating potential risks to human health, animals, and the environment. Regulatory requirements are detailed in the "Guidelines on the Data and Documents Required for Registration of Agricultural Remdies in South Africa" of 2015.

Naturally Occurring Substances: are regulated as biological remedies. They are often seen as safer due to their natural origin, but they still must be tested for efficacy and potential risks.

6. Examples (not limited to)

Synthetic Substances:
2,4-D: A synthetic auxin used as a herbicide and for promoting cell elongation.
Paclobutrazol: A synthetic growth regulator that inhibits gibberellin biosynthesis, affecting plant height and development.
6-benzyladenine: A synthetic cytokinin used in horticulture to manipulate plant or fruit development

Naturally Occurring Substances:
Indole-3-Acetic Acid (IAA): A natural auxin that regulates various aspects of plant growth and development.
Gibberellins: Natural hormones that promote stem elongation, seed germination, and flowering.
Abscisic acid(ABA): Naturally occurring hormone involved in stress regulation, seed dormancy and other physiological processes.