GERMAN FEDERAL INSTITUTE FOR RISK ASSESSMENT

Risk Assessment Approaches and Methodology – an Overview

PD Dr. Karen I. Hirsch-Ernst

Unit Nutritional Risks, Allergies and Novel Foods
Department of Food Safety, German Federal Institute for Risk Assessment (BfR)

Scope and outline of current presentation

- Considerations regarding the risk assessment of "superfoods"
- Focus on **safety aspects** concerning human health risks, not on medicinal use, health claims or purported beneficial effects
- Focus on foods that have been claimed to be superfoods, but have not been assessed as Novel Foods or are currently not listed in the EU Novel Food catalogue
- Addressing in particular **other substances with nutritional or physiological effect** (other than vitamins or minerals) that are used as ingredients of certain food products (food supplements or fortified foods), i. e. botanical extracts or concentrated isolated plant constituents
- Risk assessment examples:
  - Concentrated isolated **Piperine** as ingredient in certain food supplements
  - **Hydroxycitric acid (HCA) *& Garcinia cambogia*** extracts as ingredients in certain so-called "fat burner" products

Foods and Novel Foods

General Food Law Regulation (EC) No 178/2002 Article 14*:*

(1) Food shall not be placed on the market if it is unsafe.

In General:

Food can be placed on the market by food business operators (FBO) without prior authorisation

Exception:

Novel Food Regulation (EU) 2015/2283

- Prior to marketing: Uniform authorisation procedure including risk assessment
- High level of protection of human health and of consumers' interests
- Effective functioning of the internal market

Authorisation as Novel Food

Conditions for authorisation:

1) No safety risk to human health
2) Not misleading the consumer
3) Normal consumption not nutritionally disadvantageous

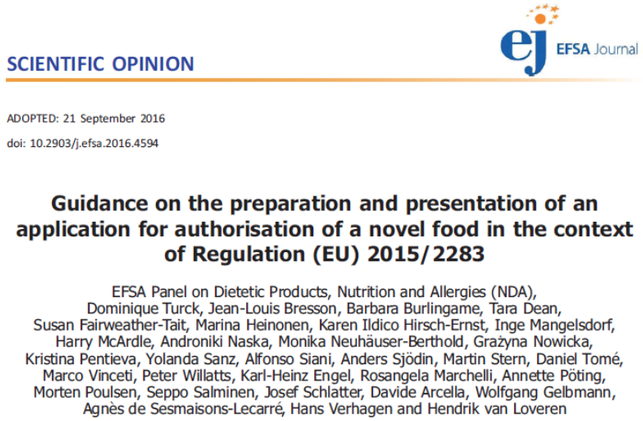
2 Authorisation procedures:

→ Article 10 procedure: "**Authorising the placing on the market within the Union of a novel food**"

→ Article 14 procedure: "**Notification of a traditional food from a third country**"

Scientific data requirements for Novel Foods according to EFSA Guidances

Application for authorization of novel foods	Notification of traditional foods from third countries
1. Identity of the novel food	1. Identity of the traditional food
2. Production process	2. Production process
3. Compositional data	3. **Compositional data**
4. Specifications	4. Specifications
5. History of use of the novel food and/or of its source	5. **Data from experience of continued use**
6. Proposed uses and use levels and anticipated intake	6. Proposed conditions of use for the EU market
7. Absorption, distribution, metabolism and excretion (ADME)	
8. Nutritional information	
9. Toxicological information	
10. Allergenicity	



SCIENTIFIC OPINION

EFSA Journal

ADOPTED: 21 September 2016

doi: 10.2903/j.efsa.2016.4594

Guidance on the preparation and presentation of an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), Dominique Turck, Jean-Louis Bresson, Barbara Burlingame, Tara Dean, Susan Fairweather-Tait, Marina Heinonen, Karen Ildico Hirsch-Ernst, Inge Mangelsdorf, Harry McArdle, Androniki Naska, Monika Neuhäuser-Berthold, Grażyna Nowicka, Kristina Pentieva, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Martin Stern, Daniel Tomé, Marco Vinceti, Peter Willatts, Karl-Heinz Engel, Rosangela Marchelli, Annette Pöting, Morten Poulsen, Seppo Salminen, Josef Schlatter, Davide Arcella, Wolfgang Gelbmann, Agnès de Sesmaisons-Lecarré, Hans Verhagen and Hendrik van Loveren

SCIENTIFIC OPINION

EFSA Journal

ADOPTED: 22 September 2016

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Guidance on the preparation and presentation of the notification and application for authorisation of traditional foods from third countries in the context of Regulation (EU) 2015/2283

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), Dominique Turck, Jean-Louis Bresson, Barbara Burlingame, Tara Dean, Susan Fairweather-Tait, Marina Heinonen, Karen Ildico Hirsch-Ernst, Inge Mangelsdorf, Harry McArdle, Androniki Naska, Monika Neuhäuser-Berthold, Grażyna Nowicka, Kristina Pentieva, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Martin Stern, Daniel Tomé, Marco Vinceti, Peter Willatts, Karl-Heinz Engel, Rosangela Marchelli, Annette Pöting, Morten Poulsen, Josef Schlatter, Wolfgang Gelbmann, Agnès de Sesmaisons-Lecarré, Hans Verhagen and Hendrik van Loveren

But what about superfoods that do not currently have Novel Food status, but are being marketed in food products, i.e. food supplements or fortified foods?

- Risk assessors may be asked by risk managers to provide scientific advice on safety-related aspects of such foods in view of e. g.
  - **General Food Law Regulation (EC) No 178/2002** Article 14 (foods must be safe for consumers)
  - **Regulation (EC) 1925/2006** (laying down provisions regarding the addition of vitamin, minerals and certain other substances to foods), which also specifies conditions under which certain other substances or ingredients might be prohibited, restricted or put under Community scrutiny, based on safety concerns
- In such cases, risk assessments are required
- No specific general data requirements for "other substances"
- **Risk assessment based on the available scientific information and data**

Scientific Risk Assessment: General Principles – Hazard - Exposure - Risk

Risk assessment represents a systematic procedure to assess the probability or likelyhood of occurrence of unwanted adverse effects in the population and involves the following principles:

1. Hazard identification:
Identification of adverse effects* on human health

* Adverse effect: "*a change in the morphology, physiology, growth, development, reproduction, or life span of an organism, system, or (sub) population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences*", WHO 2004.

2. Hazard characterisation:

- Qualitative and quantitative characterisation of adverse effects;
- Establishment of dose-response relationships;
- Identification of NOAEL or LOAEL as reference points;
- Derivation of a maximum intake level considered to be tolerable, using NOAEL or LOAEL as point of departure, taking uncertainty factors for inter- and/or interspecies extrapolation into account

3. Exposure assessment:
Estimation of intake and distribution of intake within the population

4. Risk characterisation:
Based on steps 1, 2 and 3, characterisation of the likelyhood that adverse effects might (not) occur in the population

Risk assessment: General principles – hazard identification & characterisation

- **Criteria to be considered (if available):**

- Data from animal studies
- Data from human studies (case reports, observational studies, intervention studies (with preference if available and well conducted))

- Data on mechanisms of action
- Kinetic data: ADME
- Duration of intake
- Vulnerable, sensitive parts of population
- Identification of uncertainties and data gaps, definition of appropriate uncertainty factors
- Characterisation of dose-response relationships

- Identification of critical adverse effects
- Identification of LOAEL and NOAEL

Safety Assessment of Botanicals: Discussions on conditions for considering a presumption of safety approach in certain cases

European Food Safety Authority

EFSA Journal 2014;12(3):3593

SCIENTIFIC OPINION

Scientific Opinion on a Qualified Presumption of Safety (QPS) approach for the safety assessment of botanicals and botanical preparations[1]

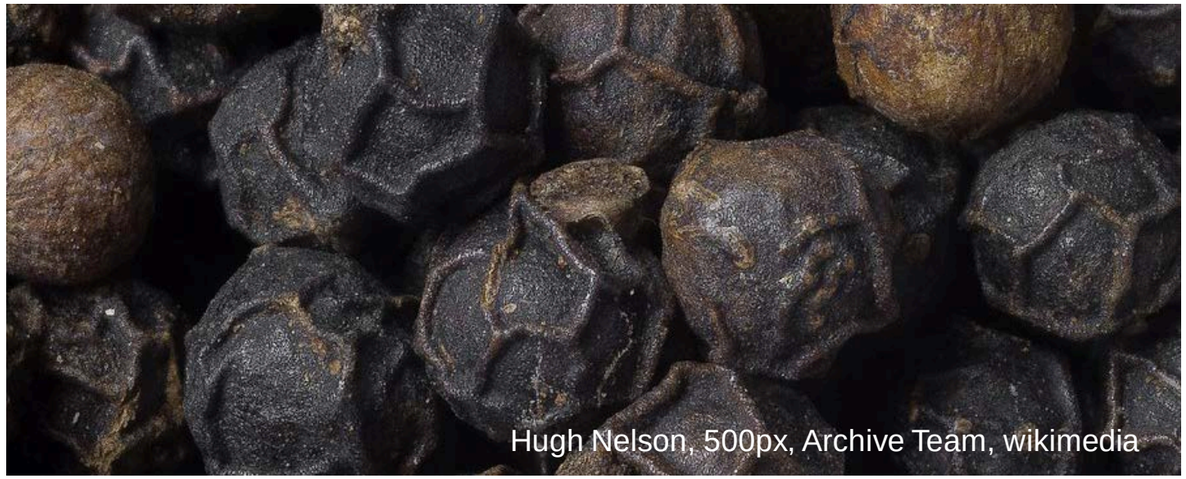
EFSA Scientific Committee[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

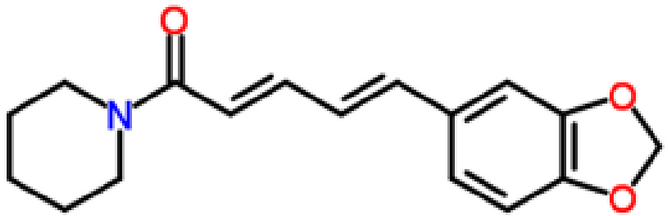
ABSTRACT

The Qualified Presumption of Safety (QPS) approach, initially developed for the assessment of microorganisms referred to EFSA and added to the food chain is equally applicable to the assessment of botanicals or botanical preparations. Using the principles to establish the suitability of a botanical preparation for QPS status, it has been possible to develop a structured assessment scheme that provides a practical method for assessing botanicals and botanical preparations for which an adequate body of knowledge exists and therefore without the need for further testing. Reiterative applications of the assessment scheme to related botanicals or different botanical preparations obtained from the same plant variety can allow a QPS status to be derived for specific groupings. However, the particularity of botanicals that may be presented in a wide variety of forms or whose morphology and chemical composition may be markedly affected by geographical and environmental factors, makes the possibility to establish QPS status at high taxonomic levels quite limited. Still, the above-mentioned structured approach for the assessment of botanicals and botanical preparations represents a considerable advancement in the development of a comprehensive, systematic and transparent methodology. The Scientific Committee recommends its use as an extension of the 2009 EFSA guidance for the safety assessment of botanicals and botanical preparations intended to be used in food supplements.

Risk assessment example:
Assessment of isolated (concentrated) Piperine in food supplements



Black peppercorns



Piperine

Piperine:

- Secundary plant ingredient, naturally occurring alkaloid (CAS no. 94-62-2)
- From black pepper (*Piper nigrum L.*), long pepper (*Piper longum L.*), Grains of Paradise (*Aframomum melegueta)*
- (E,E)-Piperine: isomeric form often used in certain food supplements
- At high doses **impact on bioavailability of other substances**, i.e. of many drugs:
  Often increase in bioavailability of the substance Piperine is combined with
- Also marketed in certain supplements on its own, claimed beneficial health effects

Former risk assessments of isolated Piperine

Piperine:

- Piperine approved as **a flavouring agent** in the European Union with no restrictions on use or max. levels set in regulation (EC) No. 1334/2008
- Assessment of Piperine as flavouring agent by EFSA (2008, 2011): NOAEL considered to be 5 mg/kg bw/day
- *"No safety concern at estimated levels of intake as flavouring substance*",
  based on the MSDI approach (estimated European per capita intake by the MSDI approach: 6.2 µg piperine/day)
  JECFA (2006), agreed on by *EFSA (2015)*

Publication in „Foods“ 2021

foods

MDPI

Review

Safety Aspects of the Use of Isolated Piperine Ingested as a Bolus

Rainer Ziegenhagen, Katharina Heimberg, Alfonso Lampen and Karen Ildico Hirsch-Ernst *

German Federal Institute for Risk Assessment (BfR), Max-Dohrn-Str. 8-10, 10589 Berlin, Germany; rainer.ziegenhagen@bfr.bund.de (R.Z.); Katharina.Heimberg@bfr.bund.de (K.H.); Alfonso.Lampen@bfr.bund.de (A.L.)
* Correspondence: Karen-Ildico.Hirsch-Ernst@bfr.bund.de

Abstract: Piperine is a natural ingredient of *Piper nigrum* (black pepper) and some other *Piper* species. Compared to the use of pepper for food seasoning, piperine is used in food supplements in an isolated, concentrated form and ingested as a bolus. The present review focuses on the assessment of the possible critical health effects regarding the use of isolated piperine as a single ingredient in food supplements. In human and animal studies with single or short-term bolus application of isolated piperine, interactions with several drugs, in most cases resulting in increased drug bioavailability, were observed. Depending on the drug and extent of the interaction, such interactions may carry the risk of unintended deleteriously increased or adverse drug effects. Animal studies with higher daily piperine bolus doses than in human interaction studies provide indications of disturbance of spermatogenesis and of maternal reproductive and embryotoxic effects. Although the available human studies rarely reported effects that were regarded as being adverse, their suitability for detailed risk assessment is limited due to an insufficient focus on safety parameters apart from drug interactions, as well as due to the lack of investigation of the potentially adverse effects observed in animal studies and/or combined administration of piperine with other substances. Taken together, it appears advisable to consider the potential health risks related to intake of isolated piperine in bolus form, e.g., when using certain food supplements.

Keywords: piperine; food safety; drug interaction; reproductive toxicity; bolus administration

Citation: Ziegenhagen, R.; Heimberg, K.; Lampen, A.; Hirsch-Ernst, K.I. Safety Aspects of the Use of Isolated Piperine Ingested as a Bolus. *Foods* **2021**, *10*, 2121. https://doi.org/10.3390/foods10092121

➢ Concentrated Piperine in food supplements - Human studies

Interactions with diverse drugs in the course of intake as a bolus:

- **20 mg Piperine/day for several days (7 or 10 days):**
  - Increase in drug serum/plasma concentrations (C_{max}) and/or increase in AUC-values (AUC = area unter the curve) of drugs applied as single dose on last day of Piperine dosing or on day after last Piperine dose
  - Observed for Propranolol, Theophyllin, Phenytoin, Carbamazepin, Nevirapin, Chlorzoxazon, Diclofenac and Fexofenadin
    (Bano et al., 1987; 1991; Pattanaik et al., 2006; 2009; Kasibhatta and Naidu, 2007; Bedada and Boga, 2017a; Bedada and Boga, 2017b; Bedada et al., 2017)

- **50 mg Piperine, single dose:**
  - Approximately 1.3-fold increase in serum/plasma C_{max}; 1.7-fold increase in AUC-value observed for single dose of 450 mg Rifampicine *(Zutshi et al., 1985)*

- **15 mg Piperine/day for 3 days:**
  - Subsequent administration of 10 mg Midazolam (benzodiazepine) on day 4: Prolonged sedation and incresed number of patients with amnesia *(Rezaee et al., 2014)*

Conclusion: In many cases increases in bioavailability and systemic levels of substances/drugs that Piperine is combined with ("**Bio-Enhancing Activity")**

➢ Concentrated Piperine in food supplements – Observed effects in animal studies

Disturbance of spermatogenesis:

- 10 mg/kg bw/Day
  - reduced sperm concentrations in caput and cauda epididymides (statistically significant, s)
  - reduced relative weight of testis (s)
  - reduced absolute weight of the cauda epididymides, vas deferens, seminal vesicle and ventral prostate

(Albino Rats: Malini et al., 1999, Wistar Rats: De`Cruz 2005, Chinta et al. 2016, 2017)

- 5 mg/kg bw/day
  - Dose-dependent increase in serum testosterone
  - Decrease in serum FSH
  - Increase in Leydig cell size and number (slight)
  - Reduced sperm count in epididymides in histological organ sections

(Sprague-Dawley Rats: Chen et al., 2018)

LOAEL of 10 mg Piperine/kg bw/day, based on significant effects on spermatogenesis

➢ Concentrated Piperine in food supplements - Animal studies

Maternal reproductive toxicological and embryotoxic effects:

- 10 mg/kg bw/day, mice
  - reduced fertility index (s)
  - reduced implantation rates (s)

  (Daware et al., 2000)

- 2 x 12.5 mg/kg bw/day, mice
  - reduced implantation rates (s)
  - abortive effects by interrupted pregnancies (s)

  (Piyachaturawat et al., 1982)

LOAEL of 10 mg Piperine/kg bw/day, lowest dose applied

Risk assessment of isolated (concentrated) Piperine in food supplements

Recommendation by BfR (2018)

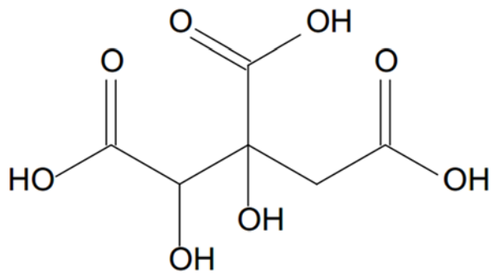
- **Not to exceed intake of 2 mg of isolated Piperine per day** as bolus dose via food supplements

- Based on:
  - LOAEL of 10 mg Piperine/kg bw/day as reference point of departure,
    - divided by 3 (Uncertainty Factor of 3 used for LOAEL to NOAEL Extrapolation),
    - divided by 100 (Uncertainty factor for inter- and intraspecies variability) and
    - multiplied with 70 (for default adult body weight in kg):

  - (3.3 mg Piperin/kg bw/day ÷ 100) × 70 kg bw = 2.3 mg/day **~ 2 mg Piperine/day**

- *"…it seems advisable **for pregnant women to abstain** from the use of food supplements containing isolated piperine…*"

Example: Hydroxycitric acid (HCA) from *Garcinia cambogia* extracts



(-)-hydroxycitric acid (HCA)

Substance:

- Hydroxycitric acid (HCA) is a fruit acid naturally occurring in fruits of the tropical plant ***Garcinia cambogia***.
- HCA is marketed in form of *Garcinia cambogia* extracts, whose composition is often not clearly specified.
- HCA is usually present as Na^+, K^+, Ca^{2+}, or Ca^{2+}/K^+ salt.


Garcinia cambogia fruits

Exposure:

- *Garcinia cambogia* (fruit rind) - used for spice purposes in South Asian countries (consumption levels - no data)
- Ingredient of dietary supplements intended for weight loss (purported appetite suppressant, "fat burner")
- Dosing via supplements – up to 3000 mg HCA/day

HCA: Hazard potential

Animal studies: Oral administration, rats

Study	preparation tested	Results
90-day	Garcinia c. extract (41,2% HCA)	**Testicular atrophies, germ cell degeneration, impaired spermatogenesis** LOAEL: 778 mg HCA/kg bw; **NOAEL: 389 mg HCA/kg bw**
90-day	Ca^{2+}/K^{+}-HCA (60% HCA)	No testicular toxicity reported; hematology, clinical chemistry, histopathology without changes **NOAEL: 1500 mg HCA/kg bw**
Reprod. toxicity	Ca^{2+}/K^{+}-HCA (60% HCA)	No effects on the reproductive system of ♂/♀ animals observed; sperm quality & reproductive parameters of ♂ animals not affected **NOAEL(♂): 611 mg HCA/kg bw** (= highest tested dose)

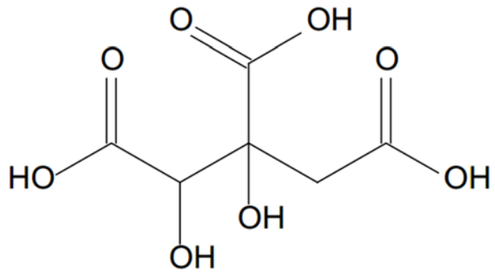
- Testicular toxicity/impaired spermatogenesis in ♂ rats at high doses with certain HCA-preparations

Human intervention studies on the safety of HCA intake:

- Ingestion of HCA preparations or *Garcinia cambogia* extracts
- Observed adverse effects mostly nonspecific; similar occurrence as in control groups
- **Parameters of potential effects on spermatogenesis (i.e. sperm quality and sperm count) not investigated.**

HCA / *Garcinia cambogia* extracts: Risk assessment

- Unclear whether the reproductive toxicological effects observed in male rats were due to possible impurities in the *Garcinia cambogia* extracts tested or were compound-specific to high doses of HCA intake
- Lowest NOAEL: **389 mg HCA/kg bw per day**
- No adequate human data on the safety of HCA-preparations with regard to the human male reproductive system are available.
- Lack of specifications for HCA preparations/*Garcinia cambogia* extracts added to food supplements. Questionable transferability of the above-mentioned observed effects to other preparations.
- Uncertainties regarding the health assessment of prolonged HCA intakes, especially in the assessment of high intakes (3000 mg HCA/day).



HCA

Garcinia cambogia

Summary

- Many substances claimed to be superfoods are currently not in the Novel Food Catalogue or on the EU-Union list, and thus have not been subjected to or are not currently foreseen for an authorisation procedure for Novel Foods
- Examples presented here (Piperine or HCA in food supplements) indicate that the use of certain foods marketed as superfoods may be associated with human health risks
- Scientific risk assessments of "other substances" used in food supplements (e.g. botanicals) often face challenges such as:
  - Incomplete information on composition of foods in question
  - Limited data from animal or human studies
  - Studies, if available, often of low quality, e.g. animal studies not conducted according to OECD guidelines
  - Assessments impeded by knowledge gaps and uncertainties

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Thank you for your attention

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German Federal Institute for Risk Assessment
Max-Dohrn-Straße 8-10 ● 10589 Berlin, GERMANY
Phone +49 30 - 184 12 - 0 ● Fax +49 30 - 184 12 – 99 0 99
bfr@bfr.bund.de ● www.bfr.bund.de/en

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