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Extensive literature search on grayanotoxins and 5-hydroxymethylfurfural

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National Food Institute, Technical University of Denmark

Abstract

An extensive literature search to identify and collect studies related to the toxicity of grayanotoxins and 5-hydroxymethylfurfural (5-HMF) was performed in the three databases PubMed, Web of Science and SciFinder® for six and four Areas, respectively. After combination of the searches from the three databases and removal of the duplicates, the total number of references for the grayanotoxins was 652 and for 5-HMF Area 1b was 3,862, for Area 2b was 37, for Area 3b was 221 and for Area 4b was 500. The evaluation of all retrieved references for relevance by screening the title and abstract (if available) and applying eligibility criteria (inclusion/exclusion) resulted in a total number of relevant references for the grayanotoxins for Area 1a of 71, for Area 2a of 3, for Area 3a of 5, for Area 4a of 75, for Area 5a of 141, and for Area 6a of 78 and for 5-HMF for Area 1b of 55, for Area 2b of 14, for Area 3b of 15 and for Area 4b of 8.

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Key words: grayanotoxin, andromedotoxin, 5-hydroxymethylfurfural, 5-HMF, toxicity, bee health, extensive literature search

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Extensive literature search on grayanotoxins and 5-hydroxymethylfurfural

Summary

The overall aim of this assignment was to identify and collect all relevant literature related to the toxicity of grayanotoxins and 5-hydroxymethylfurfural (5-HMF) to support the preparatory work for the hazard identification and characterisation steps in the human health risk assessment of these substances.

Initially, one tailored search string for grayanotoxins and four tailored search strings for 5-HMF were designed in collaboration with EFSA to retrieve all potentially relevant studies within the following Areas:

Grayanotoxins:
- Area 1a: Data on chemical identification, characterisation and formation.
- Area 2a: Data on occurrence in food.
- Area 3a: Data on toxicokinetics (absorption, distribution, metabolism, excretion) in experimental animals and humans and from in vitro studies.
- Area 4a: Data on toxicity in experimental animals.
- Area 5a: Data on in vitro and in vivo genotoxicity, in vitro studies and mode of action.
- Area 6a: Data on observations in humans (including epidemiological studies, case reports, biomarkers of exposure).

5-HMF:
- Area 1b: Data on chemical identification, characterisation and formation.
- Area 2b: Data on occurrence in bee feed and honey.
- Area 3b: Data on toxicokinetics (absorption, distribution, metabolism, excretion) in bees and from in vitro studies.
- Area 4b: Data on toxicity in bees.

The search strings were tailored to the databases PubMed, Web of Science and SciFinder® and consisted of one major step for the grayanotoxins and two major steps for 5-HMF, each designed to suit the respective databases.

Combinations of search terms were used, starting with broad searches for the two substance groups, including synonyms and abbreviations (step 1) and was for 5-HMF followed by an Area specific step with the addition of search terms relevant to each Area (step 2).

Then tailored search strings were employed to retrieve all relevant studies from the three databases. All retrieved references were exported as separate files into EndNote™ (version X9). Duplicate studies were then removed after combining the three EndNote™ files, into one file for the grayanotoxins and into one single combined file per Area for 5-HMF. The EndNote libraries are available on the Knowledge Junction community of EFSA on Zenodo, at: http://doi.org/10.5281/zenodo.3972112

The combined number of references from each database was 652 for the grayanotoxins, and was 3,862 from Area 1b, 37 from Area 2b, 221 from Area 3b and 500 from Area 4b for 5-HMF.

All retrieved references were then evaluated for relevance by applying eligibility criteria (inclusion/exclusion). The selection for relevance was conducted by screening the title and abstract (if available) and all the retrieved studies were ultimately sorted into one of the following two categories:

- Relevant to the research objectives: References ultimately evaluated to be relevant were included in this category.
The results of the reference selection process were reported in summary tables (Excel files), one for each Area, and for the grayanotoxins an additional table containing all references for the primary sorting. The summary tables are available on the Knowledge Junction community of EFSA on Zenodo, at: http://doi.org/10.5281/zenodo.3972112. The summary tables include all pertinent information for each of the references in the ‘Relevant’ category as identified by the eligibility criteria suggested by the Contractor and agreed by EFSA which could be retrieved from the title and abstract (when available). The summary tables also include references in the ‘Not relevant’ categories, but without any study details except for including the reason for exclusion for the ‘Not relevant’ references, i.e. not target compound or not relevant for the specific Area is presented.

The evaluation for relevance resulted in a total number of relevant references for grayanotoxins for Area 1a of 71, for Area 2a of 3, for Area 3a of 5 for Area 4a of 75, for Area 5a of 141, and for Area 6a of 78 and for 5-HMF for Area 1b of 55, for Area 2b of 14, for Area 3b of 15, and for Area 4b of 8.
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1. **Introduction**

1.1. **Background and Terms of Reference as provided by EFSA**

This contract was awarded by EFSA to:

**Contractor: National Food Institute, Technical University of Denmark**

**Contract title: Extensive literature search on grayanotoxins and 5-Hydroxymethylfurfural**

**Contract number: NP/EFSA/BIOCONTAM/2019/03**

1.1.1. **Background as provided by EFSA**

The Unit on Biological Hazards and Contaminants (BIOCONTAM Unit) supports the Panel on Contaminants in the Food Chain (CONTAM Panel), which provides scientific advice on contaminants in the food chain and undesirable substances such as natural toxicants, mycotoxins and residues of unauthorised substances.

EFSA expects to receive soon two new mandates from the European Commission for scientific opinions. One, on the health risks related to the presence grayanotoxins in honey and another one on the risks of 5-Hydroxymethylfurfural for bee health. These mandates will be allocated to the CONTAM Panel and Working Groups will be established to develop these opinions.

To support the preparatory work for these opinions, EFSA wishes to outsource an Extensive Literature Search (ELS) as well as the selection of relevant studies by screening of title and abstract related to

- a) the chemical identity and characterisation, occurrence in food, toxicokinetics and toxicity of grayanotoxins

- b) the chemical identity, characterisation, formation and occurrence in bee feed and honey, toxicokinetics and toxicity in bees or related species of 5-Hydroxymethylfurfural.

Grayanotoxins, also known as andromedotoxin, acetylandromedol or rhodotoxin are diterpens present in plants belonging to the Ericaceae family. Grayanotoxins can also be present in products originating from such plants in particular in honey. Uptake of grayanotoxins has been associated with a series of adverse effects on the nervous system in humans\(^1\). The EFSA compendium on botanicals mentions grayanotoxins as chemicals of concern in leaves and flowers of Rhododendron species\(^2\).

5-Hydroxymethylfurfural (HMF) is a product of the Maillard reaction i.e. is formed during the thermal treatment of carbohydrate containing foods. It can be found in a variety of foods like fruit juices, jam, chocolates, cereal bars but also in honey. HMF has been shown to exert toxicity in animal experiments and to have potentially adverse effects in humans\(^3\). It is also toxic to bees and application of HMF-containing bee feed has been associated with shorter life span and increased mortality in bees\(^4,5,6\).

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2. European Food Safety Authority; Compendium of botanicals that have been reported to contain toxic, addictive, psychotropic or other substances of concern on request of EFSA. EFSA Journal 2009; 7(9):281. [100 pp.]. doi:10.2903/j.efsa.2009.281. Available online: www.efsa.europa.eu.


The contractor should ensure that all the steps for conducting the ELS are properly documented and reported.

This call is based on EFSA’s 2019 draft Work Programme for grants and operational procurements as presented in Annex IX of the draft Programming Document 2019 – 2021, available on the EFSA’s website.

1.1.2. Objectives as provided by EFSA

The objectives of the contract are as follows:

Objective 1 a): To develop tailored search strategies to retrieve studies (including reviews and grey literature) pertinent to the risk assessment and characterisation of grayanotoxins (applying no time limit).

- Area 1a: Data on chemical identification, characterisation and formation
- Area 2a: Data on occurrence in food
- Area 3a: Data on toxicokinetics (absorption, distribution, metabolism, excretion) in experimental animals and humans and from in vitro studies.
- Area 4a: Data on toxicity in experimental animals and in vitro
- Area 5a: Data on in vitro and in vivo genotoxicity and mode of action
- Area 6a: Data on observations in humans (including epidemiological studies, case reports, biomarkers of exposure)

Objective 1 b): To develop tailored search strategies to retrieve studies (including reviews and grey literature) pertinent to the risk assessment and characterisation of 5-Hydroxymethylfurfural in bees

- Area 1b: Data on chemical identification, characterisation and formation
- Area 2b: Data on occurrence in bee feed and honey
- Area 3b: Data on toxicokinetics (absorption, distribution, metabolism, excretion) in bees and from in vitro studies.
- Area 4b: Data on toxicity in bees

The search strategies proposed by the contractor will be discussed and agreed with EFSA before proceeding with the actual searches.

- Objective 2: To carry out the extensive literature search (ELS) using the tailored search strings developed by the contractor and agreed by EFSA for identifying studies.
- Objective 3: To screen the titles and abstracts for relevance to the risk assessment. To prepare a file compatible with EndNote™ (RIS file) with the relevant literature and a table summarising the relevant studies. These should contain the studies considered as relevant applying the eligibility criteria (for inclusion/exclusion of studies) that have to be developed by the contractor. The file compatible with EndNote™ (RIS file) and table should be organised by group of compounds and by area.

2. Methodologies

The methodology for systematic reviews including guidance for development and optimisation of a search strategy and for selecting relevant studies has been described by EFSA (2010). This methodology was implemented as appropriate in the Tasks described below.

2.1. Objective 1

2.1.1. Task 1 Developing tailored search strategies and search strings for collecting relevant studies

Tailored search strings were developed for identifying all potentially relevant studies pertinent to the risk assessment and characterisation of grayanotoxins and to the risk assessment and characterisation of 5-HMF in bees.

The search strings were tailored to the databases PubMed, Web of Science and SciFinder®. The search consisted of one (grayanotoxins) or two (5-HMF) major steps designed to suit the respective databases. In PubMed, searches were made with the *All fields* [ALL] tag. In Web of Science, searches were made in *Topic* including title, abstract, author keywords and keywords plus® and in *All Databases* for the most comprehensive result. In SciFinder® CAS registry numbers were used instead of substance names as substances are indexed with links to CAS Registry, which makes search strings with CAS registry numbers preferable. Boolean operators were used for combinations of search terms. In SciFinder® patents were excluded from the search.

The first major step consisted of separate broad searches for grayanotoxins and 5-HMF including synonyms, derivatives and CAS Registry Numbers to retrieve the largest number of potentially relevant studies on grayanotoxins within Area 1a-6a and 5-HMF within Area 1b-4b. The search strings were presented and discussed with EFSA at the kick-off meeting.

2.1.1.1. Grayanotoxins

Due to the expected relatively low number of references identified in the literature search with the use of the major search string, no further limitations were applied to the search string. This means that Area-specific search strings were not applied. Instead, the selection of relevant studies was performed in two steps. The first step was a primary sorting of all references into relevant or potentially relevant for Area 1a to 6a or not relevant for any Areas. The references not considered relevant for any Areas were not considered further. This primary sorting was performed independently by two team members. The results were then compared to make sure that all relevant and potentially relevant references had been identified. In cases of doubt, references were included for final assessment of relevance by the Area-specific expert in the second step of the selection of relevant studies as described under Objective 3 (Section 3.3.).

At the kick-off meeting, it was agreed with EFSA that all relevant *in vitro* studies would be included in Area 5a, which will then include *in vitro* studies with toxicological endpoints in addition to *in vitro* and *in vivo* genotoxicity studies and mode of action (MoA) studies. The type of study (toxicity, genotoxicity and MoA) will clearly be stated for each reference in the summary table for Area 5a. Area 4a will then only include *in vivo* toxicity in experimental animals. It was also agreed to include studies in pets such as cats and dogs, but to exclude studies in livestock as relevant experimental animals in Area 4a and to include *in silico* studies in Area 5a.

2.1.1.2. 5-HMF

A second step was applied to the literature search for 5-HMF. This step was Area-specific with the addition of search terms relevant to each specific Area.

Search terms were identified in collaboration with relevant members of the project team to identify as many relevant as possible. The search strings were developed in order to retrieve the largest number
of potentially relevant studies on 5-HMF within Area 1b-4b. The search strings were presented and discussed with EFSA at the kick-off meeting.

2.2. **Objective 2**

2.2.1. **Task 2 Execution of the extensive literature searches using the tailored search strings developed in task 1**

The tailored search strings developed in Task 1 and agreed upon by EFSA were employed to retrieve all relevant studies from the databases PubMed, Web of Science and SciFinder® on grayanotoxins and 5-HMF.

No limitation to publication year was applied. Language was limited to English only.

All references identified in the extensive literature searches (ELS) in PubMed, Web of Science and SciFinder® were exported as separate files into EndNote™. Title, author, journal, year of publication and abstract were included for each study imported to EndNote™ and the number of references resulting from each of the three databases was recorded in a log file (example in Table 1). Duplicate studies were removed after combining the three EndNote™ files into one single combined file for each substance group.

<table>
<thead>
<tr>
<th>Date of search</th>
<th>Databases &amp; Search Engines</th>
<th>Search terms</th>
<th>Limitations applied to search</th>
<th>No of references</th>
<th>Comments &amp; follow-up actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>May 1, 2020</td>
<td>PubMed</td>
<td>grayano* OR andromedotoxin* OR acetylandromedol* OR rhodotoxin* OR asebotoxin* OR grayanane*</td>
<td>English only</td>
<td>250</td>
<td>Has been exported to EndNote™</td>
</tr>
</tbody>
</table>

2.3. **Objective 3**

2.3.1. **Task 3 Selection of all relevant studies retrieved by the extensive literature searches**

All studies retrieved by the ELS and imported into the combined EndNote™ files (Task 2) were evaluated for relevance by applying eligibility criteria (inclusion/exclusion) for each subject Area (1a-6a and 1b-4b) developed by the Contractor and agreed upon by EFSA.

The selection for relevance was conducted by screening their title and abstract (if available) and all the retrieved studies were ultimately sorted into one of the following two categories:

- **Relevant to the research objectives**: References ultimately evaluated to be relevant were included in this category. The reviewer consulted the full paper if possible in cases where relevance was uncertain. If relevance remained uncertain, the references were included in this category, as a conservative approach.

- **Not relevant to the research objectives**: References ultimately evaluated not to be in-scope were included in this category.
To ensure a uniform understanding of the eligibility criteria in each Area, these were discussed in an internal meeting before all references were assessed for relevance.

Each study was individually assessed by two reviewers in order to prevent the introduction of errors and personal bias. In the possible event of disagreements between reviewers a third member of the project team assisted in solving the specific issue as recommended by EFSA (2010).

The results of the reference selection process were reported in summary tables, one table per Area (1a-6a and 1b-4b), and an additional table with the primary sorting for the grayanotoxins. The summary tables include all pertinent information from each of the relevant studies as identified by the eligibility criteria developed by the Contractor and agreed with EFSA. Additional fields for potential relevance for other Areas, the person(s) responsible for the screening and comments were also included in the summary tables.

All references found relevant for the hazard identification and characterisation of grayanotoxins and the risk assessment and characterisation of 5-HMF in bees within Area 1a-6a and 1b-4b were collected in EndNote™ files (in one single EndNote™ file for grayanotoxins and in one EndNote™ file per Area for 5-HMF) including all indexed fields per reference (i.e. title, author, publication year, journal and abstract).

All relevant studies were collected in a reference list, one list per Area per substance group, see Appendix C.

3. Results

3.1. Objective 1

3.1.1. Task 1 Developing tailored search strategies and search strings for collecting relevant studies

The tailored search strings were developed in order to retrieve the largest number of potentially relevant studies related to the chemical identity and characterisation, occurrence in food, toxicokinetics and toxicity of grayanotoxins within Area 1a-6a and the chemical identity, characterisation, formation and occurrence in bee feed and honey, toxicokinetics and toxicity in bees or related species of 5-HMF within Area 1b-4b.

The suggested search strings for grayanotoxins and 5-HMF are presented below and were submitted to EFSA on 24 April 2020 (email) as part of Deliverable 1.

The search string for step 1 was developed in order to capture all known and potentially unknown grayanotoxins and their derivatives, and 5-HMF and its deviates.

The search string for step 2, Area 1a, was developed based on the experiences obtained in a similar procurement carried out for EFSA i.e. ‘Extensive literature search for studies related to fumonisins and their modified forms’, final report approved by EFSA on 2 December 2016. In this procurement, the search terms were combined and tested in the databases PubMed and Web of Science to develop the most sensitive and appropriate search string.

The search strings for step 2, Area 3b and 4b were developed by using search terms identified from OECD Test Guideline 213 (OECD 1998) and 245 (OECD 2017) and US EPA Honey Bee Acute Contact Toxicity Test (US EPA 2012).

The search strings were tested by assessing whether they retrieved relevant papers already known to the project team as recommended in EFSA (2010).

Boolean operators were used in the proposed search strings. “OR” expands the amount of references returned when used in a search string as just one of the search terms need to be present in the returned references. “AND” narrows the amount of references returned as all of the search terms need to be present in the returned references. The Boolean operator “NOT” excludes references
Extensive literature search on grayanotoxins and 5-hydroxymethylfurfural

3.1.1.1. Objective 1a Grayanotoxins

Step 1:

The search string agreed for step 1 in PubMed and Web of Science is as follows:

Grayano*
OR
Grayanane*
OR
Andromedotoxin*
OR
Acetylandromedol*
OR
Rhodotoxin*
OR
Asebotoxin*

The search term grayanane* is included to catch potential relevant references that may include grayanotoxins in grayanane diterpenoids.

The search string agreed for step 1 in SciFinder® includes 18 isomers of grayanotoxin (grayanotoxin I-XV and XVII-XIX) and is as follows:

4720-09-6
OR
4678-44-8
OR
4678-45-9
OR
30272-17-4
OR
30272-18-5
OR
30460-36-7
OR
30460-59-4
OR
30460-60-7
OR
30460-58-3
OR
3.1.1.2. Objective 1b 5-HMF

**Step 1:**

The search string agreed for step 1 in PubMed and Web of Science is as follows:

- 5-hydroxymethylfurfural
- OR HMF
- OR 5-HMF
- OR 5-hydroxymethyl-2-furfuraldehyde
- OR 5-(hydroxymethyl)furan-2-carbaldehyde

The search string agreed for step 1 in SciFinder® is as follows:

67-47-0

**Step 2:**

**Area 1b:** Data on chemical identification, characterisation and formation

For PubMed:

AND (chem* OR analy* OR identi* OR charact* OR detect* OR determin* OR method* OR form* OR degrad* OR hydroly* OR reaction* OR GC* OR HPLC OR LC-MS OR ICP-MS)
Extensive literature search on grayanotoxins and 5-hydroxymethylfurfural

AND
(honey OR syrup OR fructose OR HFCS OR sugar OR bee feed OR bee OR stingless bee OR honey bee OR honey-bee OR bumblebee OR solitary bee OR apis OR pollinator)

For Web of Science:
AND (chem* OR analy* OR identi* OR charact* OR detect* OR determin* OR method* OR form* OR degrad* OR hydroly* OR reaction* OR GC* OR HPLC OR LC-MS OR ICP-MS)
AND
(honey OR syrup OR fructose OR HFCS OR sugar OR bee feed OR bee OR stingless bee OR honey bee OR honey-bee OR bumblebee OR solitary bee OR apis OR pollinator)

For SciFinder®:
AND (chem* OR analy* OR identi* OR charact* OR detect* OR determin* OR method* OR form* OR degrad* OR hydroly* OR reaction* OR GC* OR HPLC OR LC-MS OR ICP-MS)
AND
(honey OR syrup OR fructose OR HFCS OR sugar OR bee feed OR bee OR stingless bee OR honey bee OR honey-bee OR bumblebee OR solitary bee OR apis OR pollinator)
NOT
(waste oil OR one-pot OR zirconium OR ruthenium OR silver OR fuel OR biofuel OR bamboo OR eutectic OR ferment OR humins).

Area 2b: Data on occurrence in bee feed and honey
AND (honey OR syrup OR fructose OR HFCS OR sugar)
AND
(bee feed)

Area 3b: Data on toxicokinetics (absorption, distribution, metabolism, excretion) in bees and from in vitro studies.
AND (bee* OR stingless bee* OR honey bee* OR honeybee* OR honey-bee* OR bumblebee* OR solitary bee* OR apis OR pollinator)
AND
(toxicokinetic* OR absorp* OR distribution OR metaboli* OR excret* OR vitro)

Area 4b: Data on toxicity in bees
AND (bee* OR stingless bee* OR honey bee* OR honeybee* OR honey-bee* OR bumblebee* OR solitary bee* OR apis OR pollinator)
AND


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Extensive literature search on grayanotoxins and 5-hydroxymethylfurfural

(toxic OR survi* OR morta* OR hatch* OR lethal* OR chronic* OR repro* OR offspring OR brood OR colony collapse disorder OR CCD OR diet* OR consump* OR behaviour OR feed* OR abnormalities* OR cramp* OR moribund OR apathy OR vomit* OR lethargy OR ataxia OR OECD 213 OR OECD 245 OR OPPTS 850.3020)

3.2. Objective 2

3.2.1. Task 2 Execution of four extensive literature searches using the tailored search strings developed in task 1

The number of references resulting from each of the tailored search strings in each of the three databases PubMed, Web of Science and SciFinder® were recorded in log files for grayanotoxins and 5-HMF, see Appendix A and B.

The number of references from each database, as well as the total number of references after removal of the duplicates (combined) are summarised in Table 2 (grayanotoxins) and Table 3 (5-HMF). For the grayanotoxins the number of references found relevant in the primary sorting for each Area is presented in Table 4. The duplicates in the combined files for the primary sorting for the grayanotoxins and for each Area 1b-4b for 5-HMF were removed by the EndNote™ tool. The EndNote™ tool is for various reasons not able to remove all duplicates, so remaining duplicates were removed manually as part of Task 2 and during the execution of Task 3. The revised versions of the combined EndNote™ files were submitted as part of the final deliverable.

Table 2: Total number of references from PubMed, Web of Science and SciFinder® and the combined number of references after removal of duplicates for grayanotoxins

<table>
<thead>
<tr>
<th>Area</th>
<th>PubMed</th>
<th>Web of Science</th>
<th>SciFinder®</th>
<th>Combined total</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>256</td>
<td>628</td>
<td>260</td>
<td>652</td>
</tr>
</tbody>
</table>

Table 3: Total number of references from PubMed, Web of Science and SciFinder® and the combined number of references after removal of duplicates for 5-HMF

<table>
<thead>
<tr>
<th>Area</th>
<th>PubMed</th>
<th>Web of Science</th>
<th>SciFinder®</th>
<th>Combined total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>901</td>
<td>2,127</td>
<td>2,298</td>
<td>3,862</td>
</tr>
<tr>
<td>2b</td>
<td>3</td>
<td>13</td>
<td>26</td>
<td>37</td>
</tr>
<tr>
<td>3b</td>
<td>7</td>
<td>198</td>
<td>29</td>
<td>221</td>
</tr>
<tr>
<td>4b</td>
<td>17</td>
<td>345</td>
<td>168</td>
<td>500</td>
</tr>
</tbody>
</table>

Table 4: Number of references found potentially relevant for each Area after the primary sorting for grayanotoxins

<table>
<thead>
<tr>
<th>Area</th>
<th>Number of references</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>190</td>
</tr>
<tr>
<td>2a</td>
<td>31</td>
</tr>
<tr>
<td>3a</td>
<td>7</td>
</tr>
<tr>
<td>4a</td>
<td>94</td>
</tr>
<tr>
<td>5a</td>
<td>184</td>
</tr>
<tr>
<td>6a</td>
<td>97</td>
</tr>
</tbody>
</table>
Objective 3

Task 3 Selection of all relevant studies retrieved by the extensive literature searches

The final protocol and project plan implemented by the Contractor to carry out the project was submitted to EFSA on 10 July 2020 (by e-mail) as part of the draft final deliverable.

Grayanotoxins

The total number of relevant references for grayanotoxins Area 1a-6a is presented in Table 5.

Table 5: The total number of relevant references for grayanotoxins found for each Area

<table>
<thead>
<tr>
<th>Area</th>
<th>Number of relevant references</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>71</td>
</tr>
<tr>
<td>2a</td>
<td>3</td>
</tr>
<tr>
<td>3a</td>
<td>5</td>
</tr>
<tr>
<td>4a</td>
<td>75</td>
</tr>
<tr>
<td>5a</td>
<td>141</td>
</tr>
<tr>
<td>6a</td>
<td>78</td>
</tr>
</tbody>
</table>

5-HMF

The total number of relevant references for 5-HMF Area 1b-4b is presented in Table 6.

Table 6: The total number of relevant references for 5-HMF found for each Area

<table>
<thead>
<tr>
<th>Area</th>
<th>Number of relevant references</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>55</td>
</tr>
<tr>
<td>2b</td>
<td>14</td>
</tr>
<tr>
<td>3b</td>
<td>15</td>
</tr>
<tr>
<td>4b</td>
<td>8</td>
</tr>
</tbody>
</table>

Summary tables

A proposal for the information (eligibility criteria) to be included in the summary tables for each Area (1a-6a and 1b-4b) was submitted to EFSA on 24 April 2020, (e-mail) as part of Deliverable 1. The proposed summary tables were discussed with EFSA at the kick-off meeting on 29 April 2020. EFSA had a few suggestions for revisions, which were agreed at the kick-off meeting, and reflected in the minutes accepted by EFSA 6 May 2020 (e-mail).

Summary tables (Excel files) with at least 10 motivated excluded papers per group of substances and 10 motivated included papers per group of substances were submitted to EFSA on 18 May 2020, (email) as part of Deliverable 2. These summary tables were discussed with EFSA at the interim meeting on 25 May 2020. EFSA had a few suggestions for revisions, which were agreed at the interim meeting and reflected in the minutes accepted by EFSA May 27 2020 (MS-TEAMS). At the interim meeting EFSA supplied DTU with a Technical Report from EFSA on honey from rhododendron for use in plant protection as rodenticide (EFSA, 2016). This report was not identified in the ELS, but is included in the reference list (Section 6).

Summary tables (Excel files) were prepared, one table for each Area 1a-6a (grayanotoxins) and 1b-4b (5-HMF). The summary tables include all pertinent information for each of the references in the 'Relevant' category as identified by the eligibility criteria suggested by the Contractor and agreed by EFSA, which could be retrieved from the title and abstract (when available). For the grayanotoxins an
3.3.1.1. **EndNote™ files**

In the EndNote™ files (one file for the grayanotoxins and one file per Area for 5-HMF) all references were separated in two folders:

- 1. Relevant – green: Containing references evaluated to be of relevance for this procurement.
- 2. Not relevant: Containing references evaluated not to be in-scope for this procurement.

A total of 20 EndNote™ files were submitted to EFSA on 10 July 2020, (by e-mail) as part of the draft final deliverable.

3.3.1.2. **Reference lists**

All relevant references from each Area 1a-6a (grayanotoxins) and Area 1b-4b (5-HMF) were collected in a reference list (Word file). The reference lists are included in Appendix C to this report.

4. **Conclusions**

An ELS to identify and collect all studies related to the toxicity of grayanotoxins and 5-HMF was performed in the three databases PubMed, Web of Science and SciFinder® for six and four Areas, respectively.

The combined number of references from each database was 652 for the grayanotoxins and 3862 from Area 1b, 37 from Area 2b, 221 from Area 3b, and 500 from Area 4b for 5-HMF.

The evaluation of all retrieved references for relevance by screening of the title and abstract (if available) and applying eligibility criteria (inclusion/exclusion) resulted in a total number of relevant references for grayanotoxins for Area 1a of 71, for Area 2a of 3, for Area 3a of 5 for Area 4a of 75, for Area 5a of 141, and for Area 6a of 78 and for 5-HMF for Area 1b of 55, for Area 2b of 14, for Area 3b of 15, and for Area 4b of 8.
References


EFSA (European Food Safety Authority), 2017. Technical report on the outcome of the consultation with Member States and EFSA on the basic substance application for honey from rhododendron for use in plant protection as rodenticide. EFSA supporting publication 2017:EN-1155. 54 pp.


### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS</td>
<td>Chemical abstract service</td>
</tr>
<tr>
<td>ELS</td>
<td>Extensive literature search</td>
</tr>
<tr>
<td>EPA</td>
<td>Environmental protection agency</td>
</tr>
<tr>
<td>GC</td>
<td>Gas chromatography</td>
</tr>
<tr>
<td>HFCS</td>
<td>High fructose corn syrup</td>
</tr>
<tr>
<td>5-HMF</td>
<td>5-hydroxymethylfurfural</td>
</tr>
<tr>
<td>HPLC</td>
<td>High performance liquid chromatography</td>
</tr>
<tr>
<td>ICP-MS</td>
<td>Inductively coupled plasma mass spectrometry</td>
</tr>
<tr>
<td>LC-MS</td>
<td>Liquid chromatography mass spectrometry</td>
</tr>
<tr>
<td>MoA</td>
<td>Mode of action</td>
</tr>
<tr>
<td>OECD</td>
<td>Organisation for economic co-operation and development</td>
</tr>
<tr>
<td>CAS</td>
<td>Chemical abstract service</td>
</tr>
<tr>
<td>ELS</td>
<td>Extensive literature search</td>
</tr>
</tbody>
</table>
Appendix A — Log file for the tailored search strings to retrieve all relevant data pertinent to the risk assessment and characterisation of grayanotoxins

Database: **PubMed**

Limitations applied to search: Language = English

Date of search May 1, 2020

<table>
<thead>
<tr>
<th>Search terms</th>
<th>No of references</th>
<th>Comments &amp; follow-up actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>grayano* OR andromedotoxin* OR acetylandromedol* OR rhodotoxin* OR asebotoxin* OR grayanane*</td>
<td>256</td>
<td>Imported to EndNote™</td>
</tr>
</tbody>
</table>

Database: **WoS (All Databases)**

Limitations applied to search: Language = English

Date of search May 12, 2020

<table>
<thead>
<tr>
<th>Search terms</th>
<th>No of references</th>
<th>Comments &amp; follow-up actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>grayano* OR andromedotoxin* OR acetylandromedol* OR rhodotoxin* OR asebotoxin* OR grayanane*</td>
<td>628</td>
<td>Imported to EndNote™</td>
</tr>
</tbody>
</table>

Database: **SciFinder®**

Limitations applied to search: Language = English; exclude patents.

Date of search May 7, 2020

<table>
<thead>
<tr>
<th>Search terms</th>
<th>No of references</th>
<th>Comments &amp; follow-up actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>4720-09-6 OR 4678-44-8 OR 4678-45-9 OR 30272-17-4 OR 30272-18-5 OR 30460-36-7 OR 30460-59-4 OR 30460-60-7 OR 30460-58-3 OR 36660-75-0 OR 33880-98-7 OR 35928-08-6 OR 35928-07-5 OR 39012-12-9 OR 39012-13-0 OR 59740-27-1 OR 70474-76-9 OR 75829-08-2</td>
<td>260</td>
<td>Imported to EndNote™</td>
</tr>
</tbody>
</table>
### Extensive literature search on grayanotoxins and 5-hydroxymethylfurfural

**Appendix B** — Log file for the tailored search strings to retrieve all relevant data pertinent to the risk assessment and characterisation of 5-HMF

Database: PubMed (All fields)

**Date of search May 18, 2020**

<table>
<thead>
<tr>
<th>Search #</th>
<th>Search terms</th>
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</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5-hydroxymethylfurfural OR HMF OR 5-HMF OR 5-hydroxymethyl-2-furfuraldehyde OR 5-(hydroxymethyl)furan-2-carbaldehyde</td>
<td>2312</td>
<td>#1</td>
</tr>
<tr>
<td>2</td>
<td>chem* OR analy* OR identi* OR charact* OR detect* OR determin* OR method* OR form* OR degrad* OR hydroly* OR reaction* OR GC OR HPLC OR LC-MS OR ICP-MS</td>
<td>17552028</td>
<td>#3</td>
</tr>
<tr>
<td>3</td>
<td>honey OR syrup OR fructose OR HFCS OR sugar OR bee OR stingless bee OR honey bee OR honeybee* OR honey-bee* OR bumblebee* OR solitary bee OR apis OR pollinator</td>
<td>554437</td>
<td>#6</td>
</tr>
<tr>
<td>4</td>
<td>#1 AND #2</td>
<td>2086</td>
<td>#4</td>
</tr>
<tr>
<td>5</td>
<td>#3 AND #4</td>
<td>901</td>
<td>#13 Area 1b imported to EndNote™</td>
</tr>
<tr>
<td>6</td>
<td>honey OR syrup OR fructose OR HFCS OR sugar</td>
<td>532271</td>
<td>#7</td>
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<td>7</td>
<td>bee feed</td>
<td>221</td>
<td>#8</td>
</tr>
<tr>
<td>8</td>
<td>#1 AND #6</td>
<td>947</td>
<td>#14</td>
</tr>
<tr>
<td>9</td>
<td>#7 AND #8</td>
<td>3</td>
<td>#15 Area 2b imported to EndNote™</td>
</tr>
<tr>
<td>10</td>
<td>bee feed OR bee OR stingless bee OR honeybee* OR honey bee OR honey-bee* OR bumblebee* OR solitary bee OR apis OR pollinator</td>
<td>28691</td>
<td>#12</td>
</tr>
<tr>
<td>11</td>
<td>toxicokinetic* OR absorp* OR distribution OR metaboli* OR excret* OR vitro</td>
<td>7880649</td>
<td>#9</td>
</tr>
<tr>
<td>12</td>
<td>#1 AND #10</td>
<td>40</td>
<td>#16</td>
</tr>
<tr>
<td>13</td>
<td>#11 AND #12</td>
<td>7</td>
<td>#17 Area 3b imported to EndNote™</td>
</tr>
<tr>
<td>14</td>
<td>toxic* OR survi* OR morta* OR hatch* OR lethal* OR chronic* OR repro* OR offspring OR brood OR colony collapse disorder OR CCD OR diet* OR consump* OR behaviour OR feed* OR abnormalities* OR cramp* OR moribund OR apathy OR vomit* OR lethargy OR ataxia OR OECD 213 OR OECD 245 OR OPPTS 850.3020</td>
<td>8689534</td>
<td>#10</td>
</tr>
<tr>
<td>15</td>
<td>#12 AND #14</td>
<td>17</td>
<td>#18 Area 4b imported to EndNote™</td>
</tr>
</tbody>
</table>
Database: WoS

For Area 1b only:
Limitations applied to search: Language = English.

Date of search May 15, 2020

<table>
<thead>
<tr>
<th>Search #</th>
<th>Search terms</th>
<th>No of references</th>
<th>Comments &amp; follow-up actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5-hydroxymethylfurfural OR HMF OR 5-HMF OR 5-hydroxymethyl-2-furfuraldehyde OR 5-(hydroxymethyl)furan-2-carbaldehyde</td>
<td>6,169</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>chem* OR analy* OR identi* OR charact* OR detect* OR determin* OR method* OR form* OR degrad* OR hydroly* OR reaction* OR GC OR HPLC OR LC-MS OR ICP-MS</td>
<td>30,910,682</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>honey OR syrup OR fructose OR HFCS OR sugar OR bee feed OR bee OR stingless bee OR honey bee OR honey-bee OR bumblebee OR solitary bee OR apis OR pollinator</td>
<td>325,423</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>#1 AND #2</td>
<td>5,613</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>#4 AND #3</td>
<td>2,618</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>#5 and exclusion of categories ENERGY FUELS, MATERIALS SCIENCE and POLYMER SCIENCE</td>
<td>2,127</td>
<td>Area 1b imported to EndNote™</td>
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<tr>
<td>7</td>
<td>5-hydroxymethylfurfural OR HMF OR 5-HMF OR 5-hydroxymethyl-2-furfuraldehyde OR 5-(hydroxymethyl)furan-2-carbaldehyde</td>
<td>6,324</td>
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<td>8</td>
<td>honey OR syrup OR fructose OR HFCS OR sugar</td>
<td>293,215</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Bee feed</td>
<td>2,647</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>#7 AND #8 AND #9</td>
<td>13</td>
<td>Area 2b imported to EndNote™</td>
</tr>
<tr>
<td>11</td>
<td>(bee* OR stingless bee* OR honey bee* OR honeybee* OR honey-bee* OR bumblebee* OR solitary bee* OR apis OR pollinator)</td>
<td>8,661,437</td>
<td></td>
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<tr>
<td>12</td>
<td>(toxicokinetic* OR absorp* OR distribution OR metaboli* OR excret* OR vitro)</td>
<td>6,403,659</td>
<td></td>
</tr>
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<td>13</td>
<td>#7 AND #11</td>
<td>1382</td>
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</tr>
<tr>
<td>14</td>
<td>#13 AND #12</td>
<td>198</td>
<td>Area 3b imported to EndNote™</td>
</tr>
<tr>
<td>15</td>
<td>(toxic* OR survi* OR morta* OR hatch* OR lethal* OR chronic* OR repro* OR offspring OR brood OR colony collapse disorder OR CCD OR diet* OR consump* OR behaviour OR feed* OR abnormalities* OR cramp* OR moribund OR apathy OR vomit* OR lethargy OR ataxia OR OECD 213 OR OECD 245 OR OPPTS 850.3020)</td>
<td>10,617,779</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>#13 AND #15</td>
<td>345</td>
<td>Area 4b imported to EndNote™</td>
</tr>
</tbody>
</table>
Database: SciFinder®

Limitations applied to search: Language: English, Publication types: clinical trials, journals, preprints and reviews.

Date of search May 17, 2020

<table>
<thead>
<tr>
<th>Search #</th>
<th>Search terms</th>
<th>No of references</th>
<th>Comments &amp; follow-up actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67-47-0</td>
<td>10424</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>#1 AND (chem OR analy OR identi OR charact OR detect OR deterin OR method OR form OR degrad OR hydroly OR reaction OR GC OR HPLC OR LC-MS OR ICP-MS)</td>
<td>9577</td>
<td>The 9577 are based on excluding Medline due to a large number of hits (SciFinder search in Medline and CAPLUS)</td>
</tr>
<tr>
<td>3</td>
<td>#2 AND (bee OR stingless bee OR honey bee OR honeybee OR honey-bee OR bumblebee OR solitary bee OR apis OR pollinator)</td>
<td>168</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>#2 AND (honey OR syrup OR fructose OR HFCS OR sugar)</td>
<td>3657</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>#2 AND (bee feed)</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>#3 AND #4 AND #5</td>
<td>3672</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>#6 NOT (waste oil OR one-pot OR zirconium OR ruthenium OR silver OR fuel OR biofuel OR bamboo OR eutectic OR ferment OR humins)</td>
<td>2298</td>
<td>Area 1b imported to EndNote™ (only search in CAPLUS)</td>
</tr>
<tr>
<td>8</td>
<td>#1 AND (honey OR syrup OR fructose OR HFCS OR sugar)</td>
<td>3657</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>#1 AND (bee feed)</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>#8 AND #9</td>
<td>26</td>
<td>Area 2b imported to EndNote™</td>
</tr>
<tr>
<td>11</td>
<td>#1 AND (toxicokinetic OR absorp OR distribution OR metaboli OR excret OR vitro)</td>
<td>2110</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>#1 AND (bee OR stingless bee OR honey bee OR honeybee OR honey-bee OR bumblebee OR solitary bee OR apis OR pollinator)</td>
<td>172</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>#11 AND #12</td>
<td>29</td>
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</tr>
<tr>
<td>14</td>
<td>#1 AND (toxic OR survi OR morta OR hatch OR lethal OR chronic OR repro OR offspring OR brood OR colony collapse disorder OR CCD OR diet OR consump OR behaviour OR feed OR abnormalities OR cramp OR moribund OR apathy OR vomit OR lethargy OR ataxia OR OECD 213 OR OECD 245 OR OPPTS 850.3020)</td>
<td>2663</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>#12</td>
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<td></td>
</tr>
<tr>
<td>16</td>
<td>#14 AND #15</td>
<td>168</td>
<td>Area 4b imported to EndNote™</td>
</tr>
</tbody>
</table>
Appendix C – Reference lists

Grayanotoxins Area 1a: Data on chemical identification, characterization and formation


Extensive literature search on grayanotoxins and 5-hydroxymethylfurfural


Extensive literature search on grayanotoxins and 5-hydroxymethylfurfural


**Grayanotoxins Area 2a: Data on occurrence in food**


**Grayanotoxins Area 3a: Data on toxicokinetics (absorption, distribution, metabolism, excretion) in experimental animals and humans and from in vitro studies**


**Grayanotoxins Area 4a: Data on toxicity in experimental animals and in vitro**


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Extensive literature search on grayanotoxins and 5-hydroxymethylfurfural


Extensive literature search on grayanotoxins and 5-hydroxymethylfurfural


Ottesen, A. R., & Magnuson, B. A. (2010). **Naturally Occurring Toxins in Plants.**


Grayanotoxins Area 5a: Data on in vitro and in vivo genotoxicity and mode of action


Extensive literature search on grayanotoxins and 5-hydroxymethylfurfural


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**Grayanotoxins Area 6a: Data on observations in humans (including epidemiological studies, case reports, biomarkers of exposure)**


Extensive literature search on grayanotoxins and 5-hydroxymethylfurfural


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5-HMF Area 1b: Data on chemical identification, characterisation and formation


Extensive literature search on grayanotoxins and 5-hydroxymethylfurfural


Extensive literature search on grayanotoxins and 5-hydroxymethylfurfural


5-HMF Area 2b: Data on occurrence in bee feed and honey

Extensive literature search on grayanotoxins and 5-hydroxymethylfurfural


Kilic, O., Kutlu, M. A., & Ozdemir, F. A. (2016). Examination of the various chemical properties of the Hizan region (Bitlis-Turkey) honey types. PROGRESS IN NUTRITION, 18(4), 411-420.


5-HMF Area 3b: Data on toxicokinetics (absorption, distribution, metabolism, excretion) in bees and from *in vitro* studies


**5-HMF Area 4b: Data on toxicity in bees**


