Risikobewertung von „Botanicals und „botanical preparations“ – das Vorgehen der EFSA

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Definition der Begriffe „botanical“ und „botanical preparation“

- Der Begriff “botanicals” umfasst Pflanzen, Pflanzenteile, Algen, Pilze, Flechten im Ganzen, zerteilt oder zerschnitten.

- Der Begriff “botanical preparations”umfasst alle Zubereitungen von botanicals , die durch verschiedenartige Prozesse gewonnen wurden, wie Zerdrücken, Quetschen, Extraktion, Fraktionierung, Destillation, Konzentrieren, Trocknen und Fermentieren.

Lebensmittel und Lebensmittelkomponenten botanischen Ursprungs

Aufnahme intendiert:

Traditionelle Lebensmittel
(verarbeitet/nicht-verarbeitet)
aus Pflanzen, z.B. Zerealien, pflanzliche Fette, Gemüse, Früchte, Kaffee, Tee, Kräuter, Gewürze

Novel foods
z.B. Nonisaft aus *Morinda citrifolia*

Gentechnisch veränderte Lebensmittel
z.B. GM Mais

Extrahierte, selektiv angereicherte oder isolierte Komponenten

Aromen
e.g. capsicum oleoresin

Nahrungs-ergänzungsmittel & Kräutertees
z.B. Grüner Tee

Lebensmittel-zusatzstoffe
z.B. Natürliche Pflanzenfarbstoffe

Aufnahme nicht intendiert:

botanische Kontaminanten
z.B. Opiumalkaloide in Mohnsamen

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Relevante EFSA-Dokumente und EFSA-Guidances

- **Discussion Paper on Botanicals and Botanical Preparations widely used as food supplements and related products: Coherent and Comprehensive Risk Assessment and Consumer Information Approaches (Scientific Committee 2004)**
- **Guidance on Safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements (Scientific Committee 2009)**
- **Compendium of Botanicals reported to contain naturally occuring substances of possible concern for human health when used in food and food supplements (EFSA, 2012)**

Relevante EFSA-Dokumente und EFSA-Guidances

- Scientific Opinion on a Qualified Presumption of Safety (QPS) approach for the safety assessment of botanicals and botanical preparations (Scientific Committee 2014)
- Opinion of the Scientific Committee on a request from EFSA related to A Harmonised Approach for Risk Assessment of Substances Which are both Genotoxic and Carcinogenic (2005, 2012)
- Guidance on the use of the Threshold of Toxicological Concern approach in food safety assessment (Draft), EFSA 2019

Risikobewertung nach Guidance Document (2009)

Hazardidentifizierung und Charakterisierung

- **Technische Daten (Identität, Spezifikation)**
- **ADME**
- **Toxizitätsdaten**

Charakterisierung der Exposition

- Daten zur maximaler und mittlere Aufnahme
- Information zu Gebrauch/Verbrauch

Charakterisierung des Risikos

Besonderheiten bei der Risikobewertung von Pflanzenextrakten

Technische Daten (Identität, Spezifikationen, Herstellung)

1. Das Ausgangsmaterial kann eine **komplexe Mischung** darstellen. Unerwünschte Substanzen können durch den Prozess der Extraktion angereichert werden.
2. Die **Reinheit der interessierenden Substanz ist oft sehr niedrig**, die weiteren Substanzen in der Mischung sind nicht charakterisiert *(z.B.. Farbe Lutein (E 161b): Gehalt an Farbstoff nicht weniger als 4% berechnet als Lutein)*
3. Eine botanical preparation mit gleichem Namen kann unterschiedliche **Extrakte enthalten wegen**
   - unterschiedlichen Ausgangsmaterials (Spezies, Varietät, Teile, geographischer Ursprung, Ernte) *(Beispiel: Ausgangsmaterial für Lutein E 161b: essbare Früchte und Pflanzen, Gras, Luzerne)),*
   - unterschiedlicher Lösemittel, Extraktionsmethoden
4. Oft besteht **keine Standardisierung** des Ausgangsmaterials und des Herstellungsprozesses

Besonderheiten bei der Risikobewertung von Pflanzenextrakten

Toxizität

1. Die aktive Substanz in einer botanical preparation kann in einer Mischung mit **chemisch ähnlichen Substanzen** vorkommen, die
   - sich als Agonisten oder Antagonisten bei Rezeptor-vermittelten Reaktionen verhalten *(z.B. Codeine und Morphine als Agonisten am μ Opiate-Rezeptor)*
   - metabolische Interaktionen (Induktion, Hemmung) hervorrufen können *(Beispiel: langsamere Elimination von EGCG, einer Komponente in grünem Tee, wenn als isolierte chemische Substanz untersucht)*
2. Idealerweise sollte die Bewertung eines Extraktes anhand **toxikologischer Daten von einem identischen Extrakt** vorgenommen werden *(gleich in Ausgangsmaterial, Herstellungsprozess, und Spezifikation). Ansonsten Frage des read across.*

Interaktionen zwischen den Komponenten eines Gemischs (sog. Matrixeffekte) können verstärkende oder abschwächende Wirkung haben.

Botanical food components
- Beispiele für publizierte Bewertungen-

- **Food supplements**
- Green tea extracts
- Isoflavones from soybeans & red clover
- Yohimbe bark
- Ephedra herb
- **Food Additives**
- Rosemary extracts
- Curcumin (E100)
- Mixed carotenes (E160a i)
- Lutein (E161b)

Food contaminants

- Opium alkaloids in poppy seeds
- Pyrrolizidine alkaloids
- Ergot alkaloids in grain products
- Tropane alkaloids in grain products

Anforderungen entsprechend Guidance for submission for food additive evaluations

TIER 1

- Absorption
- Genotoxicity
  - In vitro testing
- Toxicity
  - Extended 90-day toxicity study

Triggers for considering Tier 2

- *Systemic availability*
- *Toxicity in the 90-day study*
- *Genotoxicity in vitro*

TIER 2

- ADME
  - Single dose
- Genotoxicity
  - In vivo testing
- Toxicity (stand-alone or combined)
  - Chronic toxicity
  - Carcinogenicity
- Reproductive & Developmental toxicity
  - EOGRTS
  - Prenatal developmental toxicity

Triggers for considering Tier 3

- *Bioaccumulation*
- *Positive in vivo genotoxicity*
- *Chronic toxicity/carcinogenicity*
- *Reproductive & Developmental toxicity*

TIER 3

- ADME
  - Repeated dose, volunteer studies
- Carcinogenicity
  - Mode of action
- Reproductive & Developmental toxicity
- Specialised studies
  e.g. immunotoxicity, neurotoxicity, endocrine activity, mode of action

Vorgehen der Bewertung

- Bewertung vorhandener Daten in **Level A**
- Wenn nicht ausreichend: Nachforderungen
- Kondition: „In the case of a botanical ingredient whose anticipated intake is significantly higher than the estimated historical intake level, or for which the historical intake level cannot be assessed, additional data should be provided for the safety assessment, as described in the following sections."

➢ **Die Bewertung der nachgeforderten Studien erfolgt in Level B**

Vorgehen der Bewertung von Pflanzenextrakten

- **Level A:** Bewertung aller existierender Daten

Technische Daten: Identität des Ausgangsmaterials, Herstellungsprozess, chemische Zusammensetzung, Spezfikationen, Stabilität, Uses and use levels, vorhandene Bewertungen

Exposition: Daten zu maximaler und mittlere Aufnahme, Information zu Gebrauch/Verbrauch Vergleich mit der historischen Exposition

Vorgehen der Bewertung in 2 Schritten (Level A und Level B)

Toxizität

- *Toxicokinetics including metabolism*
- *Genotoxicity testing* (gene and chromosome levels)

  in vitro: z.B. Ames test, Chromosomalabb test, Mironucleus test

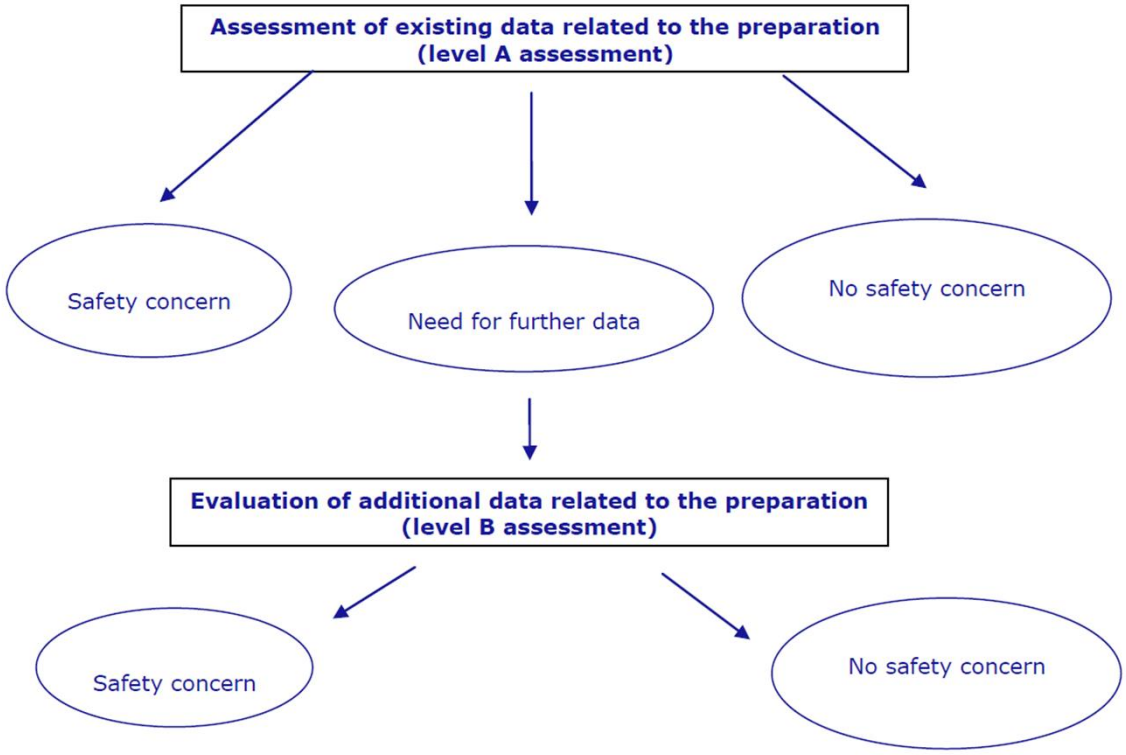
  in vivo: flexibel
- *Subchronic toxicity testing* (oral, via diet)

- *Other studies*

- Depending on the outcome of the genotoxicity and subchronic toxicity studies, or other specific relevant information,

  further studies may be required (e.g. reproductive toxicity, developmental toxicity, neurotoxicity, immunotoxicity, chronic toxicity/carcinogenicity).

Ergebnis der Bewertung



Presumption of safety approach

- A conceptual framework for safety assessment was advocated, in which botanicals or botanical preparations for which an adequate body of knowledge exists could benefit from a “presumption of safety” without any need for further testing (first level of the framework).

➢ **Conditions**

- Available data would allow to conclude that exposure to known levels of the botanical ingredient has occurred in large population groups for many years without reported adverse effects.
- That not only use levels but also chemotypes of botanicals and the chemical composition of the botanical preparations should be in line with historically used ones
- The objective is of not significantly increasing exposures beyond the levels linked to the safe history of use

Beispiel
Risikobewertung von Yohimbe als Nahrungsergänzungsmittel

* Data search for the botanical (preparation) and its components

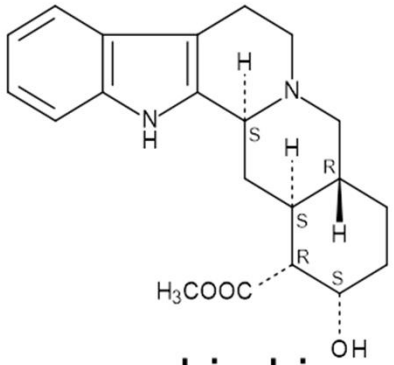
- 1. **Technical data***
- - Identity of the source material
- - Manufacturing process
- - Chemical composition and specifications
- - Uses in food supplements and common foods
- - Uses in medicinal products and associations with adverse effects
- - Existing assessments and authorisations
- 2. **Exposure data***
- - Exposure through food supplements
- - Exposure through common food (incl. historical intake levels) and medical use

3. **Toxicological data***

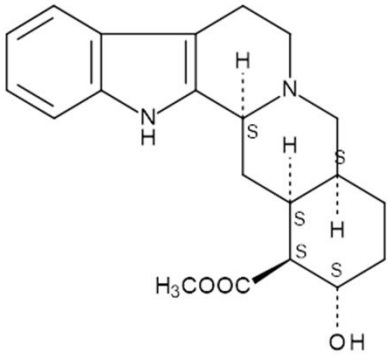
- - Studies on toxicokinetics and toxicity (e.g. genotoxicity, short- and long-term, reproductive and developmental toxicity, carcinogenicity)
- - Human data (case reports, clinical and epidemiological studies)

*in Arzneimitteln

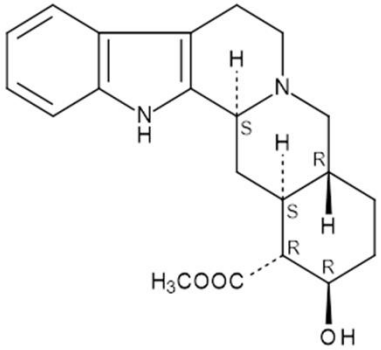
Relevante Komponenten in Yohimberinde



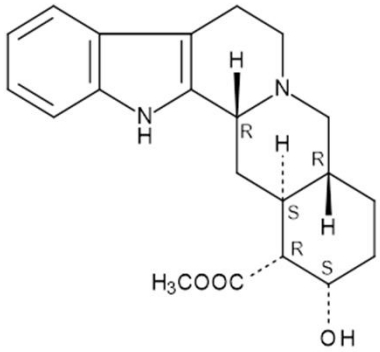
yohimbine*



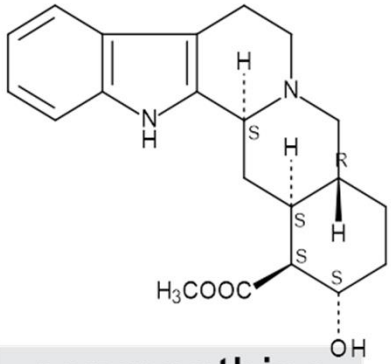
α-yohimbine



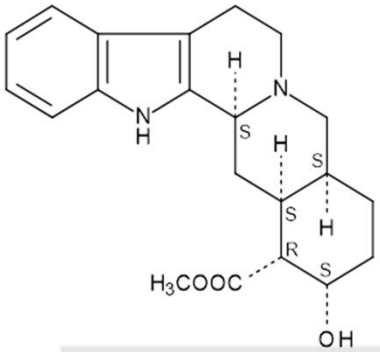
β-yohimbine



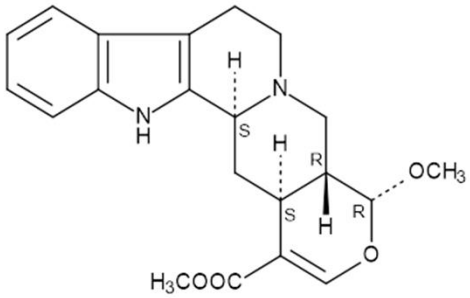
pseudoyohimbine



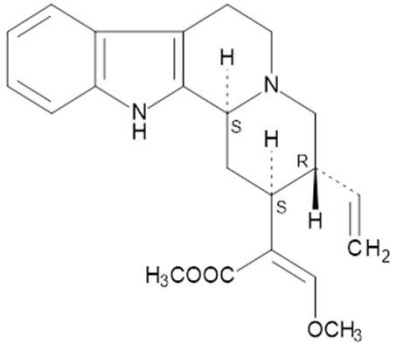
corynanthine



alloyohimbine



raubasine*
(ajmalicine)



corynantheine

Expositionsbewertung – yohimbe bark and dietary supplements

Table 3: Yohimbine in yohimbe bark and dietary supplements

Dietary supplement type	Yohimbine (analytically determined)						Max No of suggested servings per day	Content of yohimbe bark, extract or yohimbine as reported in the label (mg/serving)	Estimated exposure to yohimbine (mg/ kg bw/day)[a]		Reference
	mg/g or mg/ml			mg/serving					Minimum	Maximum	
AHP[b] bark	13.95	±	0.1	-		-	Not available	-	-		Sun and Chen, 2012
Capsule	0.96	±	0.0	0.52	±	0.05	Not available	-	0.01	0.03	Sun and Chen, 2012
	16.54	±	0.2	9.93	±	0.11	Not available	500	0.28	0.57	Sun and Chen, 2012
	5.49	±	0.1	4.14	±	0.06	Not available	750	0.12	0.24	Sun and Chen, 2012
	1.78	±	0.0	1.59	±	0.09	Not available	600	0.05	0.09	Sun and Chen, 2012
		NA[c]		0.50	±	0.08	4	150 (Yohimbe)	0.03		Zanolari et al., 2003
	0.88	±	0.0	1.09	±	0.04	Not available	1200	0.03	0.06	Sun and Chen, 2012
	8.89	±	0.1	5.33	±	0.02	Not available	400	0.15	0.30	Sun and Chen, 2012
		NA[c]		9.52	±	0.52	2	250 (extract)/5 (2 %)	0.27		Zanolari et al., 2003
	12.67	±	0.0	3.91	±	0.00	Not available	-	0.11	0.22	Sun and Chen, 2012
		NA[c]		0.59	±	0.10	2	125 (bark)	0.02		Zanolari et al., 2003
		NA[c]		0.88	±	0.16	4	Not specified	0.05		Zanolari et al., 2003
Liquid	2.4	±	0.0	2.40	±	0.01	Not available	1000	0.10		Sun and Chen, 2012
	0.14	±	0.0	0.14	±	0.01	Not available	333	0.01		Sun and Chen, 2012
		NA[c]		0.99	±	0.18	3	NA[c]	0.04		Zanolari et al., 2003
Mass				2.33	±	0.06	5	Not specified	0.17		Zanolari et al., 2003
Tablet	0.54	±	0.0	0.68	±	0.05	Not available)	800	0.02	0.04	Sun and Chen, 2012
	0.15	±	0.0	0.65	±	0.00	Not available	250	0.02	0.04	Sun and Chen, 2012
		NA[c]		5.80	±	1.10	4	200 (extract)/4 (2 %)	0.33		Zanolari et al., 2003
		NA[c]		1.24	±	0.14	2	270 (extract)/2.7	0.04		Zanolari et al., 2003
	7.46	±	0.0	18.8	±	0.12	Not available	750	0.54	1.07	Sun and Chen, 2012
	0.51	±	0.2	0.7	±	0.00	Not available	100	0.02		Sun and Chen, 2012
		NA[c]		1.21	±	0.18	2	125 (extract)/2.5 (2 %)	0.03		Zanolari et al., 2003
		NA[c]		0.53	±	0.00	3	250 (extract)/5 (2 %)	0.02		Zanolari et al., 2003
		NA[c]		3.15	±	0.34	4	NA[c]	0.18		Zanolari et al., 2003

a): minimum and maximum exposure to yohimbine have been estimated by multiplying the yohimbine content per serving, as analysed, by the minimum and maximum number of suggested servings per day for the same dietary supplement type, respectively. A body weight of 70 kg has been used to express the exposure results in mg/day per kg body weight

(b): American Herbal Pharmacopoeia

(c): Not available

Expositionsbewertung – medicinal products

Table 4: Summary of information reported for the authorisation medicinal products for oral use containing yohimbine or raubasine as single ingredient.

Substance	Posology [(a)]		Therapeutic indications [(a)]	Contraindications and warnings [(a)]	Adverse effects [(a)]
	Single dose range	Daily dose range			
yohimbine HCl	5 mg (may be increased to 10 mg)	10-15 mg (may be increased to 30 mg) for at least 8 weeks	(psychogenic) erectile dysfunction; male climacterium or Disorders of the sexual potency, e.g. of the potentia coeundi; libido disorders; reduced reflex agitation of the lumbosacral mark; general and sexual-specific symptoms of the male climacterium. or supportive treatment of mild to moderate erectile dysfunction in the context of other therapeutic actions	Hypersensitivity to the active ingredient. Cardiac disorders (especially heart disease, tachycardic arrhythmia). Hypertension, hypotension. Greatly impaired kidney or liver function. Ulcer (stomach or intestine). Glaucoma. Psychiatric disorders, particularly mood disorders and anxiety. Concomitant use of central nervous acting drugs. There exist no adequate clinical experiences with treatment in women. It is also not possible to determine effects on a fetus during pregnancy. Not be used in women. Not indicated for treatment in patients less than 18 years. Warning: the oral intake of 200 mg yohimbine hydrochloride led to intoxication symptoms (e.g. with weakness, general paresthesia, loss of coordination and memory performance, epileptic seizures, headaches with dizziness, tremor, palpitations and anxiety, chest pain) The usage may lead to positive results in doping tests.	*Cardiac disorders* Uncommon: increase of blood pressure and pulse rate, palpitation Very rare: hypotension *Nervous system disorders* Common: headache Uncommon: dizziness Very rare: tremor *Respiratory, thoracic and mediastinal disorders* Very rare: bronchospasm *Gastrointestinal disorders* Common: nausea Uncommon: vomiting, anorexia, gastric complaints, diarrhoea *Renal and urinary disorders* Common: increased urge Very rare: dysuria, decreased urge, genital pains *Skin and subcutaneous tissue disorders* Uncommon: flush Very rare: exanthema *General disorders* Uncommon: sweating, shivering *Immune system disorders* Uncommon: allergic reactions
raubasine	10-20 mg	20-60 mg	Adjuvant in the treatment of peripheral arterial disorders	Hypersensitivity to the active substance. Serious heart disease. Haemorrhagic syndrome or intracranial hypertension. Uncompensated heart failure, valvular stenosis, significant reduction of the pulmonary circulatory bed, glaucoma. First three months of pregnancy. During or within two weeks after treatment with MAOIs	Rare: dizziness, hypotension, sweating, flushing Occasionally: appearance of confusion, tachycardia, nausea, allergic reactions In the case of heart disease or other general disorders may require discontinuation of therapy.

(a): As reported in the Summary of Product Characteristics of the authorised medicinal products.

Vergleich Exposition via Nahrungsergänzungsmittel mit traditioneller/historischer Exposition

Exposition via Nahrungsergänzungsmittel

- Maximale tägliche Exposition: 1,07 mg/kg bw/d

Exposition via Arzneimittel (traditionell/historisch)

- 0,14 -0,43 mg/kg bw/d

Vorhandene Daten

ADME No ADME data on yohimbine alkaloids. Yohimbine given as single substance had ADME data indicating variable bioavailability (7-87%). Metabolism to 11-hydroxy-yohimbine by CYP 2D6. Low renal excretion of yohimbine and its metabolites. For radioactive labelled raubasine the urinary excretion was 29% and 24% were found in the feces.

Toxizität Subchronic toxicity: **No data** for yohimbe bark, its preparations and its alkaloids are available

Genotoxizität: no *in vitro* data are available for yohimbe bark or its preparations; one *in vivo* study had major flaws

Chronic toxicity: No data are available for yohimbe bark or its preparations. A poorly reported study in rats on raubasine (24 weeks, =,5,10,20, and 40 mg/kg bw/d) (1958) gave no indications for chronic intoxication.

Reproductive and developmental toxicity: Study in mice (2006) with a suspension of y. b. powder (no y. content given) resulted in an unclear pattern for male reproduction (with non-classical endpoints). **No data on developmental toxicity.**

Schlussfolgerung

The Panel concluded that according to the Guidance on safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements yohimbe bark and its preparations belong to the category of botanicals/botanical preparations for which the available data are not sufficient to conclude on their safety or to establish a health based guidance value.

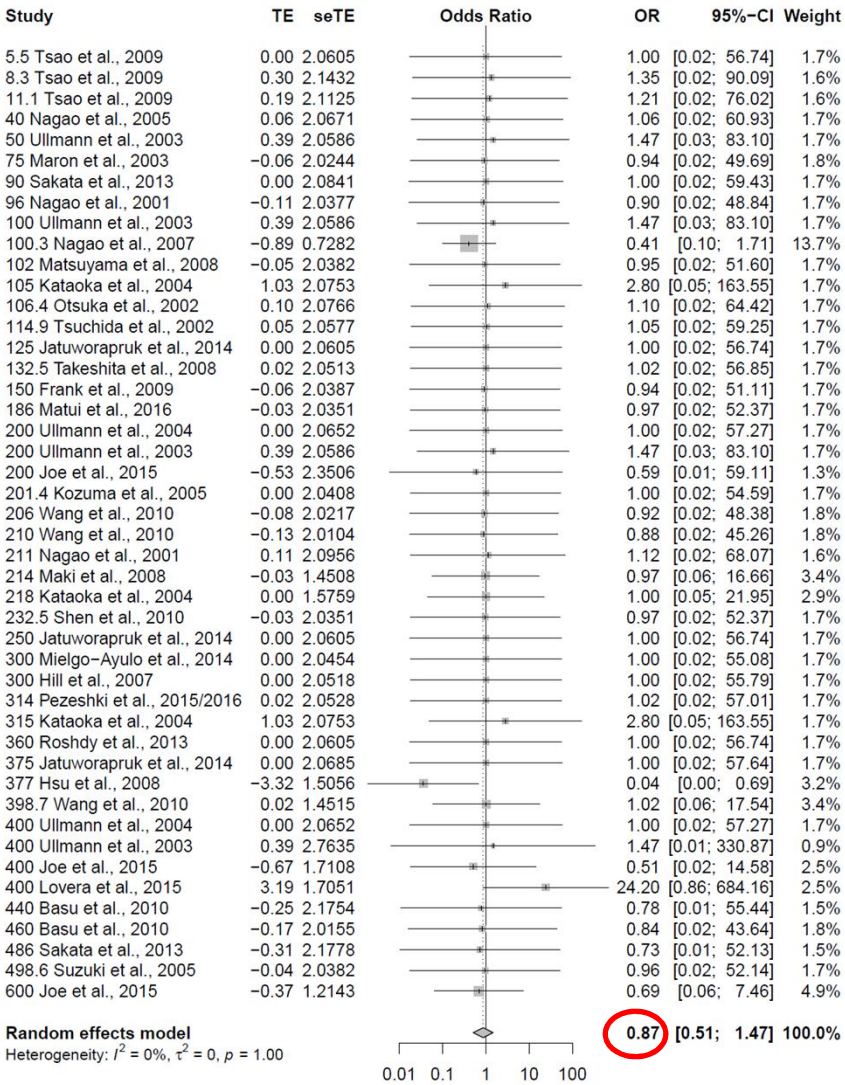
The safety assessment based on available knowledge revealed the need for further data.

Anlassbezogene Bewertung von grünem Tee

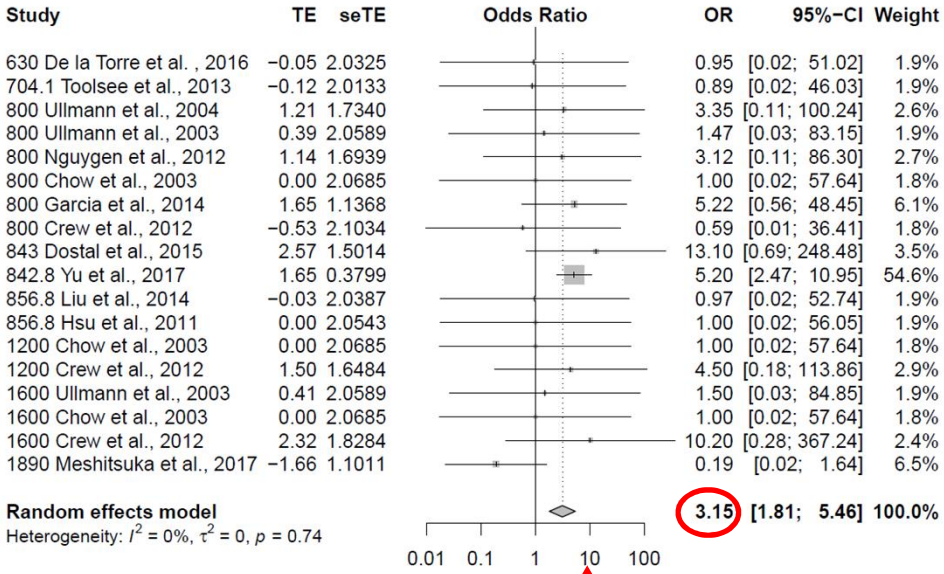
- Anlass: Fälle von Lebertoxizität im schwedischen Überwachungssystem
- Primäre Einschätzung: grüner Tee – Lebensmittel
- Sekundär: Food supplements auf dem Markt
- Toxische Komponenten mit Fokus auf

(-)Epigallocatechin-3-gallate (EGCG)

Lebertoxizität von grünem Tee – QPS?



(-)Epigallocatechin-3-gallate (EGCG)



Metaanalyse von interventionellen Studien beim Menschen

- EGCG Dosis bis 600 mg tgl. (8,6 mg/kg bw/d)
- EGCG Dosis über 600 mg tgl.

Result of the assessment

The Panel concluded that it was not possible to identify an EGCG dose from **green tea extracts** that could be considered safe.
From the clinical studies reviewed there is no evidence of hepatotoxicity below 600 mg EGCG/day up to 12 months.

Allerdings: Für Grünen Tee in normalen Mengen wie in historischem Gebrauch der Presumption of safe use Approach kann angewendet werden.

The „Qualified Presumption of Safety Approach“

The QPS approach was initially developed for the assessment of microorganisms referred to EFSA and added to the food chain

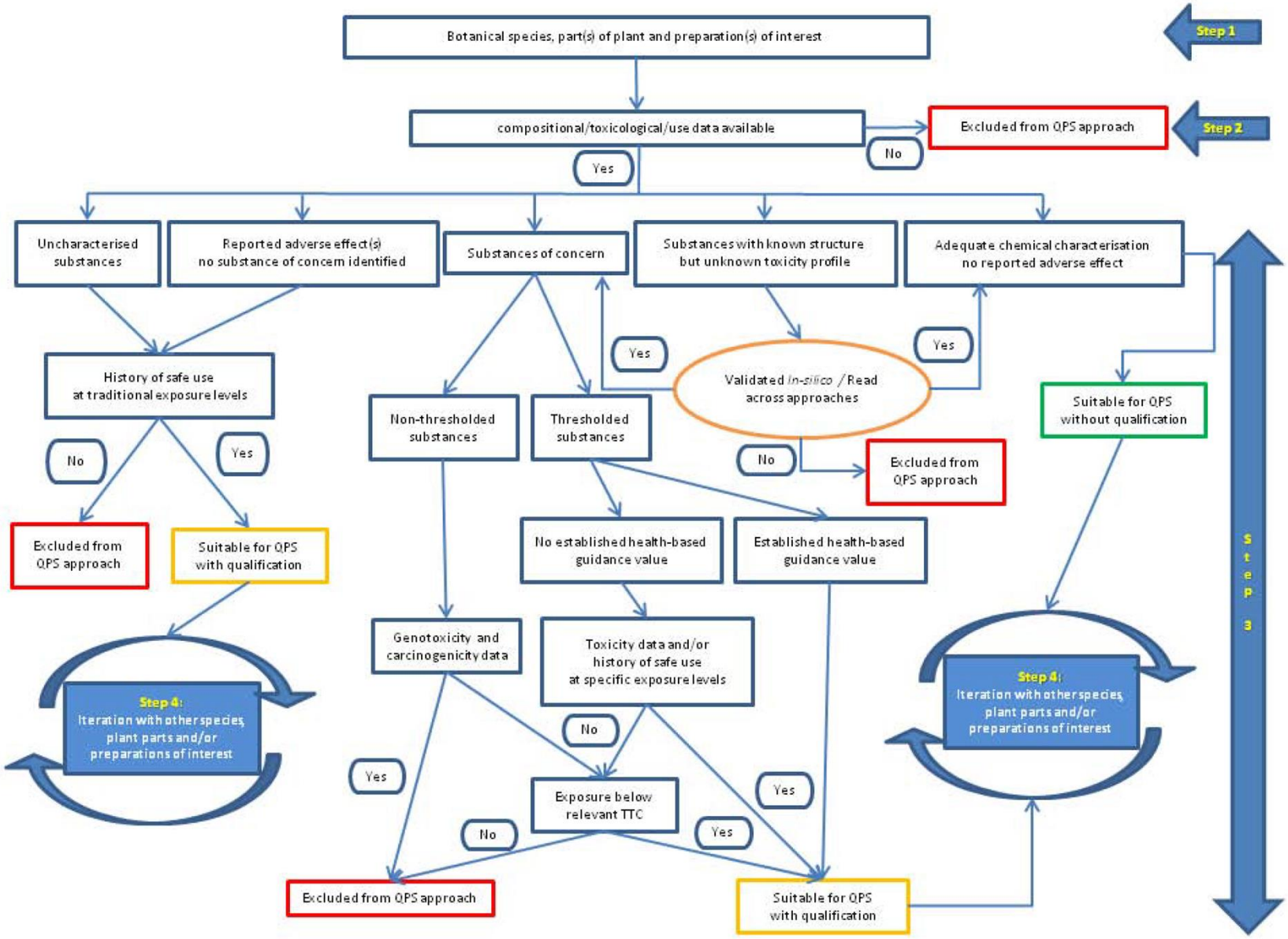
i) the ability to establish the identity of the group of organisms considered

ii) the need for a sufficient body of knowledge to define its nature

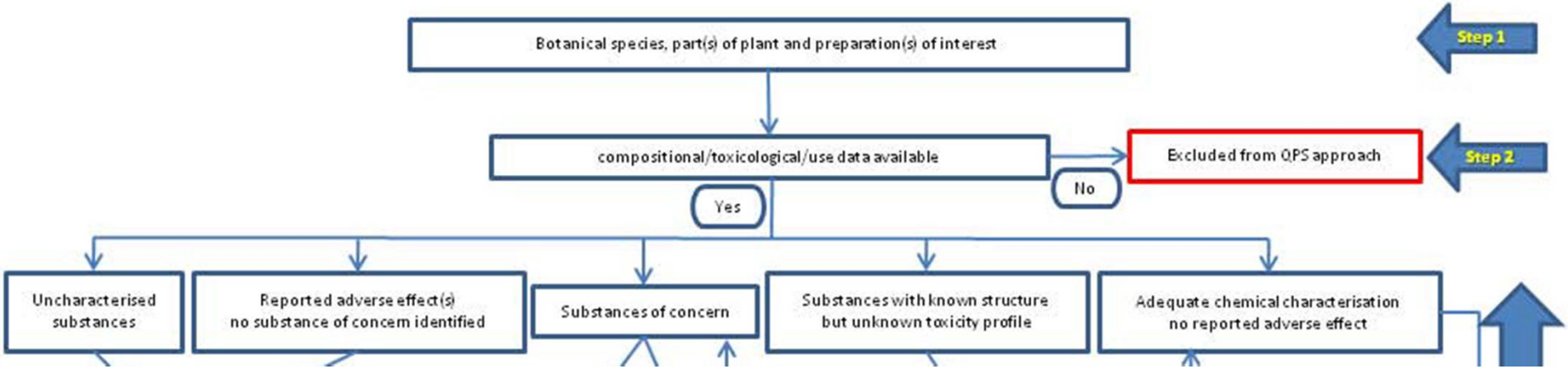
iii) the consideration of possible pathogenicity and whether a qualification could be introduced to exclude pathogenic strains

iv) information on the intended use.

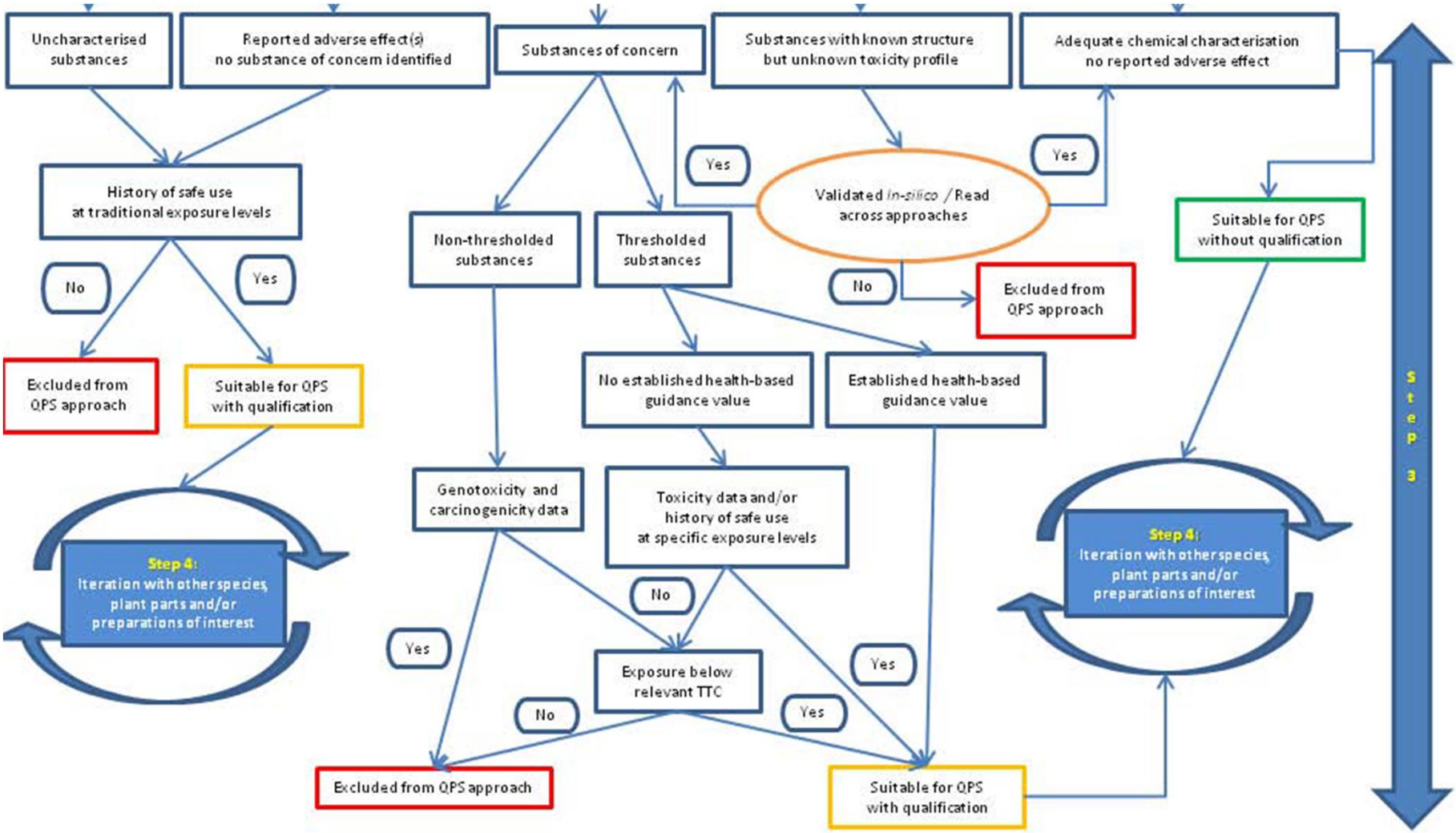
Flow diagram of the proposed methodology for QPS assessment of botanicals and botanical preparations



Stepwise approach of QPS
Steps 1 & 2

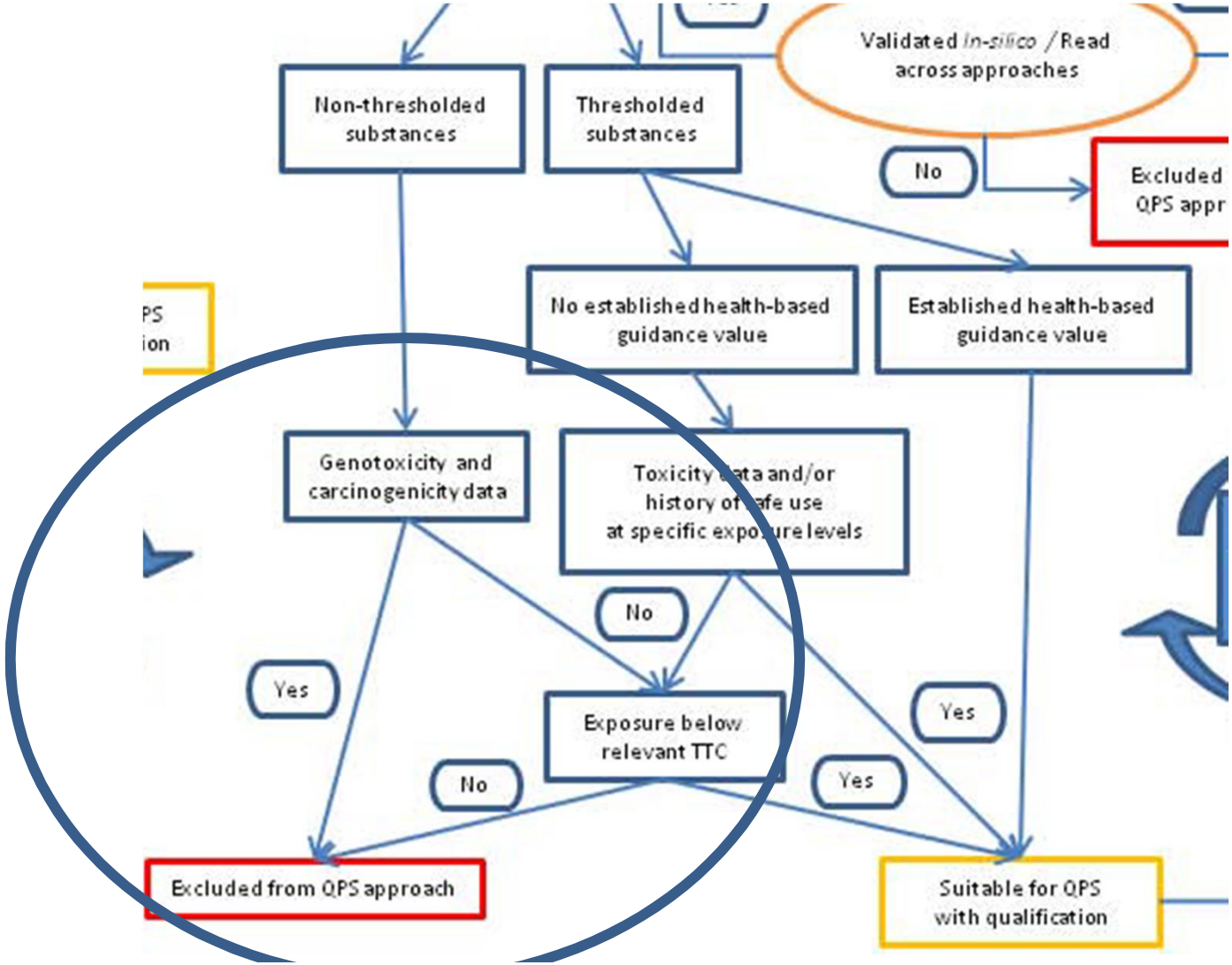


Stepwise approach of QPS
Step 3



Dealing with Substances of concern

Substance of concern



A Harmonised Approach for Risk Assessment of Substances Which are both Genotoxic and Carcinogenic

* The margin of exposure approach is proposed for the risk assessment of substances that have both genotoxic and carcinogenic properties. The margin of exposure is defined as the reference point on the dose-response curve (usually based on animal experiments in the absence of human data) divided by the estimated intake by humans.

* The use of a BMDL10 (benchmark dose lower confidence limit 10%), representing the lower bound of a 95% confidence interval on a BMD (benchmark dose) corresponding to a 10% tumour incidence is recommended as a reference point on the dose-response curve. The T25, representing the (corrected) dose corresponding to a 25% tumour incidence, should be used if the data are inadequate for estimation of a benchmark dose lower confidence limit.

Opinion SC, EFSA 2005

A Harmonised Approach for Risk Assessment of Substances Which are both Genotoxic and Carcinogenic

* The Scientific Committee is of the view that in general a margin of exposure of 10,000 or higher, if it is based on the BMDL10 from an animal study, and taking into account overall uncertainties in the interpretation, would be of low concern from a public health point of view and might be reasonably as a low priority for risk management actions.
However, such a judgement is ultimately a matter for the risk managers. Moreover a margin of exposure of that magnitude should not preclude the application of risk management measures to reduce human exposure.

* The Scientific Committee is of the opinion that in principle substances which are both genotoxic and carcinogenic should not be deliberately added to foods or used earlier in the food chain if they leave residues which are both genotoxic and carcinogenic in food.

Opinion SC, EFSA 2005

Beispiel für die Berechnung eines MOE – Nitrosamine in bearbeitetem (Nitrit + Nitrat) Fleisch

Table 15: Dietary exposure to volatile nitrosamines (NDMA + NDEA, expressed in ng/kg bw per day) from processed meat with estimation of MoE*,(a)

NDMA + NDEA	Infants (12 weeks–11 months)	Toddlers (12–35 months)	Children (3–9 years)	Adolescents (10–17 years)	Adults (18–64 years)	The elderly (≥ 65 years)
Mean exposure	0.2–1.4	1.2–3.5	0.3–2.6	0.4–2.1	0.6–1.7	0.5–1.2
MoE	12,800–90,000	5,100–15,000	6,900–60,000	8,600–45,000	10,600–30,000	15,000–36,000
High level exposure	0.5–5.8	5.0–8.3	1.6–7.3	1.4–6.3	1.9–5.1	1.5–3.1
MoE	3,100–36,000	2,200–3,600	2,500–11,200	2,800–12,800	3,500–9,500	5,800–12,000

*: Based on a $BMDL_{10}$ of 0.018 mg/kg bw (for NDEA).

(a): MoE are expressed as a range – the lower end of the range relates to upper end of the mean and the high percentile exposures ranges as reported in Table 11 and the higher end of the range relates to lower end of the mean and the high percentile exposures ranges as reported in Table 11.

ANS Panel, 2017

Guidance on the use of the Threshold of Toxicological Concern approach in food safety assessment

	TTC value in µg/person per day	TTC in µg/kg bw per day
Potential DANN-reactive mutagens and/or carcinogens	0.15	0.0025

Draft, SC EFSA, 2019

Bewertung von nicht-vermeidbaren Kontaminanten und Rückständen MOE approach for genotoxic and carcinogenic substances

- In assessing the risk from levels of unavoidable contaminants or residuals in the additive which are genotoxic and carcinogenic, the Panel generally uses the Margin of Exposure (MOE) approach described in the European Food Safety Authority (EFSA) Scientific Committee opinion

Guidance for submission for food additive evaluations, ANS Panel 2012

Bewertung von nicht-vermeidbaren Kontaminanten und Rückständen TTC approach for genotoxic substances

- The Panel noted that for the unavoidable genotoxic residuals, for which carcinogenicity data are not available, the TTC approach would be considered. The Panel would expect exposures for high level consumers at the proposed maximum use levels to be below the TTC for genotoxic compounds of 0.15 µg/person/day (= 0.002 µg/kg bw/day)

Guidance for submission for food additive evaluations, ANS Panel 2012

Bewertung von nicht-vermeidbaren Kontaminanten und Rückständen in botanicals or botanical preparations

- Botanical or botanical preparations for which the MOE approach indicates a low priority for risk management of the genotoxic and carcinogenic constituent of concern,
- or for which the exposure to this constituent resulting from the proposed use and use levels of the botanical or botanical preparation would be negligible compared to normal dietary intake of the constituent from other dietary sources,
- might be considered of no safety concern, given that the database on other toxicological endpoints also does not give reason for concern

ESCO advice on the EFSA guidance for the safety assessment of botanicals , 2009

Beispiel für eine Bewertung von botanical preparations, die kanzerogene Stoffe enthalten (QPS)
- Fenchelöl und wässrigen Fenchelextrakten -

- ***Foeniculum vulgare***
- **Species, plant parts and preparations used**
- For *Foeniculum vulgare* two varieties can be defined including *Foeniculum vulgare* Mill. var. *dulce* and *Foeniculum vulgare* Mill. var. *vulgare*. From both species preparations based on the essential oil as well as preparations containing water based extracts might be considered.
- **Composition**
- *Essential oil*
- The essential oil of both species is known to contain substances of concern including *trans*-anethole and estragole (SCF, 2001a; SCF, 2001b; Council of Europe, 2006). The latter is known to be genotoxic and carcinogenic.
- *Water based extracts*
- Given the limited water solubility of these compounds of concern their concentrations in water extracts is expected to be significantly lower than in the essential oils.

Beispiel für ein QPS Bewertung
Foeniculum vulgare

Use

- Fennel based teas are traditionally used in many parts of Europe including France, Germany, Austria, Czech Republic and Poland in for example the symptomatic treatment of digestive disorders alleviating mild spasmodic gastro-intestinal ailments and for the relief of symptoms during inflammations of mucous membranes of the upper respiratory tract (EMA, 2008). Homemade fennel tea is often used as a remedy for gastrointestinal complaints in infants and young children (Crotteau et al., 2006; Perry et al., 2011). In addition various fennel-based food supplements are on the market containing for example the essential oil, dried extract or seeds.

Beispiel für ein QPS Bewertung
Foeniculum vulgare

Toxicity

- For *trans*-anethole JECFA derived a temporary ADI of 0-2.0 mg/kg bw (JECFA, 1998), which can be used to define whether exposure of proposed uses and use levels will be safe and can be assigned QPS status with defined exposure restrictions.
- For estragole there are carcinogenicity data from which a BMDL10 could be derived and one could use the MOE approach to characterise the level of concern resulting from the exposure to this substance through food.

Beispiel für ein QPS Bewertung
Foeniculum vulgare

Result of evaluation

- Given the recommendation of the Scientific Committee to not introduce into the food chain substances that are known to be genotoxic and carcinogenic (EFSA, 2005), preparations from *Foeniculum vulgare* containing estragole will have to be excluded from the QPS approach and therefore subject to a case-by-case assessment.
- In this particular case, it should be noted that the level of estragole extracted into the essential oils of *Foeniculum vulgare* species will be higher than the levels extracted into water based preparations. For risk management purposes, it may be of interest to assess preparations of these species on a case-by-case basis, using the carcinogenicity data for estragole from which a BMDL10 could be derived and for which it is therefore possible to apply the MOE approach. The fact that some preparations e.g. essential oils of *Foeniculum vulgare* and *Ocimum tenuiflorum* species will show higher levels of estragole than the levels extracted into (traditional) water based preparations should then be taken into account (Case-by case with respect to exposure).

Zusammenfassung: Wichtigste Punkte (I)

- Die Bewertung von Botanicals und Botanical Preparations erfolgt nach Prinzipien, die ähnlich sind den Prinzipien zur Bewertung von chemisch definierten Stoffen
- Es gibt Besonderheiten, insbesondere im Hinblick auf die zu bewertende(n) Substanz(en): z.B. Mischung, nicht genau identifizerbare Substanzen
- Vergleich der Exposition mit der Exposition im traditionellen Gebrauch
- Genotoxische und kanzerogene Substanzen werden wie Chemikalien bewertet: genotoxische (DNA-reaktive) Substanzen mit TTC, Genotoxische (DNA-reaktive) und kanzerogene Substanzen mittels MOE

Zusammenfassung: Wichtigste Punkte (II)

- Der TTC Wert von 0,0025 µg/kg bw per Tag bedeutet, dass die Exposition gegenüber einem genotoxischen Botanical nicht höher als 0,0025 µg/kg bw per Tag betragen darf, um als unbedenklich/low concern eingestuft zu werden.
- Ein MOE von 10.000 bedeutet, dass die Exposition 10.000 fach unterhalb des Referenz Points (BMDL) liegen soll, damit sie als „low concern“ eingestuft werden kann.
- Fenchelöl ist ein Beispiel für das Vorhandensein von einer Botanical preparation mit einer genotoxischen und kanzerogenen Komponente (Estragole), möglicherweise enthalten auch wässrige Extrakte aus Fenchel Estragol. Eine anschließende Bewertung steht noch aus.