Webinar | 22 April 2026

EFSA'S DRAFT OPINION ON THE SAFETY OF PLANT PREPARATION CONTAINING BERBERINE

EFSA, NUTRITION AND FOOD INNOVATION UNIT

EUROPEAN FOOD SAFETY AUTHORITY

SCOPE

- In line with EFSA's Catalogue of services and commitment to engaging with its stakeholders and improving understanding of its work

- **The meeting objective**:
  - To present the scientific basis, rationale, and data gaps identified in EFSA's draft assessment
  - To support food business operators'/representatives' engagement during the public consultation.

WELCOME TO ATTENDEES

- **Participants**:
  - Interested Food Business Representatives
- **Observers**:
  - Representatives of governmental organisations

HOUSEKEEPING RULES

- Questions pre-submitted are grouped and addressed in the presentation
- Additional questions will be addressed after the presentation
- Use “raise hand” function to ask the floor during Q&A session
- Keep your microphone muted & camera off, unless you are given the floor
- Please use the chat for technical issues only. Do not write questions or comments in the chat.
- If you have problems with the connection, exit the meeting & rejoin
- Audio, video, or text recording — including the use of AI for such purposes — and taking screenshots or photos to the slides presented is not allowed.

POST MEETING - Publication on EFSA’s website: the presentation including the agenda, questions from stakeholders (anonymised) & list of participating organisations.

AGENDA

Starting time 9:00

Introductory remarks
Ana Afonso

Background and mandate, charaterisation of plant preparations and exposure
Lucia Fabiani

Genotoxicity
Leonard Matijević

General toxicity, human data and overall conclusions
Agnès de Sesmaisons Lecarré

Data gaps
Agnès de Sesmaisons Lecarré

Next steps and Art 8(4) procedure
Ana Afonso, Federico Morreale

Q&A
All

Ending time 12:00

BACKGROUND AND MANDATE

BACKGROUND

anses
French agency for food, environmental and occupational health & safety

ANSES Opinion
Request No 2018-SA-0095 - Berberine

August 2019

Concerns regarding a potential risk to consumers linked with the **consumption of plant preparations containing berberine** used as ingredient in food supplements

European Commission

ART 8.2
Reg (EC) 1925/2006

Upon request from a Member State of the EU, EFSA may be requested to **assess the available information** to support a decision on the safety of the substance/ingredient

efsa

June 2022: EC mandate to EFSA

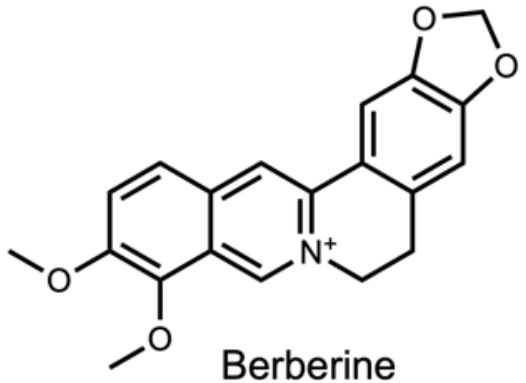
MANDATE OF THE EUROPEAN COMMISSION TO EFSA

- Review the existing scientific data on the possible link between the intake of **preparations of 13 berberine-containing plant parts** and harmful effects on health
- Provide advice on a daily intake of **plant preparations containing berberine** that does not give rise to concerns about harmful effects to health for the general population, and as appropriate, for vulnerable subgroups of the population

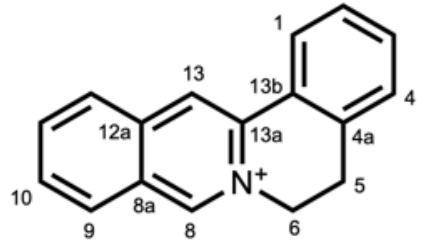
Scientific name	Plant part in the mandate	Common names
Berberis aquifolium Pursh	Root	Oregon grape; holly-leaved barberry
Berberis aristata DC.	Root, bark	Indian barberry
Berberis vulgaris L.	Root, bark	Common barberry
Chelidonium majus L.	Herb	Greater celandine
Coptis japonica (Thunb.) Makino	Rhizome	Japanese goldthread
Coptis teeta Wall.	Rhizome	Indian goldthread
Coptis trifolia (L.) Salisb.	Rhizome	Three-leaf goldthread; savoyane
Cosciniium fenestratum (Goetgh.) Colebr.	Root, stem	Tree turmeric; false calumba
Hydrastis canadensis L.	Rhizome	Goldenseal; orange root; eye-balm
Jateorhiza palmata (Lam.) Miers	Root	Calumba
Phellodendron amurense Rupr.	Bark	Amur cork tree
Thalictrum flavum L.	Root	Common meadow-rue
Tinospora sinensis (Lour.) Merr.	Root, stem, leaf	Chinese tinospora

BERBERINE AND PROTOBERBERINE ALKALOIDS

Substance	Structural similarity score[a]
Berberine	1
Epiberberine	0.989
Thalifendine	0.983
Berberrubine	0.983
Coptisine	0.981
Corysamine	0.978
Palmatine	0.976
Columbamine	0.973
Jatrorrhizine	0.972
Groenlandicine	0.971
Berberastine	0.967
Demethyleneberberine	0.962
Thalidastine	0.957
Fissisaine	0.946
Stephabine	0.94



Berberine



Protoberberine skeleton

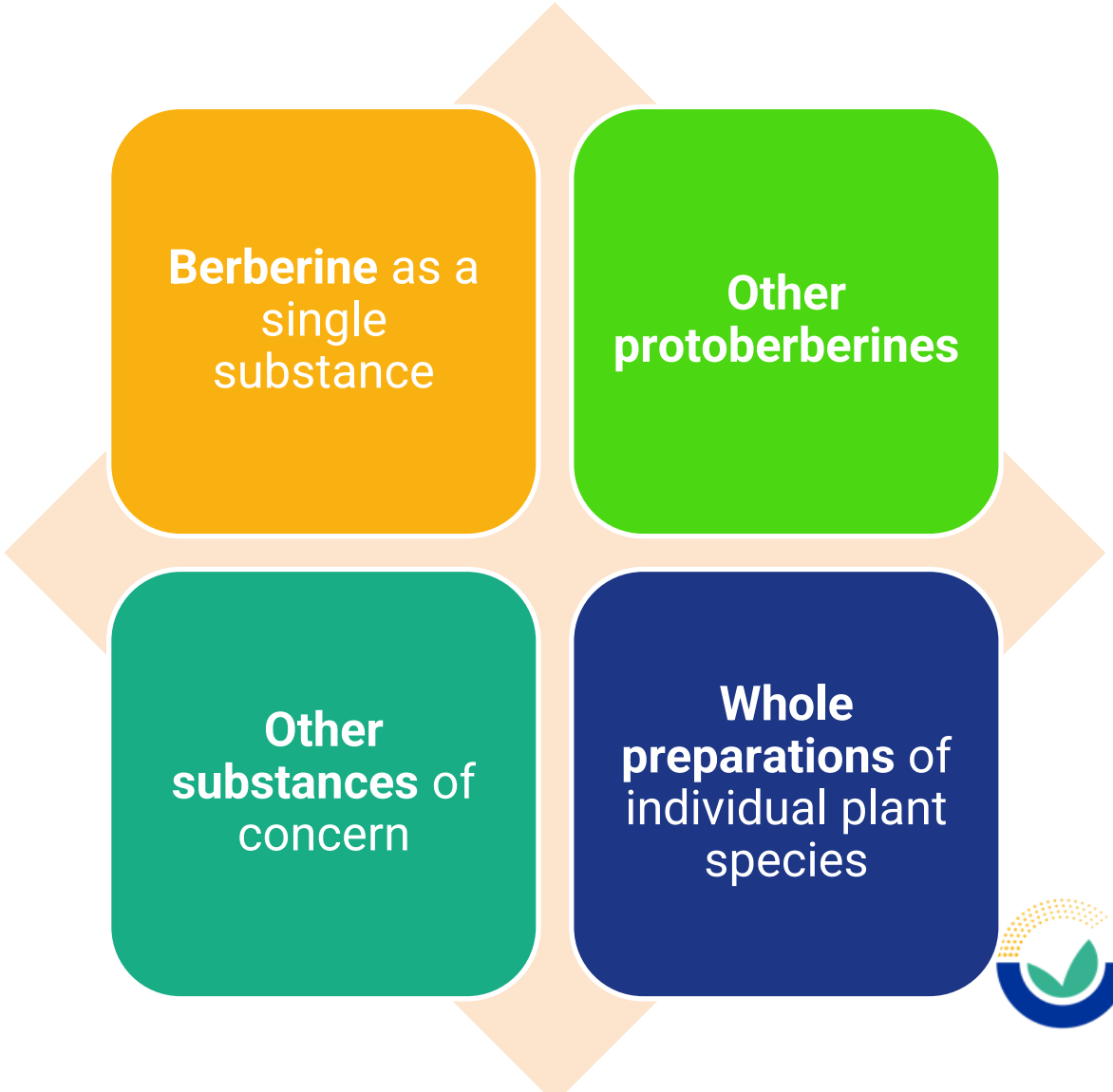
- berberine is ingested as part of complex plant preparations containing multiple protoberberine alkaloids
- structurally related compounds may interact during absorption and first-pass metabolism, leading to a modified internal exposure profile compared with berberine alone
- contribution of individual protoberberine alkaloids to (adverse) effects requires consideration
- other substances of concern must also be considered

[a] Similarity score of each substance with berberine as reference, using VEGA similarity algorithm as described by Floris et al. (2014)

INTERPRETATION OF THE TOR

- risk assessment of the plant preparations in the mandate followed a holistic approach, beyond their berberine content

- evidence on health effects were integrated across different exposures



OUT OF SCOPE

- possible **beneficial health effects** of plant preparations containing berberine
- risk assessment of **synthetic berberine** used **in food supplements** or added to foods, as it is covered by the Novel Foods regulation (Reg (EU) 2015/2283)
- **medicinal products** regulated under Directive 2001/83/EC (separate legal provisions and authorisation processes)

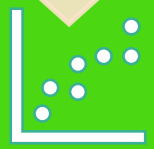
EFSA RISK ASSESSMENT PRINCIPLES

Hazard identification

- What adverse effects are caused by the substance/plant preparation?

Hazard characterization

- What are the adverse effects at different levels of exposure (dose-response relationship)? Can safe levels of consumption be characterised?



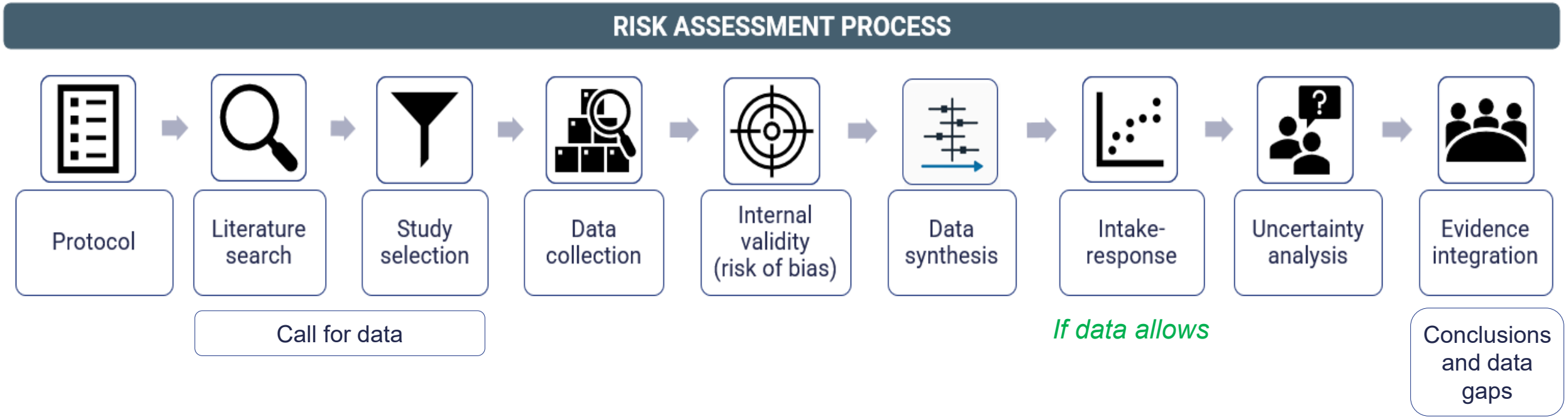
Exposure assessment

- How much of the substance/plant preparation are consumers exposed to?

Risk characterization

- What is the risk of adverse effects in the exposed population?

DATA & METHODOLOGY



CHARACTERISATION OF PLANT PREPARATIONS CONTAINING BERBERINE AND EXPOSURE

CONCLUSIONS REGARDING PROTOBERBERINES CONTENT

- **Berberine content data** are heterogeneous.
- For several plant species, quantitative data are **limited or absent**.
  - inly 1 study on *C. trifolia* rhizome and *T. sinensis* root
  - no quantification on *T. sinensis* stem and leaves, *J. palmata* root, or *T. flavum* root
- **Highest berberine contents** were reported in *B. aristata* root, *C. japonica* and *C. teeta* rhizome, *C. fenestratum* stem, *H. canadensis* root/rhizome, and *P. amurense* bark, with **wide variability between samples of the same species, depending on intrinsic and extrinsic factors**
- The **identification and characterisation of other protoberberine alkaloids** were inconsistent across studies, as they were **not systematically investigated**.
- The **most comprehensive chemical characterisation** is available for preparations of *B. aristata* root and bark (call for data).

QUESTION FROM STAKEHOLDERS

- Request to consider how **matrix effects in complex botanical preparations** may alter absorption and influence risk compared with isolated berberine

IDENTIFICATION OF DIETARY SOURCES

- Intake of berberine from foods expected to be **negligible in the general EU population**
- limited data available regarding foods containing berberine plant preparations in Mintel GNPD (e.g. infusions, liqueurs, other beverages)
- limited individual eating occasions in EFSA Comprehensive European food consumption database

- **berberine chloride and berberine sulphate** are the most common forms in food supplements; form and purity often not reported on product labels.
- berberine is found in **plant preparations or concentrated extracts** (variable composition)

- most frequent plants species in food supplements on EU Market: *B. aristata* and *B. vulgaris* (SISTE, EHPM, Mintel GNPD)
- other preparations on EU Market: *P. amurense*, *H. canadensis*, *C. majus*, other *Berberis* species (EHPM); *C. Teeta* (Mintel)

THEORETICAL DAILY EXPOSURE, FROM FOOD SUPPLEMENTS ONLY

❑ Theoretical daily berberine exposure from food supplements only:

berberine content in food supplement (mg/unit) x recommended daily use level (units/day)

- **Call for data**
  - *B. aristata*; bark/root; 47 analytical samples; median **445 mg/day**; Max **496 mg/day**.
- **Mintel GNPD**
  - *B. aristata*; bark/root/unspecified; 30 products; median **274 mg/day**; Max **1000 mg/day**.
  - *B. vulgaris*; root/root bark; 3 products; range **200-1164 mg/day**
  - *C. teeta*; root/rhizome; 2 products; range **6–8 mg/day**

❑ Assumptions

- consumers follow the use levels recommended by the manufacturers (no actual consumption data)
- regarding Mintel GNP database, content complies with the content declared on the label

QUESTION FROM STAKEHOLDERS

- **In Table 11 of the Opinion, the SISTE data reported under the entry "Alkaloids content in root and bark of *B. aristata*" are presented in a manner that is insufficiently transparent and may lead to misinterpretation. The data provided by SISTE referred to extracts of *Berberis aristata* and not to plant parts; in particular, the items indicated as N.Q. refer in particular to the presence of alkaloids in food supplements containing *Berberis aristata* extracts. Therefore, in terms of actual exposure, protoberberines are not present.**

Questions

GENOTOXICITY

METHODOLOGY

Assessment framework

- Genotoxicity assessment followed EFSA SC Guidance on chemical mixtures - *«if the mixture contains one or more chemical substances that are evaluated to be genotoxic in vivo via a relevant route of administration, the whole mixture raises concern about genotoxicity»*
- Default approach is **component-based.** Once genotox. concern for individual components of plant preparations is ruled-out, the risk assessment can be moved to the **mixture-level.**

Study eligibility and evaluation

- All eligible **mechanistic, in vitro and in vivo genotoxicity studies** were considered.
- Results classified as **positive, negative, equivocal or inconclusive**, accounting for study limitations.

QSAR and read-across strategy

- QSAR (quantitative structure-activity relationship) and read-across approaches were used as **supporting evidence** to **complement experimental and mechanistic evidence and** to identify **structural alerts** relevant for genotoxicity.
- Identification of structural alerts (endpoints included **mutagenicity (Ames test)** and **micronucleus induction)**

WoE APPROACH FOR BERBERINE GENOTOXICITY

	Berberine	Other protoberberines	*B. aristata*	*C. majus*	*C. japonica*	*C. fenestratum*	*H. canadensis*	*P. amurense*	*T. sinensis*	Total
In vitro and in vivo genotoxicity studies	26	3	1	0	1	0	3	1	0	35

Each assay evaluated:

- **Klimisch score (1-4)** for reliability
- Relevance of test system (type of assay)
- Relevance of the study results

Each study results were classified as:

- Positive,
- Negative,
- Equivocal, or
- Inconclusive

Technical report on Harmonised approach for reporting reliability and relevance of genotoxicity studies - https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/sp.efsa.2023.EN-8270

WEIGHTING AND INTEGRATION OF THE EVIDENCE

Weight-of-Evidence approach

- ❑ Qualitative, expert-based integration of all available evidence.
- ❑ Consistency across **experimental data, mechanistic information and QSAR results** evaluated.

Evidence integration

- ❑ Greater weight given to **high-quality, biologically relevant studies as assessed by our WG experts**.
- ❑ Mechanistic data used to support interpretation of positive in vitro findings.
- ❑ Uncertainties explicitly considered in the overall assessment.

Outcome

- ❑ Integrated evidence used to inform conclusions on **genotoxic potential**.
- ❑ Basis for identifying **data gaps** and guiding further testing needs

WoE APPROACH FOR GENOTOXICITY: BERBERINE AND PROTOBERBERINE ALKALOIDS

Berberine

- ❑ WoE largely based on **in vitro studies**, showing a **consistent pattern of positive findings** for DNA damage and gene mutation.
- ❑ Mechanistic evidence supports biological plausibility, with **topoisomerase inhibition and DNA intercalation** identified as key modes of action.
- ❑ **No adequate in vivo evidence** available, resulting in residual uncertainty.
- ❑ The **genotoxic potential of berberine in vivo requires elucidation**, both at the level of systemic exposure and at first-contact sites of exposure, namely the liver and the GI tract, which represent the major site of metabolism and the highest local exposure, respectively.

Protoberberine alkaloids

- ❑ **High structural similarity** to berberine supports read-across for several protoberberine alkaloids.
- ❑ QSAR predictions indicate **mutagenic potential with high certainty**, while micronucleus predictions are associated with higher uncertainty.
- ❑ Experimental data for most protoberberine alkaloids are **limited or absent, insufficient for firm conclusions**.

WoE APPROACH FOR GENOTOXICITY: PLANT PREPARATIONS

Chelidonium majus (herb)

- **sanguinarine (and chelerytrine)** identified as DNA intercalators and of genotoxic concern by **FEEDAP Panel (2023–2024)**, based on experimental data and plausible mode of action.
- these concerns were confirmed by the NDA Panel.

Plant preparations with evidence of low or limited relevance

- *Berberis aristata* (root, bark): one Ames test with low relevance
- *Coptis japonica* (rhizome): one Ames test with limited relevance (positive results)
- *Phellodendron amurense* (bark): one immunofluorescence analysis of DBS markers with low relevance (positive results)
- *Hydrastis canadensis* (rhizome, root): a couple of *in vitro* studies with low or limited relevance and one *in vivo* MN assay with low relevance (negative results)

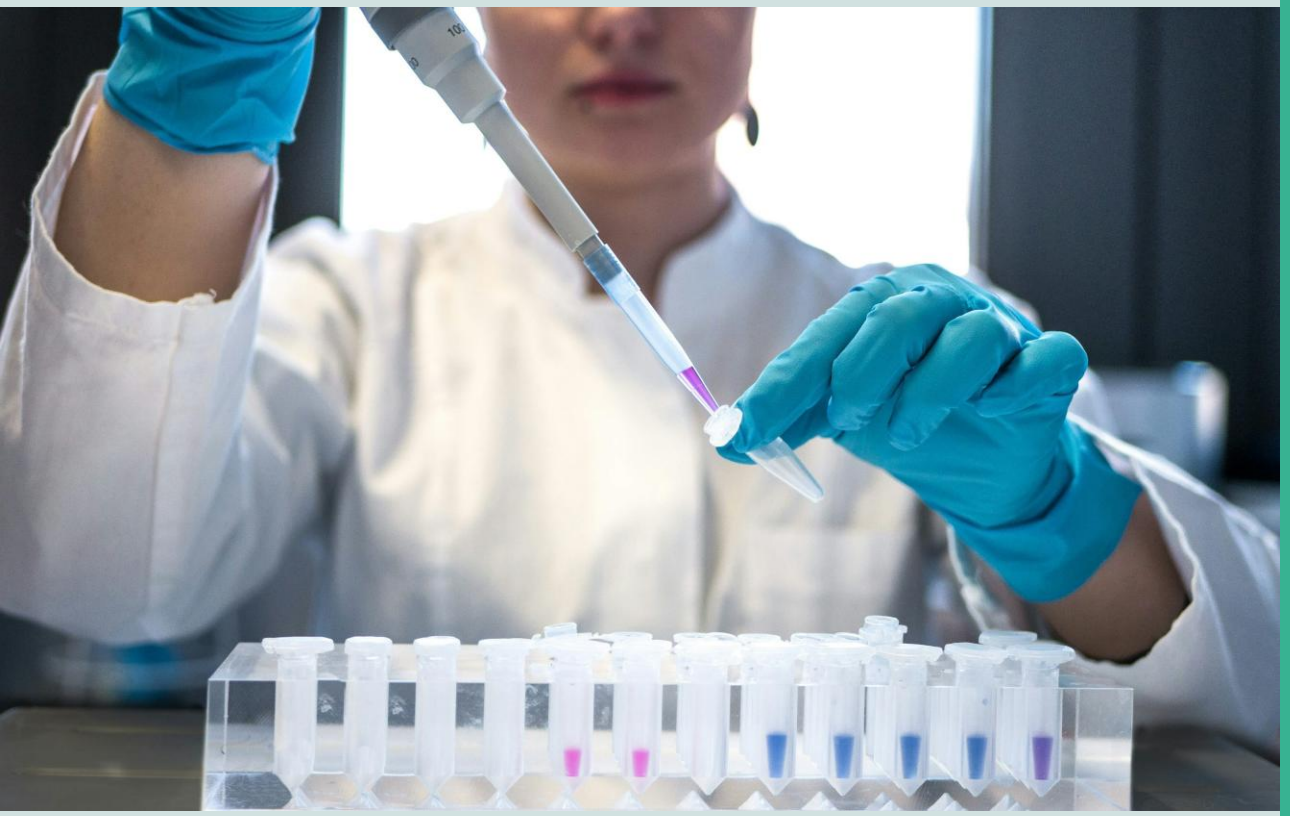
Plant preparations with no evidence

- *Berberis aquifolium* (root), *Berberis vulgaris* (root, bark), *Coptis teeta* (rhizome), *Coptis trifolia* (rhizome), *Coscinium fenestratum* (root, stem), *Jateorhiza palmata* (root), *Thalictrum flavum* (root), *Tinospora sinensis* (root, stem, leaf)

QUESTIONS FROM STAKEHOLDER

- EFSA concludes that the MOA for genotoxicity of berberine and berberine containing plants includes non-DNA reactive Modes of Action (line 2681-2687), but it seems unclear if that information was considered in the risk assessment and data request.
- What is the reason to exclude the existing in vivo micronucleus for berberine from the dataset? This study was done using i.p. administration which is a non-physiological route that can be considered worst-case for compounds that may react stronger in the absence of metabolic competency - the profile that was observed for berberine (see, e.g., Sun et al, 2025). There seem other cases where EFSA has accepted i.p. for exactly that reason, e.g., in context of the current public consultation for acetaldehyde as a substance that is shows stronger genotoxicity in the absence of a metabolism system than in its presence

Questions



GENERAL TOXICOLOGY AND HUMAN DATA & CONCLUSIONS

METHODOLOGY

Study appraisal

- ❑ Animal studies: grouped into tiers reflecting overall risk of bias (reliability): Tier 1 (low), Tier 2 (moderate), Tier 3 (high)
- ❑ Human studies: collective narrative appraisal

Integration (Weight of Evidence-WoE)

- ❑ Expert-guided WoE considering:
  - Reliability & relevance
  - Consistency across studies (including humans vs animals)
  - Biological plausibility (mechanistic support)
- ❑ Berberine/protoberberines evidence integrated narratively; then combined with plant-preparation evidence considering critical doses, dose–response, and uncertainties/data gaps

BERBERINE AND PROTOBERBERINE ALKALOIDS

General toxicology

- ❑ **90-day toxicity studies** for berberine, berberrubine, jatrorrhizine, coptisine, columbamine
  - Mostly no observed effects; data on berberrubine suggestive of liver toxicity
  - But methodological (not following accepted test guidelines; limited number of endpoints)/reporting limitations
- ❑ **Other animal studies** (**18**): do not raise safety concerns but investigated a restricted number of safety-related endpoints

Maternal, reproductive and developmental toxicity

- ❑ Maternal and offspring toxicity observed in rats/mice for **berberine (2 studies commissioned by US NTP)**
- ❑ No data on **other protoberberine alkaloids**

Data from human case reports and clinical trials

- ❑ **Case reports (3)**: adverse effects (sinus bradycardia, rash) associated with berberine supplement consumption, but causality remains uncertain
- ❑ **Clinical trials (28)**: GI symptoms most frequent (constipation, diarrhea, nausea, abdominal discomfort) with berberine supplements (400–1500 mg/day vs placebo); 2 cases with elevated transaminases, but link not well established.
  - Study address a limited number of safety related endpoints and often lacks detail on source and form of berberine

Interactions with medicinal products (6 human and 12 animal studies)

- ❑ Berberine may inhibit CYP3A4, and possibly CYP2D6/CYP2C9 → potential interactions with medicinal products

CONCLUSIONS - BERBERINE

- There is **evidence for berberine genotoxicity in vitro**, indicating gene mutation and chromosomal damage, which are supported by mechanistic evidence. Confirmation in vivo is lacking, especially at contact sites of exposure, namely the gastrointestinal tract and the liver.
- There is **no adequate repeated dose toxicity study** on berberine alone that would allow identification of a reference point.
- The consumption of berberine-containing food supplements may lead to **transient gastrointestinal symptoms** such as constipation, diarrhoea, nausea, and abdominal pain.
- Berberine may inhibit CYP3A4 and possibly other CYP450 enzymes, indicating a **risk for interaction between berberine-containing plant preparations and various medicinal products**.

CONCLUSIONS – OTHER PROTOBERBERINE ALKALOIDS AND OTHER SUBSTANCES

- Available **experimental data are sparse and inconclusive**.
- In view of their high structural similarity with berberine, the **genotoxic potential of other protoberberine alkaloids** also requires consideration.
- **Other alkaloids** present in the plant preparations included in the mandate, including **sanguinarine and chelerythrine in C. Majus**, also raise some **genotoxic concerns**.

HYDRASTIS CANADENSIS (ROOT-RHIZOME)

General toxicity and carcinogenicity

- Consistent and dose-dependent hepatotoxicity in rodents in several standard toxicological studies **(US NTP)**
- Evidence of carcinogenic activity of a root powder of *H. canadensis*, with increased incidence of **liver adenomas observed in rodents** (US NTP).

Maternal, reproductive and developmental toxicity

- No effects observed (1 study), but limitations of the study preclude firm conclusions on potential developmental toxicity.
- No data on reproductive toxicity.

Interactions with medicinal products

- Preparations inhibit **CYP3A and CYP2D6**, and possibly intestinal uptake transporters (e.g. OCTs).
- Besides berberine, **(–)-β-hydrastine** may significantly contribute to potential interactions with medicinal products.

CONCLUSIONS- RHIZOME/ROOT OF *H. CANADENSIS*

- **Preparations from rhizome/root of *H. canadensis*** showed **evidence of carcinogenic activity in rodents, particularly causing liver adenomas**. The mechanisms remain unclear, including potential genotoxic modes of action.
- The consumption of preparations of rhizome/root of *H. canadensis* represents a carcinogenic risk for humans.

Image: https://www.omafra.gov.on.ca

CHELIDONIUM MAJUS (AERIAL PART)

Data from human case reports, case series

- 45 human cases of liver injury (CM only ingredient or multi-ingredient, DE, IT, ES; AUS; South Korea)
- The latency periods to first symptoms varied from some weeks to some months.
- Causality assessment performed using validated scales:
  - highly probable in 5 cases, probable in 13 cases and possible in 20 cases
- Very likely that cases of liver injury can be attributed to the consumption of C. majus products.
- Reactions consistent with an idiosyncratic form of herb-induced liver injury and dependent on individual susceptibility.
- The role of berberine in these effects remains uncertain

CONCLUSIONS- AERIAL PARTS OF *C. MAJUS*

- In humans, **consumption of preparations of C. majus aerial parts** has been linked to **idiosyncratic herb-induced liver injury**;
- Susceptible individuals cannot currently be identified
- **No dose** below which such reactions would not occur can be established

Image: by Hans from Pixabay

CONCLUSIONS - OTHER PLANT SPECIES

- Except for *H. canadensis*, the **toxicity profiles of preparations of the other plant species included in the mandate, beyond their berberine content, remain largely unknown** due to the lack of adequate toxicity studies, resulting in significant uncertainty in the identification and characterisation of hazards
- The available data **do not allow establishing a safe intake for humans for any preparations** of the plant species, and plant parts thereof, included in the assessment.

Scientific name	Plant part in the mandate	Common names
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Berberis vulgaris L.	Root, bark	Common barberry
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Phellodendron amurense Rupr.	Bark	Amur cork tree
Thalictrum flavum L.	Root	Common meadow-rue
Tinospora sinensis (Lour.) Merr.	Root, stem, leaf	Chinese tinospora

QUESTION FROM STAKEHOLDERS

- *Hydrastis canadensis* L. and *Chelidonium majus* L., are **not allowed to be used in FS** in most EU countries.
- Question the application of safety concerns related to those plants **to all plant preparations** containing berberine.
- For many of the plant species (e.g. B vulgaris, root, bark), **no data** were retrieved. Question the application of conclusions to species for which no adverse data have been identified. Refer to the **proportionality principle** of Regulation (EC) No 178/2002 Art. 7

QUESTION FROM STAKEHOLDERS

- Consideration of **distinct exposure scenario for food supplements used at “nutritional/low doses” vs “pharmaceutical doses”,** accounting for different systemic bioavailability and interaction profiles

QUESTION FROM STAKEHOLDERS

- Weight of **post-market surveillance evidence from national competent authorities** in risk characterization/risk assessment compared to in vitro or animal studies?

Questions

DATA GAPS

SECTION 6 OF THE DRAFT OPINION

- Outlined the **additional data needed** to address identified concerns, and the **stepwise approach to generating these data** (flowcharts).
- **All studies generated should follow OECD TGs** if existing and be conducted in accordance with **GLP**.
- The test material should be **well characterised and representative** of the plant preparation to be used for the European market.
- For newly generated studies, **full study reports** should be provided.
- If additional searches were conducted, a **complete description of the literature search strategy and results** should be given.

STEP 1 CHARACTERISATION

- **Characterisation of the plant preparation**
  - Requirements in the Guidance on safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements should be applied (EFSA Scientific Committee, 2009)
- The **conditions of use** of the plant preparation of interest, including the **target population and recommended doses**, should be provided.

STEP 2A GENOTOXICITY OF BERBERINE

1. **In vivo mutagenicity**: transgenic rodent mutation assay (OECD TG 488) - both the liver and gastrointestinal tract tissues
   - Positive -> GENOTOXICITY CONCERN
   - Negative: NO mutagenicity concern for BBR and other protoberberines -> PROCEED WITH IN VIVO TESTS ON CHROMOSOMAL AND DNA DAMAGE

2. **In vivo chromosomal damage**: in vivo micronucleus assay - in the liver of male juvenile rats & **In vivo DNA strand breaks:** in vivo comet assay (OECD TG 489) - both the liver and gastrointestinal tract tissues
   - One positive -> GENOTOXICITY CONCERN
   - Both negative: NO genotoxicity concern for berberine -> PROCEED TO STEP 2B

STEP 2B GENOTOXICITY OF OTHER PROTOBERBERINES

- ❑ **For mutagenicity,** read-across from berberine to the other protoberberines is possible
- ❑ **On one selected protoberberine (to be justified)**

1. **In vitro chromosomal damage**: in vitro micronucleus assay (OECD TG 487)
   - ➢ Positive -> GENOTOXICITY CONCERN
   - ➢ Negative: NO genotoxicity concern for protoberberines -> PROCEED WITH IN VIVO TESTS ON CHROMOSOMAL AND DNA DAMAGE

2. **In vivo chromosomal damage**: in vivo micronucleus assay & **In vivo DNA strand breaks:** in vivo comet assay (OECD TG 489)
   - ➢ One positive -> GENOTOXICITY CONCERN
   - ➢ Both negative: NO genotoxicity concern regarding protoberberines -> PROCEED WITH STEP 3

STEP 3 GENOTOXICITY OF THE PLANT PREPARATIONS

1. **Other identified substances** present in the plant preparation
   - Based on the composition data of the plant preparation
   - **Literature searches** to identify additional potential concerns for genotoxicity.
   - Should concerns be identified, **genotoxicity testing** needs to be carried out in line with EFSA SC testing strategy for genotoxicity

2. When genotoxicity of identified substances is ruled out, testing can proceed to investigating genotoxicity of the **unidentified fraction** (if not feasible, whole mixture)

- ❑ POSITIVE -> GENOTOXICITY CONCERN
- ❑ NEGATIVE: NO genotoxicity concern for the plant preparation -> PROCEED WITH STEP 4

STEP 4 IN CASE GENOTOXICITY IS RULED OUT

- **A 90 day study,** performed according to **guidelines (OECD TG 408)**, is the minimum requirement to identify a RP to establish safe doses.
- In case the plant preparation is intended for pregnant and/or lactating women: Reproductive and developmental toxicity should be assessed through a **standard reproduction and developmental toxicity** study (**OECD TG 422**), unless justified
- Extrapolation of the results from the submitted studies to **other plant preparations** will need to be evaluated based on the data provided and will be an expert judgement.

SPECIFIC CONSIDERATIONS

- ***Specific considerations regarding preparations of rhizomes/root of H. canadensis***
  - The consumption of preparations of rhizome/root of *H. canadensis* represents a carcinogenic risk for humans. Without evidence excluding a genotoxic mechanism, a safe level of exposure cannot be determined.
  - In case a genotoxic mechanism was reliably ruled out, the **available toxicity studies on rhizomes/root of *H. canadensis* can be used to identify a reference point** for establishing a safe level of intake in humans

- ***Specific considerations regarding preparations of aerial parts of C. majus***
  - Idiosyncratic drug reactions are rare, unpredictable adverse responses that typically lack a clear dose-response relationship and are not reliably reproduced in animal models (EMA (European Medicines Agency), 2010).
  - The Panel **did not identify an experimental approach** that could be used to address this concern.

FOLLOW UP STUDIES

- Can the submission of new studies conducted according to official guidelines change a previous EFSA opinion?
- If studies are published in scientific journals after the deadline, will they still be considered by EFSA?

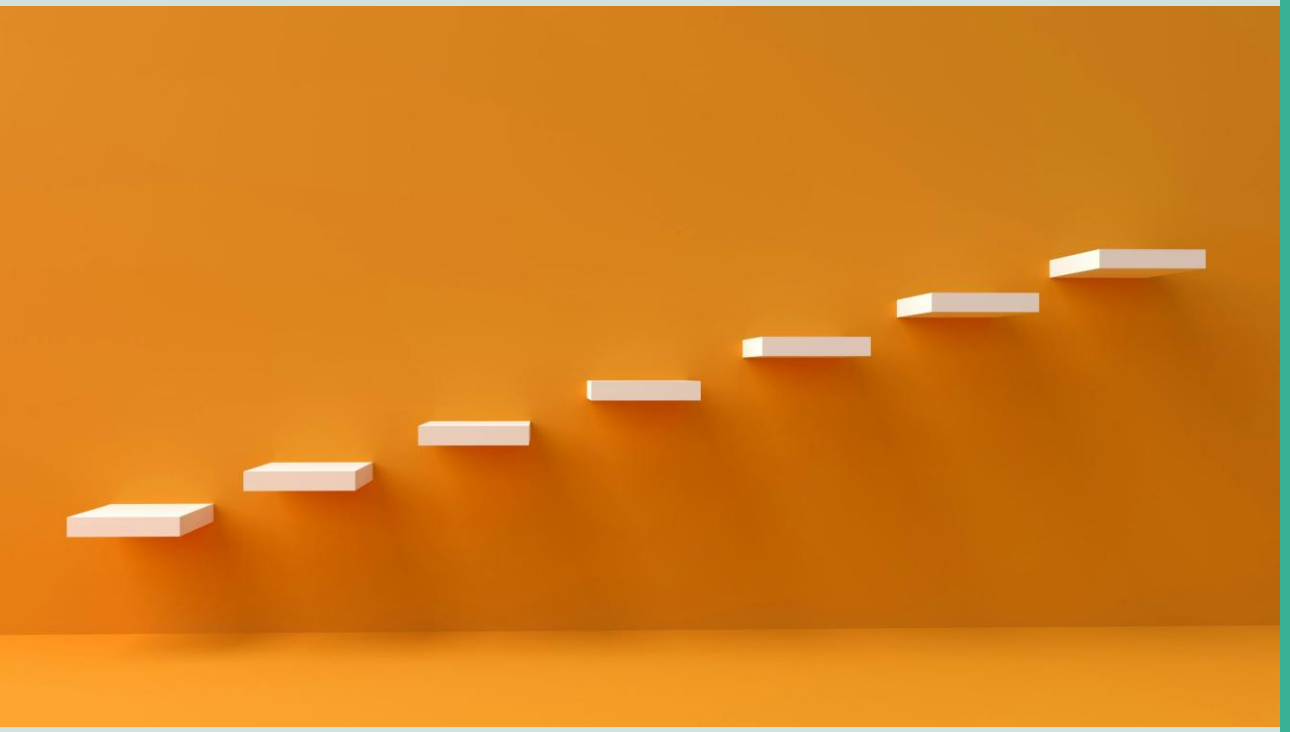
FOLLOW UP STUDIES

- Considering the intrinsic variability of plant extracts, is it more appropriate to conduct **studies on isolated berberine or on whole extracts**?
- Which **types of preparations** should be considered (e.g. extracts, powders, or other forms) and according to which criteria should they be selected?
- Considerations required when conducting in vivo toxicity studies with **berberine-containing extracts with modified bioavailability** (e.g., increased solubility in water, higher absorption in the gastrointestinal tract)

GENOTOXICITY TESTING STRATEGY

- Questions regarding step 2 of the testing strategy
  - Berberine: Is the assumption correct that the Comet assay and the in vivo micronucleus assay could be combined?
  - Berberine: If a Comet assay would be done, a study type that is considered to include DNA damage that leads to mutation (e.g. by EFSA), what would be the rationale to also run an OECD 488 study?
  - Protoberberines: what is the rationale to request in vivo studies before checking the genotoxicity potential in vitro?
  - Protoberberines: will EFSA accept read across to all protoberberines listed?

Questions



NEXT STEPS
ART 8(4) PROCEDURE

NEXT STEPS

- **Public consultation**: until 11 May (deadline extended by 7 days) - https://connect.efsa.europa.eu/

- **Review of the comments**: May-June

- **Submission of the opinion for adoption by the NDA Panel**: 1/2 July (pending the amounts of comments received during the PC)

REGULATORY FRAMEWORK: ARTICLE 8 REG (EC) 1925/2006

Art 8.2

If a harmful effect on health is identified, the substance shall be:

Prohibited
in the addition and manufacture of foods. (**Part A** of Annex III)

Allowed under specific conditions
in the addition and manufacture of foods. (**Part B** of Annex III)

If the possibility of harmful effect on health is identified but **scientific uncertainty persists:**

the substance shall be placed under **Community scrutiny** (**Part C** of Annex III) (scrutiny period) → Food business operators may submit for evaluation to EFSA scientific data demonstrating the safety of a substance/ingredient **(dossier)**

ART 8.4

EFSA's legal deadline to assess new data (dossier) 9 months

HIGHLIGHTS ABOUT THE SUBMISSION OF SCIENTIFIC DATA

e-submission system

- Food business operators (FBOs) **use Portalino to submit a file containing scientific data** that demonstrate the safety of a substance listed in Annex III, part C of Regulation (EC) 1925/2006.

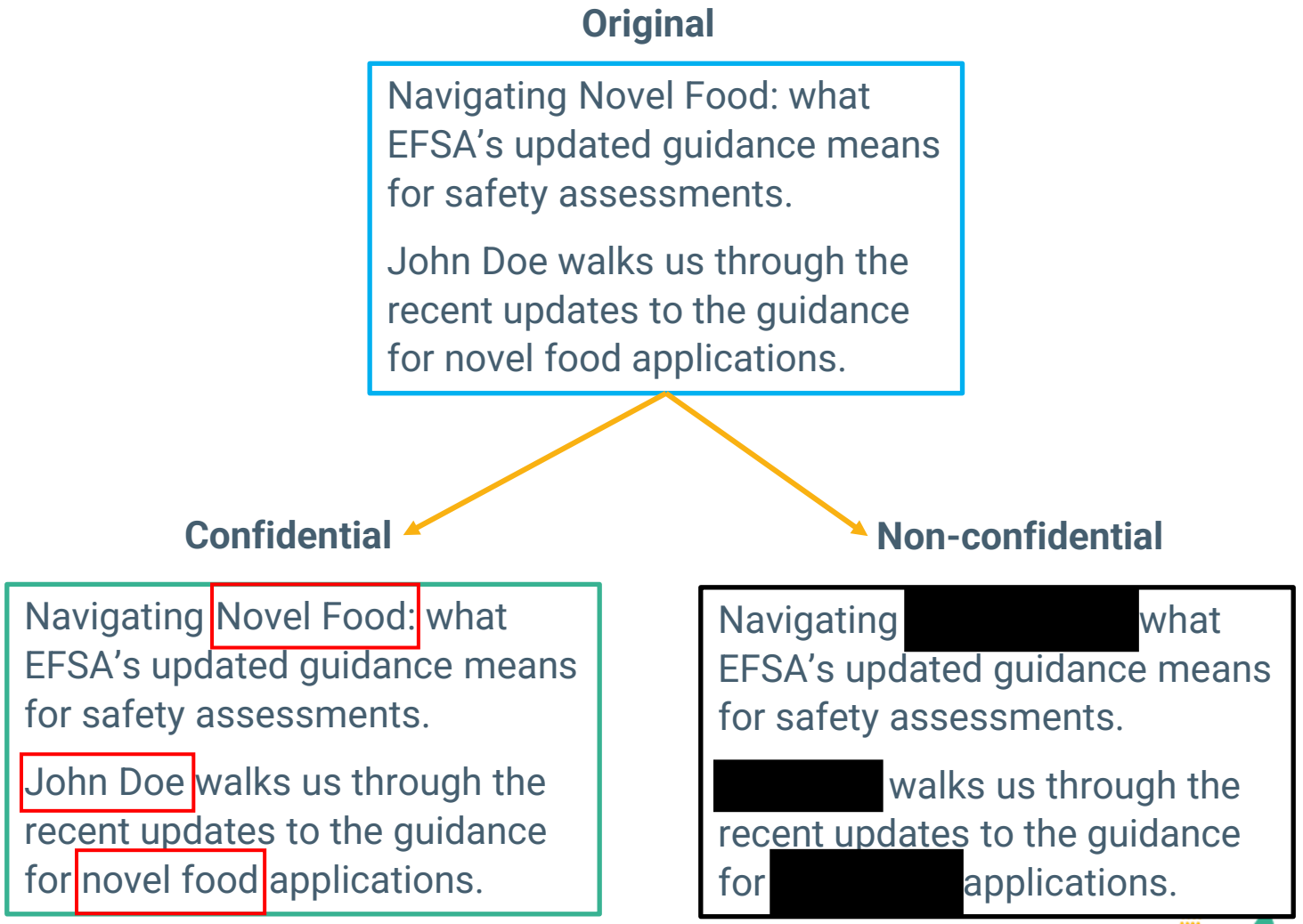
Regulation (EU) 307/2012 sets the rules for the submission

- FBOs **notify the studies** commissioned or carried out **to demonstrate the safety of a substance**, **without delay** (i.e. before the starting date of the study).
- FBOs **consult Article 4** for details about the **content of the submission**.
- FBOs **may request pre-submission advice** for a potential submission.
- FBOs **may submit confidentiality request(s)** on certain parts of a submission.

HOW TO SUBMIT DOCUMENTATION CONTAINING CONFIDENTIAL INFORMATION?

- Two versions of each document containing confidential information are needed:
  - **Confidential version**: all information visible, confidential elements and personal data* boxed or earmarked
  - **Non-confidential (Public) version**: identical document, confidential elements and personal data* irreversibly blackened

- **Use of an appropriate software for earmarking and redacting the documentation, is highly recommended.**



***Personal data** stands for names, signatures, contact details, etc, which relates to identifiable natural persons contained in unpublished documents and as such qualifies as personal data to be protected in accordance with Regulation (EU) 2018/1725

SUPPORT FOR APPLICANTS

Useful guidance documents:

- User guide on Portalino: describes the steps to request the access to this portal and provides general guidance on the submission process.
- Connect.EFSA registration user manual: describes the registration process and provides information on the steps to follow. For the purpose of this submission, interested parties **may need to request a pre-submission activities profile**. Please follow the indications identifiable with a pink banner on the left side of the pdf**.**
- EFSA's user guide on confidentiality: provides instructions on how to submit confidentiality requests using Portalino, see Section D, Chapter 3.

How to contact EFSA in case of need:

- In case of any technical issues during the registration on Connect.EFSA or the submission of your file: servicedesk@efsa.europa.eu.
- If you have any question or doubt you can contact EFSA by using the Ask a Question tool. We kindly suggest to put in the subject of the request a reference to the substance under scrutiny or to your submission.

Q&A Session

RISK MANAGEMENT

- **Expected timeframe** for the European Commission and Member States to **implement decisions** after the adoption of the opinion
- Consideration of risk-management approaches other than restriction, such as **limiting the duration of use or introducing specific usage warnings on labels**?
- **Proportionality assessment** quantifying the **economic and public health consequences** of the restrictions or bans of products
- **Monacolin, berberine and HCA** : current regulatory status in the EU and MSs

DIHYDROBERBERINE (DHB)

- Several questions regarding the safety assessment of dihydroberberine

ANY OTHER QUESTIONS?

After the event, attendees will receive a **link to a survey** to evaluate the EFSA event

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