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Overall conclusions on the application for approval of *Quassia amara* L. wood as a basic substance to be used in plant protection as an insecticide and repellent in pome fruit, stone fruit, hop and ornamentals

European Food Safety Authority (EFSA)

Abstract

The European Food Safety Authority (EFSA) was asked by the European Commission to provide scientific assistance with respect to the evaluation of applications received in accordance with Article 23 of Regulation (EC) No 1107/2009 concerning basic substances. This evaluation was requested by way of a specific mandate from the European Commission following the submission of an application for approval of *Quassia amara* L. wood as a basic substance to be used in plant protection as an insecticide and repellent in pome fruit, stone fruit, hop and ornamentals. This report summarises the outcome of the public and targeted consultations with Member States and EFSA, and presents EFSA's scientific views on the individual comments received including the overall conclusions with the main findings on the application.

Key words: *Quassia amara* L. wood, basic substance, application, consultation, plant protection, pesticide

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Correspondence: pesticides.peerreview@efsa.europa.eu

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Summary

In accordance with Article 23(3) of Regulation (EC) No 1107/2009, the European Commission received an application from IFOAM (International Federation of Organic Agriculture Movements) Organics Europe for approval of *Quassia amara* L. wood as a 'basic substance'. Regulation (EC) No 1107/2009 defines 'basic substances' as active substances, not predominantly used as plant protection products but which may be of value for plant protection and for which the economic interest in applying for approval may be limited. Article 23 of Regulation (EC) No 1107/2009 lays down specific provisions for consideration of applications for approval of basic substances.

The current report summarises the outcome of the public and targeted consultations organised by EFSA on the application for approval of *Quassia amara* L. wood as a basic substance for use for plant protection purpose, and presents EFSA's scientific views on the individual comments received in the format of a reporting table, including EFSA's overall conclusions with the main findings on the application.

Quassia amara L. wood is a botanical active substance and it is available on the **EU market** with a description for use in the preparation of a herbal infusion, both with and without medicinal claims. The **formulation** to be used **for plant protection purpose** is a soluble concentrate (SC) prepared by the farmer/operator by boiling *Quassia amara* L. wood in water. After cooling down, the extract is sieved and diluted with water before application. The extract of the wood of *Quassia amara* L. is intended to be used as an **insecticide** and **repellent** against aphids, sawflies in pome fruit and stone fruit, against aphids in hop and against white fly in ornamentals. Application is performed by field spraying, or drenching in greenhouse (permanent) ornamental crops.

It is noted that the use on ornamentals via drench application in greenhouse (permanent) was proposed by the applicant after the applicant's commenting window during the ongoing assessment and included in the updated application (IFOAM Organics Europe, 2024). Since this proposed additional use was not part of the initial application, it could not be commented on by Member States and the public. The EFSA considerations on this additional use have been presented in the relevant sections as appropriate.

The impact on **human and animal health** of the proposed basic substance (and the formulation prepared by the farmer for the intended uses) has been assessed on the basis of toxicological studies and published studies identified through a literature search. Further information is needed to conclude on genotoxicity and on the possible reproductive and endocrine effects. Robust toxicological reference values cannot be derived on the basis of the available information, and the non-dietary risk assessment could not be concluded.

In the area of **residues**, the consumer risk assessment could not be finalised for all intended uses except ornamentals. Notably, sufficient information on the toxicological profile of this proposed basic substance (and the formulation intended for plant protection use) is not available. Neither could an alternative assessment approach conclusively demonstrate that the additional exposure to *Quassia amara* L. wood from the plant protection use is negligible compared to the exposure by other dietary routes, e.g. from the use of *Quassia amara* L. as a source material to produce flavourings or food ingredients with flavouring properties. For the use on ornamentals, a consumer risk assessment can be waived due to an insignificant dietary exposure potential.

In the area of **fate and behaviour in the environment,** the exposure assessment of the components of the *Quassia amara* L. wood aqueous extract and its transformation products other

than quassin is not addressed. A robust justification for the consideration of quassin as the only relevant lead compound for the environmental exposure assessment of *Quassia amara* L. wood extract is not available. A groundwater exposure assessment addressing the various components of this proposed basic substance (and the formulation intended for plant protection use) is not available. Should any of these components leach through soil to groundwater, their toxicological profile would require clarification.

As regards the **effects on non-target organisms**, a low risk can be concluded for aquatic organisms (acute risk), bees and non-target arthropods other than bees, and soil organisms for the proposed field uses. For other non-target organisms, it was not possible to conclude a low risk for the proposed field uses. Considering the intended use in greenhouses (permanent), minimal exposure can be expected for birds and mammals, bees and other non-target arthropods, soil organisms, biological methods of sewage treatment and non-target terrestrial plants, and a low risk can be concluded. For aquatic organisms, a low acute risk can be concluded for the use in permanent greenhouses, while further data are needed to confirm a low chronic risk. Further data are also needed to conclude on the potential concern for endocrine disruption in wild mammals and fish.

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1. Introduction

1.1. Background and terms of reference as provided by the requestor

Regulation (EC) No 1107/2009[1] (hereinafter referred to as 'the Regulation') defines 'basic substances' as active substances, not predominantly used as plant protection products but which may be of value for plant protection and for which the economic interest of applying for approval may be limited. Article 23 of the Regulation lays down specific provisions to identify a substance as a basic substance with a view to ensure that such active substances that do not have an immediate or delayed harmful effect on human and animal health nor an unacceptable effect on the environment can be approved as 'basic' and used for plant protection purposes.

Quassia amara L. wood is an active substance for which, in accordance with Article 23(3) of the Regulation, the European Commission received an application from IFOAM (International Federation of Organic Agriculture Movements) Organics Europe for approval as a basic substance to be used in plant protection as an insecticide and repellent in pome fruit, stone fruit, hop and ornamentals.

The European Food Safety Authority (EFSA) organised the following consultations on the application for approval of *Quassia amara* L. wood as a basic substance in accordance with the procedure described in the Commission working document on the approval of basic substances (SANCO/1063/2012, revision 10; European Commission, 2021):

- From 27/04/2023 – 18/05/2023, EFSA conducted a **public consultation** on the non-confidential version of the application with a view to identify whether other relevant scientific data or studies are available. In addition, interested parties were also invited to provide additional information on eventual further uses of the substance for plant protection purpose which are beyond the uses supported by the applicant.

  Additional uses were not proposed as a result of the public consultation.

- From 11/07/2023 – 12/09/2023, EFSA conducted a **targeted consultation** with Member States on the application for approval of *Quassia amara* L. wood as a basic substance and on eventual comments received during the public consultation. In this context, Member States were further given the possibility to provide additional information on possible uses of the substance which are beyond the uses supported by the applicant, and / or proposing extensions of the scope of the application to further crops, if any.

  Additional uses were not proposed as a result of the targeted consultation.

All the comments received during the public and targeted consultations, including EFSA's own comments and observations, were collated and consolidated by EFSA in the format of a structured reporting table. Subsequently, the applicant was invited to address the comments and to provide an updated application as appropriate, within a period of 60 days. This deadline was extended upon the request of the applicant to 29 February 2024 and then to 30 June 2024. The comments received and the response of the applicant thereon, together with the updated

[1] Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ L 309, 24.11.2009, p. 1-50.

application submitted by the applicant on 28 June 2024, were considered by EFSA when finalising the reporting table.

The current report summarises the outcome of the public and targeted consultations organised by EFSA on the application for approval of *Quassia amara* L. wood as a basic substance for use for plant protection purpose, and presents EFSA's scientific views on the individual comments received, including EFSA's overall conclusions with the main findings on the application.

As an endorsement before finalisation of the Technical Report, a written consultation with Member States on the final conclusions reached took place in November 2024.

The application and, where relevant, any update thereof submitted by the applicant for approval of *Quassia amara* L. wood as a basic substance in the context of Article 23 of the Regulation, is a key supporting document, therefore it is considered as background documentation to this report and is also made publicly available (IFOAM; 2024). Likewise, supporting documents, if any, provided during the public or targeted consultations are also considered as background documents to the Technical Report. Member State comments received on the draft Technical Report have also been made publicly available.

EFSA carried out a literature search to complement the application dossier provided, where impact on human and animal health, fate and behaviour in the environment and effects on non-target organisms was the search target. The search terms and strings used to conduct this literature search and the search results are reported in Appendix H.

1.2. Interpretation of the Terms of Reference

On 20 August 2021, by means of a general framework mandate, the European Commission requested EFSA to provide scientific assistance with respect to the evaluation of applications concerning basic substances in accordance with the procedure described in the Commission working document on the approval of basic substances (SANCO/1063/2012 revision 10; European Commission, 2021) in view of the implementation of Regulation (EU) No 2019/1391 (i.e. the 'Transparency Regulation' [2]).

On the basis of a specific mandate received from the European Commission in July 2024, after the end of the applicant's consultation period, EFSA was requested to complete the reporting table concerning the risk assessment for approval of *Quassia amara* L. wood as basic substance and, based thereon, provide its scientific opinion on the application to the Commission in accordance with Article 23 of Regulation (EC) No 1107/2009, within 3 months from the reception of the specific mandate.

For this purpose, a Technical Report has been prepared by EFSA containing the finalised reporting table and EFSA's overall conclusions with the main findings on the application for approval of *Quassia amara* L. as a basic substance for use in plant protection as an insecticide and repellent in pome fruit, stone fruit, hop and ornamentals.

On the basis of the Technical Report, the European Commission will decide on a case-by-case basis whether to request EFSA for further scientific or technical assistance as deemed appropriate for decision making purpose.

[2] Regulation (EU) 2019/1381 of the European Parliament and of the Council of 20 June 2019 on the transparency and sustainability of the EU risk assessment in the food chain; OJ L 231, 6.9.2019, p. 1–28

2. Assessment

The comments received on the application for approval of *Quassia amara* L. wood as a basic substance for use in plant protection as an insecticide and repellent in pome fruit, stone fruit, hop and ornamentals, and the conclusions drawn by EFSA on the specific points raised have been presented in the format of a reporting table.

The comments including eventual proposals for updating the application received during the public and targeted consultations with Member States and EFSA are summarised in columns 2 and 3 of the reporting table. The applicant's consideration of the comments, where available, has been provided in column 4, while EFSA's scientific views and conclusions have been outlined in column 5 of the reporting table.

The finalised reporting table is provided in Appendix A of this report. In addition, an overview table on the identity, mode of use and function of the substance, as well as the list of intended uses for plant protection purpose (GAP table) are provided in Appendix C and E, respectively. The EFSA considerations with respect to compliance with the eligibility criteria for the substance to be approved as a basic substance as set out in Article 23 of Regulation (EC) No 1107/2009 have been provided in Appendix D.

An overview of the main findings for each area of the risk assessment, also considering the comments in the completed reporting table as well as EFSA's overall conclusions on the application, including EFSA's views on whether the substance has neither an immediate or delayed harmful effect on human or animal health nor an unacceptable effect on the environment taking into consideration the proposed conditions of use, are presented below.

3. Overall conclusions and main findings on the application for approval as a basic substance

3.1 Identity of the substance/product as available on the market and predominant use, and as proposed for plant protection purpose

The proposed **basic substance is the *Quassia amara* L. wood**. *Quassia amara* L. wood is a botanical active substance and it is available on the EU market with a description for use in the preparation of a herbal infusion, both with and without medicinal claims (see reporting table point 2(4)), and it is sold as pure *Quassia amara* L. wood or in a blend with other botanicals e.g. *Picrasma excelsa* Planch[3]. Relevant **specifications** for *Quassia amara* L. wood do not exist in authorisations/approvals/evaluations in other regulatory context. Based on the information provided by the applicant, it is proposed that the *Quassia amara* L. wood should contain 0.5 to 1.18 g quassin/kg wood, measured using an ethanol:water (30:70) extraction (see reporting table point 2(15)).

The **formulation to be used for plant protection purpose** is a soluble concentrate (SC) prepared by the farmer/operator by boiling 20 kg of *Quassia amara* L. wood in 100 L of water for 1 hour. After cooling down, the extract is sieved, and diluted with water according to the intended GAP uses before application. During the drafting of this report EFSA became aware that material described as '*From the wood of the Quassia plant*' may be available in Germany with

[3] e.g. Quassia, wood (Picrasma excelsa Planch./Quassia amara L.) https://www.officinaliserboristeria.it/en/negozio/quassia-wood-picrasma-excelsa-planch-quassia-amara-l/

indications for use to control sawflies (*Hoplocampa* spp.) in pome and stone fruit in the field under the name Quassia-Extract-MD[4]. According to the company's website[4], the active ingredient is obtained as a powdery plant extract in a specially developed process. Based on this finding it might be considered that Article 23(d) of Regulation (EC) No 1107/2009 is not fulfilled.

The water extract of *Quassia amara* L. wood is a **mixture of several components** which occur in the wood of this shrub. The main component in the water extract is quassin, which is used as a lead substance to qualify the extract. It is noted that not all analytical lead substances in the water extract, prepared according to the description of the preparation to be used, were identified or quantified (see reporting table points 2(12), 2(14) and 7(22)) (**data gap**, see section 4). In addition, the applicant claimed that the amount of quassin extracted with water equals to 50% of the quassin extracted when ethanol:water (30:70) is used, however no data were provided to support such a claim.

The water extract of the wood of *Quassia amara* L. is intended to be used as an **insecticide** and **repellent** against aphids, sawflies in pome fruit and stone fruit, against aphids in hop and against white fly in ornamentals. Application is performed by field spraying, or drenching in greenhouse (permanent) ornamental crops. Sufficient information was provided to demonstrate the **usefulness** of the water extract of *Quassia amara* L. wood for plant protection purposes against aphids and sawflies, though that to support the control of white fly in ornamentals by drenching was limited.

3.2 Impact on human and animal health

Quassia amara L. wood extracts (aqueous, others) have been tested for **genotoxicity** *in vitro* and *in vivo*, partially addressing the assessment of the formulation intended for plant protection use. Detailed *in silico* analyses of the mixture components (once they are adequately identified) should be provided to conclude on genotoxicity (**data gap,** see section 4.1 and reporting table point 5(1)).

Based on the available information, *Quassia amara* L. wood extracts and the component quassin could cause adverse effects on the mammalian male and female reproductive system; moreover, it is not possible to exclude that such effects would be related to an endocrine mode of action. However, the available information is insufficient to derive solid toxicological conclusions, and currently meaningful NOAELs/LOAELs cannot be derived. Further evidence is needed to clarify the toxicological profile of this proposed basic substance (and the formulation intended for plant protection use), particularly as regards **reproductive toxicity** and **endocrine activity** (**data gap**, see section 4.1 and reporting table point 5(2)).

A **non-dietary exposure assessment** has been carried out by the applicant according to EFSA, 2022, however, in the absence of solid toxicological reference values and clear information on the composition of the extract, it cannot be finalised (**data gap**, see section 4.1).

3.3 Residues

Information of the nature of residues was not provided while some information on the magnitude of residues was submitted by the applicant. As far as the information allows, EFSA provided an assessment of the residues and provisional consumer exposure assessments in a separate **Appendix F**.

[4] https://www.trifolio-m.de/en/produkt/quassia-extract-md/?sfw=pass1730373675

To further characterise possible residues from *Quassia amara* L. wood and to evaluate the nature of the residues, i.e. the possible metabolism of the components in the wood extract after application to crops, information on the composition of the extract is a prerequisite (see **data gap** in section 3.1), but the information currently available on this is unsatisfactory. Therefore, EFSA considers that a reliable dietary exposure assessment for *Quassia amara L.* wood or its components quassin and neoquassin (and other possibly extracted biologically active components) is not possible as there isn't any robust information on the composition of the prepared and applied extract and its actual quassinoid levels.

Furthermore, a quantitative consumer risk assessment cannot be conducted for the intended uses on crops for human consumption in the absence of sufficient information on the toxicological profile of *Quassia amara* L. wood and its extract (see section 3.2 and **data gaps** in section 4.1). Neither could an alternative assessment approach conclusively demonstrate that the additional exposure to *Quassia amara* L. wood (and relevant components e.g. quassin) from the plant protection use is negligible compared to the exposure by other dietary routes, e.g. from the use of *Quassia amara* L. as a source material to produce flavourings or food ingredients with flavouring properties according to Regulation (EC) No 1334/2008 (**data gap**, see section 4.1).

EFSA is of the opinion that there is currently insufficient robust evidence to demonstrate a negligible contribution of residues from the proposed plant protection use to the dietary exposure of the EU population to *Quassia amara* L. or its components from other dietary sources. Should risk managers want to use the comparison of exposure from the plant protection use to exposure from other sources in lieu of a risk assessment using toxicological data, a more detailed study of the actual chronic and acute exposure of the general EU population to *Quassia amara* L. and its components is necessary (**data gap**, see section 4.1).

Overall, the consumer risk assessment for the intended uses on crops for human consumption cannot be finalised. A consumer risk assessment can be waived for the use on ornamentals due to an insignificant dietary exposure potential.

To mitigate the occurrence of measurable residues on crops for human consumption, an adjustment of the growth stage for the latest time of application in the GAP (currently BBCH 69, i.e. after formation of the edible part of crops) to a growth stage before BBCH 65 could be considered by the applicant and risk managers if this would make agronomic sense.

With regard to the five assessment criteria according to the Commission guidance SANCO/11188/2013 Rev. 2 (European Commission, 2015) for inclusion in Annex IV of Regulation (EC) No 396/2005, i.e.: approval as basic substance (criterion I), listed in Annex I of Regulation (EC) No 396/2005 (criterion II), having no identified hazardous properties (criterion III), exposure linked to the use as plant protection product is negligible compared to natural exposure (criterion IV) and consumer exposure is not expected considering the mode of application for the intended uses (criterion V); criteria I, II, III and V are not met while criterion IV is considered inconclusive.

3.4 Fate and behaviour in the environment

In the area of **fate and behaviour in the environment,** the exposure assessment of the components of the *Quassia amara* L. wood aqueous extract and its transformation products other than the component quassin is not addressed.

Quassia amara L. wood is acknowledged to contain a number of biologically active components besides quassin (chosen by the applicant as lead compound for the environmental exposure assessment). For example, other quassinoid derivatives, carboline derivatives and canthin derivatives have been reported by the applicant as components of the *Quassia amara* L. wood extracts, the environmental fate of which in soil cannot be considered addressed by what has been provided to date. In the updated application the following compounds were listed by the applicant: neoquassin, isoquassin, parain, quassimarin and quassinol. However, the relative amount of these compounds in the water extract of *Quassia amara* L. wood is unknown. A detailed consideration of all the known biological active components of *Quassia amara* L. wood and the necessary information on their persistence and fate in the environment is not available. A robust justification for the consideration of quassin as the only relevant lead compound for the environmental exposure assessment is not available (see **data gaps** and outstanding issues identified in sections 4.1 and 4.2).

A groundwater exposure assessment addressing the various components in the wood extract is not available. Should any of these components leach through soil to groundwater, their toxicological profile would require clarification (**data gap**, see section 4.1).

3.5 Effects on non-target organisms

Overall, the available toxicity data do not allow to conclude on effects for **birds**. Few details are available regarding non-dietary route of exposure through the skin due to detergent uses. Repellent effects are reported. The dietary route of exposure has not been assessed by the applicant. The information provided is quantitatively and qualitatively scarce. A risk assessment has not been provided, nor a sound and scientifically justified weight of evidence (**data gap**, see section 4.1). A safe use cannot be identified for the proposed field uses. Considering the proposed intended use in greenhouses (permanent), minimal exposure can be expected for birds and a low risk can be concluded.

For **wild mammals**, limited information was provided in the application. Few details on the potential repellent effect are reported. While it is reported that *Q. amara wood* has a long history of safe use, no quantitative information is provided to support this statement. Literature studies seem to indicate that an effect on reproduction can be observed (see section 3.2 and **data gap** in section 4.1). Based on the data from Raji et al. (2010), an illustrative NOAEL of 1.0 mg quassin/kg bw per day can be derived based on effects on reproduction in mammals. This is much lower than what is indicated in the application (i.e. NOAEL > 17.4 mg/kg bw per day). The outcome of the reproductive screening assessment with a NOAEL of 1.0 mg quassin/kg bw per day indicates a high risk to mammals from the intended uses in hop, pome- and stone fruits. Considering the proposed intended use in greenhouses (permanent), minimal exposure can be expected for mammals and a low risk can be concluded.

Acute toxicity data are available for fish and aquatic invertebrates. The dossier lacks chronic toxicity data and an appropriate assessment for the chronic risk to fish and aquatic invertebrates. However, the available data and lack of reported adverse effects in literature can indicate a favourable ecotoxicological profile for **aquatic organisms**. Consequently, for fish, aquatic invertebrates and algae a low acute risk can be concluded based on the available information for all intended uses. However, considering (i) the lack of data to address potential long-term and delayed effects, (ii) the potential concern identified for the endocrine disruption potential in mammals (see section 3.2), and (iii) that the assessment is based only on acute toxicity data, further data would be needed to confirm a conclusion of low chronic risk for all intended uses,

and exclude any potential effect related to an endocrine mode of action (see **data gap** in section 4.1 and minor outstanding issues in section 4.2).

For **bees**, acute oral and contact toxicity studies and literature studies were available. For **non-target arthropods** other than bees, information was available from the open peer reviewed literature. The available data and the lack of adverse effects reported in literature indicate a favourable ecotoxicological profile for bees and non-target arthropods. Therefore, a low risk can be concluded for all intended uses (see also minor outstanding issues in section 4.2).

A low risk can be concluded for **earthworms, soil macro and microorganisms** based on the information available for all intended uses (see also minor outstanding issues in section 4.2).

Information was not provided to address the risk for **non-target terrestrial plants** and for **biological methods of sewage treatment**. Therefore, it is not possible to conclude on the risk for non-target terrestrial plants and biological methods of sewage treatment for the proposed field uses (**data gap**, see section 4.1). Considering the proposed use in greenhouses (permanent), minimal exposure can be expected, and therefore a low risk can be concluded.

4. Data gaps

4.1 Potential concerns

The following potential concerns and/or issues or assessments that could not be finalised have been identified that **impact on the evaluation of compliance with the criteria for eligibility** of the substance to be approved as a basic substance, as set out in Article 23 of Regulation (EC) No 1107/2009:

Preparation to be used vs test item of several studies regarding the effect on human health or on the environment:

- Applicant to provide a robust comparison of the chromatograms obtained from the water extract of *Quassia amara* L. wood chips as prepared according to the proposed recipe and the ready extract Quassia MD (i.e. the extract used as a test item in several studies regarding the effect on human health or on the environment). Further identification of the unidentified peaks in the water extracts should be provided as appropriate. In addition, this information would be needed for water extracts of five batches of commercially available *Quassia amara* L. wood in the EU (currently this information is only available for 1 or 2 batches, depending if the *Picrasma* wood is considered to represent quassia wood basic substance) (see sections 3.2-3.5 and reporting table points 2(7), 2(12), 7(2), 7(22)).

- A justification of the equivalence of the application rate in terms of kg of wood pellets and amount of quassin in the resulting extract has not been provided. The applicant should at the least provide the analysis of several (at least 5) extracts obtained from different *Quassia amara* L. wood batches in order to justify the levels of quassin (and other *Quassia amara* extract biologically active components) to have a robust justification of the levels (and associated uncertainty) assumed to be applied on the crops (see reporting table point 7(22)).

Impact on Human and Animal Health:

- Further evidence is needed to clarify the toxicological profile of the proposed basic substance (and the prepared formulation intended for plant protection use), particularly as regards genotoxicity, effects on the reproductive system and endocrine activity, taking into account the clarifications on the composition of the formulation intended for plant protection use (relevant for all intended uses, see section 3.2 and reporting table points 5(1), 5(2) and 2(12)).

  The following data are necessary:

  - Strengthened genotoxicity assessment of the formulation intended for plant protection use, with a detailed analyses of the mixture components (e.g. *in silico)*, once they are adequately identified; in general, the genotoxicity assessment of the formulation intended for plant protection use should be carried out according to EFSA Scientific Committee, 2019.

  - Robust data on the toxicological effects of the proposed basic substance, derived preparations, as well as on individual components, once identified. Focus should be, but not limited to, on effects on the reproductive system; the endocrine mode of action for the identified effects should be thoroughly discussed. The relevance of the retrieved information for the basic substance matter of this application and the formulation intended for plant protection use should be thoroughly justified.

- A risk assessment for non-dietary exposure for the proposed uses cannot be finalised (relevant for all intended uses, see section 3.2 and reporting table point 5(26)).

  The following data are necessary:

  - Toxicological data are needed to set reference values based on adequate information on the composition of the extract (see section 3.2 and reporting table point 5(26)).

Residues:

- A consumer risk assessment cannot be finalised for uses on crops for human consumption whilst sufficient information on the toxicological profile of *Quassia amara* L. wood and its prepared extract, and on the actual composition of the extract is not available (relevant for all intended uses except ornamentals, see section 3.3).

- An alternative assessment whether the dietary exposure to *Quassia amara* L. wood (and relevant components e.g. quassin) from the plant protection use is negligible compared to the exposure by other dietary routes, e.g. the use of Quassia as a source material for the production of flavourings / food ingredients having flavouring properties is provisional and inconclusive (relevant for all intended uses except ornamentals, see section 3.3).

  The following data are necessary:

  - An updated consumer exposure and risk assessment for the intended uses on crops (pome fruit, stone fruit, hops), upon demonstration that the residues at LOQ level (fruit) and actual measured residue levels (hops) in the submitted residues trials with the commercial product are applicable to the intended uses. The requested clarification on compounds that could be expected as residues on crops after application of the prepared extract from *Quassia amara* L. wood (besides quassin /

neoquassin) as well as clarification on the levels of quassin (and other extracted biologically active components) in the extract, and the requested clarification with regard to the toxicology of *Quassia amara* L. extract and its components are required for a reliable consumer risk assessment (see section 3.3 and reporting table point 6(6)).

- A robust, comprehensive assessment of chronic and acute dietary exposure to *Quassia amara* L. wood and its components from other dietary sources is required (see section 3.3 and reporting table point 6(7)).

Fate and behaviour in the environment:

- A groundwater exposure assessment addressing the various components in the wood extract is not available. Information on soil transformation products of these components is also absent from the dossier. Should any of these components or their transformation products leach through soil to groundwater, their toxicological profile would require clarification (relevant for all intended uses, see section 3.4).
- Reliable groundwater exposure modelling for quassin considering what would be the most reliable endpoints was not available. Assessments of groundwater exposure potential to quassin soil transformation products (currently unknown) and other biologically active components of *Quassia amara* L. wood extract and their soil transformation products were not available (see reporting table point 7(28)).

The following data are necessary:

- Fate and behaviour information on the biologically active components and their transformation products, particularly persistence and mobility in soil. In detail:
    - Besides quassin, *Quassia amara* L. wood extract is acknowledged to contain a number of other biologically active components. For example, other quassinoid derivatives, carboline derivatives and canthin derivatives have been reported by the applicant as components of the *Quassia amara* extract, the environmental fate of which in soil cannot be considered addressed by what has been provided to date. In the updated application the following compounds were listed by the applicant: neoquassin, isoquassin, parain, quassimarin and quassinol. However, the relative amount of these compounds in the water extract of *Quassia amara* L. wood is unknown. The applicant should discuss in detail all the known biologically active components of *Quassia amara* L. wood and provide the necessary information on their persistence and fate in the environment. Information from soil incubations in at least four soils is needed for the biologically active components of *Quassia amara* L. wood extract, in addition to quassin. Alternatively, a valid argumentation to demonstrate that such information is not necessary, such as a read across from quassin supported by scientific publications, is needed for the biologically active compounds present in the extract. If lead compounds are selected for the environmental risk assessment, their selection should be adequately justified (see section 3.4 and reporting table point 7(2)).

- Information is only available on the rate of degradation of quassin (one of the biologically active components of *Quassia amara* L. wood) in four soils. However, there is no information on its degradation products. Since soil metabolites of quassin may retain its biological activity, they need to be identified with appropriate studies (see reporting table point 7(3)).

- Information or data on the photodegradation of quassin in soil and water was not available. Also, information on the photodegradation of other *Quassia amara* L. wood components with known or presumed biological activity was not available. UV spectra can be provided for the different components of *Quassia amara* L. wood to justify the arguments provided to waive further data (e.g. in the absence of significant UV adsorption, photodegradation may be considered not relevant) (see reporting table point 7(15)).

- Batch adsorption/desorption studies on the other active components of *Quassia amara* L. wood extract that may be identified as biologically active and/or responsible for a potential impact on human health were not available. In case bridging of data on quassin is proposed, a sound scientific argumentation would need to be provided (see reporting table point 7(19)).

- Groundwater FOCUS modelling of the biologically active components and their transformation products. In the absence of reliable end points for modelling, default values can be used to demonstrate groundwater exposure potential.

Effects on non-target species:

- Data are needed to address the uncertainty regarding the derivation of the endpoints based on quassin for all non-target organisms. Any test performed with purified quassin might not cover the other components and an assessment to demonstrate that quassin is the most adequate lead compound to address the ecotoxicological risk assessment is still missing (see reporting table points 7(3), 8(24)).

- Further data are needed to clarify the ecotoxicological profile of the proposed basic substance, and in particular effects on the reproductive system and potential endocrine activity for fish and wild mammals (see also the data gap indicated under the subsection 'Impact on Human and Animal Health' in section 4.1 above).

- A risk assessment for terrestrial vertebrates relevant for the proposed field uses was not available (relevant for the intended field uses, see section 3.5 and reporting table points 8(3), 8(7)).

  The following data are necessary:

  - Toxicity data for terrestrial vertebrates to allow deriving a robust endpoint (see section 3.5 and reporting table point 8(7)).

  - Robust data on the ecotoxicological effects of the proposed basic substance considering the potential for endocrine disruption for wild mammals and fish (see section 3.5 and reporting table points 8(3), 8(10)).

- A risk assessment for non-target terrestrial plants for the proposed field uses was not available (relevant for the intended field uses, see section 3.5 and reporting table point 8(26)).

  The following data are necessary:

  - Toxicity data for non-target terrestrial plants, expanding the literature search or providing a well-substantiated weight of evidence consideration to address the risk assessment (see section 3.5 and reporting table point 8(26)).

- A risk assessment for biological methods of sewage treatment for the proposed field uses was not available (relevant for the intended field uses, see section 3.5 and reporting table point 8(27)).

  The following data are necessary:

  - Toxicity data for biological methods of sewage treatment, expanding the literature search or providing a well-substantiated weight of evidence consideration to address the risk assessment (see section 3.5 and reporting table point 8(27)).

4.2 Minor outstanding issues

The following minor outstanding issues have been identified that, although **not critically affect the assessment**, nevertheless lead to uncertainties:

- Not all analytical lead substances in the *Quassia amara* L. wood water extracts, reported in the study ENV-18-173, have been identified (relevant for all intended uses, see Section 3.1 and reporting table points 2(12), 5(1), 5(2), 6(1), 7(2)).
- Further information on possible effects of the proposed basic substance and the formulation for the intended plant protection uses on the immune system (see reporting table point 5(12)).
- An updated literature search addressing biologically/toxicologically relevant components of the substance, once identified (see reporting table point 10(1)).
- Storage stability data for quassin and neoquassin in stone fruit commodities to validate the results of the residue trials in plums (see reporting table point 6(3)).
- Information on the analytical method, including validation data, used in the 2013 residue trials in apple, plum and hops (report by [redacted], 2013) (see reporting table point 6(5)).
- Information whether the hop cone samples submitted to residue analysis from the residue trials 2013, 2014, 2015, 2018, 2019 were fresh or dried (see reporting table point 6(5)).
- The applicant would need to update the soil, surface water and groundwater exposure assessment of the component quassin with the soil DT values indicated in reporting table point 7(4), once the other data gaps in relation to the composition of the water extract that is applied, have been addressed (see also reporting table point 7(29)).
- Predicted exposure of the aquatic environment to quassin (updated with peer reviewed end points) and the other known or presumed biologically active components of *Quassia*

amara L. wood and transformation products of quassin and the other biologically active components were not available (see reporting table points 7(29) and 7(30)).

- Further data showing the lack of potential chronic and delayed adverse effects for aquatic invertebrates and for fish for all proposed uses and to allow to finalise the chronic risk assessment are needed (see section 3.5). In addition, the potential insecticidal effects should have been investigated for aquatic invertebrates (see reporting table points 8(9), 8(10), 8(28)).
- Further data are needed to address the uncertainty regarding the exposure assessment for soil organisms and as regards bees (see sections 3.4, 3.5 and reporting table points 7(2), 7(3), 7(4), 8(16)).

Documentation provided to EFSA

1. IFOAM Organics Europe, 2022. Basic substance application on *Quassia amara* L. wood submitted in the context of Article 23 of Regulation (EC) No 1107/2009. March 2022 (initial dossier).
2. IFOAM Organics Europe, 2024. Basic substance application update on *Quassia amara* L. wood submitted in the context of Article 23 of Regulation (EC) No 1107/2009. June 2024.

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EFSA (European Food Safety Authority), 2011. Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009. EFSA Journal 2011;9(2):2092, 49 pp. doi:10.2903/j.efsa.2011.2092

EFSA (European Food Safety Authority), 2018. Technical report on the outcome of the consultation with Member States and EFSA on the basic substance application for Quassia amara L. wood extract for use in plant protection as insecticide and repellent. EFSA supporting publication 2018:EN-1382. 76 pp. doi:10.2903/sp.efsa.2018.EN-1382

EFSA Scientific Committee, 2011. Scientific Opinion on genotoxicity testing strategies applicable to food and feed safety assessment. EFSA Journal 2011;9(9):2379. [69 pp.] doi:10.2903/j.efsa.2011.2379

EFSA (European Food Safety Authority), 2007. Reasoned opinion on the potential chronic and acute risk to consumers health arising from proposed temporary EU MRLs. EFSA Journal 2007; 5(3):RN-32. [1141 pp.] doi:10.2903/j.efsa.2007.32r

EFSA (European Food Safety Authority), Charistou A, Coja T, Craig P, Hamey P,Martin S, Sanvido O, Chiusolo A, Colas M and Istace F, 2022. Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment of plant protection products. EFSA Journal 2022;20(1):7032, 134 pp. doi: 10.2903/j.efsa.2022.7032

EFSA Scientific Committee, Hardy A, Benford D, Halldorsson T, Jeger MJ,Knutsen HK, More S, Naegeli H, Noteborn H, Ockleford C, Ricci A, Rychen G, Schlatter JR, Silano V,Solecki R, Turck D, Benfenati E, Chaudhry QM, Craig P, Frampton G, Greiner M, Hart A, Hogstrand C,Lambre C, Luttik R, Makowski D, Siani A, Wahlstroem H, Aguilera J, Dorne J-L, Fernandez Dumont A,Hempen M, Valtuena Martınez S, Martino L, Smeraldi C, Terron A, Georgiadis N and Younes M, 2017. Scientific Opinion on the guidance on the use of the weight of evidence approach in scientific assessments. EFSA Journal 2017;15(8):4971, 69 pp. doi: 10.2903/j.efsa.2017.4971

EFSA Scientific Committee, More S, Bampidis V, Benford D, Boesten J, Bragard C,Halldorsson T, Hernandez-Jerez A, Hougaard-Bennekou S, Koutsoumanis K, Naegeli H, Nielsen SS,Schrenk D, Silano V, Turck D, Younes M, Aquilina G, Crebelli R, Gurtler R, Hirsch-Ernst KI, Mosesso P,Nielsen E, Solecki R, Carfı M, Martino C, Maurici D, Parra Morte J and Schlatter J, 2019. Statement on the genotoxicity assessment of chemical mixtures. EFSA Journal 2019;17(1):5519, 11 pp. doi: 10.2903/j.efsa.2019.5519

European Commission, 2002. Scientific Committee on Food. Opinion of the Scientific Committee on Food on quassin. SCF/CS/FLAV/FLAVOUR/29 Final. 25 July 2002.

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

European Commission, 2015. Guidance document on criteria for the inclusion of active substances into Annex IV of Regulation (EC) N° 396/2005. SANCO/11188/2013. Rev. 2, 14 September 2015.

European Commission, 2019. Appendix D - Data requirements for setting maximum residue levels, comparability of residue trials and extrapolation of residue data on products from plant and animal origin - SANTE/2019/12752 rev.1

European Commission, 2021. Working document on the procedure for application of basic substances to be approved in compliance with Article 23 of Regulation (EC) No 1107/2009. SANCO/10363/2012 rev.11, 12 July 2023.

FOCUS (Forum for the Co-ordination of Pesticide Fate Models and their Use), 2006. Guidance document on estimating persistence and degradation kinetics from environmental fate studies on pesticides in EU Registration Report of the FOCUS Work Group on Degradation Kinetics. EC Document Reference SANCO/10058/2005-v. 2.0, 434 pp., as updated by the Generic guidance for Estimating Persistence and Degradation Kinetics from Environmental Fate Studies on Pesticides in EU Registration, v. 1.1, December 2014

Abbreviations

ADI	acceptable daily intake
a.i.	active ingredient
AOEL	acceptable operator exposure level
a.s.	active substance
BBCH	growth stage of mono- and dicotyledonous species
BMEL	Federal Ministry of Food and Agriculture (Germany)
BSA	Basic substance application
CA	competent authority
CAS	Chemical Abstracts Service
CEZ	Central European zone
C&L	classification and labelling
CLH	harmonized classification and labelling
CLP	classification, labelling and packaging
DALA	days after last application
DFOP	Double First-Order in Parallel kinetic
DNA	Deoxyribonucleic acid
DT_{50}	period required for 50% dissipation (define method of estimation)
EAS	estrogen-androgen-steroidogenesis
ECHA	European Chemicals Agency
ED	endocrine disruption
EINECS	European Inventory of Existing Commercial Chemical Substances
EPPO	European and Mediterranean Plant Protection Organization
FAO	Food and Agriculture Organization of the United Nations
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP	good agricultural practice
GD	guidance
GLP	good laboratory practice
GS	growth stage
HPLC	high-pressure liquid chromatography or high-performance liquid chromatography
HR	highest residue
HS	hockey stick kinetic
IESTI	International estimated short-term intake
ISO	International Organization for Standardization
JKI	Julius Kühn Institute (Federal Research Centre for Cultivated Plants, Germany)

LOAEL	lowest observable adverse effect level
LOQ	limit of quantification
MNA	Micronucleus assay
MRL	maximum residue level
MS	Member State
NDE	non-dietary exposure
NEU	Northern Europe
NOAEL	no observed adverse effect level
NOEL	no observed effect level
OC	organic content
OECD	Organisation for Economic Co-operation and Development
PHI	pre-harvest interval
PEC	predicted environmental concentration
PECgw	predicted environmental concentration in groundwater
PECsed	predicted environmental concentration in sediment
PECsoil	predicted environmental concentration in soil
PECsw	predicted environmental concentration in surface water
PPE	personal protective equipment
PPP	plant protection product
PRIMo	Pesticide Residue Intake Model
QSAR	quantitative structure–activity relationship
REACH	Registration, Evaluation, Authorisation of Chemicals Regulation
RPE	respiratory protective equipment
SC	suspension concentrate
SEU	Southern Europe
SFO	Single First-Order kinetic
STMR	Standard Trial Median Residue
TGL	Test guideline
UV	ultra violet
WoE	weight of evidence

Appendix A – Collation of comments received from Member States and EFSA during the targeted consultation conducted in July – September 2023 on the application for approval of *Quassia amara* L. wood as a basic substance including consideration of comments/information, if any, received during the public consultation (27/04/2023 – 18/05/2023) and the conclusions drawn by EFSA on the specific points raised

1. Purpose of the application

General					
No.	**Column 1 Reference to Application Template**	**Column 2 Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4 Follow up response from applicant**	**Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
1(1)		DE: Contact details of the applicant are missing in the application. Please provide this information.		Applicant: The contact details of the applicant can be found in the respective IUCLID element (UUID: 447b4b4d-d242-49de-a74b-f3b4680f047b). The contact persons have been adapted due to personnel changes.	Addressed. The relevant contact details of the applicant are available in the updated IUCLID dossier (dedicated part on identity of the applicant).
1(2)	1. General	NL: It is generally felt by the CAs that the basic substance route provides		Applicant: see comments to 2(17) and 9 (1).	Comment noted.

General					
No.	**Column 1 Reference to Application Template**	**Column 2 Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4 Follow up response from applicant**	**Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
		an ill fit for *Q. amara* L wood extract. As already pointed out by other MSs, considering assessment purposes, the case would be far more compatible with the regular botanical active substance framework.			The application has been deemed admissible by the European Commission under Article 23 of Regulation (EC) No 1107/2009. Further considerations as a result of the present evaluation on the possible approval of *Quassia amara* L. wood under the basic substance framework are risk manager matters. The overall considerations with respect to compliance with the criteria for eligibility of the substance to be approved as a basic substance are outlined in Appendix D.

2. Identity of the substance/product as available on the market and predominant use

2.1. Predominant uses for purposes other than plant protection

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
2(1)	2.1	DK: Regarding the "Anonymous, Quassia wood – Availability of the substance on the market": The link for the Italian example for a product placed on the market is dead, this link works instead: https://www.erbesalute.it/erbe/216-693-quassio.html#/29-quantita-1_kg Please note, that as 1 kg wood chips cost 75 euro and the proposed GAP is for 20-30 kg wood chips pr. hectare, the total price pr. treated hectare in Italy will be 1500-2250 euro. DK therefore conclude that yes Quassia is technically on the market in the EU as a health food stuff (not widely distributed); however, it is not available on the market in a form that will be practical for farmers (incl. organic farmers). As basic substances may not be placed on the market as PPP, this situation will not change by an approval as a basic substance. Therefore, please consider to apply for a botanical active substance, which will then be legal to		Applicant: The reference is updated in the application. The new reference can be found in IUCLID. The reference was given to underline that *Quassia amara* chips are just freely available with a normal web search. Of course, the price corresponds to small scale orders and is not feasible for farmers. In the past, farmers organized as a group and made bulk orders for chips in big packs where also a batch analysis could be requested in advance. Several large scale retailers of botanicals can organize chips of *Quassia amara* wood in higher quantities on request. Currently such bulk orders are possible for example at	Addressed. The information on the market availability of *Q. amara* wood chips was updated in the application. It is noted that the proposed basic substance is the *Q. amara* L. wood and the preparation to be used is *Quassia amara* L. wood extract obtained by extraction with water. See also 2(3).

2.1. Predominant uses for purposes other than plant protection

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
		market as a PPP, which will benefit all potential users especially organic farmers. Or maybe considers applying for pure quassin (the proposed lead component) to be an active substance (not basic substance); a PPP is likely to be more affordable for the farmers in this case. Quassia is also not grown in the EU, therefore it is not like e.g. the basic substance nettle (you may harvest your own nettle and use as a basic substance).		https://www.martin-bauer.com/ or Horticon BV in NL-Vlaadingen. The prices depend of course on the quantity ordered and the year, but they are approximately about 10-15 € per kg. For 20 kg, this means 200-300 €/ha. This is e.g. comparable to the cost of an application with NeemAzal-T/S against aphids in apple and perfectly feasible for organic fruit growers. Considering the damage caused by sawfly even much higher prices would be tolerated by the farmers.	
2(2)	2.1	DK: What is the relevance of examples of available food stuff with the ingredient Quassia in this chapter of the application? Chapter 2 is for Identity of the substance as available on the market. As the foodstuff (or cosmetics) with the ingredient Quassia is not proposed as the basic substance please		Applicant: According to SANCO/10363/2012, the applicant shall describe predominant use(s) of the substance and provide evidence that these are not for purposes of plant protection. Provide	The applicant provided a reply that does not justify the relevance of examples of available foodstuff with the ingredient quassia in this chapter. EFSA notes that the basic

2.1. Predominant uses for purposes other than plant protection

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
		delete those parts from this chapter. Please also delete the reference and mention of "quassin" here, as this is not the proposed basic substance. This information may be relevant later in the application e.g. with regard to exposure, however not here in chapter 2.		arguments why they shall be considered as predominant compared to the intended use in plant protection. We consider that the demonstration of uses of *Q. amara* for addition to food or the presence of the lead substance Quassin, as well as uses in cosmetics, are suitable here.	substance is the *Quassia amara* L. wood and not quassia, thus any reference to the predominant use(s) of quassia in this chapter is irrelevant.
2(3)	2.1 Market availability	NL: The information on the market availability of *Q. amara* wood does not suggest that the proposed use as basic substance is commercially viable. To illustrate, only small scale, herbalist internet shops are mentioned (indeed, the reviewer was not able to find larger scale suppliers). Typically, *Q. amara* chips can be purchased for €50 per kg. According to the GAP, at least 20 kg of wood is required per ha, which makes at least €1000 per ha per annum. For this amount of money, the intended customers are likely to find more		Applicant: The reference is updated in the application. The new reference can be found in IUCLID. Several large scale retailers of botanicals can organize chips of *Quassia amara* wood in higher quantities on request. Currently such large scale orders are possible for example at https://www.martin-bauer.com/ or Horticon BV in NL-Vlaadingen. The prices depend of course of the	Addressed. The information on the market availability of *Q. amara* L. wood chips was updated in the application. It is noted that Article 23 of Regulation (EC) No 1107/2009 lays down specific criteria to identify an active substance as eligible as basic and commercial viability is not one of them.

2.1. Predominant uses for purposes other than plant protection

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
		attractive alternatives. Applicant is requested to respond.		quantity ordered and the year, but they are approximately about 10-15 € per kg. For 20 kg, this means 200-300 €/ha. This is e.g. comparable to the cost of an application with NeemAzal-T/S against aphids in apple and f perfectly feasible for organic fruit growers. Considering the damage sawfly even much higher prices would be tolerated by the farmers. See also our comments in 2 (1).	
2(4)	2.1 Predominant uses for purposes other than plant protection	EFSA acknowledges the submission of [redacted] 2021 Legal statement. The issue whether *Quassia amara* L. wood should be classified as a foodstuff within the meaning of Art. 2 of EU Regulation (EC) No. 178/2002 is considered by EFSA as debatable.		Applicant: A legal examination on the classification as foodstuff was performed by [redacted] (2021) and the substance is an ingredient of several foodstuffs on the market. See also comment to 9 (1).	As regards the food status of the substance, it is noted that the term 'foodstuff' is not precisely defined in the legislation. The decision on whether it should be considered as a foodstuff within the meaning of Art. 2 of Regulation (EC) No

2.1. Predominant uses for purposes other than plant protection					
No.	**Column 1** **Reference to Application Template**	**Column 2** **Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4** **Follow up response from applicant**	**Column 5** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
					178/2002 is to be taken by the European Commission. EFSA stated in its Technical Report the fact that in the EU market *Quassia amara* L. wood is sold with a description for use in the preparation of a herbal infusion both with and without medical claims, i.e. its water extract may be consumed by humans. It is noted that on websites selling the product, advice is usually included that it should not be consumed without having consulted a doctor. It is noted that based on the information

2.1. Predominant uses for purposes other than plant protection					
No.	**Column 1 Reference to Application Template**	**Column 2 Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4 Follow up response from applicant**	**Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
					provided by the applicant, extracts of the wood of *Quassia amara* L. are used in cosmetics as denaturant, tonic and for skin conditioning; in food industry to flavour certain foods and beverages[5]. However, considering that wood of *Quassia amara* L. is a botanical substance, the solvent and the extraction procedure employed to produce its extract affect the type of components and their levels in the final extract. Such information was not available for the

[5] Regulation (EC) No 1334/2008, ANNEX IV List of source materials to which restrictions apply for their use in the production of flavourings and food ingredients with flavouring properties

2.1. Predominant uses for purposes other than plant protection					
No.	**Column 1 Reference to Application Template**	**Column 2 Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4 Follow up response from applicant**	**Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
					Quassia amara L. wood extracts used in the context of the above-mentioned uses, thus they have not been included in the EFSA Technical Report.
2(5)	2.1 Predominant uses for purposes other than plant protection 2.3 Identity of the substance	EFSA: The following 2 publications are relevant for point 2.1 and 2.3, please include them in your updated application together with your assessment: 1. Patel, Kanika & Patel, Dinesh. (2018). Health Benefits of Quassin from *Quassia amara*: A Comprehensive Review of their Ethnopharmacological Importance, Pharmacology, Phytochemistry and Analytical Aspects. Current Nutrition & Food Science. 14. 10.2174/1573401314666181023094645. 2. Balkrishna, Acharya & Singh, Shalini & Srivastava, Deepika & Mishra, Shalini & Rajput, Satyendra & Arya, Ved. (2022). *Quassia amara* L.: A Comprehensive Review of its Ethnomedicinal Uses, Phytochemistry, Pharmacology and		Applicant: Both publications are included in section 2.1 and 2.3 of the updated application form and were also added to Table 5-2.	Addressed. The relevant publications were included in the application.

2.1. Predominant uses for purposes other than plant protection					
No.	**Column 1** **Reference to Application Template**	**Column 2** **Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4** **Follow up response from applicant**	**Column 5** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
		Toxicity. Phytomedicine: International Journal of Phytotherapy and Phytopharmacology. 11. 194-199. 10.31254/phyto.2022.11310.			

2.2. Relevant evaluations, carried out in accordance with other Union legislation as referred to in Art 23 of Regulation (EC) No 1107/2009

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
2(6)	2.2 Relevant evaluations, carried out in accordance with other Union legislation as referred to in Art 23 of Regulation (EC) No 1107/2009	EFSA: The previous application was for the *Quassia amara* L. wood extract obtained by extraction with water or ethanol-water mixture (https://www.efsa.europa.eu/en/supporting/pub/en-1382), while this application is for *Quassia amara* L. wood and the preparation to be used is a water extract of the *Quassia amara* L. wood.	EFSA: Please include a text in the updated application describing the differences in the basic substance and the preparation to be used, between the current application and the previous one.	Applicant: In the previous application, two different modes of preparation were suggested: 1. The preparation of the extract by "cooking" of the wood on farm – this corresponds to the current application. 2. The use of a ready extract "Quassia extract MD" which is an ethanolic extract. This extract was removed in the updated current application.	Addressed. The preparation to be used proposed in the current application is a water extract of the *Quassia amara* L. wood prepared by the operator/ farmer.

2.3. Identity of the substance

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
2(7)	2.3.6, Description and specification of purity of the substance	DE: Studies on acute toxicity were conducted with Quassia MD. The substance for approval is *Quassia amara* wood chips. For both substances, a HPLC-UV chromatogram was presented by the applicant to demonstrate the similarity of the compounds. Both chromatograms differ in the signals of quassin peaks and other unspecified peaks.	DE: Please provide further information to explain the proposed similarity of the compounds.	Applicant: The HPLC-UV chromatograms of the extract as well as that of Quassia MD show that the main peak is Quassin. The signal is slightly shifted but nevertheless shows that quassin is the main component. Neoquassin could also be found. Concerning other peaks in the chromatograms, the extract is obtained from natural woods, so it is expected to have variation in terms of the chromatographic profile. Furthermore, Quassia MD is a dried extract and received further treatment than the aqueous extract which further explains that there are some differences in the chromatographic profiles. Overall, there are still several signals which can be found in both samples (e.g. the signals between 11 and 12 minutes) which shows	This point was partially addressed by the applicant. EFSA notes that, as indicated by DE, there are peaks in the quassia wood extract (ethanol: water) that are not found in the Quassia MD extract. With respect to the water extracts, the peaks with elution time 5 min and 10.92 min, that appear in the aqueous extract of *Quassia amara* wood chips, have not been discussed and are not identified (and do not match with any peak in the quassin standard). Also, the area of the peak at ~17.5 minutes in Fig 2-2 is larger than the area in Fig 2-1. In addition, it is noted that one of the extracts investigated was of another species or variant (*Picrasma*). Wood of Picrasma is commercialised in the EU under the generic name of Quassia too. As farmers may not be aware of the origin of the quassia they use for the

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				that the chromatographic profiles are comparable.	insecticide preparation, the results of this extract are also relevant for the assessment of quassia as a basic substance. Therefore, the identity of the peak at 14.89 min, that appears on the chromatogram of the water extract of Picrasma wood, needs to be further investigated (as it is not corresponding to any of the components of the standard of quassin; i.e quassin, isoquassin and neoquassin). These issues need to be clarified before concluding on the similarity of the extracts used in the toxicological studies and the appropriateness of the acute studies provided to support the assessment of acute toxicity of the proposed basic substance (see also 2(12)). **Data gap:** Applicant to provide a robust comparison of the chromatograms obtained from the water extract of *Quassia amara* L. wood chips as

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					prepared according to the proposed recipe and the ready extract Quassia MD (i.e. the extract used as a test item in several studies regarding the effect on human health or on the environment). Further identification of the unidentified peaks in the water extracts of the *Quassia amara* L. wood and Picrasma wood should be provided as appropriate. In addition, this information would be needed for water extracts of five batches of commercially available *Quassia amara* L. wood in the EU (currently this information is only available for 1 or 2 batches, depending on whether the *Picrasma* wood is considered to represent quassia wood basic substance). See also point 2(12)
2(8)	2.3 Identity	DK: Please clearly include what the proposed basic substance is. The name is		Applicant: The proposed basic substance is the wood of *Q. amara* which is used to prepare a water extract	Addressed. The proposed basic substance is the *Q. amara* L. wood and the preparation to be used is

2.3. Identity of the substance

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		"Quassia amara L. wood" however it is an extract that is to be sprayed that is the basic substance?! If so, then this basic substance has a CAS number according to ECHA.		on farm. Since in the GAP table the concentration is quantified using the amount of wood chips per ha to use for the preparation of the extract, we defined the wood as basic substance. For the wood chips of *Quassia amara,* no CAS number is available.	*Quassia amara* L. wood extract obtained by extraction with water. The formulation to be used is prepared by boiling 20 kg of quassia wood chips in 100 L of water for one hour.
2(9)	2.3.4	DK: Please add that these retailers of herb only sell relatively small amounts of wood chips e.g. bags of 500 g or 1 kg. No larger bags are currently put on the market for teas etc, which should be considered as the proposed GAP is for 20-30 kg pr. hectare (this type of plant protection will therefore be expensive for farmers).		Applicant: The reference is updated in the application. The new reference can be found in IUCLID. Several large scale retailers of botanicals can organize chips of *Quassia amara* wood in higher quantities on request. Currently such bulk orders are possible for example at https://www.martin-bauer.com/ or Horticon BV in NL-Vlaadingen. The prices depend of course on the quantity ordered and the year, but they are approximately about 10-15 € per kg. For 20 kg, this	Addressed. Additional clarification and information on the market availability of *Q. amara* L. wood has been included in the application. It is noted that Article 23 of Regulation (EC) No 1107/2009 lays down specific criteria to identify an active substance as eligible as basic, and commercial viability is not one of them.

2.3. Identity of the substance

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				means 200-300 €/ha. This is e.g. comparable to the cost of an application with NeemAzal-T/S against aphids in apple and perfectly feasible for organic fruit growers. Considering the damage sawfly even much higher prices would be tolerated by the farmers. See also our comments in 2 (1) and 2(3).	
2(10)	2.3.2 CAS no	DK: Please add the CAS number for *Quassia amara* ext. 84604-10-4 according to ECHA.	EFSA: Applicant to consider his/her reply under point 2(6) when replying to this comment, i.e. is the basic substance the Quassia amara, ext. or the Quassia amara L. wood? In addition, according to the ECHA website, the classification provided by companies to ECHA in CLP notifications the substance with CAS 84604-10-4 is a highly flammable liquid and vapour (https://echa.europa.eu/el/substance-information/-/substanceinfo/100.075.690, accessed 06/11/2023). Is this classification applicable to your Quassia amara, extract.? If not, then	Applicant: The proposed basic substance is the wood of *Q. amara* which is used to prepare an extract on farm. Since in the GAP table the concentration is quantified using the amount of wood chips per ha to use for the preparation of the extract, we defined the wood as basic substance. For the wood chips of *Quassia amara,* no CAS number is available. The extract referred to in the comment is very likely no aqueous extract, but an	Addressed.

2.3. Identity of the substance

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			this CAS number cannot be applicable to your extract. If this is the case please provide a justification, e.g. your extract is a 100% water extract so cannot be classified a highly flammable etc.	alcoholic extract containing alcohol. Therefore, the extract mentioned by ECHA is probably for this reason highly inflammable. The extract we refer to is an 100 % water extract and as such not highly flammable.	
2(11)	2.3.2 Chemical name with CAS, EC and CIPAC numbers 2.3.3 Molecular and structural formula, molar mass 2.3.4	EFSA: Please include the relevant information under points 2.3.2 and 2.3.3 for the other quassinoids stated as present in the wood i.e.: neoquassin, isoquassin, parain, quassimarin, quassinol and quassol.		Applicant: The requested information was included in the application form.	Point partially addressed. Information on the structure of quassol and its IUPAC name is missing.
2(12)	2.3.6 Specification	NL: The description lacks a discussion on the components in *Q. amara* extract		Applicant: We agree that Neoquassin is present in the extract and there is some weak efficacy even if much	EFSA considers that not all analytical lead substances in the *Quassia amara* L. wood water extract have been identified.

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		besides quassin. For instance, neoquassin may also be present in the extract, and in similar quantities. Given its related molecular structure, contributary efficacy may be expected for neoquassin. In short: are all relevant lead components identified? Likewise: are the toxicologically relevant components that do not contribute to plant protection action sufficiently discussed?		lower than of Quassin (Kienzle et al., 2005). For this reason, Neoquassin was included in the analysis of the residues. Regarding other components, applicant wants to highlight the fact that *Quassia amara* was evaluated for food use based on a literature evaluation summarized in the report of the EUROPEAN COMMISSION HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL, Scientific Committee on Food (SCF/CS/FLAV/ FLAVOUR/29/FINAL) of 25.7.2002. Thus, it complies with Art 23(2) of the Regulation (EC) 1107/2009 that the substance should have already been evaluated in the view of other uses. Due to this evaluation, the limits in Regulation (EC) 1334/2008 were set as follows:	Looking at the chromatogram of the water extract of *Quassia amara* wood corresponding to the test item Q02 (see study Extract of a Wood (Quassia amara): Initial Extraction and Profiling Study Number: ENV-18-173) and the Table 2-7: *HPLC Area Normalisation Results by extraction with water only*, it is clear that the most frequently occurring substance is quassin as its peak accounts roughly for 21% of the normalised area. However, based on the same chromatogram, it is clear that there is another major component with a retention time of 5 min and its peak accounts for 16.6% of the normalised peak area, while for the remaining 17 components, their normalised peak area ranges from 1 to 8% roughly. It is noted that in the study Extract of a Wood (Quassia amara): Initial Extraction and Profiling Study Number: ENV-

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				In **Part A of Annex III** of Regulation (EC) 1334/2008 Quassin is listed as a substance that shall not be added as such to food. However, in **Part B of Annex III** are listed substances naturally present in flavouring and food ingredients with flavouring properties, for which a maximum level was set. In this Part B of Annex III of Regulation (EC) No 1334/2008 the limits for Quassin of 0.5 mg/kg in non-alcoholic beverages, 1 mg/kg in bakery wares and 1.5 mg/kg in alcoholic beverages are specified. In **Part B of Annex IV** of the same regulation the conditions of use for flavourings and food ingredients with flavouring properties produced from certain source materials are specified. There, *Quassia amara* is listed as a source	18-173) the chromatogram of a different *Quassia amara* wood sample is reported (test item Q04, *Picrasma*); in that chromatogram a major peak at 14.85 min is present and this peak has not been identified. The applicant proposed to use quassin as a lead component, but this selection was justified based on efficacy reasons, not based on the risk assessment (e.g. metabolism, residues, environmental fate). As the botanical guidance SANCO/11470/2012– rev. 8 (European Commission, 2014) notes, there can be different 'lead components' used for different sections and lead component(s) that is/are used should be justified in terms of its/their properties and quantities, in particular with regard to representativeness of biological activity. EFSA notes that the report of the European Commission

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				material with the specification "Flavourings and food ingredients with flavouring properties produced from the source material may only be used for the production of beverages and bakery wares." Thus, *Quassia amara* is clearly defined as a possible source material for the addition to food. Since the addition of pure Quassin to food is not allowed, the full extract with all ingredients is definitively the substance that was evaluated in view of the use in food. Since for bakery wares and beverages, a limit of the Quassin content is specified in Annex III Part B, Quassin	Health & Consumer Protection Directorate-General, Scientific Committee on Food SCF/CS/FLAV/ FLAVOUR/29/FINAL[6] (European Commission, 2002) is an opinion on quassin, not on the water extract of *Quassia amara* L. wood or the *Quassia amara* L. wood. In addition, Regulation (EC) 1334/2008 (Annex III and IV)[7] refers again to quassin that is produced from the source material (i.e. starting material) *Quassia amara* L. and *Picrasma excelsa* (Sw) and not to *Quassia amara* L. wood. Finally, the production /manufacturing process of the flavouring extracts of *Quassia amara* L. or *Picrasma excelsa* has to be compared against the preparation process of this basic

[6] https://food.ec.europa.eu/system/files/2020-12/sci-com_scf_out134_en.pdf

[7] Regulation (EC) No 1334/2008 of the European Parliament and of the Council of 16 December 2008 on flavourings and certain food ingredients with flavouring properties for use in and on foods and amending Council Regulation (EEC) No 1601/91, Regulations (EC) No 2232/96 and (EC) No 110/2008 and Directive 2000/13/EC. *OJ L 354, 31.12.2008, p. 34–50.*

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				is used in European legislation as lead substance to quantify and to limit the use and an eventual toxicological risk of *Quassia amara* when used as food ingredient. Since Quassin is also the active ingredient of the *Quassia amara* regarding the effect on insects, it is chosen as lead substance. In the numerous publications regarding the effects of *Quassia amara* bark or wood on insects or mammals, if there is a lead substance given this is Quassin.	substance water extract, i.e. does the production process of the extracts of *Quassia amara* L. or *Picrasma excelsa* as flavouring include a purification/isolation step that aims at removing any other component that has been extracted from the *Quassia amara* L. wood? The lack of comprehensive information on the composition of the preparation to be used for plant protection purposes impacts on its toxicological assessment, since 1) it is not clear which are the types and levels of biologically and/or toxicologically relevant components of the proposed preparation to be used, 2) although some of the provided studies are on extracts (mixtures), in some cases these are prepared in a different way than the proposed preparation to be used, and their relevance

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					is unclear (e.g. acute toxicity). See also 5(1) and 5(2). **Data gap:** Not all analytical lead substances in the *Quassia amara* L. wood water extracts reported in the study ENV-18-173 have been identified. See also data gap in point 2(7), 5(1), 5(2) and 7(2).
2(13)	2.3.6 Origin of wood batches	NL: The data in Table 2-1 and 2-2 are critical with regard to quality assurance. Unfortunately, they are also critically incomplete due to the fact that the tested batches are only characterized as 'Quassia wood', which is too generic to be useful. Would the origin be known for these batches, to offer potential users		Applicant: "Quassia wood" is the common denomination of the wood chips in commerce. It is impossible to investigate the origin of these wood chips after considerable time. A hint where acceptable material can be obtained is given in 2.9.	Addressed. See also data gaps in 2(7) and 2(12).

2.3. Identity of the substance

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		some hint as to where acceptable material may be obtained?			
2(14)	2.3.6 Purity	NL: It is not clear how the user has a way of telling what the quassin content in a purchased batch of chips may be, and subsequently, which wood:extraction solvent ratio should be used during extraction.		Applicant: It is written in the dossier that due to natural variation of Quassin contents in *Q. amara* wood, farmers will apply 5-11.8 g Quassin / ha in apples and stone fruits and 7.5 – 17.7 g Quassin/ha for hop if the extraction and application is according to the GAP. As described in Section 3, *Quassia amara* wood with lower Quassin levels (0.5 g Quassin/kg wood) are still effective for uses in agriculture. For the evaluation of the effects of *Quassia amara* wood on humans, animals and the environment, wood with high Quassin content was used, which would lead to the application of 12 g Quassin/ha in pome and	It is noted that the applicant assumed that 50% of the total quassin content of *Q. amara* L. wood will be extracted when the description for preparation is used, however no data or a robust justification was provided to support such an assumption. See data gap in 7(22)

2.3. Identity of the substance					
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				stone fruit or 18 g Quassin/ha in hop. Additionally, farmers usually buy Quassia chips "en gros" in a concerted action and in this case they can and do ask the retailer to present an analysis of Quassin content of the batch.	
2(15)	2.3.6 Purity	NL: Please derive a recommended specification range along with reliable sources.		Applicant: It is written in the dossier that due to natural variation of Quassin contents in *Q. amara* wood, farmers will apply 5-11.8 g Quassin / ha in apples and stone fruits and 7.5 – 17.7 g Quassin/ha for hop if the extraction and application is according to the GAP.	Based on the information provided by the applicant under point 2.3.6 Description and specification of purity of the substance, EFSA proposed that the basic substance *Q. amara* L. wood should contain quassin content in a range between 0.5 g quassin / kg wood and 1.18 g quassin / kg wood, measured following ethanol:water (30:70) extraction. See data gap in 7(22)
2(16)	2.3.9 Methods of analysis	EFSA: For the following analytical methods please include in the updated application their complete		Applicant: The method summaries were extended in an updated application.	Addressed.

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		summary and validation data to justify the statement that these methods are validated according to SANCO/3029/99, rev. 4 and/or SANTE/2020/12830 rev. 1 1. Method validation in support of in vivo COMET assay 2. Method validation in support of adsorption/desorption study 3. Method validation in support of dermal adsorption study			

2.4. Type of preparation of the substance					
No.	**Column 1 Reference to Application Template**	**Column 2 Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4 Follow up response from applicant**	**Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**

No comments.

2.5. Description of the preparation of the substance for use in plant protection					
No.	**Column 1 Reference to Application Template**	**Column 2 Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4 Follow up response from applicant**	**Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
2(17)	2.5	DK: Which farmers or persons have a 100 or 150 L pot and a way to heat it to boiling for an hours. Also, the pot must be bigger than that as 20 or 30 kg wood chips are to be added as well.		Applicant: In commercial agriculture, 100 to 150 L pots are available. Usually, famers always boil 20 kg for 1 hour, pump the extract in a collecting tank and subsequently prepare the next 20 kg until the	Addressed.

2.5. Description of the preparation of the substance for use in plant protection					
No.	**Column 1 Reference to Application Template**	**Column 2 Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4 Follow up response from applicant**	**Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
		Furthermore, which person/persons can then sieve this extract within a reasonable time frame? It appears to not be practical for a normal farmer/person to manufacture the *Quassia amara* extract needed for further dilution. Is this extract the basic substance?! It also would not make sense to produce less than what is described as this is the volume required for treatment of just one hectare. Please consider to apply for a botanical active substance (e.g. pure quassin or Quassia extract) and		amount of quassia extract needed is achieved. This has been done during the past nearly 100 years, so it has proven to be feasible. Applicant agrees that the availability of a botanical active substance would be an easy solution for our farmers and highly appreciated, however, until now, this was not feasible due to the small market of this niche product. When the Reg. 1107/2009 was introduced, the problem, that *Quassia amara* was a niche product for which no return of investment for regulatory studies and dossier preparation was to be expected by a company. However, an essential use was discussed with German BMEL and the Commission.	

2.5. Description of the preparation of the substance for use in plant protection					
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		then place a concentrated PPP on the market in all relevant MS. This is likely to be a more affordable and practical solution for (organic) farmers.		This problem was mentioned in the meantime often by IFOAM Organics Europe without any solution. In 2010, both authorities advised the applicant to apply for approval as basic substance. Thus, *Quassia amara* was also listed in the first list of candidates for basic substances of the Commission and was part of the pilot project for application. See also comments to 9 (1).	
2(18)	2.5 Extraction	NL: Given the cost of Quassia wood, would it be possible to improve the extraction efficiency, e.g. by adding a co-extractant, like ethanol?		Applicant: In the past, this was never done when the extract was prepared on farm. Only producers of commercial extract used ethanol as co-extractant.	Addressed.
2(19)	extraction	NL: seem quite a lot of work first to boil the wood	NL: can the extract be store bought?	Applicant: It is a lot of work, but it is an essential use and if	Addressed.

2.5. Description of the preparation of the substance for use in plant protection					
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		shavings, sieve and then dilute the extract.		there is no alternative farmers have to do this.	

3. Uses of the substance and its product

3.1. Field of use / function

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
3(1)	GAP Table	DE: There are inconsistencies regarding the provided values for concentrations in the GAP table. A concentration of 200 g/L (a.i. g/L), as stated here, corresponds to 20 kg/hL (g a.s./hL) and 200 kg wood chips per ha. However, according to section 2.5, it is foreseen to use 20 kg Quassia chips/ha (for use in hop: 30 kg/ha).	DE: Please clarify and provide coherent values for "Conc of a.i. g/L", "g a.s./hL" and "g as/ha Quassia wood chips/ha".	Applicant: The *Q. amara* wood extract is used in a 1:10 dilution. 20 kg *Q. amara* wood chips are used per hectare, whereas the volume applied is 1000 L in total. In these 1000 L, only 10 % Quassia extract are used, *i.e.* 100 L *Q. amara* wood extract (for which 20 kg *Q. amara* wood decocted) in 1000 L tank mix. The 100 L *Q. amara* wood extract is prepared by cooking 20 kg wood in 100 L water. If the content of *Q. amara* wood per hL of the tank mix is calculated, this corresponds to 2 kg *Q. amara* wood in 1 hL tank mix. Moreover, the GAP has been amended in the updated application, as the use of 500 litres of water is no longer envisaged for plum, pome fruits	Addressed. The GAP table has been amended in the updated application. See also Appendix E. See also data gap in 7(22)

3.1. Field of use / function

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
				and stone fruits. Furthermore, a new use in ornamentals was added.	
3(2)	3. GAP	DK: Column 3 "example product name as available on the market". Please consider to rename this column to "basic substance" which is then "Quassia amara extract". As mentioned in previous comment it is not clear if it is the wood chips or in fact the extract that is the proposed basic substance.		Applicant: The application is for *Q. amara* wood, which is used for extract preparation on farm. The description of the substance can be found in the application form (section 2.3.2) and further information was also added in IUCLID in the reference substance entity. Available on the market are the wood chips.	Addressed. The proposed basic substance is the *Q. amara* L. wood and the preparation to be used is *Quassia amara* L. wood extract obtained by extraction with water.
3(3)	Insecticide and repellent in pome	NL: good efficacy		Applicant: Noted.	Addressed. Efficacy has been demonstrated for the intended uses on pome fruit, stone fruit and hops. Efficacy on white fly, when watering

3.1. Field of use / function					
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	fruits, pitfruits and hop				plants in pots, is mentioned in old literature. Application seems needed before egg laying and at least before egg hatching. So, the evidence for the control of white fly is weaker.
3(4)	GAP table	EFSA: For the proposed GAP uses on pome fruit, stone fruit and plum a water application rate of 500-1000 L/ha is proposed, thus the kg a.s/hL should be 2-4 kg/hL and not only 2 kg/hL as stated. Please clarify.		Applicant: The GAP has been amended in the updated application, as the use of 500 litres of water is no longer envisaged for plum, pome fruits and stone fruits. Therefore, only the 2 kg/hL are mentioned. Furthermore, a new use in ornamentals was added.	Addressed. The GAP table has been amended in the updated application. See also Appendix E.

3.2. Effects on harmful organisms or on plants (including mode of action)					
No.	**Column 1** **Reference to Application Template**	**Column 2** **Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4** **Follow up response from applicant**	**Column 5** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
3(5)	Control of sawflies and aphids	NL: Good efficacy on primary and even on secondary infestations even at high infestation.		Applicant: Noted.	Addressed. See also point 3(3).
3(6)	Phytotoxicity on plants	NL: absence of negative effects on plants was not demonstrated.	NL: demonstrate absence of phytotoxicity	Applicant: Extracts of the wood of *Quassia amara* are used for about 100 years for some of the proposed uses. For more than 20 years it is an essential use in organic farming. In all this time, no negative effects on plants or phytotoxic effects were observed.	See point 8(26).

3.3. Usefulness in the framework of plant protection / intended uses					
No.	**Column 1** **Reference to Application Template**	**Column 2** **Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4** **Follow up response from applicant**	**Column 5** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
3(7)	Table 3-1	DK: We do not question that this proposed basic substance would be useful for farmers across the EU. This list of organisations that would use *Quassia amara* were it to be approved as a basic substance would likely also use *Quassia amara* were it to be approved as a regular active substance with marketed PPPs. If this proposed basic substance is so essential and useful, then please consider to market it as a PPP as there apparently is a great market for it.		Applicant: It is essential and useful, however only for a niche market of few insect species. For fruit and hop, about 2000 to maximum 5000 ha over whole Europe currently are concerned. For organic fruit and hop, high economic losses in these areas are intolerable. For a company, however, this market does not at all justify the high investment in the application for a botanical active substance. Furthermore, the areas where sawfly is a problem are variable, so the calculation of the market is not at all reliable.	Addressed. See comment 1(2).
3(8)	As an insecticide on hop/pome fruits	NL: Quite useful as the diluted extract gives good control.		Applicant: Noted.	Addressed.

4. Classification and labelling of the substance

Classification and labelling of the substance					
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4(1)	4	DK: The lack of classification of the proposed basic substance on ECHAs webpage is not an argument for no classification, as this is likely due to lack of any notified classifications (registrations). Also, if the proposed basic substance is actually *Quassia amara* extract, then is likely classified as Flam. Liq. 2. Most likely the classification is simply not known.	DK: Please add more information regarding the basis for the statement "not classified".	Applicant: See also 2.3.2: The proposed basic substance is the wood of *Q. amara* which is used to prepare an extract on farm. Since in the GAP table the concentration is quantified using the amount of wood chips per ha to use for the preparation of the extract, we defined the wood as basic substance. For the wood chips of *Quassia amara,* no CAS number is available. The extract referred to in the comment is very likely not an aqueous extract but contains flammable solvent and is probably for this reason highly flammable. The extract we refer to is an 100 % water extract prepared on farm and as such not highly flammable. Moreover, *Quassia amara* was evaluated for food use and is listed in **part B of Annex IV** of Regulation **1334/2008**. There, *Quassia amara* is listed as a source material with the specification	Addressed. As regards the use of *Quassia amara* as food, please see point 2(4).

Classification and labelling of the substance					
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				"Flavourings and food ingredients with flavouring properties produced from the source material may only be used for the production of beverages and bakery wares." Thus, *Quassia amara* is clearly defined as a possible source material for the addition to food. Therefore, critical classification of *Q. amara* is not expected.	

5. Impact on Human and Animal Health (effects having relevance to human and animal health arising from exposure to the substance/its products or to impurities contained in the substance/product or their transformation products)

5.1. Toxicity

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
5(1)	5.1.4, Genotoxicity	DE: The existing dataset is not sufficient to conclude the genotoxicity assessment of *Quassia amara* L. wood extract. The main unresolved issue pertains to the "equivocal" conclusion from the micronucleus (MN) test in human lymphocytes ([redacted], 2021; performed according to OECD Test Guideline/TG 487). An appropriate follow-up test would have been the mammalian erythrocyte micronucleus test (OECD TG 474), which is not available in the application for review. The negative outcomes from the Comet assay ([redacted], 2022; performed according to OECD TG 489) do not	DE: Please provide further data or evidence for the genotoxicity assessment, e. g. outcomes of the mammalian erythryocyte micronucleus test (OECD TG 474), to address the equivocal findings in the human MN test of [redacted] (2021).	Applicant: An evaluation of the genotoxic potential of *Quassia amara* L. wood was performed based on all available study data on this topic and considering the recommendations for genotoxicity testing as outlined by the EFSA Scientific Committee (EFSA, 2011; EFSA, 2017; EFSA 2019). Furthermore, profiling for endpoints genotoxicity/carcinogenicity (OECD QSAR Toolbox v.4.6) for the known extract components quassin (main component, analytical lead substance), neoquassin and 18-hydroxyquassin (both tentatively identified by mass spectrometry analysis) was performed to support the present evaluation.	*Quassia amara* wood extracts were tested for genotoxicity by *in vitro* and *in vivo* studies. Quassia extract MD resulted negative in a bacterial gene mutation assay (with and without metabolic activation). *Quassia amara* L. wood water extract (prepared as for the use in plant protection, batch Q02) showed equivocal results in an *in vitro* micronucleus assay on human lymphocytes (in the absence of metabolic activation). As a follow up, the same extract was tested *in vivo* (Comet assay in male rats) and proven to be negative (small intestine and liver cells). The above studies on the water extract

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		resolve the equivocal findings from the MN test. The Comet assay is used for detecting DNA damage *in vivo*, whereas MN formation provides indications of chromosomal aberrations. Therefore, a genotoxic potential remains of concern for *Quassia amara* L. wood extract.		The study database comprised *in vitro* and *in vivo* genotoxicity assays (GLP and OECD guideline compliant) related to all relevant endpoints, *i.e.*, gene mutation, structural and numerical chromosomal aberrations and was thus considered complete and adequate for the evaluation of genotoxicity. In the Ames test, *Quassia amara* L. wood was non-mutagenic in the bacterial strains *Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537, and *Escherichia coli* WP2*uvrA*. In a micronucleus assay (MNA) *in vitro* in human lymphocytes, there was no relevant effect on micronuclei incidences in the presence of metabolic activation (S9 mix), but slightly increased incidences in micronuclei in the absence of metabolic activation were observed. These increases, which were assessed as equivocal	are GLP and OECD compliant. The applicant reported that the components of Quassia extracts show profiles indicating potential DNA damage (by QSAR toolbox). Therefore, a Comet test evaluating tissues exposed to the mixture would be appropriate to follow up the equivocal outcome of the *in vitro* micronucleus test. However, no details on the QSAR analysis have been provided to support the possible mechanisms of genotoxicity. **Data gap:** To conclude on genotoxicity, the applicant should provide detailed *in silico* analyses of the mixture components, once they are adequately

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				in the study report, were only observed at cytotoxic concentrations. Since the increases in micronucleus incidences were marginal and that cytotoxicity is a known confounder under *in vitro* testing conditions, the overall assessment of the study indicates low concern for genotoxicity. To follow up on these slight increases a Comet assay in male rats was chosen as *in vivo* follow-up test. The investigation of potential DNA damage *in vivo* revealed that *Quassia amara* L. wood was not genotoxic in cells of the small intestine (site of direct contact) and in liver cells. The Comet assay was selected as the adequate test system for the complex *Quassia amara* L. wood since potential cytotoxic effects determined in a mouse bone marrow MNA, which represents the potential alternative to the *in*	identified (see data gaps in 2(7), 2(12)).

5.1. Toxicity

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				vivo Comet assay in this case, could not be unequivocally attributed to a defined component of the wood. By choosing a tissue with site of direct contact (*e.g.* small intestine), tissue exposure for components not requiring metabolic activation can be demonstrated in the Comet assay after oral exposure. For an *in vivo* MNA, however, bone marrow exposure to all components of the test substance (confirmed bone marrow exposure is a prerequisite for regulatory acceptance of this assay) can neither be predicted nor reliably analytically demonstrated. Alerts depicted in the genotoxicity/carcinogenicity profiling for the components quassin (main component), neoquassin and 18-hydroxyquassin using the OECD QSAR Toolbox v.4.6 indicated	

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				that direct interaction with DNA might be the underlying mechanism to the equivocal finding in the *in vitro* MNA, supporting the choice of the Comet assay as the adequate follow up test *in vivo*. Overall, it can be concluded that *Quassia amara* L. wood is of low concern regarding the endpoint genotoxicity and the level of uncertainty remains low and acceptable. Moreover, *Quassia amara* is clearly defined as a possible source material for the addition to food. The application was updated accordingly.	
5(2)	5.1.5, Long-term toxicity and carcinogenicity	DE: Data on long-term toxicity and carcinogenicity are lacking. The existing text in the application is not sufficient to draw any	DE: Please provide further scientific evidence and evaluation on these endpoints.	Applicant: Regarding the genotoxicity assessment, please see our answer to the comment above.	As regards genotoxicity, see 5(1). As regards general toxicity, the provided dataset indicates effects on the

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		conclusion on these endpoints. Considering the genotoxicity assessment is inconclusive (especially regarding chromosomal aberrations), it is necessary to provide scientifically valid evaluation on these endpoints to ensure that the active substance does not have any chronic toxic and carcinogenic concerns.		Please consider also that *Quassia amara* was evaluated for food use based on a literature evaluation summarized in the report of the EUROPEAN COMMISSION HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL, Scientific Committee on Food (SCF/CS/FLAV/ FLAVOUR/29/FINAL) of 25.7.2002. Thus, it complies with Art 23(2) of the Regulation (EC) 1107/2009 that the substance should have already been evaluated in the view of other uses. Due to this evaluation, the limits in Regulation (EC) 1334/2008 were set as follows: In **Part A of Annex III** of Regulation (EC) 1334/2008 Quassin is listed as a substance that shall not be added as such to food. However, in **Part B of Annex III** are listed substances	reproductive system of mammals by quassin and Quassia extracts. It is noted that no OECD studies are provided, and that the evidence derives from non-regulatory studies, nevertheless sperm parameters and male/female fertility are consistently affected in rodents. *In vitro* investigations indicate an effect of quassin on androgen synthesis. Based on the available information, it cannot be excluded that quassin/Quassia extracts can affect the reproductive system in mammals. Moreover, it is not possible to exclude that the reproductive effects are related to an endocrine mode of action. It is noted that Article 23 of Regulation (EC) No

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				naturally present in flavouring and food ingredients with flavouring properties, for which a maximum level was set. In this Part B of Annex III of Regulation (EC) No 1334/2008 the limits for Quassin of 0.5 mg/kg in non-alcoholic beverages, 1 mg/kg in bakery wares and 1.5 mg/kg in alcoholic beverages are specified. In **Part B of Annex IV** of the same regulation the conditions of use for flavourings and food ingredients with flavouring properties produced from certain source materials are specified. There, *Quassia amara* is listed as a source material with the specification "Flavourings and food ingredients with flavouring properties produced from the source material may only be used for the production of beverages and bakery wares."	1107/2009 clearly indicates that, among others, a basic substance is not a substance of concern and does not have an inherent capacity to cause endocrine disrupting effects. The limited toxicological information available does not allow to derive solid conclusions on the toxicity of quassin/Quassia extracts and to identify robust NOAELs, consequently no risk assessment can be performed. **Data gap:** Further evidence is needed to substantiate the toxicological profile of the proposed basic substance *Quassia amara* L. wood (and the formulation proposed for plant protection use, i.e.

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				Thus, *Quassia amara* is clearly defined as a possible source material for the addition to food. Since the addition of pure Quassin to food is not allowed, the full extract with all ingredients is definitively the substance that was evaluated in view of the use in food.	aqueous extract) and/or its components (quassin, other relevant ones), particularly as regards reproductive toxicity; and to exclude an endocrine activity considering the observed reproductive effects. The above should be addressed taking into account the clarifications on the extract composition, as indicated in 2(7) and 2(12).
5(3)	5.1.6, Reproductive toxicity	DE: From this section of the application as well as the other published reports (e. g., SCF 2002, SCF/CS/FLAV/FLAVOUR/29 Final) it is quite evident that *Quassia amara* L. wood extract has reproductive toxicity concerns. The provided list of literature by the applicant also seems to confirm this, and there is no	DE: As proposed by DE already during the public consultation in 2017 (EFSA 2018:EN-1382), a botanical active substance dossier prepared in line with Guidance Document SANCO/11470/2012 should be generated for *Quassia amara* L. wood extract if the substance is to be considered for plant	Applicant: *Quassia amara* was evaluated for food use based on a literature evaluation summarized in the report of the EUROPEAN COMMISSION HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL, Scientific Committee on Food (SCF/CS/FLAV/ FLAVOUR/29/FINAL) of 25.7.2002. Thus, it complies with Art 23(2) of the Regulation	As regards reproductive toxicity see 5(2). As regards the food status, see 2(4).

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		other new evidence or scientific understanding to fully disprove the reprotoxic findings in the published literature. SCF (2002) also expressed concerns regarding reproductive toxicity of quassin or *Quassia* extract. Lastly, we already commented during the public consultation in 2017 that there is evidence of reproductive toxicity (EFSA 2018:EN-1382; pages 29-30), and therefore, *Quassia amara* L. wood extract does not comply with the approval conditions of article 23 (1b) and 23 (2) of Regulation (EC) No 1107/2009.	protection use in the EU. There are sufficient human health concerns of *Quassia amara* extract identified that cannot be ignored or disregarded. We do not find "simple economic reasons", as replied by the applicant in EFSA 2018:EN-1382 to our proposal, an appropriate reason to avoid generation of a full active substance dossier.	(EC) 1107/2009 that the substance should have already been evaluated in the view of other uses. Due to this evaluation, the limits in Regulation (EC) 1334/2008 were set as follows: In **Part A of Annex III** of Regulation (EC) 1334/2008 Quassin is listed as a substance that shall not be added as such to food. However, in **Part B of Annex III** are listed substances naturally present in flavouring and food ingredients with flavouring properties, for which a maximum level was set. In this Part B of Annex III of Regulation (EC) No 1334/2008 the limits for Quassin of 0.5 mg/kg in non-alcoholic beverages, 1 mg/kg in bakery wares and 1.5 mg/kg in alcoholic beverages are specified.	

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				In **Part B of Annex IV** of the same regulation the conditions of use for flavourings and food ingredients with flavouring properties produced from certain source materials are specified. There, *Quassia amara* is listed as a source material with the specification "Flavourings and food ingredients with flavouring properties produced from the source material may only be used for the production of beverages and bakery wares." Thus, *Quassia amara* is clearly defined as a possible source material for the addition to food. Since the addition of pure Quassin to food is not allowed, the full extract with all ingredients is definitively the substance that was evaluated in view of the use in food. As a foodstuff already evaluated it complies with the approval conditions of article 23 (1b) and	

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				23 (2) of Regulation (EC) No 1107/2009 as long as the proposed use is comparable to the food uses respecting the limits. This is shown in section 5.3.1. Just to explain: Applicants have no commercial interest in selling substances used in plant protection, but they have interest in using them. When the Reg. 1107/2009 was introduced, the problem, that *Quassia amara* was a niche product where no return of investment for dossier preparation was to be expected for a company, but an essential use was discussed with German BMEL and the Commission. This problem was mentioned in the meantime often by IFOAM Organics Europe without any solution. In 2010, both authorities advised applicants to apply for basic substance. Thus, *Quassia amara* was also listed in	

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				the first list of candidates for basic substances of the Commission and was part of the Pilot project for application. See also comments to 9(1).	
5(4)	5.1.8, Endocrine disruption	DE: We highly disapprove of the applicant's justification of disregarding the endocrine disruptive (ED) potential of *Quassia amara* L. wood extract by referring to other foodstuff or basic substances with reported ED properties. The peer review of a basic substance should be performed independent of the outcomes of other (basic) substances. In this case, the applicant appears to acknowledge the ED potential of *Quassia amara* L. wood extract, and there is no other new evidence or scientific understanding to disprove	DE: As proposed by DE already during the public consultation in 2017 (EFSA 2018:EN-1382), a botanical active substance dossier prepared in line with Guidance Document SANCO/11470/2012 should be generated for *Quassia amara* L. wood extract if the substance is to be considered for plant protection use in the EU. There are sufficient human health concerns of *Quassia amara* extract identified that cannot be ignored or disregarded. We do not find "simple economic reasons", as	Applicant: *Quassia amara* was evaluated for food use based on a literature evaluation summarized in the report of the EUROPEAN COMMISSION HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL, Scientific Committee on Food (SCF/CS/FLAV/ FLAVOUR/29/FINAL) of 25.7.2002. Thus, it complies with Art 23(2) of the Regulation (EC) 1107/2009 that the substance should have already been evaluated in the view of other uses. Due to this evaluation, the limits in Regulation (EC) 1334/2008 were set as follows:	See 5(2) and 2(4).

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		the ED-related findings in the published scientific literature. Lastly, we already commented during the public consultation in 2017 that there is evidence of ED effects (EFSA 2018:EN-1382; pages 29-30), and therefore, *Quassia amara* L. wood extract does not comply with the approval conditions of article 23 (1b) and 23 (2) of Regulation (EC) No 1107/2009.	replied by the applicant in EFSA 2018:EN-1382 to our proposal, an appropriate reason to avoid generation of a full active substance dossier.	In **Part A of Annex III** of Regulation (EC) 1334/2008 Quassin is listed as a substance that shall not be added as such to food. However, in **Part B of Annex III** are listed substances naturally present in flavouring and food ingredients with flavouring properties, for which a maximum level was set. In this Part B of Annex III of Regulation (EC) No 1334/2008 the limits for Quassin of 0.5 mg/kg in non-alcoholic beverages, 1 mg/kg in bakery wares and 1.5 mg/kg in alcoholic beverages are specified. In **Part B of Annex IV** of the same regulation the conditions of use for flavourings and food ingredients with flavouring properties produced from certain source materials are specified. There, *Quassia amara* is listed as a source material with the	

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				specification "Flavourings and food ingredients with flavouring properties produced from the source material may only be used for the production of beverages and bakery wares." Thus, *Quassia amara* is clearly defined as a possible source material for the addition to food. Since the addition of pure Quassin to food is not allowed, the full extract with all ingredients is definitively the substance that was evaluated in view of the use in food. Since for bakery wares and beverages, a limit of the Quassin content is specified in Annex III Part B, Quassin is used in European legislation as lead substance to quantify and to limit the use and an eventual toxicological risk of *Quassia amara* when used as food ingredient. This was one of the main reasons why this ingredient	

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				was also chosen as a lead substance by applicants. In section 5.3.1 it is shown that the proposed use is comparable to the food uses respecting these limits. After the evaluation of 2002 other scientific literature was published. However, the amounts of Quassin where effects were shown is not lower than the amount in the previous publications that were subject of the evaluation of 2002 (See table 5.2.1). Thus, there is no reason not to accept the limits for the content of Quassin in food defined already for food uses in Reg. (EC) No 1334/2008 as levels to avoid toxicological risks for humans.	
5(5)	5.1.1 Toxicokinetics and	DK: The extract contains many components, so while it might not be possible to do studies on the mixture, could		Applicant: The studies presented were done with the full extract prepared as proposed in this	Noted. The assessment considered both studies on Quassia extracts (here defined as

5.1. Toxicity

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	metabolism in humans	it be that data on the individual ingredients is available?		application. Thus, all ingredients are included.	"mixtures") and on individual components of Quassia. Studies on mixtures include GLP genotoxicity studies, some on a mixture prepared as proposed as basic substance in this application; this information is considered highly relevant, provided that the tested mixture is sufficiently representative. The assessment has been complemented by studies on individual components relevant for the mixture, and in particular on quassin (mainly published literature). The composition of the preparation intended for use however needs further clarification - see data gaps at 2(7) and 2(12) – therefore further consolidation of the provided information to address the toxicity of the

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					basic substance/preparation could be possible.
5(6)	5. regarding foodstuff	DK: Agree with DE that according to Regulation (EC) 1334/2008 Quassin should not be added to food intentionally. Thus, it is not relevant to mention the content in beverages as an argumentation for acceptable exposure in all the cases where exposure estimates from the EFSA calculator exceeds the acceptable level		Applicant: *Quassia amara* was evaluated for food use based on a literature evaluation summarized in the report of the EUROPEAN COMMISSION HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL, Scientific Committee on Food (SCF/CS/FLAV/ FLAVOUR/29/FINAL) of 25.7.2002. Thus, it complies with Art 23(2) of the Regulation (EC) 1107/2009 that the substance should have already been evaluated in the view of other uses. Due to this evaluation, the limits in Regulation (EC) 1334/2008 were set as follows: In **Part A of Annex III** of Regulation (EC) 1334/2008 Quassin is listed as a substance that shall not be added as such	See comment 2(4)

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				to food. However, in **Part B of Annex III** are listed substances naturally present in flavouring and food ingredients with flavouring properties, for which a maximum level was set. In this Part B of Annex III of Regulation (EC) No 1334/2008 the limits for Quassin of 0.5 mg/kg in non-alcoholic beverages, 1 mg/kg in bakery wares and 1.5 mg/kg in alcoholic beverages are specified. In **Part B of Annex IV** of the same regulation the conditions of use for flavourings and food ingredients with flavouring properties produced from certain source materials are specified. There, *Quassia amara* is listed as a source material with the specification "Flavourings and food ingredients with flavouring properties produced from the source material may only be	

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				used for the production of beverages and bakery wares." Thus, *Quassia amara* is clearly defined as a possible source material for the addition to food. Since the addition of pure Quassin to food is not allowed, the full extract with all ingredients is definitively the substance that was evaluated in view of the use in food. Since for bakery wares and beverages, a limit of the Quassin content is specified in Annex III Part B, Quassin is used in European legislation as lead substance to quantify and to limit the use and an eventual toxicological risk of *Quassia amara* when used as food ingredient. This was one of the main reasons why this ingredient was also chosen as a lead substance by applicants.	
5(7)	5. Impact on human and	DK: Do you mean the "state of knowledge" in 2022?		Applicant: We refer to the state of knowledge of 2002, the year	Addressed.

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	animal health, p 38			when the report of the EUROPEAN COMMISSION HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL, Scientific Committee on Food (SCF/CS/FLAV/ FLAVOUR/29/FINAL) of 25.7.2002 was published. This report is the basis of the evaluation in the view of other uses (foodstuff) where the limits in Regulation (EC) 1334/2008 we refer to were set. In Table 5-2 the publications are listed that were not included in the report. It is shown that no results were published since 2002 that show effects with lower concentrations than those that were published before 2002.	
5(8)	5.1.2. Acute toxicity	DK: The conclusion is phrased as if the substance display no toxicologically relevant effects. However, based on the section of the report this	DK: Please rephrase.	Applicant: Further clarification was added.	Addressed.

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		is only in terms of acute toxicity.			
5(9)	5.1.5 long term toxicity and carcinogenicity	DK: A number of references are mentioned briefly, however no conclusion on long term effects or carcinogenicity is drawn in the application. Also, it appears from the paragraph that no studies of this were available.		Applicant: We refer to the state of knowledge of 2002, the year when the report of the EUROPEAN COMMISSION HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL, Scientific Committee on Food (SCF/CS/FLAV/ FLAVOUR/29/FINAL) of 25.7.2002.was published. This report is the basis of the evaluation in the view of other uses (foodstuff) where the limits in Regulation (EC) 1334/2008 we refer to were set. In Table 5-2 the publications are listed that were not included n the report. It is shown that no results were published since 2002 that show effects with lower concentrations than those that were published before 2002.	See 2(4) and 5(2).

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5(10)	5.1.6 Reproductive toxicity	DK: The text is not very reader friendly, several studies are mentioned in brief without much details on the parameters studies or the negative or positive findings and the significance of this.		Applicant: Noted. In table 5-2, we refer to the state of knowledge of 2002, the year when the report of the EUROPEAN COMMISSION HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL, Scientific Committee on Food (SCF/CS/FLAV/ FLAVOUR/29/FINAL) of 25.7.2002.was published. This report is the basis of the evaluation in the view of other uses (foodstuff) where the limits in Regulation (EC) 1334/2008 we refer to were set. In Table 5-2 the publications are listed that were not included in the report. It is shown that no results were published since 2002 that show effects with lower concentrations than those that were published before 2002.	See 5(2).
5(11)	5.1.8 Endocrine disruption	DK: No assessment of endocrine disruption is included in this section. Listing other studies		Applicant: *Quassia amara* was evaluated for food use based on a literature evaluation	See 2(4) and 5(2)

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		and effects for other substances for other uses does not seem relevant for the ED assessment. In section 5.1.6 it is mentioned that the basic substance applied for has been found to have effects on male fertility in several studies (the quality of the studies are not mentioned in the text or put into context), notably, some of the studies had the aim of investigating the potential of quassia as male contraceptive. Other studies are listed but it is not mentioned in the text what was investigated or what was found. Thus, from section 5.1.6 it appear that the extract might affect male fertility. This should be somewhat addressed in the ED assessment. Also, it is not clear if there is any		summarized in the report of the EUROPEAN COMMISSION HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL, Scientific Committee on Food (SCF/CS/FLAV/ FLAVOUR/29/FINAL) of 25.7.2002. Thus, it complies with Art 23(2) of the Regulation (EC) 1107/2009 that the substance should have already been evaluated in the view of other uses. Due to this evaluation, the limits in Regulation (EC) 1334/2008 were set as follows: In **Part A of Annex III** of Regulation (EC) 1334/2008 Quassin is listed as a substance that shall not be added as such to food. However, in **Part B of Annex III** are listed substances naturally present in flavouring and food ingredients with flavouring properties, for which a maximum level was set. In	

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		knowledge on effects on females or if any studies have been carried out to investigate this.		this Part B of Annex III of Regulation (EC) No 1334/2008 the limits for Quassin of 0.5 mg/kg in non-alcoholic beverages, 1 mg/kg in bakery wares and 1.5 mg/kg in alcoholic beverages are specified. In **Part B of Annex IV** of the same regulation the conditions of use for flavourings and food ingredients with flavouring properties produced from certain source materials are specified. There, *Quassia amara* is listed as a source material with the specification "Flavourings and food ingredients with flavouring properties produced from the source material may only be used for the production of beverages and bakery wares." Thus, *Quassia amara* is clearly defined as a possible source material for the addition to food. Since the addition of pure	

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				Quassin to food is not allowed, the full extract with all ingredients is definitively the substance that was evaluated in view of the use in food. In Table 5-2 we refer to the state of knowledge of 2002, the year when the report of the EUROPEAN COMMISSION HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL, Scientific Committee on Food (SCF/CS/FLAV/ FLAVOUR/29/FINAL) of 25.7.2002.was published. This report is the basis of the evaluation in the view of other uses (foodstuff) where the limits in Regulation (EC) 1334/2008 we refer to were set. In Table 5-2 the publications are listed that were not included in the report. It is shown that no results were published since 2002 that show effects with lower concentrations	

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				than those that were published before 2002.	
5(12)	5.1.7 Immmunotoxicity	DK: The assessment of immunotoxicity is not included in the application, only a brief conclusion. A more thorough assessment is needed where the studies included in the application should be taken into account, e.g. effects on white blood cells, on inflammation etc. It is mentioned in the ED section that the mode of action is anti-inflammatory, such effects should be addressed in the application. Immunotoxicity is one other endpoints that are specifically mentioned in art. 23.		*Quassia amara* was evaluated for food use based on a literature evaluation summarized in the report of the EUROPEAN COMMISSION HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL, Scientific Committee on Food (SCF/CS/FLAV/ FLAVOUR/29/FINAL) of 25.7.2002. Thus, it complies with Art 23(2) of the Regulation (EC) 1107/2009 that the substance should have already been evaluated in the view of other uses. Due to this evaluation, the limits in Regulation (EC) 1334/2008 were set as follows: In **Part A of Annex III** of Regulation (EC) 1334/2008 Quassin is listed as a substance that shall not be added as such to food. However, in **Part B of**	The applicant stated that there are no indications for possible immunotoxicity of *Quassia amara* L. wood (and derived preparations), without substantiating the rationale for such statement (5.1.7 Immunotoxicity). Indeed, no indication of immunotoxicity has been identified in the proposed dataset, however, some studies on Quassia extracts/quassin have shown effects on cells of the immune system modulating their function. **Minor outstanding issue:** The applicant should substantiate why no immunotoxicity effects are expected for the proposed basic substance (and its

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				Annex III are listed substances naturally present in flavouring and food ingredients with flavouring properties, for which a maximum level was set. In this Part B of Annex III of Regulation (EC) No 1334/2008 the limits for Quassin of 0.5 mg/kg in non-alcoholic beverages, 1 mg/kg in bakery wares and 1.5 mg/kg in alcoholic beverages are specified. In **Part B of Annex IV** of the same regulation the conditions of use for flavourings and food ingredients with flavouring properties produced from certain source materials are specified. There, *Quassia amara* is listed as a source material with the specification "Flavourings and food ingredients with flavouring properties produced from the source material may only be	components, once clarified), and further elaborate on its effects on the immune system. See 2(4), 2(12) and 5(2)

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				used for the production of beverages and bakery wares." Thus, *Quassia amara* is clearly defined as a possible source material for the addition to food. Since the addition of pure Quassin to food is not allowed, the full extract with all ingredients is definitively the substance that was evaluated in view of the use in food	
5(13)	5.1.9 neurotoxicity	DK: Also for this section no assessment has been performed, and it is not clear on what basis the conclusion on no effect is drawn. A more thorough assessment is needed also for this endpoint. As mentioned in the comment to section 5.1.7 on immunotoxicity the applicant describes an anti-inflammatory mode of action for the extract. Please consider the impact of this on the brain.		Applicant: *Quassia amara* was evaluated for food use based on a literature evaluation summarized in the report of the EUROPEAN COMMISSION HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL, Scientific Committee on Food (SCF/CS/FLAV/ FLAVOUR/29/FINAL) of 25.7.2002. Thus, it complies with Art 23(2) of the Regulation (EC) 1107/2009 that the substance should have already been evaluated in the view of	Agree with the comment. Also, it is acknowledged that the argumentation by the applicant to dismiss neurotoxicity is not relevant (see also 2(4)). Nevertheless, it is highlighted that in the proposed dataset there is no indication of possible effects on the nervous system by Quassia/its components, therefore neurotoxicity is considered unlikely.

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No.	**Column 1** **Reference to Application Template**	**Column 2** **Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4** **Follow up response from applicant**	**Column 5** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
				other uses. Due to this evaluation, the limits in Regulation (EC) 1334/2008 were set as follows: In **Part A of Annex III** of Regulation (EC) 1334/2008 Quassin is listed as a substance that shall not be added as such to food. However, in **Part B of Annex III** are listed substances naturally present in flavouring and food ingredients with flavouring properties, for which a maximum level was set. In this Part B of Annex III of Regulation (EC) No 1334/2008 the limits for Quassin of 0.5 mg/kg in non-alcoholic beverages, 1 mg/kg in bakery wares and 1.5 mg/kg in alcoholic beverages are specified. In **Part B of Annex IV** of the same regulation the conditions of use for flavourings and food ingredients with flavouring	

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				properties produced from certain source materials are specified. There, *Quassia amara* is listed as a source material with the specification "Flavourings and food ingredients with flavouring properties produced from the source material may only be used for the production of beverages and bakery wares." Thus, *Quassia amara* is clearly defined as a possible source material for the addition to food. Since the addition of pure Quassin to food is not allowed, the full extract with all ingredients is definitively the substance that was evaluated in view of the use in food.	
5(14)	Impact on human and animal health, 5.1 Toxicity	NL: Quassin is not an approved flavouring substance. It is included in Annex III of Regulation (EC) 1334/2008 (part A) as a substance that shall not be added as such		Applicant: *Quassia amara* was evaluated for food use based on a literature evaluation summarized in the report of the EUROPEAN COMMISSION HEALTH & CONSUMER	See 2(4) and 5(2).

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		to food. In Annex III are listed substances that are naturally present in food, for which a maximum level was set. Specifically, in Regulation (EC) No 1334/2008 the limits for quassin of 0.5 mg/kg in non-alcoholic beverages, 1 mg/kg in bakery wares and 1.5 mg/kg in alcoholic beverages are for substances naturally present in flavouring and food ingredients with flavouring properties. This puts into question if the maximum levels from Regulation EC 1334/2008 should be regarded as safe levels and we question the use of this levels in the exposure assessment to explain/argue the use of an unrealistic low AOEL value		PROTECTION DIRECTORATE-GENERAL, Scientific Committee on Food (SCF/CS/FLAV/ FLAVOUR/29/FINAL) of 25.7.2002. Thus, it complies with Art 23(2) of the Regulation (EC) 1107/2009 that the substance should have already been evaluated in the view of other uses. Due to this evaluation, the limits in Regulation (EC) 1334/2008 were set as follows: In **Part A of Annex III** of Regulation (EC) 1334/2008 Quassin is listed as a substance that shall not be added as such to food. However, in **Part B of Annex III** are listed substances naturally present in flavouring and food ingredients with flavouring properties, for which a maximum level was set. In this Part B of Annex III of Regulation (EC) No 1334/2008 the limits for Quassin of 0.5	

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		(according to the applicant) causing unacceptable exposure. Using higher AOEL values based on bitterness of higher concentrations e.g. 0.2 g Quassia/L is therefore also questionable without more data related to toxicity.		mg/kg in non-alcoholic beverages, 1 mg/kg in bakery wares and 1.5 mg/kg in alcoholic beverages are specified. In **Part B of Annex IV** of the same regulation the conditions of use for flavourings and food ingredients with flavouring properties produced from certain source materials are specified. There, *Quassia amara* is listed as a source material with the specification "Flavourings and food ingredients with flavouring properties produced from the source material may only be used for the production of beverages and bakery wares." Thus, *Quassia amara* is clearly defined as a possible source material for the addition to food. Since the addition of pure Quassin to food is not allowed, the full extract with all ingredients is definitively the	

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				substance that was evaluated in view of the use in food. Normal consumption of beverages and bakery wares containing the allowed maximum levels of quassin, would lead to quassin uptake above the proposed AOEL from EFSA.	
5(15)	5.1.4 Genotoxicity	NL: No clear negative results of the *in vivo* Comet assay in rat liver and small intestine cells can be presented as there are no positive controls shown to induce DNA breaks. Also gene mutation has not been excluded yet based on the *in vitro* micronucleus test.		Applicant: An evaluation of the genotoxic potential of *Quassia amara* L. wood was performed based on all available study data on this topic and considering the recommendations for genotoxicity testing as outlined by the EFSA Scientific Committee (EFSA, 2011; EFSA, 2017; EFSA 2019). Furthermore, profiling for endpoints genotoxicity/carcinogenicity (OECD QSAR Toolbox v.4.6) for the known extract components quassin (main component, analytical lead substance), neoquassin and 18-	The genotoxicity assessment strategy proposed by the applicant is in principle appropriate, however further substantiation is needed, see 5(1).

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				hydroxyquassin (both tentatively identified by mass spectrometry analysis) was performed to support the present evaluation. The study database comprised *in vitro* and *in vivo* genotoxicity assays (GLP and OECD guideline compliant) related to all relevant endpoints, *i.e.*, gene mutation, structural and numerical chromosomal aberrations and was thus considered complete and adequate for the evaluation of genotoxicity. In the Ames test, *Quassia amara* L. wood was non-mutagenic in the bacterial strains *Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537, and *Escherichia coli* WP2*uvrA*. In a micronucleus assay (MNA) *in vitro* in human lymphocytes, there was no relevant effect on micronuclei incidences in the presence of metabolic activation (S9 mix), but slightly increased	

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				incidences in micronuclei in the absence of metabolic activation were observed. These increases, which were assessed as equivocal in the study report, were only observed at cytotoxic concentrations. Since the increases in micronucleus incidences were marginal and that cytotoxicity is a known confounder under *in vitro* testing conditions, the overall assessment of the study indicates low concern for genotoxicity. To follow up on these slight increases a Comet assay in male rats was chosen as *in vivo* follow-up test. The investigation of potential DNA damage *in vivo* revealed that *Quassia amara* L. wood was not genotoxic in cells of the small intestine (site of direct contact) and in liver cells. The Comet assay was selected as the adequate test system for the complex *Quassia amara* L. wood	

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				since potential cytotoxic effects determined in a mouse bone marrow MNA, which represents the potential alternative to the *in vivo* Comet assay in this case, could not be unequivocally attributed to a defined component of the wood. By choosing a tissue with site of direct contact (*e.g.* small intestine), tissue exposure for components not requiring metabolic activation can be demonstrated in the Comet assay after oral exposure. For an *in vivo* MNA, however, bone marrow exposure to all components of the test substance (confirmed bone marrow exposure is a prerequisite for regulatory acceptance of this assay) can neither be predicted nor reliably analytically demonstrated. Alerts depicted in the genotoxicity/carcinogenicity profiling for the components	

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				quassin (main component), neoquassin and 18-hydroxyquassin using the OECD QSAR Toolbox v.4.6 indicated that direct interaction with DNA might be the underlying mechanism to the equivocal finding in the *in vitro* MNA, supporting the choice of the Comet assay as the adequate follow up test *in vivo*. Overall, it can be concluded that *Quassia amara* L. wood is of low concern regarding the endpoint genotoxicity and the level of uncertainty remains low and acceptable.	
5(16)	5.1.5 Long-term toxicity	NL: NL would consider more appropriate to exclude first the genotoxic potential of the extract of the wood of *Quassia amara* and then to set specific health-based guideline values (e.g. Acceptable Operator Level)		Applicant: An evaluation of the genotoxic potential of *Quassia amara* L. wood was performed based on all available study data on this topic and considering the recommendations for genotoxicity testing as outlined	See 5(1).

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		on the basis of available toxicity studies. Presenting positive/beneficial effects is not enough to exclude long-term toxicity and carcinogenicity.		by the EFSA Scientific Committee (EFSA, 2011; EFSA, 2017; EFSA 2019). Furthermore, profiling for endpoints genotoxicity/carcinogenicity (OECD QSAR Toolbox v.4.6) for the known extract components quassin (main component, analytical lead substance), neoquassin and 18-hydroxyquassin (both tentatively identified by mass spectrometry analysis) was performed to support the present evaluation. The study database comprised *in vitro* and *in vivo* genotoxicity assays (GLP and OECD guideline compliant) related to all relevant endpoints, *i.e.*, gene mutation, structural and numerical chromosomal aberrations and was thus considered complete and adequate for the evaluation of genotoxicity.	

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				In the Ames test, *Quassia amara* L. wood was non-mutagenic in the bacterial strains *Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537, and *Escherichia coli* WP2*uvrA*. In a micronucleus assay (MNA) *in vitro* in human lymphocytes, there was no relevant effect on micronuclei incidences in the presence of metabolic activation (S9 mix), but slightly increased incidences in micronuclei in the absence of metabolic activation were observed. These increases, which were assessed as equivocal in the study report, were only observed at cytotoxic concentrations. Since the increase in micronucleus incidences were marginal and that cytotoxicity is a known confounder under *in vitro* testing conditions, the overall assessment of the study indicates low concern for genotoxicity. To	

5.1. Toxicity

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				follow up on these slight increases a Comet assay in male rats was chosen as *in vivo* follow-up test. The investigation of potential DNA damage *in vivo* revealed that *Quassia amara* L. wood was not genotoxic in cells of the small intestine (site of direct contact) and in liver cells. The Comet assay was selected as the adequate test system for the complex *Quassia amara* L. wood since potential cytotoxic effects determined in a mouse bone marrow MNA, which represents the potential alternative to the *in vivo* Comet assay in this case, could not be unequivocally attributed to a defined component of the wood. By choosing a tissue with site of direct contact (*e.g.* small intestine), tissue exposure for components not requiring metabolic activation can be	

5.1. Toxicity

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				demonstrated in the Comet assay after oral exposure. For an *in vivo* MNA, however, bone marrow exposure to all components of the test substance (confirmed bone marrow exposure is a prerequisite for regulatory acceptance of this assay) can neither be predicted nor reliably analytically demonstrated. Alerts depicted in the genotoxicity/carcinogenicity profiling for the components quassin (main component), neoquassin and 18-hydroxyquassin using the OECD QSAR Toolbox v.4.6 indicated that direct interaction with DNA might be the underlying mechanism to the equivocal finding in the *in vitro* MNA, supporting the choice of the Comet assay as the adequate follow up test *in vivo*. Overall, it can be concluded that *Quassia amara* L. wood is of low	

5.1. Toxicity

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				concern regarding the endpoint genotoxicity and the level of uncertainty remains low and acceptable. Moreover, *Quassia amara* was evaluated for food use based on a literature evaluation summarized in the report of the EUROPEAN COMMISSION HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL, Scientific Committee on Food (SCF/CS/FLAV/ FLAVOUR/29/FINAL) of 25.7.2002. Thus, it complies with Art 23(2) of the Regulation (EC) 1107/2009 that the substance should have already been evaluated in the view of other uses. Due to this evaluation, the limits in Regulation (EC) 1334/2008 were set as follows: In **Part A of Annex III** of Regulation (EC) 1334/2008	

5.1. Toxicity

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
				Quassin is listed as a substance that shall not be added as such to food. However, in **Part B of Annex III** are listed substances naturally present in flavouring and food ingredients with flavouring properties, for which a maximum level was set. In this Part B of Annex III of Regulation (EC) No 1334/2008 the limits for Quassin of 0.5 mg/kg in non-alcoholic beverages, 1 mg/kg in bakery wares and 1.5 mg/kg in alcoholic beverages are specified. In **Part B of Annex IV** of the same regulation the conditions of use for flavourings and food ingredients with flavouring properties produced from certain source materials are specified. There, *Quassia amara* is listed as a source material with the specification "Flavourings and food ingredients with flavouring	

5.1. Toxicity

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
				properties produced from the source material may only be used for the production of beverages and bakery wares." Thus, *Quassia amara* is clearly defined as a possible source material for the addition to food. Since the addition of pure Quassin to food is not allowed, the full extract with all ingredients is definitively the substance that was evaluated in view of the use in food.	
5(17)	5.1.6 Reproductive toxicity	NL: The lowest LOAEL should be used to derive the threshold. So, still 0.1 mg/kg bw of quassin as previously stated.		Applicant: *Quassia amara* was evaluated for food use based on a literature evaluation summarized in the report of the EUROPEAN COMMISSION HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL, Scientific Committee on Food (SCF/CS/FLAV/ FLAVOUR/29/FINAL) of 25.7.2002. Thus, it complies with Art 23(2) of the Regulation (EC)	The available dataset is not robust enough to derive a sufficiently solid NOAEL/ LOAEL. See 5(2).

5.1. Toxicity					
No.	**Column 1** **Reference to Application Template**	**Column 2** **Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4** **Follow up response from applicant**	**Column 5** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
				1107/2009 that the substance should have already been evaluated in the view of other uses. Due to this evaluation, the limits in Regulation (EC) 1334/2008 were set as follows: In **Part A of Annex III** of Regulation (EC) 1334/2008 Quassin is listed as a substance that shall not be added as such to food. However, in **Part B of Annex III** are listed substances naturally present in flavouring and food ingredients with flavouring properties, for which a maximum level was set. In this Part B of Annex III of Regulation (EC) No 1334/2008 the limits for Quassin of 0.5 mg/kg in non-alcoholic beverages, 1 mg/kg in bakery wares and 1.5 mg/kg in alcoholic beverages are specified. In **Part B of Annex IV** of the same regulation the conditions of use for flavourings and food	

5.1. Toxicity

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
				ingredients with flavouring properties produced from certain source materials are specified. There, *Quassia amara* is listed as a source material with the specification "Flavourings and food ingredients with flavouring properties produced from the source material may only be used for the production of beverages and bakery wares." Thus, *Quassia amara* is clearly defined as a possible source material for the addition to food. Since the addition of pure Quassin to food is not allowed, the full extract with all ingredients is definitively the substance that was evaluated in view of the use in food. Thus, it should be appropriate to refer to these limits.	
5(18)	5.1.8 Endocrine disruption	NL: As stated "In 2018, EFSA raised concerns for reproductive toxicity and		Applicant: *Quassia amara* was evaluated for food use based on a literature evaluation	See data gap at 5(2).

5.1. Toxicity

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		endocrine disrupting potential in the Technical report. It was already discussed by the applicant, that effects on the hormone system may arise by various natural substances – also substances which are approved basic substances under plant protection law." In this paragraph 5.1.8. the inherent endocrine capacity of *Quassia amara* should be addressed according to the endocrine disruption guidance.		summarized in the report of the EUROPEAN COMMISSION HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL, Scientific Committee on Food (SCF/CS/FLAV/ FLAVOUR/29/FINAL) of 25.7.2002. Thus, it complies with Art 23(2) of the Regulation (EC) 1107/2009 that the substance should have already been evaluated in the view of other uses. Due to this evaluation, the limits in Regulation (EC) 1334/2008 were set as follows: In **Part A of Annex III** of Regulation (EC) 1334/2008 Quassin is listed as a substance that shall not be added as such to food. However, in **Part B of Annex III** are listed substances naturally present in flavouring and food ingredients with flavouring properties, for which a maximum level was set. In	

5.1. Toxicity

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
				this Part B of Annex III of Regulation (EC) No 1334/2008 the limits for Quassin of 0.5 mg/kg in non-alcoholic beverages, 1 mg/kg in bakery wares and 1.5 mg/kg in alcoholic beverages are specified. In **Part B of Annex IV** of the same regulation the conditions of use for flavourings and food ingredients with flavouring properties produced from certain source materials are specified. There, *Quassia amara* is listed as a source material with the specification "Flavourings and food ingredients with flavouring properties produced from the source material may only be used for the production of beverages and bakery wares." Thus, *Quassia amara* is clearly defined as a possible source material for the addition to food	

5.1. Toxicity

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
				with the limits set in Reg. (EC) 1334/2008 referring to the lead substance Quassin. Since the addition of pure Quassin to food is not allowed, the full extract with all ingredients is definitively the substance that was evaluated in view of the use in food. Applicants followed this evaluation in their risk assessment.	
5(19)	5.1 Toxicity	EFSA: Based on the information provided by the applicant, it is highlighted that *Quassia amara* contains various quassinoids (terpenes) and other compounds (e.g. alkaloids) that show biological properties. Most studies proposed by the applicant inform on effects by quassin, considered as the lead analytical compound; instead, the impact on human and animal health of other quassinoids	EFSA: Please integrate the information on the potential impact on human and animal safety of *Quassia amara* and its individual components other than quassin (e.g. other quassinoids, indole alkaloids), as relevant. To this aim, please explore further the literature using search keywords on constituents other than *Quassia amara* and quassin (see also comments on	In table 5-2 all studies were summarized that were conducted or with Quassin or with full extracts of *Quassia amara*. For the extracts, all studies with extracts from bark or stem or roots of *Quassia amara* were integrated. Studies, where the part of the plant used for the preparation of the extract were also integrated. The table 5-2 was updated where the information, which part of the plant was used, were lacking. For the preparation of the	Addressed.

5.1. Toxicity

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
		and in general on other compounds is limitedly reported and discussed. It is also noted that many of the provided studies are conducted on Quassia extracts other than aqueous extracts, and from various parts of the plant (e.g. leaves, bark etc). The presence and/or levels of individual compounds may vary depending on the preparation process; therefore the relevance of these studies for the toxicological assessment of the basic substance matter of this application should be justified. See further details in the Compendium of botanicals: https://www.efsa.europa.eu/en/data-report/compendium-botanicals#information-	Section 10 -Literature search). For all the studies used in the assessment please clearly report the part of the plant used as the test substance (e.g. leaves, bark etc), the type of test substance (ethanolic extract, aqueous extract, pure individual components etc); and discuss the relevance of these for the basic substance matter of this application.	extracts, all information available were reported. Unfortunately, often in this kind of literature the preparation of the extracts is often not sufficiently characterized. Applicant could have also discarded these studies, however, for the sake of completeness, we wanted to summarize all information available.	

5.1. Toxicity					
No.	**Column 1 Reference to Application Template**	**Column 2 Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4 Follow up response from applicant**	**Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
		provided-by-the-compendium Botanical Summary Report | EFSA (europa.eu)			
5(20)	5.1.4 Genotoxicity	EFSA: The lack of a complete genotoxicity package was previously identified as a data gap (EFSA, 2018) for the basic substance *Quassia amara* L. wood extract. It is noted that additional studies have been provided in the context of the current application, however the genotoxicity assessment of the basic substance needs further corroboration, in particular as regards chromosomal aberrations, considering the equivocal result of the micronucleus test with the extract prepared from *Quassia amara* wood chips under the conditions of the test as reported.	EFSA: Please provide further evidence to support the genotoxicity assessment of this basic substance (e.g. a new *in vitro* micronucleus test). Studies and/or information (e.g. in silico) on individual components (e.g. quassin, others) can also be considered to support the assessment.	Applicant: An evaluation of the genotoxic potential of *Quassia amara* L. wood was performed based on all available study data on this topic and considering the recommendations for genotoxicity testing as outlined by the EFSA Scientific Committee (EFSA, 2011; EFSA, 2017; EFSA 2019). Furthermore, profiling for endpoints genotoxicity/carcinogenicity (OECD QSAR Toolbox v.4.6) for the known extract components quassin (main component, analytical lead substance), neoquassin and 18-hydroxyquassin (both tentatively identified by mass spectrometry analysis) was performed to support the present evaluation.	See 5(1).

5.1. Toxicity

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				The study database comprised *in vitro* and *in vivo* genotoxicity assays (GLP and OECD guideline compliant) related to all relevant endpoints, *i.e.*, gene mutation, structural and numerical chromosomal aberrations and was thus considered complete and adequate for the evaluation of genotoxicity. In the Ames test, *Quassia amara* L. wood was non-mutagenic in the bacterial strains *Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537, and *Escherichia coli* WP2*uvrA*. In a micronucleus assay (MNA) *in vitro* in human lymphocytes, there was no relevant effect on micronuclei incidences in the presence of metabolic activation (S9 mix), but slightly increased incidences in micronuclei in the absence of metabolic activation	

5.1. Toxicity

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				were observed. These increases, which were assessed as equivocal in the study report, were only observed at cytotoxic concentrations. Since the increases in micronucleus incidences were marginal and that cytotoxicity is a known confounder under *in vitro* testing conditions, the overall assessment of the study indicates low concern for genotoxicity. To follow up on these slight increases a Comet assay in male rats was chosen as *in vivo* follow-up test. The investigation of potential DNA damage *in vivo* revealed that *Quassia amara* L. wood was not genotoxic in cells of the small intestine (site of direct contact) and in liver cells. The Comet assay was selected as the adequate test system for the complex *Quassia amara* L. wood since potential cytotoxic effects	

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				determined in a mouse bone marrow MNA, which represents the potential alternative to the *in vivo* Comet assay in this case, could not be unequivocally attributed to a defined component of the wood. By choosing a tissue with site of direct contact (*e.g.* small intestine), tissue exposure for components not requiring metabolic activation can be demonstrated in the Comet assay after oral exposure. For an *in vivo* MNA, however, bone marrow exposure to all components of the test substance (confirmed bone marrow exposure is a prerequisite for regulatory acceptance of this assay) can neither be predicted nor reliably analytically demonstrated. Alerts depicted in the genotoxicity/carcinogenicity profiling for the components quassin (main component),	

5.1. Toxicity

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				neoquassin and 18-hydroxyquassin using the OECD QSAR Toolbox v.4.6 indicated that direct interaction with DNA might be the underlying mechanism to the equivocal finding in the *in vitro* MNA, supporting the choice of the Comet assay as the adequate follow up test *in vivo*. Overall, it can be concluded that *Quassia amara* L. wood is of low concern regarding the endpoint genotoxicity and the level of uncertainty remains low and acceptable.	
5(21)	5.1.6, Reproductive toxicity	EFSA: The reproductive system is a potential target for adverse effects by *Quassia amara* extracts (and/or its constituents) and, on the basis of the available information it cannot be excluded that such effects are related to an endocrine	EFSA: Please integrate the literature search to corroborate the information on reproductive toxicity to have a general overview of possible (adverse) effects on the reproductive system for *Quassia amara* and its relevant individual	Applicant: In Table 5-2 we refer to the state of knowledge of 2002, the year when the report of the EUROPEAN COMMISSION HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL, Scientific Committee on Food (SCF/CS/FLAV/ FLAVOUR/29/FINAL) of	Partially addressed (new information added). See 5(2).

5.1. Toxicity

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		mode of action (MoA). The set of studies proposed by the applicant on effects of Quassia extracts (and/or its constituents) on the reproductive system is not comprehensive enough to address this assessment; in particular, some studies available in the published literature are not identified and/or discussed by the applicant (such as Parveen et al, 2003, Adewole 2021). It is also noted that most of the provided studies are on extracts other than water; the relevance of possible impurities from the extraction process for effects on the reproductive system has to be considered.	components, and on the MoA of such effects. To this aim consider searching for *Quassia amara* and its individual constituents (see also Section 10) and introduce search terms relevant for (adverse) effects on the male and female reproductive system. Please provide an assessment of the retrieved studies, including: • Parveen et al, 2003 • Adewole 2021 Please reorganise the tabular summary (Table 5-2) by type of (adverse) effect (e.g. reproductive system effects, others) integrating the outcome of the revised literature search for reproductive effects and revise the narrative text accordingly.	25.7.2002.was published. This report is the basis of the evaluation in the view of other uses (foodstuff) where the limits in Regulation (EC) 1334/2008 we refer to were set. In Table 5-2 the publications are listed that were not included n the report. It is shown that no results were published since 2002 that show effects with lower concentrations than those that were published before 2002.	

5.1. Toxicity

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5(22)	5.1.8 Endocrine disruption (ED)	EFSA: the assessment of ED properties needs further elaboration, please see EFSA comments on Reproductive toxicity.	See EFSA comment above on reproductive toxicity	Applicant: *Quassia amara* was evaluated for food use based on a literature evaluation summarized in the report of the EUROPEAN COMMISSION HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL, Scientific Committee on Food (SCF/CS/FLAV/ FLAVOUR/29/FINAL) of 25.7.2002. Thus, it complies with Art 23(2) of the Regulation (EC) 1107/2009 that the substance should have already been evaluated in the view of other uses. Due to this evaluation, the limits in Regulation (EC) 1334/2008 were set as follows: In **Part A of Annex III** of Regulation (EC) 1334/2008 Quassin is listed as a substance that shall not be added as such to food. However, in **Part B of Annex III** are listed substances naturally present in flavouring	See data gap at 5(2).

5.1. Toxicity

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
				and food ingredients with flavouring properties, for which a maximum level was set. In this Part B of Annex III of Regulation (EC) No 1334/2008 the limits for Quassin of 0.5 mg/kg in non-alcoholic beverages, 1 mg/kg in bakery wares and 1.5 mg/kg in alcoholic beverages are specified. In **Part B of Annex IV** of the same regulation the conditions of use for flavourings and food ingredients with flavouring properties produced from certain source materials are specified. There, *Quassia amara* is listed as a source material with the specification "Flavourings and food ingredients with flavouring properties produced from the source material may only be used for the production of beverages and bakery wares."	

5.1. Toxicity

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
				Thus, *Quassia amara* is clearly defined as a possible source material for the addition to food. Since the addition of pure Quassin to food is not allowed, the full extract with all ingredients is definitively the substance that was evaluated in view of the use in food.	

5.2. Reference values: Acceptable Daily Intake, Acute reference Dose, Acceptable Operator Exposure Level, Acute Acceptable Operator Exposure Level

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
5(23)	5.2, Reference values	DE: As commented by EFSA in the public consultation (EFSA 2018-EN:1382; p. 23)		Applicant: *Quassia amara* was evaluated for food use based on a literature evaluation summarized in the	See 2(4)

5.2. Reference values: Acceptable Daily Intake, Acute reference Dose, Acceptable Operator Exposure Level, Acute Acceptable Operator Exposure Level

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
		quassin (main component of *Quassia amara*) is not an approved food flavouring substance. It is even specified that quassin should not be added in food, and the maximum level limits given in Annex III of Regulation (EC) 1334/2008 are for naturally present substances such as quassin in food. Therefore, quassin (or *Quassia amara*) does not fulfil the criteria of a 'foodstuff' since it should not be intentionally incorporated into food.		report of the EUROPEAN COMMISSION HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL, Scientific Committee on Food (SCF/CS/FLAV/ FLAVOUR/29/FINAL) of 25.7.2002. Thus, it complies with Art 23(2) of the Regulation (EC) 1107/2009 that the substance should have already been evaluated in the view of other uses. Due to this evaluation, the limits in Regulation (EC) 1334/2008 were set as follows: In **Part A of Annex III** of Regulation (EC) 1334/2008 Quassin is listed as a substance that shall not be added as such to food. However, in **Part B of Annex III** are listed substances naturally present in flavouring and food ingredients with flavouring properties, for which a maximum level was set. In this Part B of Annex III of Regulation (EC) No 1334/2008 the limits for Quassin of 0.5 mg/kg in non-alcoholic beverages, 1 mg/kg in	

5.2. Reference values: Acceptable Daily Intake, Acute reference Dose, Acceptable Operator Exposure Level, Acute Acceptable Operator Exposure Level

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
				bakery wares and 1.5 mg/kg in alcoholic beverages are specified. In **Part B of Annex IV** of the same regulation the conditions of use for flavourings and food ingredients with flavouring properties produced from certain source materials are specified. There, *Quassia amara* is listed as a source material with the specification "Flavourings and food ingredients with flavouring properties produced from the source material may only be used for the production of beverages and bakery wares." Thus, *Quassia amara* is clearly defined as a possible source material for the addition to food. Since the addition of pure Quassin to food is not allowed, the full extract with all ingredients is definitively the substance that was evaluated in view of the use in food.	
5(24)	5.2 AOEL	NL: The operator exposure is compared to the highest		Applicant: The study of Raji and Bolarinwa 1997 was integrated in the	The NL proposal is noted.

5.2. Reference values: Acceptable Daily Intake, Acute reference Dose, Acceptable Operator Exposure Level, Acute Acceptable Operator Exposure Level

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
		permitted content of Quassin in food. We do not agree with using these as reference value. Effects on male and female fertility in the Raji & Bolarinwa 1997 and Raji & Akinola 2010 already occurred at 0.1 mg/kg bw of quassin. Applying a standard safety factor of 10 and an additional safety factor of 3 to go from a LOAEL to a NOAEL would result in a reference value of 0.0003 mg Qaussin/kg bw/day. The operator, worker and resident exposure are all estimated to be far above this level. Therefore, in our opinion no safe use has been shown.		evaluation in the report of the EUROPEAN COMMISSION HEALTH & CONSUMER PROTECTION DIRECTO-RATE-GENERAL, Scientific Committee on Food (SCF/CS/FLAV/ FLAVOUR/29/FINAL) of 25.7.2002. The study on Raji & Akinola 2010 refers to similar concentrations as the study of 1997. This report is the basis of the evaluation in the view of other uses (foodstuff) where the limits in Regulation (EC) 1334/2008 we refer to were set. In Table 5-2 the publications are listed that were not included in the report. It is shown, that no results were published since 2002 that show effects with lower concentrations than those that were published before 2002.	However, EFSA considers that the available dataset is not robust enough to derive a sufficiently solid NOAEL/LOAEL on quassin and Quassia extract, therefore a risk assessment cannot be performed.
5(25)	5.2 Reference values:	EFSA: It is not clear if *Quassia amara* fulfils criteria of a 'foodstuff' as defined in	EFSA: Please corroborate the information on possible effects on human and	Applicant: *Quassia amara* was evaluated for food use based on a literature evaluation summarized in the	See 2(4) and 5(2)

5.2. Reference values: Acceptable Daily Intake, Acute reference Dose, Acceptable Operator Exposure Level, Acute Acceptable Operator Exposure Level

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
	Acceptable Daily Intake, Acute reference Dose, Acceptable Operator Exposure Level, Acute Acceptable Operator Exposure Level	Article 2 of Regulation (EC) No 178/2002, on the basis of the available information. Actually, quassin (the lead substance of *Quassia amara* as indicated in the application) is listed in Regulation (EC) 1334/2008 (Annex III) among substances that shall not be added as such to food, and maximum levels via beverages and bakery wares are set. It is not clear how these levels were determined; whether these refer to pure quassin or to a *Quassia amara* extract, and which type of. In conclusion the relevance of such information for discussing reference values and exposure of the basic substance matter of this application is unclear;	animal health by *Quassia amara* and its relevant individual components, as per previous comments and elaborate on exposure and reference values, accordingly.	report of the EUROPEAN COMMISSION HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL, Scientific Committee on Food (SCF/CS/FLAV/ FLAVOUR/29/FINAL) of 25.7.2002. Thus, it complies with Art 23(2) of the Regulation (EC) 1107/2009 that the substance should have already been evaluated in the view of other uses. Due to this evaluation, the limits in Regulation (EC) 1334/2008 were set as follows: In **Part A of Annex III** of Regulation (EC) 1334/2008 Quassin is listed as a substance that shall not be added as such to food. However, in **Part B of Annex III** are listed substances naturally present in flavouring and food ingredients with flavouring properties, for which a maximum level was set. In this Part B of Annex III of Regulation (EC) No 1334/2008 the limits for Quassin of 0.5 mg/kg in non-alcoholic beverages, 1 mg/kg in	

5.2. Reference values: Acceptable Daily Intake, Acute reference Dose, Acceptable Operator Exposure Level, Acute Acceptable Operator Exposure Level

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
		rather, toxicological relevant information on the basic substance and/or its individual constituents should be used for the assessment. It is noted that the assessment of plant "toxins" is variably regulated in the EU, if at all, and no coherent legislation on plant toxins in food exist in the EU (M. de Nijs, M.Y. Noordam and H.G.J. Mol, 2017. Short inventory of EU legislation on plant toxins in food. Quality Assurance and Safety of Crops & Foods 09 (1): 129-139)		bakery wares and 1.5 mg/kg in alcoholic beverages are specified. In **Part B of Annex IV** of the same regulation the conditions of use for flavourings and food ingredients with flavouring properties produced from certain source materials are specified. There, *Quassia amara* is listed as a source material with the specification "Flavourings and food ingredients with flavouring properties produced from the source material may only be used for the production of beverages and bakery wares." Thus, *Quassia amara* is clearly defined as a possible source material for the addition to food. Since the addition of pure Quassin to food is not allowed, the full extract with all ingredients is definitively the substance that was evaluated in view of the use in food.	

5.3. Non-dietary exposure to the substance and impurities in it

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
5(26)	5.3, Non-dietary exposure to the substance and impurities in it; **resident exposure**	DE: By using the EFSA Calculator there is no safe use for residents due to the high inhalation exposure.	DE: Please revise the statement of approval.	Applicant: As already shown in the original application, the comparison to consumption of food of several commodities (bakery wares, non-alcoholic and alcoholic beverages, respectively) with the respective allowed maximum levels of quassin showed that the total systemic exposure can be achieved by normal food consumption. This applies also for the updated calculation according to EFSA GD 2022, taking into account this and subsequent comments on 5.3, Non-dietary exposure to the substance and impurities in it.	Non-dietary exposure (NDE) is based on the active substance, quassin, as indicated by the applicant. The concentration of quassin in the preparation is inconsistently reported and, based on the description, no justification is provided for some of the reported data (i.e. 0.6 g/L quassin). See also data gap 2(12). Furthermore, no robust NOAELs/LOAELs could be identified for quassin (and Quassia extracts), see point 5(2). Therefore, a risk assessment cannot be carried out. It is also noted that the genotoxicity

5.3. Non-dietary exposure to the substance and impurities in it					
No.	**Column 1** **Reference to Application Template**	**Column 2** **Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4** **Follow up response from applicant**	**Column 5** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
					assessment needs corroboration (see 5(1)). The comparative assessment versus exposure to quassia extract or quassin via diet cannot be used as a supportive argument, considering the limited exposure data available, the lack of information on the composition of *Quassia amara* L. wood water extract, as well as the potential intrinsic hazardous properties of the substance, see 5(1) and 5(2). **Data gap:** NDE should be carried out using robust reference values and

5.3. Non-dietary exposure to the substance and impurities in it

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					based on thorough information on the composition of the extract. See also 2(12)
5(27)	5.3, Non-dietary exposure to the substance and impurities in it; **worker exposure**	DE: Worker re-entry in hops should be calculated assuming a duration of 8 hours instead of 2 hours (acc. to EFSA GD 2022) because activities like training bines or harvesting are done manually.	DE: Please revise the worker estimation.	Applicant: The exposure calculation for worker re-entry was updated assuming harvesting activities with a duration of 8 hours according to EFSA GD 2022.	Addressed. See 5(26)
5(28)	5.3, Non-dietary exposure to the substance and impurities in it; **dermal absorption**	DE: Considering the dermal absorption value for the in-use dilution incomplete absorption (i.e. T0.5 < 75 %) should be assumed as for most of the cells the residue in the receptor fluid was below the LOQ.	DE: Please revise the dermal absorption value for the in-use dilution assuming incomplete absorption (i.e. considering the residues found in tape strips 3-x as absorbed).	Applicant: The dermal absorption values were amended in the application.	Addressed.
5(29)	5.3, Non-dietary exposure to the substance	DE: According to the GAP table the lowest water volume is 500 L for applications on pome fruit.	DE: Please revise the exposure estimation with the revised input parameters.	Applicant: The GAP was changed. The use of 500 L is no longer part of the GAP.	Addressed. See 5(26)

5.3. Non-dietary exposure to the substance and impurities in it

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
	and impurities in it; **data on exposure data entry**	Moreover, the DT_{50} default value of 30 µg/cm^2/kg a.s./ha should be used in case no measured value is given.			
5(30)	5.3, Non-dietary exposure to the substance and impurities in it; **volatility**	DE: According to our information the lead substance quassin is volatile. Therefore, the air concentration might be estimated by calculating the saturated vapour concentration.	DE: Please revise the worker exposure estimation by calculating the saturated vapour concentration.	Applicant: No vapour pressure study for quassin is available, as no study was requested in the evaluation from 2018. As cited in the original application, based on the ACD lab tool vapor pressure is estimated to be 1.73 x 10^3 Pa at 25°C (9.01 x 10^2 Pa at 20°C). Based on the commenting, further investigations were conducted regarding the vapor pressure, which resulted in a substantially differing value derived from EPI suite, being 1.9 x 10^{-8} Pa at 25°C. Considering the spatial properties of the molecule the applicant considers a vapor pressure of <5 x 10^{-3} Pa at 25°C as rather realistic estimate. Thus, an updated calculation based on this estimate according to EFSA GD 2022 was conducted.	Addressed. See 5(26).

5.3. Non-dietary exposure to the substance and impurities in it

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
5(31)	5.3.	DK: According to section 2.5 the basic substance is prepared by boiling wood chips in large quantities of water (100-150L) for 1 hour on the farm. The extract is subsequently sieved and then diluted further with water, resulting in 1000-2300 L extract (for use on one hectare). This procedure will result in exposure of the manufacturer, and given the large quantities, we are of the opinion that a risk assessment is required.		Applicant: In this procedure, the wood chips are in bags and the bags are emptied in the big pot with water. On the farms, for the filtering and the transport of the liquid in other recipients, usually, pumps are used so that there will be no contact between the liquid and the manufacturer. If small quantities are needed in hobby gardens, the cooking corresponds to the preparation of herbal teas, the handling of the liquid is covered by the risk assessment.	Addressed.
5(32)	5.3.1 operator exposure	DK: According to the non-dietary exposure assessment PPE and RPE is required for safe use for operators. This is not acceptable for basic substances, that should be		Applicant: Systemic exposure without RPE/PPE was discussed and compared with the intake of beverages in relation to the permitted concentrations of quassin in these beverages. As already shown in the original application, the comparison to	See 5(26).

5.3. Non-dietary exposure to the substance and impurities in it

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
		usable for amateur and professional users alike.		consumption of alcoholic beverages with the respective allowed maximum levels of quassin showed that the total systemic exposure can be achieved by normal food consumption.	
5(33)	5.3.1 Worker exposure	DK: Disagree with the applicant. DK supports the use of the reference value proposed by EFSA in the technical report (2018).		Applicant: *Quassia amara* was evaluated for food use based on a literature evaluation summarized in the report of the EUROPEAN COMMISSION HEALTH & CONSUMER PROTECTION DIRECTO¬RATE-GENERAL, Scientific Committee on Food (SCF/CS/FLAV/ FLAVOUR/29/FINAL) of 25.7.2002. Thus, it complies with Art 23(2) of the Regulation (EC) 1107/2009 that the substance should have already been evaluated in the view of other uses. Due to this evaluation, the limits in Regulation (EC) 1334/2008 were set as follows: In Part A of Annex III of Regulation (EC) 1334/2008 Quassin is listed as a substance that shall not be added as such to food. However, in Part B of Annex III are listed substances	On the basis of the available information, no robust NOAELs/ LOAELs can be derived for the proposed basic substance. It is noted that a larger dataset is available in this application, as compared to that supporting EFSA, 2018. The available information does not allow to exclude reproductive toxicity, potentially mediated by an endocrine mode of action. See also 5(26)

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No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
				naturally present in flavouring and food ingredients with flavouring properties, for which a maximum level was set. In this Part B of Annex III of Regulation (EC) No 1334/2008 the limits for Quassin of 0.5 mg/kg in non-alcoholic beverages, 1 mg/kg in bakery wares and 1.5 mg/kg in alcoholic beverages are specified. In Part B of Annex IV of the same regulation the conditions of use for flavourings and food ingredients with flavouring properties produced from certain source materials are specified. There, *Quassia amara* is listed as a source material with the specification "Flavourings and food ingredients with flavouring properties produced from the source material may only be used for the production of beverages and bakery wares." Thus, *Quassia amara* is clearly defined as a possible source material for the addition to food. Since the addition of pure Quassin to food is not allowed,	

5.3. Non-dietary exposure to the substance and impurities in it

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
				the full extract with all ingredients is definitively the substance that was evaluated in view of the use in food. Normal consumption of beverages and bakery wares containing the allowed maximum levels of quassin, would lead to quassin uptake above the proposed AOEL from EFSA.	
5(34)	5.3.1 resident exposure	DK: The exposure of resident child in the calculator exceeds the acceptable level by far (>400% of the reference value. Disagree with the applicant's statement that this is acceptable.		Applicant: Based on the allowed maximum levels of quassin in beverages and food, the resident child must consume approximately 20 mL of a non-alcoholic beverage with the highest allowed Quassin content of 0.5 mg/kg or 10 g of bakery wares containing the maximum allowed Quassin content of 1 mg/kg. Therefore, it is considered that the exposure of the resident child to *Quassia amara*/quassin by uses in plant protection is neglectable compared to the uptake of *Q. amara* in food.	See 5(26)

5.3. Non-dietary exposure to the substance and impurities in it

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
5(35)	5.3 Non-dietary exposure	NL: The operator exposure is compared to the highest permitted content of Quassin in food. We do not agree with using these as reference value. Effects on male and female fertility in the Raji & Bolarinwa 1997 and Raji & Akinola 2010 already occurred at 0.1 mg/kg bw of quassin. Applying a standard safety factor of 10 and an additional safety factor of 3 to go from a LOAEL to a NOAEL would result in a reference value of 0.0003 mg Qaussin/kg bw/day. The operator, worker and resident exposure are all estimated to be far above this level. Therefore, in our opinion no safe use has been shown.		Applicant: *Quassia amara* was evaluated for food use based on a literature evaluation summarized in the report of the EUROPEAN COMMISSION HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL, Scientific Committee on Food (SCF/CS/FLAV/FLAVOUR/29/FINAL) of 25.7.2002. Thus, it complies with Art 23(2) of the Regulation (EC) 1107/2009 that the substance should have already been evaluated in the view of other uses. Due to this evaluation, the limits in Regulation (EC) 1334/2008 were set as follows: In **Part A of Annex III** of Regulation (EC) 1334/2008 Quassin is listed as a substance that shall not be added as such to food. However, in **Part B of Annex III** are listed substances naturally present in flavouring and food ingredients with flavouring properties, for which a maximum level was set. In this Part B of Annex III of Regulation (EC) No 1334/2008 the limits for Quassin of 0.5 mg/kg in non-	See 2(4) and 5(33).

5.3. Non-dietary exposure to the substance and impurities in it

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
				alcoholic beverages, 1 mg/kg in bakery wares and 1.5 mg/kg in alcoholic beverages are specified. In **Part B of Annex IV** of the same regulation the conditions of use for flavourings and food ingredients with flavouring properties produced from certain source materials are specified. There, *Quassia amara* is listed as a source material with the specification "Flavourings and food ingredients with flavouring properties produced from the source material may only be used for the production of beverages and bakery wares." Thus, *Quassia amara* is clearly defined as a possible source material for the addition to food. Since the addition of pure Quassin to food is not allowed, the full extract with all ingredients is definitively the substance that was evaluated in view of the use in food. In Table 5-2 we refer to the state of knowledge of 2002, the year when the report of the EUROPEAN COMMISSION	

5.3. Non-dietary exposure to the substance and impurities in it					
No.	**Column 1 Reference to Application Template**	**Column 2 Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4 Follow up response from applicant**	**Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
				HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL, Scientific Committee on Food (SCF/CS/FLAV/ FLAVOUR/29/FINAL) of 25.7.2002.was published. This report is the basis of the evaluation in the view of other uses (foodstuff) where the limits in Regulation (EC) 1334/2008 we refer to were set. In Table 5-2 the publications are listed that were not included in the report. It is shown that no results were published since 2002 that show effects with lower concentrations than those that were published before 2002.	
5(36)	5.3.1 non dietary exposure	NL: Humans are exposed to *Quassia amara* or Quassin by drinks, bakery wares, traditional medicine, cosmetics or as incense material, and furthermore *Quassia amara* can be considered as food item. So, consumers are exposed to *Quassia amara* and Quassin by uses other than		Applicant: *Quassia amara* was evaluated for food use based on a literature evaluation summarized in the report of the EUROPEAN COMMISSION HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL, Scientific Committee on Food (SCF/CS/FLAV/ FLAVOUR/29/FINAL) of 25.7.2002. Thus, it complies with Art 23(2) of the Regulation (EC) 1107/2009 that the substance should have already been evaluated in the view of other uses.	See 5(33)

5.3. Non-dietary exposure to the substance and impurities in it

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
		plant protection. However, no information is presented on the background exposure value by different exposure routes of PPP versus medicine, cosmetics or as incense material. As already commented by NL Quassin is not an approved flavouring substance. It is included in Annex III of Regulation (EC) 1334/2008 (part A) as a substance that shall not be added as such to food.		Due to this evaluation, the limits in Regulation (EC) 1334/2008 were set as follows: In **Part A of Annex III** of Regulation (EC) 1334/2008 Quassin is listed as a substance that shall not be added as such to food. However, in **Part B of Annex III** are listed substances naturally present in flavouring and food ingredients with flavouring properties, for which a maximum level was set. In this Part B of Annex III of Regulation (EC) No 1334/2008 the limits for Quassin of 0.5 mg/kg in non-alcoholic beverages, 1 mg/kg in bakery wares and 1.5 mg/kg in alcoholic beverages are specified. In **Part B of Annex IV** of the same regulation the conditions of use for flavourings and food ingredients with flavouring properties produced from certain source materials are specified. There, *Quassia amara* is listed as a source material with the specification "Flavourings and food ingredients with flavouring properties produced from	

5.3. Non-dietary exposure to the substance and impurities in it

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
				the source material may only be used for the production of beverages and bakery wares." Thus, *Quassia amara* is clearly defined as a possible source material for the addition to food. Since the addition of pure Quassin to food is not allowed, the full extract with all ingredients is definitively the substance that was evaluated in view of the use in food. Since for bakery wares and beverages, a limit of the Quassin content is specified in Annex III Part B, Quassin is used in European legislation as lead substance to quantify and to limit the use and an eventual toxicological risk of *Quassia amara* when used as food ingredient. This was one of the main reasons why this ingredient was also chosen as a lead substance by applicants. Based on the main use of *Q. amara* as food ingredient and since the use in plant protection is only once per	

5.3. Non-dietary exposure to the substance and impurities in it					
No.	**Column 1** **Reference to Application Template**	**Column 2** **Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4** **Follow up response from applicant**	**Column 5** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
				season, it is very likely that the background exposure to *Q. amara* or the lead substance quassin by the main use of *Q. amara* in food, is much higher. Normal daily consumption of beverages and bakery wares containing the allowed maximum levels of quassin, would lead to quassin uptake above exposure to the use in plant protection.	
5(37)	5.3 Impurities and toxicity	NL: NL wonders whether all relevant lead components identified? Likewise: are the toxicologically relevant components that do not contribute to plant protection action sufficiently discussed? No further, detailed information is presented in chapter 5 (see also NL comment to 2.3)		Applicant: *Quassia amara* was evaluated for food use based on a literature evaluation summarized in the report of the EUROPEAN COMMISSION HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL, Scientific Committee on Food (SCF/CS/FLAV/ FLAVOUR/29/FINAL) of 25.7.2002. Thus, it complies with Art 23(2) of the Regulation (EC) 1107/2009 that the substance should have already been evaluated in the view of other uses. Due to this evaluation, the limits in Regulation (EC) 1334/2008 were set as follows:	Agree with the comment. The composition of the proposed basic substance and clear indication of the biologically active/toxicologically relevant components needs corroboration, see 2(12).

5.3. Non-dietary exposure to the substance and impurities in it					
No.	**Column 1** **Reference to Application Template**	**Column 2** **Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4** **Follow up response from applicant**	**Column 5** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
				In **Part A of Annex III** of Regulation (EC) 1334/2008 Quassin is listed as a substance that shall not be added as such to food. However, in **Part B of Annex III** are listed substances naturally present in flavouring and food ingredients with flavouring properties, for which a maximum level was set. In this Part B of Annex III of Regulation (EC) No 1334/2008 the limits for Quassin of 0.5 mg/kg in non-alcoholic beverages, 1 mg/kg in bakery wares and 1.5 mg/kg in alcoholic beverages are specified. In **Part B of Annex IV** of the same regulation the conditions of use for flavourings and food ingredients with flavouring properties produced from certain source materials are specified. There, *Quassia amara* is listed as a source material with the specification "Flavourings and food ingredients with flavouring properties produced from the source material may only be used for the production of beverages and bakery wares."	

5.3. Non-dietary exposure to the substance and impurities in it					
No.	**Column 1** **Reference to Application Template**	**Column 2** **Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4** **Follow up response from applicant**	**Column 5** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
				Thus, *Quassia amara* is clearly defined as a possible source material for the addition to food. Since the addition of pure Quassin to food is not allowed, the full extract with all ingredients is definitively the substance that was evaluated in view of the use in food. Since for bakery wares and beverages, a limit of the Quassin content is specified in Annex III Part B, Quassin is used in European legislation as lead substance to quantify and to limit the use and an eventual toxicological risk of *Quassia amara* when used as food ingredient. This was one of the main reasons why this ingredient was also chosen as a lead substance by applicants.	

5.4. Impact on human and animal health arising from exposure to the substance or impurities contained in it					
No.	**Column 1** **Reference to Application Template**	**Column 2** **Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4** **Follow up response from applicant**	**Column 5** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
5(38)	5.4 Impact on human and animal health	NL: The operator exposure is compared to the highest permitted content of Quassin in food. We do not agree with using these as reference value. Effects on male and female fertility in the Raji & Bolarinwa 1997 and Raji & Akinola 2010 already occurred at 0.1 mg/kg bw of quassin. Applying a standard safety factor of 10 and an additional safety factor of 3 to go from a LOAEL to a NOAEL would result in a reference value of 0.0003 mg Qaussin/kg bw/day. The operator, worker and resident exposure are all estimated to be far above this level. Therefore, in our opinion no safe use has been shown.		Applicant: The highest permitted content of Quassin in food was defined in Regulation (EC) 1334/2008 based on the report of the EUROPEAN COMMISSION HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL, Scientific Committee on Food (SCF/CS/FLAV/ FLAVOUR/29/FINAL) of 25.7.2002. The findings of Raji & Bolarinwa 1997 were already evaluated in this report. The findings of Raji & Akinola 2010 refer to the same concentrations of Quassin as used in the study of 1997. Thus, the limits for the use as foodstuff were set considering the effects shown at concentrations of 0.1 mg/kg. Applicant demonstrates that the exposure of operators, workers and residents is comparable to a realistic and presumable consumption of a foodstuff containing Quassia once a year.	See 5(33)

5.5. Additional information related to therapeutic properties or health claims					
No.	**Column 1 Reference to Application Template**	**Column 2 Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4 Follow up response from applicant**	**Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
5(39)	5.5 additional information related to therapeutic properties	NL: NL would consider more appropriate to exclude first the genotoxic potential of the extract of the wood of *Quassia amara* and then to set specific health-based guideline values (e.g. Acceptable Operator Level) on the basis of available toxicity studies. Presenting positive/beneficial effects is not enough to exclude long-term toxicity and carcinogenicity.		Applicant: An evaluation of the genotoxic potential of *Quassia amara* L. wood was performed based on all available study data on this topic and considering the recommendations for genotoxicity testing as outlined by the EFSA Scientific Committee (EFSA, 2011; EFSA, 2017; EFSA 2019). Furthermore, profiling for endpoints genotoxicity/carcinogenicity (OECD QSAR Toolbox v.4.6) for the known extract components quassin (main component, analytical lead substance), neoquassin and 18-hydroxyquassin (both tentatively identified by mass spectrometry analysis) was performed to support the present evaluation. The study database comprised *in vitro* and *in vivo* genotoxicity assays (GLP and OECD guideline compliant) related to all relevant endpoints, *i.e.*, gene mutation, structural and numerical chromosomal aberrations and was thus considered	See 5(1)

5.5. Additional information related to therapeutic properties or health claims					
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				complete and adequate for the evaluation of genotoxicity. In the Ames test, *Quassia amara* L. wood was non-mutagenic in the bacterial strains *Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537, and *Escherichia coli* WP2*uvrA*. In a micronucleus assay (MNA) *in vitro* in human lymphocytes, there was no relevant effect on micronuclei incidences in the presence of metabolic activation (S9 mix), but slightly increased incidences in micronuclei in the absence of metabolic activation were observed. These increases, which were assessed as equivocal in the study report, were only observed at cytotoxic concentrations. Since the increases in micronucleus incidences were marginal and that cytotoxicity is a known confounder under *in vitro* testing conditions, the overall assessment of the study indicates low concern for genotoxicity. To follow up on	

5.5. Additional information related to therapeutic properties or health claims					
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				these slight increases a Comet assay in male rats was chosen as *in vivo* follow-up test. The investigation of potential DNA damage *in vivo* revealed that *Quassia amara* L. wood was not genotoxic in cells of the small intestine (site of direct contact) and in liver cells. The Comet assay was selected as the adequate test system for the complex *Quassia amara* L. wood since potential cytotoxic effects determined in a mouse bone marrow MNA, which represents the potential alternative to the *in vivo* Comet assay in this case, could not be unequivocally attributed to a defined component of the wood. By choosing a tissue with site of direct contact (*e.g.* small intestine), tissue exposure for components not requiring metabolic activation can be demonstrated in the Comet assay after oral exposure. For an *in vivo* MNA, however, bone marrow exposure to all components of the test	

5.5. Additional information related to therapeutic properties or health claims					
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				substance (confirmed bone marrow exposure is a prerequisite for regulatory acceptance of this assay) can neither be predicted nor reliably analytically demonstrated. Alerts depicted in the genotoxicity/carcinogenicity profiling for the components quassin (main component), neoquassin and 18-hydroxyquassin using the OECD QSAR Toolbox v.4.6 indicated that direct interaction with DNA might be the underlying mechanism to the equivocal finding in the *in vitro* MNA, supporting the choice of the Comet assay as the adequate follow up test *in vivo*. Overall, it can be concluded that *Quassia amara* L. wood is of low concern regarding the endpoint genotoxicity and the level of uncertainty remains low and acceptable.	

5.6. Additional information related to use as food					
No.	**Column 1** **Reference to Application Template**	**Column 2** **Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4** **Follow up response from applicant**	**Column 5** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**

No comments.

6. Residues

6.1 Summary of available studies

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
6(1)	6.1 Summary of available studies	NL: In EFSA's technical report (EFSA Supporting publication 2018:EN-1382), several data gaps were identified (e.g. studies on the fate of the extract in plants or during representative processing procedures, the demonstration that quassin is a valid single marker compound, …). In the present application, these data gaps were not addressed; therefore, the data gaps remain open.	EFSA agrees with the NL that some previously identified issues were still not addressed. Most notably, information of the nature of residues is not available, i.e. it is unclear whether and how quickly quassin, isoquassin, neoquassin could be possibly transformed into other compounds upon application to crops due to environmental conditions (e.g. sun light) or plant properties (metabolism), or whether these compounds extracted from *Quassia amara* wood chips would remain unchanged on the crops. Information on the fate of the compounds extracted from *Quassia amara* wood chips when applied in the field to crops should be provided. See also 7(2) requirement regarding the environment. Although quassin was apparently the main compound (but not the only one) in the preparation when *Quassia amara* wood is extracted before its use in plant protection, it is assumed by the applicant that quassin will also be a suitable marker to measure the residue levels on crops. Currently there is	Applicant: *Quassia amara* with all its ingredients was evaluated for food use based on a literature evaluation summarized in the report of the EUROPEAN COMMISSION HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL, Scientific Committee on Food (SCF/CS/FLAV/ FLAVOUR/29/FINAL) of 25.7.2002. Thus, it complies with Art 23(2) of the Regulation (EC) 1107/2009 that the substance should have already been evaluated in the view of other uses. Due to this evaluation, the limits in Regulation (EC) 1334/2008 were set as follows: In **Part A of Annex III** of Regulation (EC) 1334/2008 Quassin is listed as a substance that shall not be added as such to food.	**Refer to data gaps in 2(7), 2(12).** The applicant's reply does not address the question of whether the components of quassia wood extract would be metabolised / degraded after application to crops in the field, or, would remain stable on crops and for which period of time. However, based on the findings at different sampling intervals in the submitted residue trials in fruit and hops, it can be reasonably expected that degradation/metabolism of the applied compounds occur between application and harvest of the crops. The extent of such degradation / metabolism in each crop and the identity of the formed residue products from

6.1 Summary of available studies

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			insufficient evidence to support this assumption. More data or arguments are needed to confirm that quassin is the best marker for the residues. On which grounds was also neoquassin included for residue measurements, but other compounds present in the preparation were excluded from the analysis of the treated crops? Please provide a justification for choosing/excluding the individual components.	However, in **Part B of Annex III** are listed substances naturally present in flavouring and food ingredients with flavouring properties, for which a maximum level was set. In this Part B of Annex III of Regulation (EC) No 1334/2008 the limits for Quassin of 0.5 mg/kg in non-alcoholic beverages, 1 mg/kg in bakery wares and 1.5 mg/kg in alcoholic beverages are specified. In **Part B of Annex IV** of the same regulation the conditions of use for flavourings and food ingredients with flavouring properties produced from certain source materials are specified. There, *Quassia amara* is listed as a source material with the specification "Flavourings and food ingredients with flavouring properties produced from the source material may only be	e.g. metabolised quassin and neoquassin, is unknown, although some considerations by the applicant based on structural chemistry and general knowledge about plant metabolism would have been desirable. EFSA provided such assessment as far as possible (see Appendix F). The applicant justified the choice of quassin as lead compound for the analysis and risk assessment in the area of residues a) with the pesticidal properties of quassin, and b) because quassin limits exist in other regulatory frameworks, i.e. for flavourings. These are rather weak justifications in terms of the aspects of residue behaviour and consumer exposure with

6.1 Summary of available studies

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				used for the production of beverages and bakery wares." Thus, *Quassia amara* is clearly defined as a possible source material for the addition to food. Since the addition of pure Quassin to food is not allowed, the full extract with all ingredients is definitively the substance that was evaluated in view of the use in food. Since for bakery wares and beverages, a limit of the Quassin content is specified in Annex III Part B, Quassin is used in European legislation as lead substance to quantify and to limit the use and an eventual toxicological risk of *Quassia amara* when used as food ingredient. This was one of the main reasons why this ingredient was also chosen as a lead substance by applicants. Another reason was that Quassin is the active ingredient responsible for the	regard to agricultural uses. It is noted that the composition of the wood extract has not been clarified (see 2(7), 2(12)), which, once clarified, may trigger a need for further clarification of crop metabolism of the extracted components. Extracts of *Quassia amara* wood contain besides quassin additional extracted substances e.g. other quassinoids and derivatives (see 7(2)), and little to nothing is currently known about their residue behaviour and toxicity. The complexity of the topic is acknowledged, however, first of all, the composition of the extract to be applied to the plants must be clarified in order to assess and conclude on the possible

6.1 Summary of available studies

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				effect used in plant protection. Since Neoquassin has also a weak effect in plant protection, this ingredient was also analysed in the residue trials.	fate and behaviour of these compounds in the wood extract when applied to the plants.
6(2)	6.1 Summary of available studies	NL: The newly submitted storage stability study (Report No 19F12002-01-SSPL) is considered to be acceptable. Quassin (sum of quassin and isoquassin) and neoquassin are stable for at least 12 months under deep-frozen conditions in homogenised apple and hops samples.	See 6(3)	Applicant: Noted and agreed.	Noted. See also 6(3).
6(3)	6.1 Summary of available studies	EFSA: takes note of the new storage stability study and agrees that freezer storage stability was demonstrated for 1) the sum of quassin and isoquassin and for 2) neoquassin in pome fruit and hops. The study validates the residue trials in hops and apple.	To validate the available residue trials in plums, according to the OECD test guideline 506 freezer storage stability data in a representative stone fruit commodity should be submitted or it should be demonstrated that the analysis of all samples in these residue trials was finalised within 30 days from the sampling of the fruits in the field.	Applicant: A storage stability for residues of Quassia was conducted in apples, which belong to the crop commodity category "High water content" (Annex I of OECD guideline No 506). Based on paragraph 5 of guideline 506, representative storage stability data can be used as representative data	Paragraph 5 of OECD TGL 506 referred to by the applicant discusses commodities and representative commodities in Annex I of the OECD document, not commodity categories. Based on paragraphs 25 and 26 of OECD TGL 506 "*If residues are shown to*

6.1 Summary of available studies

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		According to OECD guideline 506, storage stability data are also required to validate the residue trials in stone fruits (plums), therefore, due to this gap the residue trials in plums are not validated.		for other crops belonging to the same category. Stone fruits (plums) are belonging to the same crop category (Annex I of OECD guideline No 506, "High water content"). For this category, representative storage stability data were provided.	*be stable in all commodities studied, a study on one commodity from each of the five commodity categories is acceptable*." However, storage stability data were not provided for one commodity in all five categories, hence paragraph 26 applies and a higher number of representative commodities may have to be tested. Apple is a representative commodity for pome fruit, and plum belongs to stone fruit. Hence, these are not the same commodities and storage stability data were only provided for the pome fruit commodity. **Minor outstanding issue:** Storage stability data for quassin and neoquassin in

6.1 Summary of available studies

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					stone fruit commodities to validate the results of the residue trials in plums.
6(4)	6.1 Summary of available studies	EFSA: In the tables with residue trials the column "Remarks" contains information with reference notes (g), (h) that are not further explained.	The applicant should complete the tables with the residue trials, providing explanation on the meaning of reference notes (g), (h).	Applicant: (g) means method of analysis and (h) means Limit of Quantification. The table was updated.	Addressed. The meaning of footnotes in the tables was added, however, in some instances this led to inconsistencies with the LOQ reported in the narrative of the applicant about the residue trials and the LOQ reported in the table with residue data.
6(5)	6.1 Summary of available studies	EFSA: Several of the residue trials in plum, apple, hops appear to be experimental replicates, i.e. conducted at the same geographical location in the same crop and variety at exactly the same time period and can therefore not be considered independent trials in the spirit of the	Applicant to clarify which of the presented residue trials in plum, apple, hops are experimental replicates (side by side trials) and not independent in the spirit of current guidance https://food.ec.europa.eu/system/files/2023-05/pesticides_mrl_guidelines_app-d.pdf and which of the trials reported separately are possibly part of a residue decline study (same experiment with different PHIs sampled).	Applicant: For apples and plum in each trial, two times samples were taken: 1st sample at BBCH 74/75 in apple and BBCH 79 in plum. At this stadium it is possible to collect a sufficient number of fruits to achieve the amount necessary for the analysis and it is still a long period until	The applicant clarified that in the residue trials the samples were taken at two different intervals. The results for different PHIs of the same residue trials were reported as separate trials. Moreover, often sets of two trials each were conducted in the same geographical

6.1 Summary of available studies

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		applicable guidelines and guidance for residue trials. The reporting of the PHI is not always clear, and it could be assumed that some trials are decline trials but are reported as separate trials. It is further noted by EFSA that the requested GAP permits application up to GS69 (End of flowering: fruit set visible). According to current guidelines for crops harvested after blossom (such as fruits or fruiting vegetables) a significant part of the consumable crop is present. The number of independent residue trials may therefore not be sufficient to establish reliable residue levels for the tested analytes and GAP scenarios (notwithstanding the fact		harvest so that there is a long "safety interval" until harvest. 2nd sample: At harvest or shortly before harvest. This sample gives information about the situation at harvest and the real possible contamination of the fruit. For hop, also two dates were chosen for sampling, one rather early and one shortly before harvest. Thus, always the two sampling dates with the same variety and application date are decline trials.	area and had the same time of application, only with slight differences that would not justify independence of the trials in line with current guidance on crop field trials. These trials are therefore not considered fully independent. Furthermore, several trials in hops were not conducted according to cGAP in terms of the latest BBCH of application but they were conducted at the earliest possible BBCH. It is also noted that the reports of the field phase of the residue trials (non GLP) are not available and therefore all information about the trial design such as type, actual rate, number and time of application, and sampling needed to be based and judged on the

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		that the suitability of the chosen analytes is still to be demonstrated – see 6(1) and the lack of storage stability data for stone fruit -see 6(3)).			narrative of the applicant as described in the application. For some trials information on the analytical method is also missing. For hops it is unknown whether the fresh or dried cones were submitted to analysis. After consolidation, the number of possible cGAP compliant independent residue trials is therefore: 4 trials in plum (NEU, season 2013, 2014, 2015, 2018) Quassin (sum of quassin and isoquassin): 4x <0.01 mg/kg STMR 0.01 mg/kg HR 0.01 mg/kg Neoquassin: 1x <0.005, 3x <0.0084 mg/kg STMR 0.0084 mg/kg

6.1 Summary of available studies

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					HR 0.0084 mg/kg 4 trials in apple (NEU, season 2013, 2014, 2015, 2018) Quassin (sum of quassin and isoquassin): 4x <0.01 mg/kg STMR 0.01 mg/kg HR 0.01 mg/kg Neoquassin: 1x <0.005, 3x <0.0084 mg/kg STMR 0.0084 mg/kg HR 0.0084 mg/kg Two additional trials in apple from SEU (2013, 2014) were not according to GAP in terms of applications and it was also unclear which batch was actually applied. It can be estimated that the application rate was approximately 1.6 - 2-fold the requested GAP rate.

6.1 Summary of available studies

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					Quantifiable residues of quassin (0.01 mg/kg and 0.009 mg/kg, resp.) were present in apples at 35-45 days after application and were <LOQ of 0.01 mg/kg at harvest (PHI 141 days) in one trial while not available for the 2nd trial (only DALA/PHI 35 days reported twice). In hop, several trials had incomplete reporting with regard to the application rate and the growth stage at treatment, and the application dates varied significantly, indicating non-comparable BBCH at application. The applicant explained that trials had two different design types, before flowering at the maximum linear growth of shoots, that corresponded to BBCH 39 or even earlier, and during end of flowering at

6.1 Summary of available studies

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					BBCH 69, which corresponded to the cGAP. 9 independent residue trials in NEU (2013, 2014, 2015, 2018, 2019) are available with the shortcomings in reporting as highlighted above. Application in June (≤BBCH 39) – not cGAP Quassin (sum of quassin and isoquassin): 6 x <0.05 mg/kg Neoquassin: 6 x <0.05 mg/kg Application mid-July (3 trials, approx. BBCH 65) Quassin (sum of quassin and isoquassin) DALA 27-29 days: 0.066, 0.1, 0.12 mg/kg Neoquassin: 0.059, 0.09, 0.11 mg/kg STMR 0.1 mg/kg HR 0.12 mg/kg

6.1 Summary of available studies

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					Quassin (sum of quassin and isoquassin) DALA 40-49 days (maturity): <0.05 (0.024), 0.08, 0.1 mg/kg STMR 0.08 mg/kg HR 0.1 mg/kg Neoquassin: <0.05 (0.019), 0.07, 0.08 mg/kg STMR 0.07 mg/kg HR 0.08 mg/kg It is unknown whether the hop cones submitted to analysis where fresh or dried, which can have an impact on the STMR and HR values for risk assessment purposes as a drying factor of approx. 3.5 would have to be considered on the residue levels if fresh cones were analysed, resulting in the following values:

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					Quassin: STMR dry 0.28 mg/kg HR dry 0.35 mg/kg Neoquassin: STMR dry 0.245 mg/kg HR dry 0.28 mg/kg **Minor outstanding issue:** Information on the analytical method, including validation data, used in the 2013 residue trials in apple, plum and hops (report by [redacted] 2013) is missing and should be provided. **Minor outstanding issue:** Information whether the hop cone samples submitted to residue analysis from the residue trials 2013, 2014, 2015, 2018, 2019 were fresh or dried.

6.2 Dietary exposure to the substance and impurities in it					
No.	**Column 1 Reference to Application Template**	**Column 2 Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4 Follow up response from applicant**	**Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
6(6)	6.2.1 Exposure through the use for plant protection purposes	NL: The exemplary dietary consumer risk assessment was conducted for hops only. However, a comprehensive consumer risk assessment should take all intended uses into account. The dietary consumer risk assessment should therefore be updated.	EFSA agrees with the NL. A dietary risk assessment with the EFSA PRIMo was only conducted for hops. Hops does not present a major food item in the diet of EU consumers while consumption of pome fruit and stone fruit is much higher. A PRIMo calculation that includes all requested uses should be submitted.	Applicant: In plums and apples no residues were found. For this reason, we did not calculate the consumer risk assessment.	**Data gap:** An updated consumer exposure and risk assessment for the intended uses on crops (pome fruit, stone fruit, hops), upon demonstration that the residues at LOQ level (fruit) and actual measured residue levels (hops) in the submitted residues trials with the commercial product are applicable to the intended uses. The requested clarification on compounds that could be expected as residues on crops after application of the prepared extract from *Quassia amara* L. wood (besides quassin / neoquassin) as well as clarification on the levels of quassin (and other extracted biologically active components) in the extract, and the requested clarification with regard to the toxicology of *Quassia amara* L. extract and its components are

6.2 Dietary exposure to the substance and impurities in it					
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					required for a reliable consumer risk assessment. The residue trials in fruit indicate a below LOQ situation and the data in hop show quantifiable residues. There are no data that demonstrate a 'zero' residue situation according to current legislation (Regulation (EU) No 283/2013). Therefore, taking also into account the toxicological properties of components in *Quassia amara* L. wood, specifically of quassin but potentially also of other quassinoids or their metabolism products on crops, a consumer exposure assessment should be conducted for food items with residues at LOQ level for fruit and the determined residues for hop to establish the maximum expected exposure from the plant protection use and enable a quantitative risk assessment. EFSA conducted

6.2 Dietary exposure to the substance and impurities in it

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
					such assessment (see section 3.3 and Appendix F). A consumer risk assessment can be waived for the use on ornamentals due to an insignificant dietary exposure potential.
6(7)	6.2.2 Background exposure (exposure to the substance through uses other than for plant protection) And 6.2.3 Comparison of exposure through use for plant protection and the background exposure	NL: While it is acknowledged that consumers are likely exposed to *Quassia amara* or quassin via uses other than for plant protection, the applicant failed to actually quantify the background exposure. Therefore, it is not possible to conclude that the additional exposure to *Quassia amara* or quassin is negligible compared to the exposure by other routes. As a minor remark, exposure via cosmetics or incense material should not be considered as dietary exposure (although it is acknowledged that these uses also contribute to the overall consumer exposure).	EFSA agrees with the NL. It has not been conclusively demonstrated that the applicant's claim that "consumer exposure to Quassia amara by consumption of treated crops in accordance with the intended GAP would be comparably low" is correct. A PRIMo calculation for all requested plant protection uses, including pome fruit and stone fruit, was not submitted (see 6(6)). Furthermore, it has not been demonstrated that this exposure from the intended use(s) for plant protection does not result in significantly higher exposure than from other (regulated) uses. The reference to section 5.3. "Non-dietary exposure" is not appropriate in the Residues section. Only consumer dietary exposure to *Quassia amara* wood (and its components) via uses other than for plant	Applicant: We assume, given that *Q. amara* is listed as ingredient in several food products, that consumers are regularly exposed to *Q. amara* by consuming these products. The consumption of treated crops and the respective uptake of *Q. amara* is considered neglectable compared to the normal daily consumption of beverages and bakery wares containing the allowed maximum level of Quassia in order to	**Data gap:** A robust comprehensive assessment of chronic and acute dietary exposure to *Quassia amara* L. wood and its components from other dietary sources. The pure assumption that dietary consumer exposure of relevant consumer groups including vulnerable groups like children or pregnant women to *Quassia amara* L. wood, its extract and the contained quassinoids will be negligible from the requested plant protection uses (apples, plums, hops), when compared to dietary exposure through

6.2 Dietary exposure to the substance and impurities in it

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			protection should be assessed in the Residues section, and not uses as cosmetics, incense materials or else. The applicant refers further to uses in traditional medicine. Information should be provided how often and how much Quassia amara is used and what is the resulting short term and long term exposure to Quassia amara wood or its individual components when consumed as herbal medicine. As the applicant claims Quassia amara wood is also a foodstuff, the assessment of consumer intake should also be done by using EU consumption data (available via the EFSA Comprehensive European Food Consumption Database: https://www.efsa.europa.eu/en/data-report/food-consumption-data).	maintain allowed quassin levels. Furthermore, no PRIMo calculations were performed for pome fruit and stone fruit since no residues were detected in the respective trials. The reference to section 5.3 was deleted. Regarding the use of *Q. amara* in traditional medicine, this is a further uptake of *Q. amara* and quassin in addition to the main use in food and beverages. The medicinal use (which is mainly homeopathic) is considered neglectable in comparison with the main use as food ingredient.	other routes, was not backed up by any sound data or calculations. The applicant mentions "*several food products that consumers are regularly exposed to*" without providing any concrete examples, including frequency and levels of such exposure. The use of *Quassia amara* L. as source material to produce flavourings and the possibly resulting quassin levels are strictly regulated and limited. It is also not the case that young children do regularly consume bitter soft drinks and alcoholic bitters as EFSA consumption data show (see also Appendix F). But children may consume treated plums and apples, and as such, a consumer intake assessment is considered necessary to compare the different sources of exposure (see above). To determine the relevant foods to which the Flavouring

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					Regulation applies in relation to the use of *Quassia amara* L. as source material, EFSA searched Mintel, an online database[8], which observes product introductions in consumer packaged goods markets worldwide (see Appendix G). No Bakery products were found in Mintel that had Quassia as an ingredient. Hence, considerations in the applicant's exposure estimate that the population would regularly consume 250 g of bakery wares that contain 1 mg/kg quassin does not seem realistic. All results retrieved from Mintel were from the category of beverages (see Appendix G). This observation is in line with the submission of the applicant to prove food uses of *Quassia amara* L. by

8 https://www.mintel.com/products/gnpd/?_bt=652169658686&_bk=mintel%20gnpd&_bm=p&_bn=g&_bg=150165006391&utm_medium=cpc&utm_source=google&utm_content=Threepipe-GO19848722604~GO150165006391&gad_source=1&gclid=EAIaIQobChMI7pyOg5axiQMVKZaDBx07hy1wEAAYASAAEgJ1SvD_BwE

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					product labels ([redacted], 2021; and Anonymous: Examples for foodstuffs actually available on the market with the ingredient "Quassia"). Only labels from alcoholic and non-alcoholic beverages containing Quassia in line with the flavouring Regulation (EC) No 1334/2008 were submitted. It has further to be noted that the market share of such beverages containing Quassia is very small (between 0%-2% depending on beverage category and country). Therefore, the claim of the applicant of an existing "*normal daily consumption of beverages and bakery wares containing the allowed maximum level of Quassia*" is not corresponding to the available facts, i.e. market data and food consumption data. Also, exposure of vulnerable groups like children or pregnant women was not

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					sufficiently considered by the applicant. EFSA provided provisional exposure estimates for toddlers and pregnant women consuming soft drinks with bitter principles as an example in Appendix F. The results are not conclusive, and the high uncertainty of these estimates is also noted. Therefore, it is not possible for EFSA to firmly conclude that the additional exposure to *Quassia amara* L. (or to its component quassin) from the plant protection use is negligible compared to the exposure by other routes.
6(8)	General	EFSA: Given that the applicant considers quassin as the best marker for residues upon application of *Quassia amara* to crops and in view of the concerns in terms of the hazardous properties reported for *Quassia amara* wood, specifically its component quassin (see EC,	The applicant is requested to elaborate on whether MRLs for quassin should be proposed for the uses in plant protection (provided its suitability as appropriate residue marker is confirmed - see 6(1)), what could be an appropriate level, or, why it is not necessary to propose any MRLs, taking into account EFSA's comment in column 2.	Applicant: We assume, given that *Q. amara* is listed as ingredient in several food products, that consumers are regularly exposed to *Q. amara* by consuming these products. It is very likely that the background exposure to	Refer to 6(7)

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		2002. Opinion of the Scientific Committee on Food on quassin; EFSA Technical report, 2018. doi:10.2903/sp.efsa.2018.EN-1382) and the restrictions for the use of *Quassia amara* as source material for flavourings including maximum concentrations of quassin imposed by Reg. 1334/2008, did the applicant consider proposing MRLs for the uses in plant protection?		*Q. amara* or the lead substance quassin by other routes than plant protection is much higher. The uptake of *Q. amara* by hop in beer is considered neglectable compared to the normal daily consumption. Therefore, the setting of a MRL is not considered justified.	

7. Fate and Behaviour in the environment (effects on the environment as degradation/dissipation in soil; risk to groundwater and risk to surface water)

7.1 Fate and Behaviour in the environment

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
7(1)	7. General	DE: The studies should be presented and cited in a consistent way, e.g. with a study header. The relevant information needs to be in the document and easily and directly to retrieve during reading. Please check the captions of the tables for correct numbering.		Applicant: Studies are now presented in consistent summary format. Captions of the tables and numbering are checked	Addressed. The two fate studies available in the dossier have been summarised properly.
7(2)	7.1 Persistence in soil	EFSA: It is noted that in EFSA (2018) (doi:10.2903/sp.efsa.2018.EN-1382) a data gap was identified for data / information on the persistence of *Quassia amara* L. wood extract active ingredients in soil. A study investigating the degradation of Quassin in four soils has been presented in this new application. However, *Quassia amara* L. wood is acknowledged to contain a number of other biological active components	EFSA: Applicant should discuss in detail all the known biological active components of *Quassia amara* L wood and provide the necessary information on their persistence and fate in the environment. Information from soil incubations in at least four soils is needed for the biological active components of *Quassia amara* L wood extract additional to quassin. Alternatively, a valid argumentation to demonstrate that such information is not necessary such as a read across from quassin supported by scientific publications is needed for	Applicant: Noted, currently data base is not available.	**Data gap:** Besides quassin, *Quassia amara* L. wood is acknowledged to contain a number of other biologically active components. For example, other quassinoid derivatives, carboline derivatives and canthin derivatives have been reported by the applicant as components of the

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		(other quassinoid derivatives, carboline derivatives and canthin derivatives have been reported by the applicant as components of the *quassia amara* extract) the fate of which in soil cannot be considered addressed by the study submitted.	the biologically active compounds present in the extract.		Q*uassia amara* extract, the fate of which in soil cannot be considered addressed by the study submitted. In the updated application the following compounds are listed by the applicant: neoquassin, isoquassin, parain, quassimarin and quassinol. However, the relative amount of these compounds in the water extract of Q*uassia amara* L. wood is unknown. The applicant should discuss in detail all the known biologically active components of *Quassia amara* L. wood and provide the necessary

7.1 Fate and Behaviour in the environment					
No.	**Column 1** **Reference to Application Template**	**Column 2** **Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4** **Follow up response from applicant**	**Column 5** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
					information on their persistence and fate in the environment. Information from soil incubations in at least four soils is needed for the biologically active components of *Quassia amara* L. wood extract, additionally to quassin. The complexity of the topic is acknowledged, however, at least a valid argumentation to demonstrate that such information is not necessary, such as a read across from quassin supported by scientific publications, is needed for the biologically active

7.1 Fate and Behaviour in the environment					
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					compounds present in the extract. If lead compounds are selected for the environmental risk assessment, their selection should be adequately justified. See data gaps in 2(7) and 2(12)
7(3)	7.1 Persistence in soil	EFSA: Further details on the available soil incubation study need to be provided in the report for a proper peer review. Tested material (purity, radiolabel position etc..), materials and methods, experimental procedure including sampling, quantitative results of the analysis of samples (providing individual replicates) etc…	EFSA: please update the application with the missing detail on the available soil incubation study that is currently summarised too briefly / inadequately in the available study report. Quality assurance in place at the organisation carrying out the work should be clarified. See also comment 7(9).	Applicant: The application is updated. In the broader soil incubation study summary details on tested material, materials and methods, experimental procedure including sampling and quantitative results of the analysis of samples are presented.	**Data gap:** The study provides information on the rate of degradation of quassin (one of the biologically active components of Q*uassia amara*) in four soils. However, there is no information on its degradation products. Since soil metabolites of quassin may retain its biological activity, they need to be

7.1 Fate and Behaviour in the environment

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					identified with appropriate studies.
7(4)	7.1 Persistence in soil	EFSA: The kinetic analysis performed needs to be better documented in the application. The level of detail currently available is inadequate.	EFSA: Are results of all data sampling points used of the analysis (covering aerobic and anaerobic phase)? How many sampling points are considered in each fit? Please provide graphical charts of the fitting in each soil and a reasoned justification of the kinetic model selected (by comparison with the alternatives). Applicant to clarify if the study that was the basis for the fitting was carried out in a GLP accredited facility and if was a GLP study.	Applicant. The application is updated. In the broader soil incubation study summary details on kinetic analysis as well as presentation of the visual best-fit of quassin degradation kinetics in the four tested soils are presented. Details on GLP accreditation of the tested facility and statement on conduction of study under GLP is provided.	**Minor outstanding issue:** The kinetic analysis has been presented in detail. However, the derived kinetic end points are not agreed. SFO fitting adequately describes the dissipation in the four soils tested. Therefore, the end points to be considered for the environmental risk assessment are: Soil I DT_{50} = 37.2 d DT_{90} = 124 d Soil II DT_{50} = 28.8 d DT_{90} = 95.7 d Soil III DT_{50} = 59.2 d

7.1 Fate and Behaviour in the environment

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					DT_{90} = 197 d Soil IV DT_{50} = 58.5 d DT_{90} = 194 d The applicant needs to update the exposure assessment of the component quassin accordingly once the other data gaps in relation to the composition of the water extract are addressed. See also 2(3), 2(12), 7(22) and 7(39)
7(5)	7.1 Persistence in soil	EFSA: The study report indicates that a modified HS is used in the kinetic analysis of three soils. In these three soils an initial lag phase is observed of around 7 d during which no significant degradation is observed (k1 =0). However, the reported DT_{50} are referring only to the second degradation phase (k2). This	See column 3 entry at comment 7(4). The comparison with alternative fitting kinetics should be reported following FOCUS kinetics guidance for this.	Applicant: The application is updated. In the broader soil incubation study summary details on kinetic analysis including the comparison with alternative fitting kinetics is provided alongside with a presentation of the visual best-fit of Quassin degradation kinetics in the four tested soils. The persistence	See data gap in 7(4)

7.1 Fate and Behaviour in the environment

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		result in an underestimation of the overall persistence of quassin in soil. The selection of the kinetic model needs to be further justified as it is not apparent from the visual examination of the charts that the HS provides a better fit than SFO or DFOP.		DT_{50} of 61.7 days and DT_{90} of 189 days were chosen considering the worst case of the best fit and is therefore derived from the HS of the overall days in accordance with the FOCUS kinetic guidance (2014). The modelling DT_{50} and DT_{90} are discussed further under the point 7(21).	
7(6)	7.1 Persistence in soil	EFSA: Only persistence of quassin in soil has been investigated. No attempts to identify soil metabolites or other transformation products has been done. Systematic review of the scientific literature on this aspect was not presented. A comparable review of the scientific literature on the known biological active components of *Quassia amara* L wood extract and their transformation products is missing.	EFSA: Determination of transformation products in soil is necessary to address ground water contamination and potential residues in rotational crops from soil transformation products. The soil transformation products of all the biological active components of *Quassia amara* L wood extract need to have been considered. Please update the application with information on these aspects.	Applicant: *Quassia amara* wood is a natural substance. All ingredients present in the wood, as well as their transformation products, are consequently also naturally occurring in the environment. Although *Quassia amara* is a (sub)tropical plant, no adverse effects in areas of its natural occurrence or farms are known to the applicant.	See data gaps in 7(2) and 7(3).
7(7)	7.1 Persistence in soil	EFSA: Not only the persistence of quassin is relevant for the environmental exposure assessment, the formation of	EFSA: Applicant to investigate the transformation products of quassia in soil. Results from soil incubation experiments would be the best way	Applicant: See answer to comment 7(6)	See data gaps in 7(2) and 7(3)

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		transformation products and metabolites would also need to be investigated. If available, information from public peer reviewed scientific literature on the fate of the different components of *Quassia amara* L. wood in soil would need to be integrated in the assessment.	to address this. As already indicated in comment 7(6), applicant to investigate the transformation products of other components of *Quassia amara* L. wood with known or presumed biological activity. Results from soil incubation experiments would be the best way to address this. Alternatively, scientific publications on these aspects retrieved by a systematic literature review approach is necessary.		
7(8)	7.1	DE: Route of degradation and reasoning for possible metabolites is missing.	DE: Please provide relevant information as already indicated in the column 3 entry at comment 7(7).	Applicant: See answer to comment 7(6).	See data gap in 7(3)
7(9)	7.1, Dissipation rate of Quassin	DE: Detailed, relevant information on the properties of the soils (eg. pH, OC, CEC) from the study is missing in the document. The caption number of the table is missing. For the rate of degradation, the normalisation and modelling endpoint need to be documented. For the documentation of the best fit for all tested kinetic	DE: Please provide relevant information e.g. in a table that allows the relation with soil number, properties and origin. See also related column 3 entry at comment 7(3).	Applicant: The application is updated. In the broader soil incubation study summary details on tested material, materials and methods, experimental procedure including sampling and quantitative results of the sample analysis are presented. Also, normalisation and modelling endpoint are documented as well as details on kinetic analysis including the	See data gap in 7(3)

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		models the Chi square values should be shown.		comparison with alternative fitting kinetics. Moreover, a presentation of the visual best-fit of Quassin degradation kinetics in the four tested soils is provided.	
7(10)	7.1 Persistence in water	EFSA: The assumption that the DT_{50} of quassin in soil is applicable to the water compartment is not substantiated by any relevant information or data.	EFSA: Applicant to provide data or information to substantiate the proposed DT_{50} in the water compartment.	Applicant: The application is updated. At this stage, no data are available regarding the degradation kinetics of Quassin or Quasia Amara extract in water. For risk assessment purposes worst-case default DT_{50}-water of 1000 d and DT_{50}-sediment of 1000 d are considered	Addressed. In the absence of data on the persistence of quassin, for risk assessment purposes worst-case default DT_{50}-water of 1000 days and DT_{50}-sediment of 1000 days are considered.
7(11)	7.1 Persistence in water	EFSA: Information and / or data on the fate and behaviour in the water compartment of quassin and other components of *Quassia amara* L. wood with known or presumed biological activity needs to be provided. In the absence of reliable data, worst case DT_{50} = 1000 d is to be assumed for surface water and sediment for the	EFSA: The fate (route and rate of degradation) of quassin and other components of quassia amara L. wood with known or presumed biological activity need to be investigated in water and water/sediment systems. The applicant is expected to provide data or information on the hydrolysis at different pHs, aerobic biodegradation and fate and	Applicant: The application is updated. At this stage, no data are available regarding the degradation kinetics of Quassin or *Quassia amara* extract in water. For risk assessment purposes worst-case default DT50-water of 1000 d and DT50-sediment of 1000 d are considered	See data gap in 7(2). In the absence of further data, the use of default values will be assumed for the other components of *Quassia amara* extract with biological activity.

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		exposure assessment to aquatic environment.	behaviour in natural surface water / sediment systems. Results from experiments with model test systems would be the best way to address this. Alternatively, scientific publications on these aspects retrieved by a systematic literature review approach are necessary.	As quassin is considered as lead substance for *Q. amara*, no assessment of further substances was performed.	
7(12)	7.1, Persistence in Water	DE: The basis of the consideration and origin of data are unclear (study, reference, testing system, reasoning).	DE: Please provide relevant information.	Applicant: Please see answers to comment 7(11)	See 7(10) and 7(11)
7(13)	7.1, Persistence in Air	EFSA: The statement needs to be substantiated with information or data on the volatility of quassin. Information and data of other *Quassia amara* L. Wood components with known or presumed biological activity also needs to be provided.		Applicant: The application is updated. At this stage, no experimental data are available regarding the Quassin behaviour in air. Reference to an external chemical database is provided.	Addressed with respect to the component quassin. See data gap in 7(2) for other biologically active components of *Quassia amara* extract.
7(14)	7.1, Persistence in Air	DE: The basis of the consideration and origin of data are unclear (study, reference, testing system, reasoning,…) and the expectation inconclusive.	DE: Please provide relevant information.	Applicant: see answer to comment 7(13).	See 7(13)
7(15)	7.1, Photostability (DT50)	EFSA: Information of data on the photodegradation of quassin	EFSA: the statement on the fast photodegradation and the estimated range of DT50 is not	Applicant: Please refer to a section 2.3.8 of the application.	**Data gap:** Information or data on the

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	(aqueous, sunlight, state pH)	in soil and water needs to be provided. Also information on the photodegradation of other *Quassia amara* L.wood components with known or presumed biological activity needs to be provided.	substantiated. Proper data or studies need to be provided. UV spectra can be provided for the different components of *Quassia amara* L. wood to justify the arguments provided to waive further data (e.g., in case no significant UV adsorption, photodegradation may be considered not relevant).	No other data than presented on the photostability of quassin are available. This information was not requested in the evaluation in 2018.	photodegradation of quassin in soil and water was not available. Also, information on the photodegradation of other *Quassia amara* L. wood components with known or presumed biological activity was not available. UV spectra can be provided for the different components of *Quassia amara* L. wood to justify the arguments provided to waive further data (e.g., in absence of significant UV adsorption photodegradation may be considered not relevant).
7(16)	7.1, Photostability (DT50)	DE: The basis of the consideration and origin of data are unclear (study, reference, testing	DE: Please provide relevant information.	Applicant: see answer to comment 7(15).	See data gap in 7(15)

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	(aqueous, sunlight, state pH)	system, reasoning,…) and the expectation inconclusive.			
7(17)		EFSA: In EFSA 2018 a data gap was identified for batch adsorption/desorption studies on quassin and other active components of *Quassia amara* L. wood extract that may be identified as biologically active and/or responsible for a potential impact on human health. These data were needed in order to address potential surface and groundwater exposure. A new study has been submitted to determine the adsorption and desorption behaviour of Quassin in four soils using the batch equilibrium method. However, the summary of this study in the application needs to be completed with the necessary information to enable an adequate peer review.	EFSA: Applicant to update the application with further details on the batch soil adsorption desorption study submitted, including test material characterisation, material and methods and the relevant calculations. Applicant to clarify if the study was performed according to GLP or if another quality assurance system was in place.	Applicant: The application is updated. In the broader soil incubation study summary details on the batch soil adsorption desorption study submitted, including test material characterisation, material and methods and the relevant calculation are presented. Details on GLP accreditation of the tested facility and statement on conduction of study under GLP are also provided.	Addressed. Reliable batch adsorption data have been made available for the component quassin. The derived end points can be used for the exposure assessment of this component.
7(18)	7.1, Determination	DE: KF,OCads-value, which test or tool was used to test for the	DE: Please provide relevant information.	Applicant: Please refer to the point 7(17)	Addressed.

7.1 Fate and Behaviour in the environment

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
	of the adsorption coefficient	correlation with soil pH. Number from table caption is missing.			
7(19)	7.1, Determination of the adsorption coefficient	EFSA: Besides for quassin, batch adsorption/desorption studies or mobility information on other active components of *Quassia amara* L. wood extract that may be identified as biologically active and/or responsible for a potential impact on human health have not been submitted.	Adsorption information is missing and is needed for other active components of *Quassia amara* L. wood extract that may be identified as biologically active and/or responsible for a potential impact on human health. Information might also be triggered for transformation products of the relevant components in the extract.	Applicant: *Quassia amara* wood is a natural substance. All ingredients present in the wood, as well as their transformation products, are consequently also naturally occurring in the environment. Although *Quassia amara* is a (sub)tropical plant, no adverse effects in areas of its natural occurrence or farms are known to the applicant. Moreover, *Quassia amara* is used in foodstuff and certain amounts of quassin are accepted in bakery wares and beverages.	**Data gap:** Batch adsorption/ desorption studies on the other active components of *Quassia amara* L. wood extract that may be identified as biologically active and/or responsible for a potential impact on human health still need to be provided. In case bridging of data on quassin is proposed, a sound scientific argumentation would be needed.
7(20)	2.1 (under IUCLID) "Preparation of the substance for use"	NL: Currently the nomenclature in IUCLID of the substance would imply that the wood itself is the active substance, which is incorrect. Please change this to "aqueous extract… " etc. as is provided	EFSA: see comment 2(6)	Applicant: The wood is the basic substance. The description of the substance can be found in the application form and further information was also added in	See 2(1), 2(8)

7.1 Fate and Behaviour in the environment

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
		in the description of the 2.1 dropdown menu under the reference substance name.		IUCLID in the reference substance entity.	
7(21)	7.1 "persistence in soil/exposure to the soil compartment"	NL: The OECD 307 study investigates the degradation of the substance, not the dissipation. Additionally, the NL does not see the need from the data presented in the 307 study to go beyond SFO for the soils II, III and IV.	NL: The SFO chi-squared errors are relatively low (~5%) and the R2 are high ~0.97. NL would prefer the line of inquiry as per FOCUS kinetics (2014) where the simpler SFO is preferred if it is good enough. It is noted that this has little bearing on the DT50 as the SFO DT50 is ~60d for soils III and IV, with ~28d for soil II, which is not drastically different than the DT50s proposed by the HS2 K_2DT50. Also see column 3 entry at comments 7(4) and 7(5).	Applicant: The application is updated. In the broader soil incubation study summary details on kinetic analysis are presented. Comparison of alternative fitting kinetic for all four soils is included in Table 7-6, showing significantly lower chi-squared values for HS in soil II, III, IV compared to SFO. The DT50 and DT90 were calculated based on the k2-value as there is not a true lag phase. The appearing lag phase is possibly the result of the fact that the pre-incubation period was not long enough.	See data gap in 7(4)

7.2 Estimation of the short and long-term exposure of relevant environmental compartment (soil, groundwater, surface water and air)					
No.	**Column 1** **Reference to Application Template**	**Column 2** **Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4** **Follow up response from applicant**	**Column 5** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
7(22)	7.2.1, Exposure through the use for plant protection purposes Table 7-1	DE: Determination of application rate is unclear. Footnote [e] is not referenced.	DE: Please show how the total application rate per season has been derived, since this is missing in the overall GAP p.30 and needs to be completed with reference to e.g. crown height and total rate.	Applicant: The amount of quassin/ha is described in section 2.3.6. See also our answer to comment 7(22). Since *Q. amara* is the basic substance, the quassin content/ha was not added to the GAP. Footnote e was an error. The footnote was deleted in the updated application.	**Data gap:** A justification of the equivalence of the application rate in terms of kg of wood pellets and amount of quassin in the resulting extract has not been provided. At least the applicant should provide the analysis of several extracts obtained from different *Quassia amara* L. wood batches in order to justify the levels of quassin (and other *Quassia amara* extract biologically active components) to have a robust justification of the levels (and associated uncertainty) assumed to be applied on the crops. See also 2(3), 2(15), 2(12), 7(3) and 7(33).
7(23)	7.2.1. Exposure through the use for plant	EFSA: According the GAP table 20 kg a.s /ha (pome fruit/stone fruit) – 30 Kg a,s /ha (hop). Since the	EFSA: Please provide a clear explanation how its possible to equate the application rate of 20 and 30 kg wood per ha to representing 12 -18 g quassin.	Applicant: Please refer to section 2.3.6. As presented in Table 2-2, wood samples from 2010-2019 revealed a Quassin content in a range between	See data gap in 7(22)

7.2 Estimation of the short and long-term exposure of relevant environmental compartment (soil, groundwater, surface water and air)					
No.	**Column 1 Reference to Application Template**	**Column 2 Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4 Follow up response from applicant**	**Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
	protection purposes	active substance is declared to be the wood pellets it should be clarified if these applications rates refer to the pellets before extraction, the raw extract or the diluted extract. Once this is clarified, the corresponding quassin application rate assumed in the exposure assessment (12 – 18 g quassin / ha) needs to be justified with data.	Any reference or experiments that are the basis of this conversion / calculation to be included in the application and transparently assessed.	0.5 g Quassin / kg wood and 1.18 g Quassin / kg wood. As presented in Table 2-4, the amount of Quassin per hectare for different concentrations of Quassin in *Q. amara* wood when applied according to the GAP is between 5-11.8 g Quassin / ha in apples and stone fruits and 7.5 – 17.7 g Quassin/ha for hop. For the evaluation of the effects of *Quassia amara* wood on humans, animals and the environment, wood with high Quassin content was used, which would lead to the application of 12 g Quassin/ha in pome and stone fruit or 18 g Quassin/ha in hop.	
7(24)	7.2.1, Table 7-4	DE: AppDate has data for the scenario hops, which differ from vines.	DE: Please give reasoning on why hops could be covered as vines as a worst case.	Applicant: Vines were chosen as surrogate crop due to the same crop interception at earlier application timing and physiological similarity of crops, while covering wider	Addressed.

7.2 Estimation of the short and long-term exposure of relevant environmental compartment (soil, groundwater, surface water and air)					
No.	**Column 1** **Reference to Application Template**	**Column 2** **Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4** **Follow up response from applicant**	**Column 5** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
				range of scenarios. Alternatively, hops could be covered by apples, which do have same interception at both stages of growth indicated. Apples are already a part of the RA presented.	
7(25)	7.2.1, Table 7-5	DE: Application dates for hops differ from AppDate (see comment table 7.4).	DE: Please check application dates for hops, at least correct for the scenario Hamburg.	Applicant: Application dates for hops are defined only for scenario Hamburg and Kremsmünster, which may not be sufficient scenarios for risk assessment in all CEZ countries considered. As a surrogate crop, vines were chosen (please see point 7(24)). For PEC_{gw} assessment of use on hops, the application dates for relevant BBCH stage of surrogate crop vines were used. These are listed in the Table 7-2-5. Those dates were defined using the AppDate3.06 tool. Found application dates for vines at BBCH53 are 14 days earlier than those for BBCH 51 for hops and 20 days	Addressed.

7.2 Estimation of the short and long-term exposure of relevant environmental compartment (soil, groundwater, surface water and air)					
No.	**Column 1** **Reference to Application Template**	**Column 2** **Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4** **Follow up response from applicant**	**Column 5** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
				earlier then BBCH55 for hops, where BBCH53 is not defined for hops. For late application at BBCH69 the application date for vines are 16 days earlier than those for hops. The impact of this time shift is considered negligible. Text of the chapter was adapted.	
7(26)	7.2.1, Table 7-6	DE: The use of the the Van't Hoff correction equation for solubility and vapour pressure data is unclear.	DE: Please explain the derivation of the solubility and vapour pressure data using the Van't Hoff correction equation.	Applicant: Derivation of solubility in water at 30°C using the Van't Hoff solubility temperature correction equation is explained in the footnote 4 of Table 7-18	Addressed.
7(27)	7.2.1 Table 7-6	EFSA: The solubility vapour pressure of quassin is stated that has been obtained from an external chemical database, but the actual reference to the source of this parameter is not given.	EFSA: Applicant to provide reliable studies determining vapour pressure and solubility of quassin. If reliable data is available in the scientific peer reviewed literature, copies of the corresponding studies should be provided in the dossier and adequately quoted in the application.	Applicant: These studies were not requested in the evaluation from 2018. Therefore, experimental data on Quassin volatility are not available. Based on the ACD lab tool vapor pressure is estimated to be 1.73×10^3 Pa at 25°C (9.01×10^2 Pa at 20°C), which was used for the originally suggested risk assessment in environmental	Addressed.

7.2 Estimation of the short and long-term exposure of relevant environmental compartment (soil, groundwater, surface water and air)					
No.	**Column 1 Reference to Application Template**	**Column 2 Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4 Follow up response from applicant**	**Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
				compartments (PEC calculations). Based on the commenting, further investigations were conducted regarding the vapor pressure, which resulted in a substantially differing value derived from EPI suite, being 1.9 x 10^{-8} Pa at 25°C. Considering the spatial properties of the molecule the applicant considers a vapor pressure of <5 x 10^{-3} Pa at 25°Cas a rather realistic estimate. An additional risk assessment in environmental compartments is presented considering a vapor pressure of 4.9 x 10^{-3} Pa at 25°C.	
7(28)	7.2.1 PEC GW	EFSA: In EFSA 2018, a data gap for PECgw calculated following FOCUS guidance and using FOCUS models and scenarios was	Reliable groundwater exposure calculations need to be provided considering what would be the most reliable endpoints for quassin, its (currently unknown) soil	Applicant: *Quassia amara* wood is a natural substance. All ingredients present in the wood, as well as potential transformation products, are consequently also naturally	**Data gap:** Reliable groundwater exposure (FOCUS GW) modelling for quassin considering what would be the most reliable endpoints for modelling were not available.

7.2 Estimation of the short and long-term exposure of relevant environmental compartment (soil, groundwater, surface water and air)					
No.	**Column 1** **Reference to Application Template**	**Column 2** **Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4** **Follow up response from applicant**	**Column 5** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
		identified for quassin and other active components of *Quassia amara* L. wood extract. PEC GW calculations have been provided for quassin in current application. However, the applicant's conclusion that the use of *Quassia amara* wood according to the GAP would be safe with respect to leaching to groundwater and contamination of drinking water and that it would not lead to groundwater concentrations above 0.1 µg/L cannot be agreed by EFSA. In relation to quassin it has been not possible to independently	transformation products and other active components of *Quassia amara* L. wood extract and their soil transformation products. I.e. considering other column 3 entries requesting further information on these aspects.	occurring in the environment. Although *Quassia amara* is a (sub)tropical plant, no adverse effects in areas of its natural occurrence or farms are known to the applicant.	Assessment of groundwater exposure potential to quassin soil transformation products (currently unknown) and other biologically active components of *Quassia amara* L. wood extract and their soil transformation products is needed. See also data gaps in 7(2) and 7(3) for quassin, its (currently unknown) soil transformation products and other active components of *Quassia amara* L. wood extract and their soil transformation products. See also 7(35)

7.2 Estimation of the short and long-term exposure of relevant environmental compartment (soil, groundwater, surface water and air)					
No.	**Column 1 Reference to Application Template**	**Column 2 Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4 Follow up response from applicant**	**Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
		validate the reliability of the application rate and input parameters used in the modelling (see EFSA and MSs comments). With respect to the other known or presumed biological active components of *Quassia amara* L. wood extract no information has been provided. Soil transformation products that may leach to groundwater is also an open issue.			
7(29)	7.2.1 Predicted Environmental Concentrations in surface water (PECsw)	EFSA: The quassin input parameters used for the PEC sw/sed calculations are not reported in the application.	EFSA: Please complete the application with the input parameters assumed for quassin in the PEC SW/sed modelling.	Applicant: The application is updated. The input parameters assumed for Quassin $PEC_{sw/sed}$ are presented in Table 7-24.	**Minor outstanding issue:** Quassin PECsw/sed need to be updated with peer reviewed input parameters (see data gap in 7(3)). See minor outstanding issue in 8(10)

7.2 Estimation of the short and long-term exposure of relevant environmental compartment (soil, groundwater, surface water and air)					
No.	**Column 1** **Reference to Application Template**	**Column 2** **Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4** **Follow up response from applicant**	**Column 5** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
7(30)	7.2.1 Predicted Environmental Concentrations in surface water (PECsw)	EFSA: The exposure of the aquatic environment to the other known or presumed biologically active components of *Quassia amara* L wood extract has not been addressed in this application. Soil and sediment water transformation products from components in the extract need to be addressed and as appropriate PEC calculated.	EFSA: please provide the predicted exposure of the aquatic environment to the other known or presumed biologically active components of *Quassia amara* L wood and transformation products of quassin and the other biologically active components.	Applicant: *Quassia amara* wood is a natural substance. All ingredients present in the wood, as well as potential transformation products, are consequently also naturally occurring in the environment. Although *Quassia amara* is a (sub)tropical plant, no adverse effects in areas of its natural occurrence or farms are known to the applicant.	**Minor outstanding issue:** Predicted exposure of the aquatic environment to the other known or presumed biologically active components of *Quassia amara* L. wood and their transformation products of quassin and the other biologically active components were not available. See data gaps 2(7) and 7(2). See minor outstanding issue in 8(10)
7(31)	7.2.2, Background exposure (exposure to the substance through uses other than for plant	DE: Reference is made to theoretical background concentration for environmental compartments for the (tropical) countries of origin without convincingly relating this to the conditions	DE: Please explain why and how the reasoning of the observations from the (tropical) countries of origin is relevant and representative for soils and climate conditions in Europe, even if *Q. amara* is planted outside its native range.	Applicant: *Quassia amara* wood is a natural substance. All ingredients present in the wood, as well as potential transformation products, are consequently also naturally occurring in the environment. Although *Quassia amara* is a (sub)tropical plant, no adverse effects in areas of its natural	Addressed. Argumentations based on the natural background levels of Q*uassia amara* L. extract components have not been considered by EFSA in its assessment as it is not relevant for EU.

7.2 Estimation of the short and long-term exposure of relevant environmental compartment (soil, groundwater, surface water and air)					
No.	**Column 1 Reference to Application Template**	**Column 2 Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4 Follow up response from applicant**	**Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
	protection purposes)	in Europe. No background concentration is given for water, only presence.		occurrence or farms are known to the applicant. Information from (sub)tropical areas are an indicative value for non-problematic background level estimations.	See also 7(36), 7(37), 7(40) and 7(41).
7(32)	7.2.1	DK: Please use the term "soil loading" or "soil deposition" instead of "soil dissipation level".		Applicant: Change in updated application.	Addressed.
7(33)	7.2.1	DK: From where comes the application rate of 12 g quassin/ha? Please include this information on the GAP in chapter 3 as well.		Applicant: The explanation why 12 g Quassin/ha was used in the calculation is provided in Section 2.3.6 and 3.3. of the application form. The 12 g/ha were calculated based on the highest Quassin content measured in *Q. amara* wood and by considering the estimated extraction of quassin when the instructions in the GAP are followed. The amount of Quassin/ha is not mentioned in the GAP, as the application is for *Q. amara*	See data gap in 7(22)

7.2 Estimation of the short and long-term exposure of relevant environmental compartment (soil, groundwater, surface water and air)					
No.	**Column 1 Reference to Application Template**	**Column 2 Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4 Follow up response from applicant**	**Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
				wood and not the lead substance quassin.	
7(34)	7.2.1 Table 7-6	DK: Please note that none of the endpoints are in accordance with EU endpoints, as there is no EFSA conclusion for quassin.	DK: Please delete the "y"s from the table.	Applicant: Change in updated application.	Addressed.
7(35)	7.2.1	DK: Appreciate that the applicant has included a FOCUS PELMO model; however, only quassin has been modelled. It is not clear, or investigated, if any other components should be risk assessed with regard to environmental fate; therefore, the conclusion that *Quassia amara* is not expected to leach into groundwater above	Groundwater modelling is needed for component and transformation products other than quassin. I.e. considering other column 3 entries requesting further information on missing substance properties and simulations necessary to conclude on the potential for groundwater exposure.	Applicant: See answer to comment 7(28)	See data gap in 7(28)

7.2 Estimation of the short and long-term exposure of relevant environmental compartment (soil, groundwater, surface water and air)					
No.	**Column 1 Reference to Application Template**	**Column 2 Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4 Follow up response from applicant**	**Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
		the threshold is only for quassin, and not in fact *Quassia amara*. Not that all components of the extract must be risk assessed, but in this case only 12 g component out of 20 kg wood chips has been risk assessed. Are there other relevant components?			
7(36)	7.2.2	DK: DK question if it is even relevant to argue for a background exposure for *Quassia amara* in the EU where the shrubs do not grow.	DK: Please consider deleting this whole section as it is not relevant for the EU.	Applicant: See our answer to comment 7(31)	Addressed. See also 7(31)
7(37)	7.2.3	Dk: please see DK comment to 7.2.2	DK: Please consider deleting this whole section as it is not relevant for the EU.	Applicant: See our answer to comment 7(31)	Addressed. See also 7(31)
7(38)	7.2.1	NL: The phrasing of "For both spray applications in pome / stone fruit and hops a		Applicant: Application is updated.	Addressed.

7.2 Estimation of the short and long-term exposure of relevant environmental compartment (soil, groundwater, surface water and air)					
No.	**Column 1 Reference to Application Template**	**Column 2 Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4 Follow up response from applicant**	**Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
		crop a soil dissipation level of 40% (crop interception level of 60%) was used." is a bit strange. Please change "dissipation level" to "loading". It would be more consistent with other documentation on the matter.		A phrase soil deposition was used as suggested in comment 7(32).	
7(39)	table 7-6	NL: The temperature correction to 30°C is unnecessary and may be deleted. The modelling software automatically corrects temperature itself.		Applicant: The correction for 30°C is not necessary for modelling by FOCUS PEARL, which is considered for RA in the NL, however, for models considered in other countries (e.g. FOCUS PELMO in DK) both values are necessary. Therefore, the correction is presented as reflected in comment 7(26).	See minor outstanding issue in 7(4)
7(40)	Background exposure 7.2.1	NL: We are unsure of the applicability to the EU of the applicant's method and arguments for the		Applicant: see our answer to comment 7(31)	See also 7(31)

7.2 Estimation of the short and long-term exposure of relevant environmental compartment (soil, groundwater, surface water and air)					
No.	**Column 1** **Reference to Application Template**	**Column 2** **Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4** **Follow up response from applicant**	**Column 5** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
		background concentration. Because the substance itself is an aqueous extract of chips themselves, and considering the slow decay of chips in the natural environment and the degradation of quassin itself, we are unsure of the implications of this release into the soil itself. NL can see that the shrubs are planted outside their native range, but to speak of a EU-wide 'background' concentration considering the presented evidence is a bit of a leap. NL would advise to use the background concentration with a			

7.2 Estimation of the short and long-term exposure of relevant environmental compartment (soil, groundwater, surface water and air)					
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		grain of salt and at most an indicative value for non-problematic background level estimations in other woodland environments with little applicability to EU agricultural lands.			
7(41)	Background exposure 7.2.1	EFSA: Background level estimations presented are not relevant to EU agricultural soil in general (where *Quassia amara* is not a usual crop) and to pome fruit and hop EU fields where *Quassia amara* can be assumed not to be present.	EFSA: Argumentations based on natural background levels of *Quassia amara* components in the EU environment are not applicable for the assessment of the use of *Quassia amara* L. wood as pesticide in EU crops.	Applicant: See our answer to comment 7(31)	See also 7(31)

8. Effects on non-target species (effects having relevance to non-target organisms arising from exposure to the substance/its products or to impurities contained in the substance/product or their transformation products)

8.1. Effects on terrestrial vertebrates

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
8(1)	8.1, Effects on terrestrial vertebrates, mammals	DE: Please provide the study on eye irritation conducted by [redacted] and [redacted], 2005.		Applicant: The study can be found in the IUCLID Dossier (UUID of the literature reference: d5d31108-7284-4547-a6da-c8e30ece2594)	Addressed.
8(2)	8.1, Effects on birds	DE: No toxicity data are available to demonstrate a low risk of *Q. amara* wood extract to birds. The applicant only refers to non-scientific literature and health care products for birds where the *Quassia* dose is unknown.	DE: The applicant should provide adequate information to demonstrate that the risk of *Quassia amara* extract to birds is low.	Applicant: It is correct that for the reference to the health care product for birds the dosage is unknown. However, the product is used for treatment of birds against mites, thus, the dosage should be high enough to make this possible and, thus, comparable to the dosage applied for. In the technical report No 1382 of 13.2.2018 EFSA did not ask for any additional studies regarding the effect on birds, thus, no such studies were started. Furthermore, please see our reply to comment 8(8)	See 8(7) and 8(8)
8(3)	8.1, Effects on mammals	DE: The studies strongly indicate endocrine disrupting properties of quassin in mammals as	DE: The results of the studies should be discussed by experts at EU level.	Applicant: *Quassia amara* was evaluated for food use based on a literature evaluation summarized in the report of the EUROPEAN	**Data gap:** The data provided seem to indicate potential adverse

8.1. Effects on terrestrial vertebrates

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
		well as reprotoxic effects were observed during these studies (e.g. Raji & Bolarinwa, 1997 and Raji et al., 2010). According to SANCO/10363/2012rev.10, a basic substance should "*not have an inherent capacity to cause endocrine disrupting, neurotoxic or immunotoxic effects*".	EFSA: We support the comment from DE on the necessity to further discuss the findings of Raji et al., 2010. If effects on reproduction and/or endocrine disrupting properties are confirmed, the substance might not meet the criteria for approval. The applicant is invited to provide a thorough evaluation of the study, with a reliability and uncertainty analysis. In addition, the applicant should provide information to support the conclusion of low-risk considering the information presented in the study. The applicant should also consider and assess the study by Faisal K, Akbarsha MA. Observations on Dag-like defect of spermatozoa induced by treatment of the phytotherapeutic *Quassia amara*/quassin in the mouse model. Andrologia. 2021 Jul;53(6):e14046. doi: 10.1111/and.14046. The study	COMMISSION HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL, Scientific Committee on Food (SCF/CS/FLAV/ FLAVOUR/29/FINAL) of 25.7.2002. Thus, it complies with Art 23(2) of the Regulation (EC) 1107/2009 that the substance should have already been evaluated in the view of other uses. Due to this evaluation, the limits in Regulation (EC) 1334/2008 were set (see section 5) In Table 5-2 we refer to the state of knowledge of 2002, the year when the report of the EUROPEAN COMMISSION HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL, Scientific Committee on Food (SCF/CS/FLAV/ FLAVOUR/29/FINAL) of 25.7.2002.was published. This report ist he basis of the evaluation in the view of other uses (foodstuff) where the limits in Regulation (EC) 1334/2008 we	effects for the reproductive system of mammals by quassin and Quassia extracts. No assessment of the potential endocrine disruption is included. It is not possible to exclude that the reproductive effects are related to an endocrine mode of action. Robust data on the ecotoxicological effects of the proposed basic substance considering the potential for endocrine disruption for wild mammals should have been provided. See comments 2(4), 5(2), 5(11) and 8(29), and data gap in section 3.5 for wild mammals and fish.

8.1. Effects on terrestrial vertebrates

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			seems to indicate potential effects and structural changes in spermatozoa that lead to angulation, flexion and coiling of the tail in mice after treatment with *Q. amara* and quassin. Please consider the relevance of this information also in the toxicology section.	refer to were set. In Table 5-2 the publications are listed that were not included in the report. It is shown that no results were published since 2002 that show effects with lower concentrations than those that were published before 2002. It was stated in the technical report from EFSA 2018: The ecotoxicology section is sufficient to consider the risk to non-target organisms as low for the representative uses. See also comment from NL 8 (29) regarding general ecotoxicology. Thus, no additional data for the effects on non-target vertebrates were prepared. However, applicants would like to recall that Quassia is a very potent bittering agent so that a strong repellent effect of treated vegetation on mammals is to be expected.	
8(4)	8.1, Effects on mammals	DE: Due to the study of Raji et al. (2010), a NOEL/NOAEL	DE: A more comprehensive risk assessment should be provided	Applicant: See answer to comment 8(3)	Considering the effects observed on fertility at

8.1. Effects on terrestrial vertebrates

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		of 2.0 mg quassin/kg bw/d (considering the recovery) on reproductive effects in mammals can be used for a risk assessment according to EFSA Journal 2009; 7(12):1438. The outcome of the reproductive screening assessment indicates an unacceptable risk to mammals from the intended *Q. amara* use in hop (17.7 g quassin/ha) and pome fruit (11.8 g quassin/ha; see Table 2-4 in section 2.3.6).	by the applicant, and the results of the non-GLP study by Raji et al. (2010) should be discussed by experts at EU level.		2 mg/kg bw/d, it is proposed to present an illustrative risk assessment with the ecotoxicological relevant NOAEL set at 1 mg/kg bw/d. See also See 8(3) and (7)
8(5)	8.1	DK: There is not risk assessment of birds.	DK: Please include a risk assessment.	Applicant: In the technical report from EFSA 2018 it was stated: The ecotoxicology section is sufficient to consider the risk to non-target organisms as low for the representative uses. See also comment from NL 8 (29) regarding general ecotoxicology. Furthermore, please see our reply to comment 8(8)	See 8(7) and 8(29)

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8(6)	8.1	DK: Please include a quantitative risk assessment for mammals. A risk assessment is the comparison of hazard to the exposure, not simply stating the hazard. Also, it is not a valid argument that no negative effects have been observed in more than 30 years, this is merely anecdotal as well as the speculation into if Quassia is a repellent. Furthermore, please delete several of the included references as they are not relevant for the use as a pesticide e.g. the "Shampoo, All natural Pet Flea away" reference.		Applicant: A risk assessment is not considered necessary since *Q. amara* is used for pest control in poultry and can be added to human food. In the technical report from EFSA 2018 it was stated: The ecotoxicology section is sufficient to consider the risk to non-target organisms as low for the representative uses. See also comment from NL 8 (29) regarding general ecotoxicology	See 8(7)
8(7)	8.1 Effects on terrestrial vertebrates - Birds	EFSA: No quantitative information was provided by the applicant. Only information on possible contact exposure is		Applicant: In the technical report from EFSA 2018 it was stated: The ecotoxicology section is sufficient to consider the risk to non-target	**Data gap:** An appropriate risk assessment was not provided for neither birds nor mammals.

8.1. Effects on terrestrial vertebrates

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		provided, although scarce and not scientifically relevant. Please note that the main route of exposure for birds to be considered is dietary. Please provide the references concerning the reported repellent effects. Please delete the references that are not relevant for the current assessment, such as information on the use of Quassia as detergent. In addition, the reliability of anonymous reference is highly questionable. No assessment is available for birds and no information is available to conclude on the risk. The applicant is invited to provide further information and carry out a quantitative risk assessment or build a solid and scientifically sound assessment based on a		organisms as low for the representative uses. See also comment from NL 8 (29) regarding general ecotoxicology. The use of Quassia as detergent is not reported, regarding the "Quassia wash" but the use refers to the control of red mites of birds by washing them with a Quassia solution. Furthermore, please see our reply to comment 8(8)	The dietary route of exposure has not been assessed by the applicant for birds. Anonymous references that are not relevant for the current assessment have not been deleted from the application, nor further supported. The applicant has not provided an updated section for the assessment of the risk to birds and mammals. Limited information on the repellent effect is reported, which does not substitute a well-supported and scientifically sound weight of evidence assessment. While it is reported that *Q. amara* has a long history of safe use, no quantitative

8.1. Effects on terrestrial vertebrates

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		weight of evidence approach (please refer to the available EFSA Guidance on Birds and Mammals and on the EFSA for the WoE approach) using all the available and referenced information (e.g. repellent effects, information on dietary exposure and effects).			information is provided to support this statement. In addition, literature studies seem to indicate that an effect on reproduction can be observed. In Raji et al. (2010), a NOEL/NOAEL of 1.0 mg quassin/kg bw per day was derived based on effects on reproduction in mammals. This is much lower than what is indicated in the basic substance application. The outcome of the reproductive screening assessment with a NOEL/NOAEL of 1.0 mg quassin/kg bw per day indicates a high risk to mammals from the intended *Q. amara* use in hop (17.7 g quassin/ha) and pome and stone fruit, and

8.1. Effects on terrestrial vertebrates

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
					plum (11.8 g quassin/ha). See also comment on the uncertainty regarding the derivation of the application rate based on quassin. See data gaps in 2(12) and 7(3). See also 8(29).
8(8)	8.1 Comparison of the use of Quassia in birds health care with the proposed applications	NL: it is stated that there are several commercial products containing Quassia for oral application, although it is not possible to quantify the uptake. The amount of Quassia will probably be on the package and a dose to be given to the bird as well so we would suspect an indication on up-take possible.	EFSA: The applicant should consider the information available to properly quantify exposure to birds.	Applicant: The recommendation for the use on canary birds to control the red mite is 2 ounces of *Quassia* chips on 10 ounces of water. The proportion is 2:10 which is much higher than the proportion we use of 20 kg in 1000 L water. For hens, the direct contact with *Quassia* wood powder in dust baths is recommended. For the external use similar or higher concentrations of Quassia than we apply for are recommended.	Addressed. Relevant information on the exposure to birds has been provided.

8.1. Effects on terrestrial vertebrates

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				As deterrent for birds, it is recommended in a concentration of 50 g in 4 cups (250 ml x 4 = 1L) of water. This is a 2-3 x higher concentrated solution than recommended by applicants. In the commercial products recommended for internal use *Quassia* is given as ingredient but the concentration is not specified.	

8.2. Effects on aquatic organisms

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
8(9)	8.2, Effects on aquatic organisms	DE: The results in Table 8-2 are based on nominal concentrations. It is likely that the toxicity endpoints are lower	DE: We ask the applicant to provide sufficient evidence that toxicity endpoints based on mean measured	Applicant: We do not see any problems with providing nominal concentrations. The study was published in the journal of the Federal Biological	**Minor outstanding issue:** The applicant has not provided the results based on mean measured concentrations. Nevertheless,

8.2. Effects on aquatic organisms

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		when they are based on mean measured concentrations.	concentrations are not needed.	Research Center for Agriculture and Forestry in Germany, which we consider as reliable source.	they can be used in the risk assessment, although this increases the uncertainty.
8(10)	8.2, Effects on aquatic invertebrates	DE: Since *Q. amara* wood extract is used as insecticide, it is likely that aquatic insects are more sensitive than other tested surrogate species. The 6-h LC_{50} of quassin for larvae of *C. quincefasciatus* was already 2.85 mg/L indicating that its 48-h LC_{50} may be lower than the lowest toxicity endpoint in Table 8-2.	DE: To also cover the risk for aquatic insects, we propose that an acute *Chironomus* sp. immobilisation test should be performed according to OECD 235. EFSA: We support the comment from the MS and would ask the applicant to provide further data to address the potential adverse effects and risk assessment for invertebrates, considering the insecticidal properties of the substance.	Applicant: Previously it was stated in the technical report from EFSA 2018: The ecotoxicology section is sufficient to consider the risk to non-target organisms as low for the representative uses. See also the comment from NL 8 (29) regarding general ecotoxicology. For this reason, no data were generated, and it is now not possible to generate data in the given time.	**Minor outstanding issue:** The applicant has not provided further data nor a sound justification to address the potential adverse effects and risk assessment for aquatic invertebrates, considering the insecticidal properties of the substance. Nevertheless, the lack of adverse effects reported in the available literature for the effects on non-target arthropods seems to indicate a favourable ecotoxicological profile. **Data gap:** A potential concern is identified for endocrine disruption, considering the concern identified regarding

8.2. Effects on aquatic organisms

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					potential for endocrine disruption in mammals. Robust data on the ecotoxicological effects of the proposed basic substance considering the potential for endocrine disruption for fish should have been provided (see also sections 3.2 and 3.5, and data gap in section 4.1).
8(11)	8.2	DK: Please justify that nominal endpoints can be used for risk assessment and not the mean measured endpoints.		Applicant: Please see our reply to comment 8(9).	See 8(9)
8(12)	8.2 table 8-4	NL: The concentration in µg/L is preferred to compare with the PECsw for an indication of risk.		Applicant: The table was adapted respectively.	Addressed.
8(13)	8.2	NL: a report with no prove of the existence of Quassin or other Quassinoids by	EFSA: The report should be deleted as it is not reliable nor relevant for the purpose of this BSA.	Applicant: The same references were evaluated in 2018 and were considered acceptable. Moreover, the analytical profile	See data gap identified in 2(7). See 8(29)

8.2. Effects on aquatic organisms

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		analytical means is unreliable.		of *Quassia* extract MD is presented in Section 2.3.6.	

8.3. Effects on bees and other arthropods species

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
8(14)	8.2.1, Effects on honeybees; Acute oral and acute contact toxicity to honeybees; Table 8-6: Summary of toxicity to bees for Quassia	DE: According to the study by [redacted] 2013, the quassin content of the product tested (Quassia extract MD) was 0.75 %.	DE: Therefore, the acute oral LD_{50} (48h) should be > 6.27 µg quassin/bee (instead of > 10.032 µg quassin/bee) and the acute contact LD_{50} (48h) should be > 5.25 µg quassin/bee (instead of > 8.4 µg quassin/bee).	Applicant: The same references were evaluated in 2018 and were considered acceptable.	The applicant has not provided a justification as to why the previously calculated endpoint should still be considered valid, considering the content of the product tested. Nevertheless, a preliminary risk assessment carried out considering the corrected endpoint expressed in quassin/bee indicates a potential low risk to bees.

8.3. Effects on bees and other arthropods species

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	extract MD and values expressed as Quassin; page 140				An uncertainty remains regarding the assessment of other components in the extract for which a biological action cannot be excluded. See data gaps in 2(7) and 7(3).
8(15)	8.2.1, Effects on honeybees; Acute oral and acute contact toxicity to honeybees; Table 8-7: Risk to bees from acute oral and contact exposure to Quassin; page 140	DE: The applicant assumes that in most cases only 50 % of the maximum available amount of quassin can be extracted. This is justified by the fact that even small deviations from the ideal preparation will reduce the amount of quassin obtained accordingly. The maximum application rate would then be 17.7 g quassin/ha.	DE: For the risk assessment, however, we recommended to consider 100 % of the maximum available amount of quassin per kg of *Q. amara* L. wood chips in order to cover the risk also in case of a perfect preparation (maximum application rate would then be 35.4 g quassin/ha).	Applicant: See next comment 8.2.1. To our knowledge, the concentration of the solution is crucial. The experimental design and the concentrations were previously discussed by the University of Hohenheim with the institute for Bienenschutz of the JKI.	Addressed. Even when considering a potential precautionary worst-case approach, as suggested by the comment from DE where the maximum application rate is 35.4 g quassin/ha, a potential low risk can be concluded for bees. This approach, however, still ignores the fact that no reliable information is available with regards to the other components of the extract and their potential biological activity, nor if any of them is more appropriate than quassin as lead compound for the risk assessment. See data gap in 8(24).

8.3. Effects on bees and other arthropods species

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8(16)	8.2.1, Effects on honeybees; Further data; Slave, J, 2017; page 141	DE: According to Slave (2017), an application rate of 6 g quassin/ha was tested in the field study. This application rate is clearly lower than the maximum application rate mentioned in the BSA maximum 35.4 g quassin/ha). The results of the study by Slave (2017) should therefore only be used as additional information.		Applicant: The test field in this study was a Phacelia field. To spray this field, 500 l water/ha were used. Thus, the concentration of the solution sprayed was 12 mg Quassin per L corresponding to 12 g Quassin in 1000 L. For the application on trees, 1000 L/ha are used since the trees are higher. With the maximum concentration of 12 g Quassin/ha this corresponds to 12 mg/L. For hop, the maximum is 18 g Quassin per ha in 2300 L/ha which corresponds to 7,8 mg/L in the solution. For the toxicity for bees, the concentration of the solution is relevant and this in the trial corresponds to the highest concentration we apply for in the GAP.	**Minor outstanding issue:** The actual amount of quassin applied is highly uncertain and the approach of DE of considering 100% of quassin present in wood could be considered a precautionary worst-case approach (without the 50% reduction factor proposed by the applicant). See 8(15)
8(17)	8.2.1, Effects on	DE: We agree that the risk to bees is considered unlikely		Applicant: Noted and agreed.	Addressed.

8.3. Effects on bees and other arthropods species

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
	honeybees; Conclusion; page 141	when quassin is properly applied.			
8(18)	8.2.2, Effects on other arthropods	DE: For predatory mites, the study reports are either not of good quality (Tsolakis et al., 1997, Vostrel, 2013, Baier, 2001) or there is not even a study report with data/results ([redacted], 2016; [redacted], 2016, Eggler et al., 1996). For example, Tsolakis et al. (1997) did not adequately describe the field trail and the results are partly not plausible. Moreover, the authors concluded that "*bitter wood could also be used, but more experiments should be carried out, using liquid formulations, as the powder ones have shown a low solubility in water*". Regarding the study by Vostrel (2013), a lot of crucial information are	DE: Therefore, the applicant is asked to submit a valid and plausible *Typhlodromus* toxicity test according to Blümel et al. (2000). We recommend to perform the test with the coffin cell method, which avoids the use of glue barriers.	Applicant: In the overview regarding the effects on non-target arthropods all available literature and information was collected and summarized. Even if the quality of the studies is of course not always good, this summary should give an indication about the effects on non-target arthropods that was commented in the technical report from EFSA 2018: The ecotoxicology section is sufficient to consider the risk to non-target organisms as low for the representative uses. See also the comment from NL 8 (29) regarding general ecotoxicology. Regarding the study of Vostrel, *Quassia* extract was applied in each case	Addressed. Overall, the available information indicates a favorable ecotoxicological profile and a low risk could be concluded for other arthropods for all proposed uses.

8.3. Effects on bees and other arthropods species

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
		missing, such as application rate and application date, which is why the study is not valid/plausible.		once to control hop aphids. Since the release of the predatory mites took place at May, 26th, the application against hop aphid had to be definitely after the release. Otherwise, it would not have been successful.	
8(19)	Bees	DK: Error in the chapter naming: "Effects on bees" is chapter 8.3, not 8.2.1. Please correct for a better overview.		Applicant: Thank you. Numbering is corrected in the updated version of the application form.	Addressed.
8(20)	History of safe use	DK: Please delete the anecdotal "evidence". It is simply not true that no case is reported where beekeepers claimed problems with bees or beehives. It may be that no one has claimed problems directly linked to use of Quassia, however, plenty of bee keepers have problems with bees where the accurate cause may not be stated or known.		Applicant: The evidence is linked to beekeepers where the bees are kept directly in the organic orchards for the whole season. There is no case reported when beekeepers with bee hives in organic orchards claimed problems.	The anecdotal information was not removed from the basic substance application. Overall, the available information indicates a favorable ecotoxicological profile and a low risk could be concluded for bees for all proposed uses.

8.3. Effects on bees and other arthropods species					
No.	**Column 1 Reference to Application Template**	**Column 2 Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4 Follow up response from applicant**	**Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
8(21)	8.2.1 Effects on honeybees	NL: no comments			Noted.
8(22)	8.2.2 Effects on other arthropods	NL: no comments			Noted.

8.4. Effects on earthworms and other soil macroorganisms					
No.	**Column 1 Reference to Application Template**	**Column 2 Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4 Follow up response from applicant**	**Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
8(23)	8.3, Effects on earthworms and other soil macro-organisms	DE: No scientific data for non-target soil meso- and macrofauna (earthworms, springtails, *Hypoaspis* mites) were submitted by the applicant demonstrating a low risk of *Q. amara* wood extract to soil invertebrates.	DE: Please, provide sufficient scientific data for soil meso- and macrofauna. EFSA: The applicant is invited to provide the necessary data to address the risk assessment and data requirements for soil organisms (e.g. by	Applicant: It was previously stated in the technical report from EFSA 2018: The ecotoxicology section is sufficient to consider the risk to non-target organisms as low for the representative uses.	Addressed. Overall, low risk can be concluded for earthworms, soil macro and microorganisms based on the information available and weight of evidence considerations for all proposed uses.

8.4. Effects on earthworms and other soil macroorganisms					
No.	**Column 1 Reference to Application Template**	**Column 2 Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4 Follow up response from applicant**	**Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
			exploring the peer reviewed scientific literature and providing a sound and scientifically justified assessment based on a weight of evidence approach). The applicant may wish to use the EFSA Guidance on Submission of scientific peer-reviewed open literature (EFSA, 2011), and the EFSA Guidance on the use of the weight of evidence approach in scientific assessments (EFSA, 2017). The information provided on the uses as traditional medicine does not seem to be relevant for the current assessment.	Thus, no additional data for this section were prepared. See also comment from NL 8 (29) regarding general ecotoxicology.	
8(24)	8.3 Effects on earthworms	NL: for ease of assessment the units could be more uniform and related to the application.		Applicant: The calculations were based on the lead substance Quassin to facilitate the interpretation. There is always the maximum amount of Quassin	**Data gap:** The applicant has not uniformed the units in relation with the application. In addition, an analysis on why quassin can be

8.4. Effects on earthworms and other soil macroorganisms					
No.	**Column 1** **Reference to Application Template**	**Column 2** **Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4** **Follow up response from applicant**	**Column 5** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
				in the application assumed: 20 kg chips per ha = max. 12 g Quassin, 30 kg ha (hop) = 18 g Quassin.	considered the adequate lead substance for the risk assessment of *Q. amara* is still missing. There is uncertainty on the amount of quassin in the extract (and therefore the amount applied). See data gaps in 2(7) and 7(3).

8.5. Effects on soil microorganisms					
No.	**Column 1 Reference to Application Template**	**Column 2 Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4 Follow up response from applicant**	**Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
8(25)	8.4 Effects on soil micro-organisms	NL: no comments.			Noted.

8.6. Effects on other non-target organisms (flora and fauna)					
No.	**Column 1 Reference to Application Template**	**Column 2 Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4 Follow up response from applicant**	**Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
8(26)	8.5 Effects on other non-target organisms (flora and fauna)	NL: an elaboration specific on non-target terrestrial plants is missing	EFSA: the applicant is invited to provide an assessment of potential effects of *Q. amara* on non-target terrestrial plants (e.g. the applicant could further expand the literature search and provide a well-substantiated weight of evidence to address the risk assessment, also	Applicant: *Quassia amara* is used for 100 years to control sawflies and some aphid species. In all this period no cases of effects of phytotoxicity or on non-target terrestrial plants were reported.	**Data gap:** The applicant has not provided an assessment of potential effects of *Q. amara* L. wood on non-target terrestrial plants, nor has further expanded the literature search or provided a

8.6. Effects on other non-target organisms (flora and fauna)					
No.	**Column 1 Reference to Application Template**	**Column 2 Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4 Follow up response from applicant**	**Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
			considering read-across). The applicant may wish to use the EFSA Guidance on Submission of scientific peer-reviewed open literature (EFSA, 2011), and the EFSA Guidance on the use of the weight of evidence approach in scientific assessments (EFSA, 2017).		well-substantiated weight of evidence consideration to address the risk assessment. A low risk can be concluded only for the proposed intended use in greenhouses (permanent).

8.7. Effects on biological methods of sewage treatment					
No.	**Column 1 Reference to Application Template**	**Column 2 Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4 Follow up response from applicant**	**Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
8(27)	8.7 effects on biological methods of	NL: The fact that the substance is already passing the sewage treatments is no argument to		Applicant: Noted.	**Data gap:** The applicant has not provided an

8.7. Effects on biological methods of sewage treatment

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
	sewage treatment	withhold any studies, however information in previous aspects do underpin that the risk on biological methods of sewage treatment is acceptable.			assessment of potential effects of *Q. amara* L. wood on biological methods of sewage treatment, nor has further expanded the literature search or provided a well-substantiated weight of evidence consideration to address the risk assessment. In addition, it is not clarified in which instances a low risk is potentially indicated, as suggested by the NL comment. A low risk can be concluded only for the proposed intended use in greenhouses (permanent).

8.8. Overall conclusion on effects on non-target organisms

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
8(28)	General	EFSA: the ecotoxicological data package does not allow to exclude potential adverse effects on non-target organisms, in particular for birds and mammals, for which a potential concern is identified, non-target arthropods, and soil organisms. The applicant should provide further data to address the data requirements and update/provide the risk assessment for each group of non-target organisms.	EFSA: To address the data requirements and the risk assessment the applicant should provide further information, obtained from regulatory studies or peer-reviewed scientific literature. The applicant might also consider read-across from peer-reviewed literature studies, however this should be duly justified. In addition, the applicant might wish to provide a qualitative risk assessment, supported by relevant and reliable studies, through a sound weight of evidence (see EFSA Guidance on the use of the weight of evidence approach in scientific assessments (EFSA, 2017)). When carrying out an updated literature search the applicant may wish to use the EFSA Guidance on Submission of scientific peer-	Applicant: In the technical report from EFSA 2018 it was stated: The ecotoxicology section is sufficient to consider the risk to non-target organisms as low for the representative uses.	The applicant has not provided all the necessary data to conclude on the safety of *Q. amara* L. wood for non-target organisms (see data gaps identified in section 4). For **terrestrial vertebrates,** a low risk can be concluded only for the proposed use in greenhouses (permanent). For the proposed field uses, potential adverse effects on reproduction and endocrine disruption for mammals, and for birds cannot be excluded and thus a low risk cannot be concluded.

8.8. Overall conclusion on effects on non-target organisms

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
			reviewed open literature (EFSA, 2011).		For **aquatic organisms,** a low acute risk could be concluded for all intended uses. Nevertheless, a potential concern is identified for fish in view of the potential endocrine disruption in mammals (see also section 3.2). In addition, the potential insecticidal effects should have been investigated for aquatic invertebrates (minor outstanding issue, see section 4.2). For **honey bees and other non-target arthropods**, a safe use can be identified for all intended uses, although further testing could have

8.8. Overall conclusion on effects on non-target organisms

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
					supported the weight of evidence for the assessment. For **soil macro- and microorganisms**, a low risk can be identified for all the proposed uses. For the intended field uses for **biological methods of sewage treatment** and t**errestrial non-target plants**, a low risk cannot be concluded since no data or a suitable scientifically sound weight of evidence assessment were provided. For the proposed use in greenhouse (permanent), a low risk can be concluded for non-target terrestrial

8.8. Overall conclusion on effects on non-target organisms

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA/public	Column 3 • Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant • Consideration by MS/EFSA on comments/information received during the public consultation	Column 4 Follow up response from applicant	Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
					plants and biological methods of sewage treatment. See also data gap in 8(24).
8(29)	General ecotox	NL: As previously stated in the technical report from EFSA 2018: The ecotoxicology section is sufficient to consider the risk to non-target organisms as low for the representative uses.		Applicant: Noted.	Noted. While in the previous EFSA Technical Report (2018) a low risk was concluded for non-target organisms, it should be noted that information was made available in the dossier and via literature submitted during the consultation phase of the present assessment. The assessment should consider all available information in the context of the evaluation. Several

8.8. Overall conclusion on effects on non-target organisms					
No.	**Column 1 Reference to Application Template**	**Column 2 Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4 Follow up response from applicant**	**Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
					data gaps are now highlighted in the Technical Report.
8(30)	General ecotox	NL: More elaboration on other substances which are found in the extract is, as stated by other aspects as well, appropriate.		Applicant: The studies presented refer all to the complete extract with all ingredients even if sometimes Quassin is used as lead substance for the quantification. Thus, all ingredients of the extract are included.	Addressed.
8(31)	General ecotox	NL: the heading numbers are not correct, just a formatting/typo issue		Applicant: Thank you. Numbering is corrected in the updated version of the application form.	Addressed.

9. Overall conclusions with respect of eligibility of the substance to be approved as basic substance

Overall conclusions with respect of eligibility of the substance to be approved as basic substance					
No.	**Column 1** **Reference to Application Template**	**Column 2** **Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4** **Follow up response from applicant**	**Column 5** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
9(1)	9, Overall conclusions with respect to the eligibility of the substance to be approved as basic substance	DE: *Quassia amara* L. wood extract does not comply with the approval conditions of Articles 23 (1b) and 23 (2) of Regulation (EC) No 1107/2009. There are evidence with *Quassia amara* showing harmful health effects (reproductive toxicity) as well as capacity to cause endocrine disrupting effects in animals. As commented earlier in Section 5.2, *Quassia amara* (or quassin) does not fulfil the criteria of a foodstuff since it is specified in Regulation (EC) 1334/2008 that quassin (main component of *Quassia amara*) should not be intentionally incorporated in food.	DE: As proposed by DE already during the public consultation in 2017 (EFSA 2018:EN-1382), a botanical active substance dossier prepared in line with Guidance Document SANCO/11470/2012 should be generated for *Quassia amara* L. wood extract if the substance is to be considered for plant protection use in the EU. There are sufficient human health concerns of *Quassia amara* extract identified that cannot be ignored or disregarded. EFSA: We would support the conclusion from the MS since no adequate information has been submitted to address the risk assessment for non-target organisms and data	Applicant: *Quassia amara* was evaluated for food use based on a literature evaluation summarized in the report of the EUROPEAN COMMISSION HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL, Scientific Committee on Food (SCF/CS/FLAV/FLAVOUR/29/FINAL) of 25.7.2002. Thus, it complies with Art 23(2) of the Regulation (EC) 1107/2009, which states that the substance should have already been evaluated in the view of other uses. Due to this evaluation, the limits in Regulation (EC) 1334/2008 were set as follows: In Part A of Annex III of Regulation (EC) 1334/2008 Quassin is listed as a substance that shall not be added as such to food. However, Part B of Annex III lists substances naturally present in flavouring and food	See 2(4), 2(12), 5(2), 6(7), 7(2), 7(3), 8(28)

Overall conclusions with respect of eligibility of the substance to be approved as basic substance					
No.	**Column 1** **Reference to Application Template**	**Column 2** **Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4** **Follow up response from applicant**	**Column 5** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
			requirements concerning the eligibility of the substance to be approved as basic substance. In particular, the considerations regarding environmental background exposure should be addressed with care, since in the environment *Q. amara* is most probably present as wood or wood chips, while this basic substance application is presented for spray applications. Thus, the natural occurrence of *Q. amara* in the environment should not be directly linked with potential exposure after application (see in details section 7 for fate and behaviour in the environment).	ingredients with flavouring properties, for which a maximum level was set. In this Part B of Annex III of Regulation (EC) No 1334/2008 the limits for Quassin of 0.5 mg/kg in non-alcoholic beverages, 1 mg/kg in bakery wares and 1.5 mg/kg in alcoholic beverages are specified. In Part B of Annex IV of the same regulation the conditions of use for flavourings and food ingredients with flavouring properties produced from certain source materials are specified. There, Quassia amara is listed as a source material with the specification 'Flavourings and food ingredients with flavouring properties produced from the source material may only be used for the production of beverages and bakery wares. '	

Overall conclusions with respect of eligibility of the substance to be approved as basic substance					
No.	**Column 1** **Reference to Application Template**	**Column 2** **Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4** **Follow up response from applicant**	**Column 5** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
				Thus, *Quassia amara* is clearly defined as a possible source material for the addition to food. Since the addition of pure Quassin to food is not allowed, the full *Quassia amara* extract with all ingredients is definitively the substance that was already evaluated in view of the use in food. It fulfils the criteria of a 'foodstuff' as defined in Article 2 of Regulation (EC) No 178/2002 (see also [redacted], 2021) and as defined in Art. 23 of the Reg. 1107/2009. It should be considered as a basic substance when the proposed uses do not lead to an exposure that exceeds a normal exposure due to food consumption within the maximum levels set in the Regulation (EC) No 1334/2008. IFOAM Organics Europe, the umbrella organization for organic food and farming, has submitted the basic substance application for	

Overall conclusions with respect of eligibility of the substance to be approved as basic substance					
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				Quassia amara wood. We are not a manufacturer of plant protection products, and we cannot, nor do we intend to, produce or market commercial formulations of products. Since 2010, we have tried to encourage any manufacturer to submit an application with the intend to market and commercialize formulated product containing *Quassia amara.* For our farmers, the availability of a standardized extract would be much more attractive than cooking the wood, because it would be more practical to handle and use. However, *Quassia amara* wood is a very selective substance with few uses and, thus, a small market segment. Thus, the return on investment in dossier preparation for a manufacturer was not to be expected. Furthermore, dossier preparation for botanical active substances is still very challenging	

Overall conclusions with respect of eligibility of the substance to be approved as basic substance					
No.	**Column 1** **Reference to Application Template**	**Column 2** **Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4** **Follow up response from applicant**	**Column 5** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
				and difficult and we did not succeed to find a company willing to invest considerable time and money in such a process for a substance with only a small market. The problem that substances with a small market segment get lost due to economic reasons has been mentioned by IFOAM since the start of Reg. 1107/2009. In this context, also the *Quassia amara* issue was discussed. Several authorities as the Commission and the German BMEL advised us to apply for basic substance approval. Thus, *Quassia amara* was also listed in the first list of candidates for basic substances of the Commission and the application of 2012 was part of the pilot project for basic substance application. When first member states started to discuss it would be more appropriate to apply for active substance approval, there was still (and still	

Overall conclusions with respect of eligibility of the substance to be approved as basic substance					
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				there is) no solution for important substances with a small market segment, as this application is economically not suitable for a company. Thus, the only possibility to have this essential niche substance available to farmers, was still the application for basic substance approval. Consequently, following the technical report of EFSA of 18-2-2018 an international Task Force was formed to organize the studies to close the data gaps with private and public money. Currently, there is some change in the situation due to the extension of the share of the agriculture land under organic management in Europe, the prospect for improved guidance for botanical active substances, and mainly to a growing interest for the use of *Quassia amara* wood in ornamentals. Therefore, we added this use to the GAP table.	

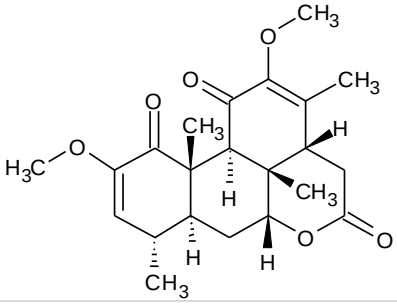
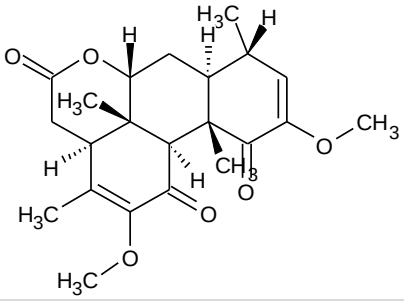
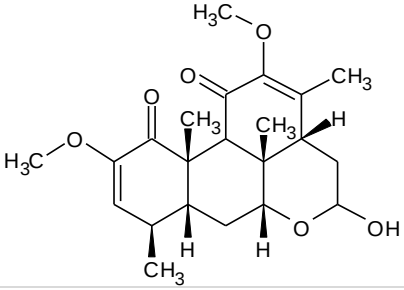
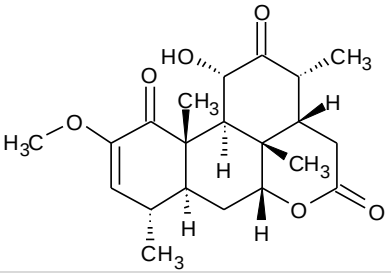
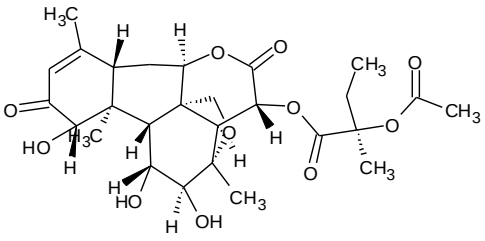
Overall conclusions with respect of eligibility of the substance to be approved as basic substance					
No.	**Column 1** **Reference to Application Template**	**Column 2** **Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4** **Follow up response from applicant**	**Column 5** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
				Even if the need for a more extended database for the fate segment is expressed, a positive evaluation of the proposed use in ornamentals should be possible in each case with the existing database. However, even if a company starts to prepare a dossier for a standardized extract as active substance, for the period until the respective application is prepared, submitted, evaluated and approved, there will be no other solution to ensure the availability of the essential uses to organic farmers other than the application for basic substance approval.	
9(2)		DK: The conclusion does not address the requirements for basic substances set out in Article 23 in sufficient detail, e.g. ED, immunotoxicity and neurotoxicity. It has not been demonstrated that the extract		Applicant: See comments in 9 (1).	See 5(2), 5(12)

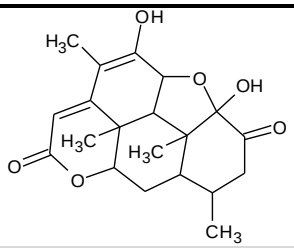
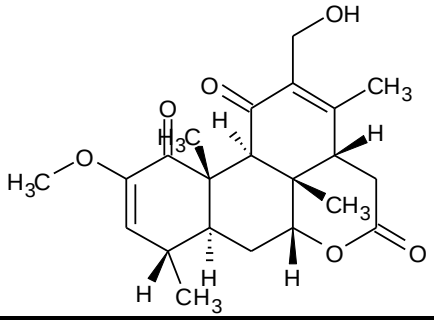
Overall conclusions with respect of eligibility of the substance to be approved as basic substance					
No.	**Column 1** **Reference to Application Template**	**Column 2** **Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4** **Follow up response from applicant**	**Column 5** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
		does not have harmful effects on humans.			

10. Other comments

Other comments					
No.	**Column 1 Reference to Application Template**	**Column 2 Comments from Member States / EFSA/public**	**Column 3** • **Proposal by Member States/EFSA on how the application should be updated to address the comment / instructions for the applicant** • **Consideration by MS/EFSA on comments/information received during the public consultation**	**Column 4 Follow up response from applicant**	**Column 5 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application**
10(1)	10 Literature search	EFSA: the information on the literature search is limited as regards the keyword and strings used (main application and Anonymous, 2022).	EFSA: Please provide an updated literature search including search terms on *Quassia amara* and its individual components other than quassin (e.g. neoquassin, 12-hydroxyquassin, 18-hydroquassin, indole alkaloids of the family of beta-carbolines) and the related CAS numbers; and focusing on reproductive (adverse) effects and genotoxicity. Please present in detail the search strategy and the outcome of the search (see also previous EFSA comments).	Applicant: The literature search was based on *Quassia amara*, which is the basic substance we apply for, and the lead substance Quassin. Since the literatures search covered *Q. amara*, it can be considered that in all studies using full extracts from this plant all ingredients are included. Moreover, literature without information on the preparation of the extracts were included for the sake of completeness.	Partially addressed. The applicant clarified the search strategy followed (i.e. focused on *Quassia amara*). It is noted that many of the retrieved studies address individual components (generally quassin); the search should be substantiated on all the biologically relevant components of the basic substance, once identified. See also 2(7). **Minor outstanding issue:** The applicant should provide an updated literature search corroborating the information on relevant biological/ toxicologically relevant components of the basic substance, once identified. See 2(7).

Appendix B – Used compound codes

Code/trivial name[a)]	IUPAC name/SMILES notation/InChiKey[b)]	Structural formula[c)]
quassin	2,12-dimethoxypicrasa-2,12-diene-1,11,16-trione COC=1C(=O)[C@@H]2[C@@]3(C)C(=O)C(=C[C@@H](C)[C@@H]3C[C@H]3OC(=O)C[C@@H](C=1C)[C@@]23C)OC IOSXSVZRTUWBHC-LBTVDEKVSA-N	
isoquassin	2,12-dimethoxy-14α-picrasa-2,12-diene-1,11,16-trione COC=1C(=O)[C@@H]2[C@@]3(C)C(=O)C(=C[C@@H](C)[C@@H]3C[C@H]3OC(=O)C[C@H](C=1C)[C@@]23C)OC IOSXSVZRTUWBHC-NYWUXZQNSA-N	
neoquassin	(9ξ)-16-hydroxy-2,12-dimethoxy-4β,5β-picrasa-2,12-diene-1,11-dione COC=1C(=O)C2[C@@]3(C)C(=O)C(=C[C@H](C)[C@H]3C[C@H]3OC(O)C[C@@H](C=1C)[C@@]23C)OC BDQNCUODBJZKIY-MPYVAXHVSA-N	
parain	11α-hydroxy-2-methoxypicras-2-ene-1,12,16-trione COC1=C[C@@H](C)[C@@H]2C[C@H]3OC(=O)C[C@H]4[C@@H](C)C(=O)[C@@H](O)[C@H]([C@@]2(C)C1=O)[C@@]34C WKQCYNCZDDJXEK-RKDOZKMISA-N	
quassimarin	1β,11β,12α-trihydroxy-2,16-dioxo-13,20-epoxypicras-3-en-15β-yl (2R)-2-(acetyloxy)-2-methylbutanoate C[C@@]12OC[C@]34[C@H]2[C@@H](OC(=O)[C@@](C)(CC)OC(C)=O)C(=O)O[C@@H]4C[C@H]2C(C)=CC(=O)[C@@H](O)[C@]2(C)[C@H]3[C@@H](O)[C@@H]1° FXMIXHYJCNZLFE-ACBKHETBSA-N	

Code/trivial name[a)]	IUPAC name/SMILES notation/InChiKey[b)]	Structural formula[c)]
quassinol	1,12-dihydroxy-1,11-epoxypicrasa-12,14-diene-2,16-dione CC12C3C4OC2(O)C(=O)CC(C)C1CC1OC(=O)C=C(C(C)=C4O)C31C WKNPIBKVHHVICI-UHFFFAOYSA-N	
quassol	No information provided see reporting table point 2(11).	
12-hydroxyquassin	No information provided see reporting table point 2(11).	
18-hydroquassin	12-(hydroxymethyl)-2-methoxypicrasa-2,12-diene-1,11,16-trione COC1=C[C@@H](C)[C@@H]2C[C@H]3OC(=O)C[C@H]4C(C)=C(CO)C(=O)[C@H]([C@@]2(C)C1=O)[C@@]34C DHIMAWQFCVIDLK-XJTLZAITSA-N	

(a): The compound name in bold is the name used in the report.
(b): ACD/Name 2023.2.4, ACD/Labs 2023.2.4 (File Version N25E41, Build 137185, 31 Jan 2024)
(c): ACD/ChemSketch 2023.2.4, ACD/Labs 2023.2.4 (File Version C45H41, Build 137017, 18 Jan 2024)

Appendix C – Identity, Mode of Use and function

Common name (ISO)	*Quassia amara* L. wood (not ISO)
Chemical name (IUPAC)	Not relevant as it is a botanical active substance.
Chemical name (CA)	Not relevant as it is a botanical substance.
Common names	Amargo, Bitter-ash, Bitter-wood, Quassia wood, Ruda, Surinam Quassia, Surinam Wood,
CAS No	Not relevant as it is a botanical substance.
CIPAC No and EEC No	Not relevant as it is a botanical substance.
FAO specification / specification in another regulatory context, if available	Not available.
Minimum purity	Not relevant as it is a botanical substance. *Quassia amara* L. wood should contain Quassin; 0.5 to 1.18 g Quassin / kg wood, measured using ethanol:water (30:70) extraction.
Relevant impurities	No robust information on the composition, components of concern as possible relevant impurities cannot be concluded.
Molecular mass and structural formula	Not relevant as it is a botanical substance.
Mode of Use	Spray and drench application.
Preparation to be used	Water decoction to be performed by operator/farmer: 20 kg of *Quassia amara* L. wood are boiled in 100 L of water for 1 hour. After cooling down, the extract is sieved, and diluted with water according to the intended GAP uses.
Function of plant protection	Insecticide, repellent

Appendix D - Considerations with respect to compliance with the criteria for eligibility of the substance to be approved as a basic substance as set out in Article 23 of Regulation (EC) No 1107/2009, taking into consideration the proposed conditions of use

Aspects for considerations as specified in Art 23 of Regulation (EC) No 1107/2009		**Conclusion**
	whether the substance has neither an immediate or delayed harmful effect on **human or animal health -** when it is present in a form in which it is **available on the market/available to the user**	*It cannot be excluded that the proposed field uses of the substance Quassia extract would result in unacceptable effects for human or animal health.*
Art 23(1a): whether the substance is **not a 'substance of concern'**[9]	whether the substance has neither an immediate or delayed harmful effect on **human or animal health -** when it is present **in the form in which it is applied (preparation to be used)**	*It cannot be excluded that the proposed field uses of the substance would result in unacceptable effects for human or animal health*. *Non-dietary exposure assessment has been carried out by the applicant according to EFSA, 2022, however, in the absence of solid toxicological reference values and clear information on the composition of the extract, it cannot be finalised.* *The consumer risk assessment cannot be finalised whilst sufficient information on the toxicological profile of Quassia amara L. wood extract and its composition is not available. Neither could an alternative assessment approach conclusively demonstrate that the additional exposure to Quassia amara L. wood extract (and relevant components e.g. quassin) from the plant protection use is negligible compared to the exposure by other dietary routes, e.g. from the use of Quassia amara wood as a source material for production of flavourings or food ingredients with flavouring properties.*

[9] "Substance of concern" is defined in Art 3(4) of Regulation (EC) No 1107/2009: *substance of concern' means any substance which has an inherent capacity to cause an adverse effect on humans, animals or the environment and is present or is produced in a plant protection product in sufficient concentration to present risks of such an effect.*
Such substances include, but are not limited to, substances meeting the criteria to be classified as hazardous in accordance with Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, and present in the plant protection product at a concentration leading the product to be regarded as dangerous within the meaning of Article 3 of Directive 1999/45/EC.

Aspects for considerations as specified in Art 23 of Regulation (EC) No 1107/2009		Conclusion
	whether the substance does not have an unacceptable effect on the **environment**	*It cannot be excluded that any of the uses would have an unacceptable effect on groundwater quality. It cannot be excluded that the intended field uses of the proposed basic substance would result in unacceptable effects for terrestrial vertebrates, terrestrial non-target plants and biological methods of sewage treatment. A low risk was identified for aquatic organisms (acute risk), bees and non-target arthropods other than bees, and soil organisms for the proposed field uses. For the proposed use in greenhouses (permanent), a low risk can be concluded for all groups of non-target organisms. Nevertheless, a potential concern is identified for wild mammals and for fish regarding the potential for endocrine disruption.*
Art 23(1b): whether a substance does not have an inherent capacity to cause **endocrine disrupting, neurotoxic or immunotoxic effects**		*On the basis of the available information, it is not possible to exclude that the proposed basic substance in subject has endocrine disrupting properties; moreover, further information is needed to exclude effects on the immune system of the substance.*
Art 23(1c): whether the substance is not predominantly used for plant protection purposes but nevertheless is **useful in plant protection** either **directly or in a product consisting of the substance and a simple diluent**		*Quassia amara L. wood is a botanical substance and it is available on the EU market with a description for use in the preparation of a herbal infusion. It is useful as an insecticide, and repellent in plant protection as a formulation prepared by the farmer/operator by boiling of Quassia amara L. wood in water. After cooling down, the extract is sieved, and diluted with water before application. It is noted however that the information available to support the control of white fly in ornamentals by drenching was limited.*
Art 23(1d): whether the substance is **not** placed **on the market** as a **plant protection product**		*Quassia amara extract might be supplied in Germany as a material for use in plant protection against sawflies (Hoplocampa spp.) in pome and stone fruit in the field, under the name Quassia-Extract-MD[10]. According to the company's website[10] the material which is a powder has the description 'The active ingredient is obtained as a powdery plant extract in a specially developed process'. Based on this finding it might be considered that Article 23(d) of the EU Regulation 1107/2009 is not fulfilled.*
Art 23(1): whether the substance fulfils the criteria of a **foodstuff** as defined in Art. 2 of Regulation 178/2002		*Please refer to reporting table point 2(4)*
Art 23(2): whether there are any **relevant EU evaluations** or other regulatory or governmental assessments showing that	the substance has **no harmful effects on human or animal health**	*There are no other relevant EU evaluations showing that the proposed basic substance has no harmful effects on human or animal health.*
	the substance does not have an unacceptable effect on the **environment**	*There are no other relevant evaluations showing that the proposed basic substance does not have an unacceptable effect on the environment.*

[10] https://www.trifolio-m.de/en/produkt/quassia-extract-md/?sfw=pass1730373675

Appendix E – List of intended uses for plant protection purpose

Crop and/or situation (a)	Member State or Country	Example product name as available on the market	F G/I (b)	Pests or Group of pest controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (m)	Remarks
					Type (d-f)	Conc of a.i. g/L (i)	Method kind (f-h)	Growth Stage and season (j)	Number min max (k) per crop/ season	Interval between applications (min)	kg a.s./hL	Water l/ha min max	kg as/ha Quassia wood chips/ha		
Pome fruit 3PMFC	EU	Quassia wood chips (decoc-	F	Sawflies	SC	200 g/l (Quassia chips)	spray	BBCH 65-69	1	n.a.	2 kg Quassia wood chips/hl	1000	20 kg Quassia wood chips/ha	n.a.	Reduction of infestation
Pome fruit 3PMFC	EU	Quassia wood chips (decoc-	F	Aphids	SC	200 g/l (Quassia chips)	spray	BBCH 53 to 69	1	n.a.	2 kg Quassia wood chips/hl	1000	20 kg Quassia wood chips/ha	n.a.	Reduction of infestation
Plum PRNDO	EU	Quassia wood chips (decoc-	F	Sawflies	SC	200 g/l (Quassia chips)	spray	BBCH 65-69	1	n.a.	2 kg Quassia wood chips/hl	1000	20 kg Quassia wood chips/ha	n.a.	Reduction of infestation
Stone fruit 3STFC	EU	Quassia wood chips (decoc- tion)	F	Aphids	SC	200 g/l (Quassia chips)	spray	BBCH 53 to 69	1	n.a.	2 kg Quassia wood chips/hl	1000	20 kg Quassia wood chips/ha	n.a.	Reduction of infestation
Hop HUMLU	EU	Quassia wood chips (decoc- tion)	F	Hop aphids	SC	200 g/l (Quassia chips)	spray	BBCH 39 (end of June) BBCH 69 (mid of July)	1	n.a.	1.3 kg Quassia wood chips /hl	2300	30 kg Quassia wood chips/ha	n.a.	Reduction of infestation

Ornamentals (young plants and cuttings in pots* 3ORTC	EU	Quassia wood chips (decoc-tion)	G	White fly	SC	200 g/l (Quassia chips)	drenching	- At occurrence of pest	1	n.a.	6.5 kg Quassia wood chips /hl	30000	1950 kg Quassia wood chips/ha Equivalent to 0.195 kg/m^2	n.a.	Reduction of infestation

* Additional use (ornamentals via drench application) proposed by the applicant after the applicant's commenting window during the ongoing assessment and included in the updated application (IFOAM Organics Europe, 2024). It is noted that the proposed additional use on ornamentals was not part of the original basic substance application and therefore it could not be commented on at all by the public and member states were only able to comment at a late stage once the final draft of this report had been drafted by EFSA. The EFSA considerations on this additional use are presented in the relevant sections as appropriate.

(a): For crops, the EU and Codex classification (both) should be taken into account; where relevant, the use situation should be described (e.g. fumigation of a structure). The codes indicated are EPPO (European and Mediterranean Plant Protection Organization) codes
(b): Outdoor or field use (F), greenhouse application, permanent structures(G) or indoor application (I)
(c): e.g. pests as biting and suckling insects, soil born insects, foliar fungi, weeds or plant elicitor
(d): e.g. wettable powder (WP), emulsifiable concentrate (EC), granule (GR) etc..
(e): GCPF Codes – GIFAP Technical Monograph N° 2, 1989
(f): All abbreviations used must be explained
(g): Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench
(h): Kind, e.g. overall, broadcast, aerial spraying, row, individual plant, between the plant – type of equipment used must be indicated
(i): g/kg or g/L. Normally the rate should be given for the active substance (according to ISO)
(j): Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
(k): Indicate the minimum and maximum number of application possible under practical conditions of use
(l): The values should be given in g or kg whatever gives the more manageable number (e.g. 200 kg/ha instead of 200 000 g/ha or 12.5 g/ha instead of 0.0125 kg/ha
(m): Pre-harvest interval

Additional uses proposed by Member States and/or other parties during the public or targeted consultations, which are beyond the uses supported by the applicant:

No additional uses have been proposed by Member States and/or other parties during the public or targeted consultations, which are beyond the uses supported by the applicant.

Appendix F – Evaluation of residue data and consumer dietary exposure assessments

Information of the **nature of residues** was not provided, i.e. it is unclear whether and how quickly the components of *Quassia amara* L. wood extract could be possibly transformed into other compounds upon application to crops due to environmental conditions (e.g. sun light) or plant metabolism, or whether compounds extracted from *Quassia amara* L. wood would remain stable on the crops and for which period of time. While the full composition of the extract still needs to be clarified (see section 3.1), some pertinent components in the extract are quassinoids. Quassinoids have a highly oxygenated polycyclic structure. Hence, their chemistry is complex. Due to several hydroxy, methoxy and carbonyl groups in the quassinoid molecules (e.g. in quassin and neoquassin), multiple metabolic products could be generated by the commonly known primary and secondary metabolic reactions in plants,[11] i.e. oxidation, hydrolytic or reduction reactions,[12] and conjugation. It may be expected that the treated crops will show a similar diversity of metabolites that are quassinoids or their derivatives and conjugates as the plants that naturally contain quassinoids and quassinoid glycosides. The extent to which after application to crops in the field the polycyclic structure of the quassinoids is broken down into smaller structures, e.g. monoterpenes, which are then further metabolised, is unknown.

However, to further characterise possible residues from *Quassia amara* L. wood and its extract, and to evaluate the possible metabolism of the components in the extract after application to crops, the full characterisation of the composition of the extract is a prerequisite (see **data gap** in section 3.1).

The fact that the quassinoids quassin (including its isomer isoquassin) and neoquassin in the wood extract of *Quassia amara* L. are actually degraded after application to crops was proven by the residue trials presented in apple, plum and hops with sampling at different time intervals after application.

To address the **magnitude of residues** after application of *Quassia amara* L. wood as extract to crops for human consumption, residue trials were conducted in Northern Europe (NEU) during four different growth seasons (2013, 2014, 2015, 2018) in apple and plum, and during five different growth seasons (2013, 2014, 2015, 2018, 2019) in hops. Several trials could not be considered independent in line with current guidelines and guidance, resulting in three independent trials of the seven trials submitted, each in apple and plum, and nine independent trials out of 19 trials in hops. Samples from two different sampling dates were analysed for quassin (sum of quassin and isoquassin) and neoquassin. As only the analytical reports are available while the reports on the field phase (non GLP) are not available, any information about the trial design, including information on application, sampling and storage of the samples was taken solely from the applicant's narrative, which required assumptions and led to some uncertainties. According to the applicant, the application rate was 12 g quassin/ha in plum and apple, and 18 g quassin/ha in hop. How this rate corresponds to the application rate in kg/ha of *Quassia amara* L. wood as proposed in the GAP table was not reported, as a commercially available standardised insecticide product, "Quassia-Extrakt-MD", was used in the trials. EFSA assumes that application rates of 20 kg wood chips/ha and 30 kg wood chips/ha for fruit and

[11] Roberts, T., 2000. Metabolism of agrochemicals in plants. John Wiley, New York
[12] Reduction of quassin produces neoquassin, oxidation of neoquassin produces quassin and isoquassin.

hops, respectively, may correspond to similar concentrations of quassin[13] as used in the residue trials when applying the commercial plant protection product. Furthermore, information on the analytical method including validation data was not available for the residue trials conducted in 2013 (**minor outstanding issue**, see section 4.2), leading to some uncertainty about the reliability of the 2013 results.

In a storage stability study with spiked samples of apples (pome fruit, high water content category) and hops (high oil content category), minimal degradation of quassin (sum of quassin and isoquassin) and neoquassin was observed but did not exceed 30% within 12 months of freezer storage. According to the applicant, none of the samples in the residue trials was stored for longer than 8 months. To validate the results of the residue trials in plum (stone fruit), an additional storage stability test would be required in line with current test guidelines (see reporting table 6(3)). As sufficient stability of residues in freezer storage has been demonstrated in at least one commodity in the category of high-water content commodities (pome fruit), the lack of a storage stability study in stone fruit is considered a **minor outstanding issue** (see section 4.2).

Residue trials in apple and plum: Two applications were reported by the applicant, one during flowering and one at the end of flowering, while the concrete BBCH stages of application are not available. Applications before formation of the edible part (BBCH 65, full flowering)[14] are commonly not expected to significantly contribute to the final residues and could be disregarded. It is therefore assumed that the residue trials in apple and plum can be used to support the intended cGAP. Residues in plums and apples at harvest were always below the LOQ of 0.01 mg/kg for the sum of quassin and isoquassin, and below the LOQ of 0.0084 mg/kg (LOQ in 2013 trials 0.005 mg/kg) for neoquassin.

In the residue trials in apple, residues of quassin and neoquassin between LOD and LOQ could be detected at the intermediate sampling interval, indicating a residue situation below LOQ but not a "zero" residue situation as defined in the legislation. This is also confirmed by two supporting trials (SEU) in apples, conducted at approx. double the application rate that had quantifiable residues (>LOQ) of quassin at the intermediate sampling intervals (35-45 days after application).

Residue trials in hops: According to the applicant, one application at a rate of 18 g quassin/ha was made. Nine independent residue trials with one application at the expected application rate in hops are available, however, only three trials were conducted with an application at BBCH 69 in line with the cGAP. In the other six trials application was made approximately at BBCH 39, in any case before the start of flowering (BBCH 60). In the three cGAP compliant trials, quantifiable residues of quassin (sum of quassin and isoquassin) and neoquassin were present in the cones in all the intermediate samples and in two out of three samples at final harvest, the third sample had detectable residues below the LOQ. It is unknown whether the hop cones submitted to analysis were fresh or dried, creating uncertainty in terms of the residue concentration in the samples and their comparability to the food item in Annex I of Regulation (EC) No 396/2005 (hops, dried) considered in dietary intake assessments. If this information can still be retrieved,

[13] A maximum content of 1.18 g quassin/kg wood and an extraction rate of 50% was stated by the applicant in section 2.3.6 of the application dossier. This would correspond to 11.8 g quassin being extracted from 20 kg of wood chips and 17.7 g quassin from 30 kg of wood chips.
[14] European Commission, 2019. Appendix D - Data requirements for setting maximum residue levels, comparability of residue trials and extrapolation of residue data on products from plant and animal origin - SANTE/2019/12752 rev.1

the applicant is requested to submit this clarification (**minor outstanding issue,** see section 4.2).

In view of the findings of residues in hops, the applicant proposed a PHI of 70 days in hops that was however not formalised in the GAP table in the application.

The conclusion by the applicant is in line with the conclusion by EFSA that, in order to avoid residues, the last application needs to be made before the edible part of the crop is starting to form, i.e. before BBCH 65[15]. Furthermore, the applicant requested uses in the whole categories of pome fruit and stone fruit, while residue data were submitted only in apple and plum. As the last application at BBCH 69 according to cGAP will take place after forming of the edible part, extrapolation to the whole categories of pome fruit and stone fruits would not be possible[15], while it would be acceptable for applications before forming of the edible part, i.e. before BBCH 65. An adjustment of the growth stage for the latest time of application in the GAP could therefore be considered by the applicant and risk managers to mitigate the occurrence of residues.

Based on the available residue trials, EFSA conducted a **provisional dietary intake calculation** to estimate consumer exposure to quassin (sum of quassin and isoquassin) and neoquassin resulting from the uses in apple, plum and hops (scenario 1) and for all intended uses (scenario 2), assuming that extrapolation to the whole categories of pome fruit and stone fruits would be acceptable to risk managers despite deviation from current guidelines. The calculations were based on EFSA PRIMo rev. 3.1 diets and calculation formulas, using the input values (STMR and HR) derived from the available cGAP compliant residue trials (see reporting table 6(5)). Results for processed products are included if the exposure exceeded that of the raw commodity. It is acknowledged that the estimates may overestimate exposure regarding pome fruit and stone fruit as the LOQ has been used in the calculation in line with current practice.

EFSA considers that a reliable dietary exposure assessment is currently not possible either for the proposed basic substance (and the formulation intended for use as a plant protection product) or for the substances quassin and neoquassin contained therein because there isn't any robust information on the composition of the extract and its actual quassinoid levels. Hence, the assessment is provisional.

Provisional chronic dietary exposure assessment

	Scenario 1		Scenario 2	
Analyte	**EU diet** (top child & top adult diet)	**Estimated exposure** (µg/kg bw per day)	**EU diet** (top child & top adult diet)	**Estimated exposure** (µg/kg bw per day)
Quassin (sum of quassin and isoquassin)	DE child	0.126	NL toddler	0.158
	DE women 14-50 yr	0.026	DE women 14-50 yr	0.032
Neoquassin	DE child	0.101	NL toddler	0.126
	DE women 14-50 yr	0.021	DE women 14-50 yr	0.025

[15] European Commission, 2019. Appendix D - Data requirements for setting maximum residue levels, comparability of residue trials and extrapolation of residue data on products from plant and animal origin - SANTE/2019/12752 rev.1

Provisional acute dietary exposure assessment - Results for children (IESTI)

	Commodity	Estimated exposure (µg/kg bw)	Estimated exposure (µg/kg bw)
Analyte		Quassin (Sum of quassin and isoquassin)	Neoquassin
Scenario 1	Apple	1.078	0.862
	Plums	0.421	0.337
	Hops (dried)	0.004	0.003
	Hops (dried)[16]	0.015	0.012
Scenario 2 (top 5 raw commodities)	Pears	1.385	1.108
	Apples	1.078	0.862
	Peaches	0.950	0.760
	Plums	0.421	0.337
	Apricots	0.350	0.280

Provisional acute dietary exposure assessment - Results for adults (IESTI)

	Commodity	Estimated exposure (µg/kg bw)	Estimated exposure (µg/kg bw)
Analyte		Quassin (sum of quassin and isoquassin)	Neoquassin
Scenario 1	Apple	0.281	0.225
	Plums	0.178	0.143
	Hops (dried)	0.018	0.015
	Hops (dried)[16]	0.064	0.051
Scenario 2 (top 5 raw commodities & processed product)	Pears	0.305	0.244
	Apples	0.281	0.225
	Peaches	0.187	0.150
	Plums	0.178	0.143
	Quinces	0.152	0.122
	Apples / juice	0.333	0.267

EFSA also attempted an estimate of consumer exposure to *Quassia amara* L. wood (and relevant components e.g. quassin) from possible other dietary routes, e.g. the use of *Quassia amara* L. (Quassia) as a source material for production of flavourings or food ingredients with flavouring properties. Reliable information was not provided by the applicant. Therefore, EFSA searched the Mintel database[17] to obtain an overview over consumer goods containing Quassia or Quassia derived ingredients or flavourings (see **Appendix G**). All results retrieved were from the category of beverages and indicate also that the market share of products prepared with Quassia is rather small (0%-2% depending on beverage category and country). It was not possible to retrieve the amount of Quassia extract added except in one case. Hence, to estimate the content of Quassia or of one of its components quassin, it will have to be assumed that all products

[16] Calculated with drying factor for hop cones of 3.5, assuming water content of 80% in wet hops and 9% (usual range 8-10%) in dried hops

[17] https://www.mintel.com/products/gnpd/?_bt=652169658686&_bk=mintel%20gnpd&_bm=p&_bn=g&_bg=150165006391&utm_medium=cpc&utm_source=google&utm_content=Threepipe-GO19848722604~GO150165006391&gad_source=1&gclid=EAIaIQobChMI7pyOg5axiQMVKZaDBx07hy1wEAAYASAAEgJ1SvD_BwE

contain quassin up to the maximum permitted concentration according to Annex III of Regulation (EC) No 1334/2008.[18]

EFSA also explored consumption data for carbonated soft drinks with bitter principle (comprising e.g. tonic water) in the EFSA food consumption database[19] as this was the most pertinent beverage category observed in the Mintel database. The relevant statistical descriptors were extracted, i.e. mean consumption for specific subgroups of the population for the chronic assessment and high percentile of the consumers-only population for the acute assessment in line with the common approach (EFSA, 2007). Only 1.1% of 73.5 thousand consumers surveyed on chronic consumption consumed soft drinks with bitter principle, and consumption days in the acute survey for such products were in average only 0.6%, hence, in the majority of cases the number of observations was so low that the consumption figures may not be statistically robust.

A reliable assessment of chronic exposure was not possible as the 50th percentile consumption was 0 g/kg bw per day for all surveyed countries and population groups because most consumers did not consume soft drinks with bitter principle. However, in view of the pending assessment of genotoxicity, reproductive toxicity and endocrine activity in mammalian toxicology (see section 3.2), a robust chronic exposure assessment is considered indispensable.

In a next step, acute consumption data (97.5th percentile) for NL, DE and IE toddlers were extracted to be used for comparison with the most critical acute EU diets of NL toddlers (apple, pears, peaches), DE children (apricots) and IE children (plums) reflected in the EFSA acute intake estimates for children for the intended uses (see above). No observation of consumption by IE children was included in the database, only one observation for NL toddlers and two for German toddlers, indicating the lack of robustness of the consumption data but confirm rare consumption of soft drinks with bitter principle by young children.

Acute Food Consumption Grams per kilogram of body weight (g/kg bw) in a single day – Consuming days only

Survey's country	Survey start year	Survey name	Population Group (L2)	Exposure hierarchy (L1)	Exposure hierarchy (L2)	Exposure hierarchy (L3)	Exposure hierarchy (L4)	Exposure hierarchy (L5)	Exposure hierarchy (L6)	Exposure hierarchy (L7)	Number of consuming days	% consuming days	Median	97.5th percentile	comment Acute
Germany	2001	Consumption Survey of Food Intake among Infants and Young Children	Toddlers	Water and water-based beverages	Water based beverages	Soft drinks	Soft drinks with minor amounts of fruits or flavours	Soft drink, flavoured, no fruit	Soft drink with bitter principle	Soft drink with bitter principle	2	0.1%	8.18	13.08	'Number of observations lower than 5, the median may not be statistically robust'
Netherlands	2006	DNFCS-Young-Children	Toddlers	Water and water-based beverages	Water based beverages	Soft drinks	Soft drinks with minor amounts of fruits or flavours	Soft drink, flavoured, no fruit	Soft drink with bitter principle	Soft drink with bitter principle	1	0.2%	1.19	1.19	'Number of observations lower than 5, the median may not be statistically robust'

Acute consumption data (97.5th percentile) were also extracted for pregnant women (in total 5 observations from 3 countries).

[18] Quassin: Non-alcoholic beverages 0.5 mg/kg; Bakery wares 1 mg/kg; Alcoholic beverages 1.5 mg/kg

[19] https://www.efsa.europa.eu/en/data-report/food-consumption-data

Acute Food Consumption Grams per kilogram of body weight (g/kg bw) in a single day – Consuming days only

Survey's country	Survey start year	Survey name	Population Group (L2)	Exposure hierarchy (L1)	Exposure hierarchy (L2)	Exposure hierarchy (L3)	Exposure hierarchy (L4)	Exposure hierarchy (L5)	Exposure hierarchy (L6)	Exposure hierarchy (L7)	Number of consuming days	% consuming days	Mean	97.5th percentile	comment Acute
Montenegro	2017	Montenegrin National Dietary Survey on the general population	Pregnant women	Water and water-based beverages	Water based beverages	Soft drinks	Soft drinks with minor amounts of fruits or flavours	Soft drink, flavoured, no fruit	Soft drink with bitter principle	Soft drink with bitter principle	2	0.5%	3.00	3.12	'Number of observations lower than 5, the median may not be statistically robust'
Serbia	2019	Serbian Food Consumption Survey on adults	Pregnant women	Water and water-based beverages	Water based beverages	Soft drinks	Soft drinks with minor amounts of fruits or flavours	Soft drink, flavoured, no fruit	Soft drink with bitter principle	Soft drink with bitter principle	2	0.7%	4.41	4.70	'Number of observations lower than 5, the median may not be statistically robust'
Spain	2013	Spanish National dietary survey in adults, elderly and pregnant women	Pregnant women	Water and water-based beverages	Water based beverages	Soft drinks	Soft drinks with minor amounts of fruits or flavours	Soft drink, flavoured, no fruit	Soft drink with bitter principle	Soft drink with bitter principle	1	0.4%	4.71	4.71	'Number of observations lower than 5, the median may not be statistically robust'

The estimated acute intakes of quassin, assuming *Quassia amara* L. extract was used and quassin was actually present in the consumed beverage at the maximum permitted concentration of 0.5 mg/kg, correspond to 0.6 µg/kg bw (NL toddler) and 6.5 µg/kg bw (DE toddler); i.e. in one estimate exposure is lower and in the other higher than in the provisional acute intake assessment for the intended uses. For pregnant women, the calculated intakes of quassin, using the same assumption as for toddlers, ranged between 1.6 µg/kg bw (ME) and 2.4 µg/kg bw (RS, ES) and are higher than in the provisional acute intake assessments for adults for the intended uses, however the difference is less than an order of magnitude. The high uncertainty of all these estimates is emphasised.

It is noted that these estimates consider also only intake of quassin, neither neoquassin nor other quassinoids, while additional knowledge is not available on how the composition of Quassia extracts used in the remit of the flavouring Regulation (EC) No 1334/2008 compares with the composition of the extract prepared for plant protection uses, and finally with the composition of the residues on treated crops.

EFSA is of the opinion that there is currently insufficient robust evidence to demonstrate a negligible contribution of residues from the proposed plant protection use to the dietary exposure of the EU population to *Quassia amara* L. or its components from other dietary sources.

Appendix G – Outcome of EFSA's search of Mintel Global New Products Database (GNPD) that observes product introductions in consumer packaged goods markets worldwide (reporting table point 6(7))

Appendix G can be found in the Open EFSA, Supporting evidence section under EFSA-Q-2022-00824.

Appendix H – Literature search carried out by EFSA targeting impact on human and animal health, fate and behaviour in the environment and effects on non-target organisms: Search terms and strings used to conduct the literature search and search results

Appendix H can be found in the Open EFSA, Supporting evidence section under EFSA-Q-2022-00824.