Data Decision Trees For BioControl:

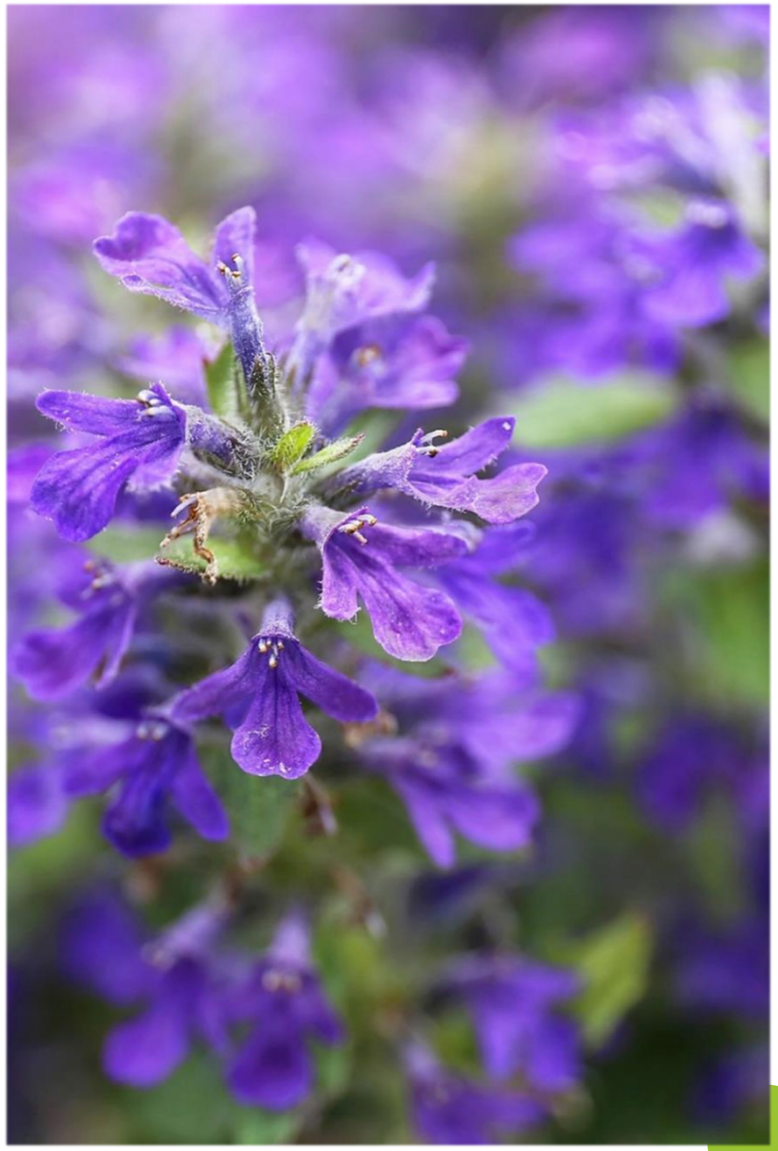
An Easy-to-Use Tool

Nov 7, 2023

IBMA
INTERNATIONAL BIOCONTROL MANUFACTURERS ASSOCIATION

Presentation Objective & Overview

- Presenting the Data DT
- Natural Substances Definition
- The Format of the Data DT
- Key Principles of the Data DT
- Details
- Case-Studies
- Wrap-Up: General Advantages of the Data DT



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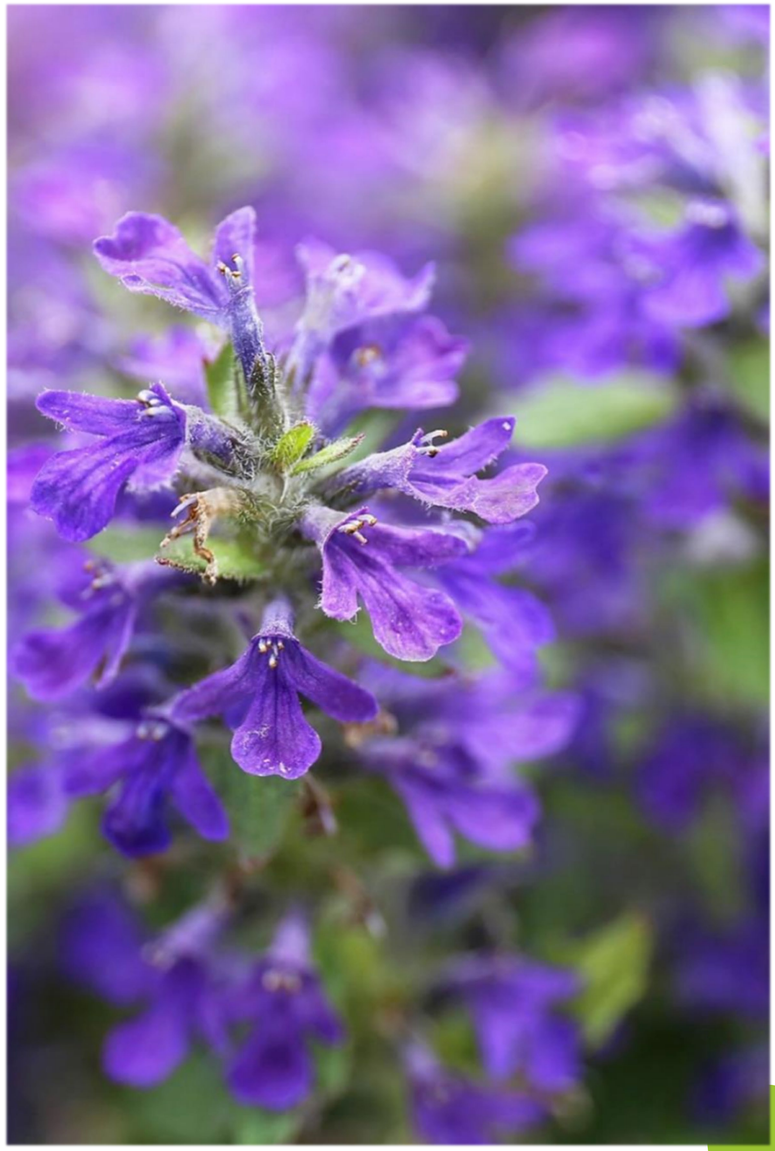
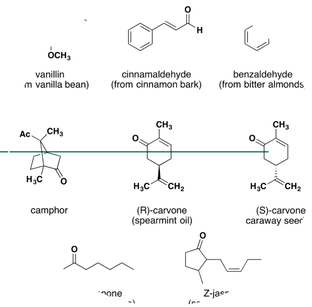


IBMA has developed Three Data Decision Trees

IBMA data decision trees



Natural substances – This presentation

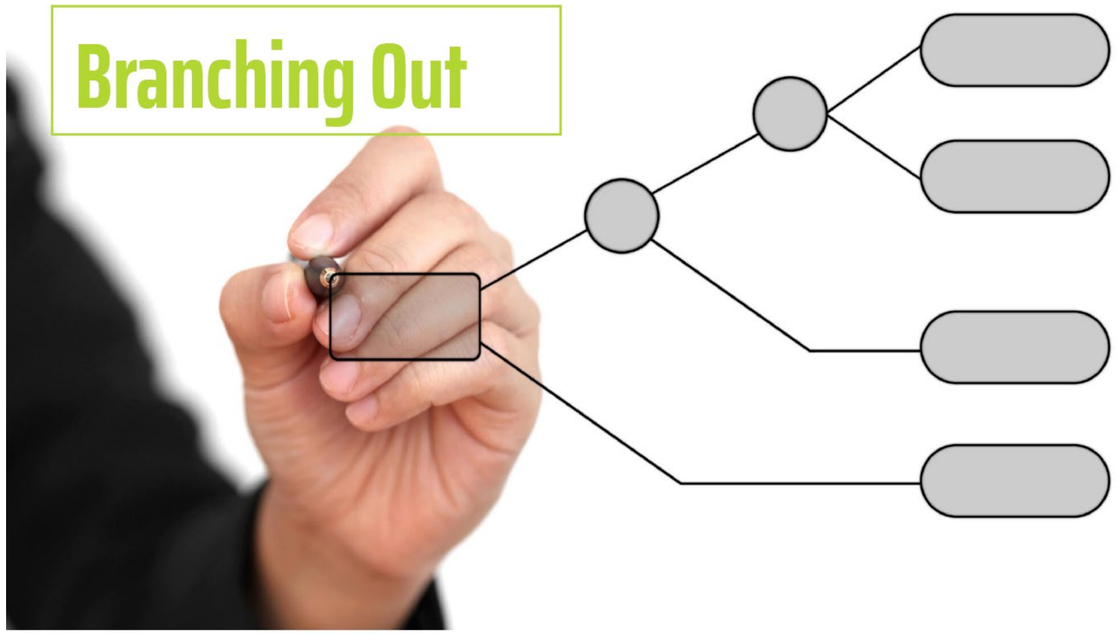
Micro-Organisms – submitted

Semiochemicals – To be submitted

What is the Data DT about?

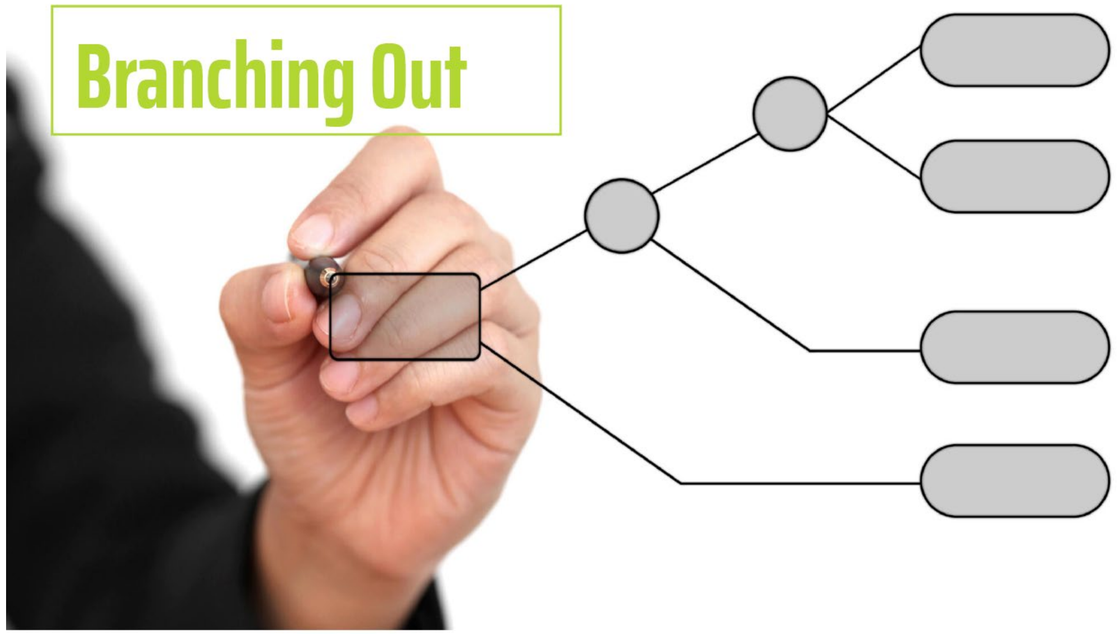
- It is all about making regulatory easier interpretable
- It contains a tiered approach used to indicate potential risk areas
- Branched Data Decision Tree that addresses:

	Identification, characterisation and analyses
	Effects on human health
	Residues
	Environmental fate and behaviour
	Effects on non-target organisms



What is the Data DT NOT about?

- New data requirements
- Detailed risk assessments
- New technologies?
- Exact studies and Guidelines to use
- Low Risk criteria
- Efficacy



Reference for Natural Substances: Citation

- **Title:** Data Decision tree for identifying potential risks for natural substances when used in plant protection
- **Authors:** Marloes Busschers, Roma Gwynn, Lara Ramaekers, Jennifer Lewis & Francesco Greco
- **Journal:** Biocontrol Science and Technology, 33:7, 597-629, 2023
- **Where to find?** DOI:10.1080/09583157.2023.2210268

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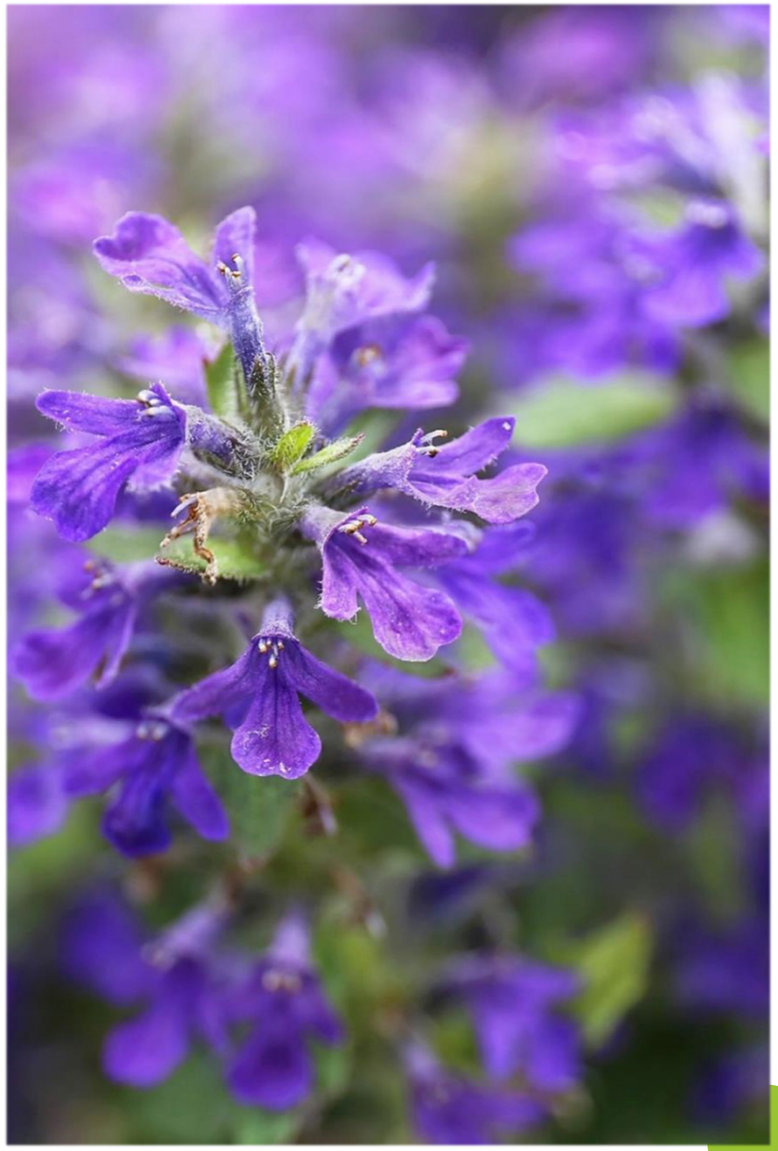

Natural Substances: Definition

IBMA Natural Substances Definition:

Natural substances consist of one or more components that originate from nature, including but not limited to: plants, algae/microalgae, animals, minerals, bacteria, fungi, protozoans, viruses, viroids and mycoplasmas. They can either be sourced from nature or are nature identical if synthetized. This definition excludes semiochemicals and microbials.

NATURAL SUBSTANCES CATEGORIES:

1. Organic or inorganic/mineral ORIGIN?

- INORGANIC/MINERAL ORIGIN
  - 3. Naturally occurring mixture OR single entities?
    - MIXTURE → Inorganic/Mineral Mixtures
    - SINGLE ENTITIES → Inorganic/Mineral Single Entities
- ORGANIC ORIGIN
  - 2. Which SOURCE?
    - PLANT SOURCE
      - 3. Naturally occurring mixture OR single entities?
        - MIXTURE → Plant Mixtures
        - SINGLE ENTITIES → Plant Single Entities
    - ANIMAL SOURCE
      - 3. Naturally occurring mixture OR single entities?
        - MIXTURE → Animal Mixtures
        - SINGLE ENTITIES → Animal Single Entities
    - MICRO-ORGANISM SOURCE**
      - 3. Naturally occurring mixture OR single entities?
        - MIXTURE → Micro-organism Mixtures
        - SINGLE ENTITIES → Micro-organism Single Entities
    - FERMENTATION*** or SYNTHETIC SOURCE
      - 3. Mixtures OR single entities?
        - MIXTURE → Nature-Identical Mixtures
        - SINGLE ENTITIES → Nature-Identical Single Entities

- **Origin**: where is the AI originally discovered/where is the AI originally present?
- **Source**: Production method.

*__Logic for question 1 and 2__: Risks are different depending on origin and source, so need to separate the origin/source. Composition needs to be addressed, does natural inventory contain any critical substance. The process drives whether critical components might appear.

*__Question 3__: The single entities need to be identifiable using analytical methods, to distinguish them from other components that have no impact on the mode of action.

**__Micro-organism source__: one or several metabolites produced by specific micro-organism(s) where in the final AI/product does not contain this viable micro-organism anymore - some overlap with microbial data decision tree

***__Fermentation source__: the micro-organism is reduced to merely a production tool (bio-factory). It is discarded from or made non-viable in the final AI/product. The micro-organism is of no importance in the final AI/product.

Comments/Examples per Category

Inorganic/Mineral Mixtures	Milled mineral mixtures obtained from mining or other inorganic source eg paraffinic oil
Inorganic/Mineral Single entities	'Pure' minerals obtained from mining/refineries/other inorganic source eg copper, sulphur, kaoline, ferric phosphate, bicarbonate
Plant Mixtures	Including natural oils from plant origin eg cinnamon oil - use botanical guideline eg garlic extract, pyrethrins
Plant Single Entities	Purified plant extracts Eg cinnamaldehyde, citric acid, abamectin, Dodecan-1-ol
Animal Mixtures	Including natural oils from animal origin - less likely to produce toxic component and less persistence eg Blood meal
Animal Single Entities	Purified Animal extracts Eg Pelargonic acid
Micro-organism Mixtures	Extracts of, and metabolites from, micro-organisms - can be covered partly by micro-organism decision tree (dead microbes)? Eg yeast cell walls, ABE-IT 56
Micro-organism Single Entities	Purified extracts of, and metabolites from, micro-organisms eg gibberellins
Nature-Identical Mixtures	Including Fermentation based extracts
Nature-Identical Single Entities	Purified fermentation based extracts/synthetic chemistry/synthetic biology Examples: – purified (poly)peptide/protein, nucleic acids (non-transformation DNA/RNA technologies including additional molecules linked to it, other single entities - Microbial sourced Sulphur - 6-benzyladenine

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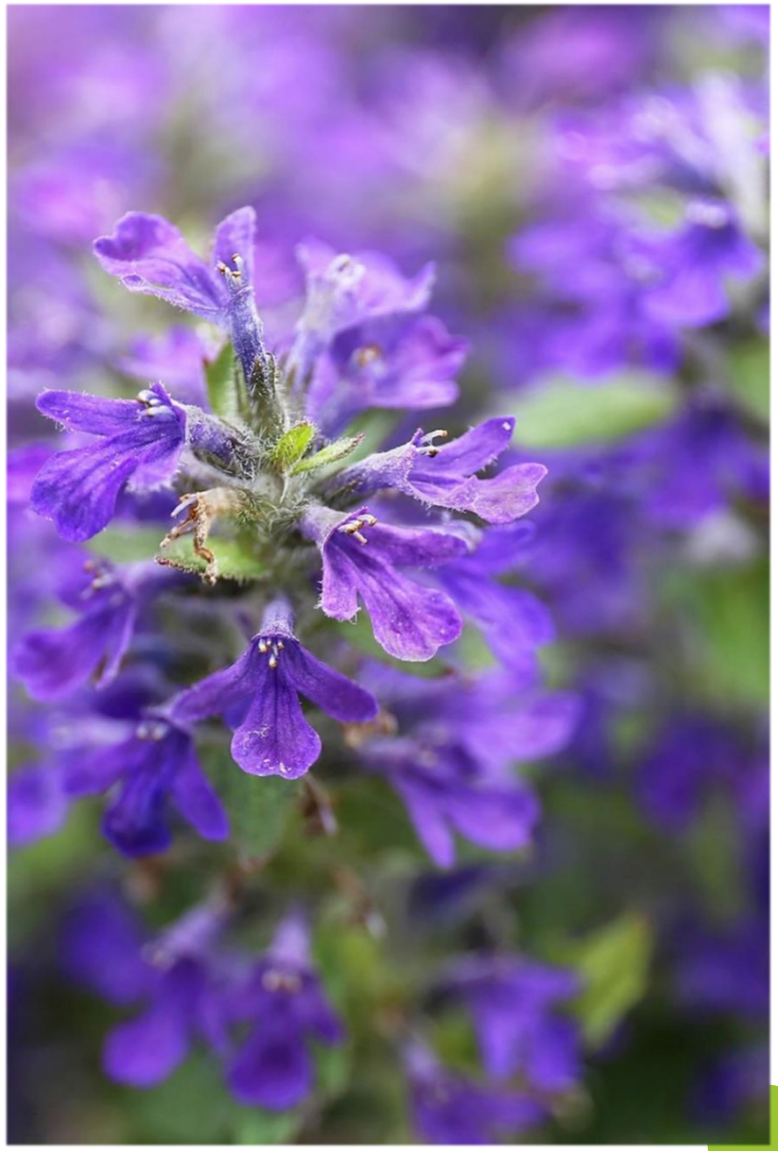


Natural Substances Data Decision Tree

THE FORMAT

- **Presentation:** Peer-reviewed Publication
- **Introduction**
- **General definitions and recommendations**
- **Section 1 to 5**: Specific data decision tree:
  - Section 1 data decision tree addresses the requirements needed for Section 1 and also determines the classification of the NS in group 1, 2 or 3 (adapted from botanical Manual).
  - This group classification needs to be used in Section 2 and 3. The groupings are not used in Section 4 and 5.
  - **Section 6 (Efficacy):** No specific data decision tree. Refer to EPPO Manual for efficacy testing of low-risk substances (PP 1/296 (1)).
- An applicant is required to go through each section data decision tree starting by the Section 1 data decision tree.

Natural Substances Data Decision Tree

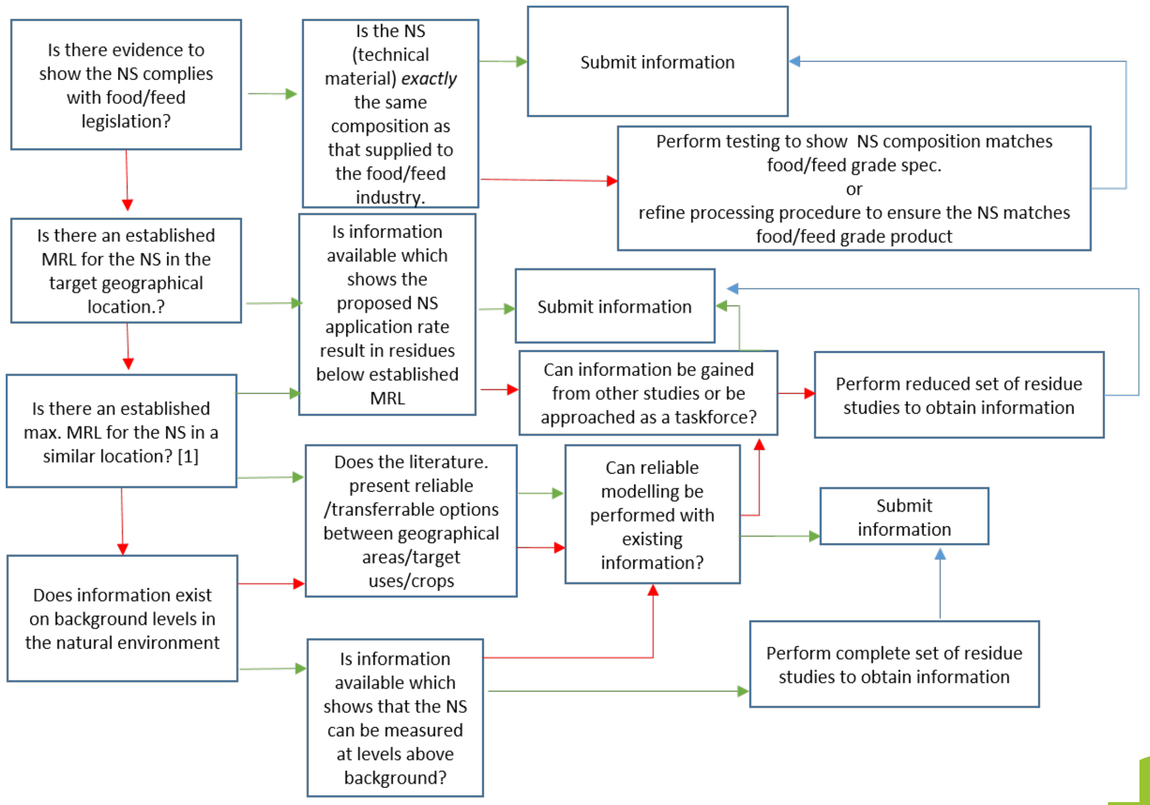
THE FORMAT

- **Presentation:**
  - Decision trees in table format and summarized in flow charts (flow charts to be done by Nov 15)

EXAMPLE

1.1 Recognized Specification			
1.1	Does the NS comply with a recognized specification?	No Define a specification (see general guidelines above). Proceed to 1.2	Yes Classification in Group 1. Proceed to Section 2 Decision Tree.

1.2 Max concentration for suspected critical components			
1.2	Has a max concentration been established for the suspected critical components ?	No Proceed to 1.3	Yes Classification in Group 2. Proceed to Section 2 Decision Tree.



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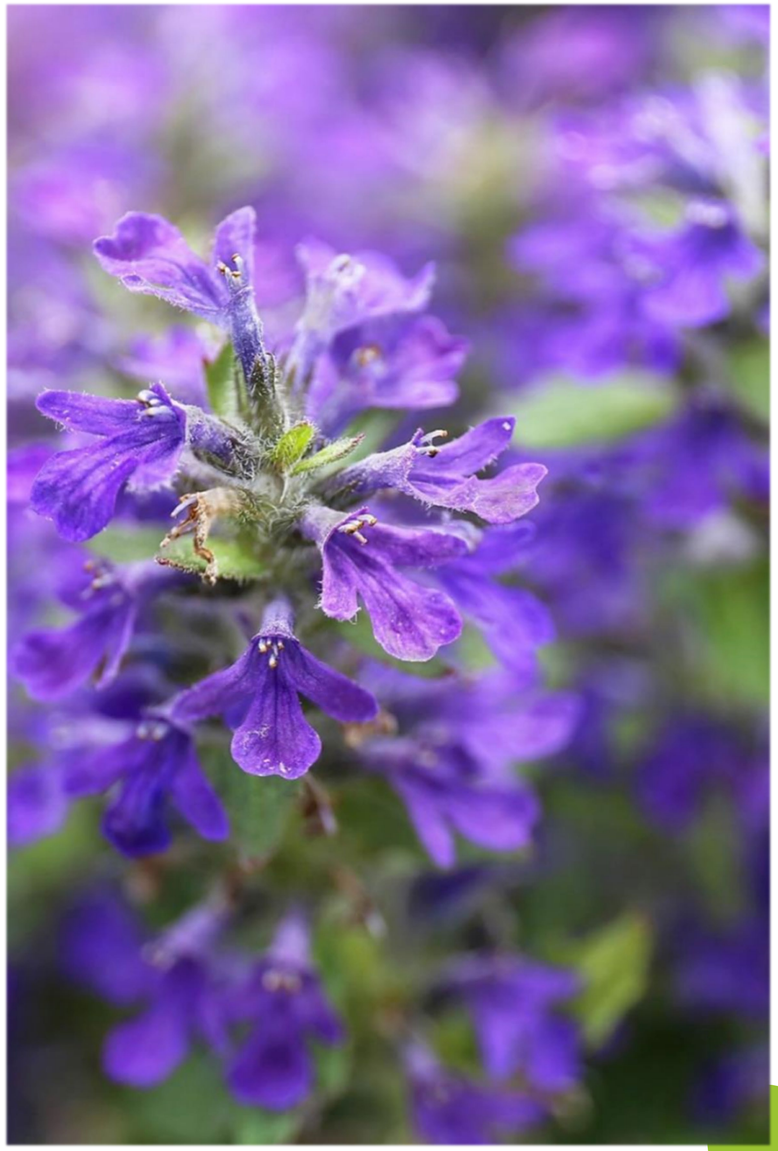

Key Principles of the Data DT: Keep it simple and pragmatic

- If the whole NS (technical grade) shows no unacceptable effects on human health/environment/NTOs, then:
  - No additional value to test its components separately.
  - Acceptable that a significant portion of components in the NS may remain unknown

- Integrate and re-use botanical guidance where relevant

- If allowed for food and feed and the natural substance is equivalent, no more action needed
- Is exposure below/similar to background level?
- Readily biodegradability of the natural substance

- Before recommending to perform higher tier studies, assess the potential use of:
  - Existing literature
  - Bridging arguments
  - Risk assessment waivers

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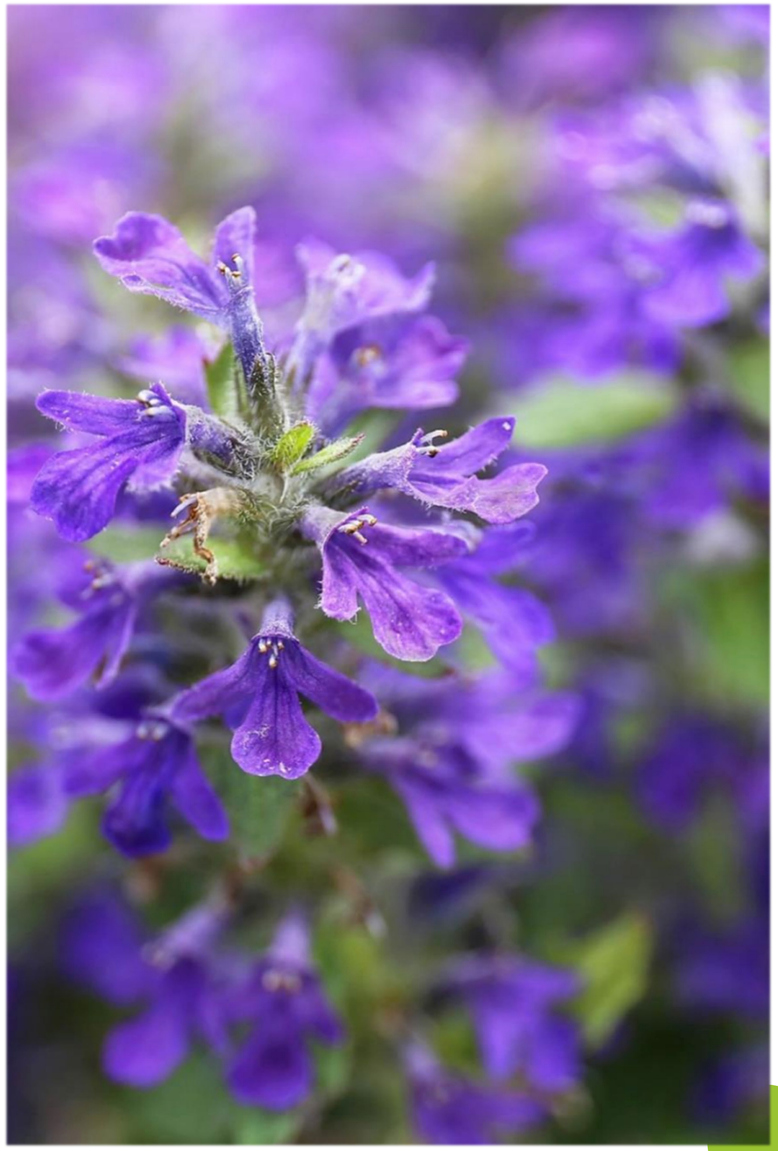


The key parameter and starting point: Identity

1

Group 1:

Natural Substances that are, with current knowledge, known to have no established effects on humans, animals and the environment with recognized specifications e.g., food/feed use

2

Group 2

Natural Substances with an established specification and for which the current knowledge indicates that the Natural Substance may contain known or suspected critical components for humans, animals and/or the environment

3

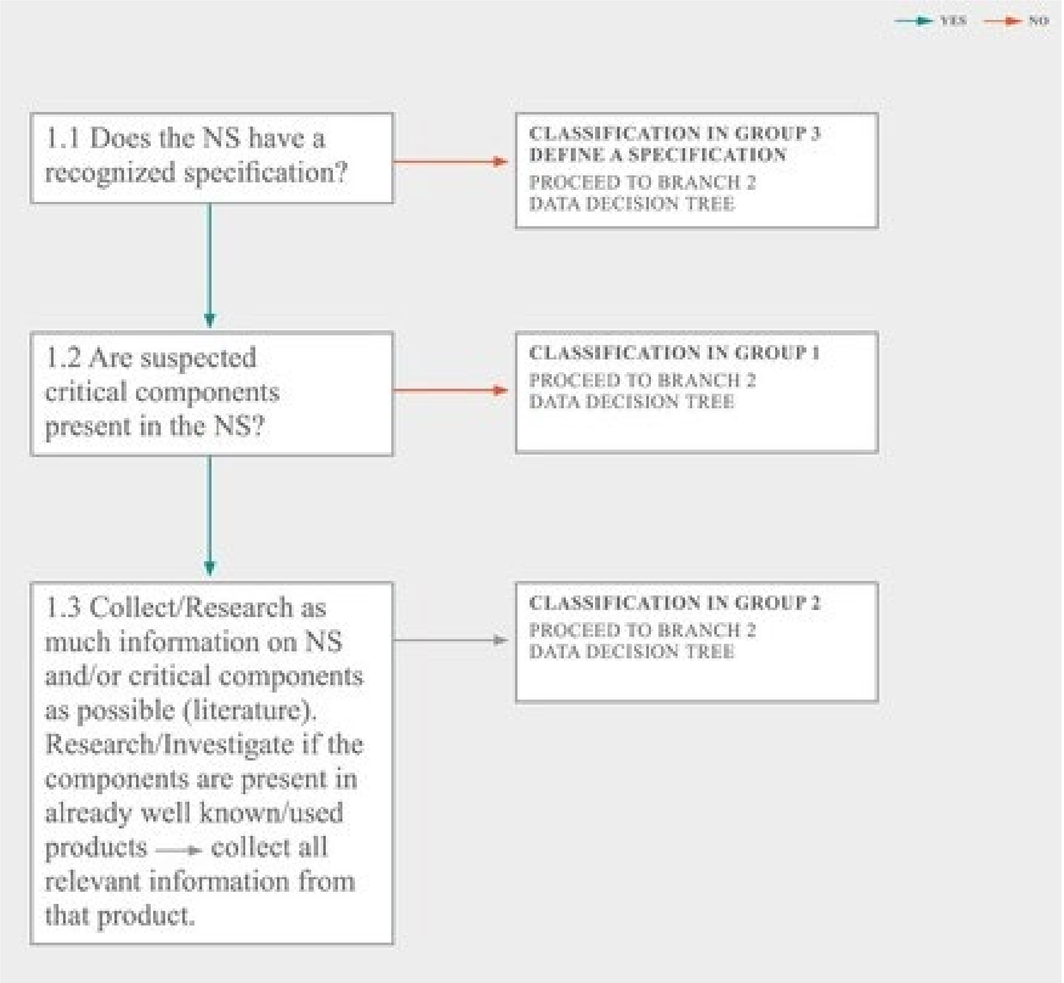
Group 3

Natural Substances that are not based on an established specification.

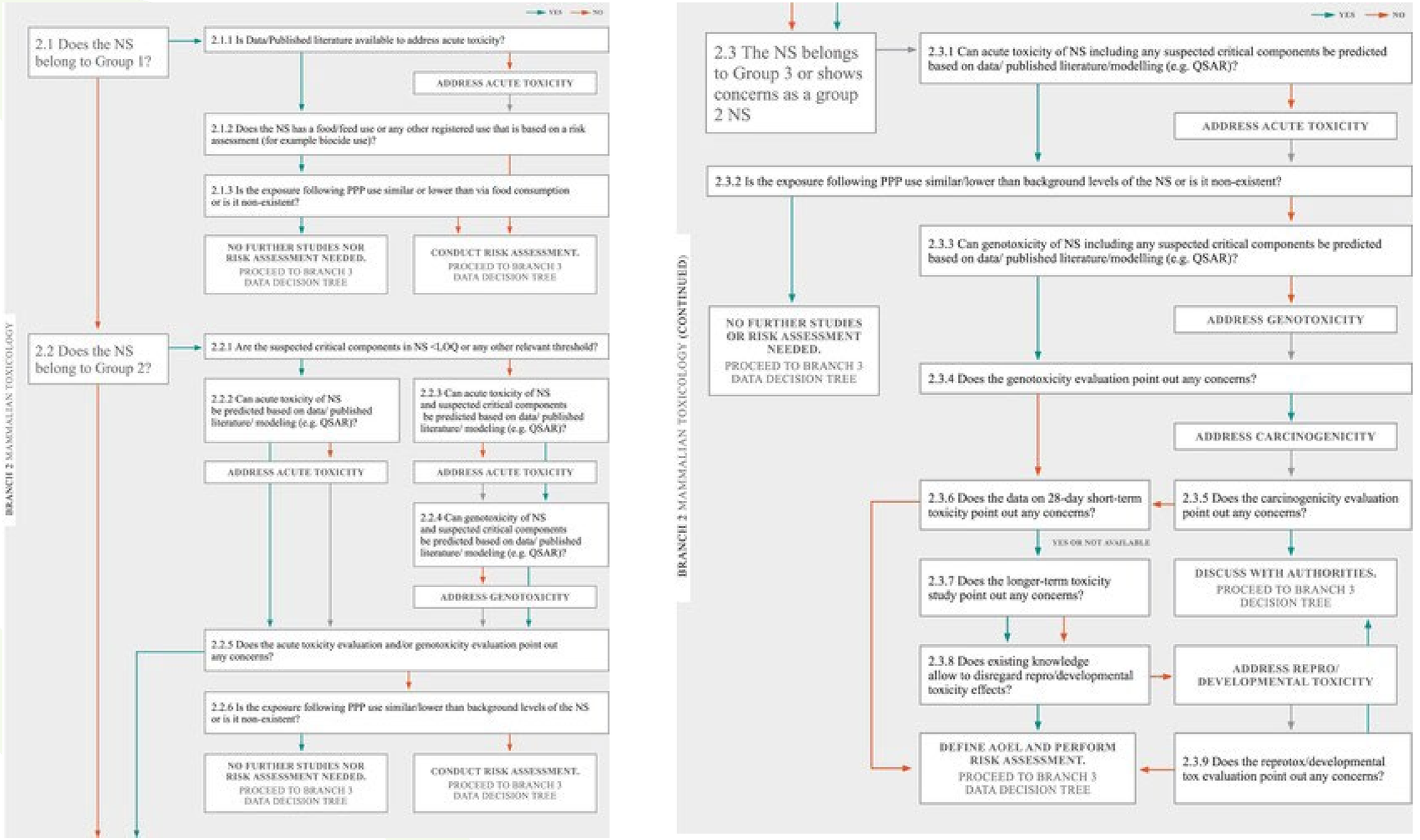
Determining the group is the starting point

The key parameter and starting point: Identity

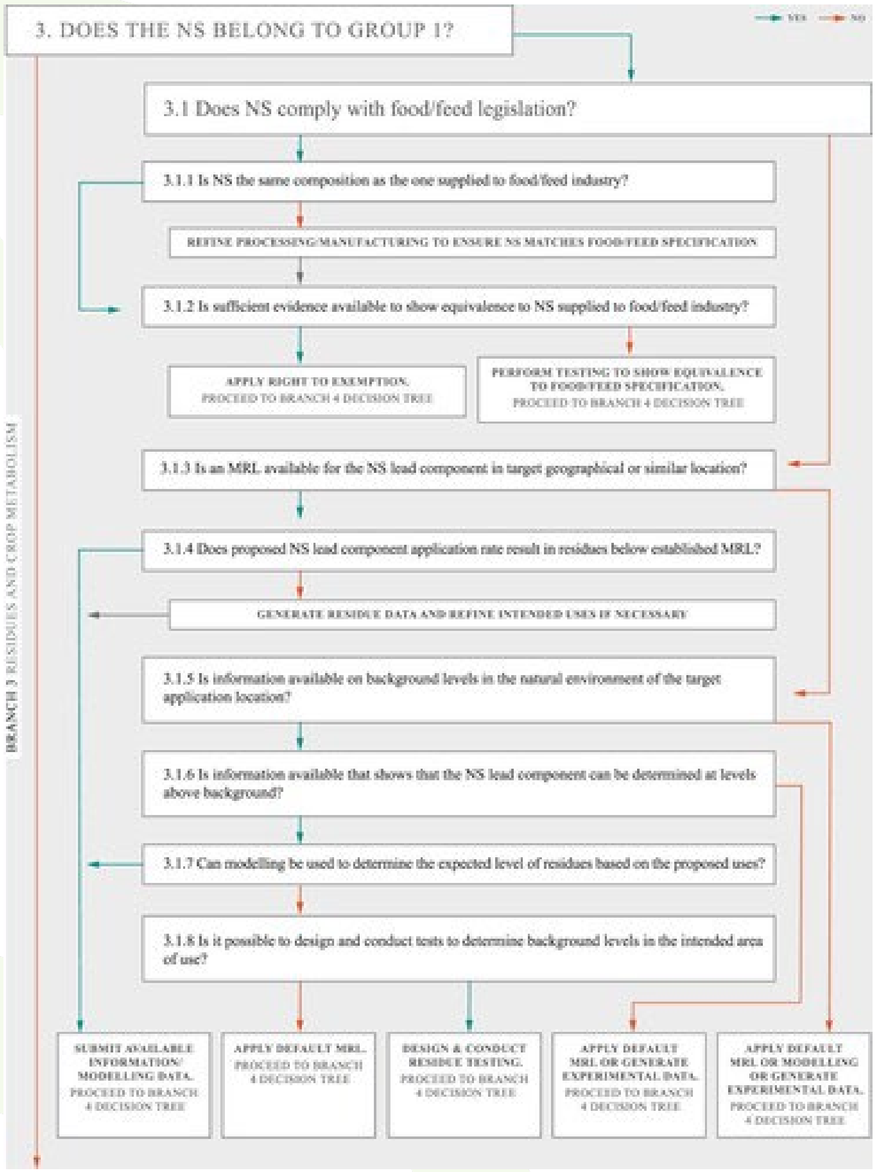
1.1 Recognised Specification			
1.1	Does the NS already have a recognised specification (e.g food/feed use)?	No Classification in Group 3. Define a specification* *Proceed to Branch 2 Data Decision Tree*	Yes *Proceed to step 1.2*
1.2 Suspected critical components			
1.2	Are suspected critical components present in the NS? **	No Classification in Group 1. *Proceed to Branch 2 Data Decision Tree*	Yes *Proceed to step 1.3*
1.3 Information about critical components and Natural Substance			
1.3	Collect/research as much information on the NS and/or the critical components as possible (literature). Research/investigate if the components are present in already well known/used products → collect all relevant information from that product.	Classification in Group 2. *Proceed to Branch 2 Data Decision Tree*	

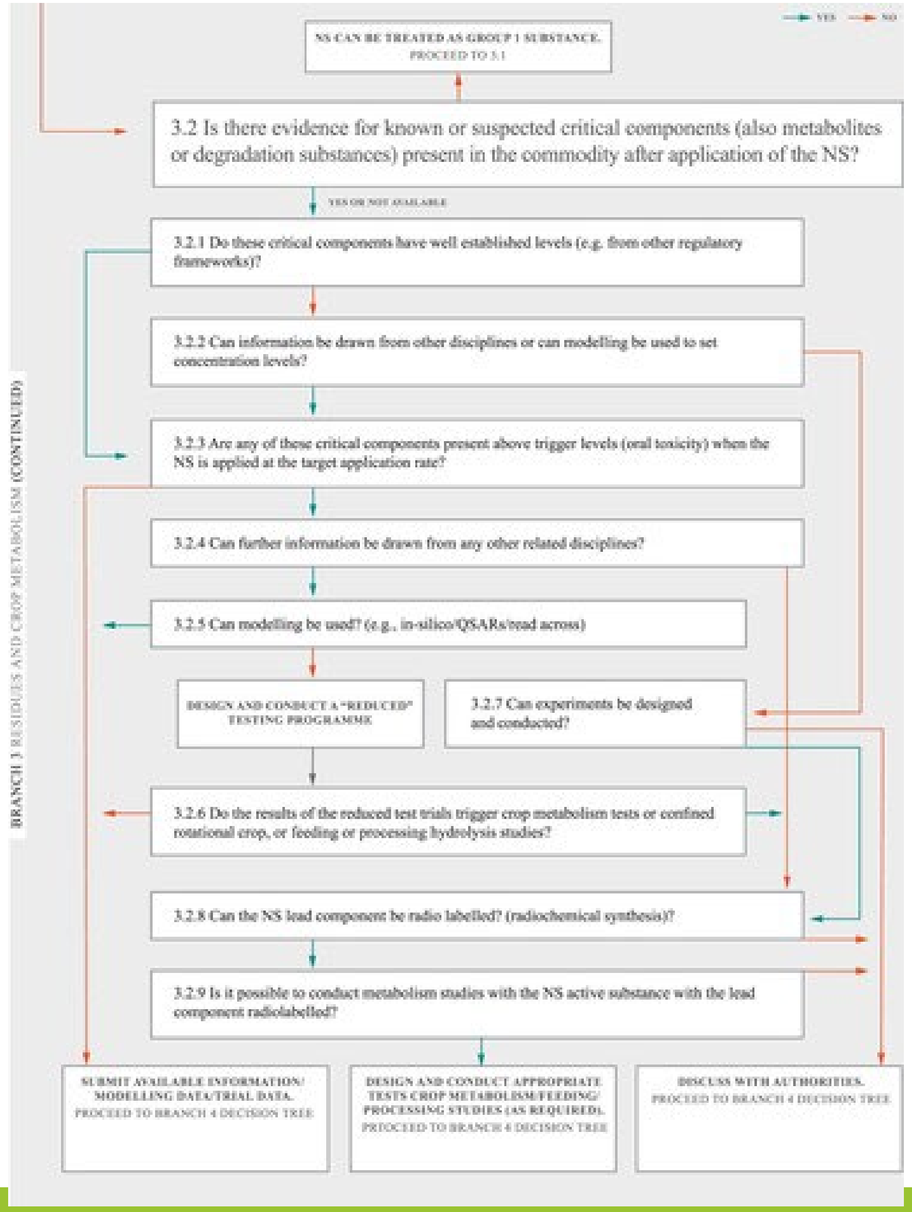


Effects on Human Health



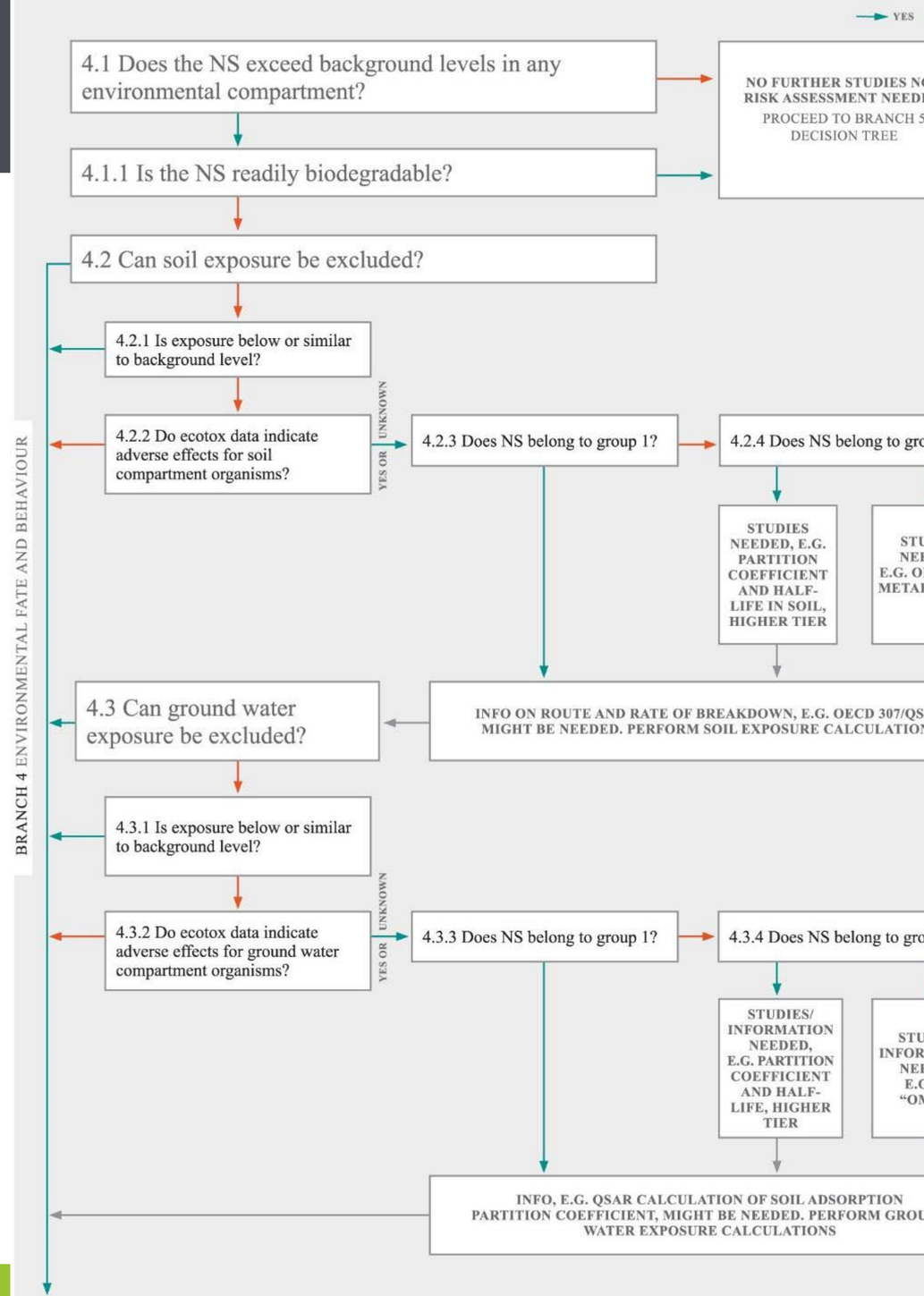
Residues


BRANCH 3 RESIDUES AND CROP METABOLISM
YES
NO
3. DOES THE NS BELONG TO GROUP 1?
3.1 Does NS comply with food/feed legislation?
3.1.1 Is NS the same composition as the one supplied to food/feed industry?
REFINE PROCESSING/MANUFACTURING TO ENSURE NS MATCHES FOOD/FEED SPECIFICATION
3.1.2 Is sufficient evidence available to show equivalence to NS supplied to food/feed industry?
APPLY RIGHT TO EXEMPTION. PROCEED TO BRANCH 4 DECISION TREE
PERFORM TESTING TO SHOW EQUIVALENCE TO FOOD/FEED SPECIFICATION. PROCEED TO BRANCH 4 DECISION TREE
3.1.3 Is an MRL available for the NS lead component in target geographical or similar location?
3.1.4 Does proposed NS lead component application rate result in residues below established MRL?
GENERATE RESIDUE DATA AND REFINE INTENDED USES IF NECESSARY
3.1.5 Is information available on background levels in the natural environment of the target application location?
3.1.6 Is information available that shows that the NS lead component can be determined at levels above background?
3.1.7 Can modelling be used to determine the expected level of residues based on the proposed uses?
3.1.8 Is it possible to design and conduct tests to determine background levels in the intended area of use?
SUBMIT AVAILABLE INFORMATION/ MODELLING DATA. PROCEED TO BRANCH 4 DECISION TREE
APPLY DEFAULT MRL. PROCEED TO BRANCH 4 DECISION TREE
DESIGN & CONDUCT RESIDUE TESTING. PROCEED TO BRANCH 4 DECISION TREE
APPLY DEFAULT MRL OR GENERATE EXPERIMENTAL DATA. PROCEED TO BRANCH 4 DECISION TREE
APPLY DEFAULT MRL OR MODELLING OR GENERATE EXPERIMENTAL DATA. PROCEED TO BRANCH 4 DECISION TREE


BRANCH 3 RESIDUES AND CROP METABOLISM (CONTINUED)
YES
NO
NS CAN BE TREATED AS GROUP 1 SUBSTANCE. PROCEED TO 3.1
3.2 Is there evidence for known or suspected critical components (also metabolites or degradation substances) present in the commodity after application of the NS?
YES OR NOT AVAILABLE
3.2.1 Do these critical components have well established levels (e.g. from other regulatory frameworks)?
3.2.2 Can information be drawn from other disciplines or can modelling be used to set concentration levels?
3.2.3 Are any of these critical components present above trigger levels (oral toxicity) when the NS is applied at the target application rate?
3.2.4 Can further information be drawn from any other related disciplines?
3.2.5 Can modelling be used? (e.g., in-silico/QSARs/read across)
DESIGN AND CONDUCT A "REDUCED" TESTING PROGRAMME
3.2.7 Can experiments be designed and conducted?
3.2.6 Do the results of the reduced test trials trigger crop metabolism tests or confined rotational crop, or feeding or processing hydrolysis studies?
3.2.8 Can the NS lead component be radio labelled? (radiochemical synthesis)?
3.2.9 Is it possible to conduct metabolism studies with the NS active substance with the lead component radiolabelled?
SUBMIT AVAILABLE INFORMATION/ MODELLING DATA/TREAL DATA. PROCEED TO BRANCH 4 DECISION TREE
DESIGN AND CONDUCT APPROPRIATE TESTS CROP METABOLISM/FEEDING/ PROCESSING STUDIES (AS REQUIRED). PROCEED TO BRANCH 4 DECISION TREE
DISCUSS WITH AUTHORITIES. PROCEED TO BRANCH 4 DECISION TREE

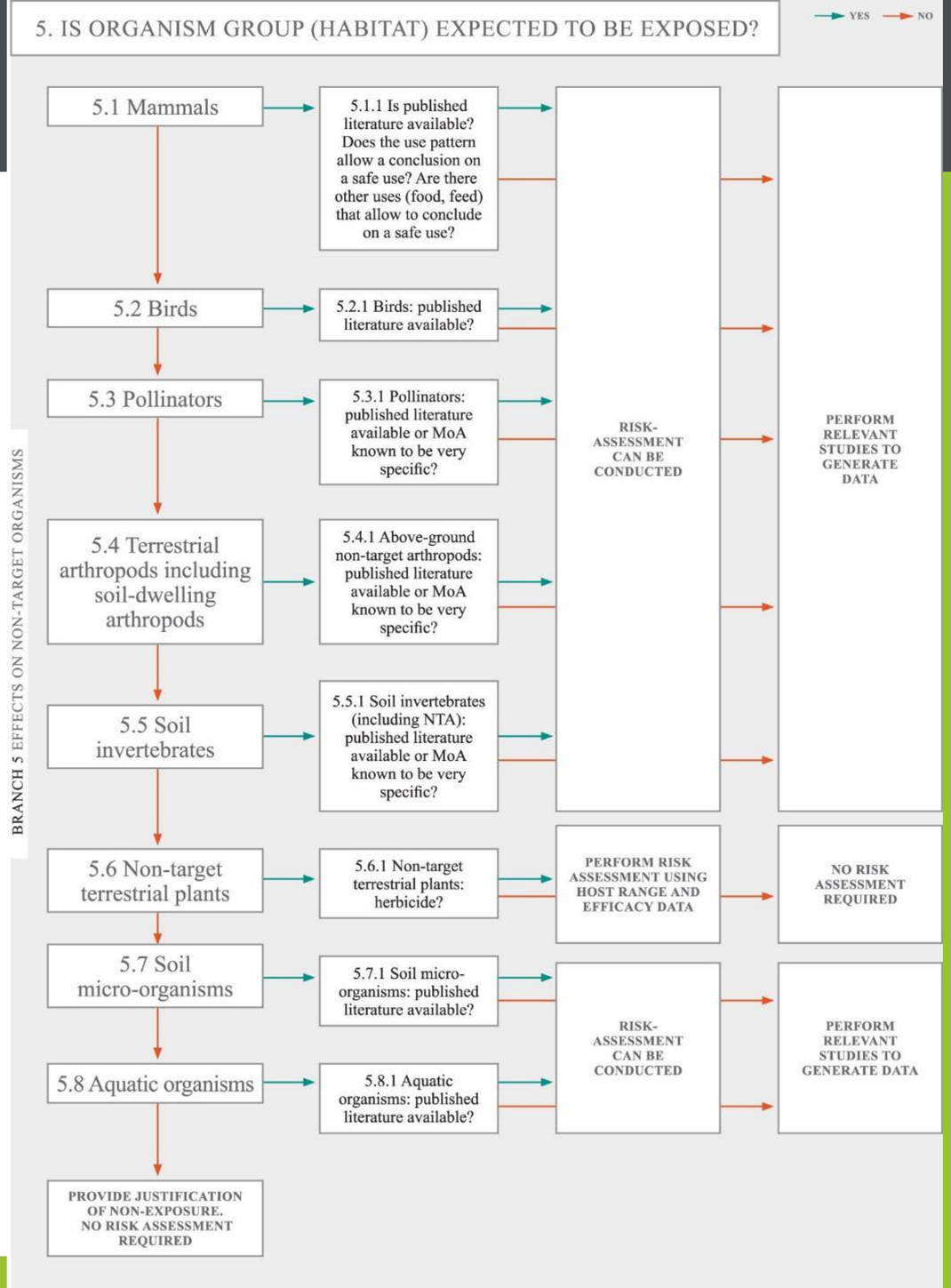
Environmental fate

- Background level check
- Biodegradation check; e.g. does the natural substance degrade?
- Exposure check: Can exposure be excluded?
- Depending on the group, either studies or QSAR & calculations



Ecotoxicology

- Literature is the backbone
- For food or feed additives or pharmaceuticals, mammals and bird studies can be waived
- If data on adverse effects of the Natural Substance active substance (other than those listed) are known from public literature, these need to be considered.
- Absence of information is insufficient; robust information or logical thinking needs to be available to conclude on a safe use.



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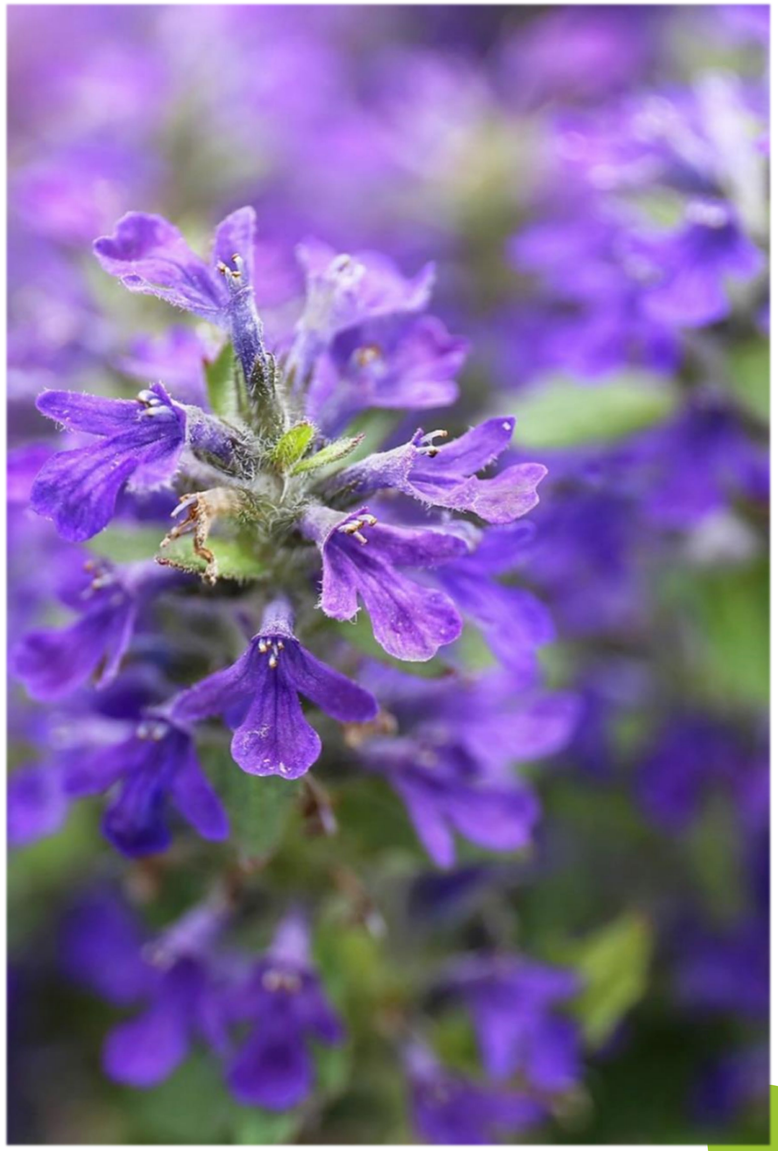

Natural Substances Data DT: let's Test the Tree

CASE STUDIES

1. **Nature Identical Single Entities:** Eva Van Hende (Biotalys NV)
2. **Plant mixtures**: M, Ina Kleeberg (Trifolio)
3. **Micro-organism mixtures**: Maggie Rodriguez (Profarm ex: Marrone Bio Inno)

→ Outputs of 2 days workshop with an expert group of IBMA members

Comparison Data DT – 1107 Regulation:

Nature-Identical Single Entity Case

Evoca/Biotalys – Antibody for use in crop protection

Nature-Identical Single Entity	1107/2009	NS Data DT
Section 1	Characterization needed of the Bioprocess-related non-relevant components	No characterization needed, testing of the full technical product in later phases (including active ingredient and bioprocess-related non-relevant components) is sufficient to characterize the product as a whole. Identification of the individual molecules is not bringing extra value.
Section 2	After discussion with the authority, we came to the same data requirement as the decision tree.	→ Run acute tox 6-pack → Run Genotox test (TIER 1) (Ames) → No need to run carcino → Run 28-day study: not a part of acute tox, but needed by default? → No need for 90-day oral study, which would be a good element out of this decision tree
Section 3	MRL exemption applied for, after agreement with the authorities in pre-submission meeting	MRL exemption would be a logic outcome because of readily biodegradability. This could be clear if there are small adaptations made to the decision tree.
Section 4	No data needed. Because the regulation is focusing on the active, the bioprocess related non-relevant components are not yet giving rise to	No data needed. Because of readily biodegradability of the protein, no e-fate studies or risk assessments need to be done. Similar conclusion on data generation as 1107.
Section 5	All studies needed.	All studies needed. Similar conclusion on data generation as 1107.

Comparison Data DT – 1107 Regulation:

Plant Mixture Case

Confidential/Trifolio – Plant extract obtained from kernels with insecticidal efficacy

Plant Mixtures	1107	NS Data DT
Section 1	Need to identify >80% and all components above 1%: irrealistic and not feasible	define raw material, process and quality (fingerprint) + lead component: more fit-for-purpose
Section 2		Similar conclusion on data generation as 1107
Section 3	Establish MRL for 4 components present in the NS: irrealistic and not feasible	Only establish MRL for lead component
Section 4	Full E-fate data package is needed, or else justification/waivers for every point	More weight given to ready biodegradability/primary degradation of the lead component
Section 5	Prone to push for higher tier studies	First questions the relevance of and need for higher tier studies

Comparison Data DT – 1107 Regulation:

Microbial Mixture Case

Chromobacterium subtsugae strain PRAA4-1T + Fermentation media (inactive microbe in final formulation)/Profarm

Microbial Mixtures	1107/2009	NS Data DT
Section 1	Unclear guidance/position around proper product characterization of NS and pushing registrants to address full product composition as an agrochemical	Allows to use biological properties as criteria for characterization of NS For example: WGS, proxy marker secondary metabolites, CFU's, biological properties Omics tools to screen for compounds of toxicological concern
Section 2		Similar conclusion on data generation as 1107
Section 3	Currently designed to assess discrete chemical compounds that is not technically feasible for natural substances that can be complex mixture of compounds	Biological property approach, e-fate data, and acute tox data allow a WoE approach to MRL exemption
Section 4	Currently designed to assess discrete chemical compounds that is not technically feasible for natural substances that can be complex mixture of compounds	Uses the biodegradability of NS to determine data requirements
Section 5		Similar conclusion on data generation as 1107 Specifically mentions the potential use of: • Existing literature • Bridging arguments • Risk assessment waivers

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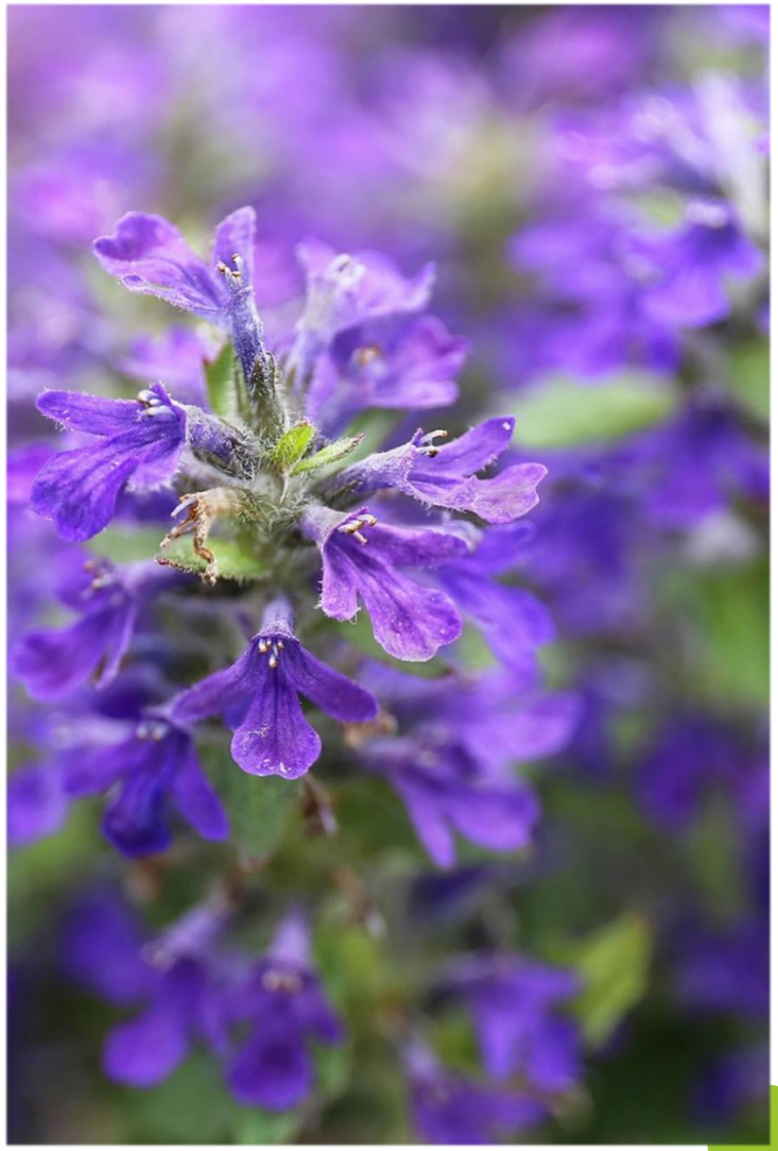


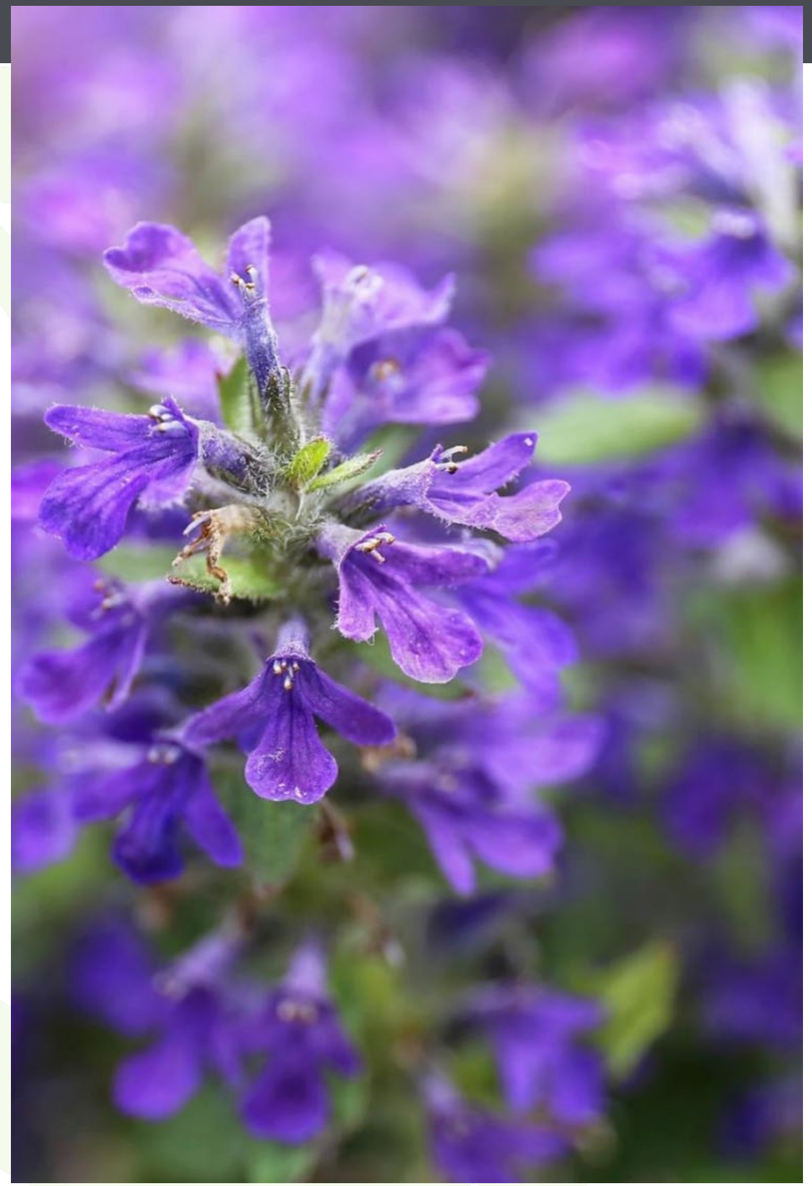
General Advantages of Data DT

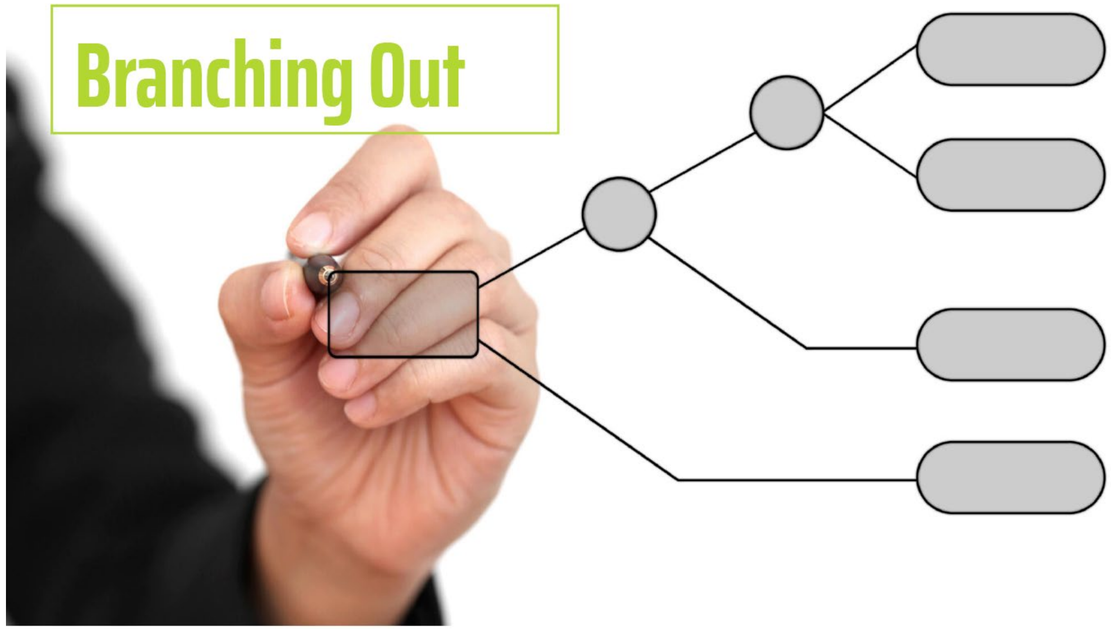
- Easy-to-Use Tool
- Fit for purpose for BioControl
- Provide focus for Pre-submission meetings: identify the right points for discussion
- Provide structure and clarity on what is needed
- The Data DT provides the possibility to develop tailored solutions which gives flexibility for registration and helps to avoid gaps in the EFSA conclusion

HELPS TO:

- Improve the time to registration by decreasing the level of uncertainty
- Helps to achieve the Green Deal ambitions of EU and to provide new BioControl solutions to help solve farmer pain points

Thank you! Questions?





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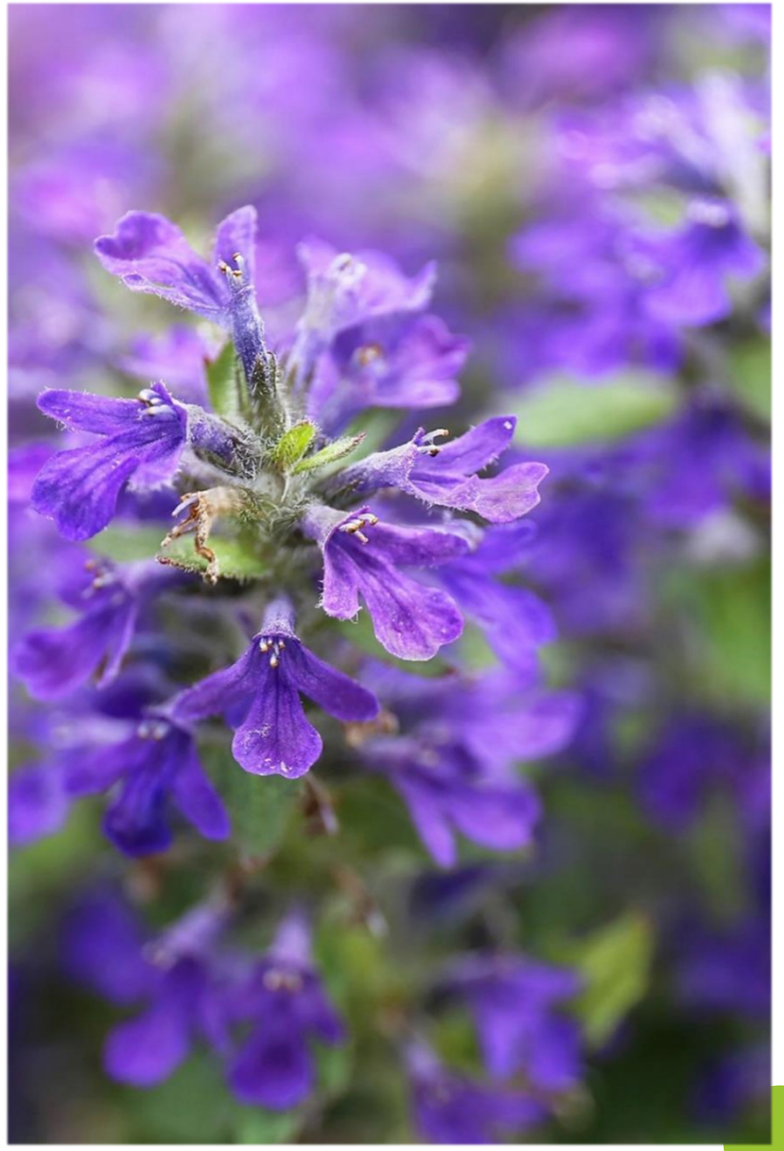
Back-Up Slides

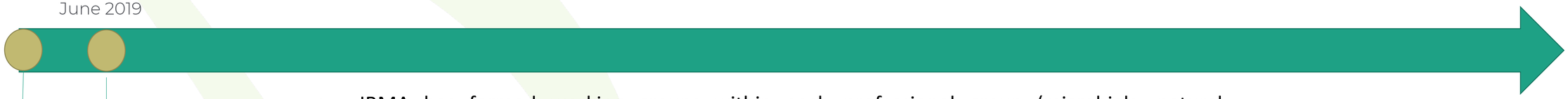


Natural Substances Data Decision Tree

THE JOURNEY

May 2019

June 2019



IBMA, DG Sante and EC agree to adapt data requirements to make them more appropriate for biocontrol classes IBMA requested to input decision trees

IBMA Kick-Off meeting

- IBMA has formed working groups within each professional group (microbials, natural substances and semiochemicals) to develop the decision trees
- All IBMA members were asked to participate in this decision tree development

	Section 1: Analytics and Identification	Section 2: Toxicity	Section 3: Residues	Section 4: E-fate	Section 5: Ecotox and non-target testing
Moderator	**David Cary**	**Lara Ramaekers**	**Dawn Williams**	**Francesco Greco**	**Ulf Heilig**
Members	Ina Kleeberg	Anne Alix	Jennifer Lewis	Annabel Levert/Cédric Bertrand	Patrick Kabouw
	José Carvalho	An Vanden Bosch	Beate Ruch	Adi Cornelese	Ruediger Hauschild
	Khalid Akdi/Loli Gomes	Karin Lauber	Sue Young (Certis)	Eva Mandrisch	Sian Ellis
	Keith Pitts		Severine PELTE <severine.pelte@sbm-company.com>		Fabien Schroeder (Certis)

Natural Substances Data Decision Tree

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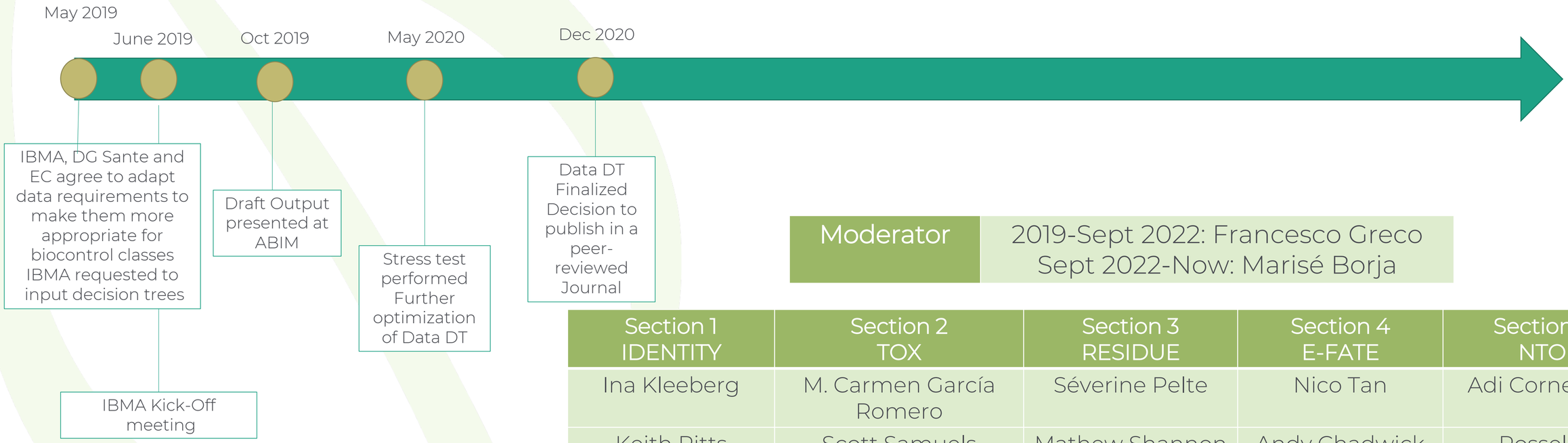

Moderator	2019-Sept 2022: Francesco Greco Sept 2022-Now: Marisé Borja

Section 1 IDENTITY	Section 2 TOX	Section 3 RESIDUE	Section 4 E-FATE	Section 5 NTO
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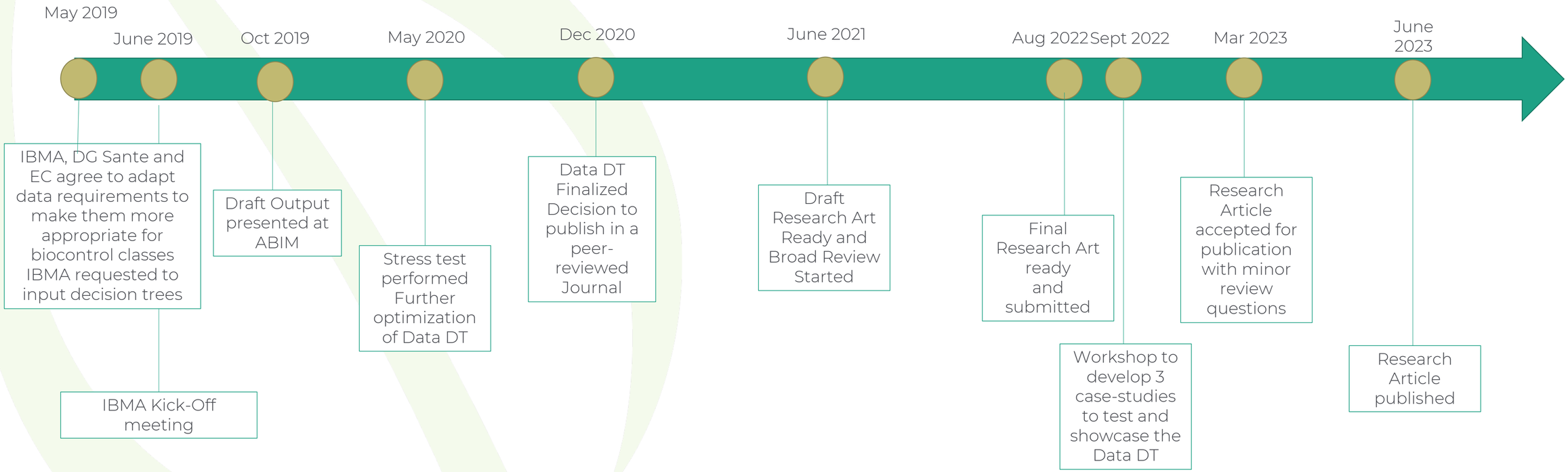

The approach is in line with 1107 (283 & 284)

1 2 3

1.1. The information shall be sufficient to evaluate the foreseeable risks, whether immediate or delayed, which the active substance may entail for humans, including vulnerable groups, animals and the environment and contain at least the information and results of the studies referred to in this Annex.

1.2. Any information on potentially harmful effects of the active substance, its metabolites and impurities on human and animal health or on groundwater shall be included.

1.3. Any information on potentially unacceptable effects of the active substance, its metabolites and impurities on the environment, on plants and plant products shall be included.

1 2 3

1.4. The information shall include all relevant data from the scientific peer reviewed open literature on the active substance, metabolites and breakdown or reaction products and plant protection products containing the active substance and dealing with side-effects on health, the environment and non-target species. A summary of this data shall be provided.

Group 2 3

1.5. 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:

Group 1

(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.

Contributing to New Data Requirements for Natural Substances
SECTION 1: ANALYTICS AND IDENTIFICATION

- Section 1 data decision tree addresses the requirements needed for Section 1 and also determines the classification of the NS in group 1, 2 or 3 (adapted from botanical guidance).
- Guidelines:
  - The fingerprint approach is good but should also incorporate a leading compound approach.
  - There should be flexibility in the fingerprint with the level of identification say 90% of peaks being identified.
  - The fingerprint should be justified and covers quantification of lead compounds in critical functions and activity functions.
  - Leading compounds may be different for different risk areas.
  - For the fingerprint no marker compounds need to be identified for each study / dilution. These can be identified at the start of the study not each time a new diluted test sample is prepared as this should not be scientifically needed or possible.

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Contributing to New Data Requirements for Natural Substances
SECTION 2: HUMAN TOXICITY

- One data decision tree per group (group 2 decision tree can be requested to also go through group 3 decision trees in case of concerns for acute tox evaluation).
- All studies preferably with the formulated product or on the NS (technical grade) in case of several similar formulations. In all cases, avoid to do studies on isolated components that are part of the NS (technical grade).

- **Group 1 Decision tree:**
  - Partial or full acute tox information
  - Published literature and food/feed use + compare exposure to food consumption
- **Group 2 Decision tree:**
  - Use Group 1 Decision tree to asses need for partial or full acute tox information
  - Focus on suspected critical components: exposure level – use of published information – modelling (eg QSARs) – studies
- **Group 3 Decision tree:**
  - By default, information needed on acute tox, genotox, 28 days short term tox
  - Exposure level – concerns in default testing? If yes, additional information needed (e.g. carcinogenicity – 90 days tox)

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Contributing to New Data Requirements for Natural Substances
SECTION 3: RESIDUES AND CROP METABOLISM

- **Guidelines:**
  - Objective: Assess NS exposure by identifying residues of the NS in food or animal feedstuffs for purposes of dietary risk assessment and setting Maximum Residue Levels (MRLs).
  - Information has been collected regarding the presence of suspected critical components in the NS (technical grade).
  - Studies with the NS (technical) or formulated product. Formulation changes or application on (some) differing crops may be addressed by bridging studies.

- One decision tree for Group 1 and one decision tree for Group 2 and 3 together

- Further improvements needed for this section
- Looking for additional expertise with residue chemistry background

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Contributing to New Data Requirements for Natural Substances
SECTION 4: E-fate and behaviour

- No use of group 1-2-3
- **Structure:**
  - **Step 1**: Data collection/information → background levels, published information, studies
  - **Step 2:** Soil AND water/sediment (cover e.g. overspray) exposure.
  - **Step 3:** Surface water exposure.
  - **Step 4:** Groundwater exposure.
  - **Step 5:** Air exposure.
- NTO-tree needs to be harmonized with e-fate approach.

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Contributing to New Data Requirements for Natural Substances
SECTION 5: Non-target organisms

- **Guidelines:**
  - Groups 1, 2, 3 (according to EU Botanicals Guidance Doc.) are not to be distinguished! NTO effects cannot be generalised for any of these groups.
  - **Starting point for all NTO groups is possible exposure**
  - All NTO groupings need to be addressed but specifications could provide good information.
  - NTOs are in groupings according to exposure of their habitat. Consider GAP! Non-exposure and/or the specificity of effect can exclude the need for information.
  - If substance rapidly degraded: no chronic studies required, unless repeated application.
  - Some natural substances also used as food, feed, food or feed additives and pharmaceuticals can be excluded for certain tests if the exposure through the PPP use is $\leq$ food/feed/pharma exposure. This is addressed at organism group level and only valid for mammals (food, food add. use) and for the animals that are targets for the feed (including feed add.) and pharma uses.
  - Estimated environmental concentrations (applied dose according to worst-case GAP) shall be considered. Those for food additives used as PPPs are expected to generally exceed those for food uses.

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Contributing to New Data Requirements for Natural Substances
SECTION 5: Non-target organisms

Which organism groups (habitats) are expected to be exposed?

Mammals
Birds
Pollinators
Terrestrial arthropods including soil-dwelling arthropods
Soil invertebrates (e.g. worms, nematodes)
Non-target terrestrial plants
Microorganisms
Aquatic organisms

For each group:

- Published information available?
- Identify need for risk assessment
- Identify need for data requirements

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