Targeted Stakeholder Meeting | 23 April 2026

EFSA'S DRAFT OPINION ON THE SAFETY OF HYDROXYCITRIC ACID (HCA) AND PLANT PREPARATIONS CONTAINING HCA

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 14:00

Introductory remarks
Ana Afonso

Background and mandate, data and methodology
Thibault Fiolet

Safety assessment of (-)-HCA, G. gummi-gutta, G. indica
Thibault Fiolet, Ariane Titz

Safety assessment of H. sabdariffa
Thibault Fiolet, Ariane Titz

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

Q&A
All

Ending time 17:00

BACKGROUND AND MANDATE

BACKGROUND

Starting point

agencia española de seguridad alimentaria y nutrición

- Spanish Agency for Food Safety and Nutrition concluded that there is sufficient clinical evidence to establish a causal association between the consumption of ***Garcinia gummi-gutta*** **(L.) Roxb.** and **acute liver injury**, based on evidence from case reports.

- Concerns were raised regarding a **potential risk to consumers** linked to the consumption of foods containing the pericarp of the fruit of ***G. gummi-gutta***.
- The rind (=pericarp) of the Garcinia fruit contains hydroxycitric acid (HCA)

EC MANDATES - TERMS OF REFERENCE

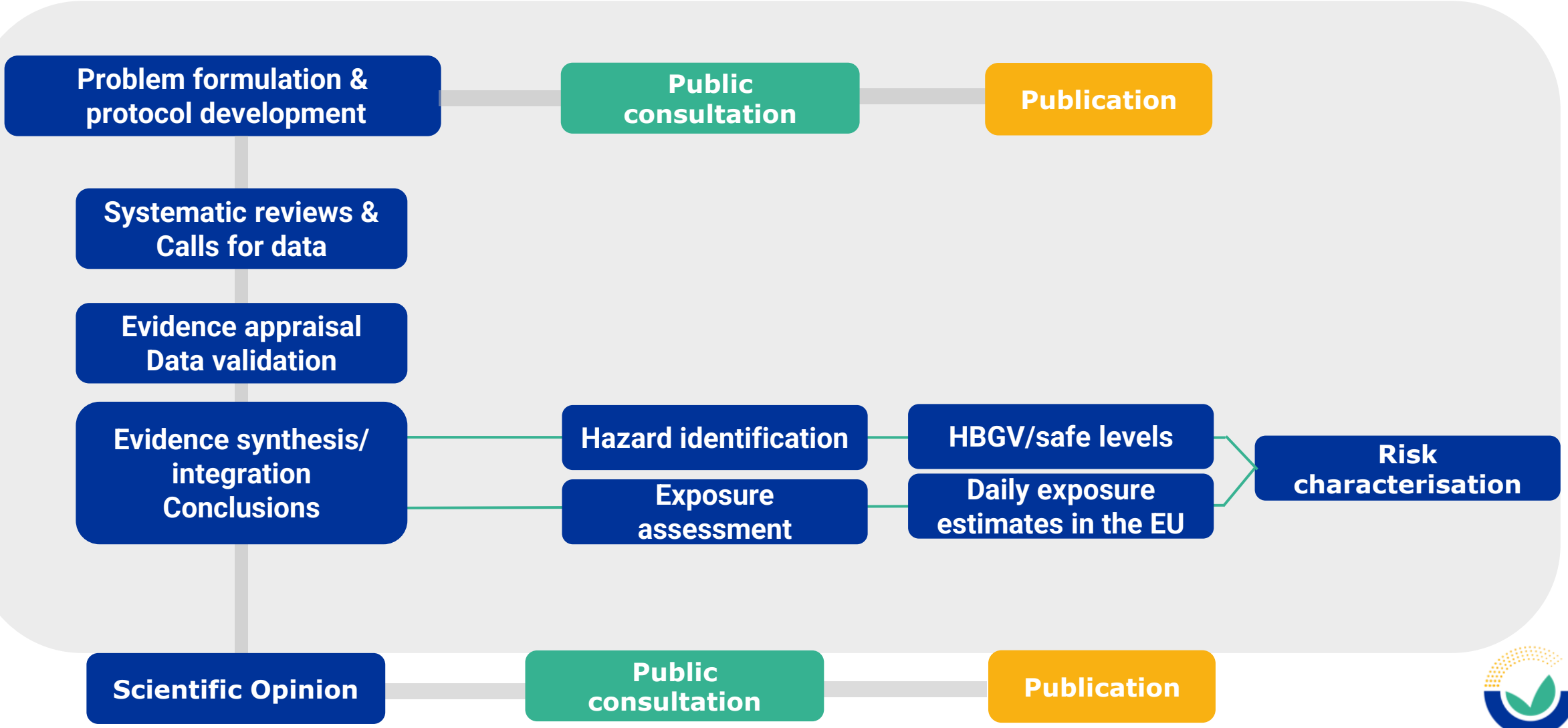
- Review the existing scientific data on the possible link between the **intake of highly purified HCA and preparations containing HCA** and a harmful effect on health
- Provide advice on a daily intake of **isolated HCA and plant preparations containing HCA** that does not give rise to concerns about harmful effects to health

ToR

- Plant preparations **not containing HCA**
- **Novel foods** (basis Novel Food Catalogue)
- **Beneficial** health effects of HCA and plants preparation containing HCA
- **Risk-benefit** assessment

Out of scope

RISK ASSESSMENT PROCESS – ART 8.2. GENERIC MANDATES



METHODOLOGY FOR HAZARD IDENTIFICATION

- Systematic review performed in PubMed, Embase and Cochrane database limited to English language for toxicity data
- Additional targeted searched performed for emerging adverse effects (reproductive toxicity)
  - These supplementary searches did not follow the systematic methodology described above
  - Publications which were not indexed in databases or published in another language than English
- Targeted searches also for the characterisation of the plant preparations, ADME data, substances of concern in the plant preparations other than HCA and the potential mechanisms of action (summarised in a narrative way)

PRESUBMITTED QUESTIONS – METHODOLOGY

- Given that a number of studies were at high risk of bias with limited or low relevance, could the applied criteria to reach conclusions be explained? In particular, it is unclear which level of evidence is considered sufficient to trigger proposals for follow-up actions.

- Were all data taken into account in the assessment, also published studies in humans with food supplements containing 2 grams of HCA per day?

Questions - methodology

SAFETY ASSESSMENT OF (-)-HCA, *G. GUMMI-GUTTA, G. INDICA*

CHARACTERISATION OF THE PLANT SPECIES

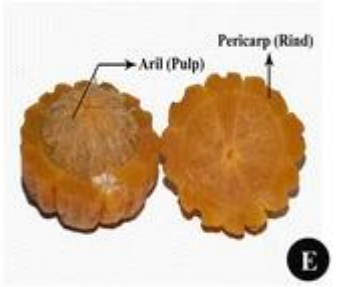
CHARACTERISATION OF THE PLANT SPECIES

G. gummi-gutta

Edibility: Too acidic to eat raw; dried pericarp used in curries

Composition of the pericarp:

- **Main acids**: (−)-HCA and (−)-HCAL
- **Other acids**: malic, tartaric, citric acid
- **Polyphenols & polyprenylated compounds**: garcinol, 14-deoxygarcinol, xanthochymol, isoxanthochymol, guttiferones I–N, oxy-guttiferone K



Composition of the aril: contains (−)-HCA, little is known about the specific composition

CHARACTERISATION OF THE PLANT SPECIES

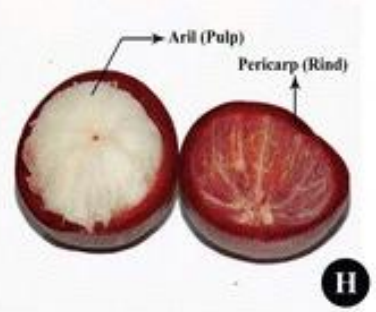
G. indica

Edibility: Dried pericarp used in drinks & curries

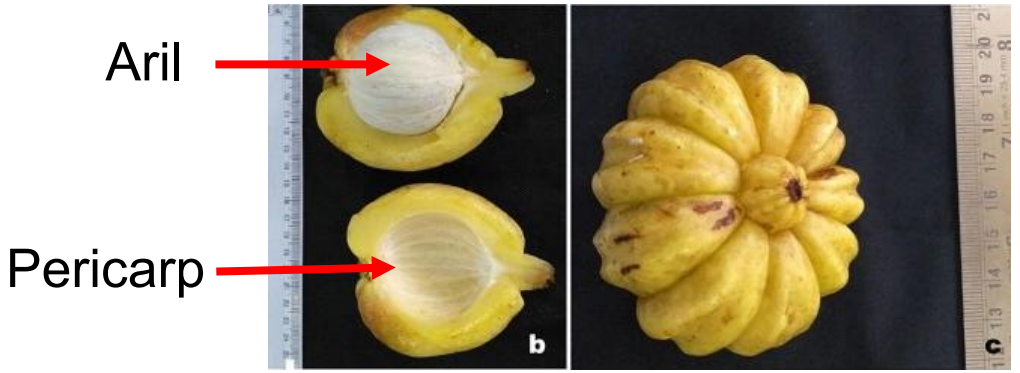
Composition of the pericarp:

- **Main acids**: (−)-HCA and (−)-HCAL
- **Other compounds:** anthocyanins (cyanidin 3-sambubioside), flavonoids (naringenin), phenolic acids (p-coumaric acid), garcinol, isogarcinol

Composition of the aril: no information retrieved



(-)-HCA CONTENT IN THE PLANT PARTS



Plant	(-)-HCA content in the pericarp	(-)-HCA content in the aril
G. gummi-gutta	11-29%	2.6%[1]
G. indica	5-19%	NA

1: based on one anlaytical study only

PRESUBMITTED QUESTIONS ON CHARACTERISATOIN

- How does variability in the different HCA forms (free acid, lactone or salt forms) in a plant preparation affect risk assessment?
- Were the analytical methods applied to quantify HCA in plant matrices reliable?
- Which analytical methods does EFSA recommend?

Questions – characterisation

HAZARD IDENTIFICATION

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) was used as **supporting evidence to** identify **structural alerts** relevant for genotoxicity

WoE APPROACH FOR GENOTOXICITY

Results from each study assessed were classified as: **positive, negative, equivocal or inconclusive** (OECD TGs, 2017)

❑ **Positive**

- criteria established in corresponding OECD TG or based on expert judgement
- e.g. > 2- or 3-fold increase in revertant colonies, statistically significant and dose-dependent increase in treatment groups vs control

❑ **Negative**

- Not meeting the criteria above

❑ **Equivocal**

- refers to a situation where not all the requirements for a clear positive result have been met.
- e.g. a positive trend was observed, but the dose-response relationship is not statistically significant. Equivocal can, therefore, be interpreted as the true result being on the borderline of the decision criteria for positive or negative

❑ **Inconclusive**

- no clear result was achieved - this may have been a consequence of some limitation of the test or procedure. In this case, repeating the test under the correct conditions should produce a clear result.

https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/sp.efsa.2023.EN-8270

GENOTOXICITY OF (-)-HCA

- **2 in vitro studies (inconclusive) –** all Klimisch score 3
  - Bacterial reverse mutation assay
  - Chromosome aberration test
- **1 in vivo micronucleus test (equivocal)** - Klimisch score 3
- **Mechanistic evidence**: concentration-dependent reactive oxygen species (ROS) increase

EFSA conclusion(s):

- Further data are needed, as the evidence is **insufficient to conclude** on the genotoxicity of (–)-HCA

GENOTOXICITY OF OTHER COMPONENTS

- **Analytical data**
  - *G. gummi-gutta* pericarp contains guttiferones, including guttiferone K, J, N, I, M and garcinol
  - *G. indica* pericarp contains garcinol
- Comet assay and micronucleus test in the bone marrow of mice suggest **in vivo genotoxicity of guttiferone A (not present in *G. gummi-gutta* and *G. indica*)**
- **QSAR**: garcinol and other guttiferones present in *G. gummi-gutta* pericarp show high structural similarity with guttiferone A

EFSA conclusion(s):

- Based on these structural and functional characteristics, **in vivo genotoxicity** of guttiferone K, garcinol, guttiferone M, xanthochymol, guttiferone J, guttiferone I, guttiferone N cannot be ruled out.

GENOTOXICITY OF PLANT PREPARATIONS (1)

- ***G. gummi-gutta* pericarp (inconclusive)**
  - 1 in vitro bacterial reverse mutation assay (Klimisch score 4)
  - 1 in vitro chromosome aberration test (Klimisch score 3)
  - 1 in vitro comet assay (Klimisch score 3)
  - 1 in vivo micronucleus test in mice (Klimisch score 3)
- ***G. gummi-gutta* aril: no data**

EFSA conclusion(s):

Further data are needed, as the evidence is insufficient to conclude on the genotoxicity of G. *gummi-gutta* pericarp preparations. No data on *G. gummi-gutta* aril was found.

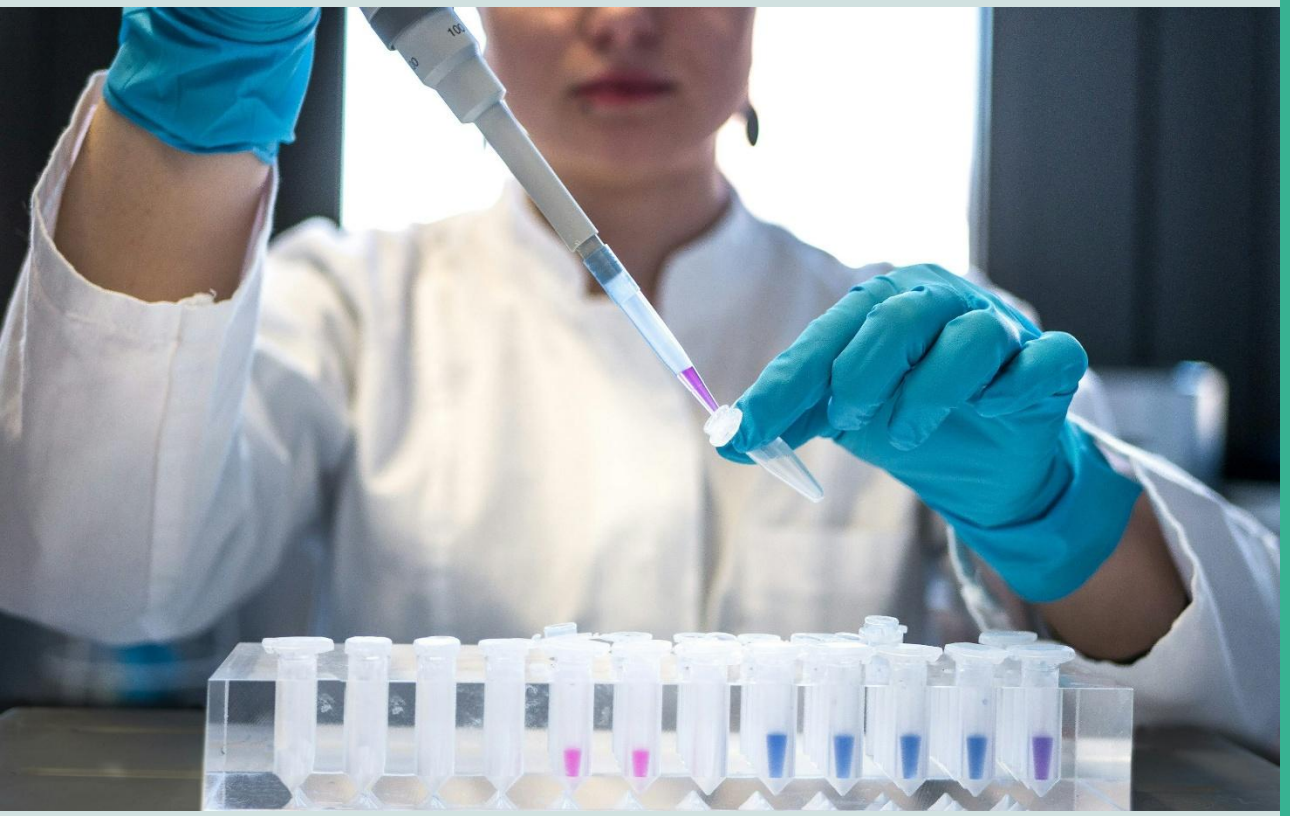
GENOTOXICITY OF PLANT PREPARATIONS (2)

- ***G. indica* pericarp**
  - 2 in vivo assays – bone marrow chromosomal aberration test + sister chromatid exchange assay (Klimisch score 2)
  - In vivo genotoxicity for a specific methanolic extract of *G. indica* dried pericarp
  - Given that the extract was not characterised, results cannot be extrapolated to other extracts
- ***G. indica* aril: no data**

EFSA conclusion(s):

Further data are needed, as the evidence is insufficient to conclude on the genotoxicity of G. *indica* preparations. No data on *G. gummi-gutta* aril was found.

Questions – genotoxicity



HAZARD IDENTIFICATION

Liver toxicity

LIVER TOXICITY – *G. GUMMI-GUTTA (1)*

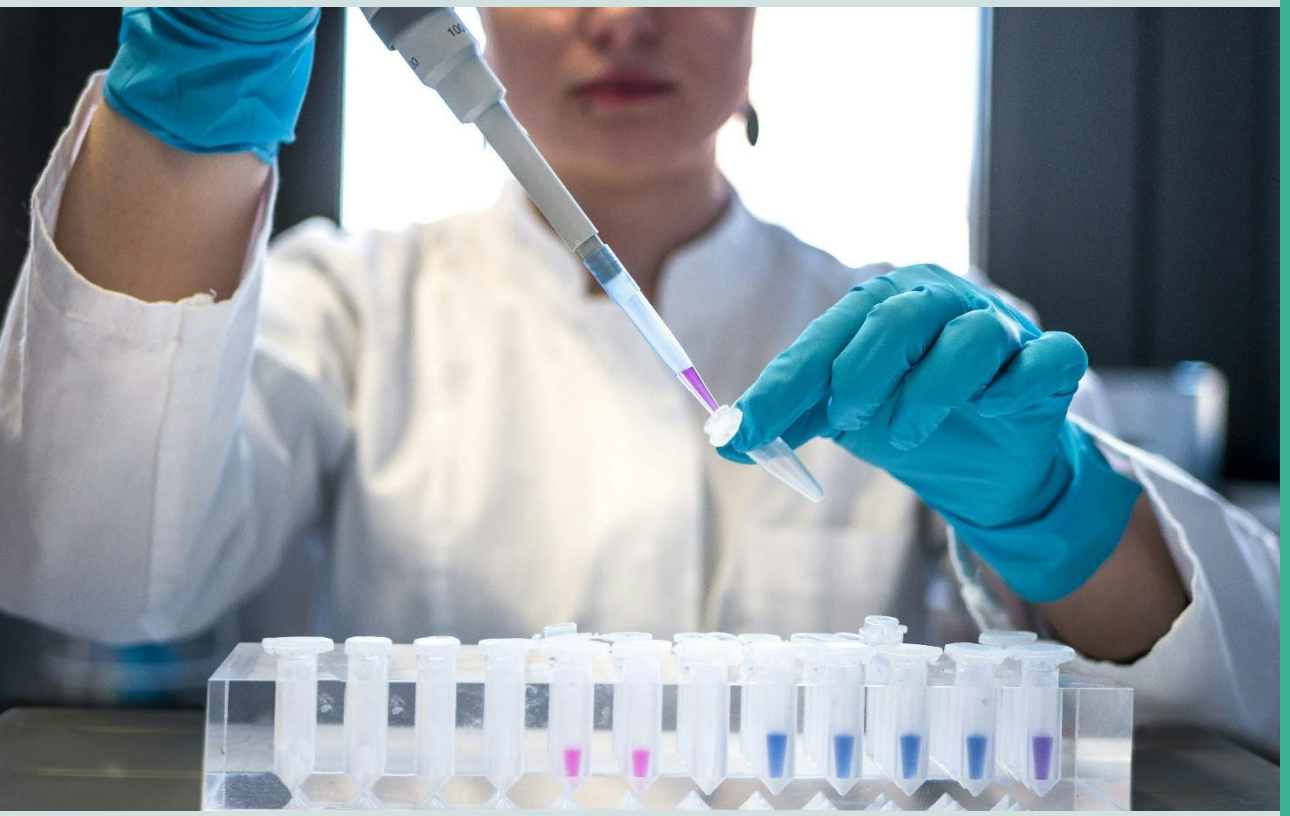
- **Human case reports (supplements with *G. gummi-gutta* as only ingredient)**
  - 4 cases of liver injury in individuals not taking concomitant medication and with no history of alcohol abuse
  - 13 cases of liver injury in individuals taking concomitant medication and/or with history of alcohol abuse and/or missing information on these variables
  - One case with a re-challenge
  - Based on causality assessments performed by the authors of the publications, causality was considered definite (n=1), highly probable (n=6), probable (n=5) or unlikely (n=1).
  - The Panel considers it **likely** (66–90% (subjective probability range)) that the cases of liver injury can be attributed to the consumption of commercial products labelled as containing *G. gummi-gutta* preparations.

LIVER TOXICITY – G. GUMMI-GUTTA (2)

- The nature of the reactions are consistent with an idiosyncratic form of herb-induced liver injury
  - may be specific to some individuals
  - characterised by unpredictability
  - lack of dose-dependency
  - variable latency periods
  - the failure to reproduce hepatotoxicity in experimental studies in animals.
- The specific composition of the commercial products which were consumed by the individuals having suffered from liver injury is mostly unknown.
- Some of these may have consisted of isolated (–)-HCA (sometimes marketed as *G. gummi-gutta* extract).

PRESUBMITTED QUESTION ON LIVER INJURY

- Does the fact that a preparation is linked to idiosyncratic liver injury necessarily imply a negative opinion for this product—as well as for future preparations with similar potential?



HAZARD IDENTIFICATION

Reproductive toxicity

REPRODUCTIVE TOXICITY OF – (–)-HCA AND *G. GUMMI-GUTTA (1)*

- **Consistent evidence for testicular toxicity of (-)-HCA (causative agent) in male rats**
  - Studies at low to moderate risk of bias on (-)-HCA and aqueous extracts from *G. gummi-gutta* pericarp (calcium salt and in free form).
  - Whether there is a difference in toxicity between the free acid form of (–)-HCA and (–)-HCA salts cannot be established based on the available evidence.
  - Effect primarily directed at Sertoli cells with mostly preserved Leydig-cell function, leading to secondary loss of germ cells at meiotic and post-meiotic stages (stage-specific losses).
  - The potential for underlying genotoxic damage in germ cells, particularly at the vulnerable meiotic and post-meiotic stages of spermatogenesis, cannot be excluded.

REPRODUCTIVE TOXICITY OF (–)-HCA AND *G. GUMMI-GUTTA* (2)

- Lowest NOAEL: 306 mg/kg bw/day (1-year study at moderate RoB), also supported by findings from a 182-day rat study.
- Insufficient data for exposure during pregnancy and lactation.
- Provided genotoxicity concern is ruled out, a safe dose for testicular toxicity could be set at 3.06 mg/kg bw per day (NOAEL÷100) for the general population except pregnant and lactating women.
- Studies investigating general toxicity of (-)-HCA and aqueous *G. gummi-gutta* preparations did not raise any other concerns.
- The safe dose may not protect susceptible individuals against idiosyncratic liver injury, for whom no safe level can be defined.

G. INDICA AND NON-AQUEOUS *G. GUMMI-GUTTA* PREPARATIONS

- For *G. indica* and for preparations other than aqueous *G. gummi-gutta* pericarp preparations, no toxicological studies were retrieved.
- The NOAEL is not applicable, as long as the safety is not demonstrated in an appropriate sub-chronic toxicity study addressing general toxicity and if no genotoxicity concerns exist.

Questions – reproductive and liver toxicity

EXPOSURE ASSESSMENT

OCCURRENCE DATA

- ***Food***
  - No data on culinary use of *G. gummi-gutta* or *G. indica* pericarps or arils

- ***Food supplements***
  - **Literature**: 36–289 mg (-)-HCA/capsule (*G. gummi-gutta*), 122–184 mg (-)-HCA/capsule (*G. indica*); measured contents often lower than labelled contents
  - **French market** (ANSES): average recommended daily (-)-HCA dose (analytical data): 412 mg (median: 203 mg, range: 21-2,000 mg n=42 measured data points)
  - **European market** (Mintel, 2020–2025, labelled content): 24–1,517 mg (-)-HCA/serving from *G. gummi-gutta*; mainly dried fruit; no supplements containing *G. indica* found

EXPOSURE TO (-)-HCA

From background diet

- Preparations of *G. gummi gutta* and *G. indica* pericarp or aril, are not part of the habitual diet of the European populations.
- May be present as condiments (but it is unknown if those are on the market).
- The dietary exposure to (–)-HCA through the background diet is expected to be **negligible** in the general European population.

Food supplements

- **Theoretical daily exposure to (-)-HCA from *G. gummi-gutta*-containing food supplements:** 412 mg per day in consumers of *G. gummi-gutta*-containing food supplements (no data for *G. indica*).
- This estimate is indicative and relies on the assumption that consumers follow the use levels recommended by the manufacturers.

Questions – exposure assessment

OVERALL CONCLUSIONS AND DATA GAPS

OVERALL CONCLUSIONS

- **Genotoxicity**: the available data are **insufficient** to confirm or exclude genotoxicity of (–)-HCA, *G. gummi-gutta* or *G. indica* aril or pericarp preparations.
- **Rodent studies**: (–)-HCA induced **testicular toxicity**; a contribution of genotoxic damage in germ cells cannot be excluded.
- **In humans:** products labelled as containing *G. gummi-gutta* have been linked to **idiosyncratic herb-induced liver injury**, with susceptible individuals currently not identifiable.
- Uncertainty remains as to whether (–)-HCA and *G. indica* preparations may also cause idiosyncratic liver injury.

OVERALL CONCLUSIONS

- A safe dose of (–)-HCA (isolated or in aqueous *G. gummi-gutta* pericarp extracts) could be established based on testicular toxicity data, if genotoxicity concerns are resolved, but it may not protect against idiosyncratic liver injury.
- No toxicological studies are available for **non-aqueous** preparations of *G. gummi-gutta*, for preparations of *G. gummi-gutta* **aril** and of *G. indica* **aril** or **pericarp**; therefore, no safe dose can be derived.
- Insufficient data to establish safe intake during pregnancy or lactation.

PRESUBMITTED QUESTIONS - CONCLUSIONS

- Are the identified safety concerns indicating that a safe intake level cannot currently be established due to insufficient data, rather than that the substances are definitively unsafe?
- Does the EFSA opinion distinguish between isolated HCA and HCA containing plant preparations?

DATA GAPS AND STEPWISE GENERATION OF DATA

1. Characterisation of plant preparations
2. Conditions of use and target population
3. Identification of substances of concern for genotoxicity other than (-)-HCA, guttiferones and garcinol
4. Component-based genotoxicity (re-run of the whole test battery)
5. For (-)-HCA, should in vitro test battery yield positive results: targeted germ cell genotoxicity assay, in addition to the in vivo somatic cell assays.
6. Genotoxicity testing of plant preparations (if component-based genotoxicity is ruled out)
7. 90-day repeated dose oral toxicity study for non-aqueous preparations of *G. gummi-gutta* pericarp as well as for all preparations from *G. gummi-gutta* aril and *G. indica* aril and pericarp, if genotoxicity is ruled out.
8. Standard developmental toxicity study, if products are intended to be used by pregnant and lactating women.
9. There is no experimental approach that can rule out the concern related to idiosyncratic liver injury

PRESUBMITTED QUESTIONS – DATA GAPS

- Should genotoxicity studies be conducted only on HCA, or also on the plant preparations as such?
- Should repeated-dose toxicity studies on the liver and reproductive system be conducted only on HCA, or also on the plant preparations as such?
- What relevance do animal studies have with respect to idiosyncratic effects in humans?
- Who shall carry out and finance the studies and which timeframe applies?

Questions – overall conclusions and data gaps

PRESUBMITTED QUESTIONS - RISK MANAGEMENT

- Does EFSA consider labelling with precautionary statements as a sufficient measure to mitigate the identified risks?
- What will happen with products which are currently on the market and contain HCA?
- Will all uses of HCA be covered by the same restrictions?
- Is it acceptable that individuals continue consuming *G. gummi-gutta* preparations?
- How likely or unlikely is it that *G. gummi-gutta* preparations will be prohibited or its use restricted?

Questions – generic

SAFETY ASSESSMENT OF HIBISCUS SABDARIFFA

CHARACTERISATION OF THE PLANT SPECIES

CHARACTERISATION OF THE PLANT SPECIES

H. sabdariffa

Edibility: Calyces, leaves, and seeds are used in foods; calyces are the most widely consumed, mainly in beverages, infusions, jams, and flavouring
Leaves and seeds are not expected to contain (+)-*allo*-HCA

Composition of the calyx:

- **Major organic acids:** (+)-*allo*-HCA (mainly as lactone, on average 266.7 mg/g calyx), citric, malic, tartaric acids

- **Other compounds:** Flavonoids and anthocyanins, phenolic acids, carotenoids, derivatives of (+)-*allo*-HCA and (+)-*allo*-HCAL

CHARACTERISATION IN THE TOXICOLOGICAL STUDIES

Variability and uncertainty in constituent characterisation

- In most publication, the origin, the authentication and the way in which the extracts were prepared were well described.
- However, characterisation of the extract in terms of individual constituents, including (+)-*allo*-HCA and (+)-*allo*-HCAL, is generally missing.
- Amounts of source material and solvent used, extraction methods and concentration steps differed across studies (mostly aqueous extracts) → limits dose comparison.
- The Panel used “calyx equivalents” to approximate dose ranking, acknowledging that this method relies on assumptions and offers limited precision.
- Reporting of administered doses was often unclear in terms of whether the referred to extract weight or calyx/petal weight, except for one publication in which this was specified.

PRESUBMITTED QUESTIONS ON CHARACTERISATOIN

- How does variability in the different HCA forms (free acid, lactone or salt forms) in a plant preparation affect risk assessment?
- Were the analytical methods applied to quantify HCA in plant matrices reliable?
- Which analytical methods does EFSA recommend?

Questions – characterisation

HAZARD IDENTIFICATION

Genotoxicity

GENOTOXICITY OF (+)-*ALLO*-HCA AND *H. SABDARIFFA* CALYX

- ***(+)-allo-HCA:*** No data. It is unclear whether genotoxicity findings for (–)-HCA can be extrapolated to (+)-*allo*-HCA.
- ***H. sabdariffa calyx/flowers***
  - 2 in vitro bacterial reverse mutation test (Klimisch score 3) - inconclusive
  - 1 in vivo micronucleus test in rats (Klimisch score 3) - inconclusive
  - 1 in vivo chromosomal aberration test in rats (Klimisch score 3) - inconclusive
  - 1 in vivo micronucleus test (Klimisch score 2) – inconclusive for pregnant rats but positive in the offspring (indicative of potential transplacental genotoxicity (chromosomal damage))

STUDY BY TOBANCHE MIRELES ET AL. (2025) (1)

In vivo micronucleus test in peripheral blood

- **Extract type:** Hydroalcoholic extract from H. sabdariffa calyces
- **Species: Wistar rats**
- **Dosing**: 0, 500, 1000, 2000 mg/kg bw/day (transplacental exposure) during gestional days 16-20

In dams, the extract did not induce micronucleated polychromatic erythrocytes (MNPCE).

In newborns,

- the frequency of MNPCE was increased at all dose levels compared with controls
- only one dose (500 mg/kg) showed increased micronucleated erythrocytes (MNE)
- Increased malondialdehyde (MDA, a marker of oxidative stress) levels were detected in liver, kidneys, brain, and muscle tissues at 500 and 2,000 mg/kg

STUDY BY TOBANCHE MIRELES ET AL. (2025) (2)

- Methodological limitations (low statistical power, restricted exposure window, and absence of long-term follow-up data) but its findings retain biological relevance as they show transplacental genotoxicity

→ Klimisch score of 2

- **Limited relevance of the study results**

These findings on **possible transplacental genotoxicity** require confirmation in independent, adequately designed studies

GENOTOXICITY OF (+)-*ALLO*-HCA AND *H. SABDARIFFA* CALYX

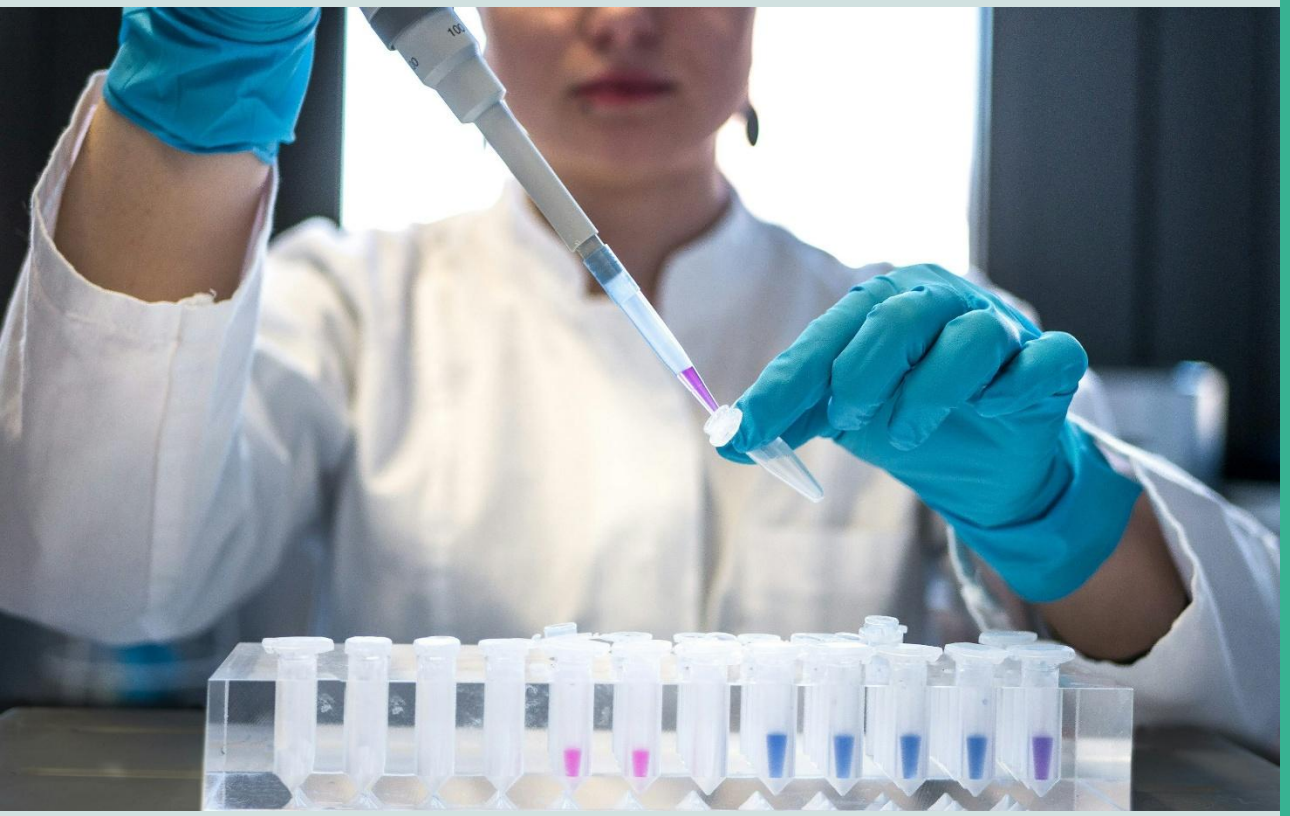
EFSA conclusion(s):

The available data are insufficient to confirm or exclude genotoxicity of (+)-*allo*-HCA or *H. sabdariffa* calyx/petal preparations; H. sabdariffa preparations may exert transplacental genotoxicity but this needs to be confirmed in an additional study

QUESTIONS - STUDY BY TOBANCHE MIRELES ET AL. (2025) (1)

- EFSA's request for transplacental micronucleus study is basing on a single published study that EFSA rates as "limited validity". This is a non-standard study type that has never been validated, no historical data exist and it is not available for testing at any CRO. Establishing this in a GLP context would require a large number of animal experiments to show that this method works and that the results are reliable, in addition to the actual study. Looking into Mireles 2025 in more detail seems strongly question such a conclusion.
- Given that the extract tested has a highly acidic pH. This indicates that the animals were exposed to extreme levels of acids, which is known from chemical testing to lead to artifactual results. Has this been considered in the draft opinion?
- Increased erythropoiesis, as observed in the study, is a known confounder of micronucleus testing and has been shown to lead to artefactual effects (at a minimum, would be considered as an indirect, thresholded MoA). Has EFSA considered this in the context of the study outcome?
- No HCA was found in the hibiscus extract tested. Why is this study considered relevant?

Questions – genotoxicity



HAZARD IDENTIFICATION

General toxicity

GENERAL TOXICITY OF H. SABDARIFFA – KIDNEY AND LIVER TOXICITY

- **Animal studies (mostly tier 3, mainly on aqueous extracts)**
  - Consistent adverse effect reported affecting **kidney biomarkers** (↑ urea/BUN and/or ↑ creatinine concentrations and changes in electrolyte concentrations) and **kidney histopathology** (vascular congestion/haemorrhage, glomerular changes, Bowman's space alterations, tubular lesions, fibrosis)
  - Several studies showed **increases in liver enzymes** and, in some cases, **liver histopathological changes** (vacuolation, inflammation, necrosis/steatosis-like features)
- **Human studies**
  - Five RCTs showed no effects on kidney or liver biomarkers, but sample sizes were small and study limitations prevent conclusions

GENERAL TOXICITY OF H. SABDARIFFA – OTHER ADVERSE EFFECTS

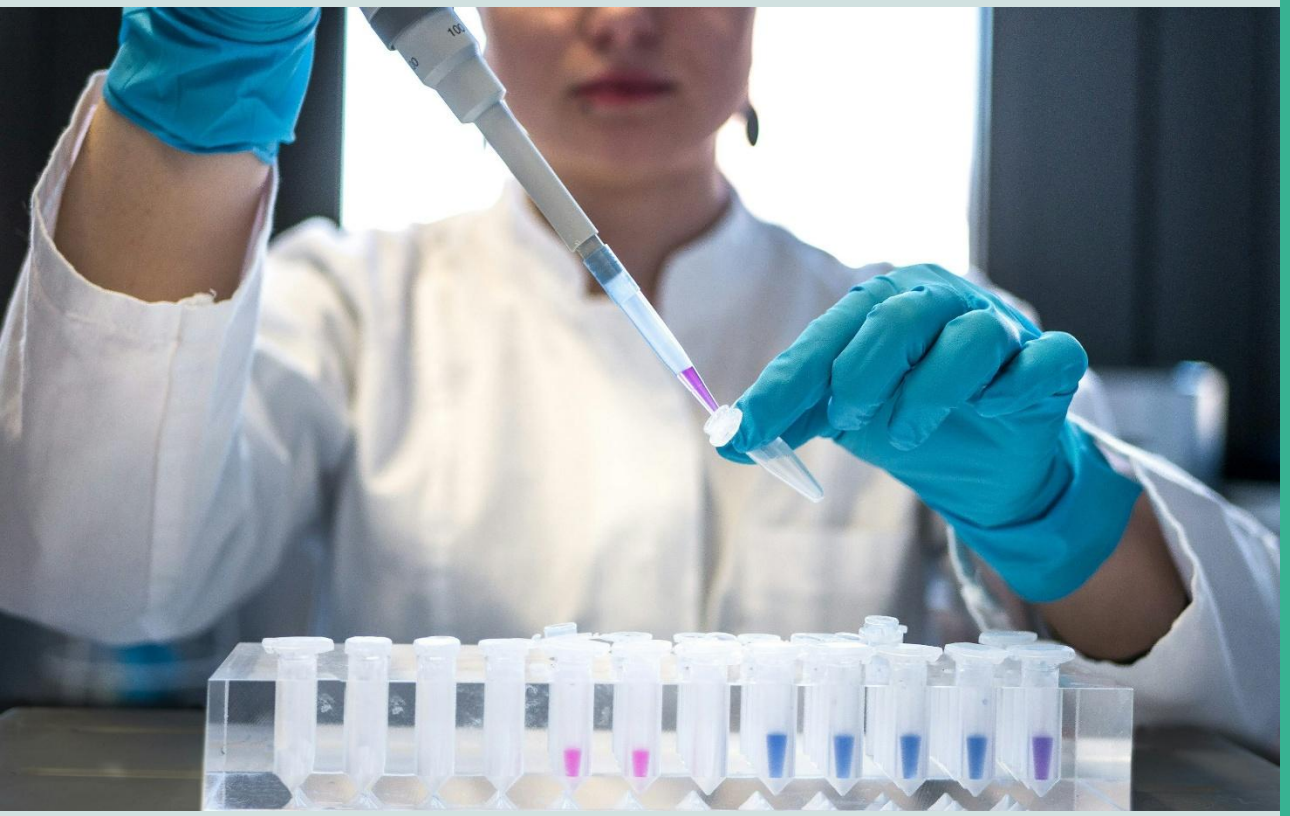
Other animal data

- Some rodent studies reported adverse effects on body weight, and one high-dose rat study observed diarrhoea accompanied by marked growth effects and mortality. However, other studies have not shown the same effects.
- Cardiovascular effects (e.g., increased blood pressure or vascular/heart changes) were reported in a few high-RoB studies in rats and rabbits.

EFSA conclusion(s):

The evidence does not allow identification of a LOAEL or NOAEL for kidney and liver toxicity, owing to uncertainty in the administered doses and the wide dose range at which effects occurred.

Questions – general toxcitiy



HAZARD IDENTIFICATION

Reproductive and developmental toxicity

REPRODUCTIVE + DEVELOPMENTAL TOXICITY OF *H. SABDARIFFA*

- **Consistent testicular toxicity observed across studies**
  - **Reported lesions** included seminiferous tubule degeneration, disrupted/arrested germ-cell development, Sertoli/myoid cell injury, germ-cell exfoliation and reduced epididymal sperm number; some studies also noted impaired sperm motility/viability and hormone changes
  - **Gestational/lactational exposure** led to reduced epididymal sperm counts in male offspring, and delayed puberty onset in female offspring.
  - **Dose:** One study clearly reported on the dose in terms of calyx equivalents administered to mice (200 mg/kg bw per day calyx equivalent) associated with adverse effects.
  - For humans this would be equivalent to approx. 14 g/day of calyx used for an infusion.
  - Applying appropriate safety factors would result in safe dose levels for humans that are lower than doses usually encountered in human consumption scenarios.
  - In addition, no NOAEL or lowest LOAEL can be established from the available data.

REPRODUCTIVE + DEVELOPMENTAL TOXICITY OF *H. SABDARIFFA*

- **Potential mechanisms:**
  - endocrine disruption and/or germ cell mutagenicity
  - (+)-*allo*-HCA unlikely to be the sole causative agent
    - 200 mg calyx (see previous slide) are expected to contain around 53 mg (+)-*allo*-HCA -> around 10 times lower than concentrations of (-)-HCA which caused an effect on the testes
    - Adverse effects have also been reported with leaves and seeds (not expected to contain (+)-*allo*-HCA)
  - Anthocyanins have also been proposed as endocrine-disrupting agents, but their negligible presence in leaves and seeds makes them also unlikely candidates.

EFSA conclusion(s):

- **Testicular toxicity** has been observed with an infusion at a dose of 200 mg/kg bw per day of calyx equivalents in mice
- The evidence is insufficient to identify a NOAEL
- Concerns for a **delayed onset in puberty** of female rats following transplacental exposure also exist

Questions – reproductive and developmental toxcitiy

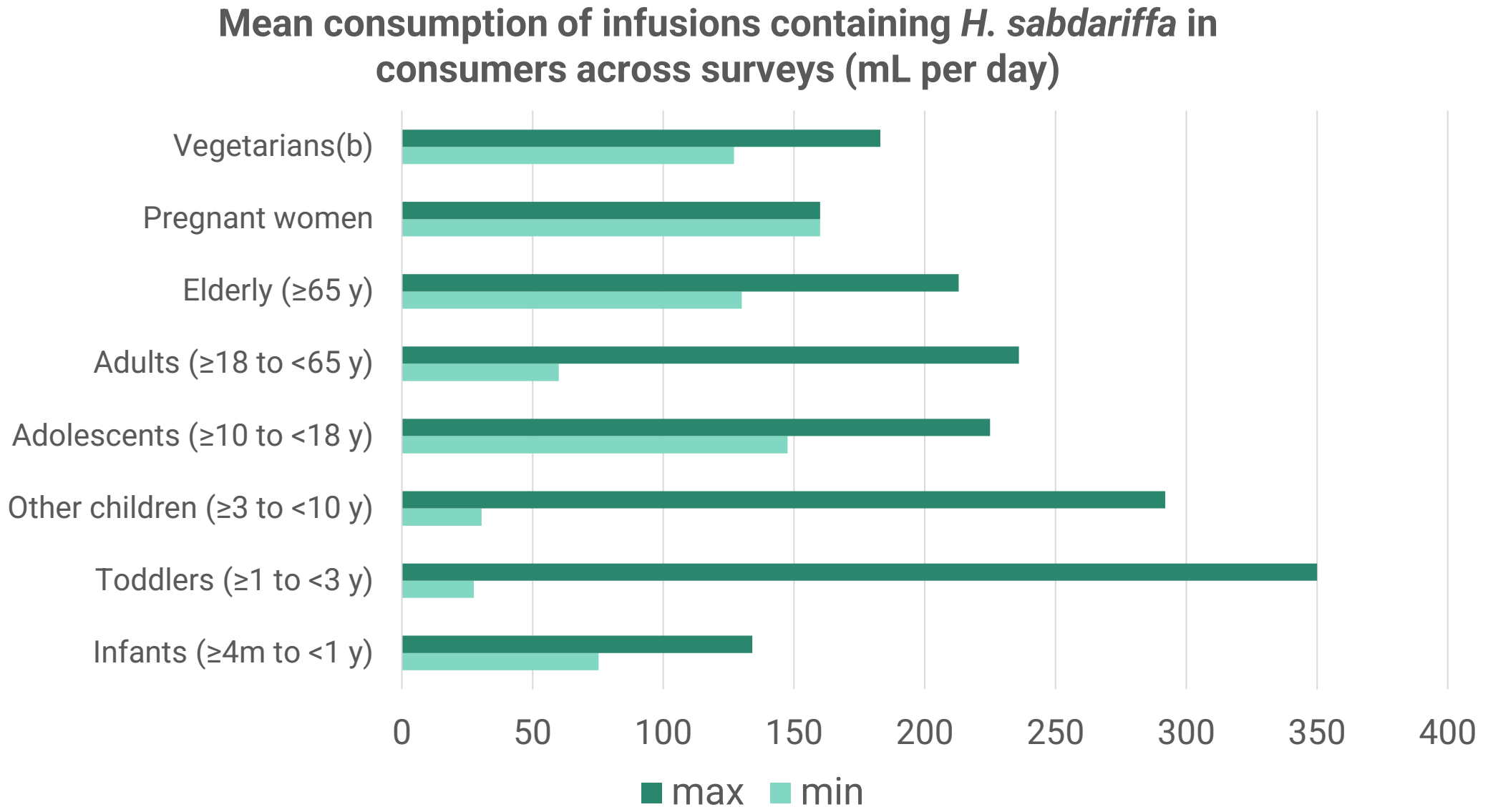
EXPOSURE ASSESSMENT

OCCURRENCE DATA

- ***Food***
  - **Literature**: 266.7 mg (+)-allo-HCA/g calyx (measured content, average of the mean concentrations reported in 3 studies)
  - **Mintel database**: Most common food containing hibiscus: infusions, fermented drinks, ready-to-drink infusions, baby juice and drinks

- ***Food supplements***
  - **Mintel database**: 30 – 500 mg *H. sabdariffa* per day (labelled content)
  - The content of (+)-*allo*-HCA and (+)-*allo*-HCAL was not reported on the labels

CONSUMPTION OF INFUSIONS CONTAINING *H. SABDARIFFA*



PRESUBMITTED QUESTIONS - EXPOSURE ASSESSMENT

- Is the data from EFSA´s Comprehensive Food Consumption Database which was used to derive intake amounts of infusions containing hibiscus publicly available?
- Which exposure hierarchy level of EFSA´s Comprehensive Food Consumption Database and category within this level was used to derive intake amounts of herbal infusions containing hibiscus (= blends) for the different population groups?
- How were the consumption levels shown in table B2 be derived.

Questions – exposure assessment

OVERALL CONCLUSIONS AND DATA GAPS

OVERALL CONCLUSIONS

- Insufficient data to confirm or exclude genotoxicity of (+)-*allo*-HCA or *H. sabdariffa* calyx/petal preparations; *H. sabdariffa* preparations may exert **transplacental genotoxicity** but this needs to be confirmed in an additional study;
- *H. sabdariffa* calyx/petal preparations induced **testicular, kidney and liver toxicity** in experimental rodent studies; concerns for a delayed onset in puberty of female rats following transplacental exposure also exist;
- **Testicular toxicity** has been observed with an infusion at a dose of 200 mg/kg bw per day of calyx equivalents in mice;
- The evidence is insufficient to identify a NOAEL; a dose which is associated with kidney and liver toxicity can also not be identified;
- The currently available data are insufficient to establish a safe intake for humans for (+)-*allo*-HCA or *H. sabdariffa* calyx/petal preparations.

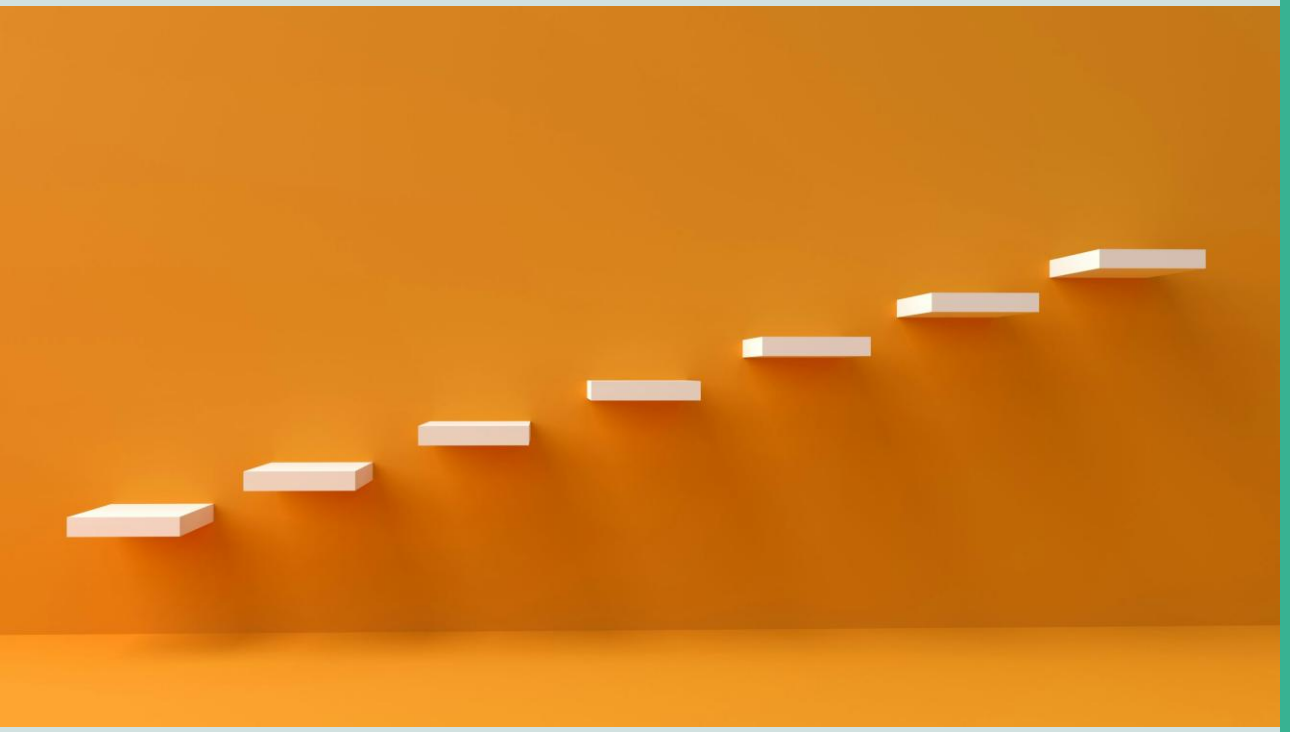
DATA GAPS AND STEPWISE GENERATION OF DATA

1. Characterisation of plant preparations, conditions of use and target population
2. Transplacental germ cell mutagenicity assay for *H. sabdariffa* calyx preparation
3. If transplacental germ cell mutagenicity is ruled out, dedicated germ cell assays are required to address the potential for heritable genotoxic effects.
4. If ruled out, identification of substances of concern for genotoxicity in the plant preparation other than (+)-*allo*-HCA
5. Component-based genotoxicity (re-run of the whole test battery)
6. Genotoxicity testing of plant preparations (if component-based genotoxicity is ruled out)
7. If genotoxicity is ruled out, studies need to be conducted which allow to identify safe intake levels for testicular, renal, and hepatic toxicity.
8. Concerns that rodent studies may replicate existing findings and yield final safe human intake values considerably below the range of current human exposures.
9. Only alternative is a well-conducted RCT in humans (at least one spermatogenic cycle, hormonal and sperm motility assessments, multiple dose levels based on typical and high consumption estimates, liverr and kidney function markers).

PRESUBMITTED QUESTIONS – TRADITIONAL USE

- Could EFSA please clarify how evidence of historical and very widespread traditional consumption of Hibiscus sabdariffa in non-EU regions has been considered in the safety assessment process and determination of safe use levels?
- In light of the extensive history of use, are there epidemiological data available documenting an association between the consumption of hibiscus tea and an increased incidence of hepatotoxic effects or other adverse effects in exposed populations.
- Given the long-standing exposure, does the absence of evidence in this regard not indicate that the hypothesis of a genuine risk of hepatotoxicity associated with the consumption of this beverage is poorly supported?

Questions – overall conclusions and data gaps



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.

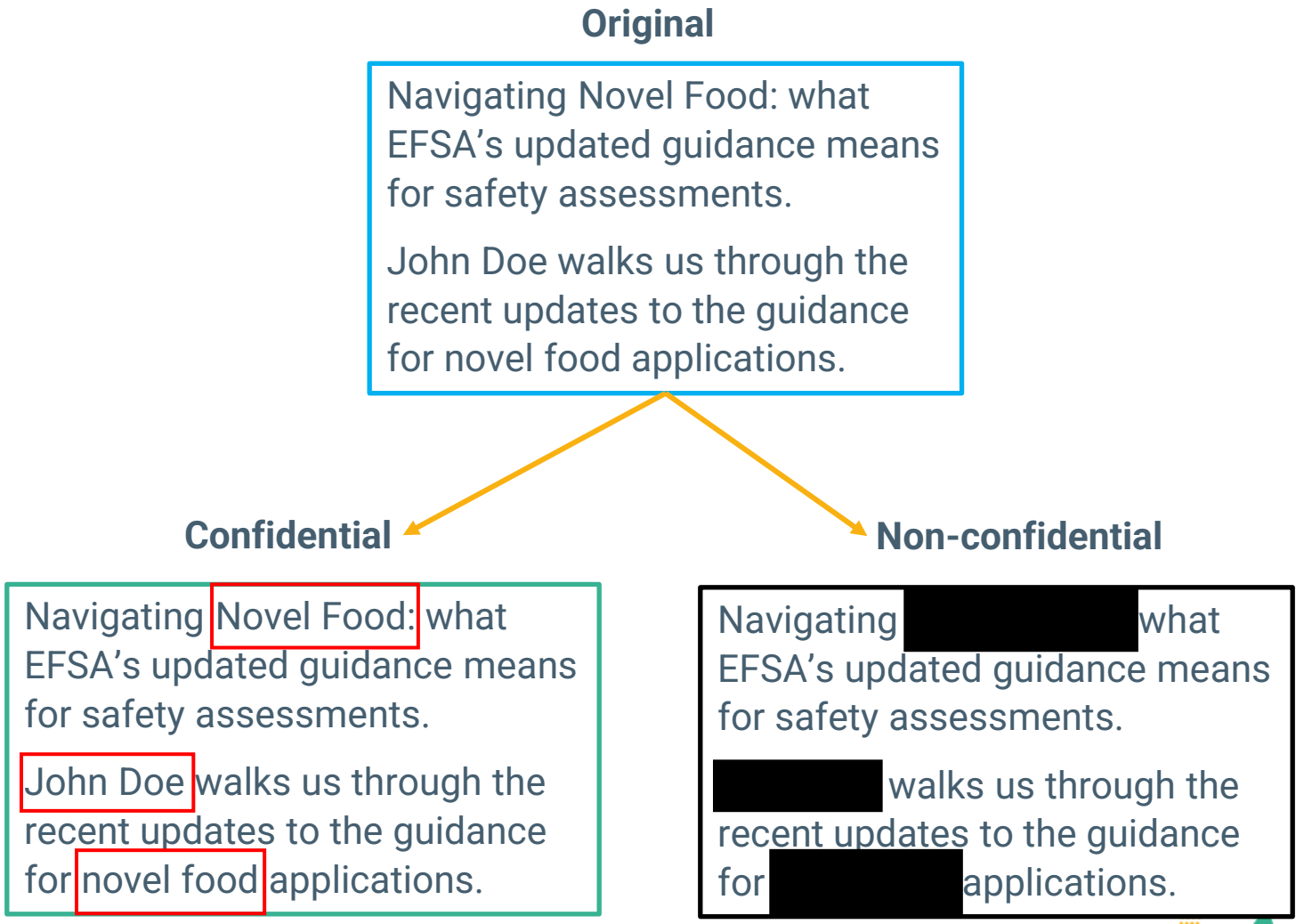
Regulation (EU) 307/2012 sets the rules for the submission

- 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

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

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