National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

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RIVM Letter report 2019-0114
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Colophon

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Synopsis

Template for safety assessment of plant food supplements

Consumers are using plant food supplements due to their 'natural' image and (supposed) health benefits. Plant food supplements must be safe according to the General Food Law and the Herbal Preparations Decree under the Dutch Commodities Act.

However, safety assessments of these products are often problematic because of the limited information available about the composition of the supplement and the toxicity of the ingredients used. RIVM has developed a template for performing safety assessments for dietary supplements, particularly plant food supplements, in a standardized way.

Firstly, the template provides an overview of the information that is required. Depending on the extent and quality of this information, RIVM provides guidance on how this can be used to assess safety.

A wide range of dietary supplements are now commercially available, including on the internet. However, no premarket assessment of the safety and composition of dietary supplements is required, for instance as part of an authorization. Such assessments are only performed if there is an indication that a particular commercially available supplement may pose a risk to human health. A possible assessment by the government is carried out after the supplements are on the market.

Keywords: dietary supplements, herbal preparation, botanical, safety, risk assessment

Publiekssamenvatting

Template voor de veiligheidsbeoordeling van voedingssupplementen met kruiden

Consumenten gebruiken voedingssupplementen met kruiden vanwege hun natuurlijke imago en (veronderstelde) gezondheidsvoordelen. Deze kruidenpreparaten moeten veilig zijn volgens de Algemene Levensmiddelen Verordening en het Warenwetbesluit Kruidenpreparaten.

Vaak is het lastig om de veiligheid te beoordelen. Er is namelijk weinig informatie beschikbaar over de samenstelling van het voedingssupplement en de mogelijk schadelijke eigenschappen van de ingrediënten. Het RIVM heeft nu een sjabloon ontwikkeld waarmee de veiligheid van voedingssupplementen, en in het bijzonder kruidenpreparaten, op eenzelfde manier beoordeeld kan worden.

Het sjabloon geeft eerst aan welke gegevens beschreven moeten worden. Afhankelijk van de hoeveelheid en kwaliteit van de beschikbare gegevens geeft het RIVM aan hoe hiermee de veiligheid beoordeeld kan worden.

Er zijn veel verschillende voedingssupplementen te koop, onder meer via internet. De veiligheid en samenstelling van voedingssupplementen worden niet beoordeeld, bijvoorbeeld in een toelatingsprocedure, vóórdat ze op de markt worden gebracht. Dit wordt alleen gedaan als er aanwijzingen zijn dat een supplement misschien een risico voor de gezondheid vormt. Een eventuele beoordeling door de overheid gebeurt pas nadat de producten al op de markt beschikbaar zijn.

Kernwoorden: voedingssupplementen, kruidenpreparaat, veiligheid, beoordeling

Contents

Summary

Consumers tend to use plant food supplements more often, mainly due to their natural image and (supposed) health benefits. Many different food supplements are commercially available, amongst others on the internet. Plant food supplements (botanical preparations) need to be safe according to the General Food Law and the Herbal Preparations Decree under the Dutch Commodities Act. No premarket assessment of the safety and composition of food supplements is, however, required. Such assessment is performed if there is an indication that a supplement on the market may pose a risk to human health. A safety assessment of these products is however often difficult because of the limited information available about the composition of the food supplement and the toxicity of the ingredients. The Netherlands Food and Consumer Product Safety Authority (NVWA) therefore commissioned RIVM to develop a template for the safety assessment of food supplements.
In 2009, the Scientific Committee of the European Food Safety Authority (EFSA) published a guidance document on how to perform safety assessments of botanicals and botanical preparations and described the data needed for such an assessment (EFSA, 2009). The template is developed using the principles described in the EFSA guidance as a basis.
Chapters one to five of the template describe the different types of information needed for an assessment, like the background of the request, information on existing assessments and legislation, results of the literature search, identification and characterization of the food supplement of interest, exposure data and toxicokinetic and toxicological information. Chapter six describes the actual safety assessment and chapter seven the conclusions and recommendations. In chapter six this report provides a decision scheme to choose the appropriate approach for performing a safety assessment and an explanation of the different approaches. The appropriate approach is dependent on the amount, type and quality of the available data and may include application of presumption of safety, an assessment based on a health-based guidance value or on a margin of exposure approach, applying read across or the threshold of toxicological concern approach.
The template will be used in the future by RIVM to perform safety assessments of (ingredients of) food supplements commissioned by NVWA or the Ministry of Health, Welfare and Sports (VWS) in a consistent way.

Preface

Food supplements containing botanical ingredients or 'other substances' are being used more often by consumers due to their natural image and their (supposed) health benefits. These supplements are easily accessed and obtained, especially through the internet. It is stated by the General Food Law and the Herbal Preparations Decree in the Dutch Commodities Act that (plant) food supplements need to be safe when placed on the market. However, no pre-market safety assessment and quality assessment is carried out. If there are indications that the food supplement may be harmful to human health, for example based on the presence of certain substances or botanicals found by analysis of the food supplement or reports about side effects by users of the supplement, a safety assessment is often requested. Limited toxicity data and limited information on the composition of (plant-based) food supplements make it however difficult to assess the potential health risks of these supplements. The Netherlands Food and Consumer Product Safety Authority (NVWA) therefore commissioned RIVM to develop a template for the safety assessment of (plant) food supplements. The development of the template is performed by RIVM within the framework of project 9.4.46.

In 2009, the Scientific Committee of the European Food Safety Authority (EFSA) published a guidance document on how to perform safety assessments of botanicals and botanical preparations and described the data needed for such an assessment (EFSA, 2009). The template is therefore developed using the principles described in the EFSA guidance as a basis. Also, safety assessments of botanicals conducted by EFSA, i.e. opinions on yohimbe and green tea catechins were considered (EFSA, 2013, 2018). In addition, other relevant guidance documents from EFSA and the World Health Organization (WHO) were consulted, i.e. guidance on the Threshold of Toxicological Concern approach (EFSA and WHO, 2016; EFSA, 2019a), guidance on biological relevance of data (EFSA, 2017), guidance on applying the margin of exposure approach for genotoxic carcinogens (EFSA, 2005) guidance on performing read-across (ECHA, 2008, 2012) and the principles for risk assessment (WHO-IPCS, 2009).

The template is drafted in the format of a RIVM report, so it can be used as a basis for future RIVM reports on safety assessments of food supplements commissioned by Netherlands Food and Consumer Product Safety Authority (NVWA) and the ministry of Health, Welfare and Sports (VWS) in a consistent way. The template applies to safety assessments of food supplements containing herbs (botanicals or botanical preparations) or 'other substances', where 'other substances' are defined as 'a substance other than a vitamin or a mineral that has a nutritional or physiological effect' (EC No. 1925/2006).

From the next page onwards, the template is presented in seven chapters describing the information that is needed to assess the safety of botanicals or their ingredients.

For each chapter the subheadings to be included are given as well as an explanation of the information that needs to be written down under that specific subheading. The clean template is provided in Appendix I.

1 Introduction

1.1 Background

This section will shortly state the reason why and upon whose request this substance, botanical, or botanical preparation is assessed. This, in general, will include NVWA or VWS commissioning a risk assessment performed by RIVM. Furthermore, general information such as its definition, the recommended daily consumption, as well as the (supposed) health benefits is also mentioned here.

1.2 Information on existing assessments

The existing toxicological evaluations by international committees and institutes (EFSA, EMA, JECFA) or national organizations (RIVM, BfR, ANSES etc.) for the potential adverse effects should be mentioned as well as derived health based guidance values, effect levels etc..

1.3 Information on existing legislations

In this section, information regarding the regulatory status and legislation that apply to the respective substance, botanical, or botanical preparation should be mentioned.

2 Literature search

In this section, the literature search should be described. This consists of the search terms, search machines, as well as other data sources (websites, grey literature[1]) that have been used in order to gain information, including toxicological information, concerning the substance, botanical, or botanical preparation that is going to be assessed.

[1] Grey literature refers to research that is either unpublished or has been published in a non-commercial form. Examples include RIVM reports or EFSA's Compendium of Botanicals.

3 Description of the product

The paragraphs in this chapter may differ depending on which type of sample is going to be assessed, i.e. whether it is a substance, botanical, or botanical preparation. A botanical is defined as all botanical materials, e.g. the whole, fragmented or cut plants or plant parts. A botanical preparation is defined as all preparations obtained from botanicals by several processes, e.g. pressing, squeezing, extraction, fractionation, distillation, concentration, drying up and fermentation (EFSA, 2009). Paragraph 3.1 will differ with respect to the type of information that should be included (see also below). Overall, it is the main objective of this chapter that the botanical (preparation) or substance is clearly characterized.

3.1 Identity and nature of the source material

In case of assessment of botanical (preparation):

3.1.1 Botanical (preparation)

Information regarding the scientific (Latin) name, synonyms, common names (vernacular name), part(s) used (e.g. root, leaf, seed), geographical origin, as well as the growth and harvesting conditions should be mentioned here.
The identification and characterization of a botanical source may be complicated in certain cases. Therefore, it is recommended by EFSA to follow as much as possible the nomenclature of the European Pharmacopeia, as well as the additional nomenclature sources such as: - World Checklist of Selected Plant Families (WCSP, 2019); the books by Hanelt (2001) which are available on the Internet as Mansfeld's World Data base of Agricultural and Horticultural Crops; and the database by the United States Department of Agriculture. The existence of a scientific name which is not found in the above-named references could also be checked in The International Plant Names Index (EFSA, 2009).

In case of assessment of a substance:

3.1.1 Substance

Information regarding the IUPAC name, CAS number, the chemical structure, form, source of origin, as well as the classification should be mentioned here.

3.2 Manufacturing process

3.2.1 Information on the method(s) of manufacture

(e.g. the process by which the raw material is converted into a substance or preparation, such as extraction or other procedure(s), and plant extract ratio or how the substance is manufactured in case of synthetic manufacturing)

3.2.2 Information on substances entering the manufacturing process

(e.g. identity of the extraction solvent, reagents, special precautions)

3.3 Chemical composition

Data on the chemical composition of the botanical (preparation) should be described with emphasis on the concentrations of constituent(s) of relevance for the safety assessment. This includes the concentrations of substances classified according to their chemical nature, constituents to characterize the quality, chemical fingerprint, production process and or/biological activity of the preparation, as well as the constituents that provide reasons for concern due to their chemical, physiological or toxicological properties. Also, information on possible contaminants and impurities should be included.

3.4 Stability

The stability of a substance or botanical (preparation) is dependent on the pH, temperature, concentration, shelf-life time and solvent used.

3.5 Use and use levels

Information on intended uses of food supplements containing the substance or botanical (preparation) under evaluation should be listed here. The recommended intakes of the food supplement, based on information on the leaflet, should be included, as well as information on the recommended duration of use. Special attention should be given to population groups with specific uses like for example young children. In addition, information on the intended use of the substance or botanical (preparation) in common food or medicinal products should be given.

4 Exposure: extent and duration

4.1 Exposure from food supplement use

This includes the amount (e.g. maximum and average daily intake or exposure), frequency and duration of the exposure to the substance or botanical (preparation). Use levels as mentioned in 3.5 can be used for exposure estimations.
Clear distinction should be made between the intake of a botanical itself, intake of its essential oil and intake of other preparations made of it.

4.2 Possibility of additional/combined human exposure

This is assessed by taking into account exposure to the substance or the botanical (preparation) from different sources (other foods, food supplements and/or medicinal products).

4.3 Information on historical use of the ingredient

This is evaluated in human population groups in relation to the use and resulting exposure levels if known from existing authorizations, evaluations, and regulations.

A matter to be specifically addressed in the evaluation is whether the proposed use and use levels will significantly increase already existing human exposure.

This information is a prerequisite to apply the approach ´Application of presumption of safety' (see chapter 6).

5 Toxicological data

Chapter 5 describes the available toxicokinetic and toxicological data of the substance or botanical (preparation). EFSA's Compendium of Botanicals (EFSA, 2012) can be used to identify substances of possible concern. All relevant studies belonging to the different paragraphs will be described. In case no studies are available, this will be stated. Some details are provided below.

5.1 Toxicokinetics

5.1.1 Absorption, distribution, metabolism, excretion

Special attention should be paid to biotransformation, and the enzymes involved should be mentioned. This information can be used to assess potential interactions with drugs/herbs/other substances.

5.2 Toxicological data

5.2.1 Acute toxicity

5.2.2 Short-term and sub-chronic toxicity

5.2.3 Genotoxicity

5.2.4 Chronic toxicity and carcinogenicity

5.2.5 Reproduction and developmental toxicity

5.2.6 Other studies

Studies investigating other endpoints of toxicity, such as neurotoxicity, immunotoxicity, phototoxicity etc. can be described here. Otherwise, it should be reported that there are no studies available.

5.2.7 Human data

All available human data should be described here, including case reports, biomonitoring and epidemiological studies.

5.2.8 Interactions

The possible interactions between a botanical, chemical, and/or drug should be mentioned and explained here, and the possible adverse effects due to alterations in the toxicokinetics and toxicodynamics of the substances involved should be discussed.

5.3 Derivation of toxicological reference value

In this section the availability of a toxicological reference value based on the available toxicological information is described. In some cases an existing health-based guidance value (HBGV) might be available. In such cases, it should be checked whether or not the newly available toxicological data might warrant revision of the HBGV. If no HBGV is available, it should be explored if the available toxicological data in animals and humans enable derivation of a HBGV (see for more explanation the next paragraphs). If a HBGV cannot be derived, it should be explored whether an other reference value can be obtained, like a no observed adverse effect level (NOAEL), lowest observed adverse effect level (LOAEL), BMDL (benchmark dose lower confidence limit) or other effect level.

Derivation of health-based guidance value

Using human data
The following is based on the WHO-IPCS document on principles for risk assessment of chemicals in food (WHO-IPCS, 2009). It is generally recognized that for toxicological risk assessment for humans, data obtained from studies in humans would be preferable over animal data. Use of human data avoids the necessity of interspecies extrapolation (quantitatively) and observations in studies with humans are less disputable with respect to their relevance (qualitatively) than observations obtained in animal studies. In addition, epidemiological studies may provide direct information on e.g. sensitive sub-populations. Obviously, when a study in humans involves intended administration of substances (in controlled studies), this can only be done under the condition that the effects in humans will remain within what is considered acceptable from an ethical point of view. This requirement could restrict exposure to such an extent that no effect will be observed at all, thereby greatly reducing the informative value of the study.
However, as indicated by WHO-IPCS (2009), some general considerations should be taken into account, that may be useful for the evaluation of the value of human data in toxicological risk assessment.

At least studies should be properly designed and conducted. Poorly designed studies should not be used for toxicological risk assessments or for derivation of HBGVs. Group size, composition of the group(s) of demographic description of participants (gender, age, ethnic background) and life style factors should be sufficiently reported to judge whether a study is sufficiently sensitive and representative for the target population. The evaluation criteria as described by Bradford Hill (1965) are very helpful to substantiate whether an association between exposure (or an exposure estimate or a proxy for that) and an effect does indeed reflect a causal relationship. Like all scientific research, epidemiological studies are sensitive to systematic errors. Controlled studies are less sensitive to bias than observational studies[2].
Ideally, the studies should look at a great variety of toxicological parameters, but for medical, ethical and practical reasons, this will usually be limited to monitoring of a number of specific parameters, which were selected from results from animal studies or previously reported human studies. Different general study designs are available for human studies, each with its own advantages and disadvantages.

- When performed and reported adequately, controlled ((clinical) intervention) studies can provide a good basis for a toxicological risk evaluation; at least for the period of exposure (usually acute or sub-chronic) for which the study population was exposed.
- Case reports are usually not very useful as a basis for a toxicological risk evaluation. This is because exposures usually result from overdosing or occur in an occupational setting, and the actual level of exposure can only be estimated with a large margin of uncertainty e.g. due to recall bias.

[2] For a further introductory overview of various types of bias, including confounding see: https://www.healthknowledge.org.uk/public-health-textbook/research-methods/1a-epidemiology/biases

- Case-control studies may provide a basis for a toxicological risk evaluation under certain conditions, like an adequate matching process of the control group, sufficient exposure estimation and a wide enough range of measured effects.
- Cohort studies may be used as a basis for a toxicological risk evaluation, provided that they address effects that can be ascribed to the exposure with sufficient certainty, the estimation of exposure is sufficiently robust and various types of bias, including recall bias is sufficiently controlled.
- Cross-sectional studies are usually too weak to provide a basis for a toxicological risk evaluation due to their high sensitivity to bias.

In reality, in most cases human data alone are insufficient to be used as starting points for derivation of HBGVs. However, some examples are available where the derivation of an HBGV has been done on the basis of epidemiological studies, supported by data from studies in animals, rather than the other way around[3].
The strongest human data would come from properly designed and conducted clinical trials. But even then it is questionable if such studies would allow for the derivation of HBGVs for chronic exposure. Also, depending on the number of parameters studied, the clinical trial and its outcome might not cover all possible kinds of toxicity. The applicability and usefulness of human data in the risk assessment of botanicals should therefore be evaluated for every assessment separately.

Using animal data
As described in the EFSA guidance (2009) the following data can be seen as a minimum requirement in order to derive an HBGV based on animal data:

- Toxicokinetics including metabolism (and interactions)
- Genotoxicity testing
  This includes at least two in vitro tests addressing both effects at gene and chromosome level.
- Subchronic toxicity testing
  This includes a 90-day study in the rat with administration of the test item via the diet, in order to derive a NOAEL or a BMD.
- Other toxicity studies
  Based on the outcome of the genotoxicity and subchronic toxicity studies or other information it can be decided that other toxicity data, like information on neurotoxicity, developmental toxicity or in vivo genotoxicity data is necessary.

In addition to this minimum set of information requirements as defined by EFSA, in our opinion, the following information is needed for a possible derivation of an HBGV:

- Pharmacological profile
  This information may provide an indication about what kind of possible adverse effects may occur. The toxicological studies, especially the repeated-dose studies, must then include

[3] e.g. the EFSA opinion on dioxins and dioxin-like PCBs: https://www.efsa.europa.eu/en/efsajournal/pub/5333

parameters that are able to address these possible adverse effects, e.g. cardiac toxicity or neurotoxicity
- A 90-days subchronic study with additional study parameters based on pharmacological profile
- Developmental toxicity

Nevertheless, it still needs to be assessed on a case-by-case basis if the data are sufficient to derive a HBGV when taking into account available information about the toxicodynamics and –kinetics of the substance(s).

Critical effect size

To establish an adequate NOAEL, LOAEL or BMD it must be known when an observed effect can be considered adverse. The EFSA opinion on critical effect size discusses this topic (EFSA, 2017).
EFSA recognizes the fact that a statistically significant effect not necessarily means a biological relevant effect as well. Therefore, EFSA argues that a biologically relevant effect size should be predefined based on its background variability. The background variability of a parameter may differ between persons and between a person and the population. Roughly, three options can be defined for assessing the critical effect size.
For various parameters critical effect sizes have been agreed, such as a 10% change in body weight gain and a 20% inhibition in acetylcholinesterase inhibition (WHO, 2015).
However, it is not always clear at which size an effect should be considered to be adverse. In such cases the data can be assessed by a group of experts on the subject (e.g. toxicologists, pharmacologists, clinicians). Factors such as reliability, relevance and natural variability should be taken into account. An expert knowledge elicitation can be used to facilitate the decision-making process. Based on the available information and using a weight of evidence approach, a critical effect size for risk assessment could be established. The justification for the choice of the critical effect size should be presented.
If no generally agreed critical effects sizes are available and no critical effect can be established, based on the available knowledge default values of 10% (extra risk for quantal data) and 5% (change in mean response) for continuous data from animal studies can be used, as proposed by EFSA (2017). However, EFSA notes that based on toxicological or statistical considerations a different benchmark response (BMR) may be used. Default values when relying on human data are not provided by EFSA (2017).
It is more difficult to determine the critical effect size when there are more factors influencing a certain effect. For instance, some food supplements are used in combination with exercise to enhance performance. This kind of supplements often has an effect on the adrenergic system leading to changes in parameters such as blood pressure and heart rate. These parameters are also affected by exercise itself. This may lead to an additive or synergistic effect causing the overall effect(s) to become adverse.

6 Safety assessment

The way the safety assessment should be done for a substance or botanical (preparation) depends on the type, amount and quality of the information available, as is gathered in the preceding chapters. This chapter describes the different approaches for safety assessment and the information that is required to apply them. Figures 6-1 to 6-3 provide a schematic overview of the different approaches. Together with the information provided in the text, the figures can be used as decision schemes to decide on the approach for the safety assessment.

6.1 Short summary of the available data

This section provides a concise summary of the relevant information from the description of the food supplement and the dietary exposure assessment. Also, it contains a concise summary of the toxicokinetic and toxicological data and its interpretation (in the same order as listed in chapters 3-5).
Based on this information it can be decided how to perform the actual safety assessment using the decision scheme (see figures 6-1 – 6-3).

6.2 Safety assessment

Decision schemes for the safety assessment
There are different approaches for the safety assessment, dependent on the available data, these are explained below. Figures 6-1 – 6-3 provide decision schemes to determine which approach should be used in a specific case. By answering a series of questions, a choice for the available approaches is made. These approaches are represented by the ellipses in the figures. For each approach additional explanation is given under the subheadings below (the subheadings correspond to the ellipses in the figure).

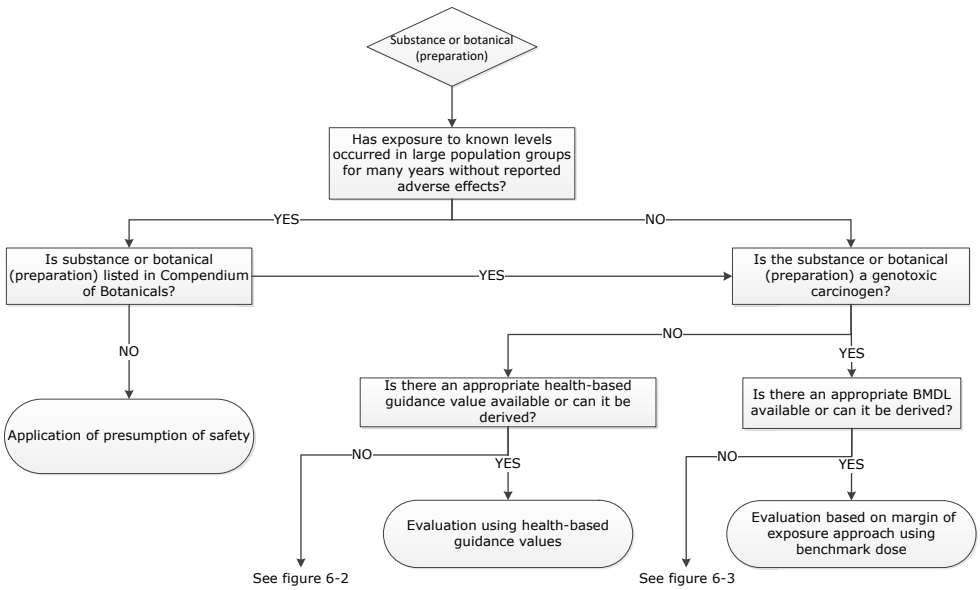

Figure 6-1. Decision scheme for determination which approach to use in the safety assessment based on type, amount and quality of available data.

Evaluation using presumption of safety
Safety of the substance or botanical (preparation) can be presumed when "available data would allow concluding that exposure to known levels of the botanical ingredient has occurred in large population groups for many years without reported adverse effects" (EFSA, 2009). EFSA adds to this that "it is recognized that for botanical ingredients lacking a history of food use, or for botanicals whose intended use levels will significantly exceed historical intake levels, an assessment of safety generally relies on experimental toxicity data" (EFSA, 2009).
Further, it is stated that for "botanicals and botanical preparations with a potential to contain toxic, addictive, psychotropic or other substances that may be of concern, presumption of safety can be applied if there is convincing evidence that these undesirable substances in the specific plant parts or preparations are either absent in the source material, or significantly reduced if not excluded, or inactivated during processing" (EFSA, 2009).
Prerequisites for this option are that data on historical use are available (see paragraph 4.3) and that the substance or botanical (preparation) is not listed in the Compendium of Botanicals (EFSA, 2012). This is reflected in the left pathway of the decision scheme presented in figure 6-1.

Evaluation using health-based guidance values
When presumption of safety cannot be applied, the safety assessment should be based on additional data. One way of doing this is by comparing the overall exposure estimate (from the diet plus supplement use) to the substance or botanical (preparation) of interest with a health-based guidance value (HBGV) to assess whether the estimated exposure is safe. This is reflected in the pathway in the middle in the decision scheme presented in figure 6-1.

This approach is not applicable for (botanicals that contain) substances that are genotoxic and carcinogenic. For these substances, a Margin of Exposure (MOE) approach needs to be applied (see the subheading Evaluation using the Margin of Exposure approach).

Evaluation using the Margin of Exposure approach
The Margin of Exposure (MOE) is an approach, in which exposure is compared to a BMDL value derived from an animal study or a BMDL from human data. It is applied to substances that are both genotoxic and carcinogenic (EFSA, 2005) and can therefore be applied to botanicals that contain such substances. This is depicted in the right pathway in the decision scheme presented in figure 6-1. The exposure resulting from using the botanical (preparation) needs to be taken into account as well as exposure from other dietary sources. A MOE of 10,000 or higher, "if it is based on the $BMDL_{10}$ 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 considered as a low priority for risk management actions" (EFSA, 2005). If lower, there is a possible concern for human health.

The MOE approach can also be used for non-genotoxic substances when the toxicological data do not allow the derivation of a HBGV (see figure 6-2). In that case, the exposure can be compared to a NOAEL, LOAEL or

BMDL or other effect level. When the MOE is considered sufficiently large (based on amongst others the reliability of the data on which the MOE is based), the exposure to this substance or botanical (preparation) would be of low concern from a public health point of view.

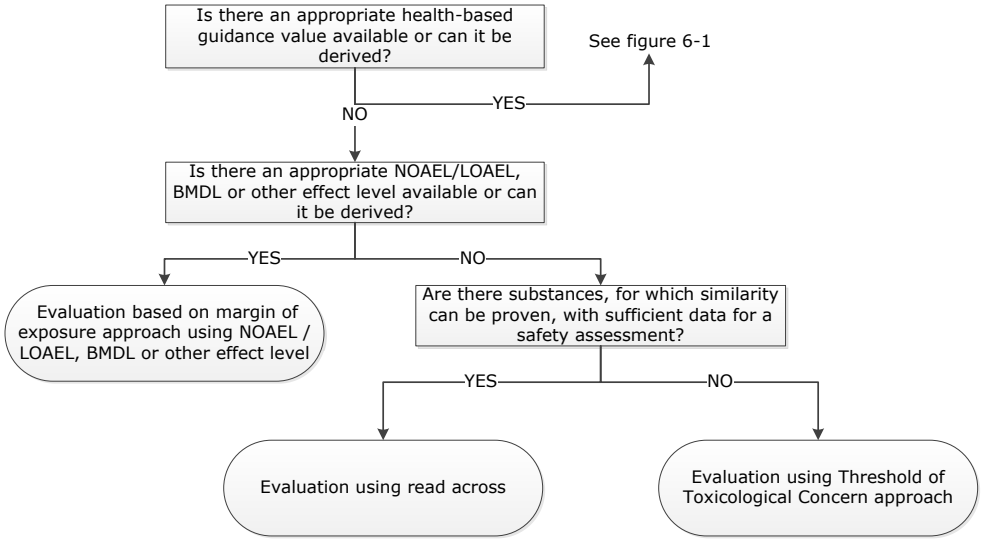

Figure 6-2. Decision scheme to use when presumption of safety cannot be applied, the substance or botanical (preparation) of interest is not a genotoxic carcinogen and no appropriate HBGV is available or can be derived.

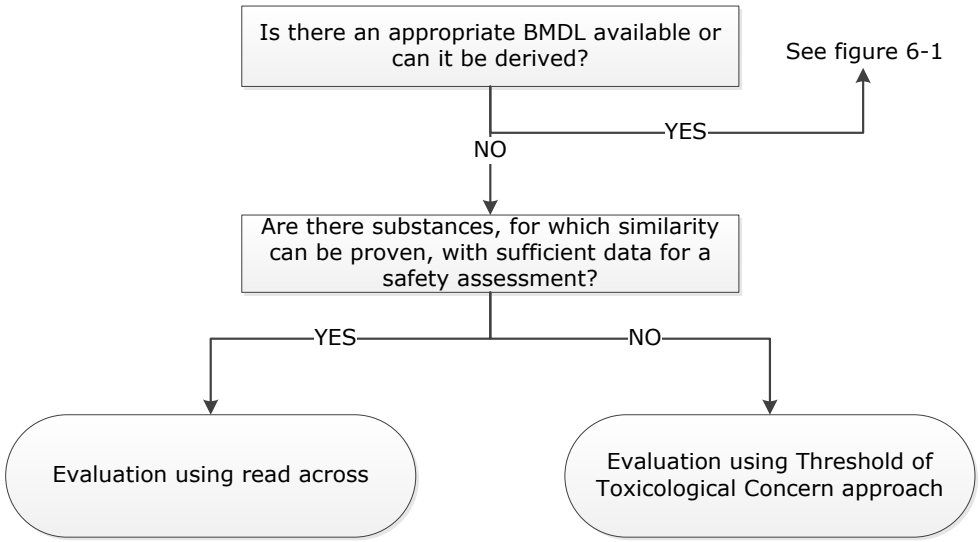

Figure 6-3. Decision scheme to use when substance or botanical (preparation) is a genotoxic carcinogen but no appropriate BMDL is available or can be derived.

Comparison with other substances (read across)

When above mentioned approaches are not possible, the safety assessment may be performed by applying read across to estimate potency based on data from (a) highly similar substance(s) (see figures 6-2 and 6-3).

Substances that are structurally similar are expected to have similar (eco)toxicological properties. This structural similarity can be supported by showing that the substances also have similar physicochemical properties (this provides answer to question Are there substances for

which similarity can be proven). Ideally, these physicochemical properties determine for a large part the (differences in) environmental fate and/or toxicokinetic behavior. Such substances may be considered as a group of substances.
These similarities may be due to a number of factors:

- common functional group (i.e. chemical similarity within the group)
- common precursors and/or likely common breakdown products via physical and/or biological processes which result in structurally-similar degradation products/metabolites
- a constant pattern in the properties across the group (i.e. of physicochemical and/or biological properties)

Read across is then the prediction of endpoint information for one substance (target substance), by using data on the same endpoint from (an)other substance(s), (source substance(s)) within a group of similar substances. Depending on the number of source substances, different read-across practices are distinguished: One-to-one, One-to-many, Many-to-one, and Many-to-many (ECHA, 2008; ECHA, 2012).
In order to perform a good read across several steps need to be fulfilled. First, a read across hypothesis is needed that describes the structural similarities and any other similarities (like similar physicochemical properties), and explains why the properties of the target substance can be predicted from data on the source substance(s) for each endpoint concerned, preferably with a mechanistic underpinning. Secondly, justification is needed to demonstrate that the hypothesis is supported by referring to a data set: all claims must be supported by data. Thirdly, the structural similarities between the source and target substances must be assessed as well as the impact of the structural differences on the toxicity profiles/potential of the source and target substances. Toxicokinetic information on the source and target substances can considerably strengthen the robustness of the hypothesis. If the read across hypothesis is based on same metabolic pathway, information must be provided on how likely the existence, rate and extent of metabolism are similar for the target and source chemicals. Is this metabolic pathway the main biotransformation process or could there be (toxicological) impact of alternative metabolic pathways?
Further information on the read-across approach and how to prepare substance grouping can for instance be found in guidance documents (ECHA, 2008; ECHA, 2012).
Crucial for read across is the definition of similarity, which is specific for the toxicological endpoint for which read across is performed, and that there are similar substances (according to the definition) for which experimental data is available for the endpoint of interest. Software tools like the OECD QSAR Toolbox (https://qsartoolbox.org/about) allow for a systematic search of similar substances (structural analogues) in various publicly available databases of toxicological information.

If read across is used for the safety assessment, the additional uncertainty introduced by this approach should be addressed, by adding an additional uncertainty factor, or by showing that the read across procedure is very likely to lead to a conservative (worst-case) estimate of the toxicological potency of the substance of interest. If several similar substances are available for read across, using the most toxic

source chemical for the read across would lead to such a worst-case estimate. It should then be hypothesized or shown that the target chemical (the chemical of interest) is likely to be less toxic than the source chemical.

Threshold of Toxicological Concern (TTC) approach
When there is also no possibility for read across, the Threshold of Toxicological Concern (TTC) concept may be applied (EFSA & WHO, 2016; EFSA, 2019a) (see figures 6-2 and 6-3). This approach considers five different so-called TTC values depending on which class of substances the substance of interest belongs. These values are presented in Table 6-1. For the determination of the appropriate (Cramer) Class, programs like the OECD QSAR Toolbox and Toxtree can be used provided that the chemical structure is known. The TTC concept cannot be used for aflatoxin-like, nitrosamine and azoxy-compounds, steroids, benzidines and polyhalogenated dibenzo-p-dioxins and -dibenzofurans.

Table 6-1 Overview of TTC values

Class	***TTC value in µg/person per day***	***TTC value in µg/kg bw per day****
With structural alert for genotoxicity	*0.15*	*0.0025*
Organophosphates and carbamates	*18*	*0.3*
Cramer class III	*90*	*1.5*
Cramer class II	*540*	*9.0*
Cramer class I	*1800*	*30*

[*] *Based on an average human body weight of 60 kg*

The total exposure (exposure from all dietary sources) to a substance is compared to the appropriate TTC value. The decision scheme (see EFSA, 2019a) shows that if the exposure is below the TTC value, the substance would have a low probability of adverse health effects. On the other hand, if the exposure exceeds the TTC, a (full) risk assessment is required.
The TTC concept may therefore have a good application to substances that appear in trace amounts in a botanical (preparation) or are present as a contamination, as this generally leads to low exposures. However, the outcome of applying the TTC approach in the case of exposure to botanical(s) (preparations) would generally result in exceeding the TTC value, leading to the conclusion that a full risk assessment should be conducted.

Since sufficient data for a full risk assessment are lacking (the reason for using the TTC approach for botanicals), the TTC value for a given substance or botanical (preparation) might be seen as the upper level of safe exposure. In other words, when exposure is beneath the applicable TTC value there is a low probability of adverse health effects. When the exposure is above the TTC value, it is not possible to assess the probability of adverse effects because sufficient data are lacking. This means that a safety concern cannot be ruled out.

Extra note in case of dealing with food supplements containing multiple substances with the same effect

Food supplements often contain multiple ingredients. In case these ingredients are expected to have a similar effect or mode of action, a risk assessment for the mixture could be done by assuming dose addition and assuming that all ingredients have the same potency (i.e. a relative potency factor of 1 – unless scientific evidence shows otherwise). In this way an indication of the consequences of having a mixture with ingredients having a similar effect might be given, however, the usefulness of this approach should be evaluated on a case by case basis (see also EFSA, 2019b).

6.3 Interactions

The consequences for the safety of the supplement due to possible interactions of the food supplement with medicines, other food supplements or other components from the diet should be discussed. Interactions may lead to alterations in toxicokinetics (eg. lower/higher plasma levels) as well as toxicodynamics (eg. synergistic or additive effects) of both the food supplement under evaluation and the medicine, food supplement or other component from the diet that is used concomitantly.

6.4 Sensitive/vulnerable groups

Information regarding the safety for sensitive/vulnerable sub-groups, which include infants, children, pregnant/breastfeeding woman, athletes and sportsmen, people with a specific health disease or condition, and elderly people, should be described in this section.

6.5 Uncertainties

In this section, the uncertainties that have been encountered during the assessment should be mentioned. If possible, it is also stated what influence the identified uncertainty has on the assessment, i.e. if it leads to an over- or underestimation of the risk (EFSA, 2006).

7 Conclusions and recommendations

The final conclusions on the safety of the substance or botanical (preparation) as well as the recommendations for further improvements should be mentioned in this section.

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The literature/references that were used in this assessment should be stated in this section.

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Appendix I

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