Nederlandse Voedsel- en Warenautoriteit
Ministerie van Landbouw, Natuur en Voedselkwaliteit

> Return address PO Box 43006 3540 AA Utrecht

To the Inspector-General of the Netherlands Food and Product Safety Authority

Advice of the Director of the Office for Risk Assessment and Research on

Pharmacologically active substances in food supplements

Office for Risk Assessment & Research

Catharijnesingel 59
3511 GG Utrecht
PO Box 43006
3540 AA Utrecht
www.nvwa.nl

Contact

T +31 (0)88 223 33 33
risicobeoordeling@nvwa.nl

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Introduction

In the Netherlands, food supplements that target weight control, weight loss, performance improvement and/or libido enhancement are available on the market. These supplements may contain pharmacologically active substances. Research by the Netherlands Food and Product Safety Authority (NVWA) in 2016 showed that more than 60% of the 160 libido-enhancing supplements, slimming preparations, fat burners and pre-workout products examined contained one or more regulated pharmacologically active substances. These products were also found to contain non-regulated pharmacologically active substances in concentrations with potentially adverse health effects after ingestion.

A pharmacologically active substance (which, in this advice, is a substance that targets weight control, weight reduction, performance improvement and/or libido enhancement) influences a particular physiological function (e.g. blood pressure or metabolism) in humans or animals. Substances can either occur naturally in a foodstuff or be man-made (i.e. not of natural origin) and added to, for example, a supplement. Consumers may not be aware of the presence of such a substance if it is not identified, or not identified correctly, on the label. Adverse health effects may occur when a consumer takes one or more food supplements, possibly without reading the instructions (e.g. by taking more pills than prescribed), uses medication (potential interaction with medicines) or engages in particularly strenuous physical exercise (e.g. extreme sports). In addition, top athletes run the risk of a positive doping test because the use of performance-improving drugs in competition is prohibited. In the past, athletes indeed have tested positive where the source was a contaminated food supplement.

Within the NVWA's Enforcement Directorate, the Special Food & Drink Products (BED) domain is charged with the supervision of, among other things, food supplements, herbal preparations, novel foods, baby and infant formulae and food for medical use. The supervision and enforcement of food supplements is complex. At the end of December 2020, the Minister for Medical Care and Sport

informed the House of Representatives about the approach to food supplement safety[1]. The approach consists of four components:

1. compiling a national list of unsafe substances;
2. targeted monitoring of Internet trade and of trade from third countries;
3. information and communication about risks;
4. exploring possibilities for the introduction of a notification system.

This approach represents the steps the Minister is taking to improve the monitoring of the safety of active substances in food supplements.

In November 2020 the first meeting of the Heads of Food Safety Agencies[2] (HoA) working group on food supplements took place. The working group is chaired by Germany and Ireland and its objective is to establish a common European list of substances in food supplements that should be forbidden or limited.

The BED domain has compiled a list of substances that are regularly found in food supplements and are not regulated by law:

- DMAA (1,3-dimethylamylamine)
- DMBA (1,3-dimethylbutylamine; nor-DMAA)
- DMHA (1,5-dimethylhexylamine; octodrine)
- BMPEA (β-methylphenethylamine)
- PEA (phenethylamine)
- N,N-DMPEA (N,N-dimethylphenethylamine)
- Halostachine
- Higenamine
- Hordenine
- Icariin
- Isopropyloctopamine
- Methylsynephrine

The BED domain has asked the Office for Risk Assessment & Research (BuRO):

1. to draw up fact sheets listing the information available on these substances (including toxicological features), and
2. if possible, to determine a health-based guidance value for these substances.

BuRO used the answers to these 2 questions to carry out a risk assessment.

Approach

Given the scope of the request, BuRO decided to split it up and asked the Front Office Food and Product Safety (FO) and the Department of Pharmacology & Toxicology of Maastricht University (UM) to conduct the associated research.

BuRO asked FO to prepare a fact sheet for DMAA, DMBA and DMHA and, if possible, to establish a health-based guidance value. The fact sheet contains data on the following aspects:

- trivial names or synonyms
- (toxico)kinetics (absorption, distribution, metabolism and excretion)
- (toxico)dynamics

[1]Letter to the House of Representatives on the approach to the safety of food supplements, 14 December 2020. Available at https://www.tweedekamer.nl/kamerstukken/brieven_regering/detail?id=2020Z24798&did=2020D52042

[2]See https://webgate.ec.europa.eu/hoa/ for detailed information.

- interactions with other substances

BuRO asked UM to prepare fact sheets for BMPEA, PEA, N,N-DMPEA, halostamine, hordenine, icariin, isopropyloctopamine and methylsynephrine, focusing on the following aspects:
- trivial names or synonyms
- (toxico)kinetics (absorption, distribution, metabolism and excretion)
- (toxico)dynamics
- interactions with other substances

Based on substance name and synonyms, UM scanned Pubmed, Medline, Embase and the Hazardous Substances Data Bank (HSDB) for information to be included in the fact sheets. Toxline was searched using the relevant CAS number. Articles dealing with the detection of the substance in question were not considered.

Subsequently, BuRO asked FO to establish, where possible, a health-based guidance value[3] or an effect level[4] based on the fact sheets provided by UM. In addition, it asked FO to identify any potentially sensitive groups of consumers that required special attention in the assessment and whether it was possible to apply the 'read-across' approach[5] where the data available on a substance were insufficient. FO used the fact sheets as the basis for its research and only conducted a limited literature review to check whether essential literature was missing.

Ultimately, BuRO integrated UM's fact sheets and FO's assessments and used them as the basis for this advice.

In addition, BuRO also examined the relevant legislation. Finally, BuRO developed a structured approach for the risk assessment of food supplements where insufficient toxicological data is available to establish a health-based exposure value.

This advice has been subjected to an independent peer review.

Findings

- The legal basis regarding specific legal standards for pharmacologically active substances in food supplements is limited. Regulation (EC) No 1925/2006 and the Dutch Herbal Preparations (Commodities Act) Decree only regulate a relatively small number of pharmacologically active substances in food supplements.

[3] A health-based guidance value (*gezondheidskundige grenswaarde*) is the quantity of a chemical substance to which a person can be exposed without any significant health risk. There are different types of health-based guidance values, for example for oral exposure or exposure through inhalation. In addition, a distinction is made between once-only exposure and lifelong exposure. For oral exposure, the health-based guidance value is usually expressed in milligrams per kilogram of body weight (mg/kg bw) per day.
[4] An effect level is the lowest dose at which effects have been observed in humans. This is not to say that no effects might occur with even lower doses, but there is no information on this (yet).
[5] 'Read-across' is an approach in which the available information on the potential effects of a substance is used to estimate the potential effects of a similar substance for which information is lacking.

- If a food supplement is shown to contain a pharmacologically active substance that is not specifically regulated, enforcement measures can be based on 3 pieces of legislation:
  1. The Medicines Act (*Geneesmiddelenwet*), if a supplement meets the definition of a medicinal product;
  2. the Novel Foods Regulation (Regulation (EU) No 2015/2283), if a supplement meets the definition of a novel food;
  3. the General Food Law Regulation (Regulation (EC) No 178/2002), a risk assessment is carried out to determine whether the intake of a particular supplement poses a risk to public health (i.e. is injurious to health). A risk assessment is carried out when the other statutory options are not sufficient. If a substance cannot be demonstrated to be injurious to health, the NVWA is unable to take enforcement measures. In such a case, food supplements containing potentially harmful pharmacologically active substances will continue to be available on the Dutch market.
- Where there is insufficient or no toxicological information to establish a health-based guidance value for a pharmacologically active substance in food supplements, there may still be information that can help provide an indication as to the potential risks to consumers. This could include information from answers to the following questions:
  1. Is the substance naturally present in a foodstuff (which may give indications of its historical safe use)?
  2. Has the substance been used as (an ingredient in) a medicine?
  3. Are there any studies in which the substance produced adverse effects after oral ingestion in humans or animals?
  4. Is there any other information that might point to potential risks for consumers (e.g. case reports)?
  5. In some cases, little or no information will be available to indicate the potential risks to consumers. In these cases, the read-across approach or the Threshold of Toxicological Concern (TTC) approach could be applied[6].

Hazard identification

- In addition to the 12 substances that are subject to a risk assessment in this opinion, food supplements contain many other pharmacologically active substances. For more details, see the substantiation of this advice.

Hazard characterisation

- Since the European Food Safety Authority (EFSA), the Joint FAO/WHO Expert Committee on Food Additives (JECFA) nor any other scientific institution have assessed the available toxicological data for DMAA, DMBA, DMHA, BMPEA, PEA, N,N-DMPEA, halostamine, higenamine, hordenine, icariin, isopropyloctopamine and methylsynephrine, they have not established health-based guidance values for these substances either. Both BuRO and FO have assessed the available toxicological data for these substances, but they were unable to establish health-based guidance values because no good-quality dose-effect studies with humans or animals are available. Only for hordenine did BuRO establish a health-based guidance value (but FO did not). For more details on the available information, please refer to the substantiation of and annexes to this advice.

[6] The TTC approach provides generic thresholds for chronic exposure in humans, which are established by grouping experimental toxicity data from animal bioassays. These TTC thresholds are such that the likelihood of adverse effects at exposures below these thresholds is considered low. For more details, see the substantiation of this advice.

- Based on the available toxicity information and the FO assessments, BuRO provides an overview of the daily doses that involve a low risk of adverse effects on the health of consumers.

***Table 1**. Overview of the daily doses (µg/day) with a low probability of adverse health effects for a series of pharmacologically active substances in food supplements.*

Substance	**Daily dose (µg/day) with low risk of adverse effects**	**Substantiation**
DMAA	4,000	BuRO advice, 2012
DMBA	4,000	Read across
DMHA	4,000	Read across
BMPEA	90	TTC approach
PEA	5,000	Comparison with dietary intake
N,N-DMPEA	90	TTC approach
Halostachine	90	TTC approach
Higenamine	0.15	TTC approach
Hordenine	2,340	ADI, comparison with dietary intake
Icariin	0.15	TTC approach
Isopropyloctopamine	90	TTC approach
Methylsynephrine	90	TTC approach

- Supplements consist of mixtures of different substances which potentially enhance each other's effects. In general, it can be concluded that the effects of the stimulants listed in Table 1 on the heart rate, cardiac contraction and blood pressure may increase when these substances are used in combination with substances that have similar stimulating effects (such as synephrine, yohimbine, caffeine etc.). For more details on each substance, please refer to the substantiation of this advice.

Exposure

- Between October 2013 and December 2019, the NVWA sampled 502 food supplements that were subsequently analysed for the presence of pharmacologically active substances. In all, 314 supplements were found to contain one or more regulated or non-regulated pharmacologically active substances. The daily dose was determined by multiplying the concentration of a substance found in a supplement by the recommended daily intake stated on the label.
- Table 2 presents an overview of the daily dose for the pharmacologically active substances in food supplements relevant to this advice.

***Table 2**. Overview of the average, median, minimum and maximum daily doses (µg/day) for a series of pharmacologically active substances in food supplements.*

Substance	N	Daily dose (µg/day)			
		Mean	Median	Minimum	Maximum
DMAA	14	60,400	62,300	0.1	143,400
DMBA	8	133,200	57,100	51,500	286,000
DMHA*	0				
BMPEA	10 (9)**	139,200	136,500	115,500	162,000
N,N-DMPEA*	0				
PEA	16	12,200	9	1	127,700
Halostachine	1	34,000	34,000	34,000	34,000
Higenamine	32 (27)	31,200	14,300	0.01	90,700
Hordenine	23 (19)	83,200	24,600	25	668,600
Icariin	31 (29)	29,900	40	0.02	402,900
Isopropyloctopamine	1	140,000	140,000	140,000	140,000
Methylsynephrine	17 (15)	56,700	63,000	3	137,800

* No data available.

** The number in brackets represents the actual number of detections for which the substance content has been quantified and dose information was available to determine the daily dose.

Risk assessment

- The mean and maximum daily doses of all the substances listed in Table 2 were found to exceed the daily dose that involves a low risk of adverse effects (Table 1). This also applies to the median daily dose for all substances, except PEA. When looking at the minimum daily dose, DMBA, BMPEA, halostachine and isopropyloctopamine exceed the daily dose which involves a low risk of adverse effects.
- Several groups of consumers may run an elevated risk when taking food supplements containing the substances described in this advice. In general, this concerns children and pregnant and lactating women. More specifically, this concerns athletes and other users who deliberately take these supplements to benefit from their stimulating effects. Consumers who already have a high blood pressure or heart rate (consumers with cardiovascular disease or obesity) or who use specific medicines (MAO-inhibitors) are also at extra risk.

Answer to the main question

1. Preparing fact sheets with information on these substances (including toxicology).

Fact sheets with toxicology data have been prepared. For details, please refer to the substantiation of and annexes to this advice.

2. Establishing a health-based guidance value (if possible).

BuRO was unable to establish a health-based exposure value for the above substances (with the exception of hordenine) based on toxicological data for the substances themselves.

For DMAA, DMBA, DMHA, BMPEA, PEA, N,N-DMPEA, halostachine, higenamine, hordenine, icariin, isopropyloctopamine and methylsynephrine, BuRO has established daily doses with a low probability of adverse effects (Table 1). In the case of hordenine, this daily dose was established on the basis of an ADI and a comparison with intake through food. Also in the case of PEA, BuRO made a comparison with the levels that consumers ingest through food. For the other substances, no toxicological data were available and read-across or the TTC approach was applied.

Advice

To the Inspector-General of the NVWA

- Prevent the marketing of food supplements containing DMAA, DMBA, DMHA, BMPEA, PEA, N,N-DMPEA, halostachine, hordenine, icariin, isopropyloctopamine or methylsynephrine at daily doses exceeding those specified in Table 1.
- Present this advice to the members of the HoA working group on food supplements and propose to follow the approach used to assess (other) pharmacological active substances in food supplements.

To the Minister for Medical Care and Sport

- Add DMAA, DMBA, DMHA, BMPEA, PEA, N,N-DMPEA, halostachine, higenamine, hordenine, icariin, isopropyloctopamine and methylsynephrine to the national list of unsafe substances to be compiled.

Yours sincerely,

Office for Risk Assessment & Research
Prof. Antoon Opperhuizen

Substantiation

Office for Risk Assessment & Research

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Introduction

Directive 2002/46/EC[7] defines food supplements as 'foodstuffs the purpose of which is to supplement the normal diet and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination, marketed in dose form, namely forms such as capsules, pastilles, tablets, pills and other similar forms, sachets of powder, ampoules of liquids, drop dispensing bottles, and other similar forms of liquids and powders designed to be taken in measured small unit quantities.'

Like all food companies, companies selling food supplements must comply with the applicable food legislation[8]. This means that a food supplement:

1. cannot be defined as a medicinal product;
2. is not injurious to health;
3. contains no or only limited amounts of regulated ingredients (e.g. aristolochic acids and yohimbe);
4. does not contain 'novel foods' that have not been admitted;
5. contains only vitamin and mineral substances listed in Annexes I or II to Directive 2002/46/EC;
6. is accompanied by the correct mandatory food information according to the legal requirements[9].
7. only contains claims that comply with the Claims Regulation[10] and have been assessed and approved.

A pharmacologically active substance affects a particular physiological function (e.g. blood pressure or metabolism) of humans or animals. A substance can occur naturally in a foodstuff or be man-made (i.e. not of natural origin) and added to the foodstuff. Consumers may not be aware of the presence of such a substance because it has not been declared on the label or has been declared incorrectly. This may lead to a positive doping test, for example because the use of performance-enhancing drugs in competition is prohibited (Rocha et al., 2016; Denham, 2017; Duiven & Koert, 2020). In the past, athletes have tested positive where the source was a contaminated food supplement. Adverse health effects may occur when a consumer takes one or more supplements, possibly without heeding the instructions (e.g. by taking more pills than prescribed), uses medication (interaction with medicines) or engages in particularly strenuous physical exercise (e.g. extreme/intensive sports) (Biesterbos et al., 2017; NVWA, 2017; Biesterbos et al., 2019). In May 2017, the NVWA published a fact sheet on this subject. Research had shown that over 60% of 160 libido-enhancing supplements, slimming agents, fat burners and pre-workout products examined contained at least 1 regulated pharmacologically active substance. These products

[7] Directive 2002/46/EC of the European Parliament and the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements.
[8] See also https://www.nvwa.nl/onderwerpen/voedingssupplementen-en-kruidenpreparaten/regelgeving-voedingssupplementen-en-kruidenpreparaten/regels-voedingssupplementen-met-farmacologisch-actieve-stoffen for an overview of the regulations.
[9] Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers, amending Regulations (EC) No 1924/2006 and (EC) No 1925/2006 of the European Parliament and of the Council, and repealing Commission Directive 87/250/EEC, Council Directive 90/496/EEC, Commission Directive 1999/10/EC, Directive 2000/13/EC of the European Parliament and of the Council, Commission Directives 2002/67/EC and 2008/5/EC and Commission Regulation (EC) No 608/2004.
[10] Regulation (EC) No 1924/2006 on nutrition and health claims made on foods.

also contained unregulated pharmacologically active substances in concentrations that could lead to adverse health effects after ingestion (NVWA, 2017).

Legislation
Once a food supplement has been shown to contain a pharmacologically active substance, the enforcement procedure is complex. First of all, the NVWA - possibly in consultation with the Inspectorate for Health and Youth Care - decides for each supplement whether it qualifies as a medicine or as a product under the Opium Act (*Opiumwet*). If it does not, the supplement is a foodstuff.

Medicines
According to the Medicines Act, a medicine is a substance or a combination of substances that is intended to be administered or used, or is presented in any way as being suitable for curing or preventing a disease, defect, wound or pain in humans, making a medical diagnosis in humans, or restoring, improving or otherwise modifying physiological functions in humans by exerting a pharmacological, immunological or metabolic effect.

A food supplement can be classified as a medicine in 2 ways: on the basis of food information (i.e. claims) or on the basis of the presence of a pharmacologically active substance. In the first case, the product is a medicine 'by presentation', and in the second case a medicine 'by administration'. This BuRO advice focuses exclusively on ingredients of food supplements. It does not consider the legal aspects of medicines 'by presentation'.

Until 2009, the presence of a pharmacologically active substance in a food supplement was sufficient to trigger intervention under the Medicines Act. However, case law has since narrowed down the interpretation of the definition of a medicine (HvJ-EU, 2009;2014). A product is a medicine if the amount of a pharmacologically active substance can, when used according to the instructions, significantly influence physiological functions in humans (HvJ-EU, 2009) and if the product is intended to prevent or cure a disease (HvJ-EU, 2014). In addition, in order for a product to be classified as a medicine, the following criteria must be assessed: its manner of use, extent of distribution, consumer awareness and the risks which its use may entail (HvJ-EU, 2009).

If a food supplement containing a pharmacologically active substance is found, the above criteria must be met before intervention is possible under the Medicines Act. The substance content must be sufficient for it to have an actual effect. The product must be intended to prevent or cure a disease and consumers must be able to know that the product is in fact a medicine. If these criteria are not met, the product is a food supplement.

Food supplements

Regulated ingredients

Since it was amended on 1 July 2020, the Herbal Preparations (Commodities Act) Decree (*Warenwetbesluit Kruidenpreparaten*)[11] prohibits the presence of aconitine, aristolochic acids, atropine, colchicine, hyoscyamine, m- and o-

[11] Bulletin of Acts and Decrees 2020, 100 see https://zoek.officielebekendmakingen.nl/stb-2020-100.html

synephrine, *Artemisia absinthium* oil, pilocarpine, scopolamine, strychnine or yohimbe alkaloids in herbal preparations. In addition, herbal preparations may not contain more than 27 mg of p-synephrine per daily dose. Regulation (EC) No 1925/2006[12] bans the use of ephedra and yohimbe in food supplements.

Novel foods

The Novel Foods Regulation (Regulation (EC) No. 2015/2283[13]) addresses the placing on the market of foods and food ingredients that were not used for human consumption to a significant degree within the European Union before 15 May 1997. These new foodstuffs and food ingredients are also known as 'novel foods'. Before a novel food/ingredient can be placed on the market, approval must be requested from the European Commission. A dossier must be submitted to demonstrate that the foodstuff is safe for human consumption. As long as the European Commission has not granted a licence, the product cannot be used in/as food.

General Food Law Regulation

Pursuant to the General Food Law Regulation (GFLR; Regulation (EC) No 178/2002[14]), food must be safe. The responsibility for this lies with the food business operator (FBO). The NVWA has a monitoring task. Article 14 of the GFLR is the article that prohibits the placing on the market of unsafe food. In order to take measures on the basis of this article (e.g. to oblige a FBO to withdraw a food supplement containing a pharmacologically active substance from the market), the NVWA must demonstrate that the food supplement in question is unsafe (i.e. injurious to health of consumers). To this end, the NVWA carries out a risk assessment. Performing a risk assessment can be complicated when toxicity data are lacking and it is impossible to demonstrate to a sufficient degree that the supplement is injurious to health. In such cases, the NVWA will be unable to effect enforcement.

Figure 1 presents an overview of the enforcement routes when a food supplement with a pharmacologically active substance is found. At present, a food supplement containing a pharmacologically active substance can be classified as a medicine or as a food. In the future, the 'Opium Act product' option (New Psychoactive Substance (NPS)[15]) will be added. In Figure 1 this option is shown with a dotted line.

[12] Regulation (EC) No 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods.
[13]Regulation (EU) 2015/2283 on novel foods, amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and repealing Regulation (EC) No 258/97 of the European Parliament and of the Council and Commission Regulation (EC) No 1852/2001.
[14] Regulation (EC) No. 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety.
[15] New psychoactive substances are substances which appear regularly on the market and are similar in effect to traditional illegal drugs, but which are not (yet) covered by drugs legislation.

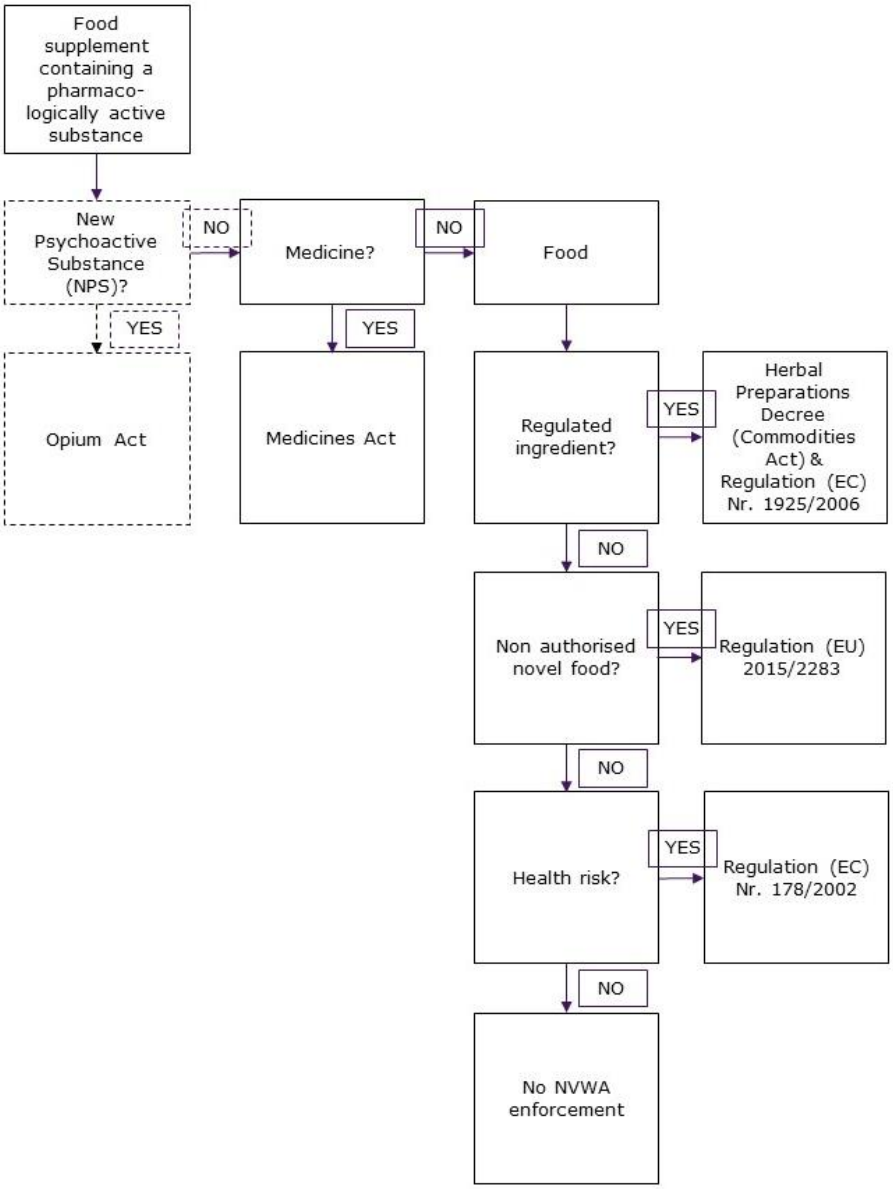

Figure 1. *Overview of enforcement routes when a food supplement containing a pharmacologically active substance is found. The dotted line represents the NPS route (currently draft legislation).*

New Psychoactive Substance (NPS)
The Ministry of Health, Welfare and Sport (VWS) intends[16] to amend the Opium Act by including a List IA in addition to List I and List II. List IA will contain a number of psychoactive substance groups whose chemical structure is derived from several substances in List I of the Opium Act. These are substances that produce, or are intended to produce, similar psychoactive effects to those produced by known List I drugs (e.g. THC, MDMA and heroin). NPSs may pose health risks unknown to the user. While the exact health risks of these NPSs have

[16] Public consultation until 20 April 2020 (https://www.internetconsultatie.nl/opiumwet_nps).

not yet been identified, it is plausible that they can cause health damage since they are related to substances that are already on List I of the Opium Act. Many NPSs are produced to circumvent drug laws. By making small structural changes to the chemical structure of an illegal drug, it is possible to create a new psychoactive substance that is still legal (i.e. not yet banned at the moment of production) and has effects similar to those of illegal drugs. Adding an individual NPS to existing drug legislation usually takes a long time. The addition of List IA to the Opium Act will make it possible to ban groups of NPSs in advance on account of the basic chemical structure of a substance.

The proposed List IA contains 3 substance groups:

1. substances derived from 2-phenethylamine. This also includes substances that have the basic structure of cathinone;
2. cannabimimetics or synthetic cannabinoids;
3. substances derived from 4-aminopiperidine.

The draft legislation excludes foodstuffs, including herbal preparations, which naturally contain a substance derived from 2-phenethylamine. 'Naturally' is understood to mean present and with a content that has been described in scientific literature. The NVWA is not authorised to intervene under the Opium Act. The Inspectorate for Health and Youth Care is responsible for supervision.

Approach to the safety of food supplements
As appears from the above, enforcement is complex in the case of food supplements containing pharmacologically active substances. At the end of 2020, the Minister for Medical Care and Sport informed the House of Representatives about the approach to the safety of food supplements[17]. That approach consists of 4 components:

1. compiling a national list of unsafe substances;
2. targeted monitoring of Internet trade and of trade from third countries;
3. information and communication about risks;
4. exploring possibilities for the introduction of a notification system.

This approach represents the steps the Minister is taking to improve the monitoring of the safety of active substances in food supplements.

HoA working group on food supplements
In November 2020 the first meeting of the Heads of Food Safety Agencies[18] (HoA) working group on food supplements took place. The working group is chaired by Germany and Ireland. Its objective is to establish a common European list of substances in food supplements that should be forbidden or limited.

Hazard identification

The NVWA's analyses
Between October 2013 and December 2019, the NVWA sampled 502 food supplements in the following 2 ways.

[17]Letter to the House of Representatives on the approach to the safety of food supplements, 14 December 2020. Available at https://www.tweedekamer.nl/kamerstukken/brieven_regering/detail?id=2020Z24798&did=2020D52042
[18]See https://webgate.ec.europa.eu/hoa/ for detailed information.

1. Proactive: project-based sampling of food supplements that are intended to enhance sexual performance, improve physical performance or induce weight loss.
2. Reactive: sampling following an RASFF notification or a complaint from a consumer regarding a specific product.

The range of products that claim to enhance sexual or physical performance or stimulate weight loss is large and reaches consumers through physical shops or the Internet. In addition, such products are also traded and sold via other channels, including social media and illegal routes. As a result, it is not possible to sample the entire range of food supplements available. The NVWA made choices and set up projects that enable the targeted search for supplements with pharmacologically active substances. Due to the complexity of the sector, the sampled products do not represent the wide range of products available on the Dutch market (NVWA, 2017).

Products supposedly enhancing sexual performance were sampled when they looked like a herbal preparation or food supplement on the outside and made a claim about enhancing sexual performance. Products supposedly improving physical performance or inducing weight loss were sampled based on claims stated on the label, the presence of substances in the ingredients list and reports from abroad (RASFF) (NVWA, 2017).

The sampled food supplements were then analysed by RIVM or Wageningen Food Safety Research (WFSR). Of the 502 food supplements sampled, 314 were found to contain one or more pharmacologically active substances (

Table **3**). The table does not distinguish between supplements based on sampling method (proactive or reactive).

***Table 3**. Overview of the number of food supplements analysed between October 2013 and December 2019 and the number of pharmacologically active substances detected per supplement.*

	2013	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**Total**
Analysed (N)	54	56	169	93	72	49	9	502
Number of supplements found to contain one or more pharmaco-logically active substances	33 (61%)	36 (64%)	103 (61%)	68 (73%)	52 (72%)	15 (31%)	7 (78%)	314 (63 %)
• 1 substance	15	16	45	25	35	11	1	148 (47 %)
• 2 substances	9	12	32	16	11	0	3	83 (26 %)
• 3 substances	3	4	17	11	5	2	2	44 (14 %)
• 4 substances	3	2	8	12	1	2	1	29 (9%)
• 5 substances	2	1	0	3	0	0	0	6 (2%)
• 6 substances	0	1	0	0	0	0	0	1 (0%)
• 7 substances	1	0	0	1	0	0	0	2 (1%)
• 8 substances	0	0	0	0	0	0	0	0 (0%)
• 9 substances	0	0	1	0	0	0	0	1 (0%)

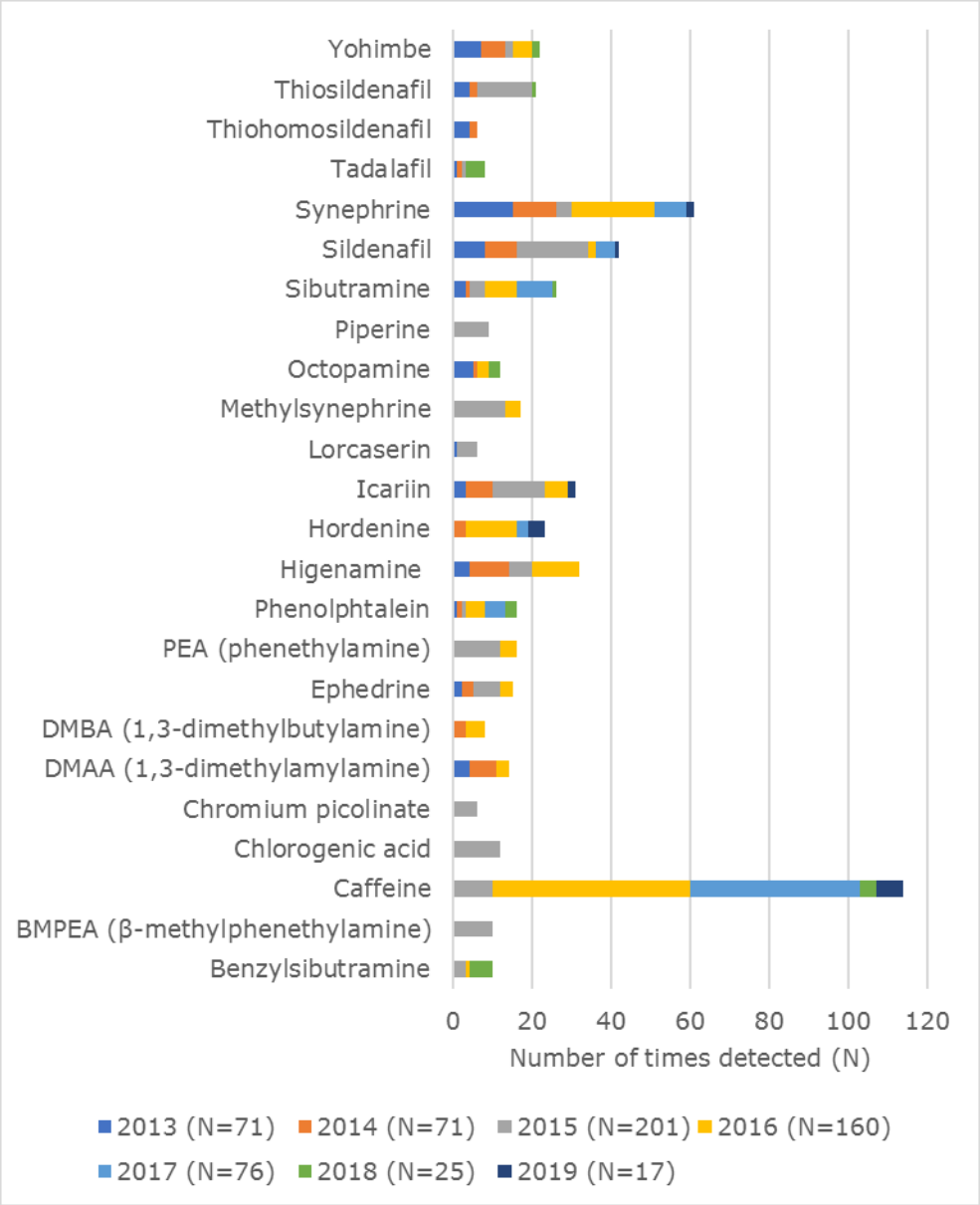

Figure 2. *Overview of the number of times a substance was found in food supplements analysed between October 2013 and December 2019. For reasons of readability, only substances that were detected more than 5 times are shown. The total number of substances found per year is shown in brackets. This can also be calculated with the data available from Table 3. For example, N=71 in 2013; ((15x1)+(9x2)+(3x3)+(5x2)+(7x1))=71 detections / substances found.*

Figure 2 provides an overview of the number of times a substance was found in a food supplement sampled by the NVWA between October 2013 and December 2019. For the sake of readability, only substances that were detected more than 5 times are shown. The complete list of substances found is shown in Annex I.

Caffeine (N=114) is the substance most commonly found, followed by synephrine (N=61), sildenafil (N=42), higenamine (N=32), icariin (N=31), sibutramine (N=26), hordenine (N=23), yohimbine (N=22) and thiosildenafil (N=21).

In 2017, the NVWA visited 16 companies that together represented the largest share of the Dutch market with regard to the sale of libido enhancers, slimming preparations, fat burners and pre-workout products. After an initial audit and possible re-inspection, half of the companies were found to have an adequate food safety plan. The other half of the companies did not have a proper food safety plan (yet).

RASFF reports
The RASFF system[19] shows 1,225 notifications in the product category of 'dietetic foods, food supplements, fortified foods' from 2015 to 2019. When notifications relating to microbiological or physical hazards are disregarded, there remain 1,085 reports of the presence of potentially harmful chemical substances in food supplements. The Netherlands is mentioned in 280 notifications. This either means that the Netherlands itself made an RASFF notification or was alerted to the fact that a product from a notification was traded in the Netherlands. In general, a RASFF notification is made after a substance has been found on a food supplement label. In some cases, an analysis result is reported.
On 411 occasions a substance is mentioned. Annex II contains a list of all the substances mentioned. Agmatine sulphate (N=40) was the substance most frequently mentioned, followed by caffeine (N=21), CBD (N=20) and vitamin B6 (N=17). The RASFF notifications mainly show which substances are the focus of monitoring in the EU Member States. Those substances are not necessarily the substances that involve the highest risk.

Questions to NVIC
The National Poisons Information Centre (NVIC)[20] receives hundreds of questions each year about the intake of food supplements. These questions partly concern unintentional intake of food supplements by young children, but the centre also receives questions about symptoms following intentional use, or misuse, of food supplements. The NVIC performs constant monitoring and warns the NVWA about potentially harmful food supplements (Roelen et al., 2016). In its annual report, the NVIC divides the questions into 5 intended-effect categories: tranquillising supplements[21], stimulating sports and slimming agents (energisers)[22], non-stimulating sports and slimming agents[23], superfoods[24], and other food supplements[25]. Figure 3 provides an overview of the number of exposures to food supplements reported to the NVIC between 2015 and 2019 (Roelen et al., 2016;

[19] Rapid Alert System for Food and Feed, see https://ec.europa.eu/food/safety/rasff_en
[20] The NVIC can only be contacted by healthcare providers (e.g. general practitioners or doctors in the emergency room). The number of requests for advice that the NVIC receives only gives an indication of the number of potential poisoning incidents due to exposure to a food supplement. This is because healthcare providers only approach the NVIC when they lack the knowledge required for treatment. Care providers who do have the knowledge required are less likely to contact the NVIC in such a case.
[21] Substances intended to induce relaxation. These are often used to help people stay calm and sleep (or fall asleep) better.
[22] Substances intended to give an energy boost. These are often used to improve performance, for example for people who engage in intensive sports training, need to stay awake or want to lose weight.
[23] Substances that are intended to help people lose weight but work in a different way than the usual energisers.
[24] Foodstuffs which are claimed to have special positive attributes.
[25] Usually intended to improve or support specific organ functions. Examples of claims found on such products are 'for natural bowel movement' and 'good for your heart and blood vessels'.

Roelen et al., 2017; Verputten et al., 2018; Roelen et al., 2019; van Riel et al., 2020). The total number of exposures per year is shown in brackets. The number of exposures does not correspond to the number of people exposed. A question about the use of 2 different products by 1 person counts as 2 exposures.

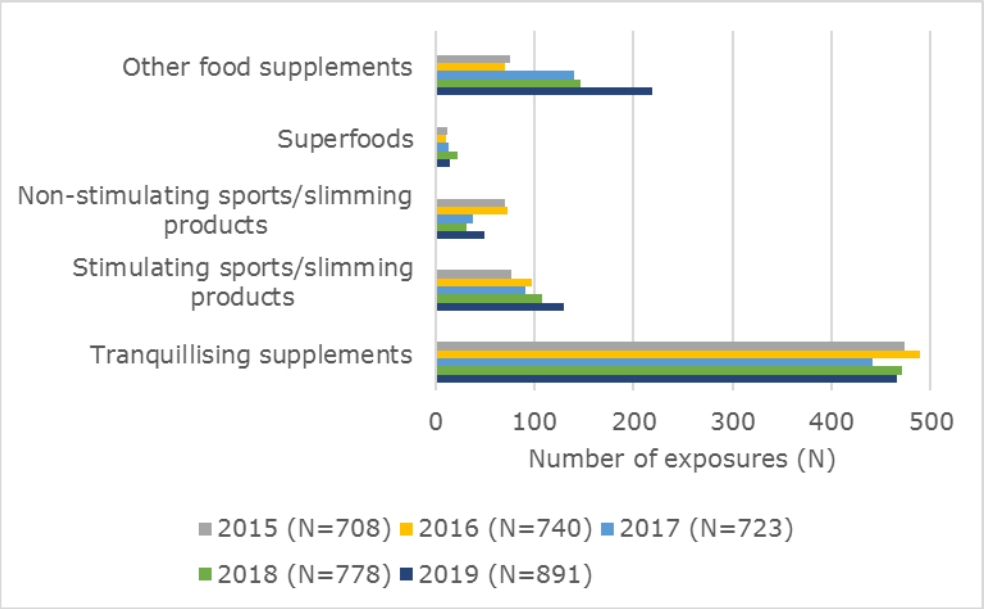

Figure 3. *The number of food supplement exposures reported to the NVIC between 2015 and 2019. The total number of exposures per year is given in brackets.*

Compared to tranquillising supplements, the number of reported exposures to stimulating sports/slimming products is small. The latter group includes food supplements with the highest risk profile, because they contain substances to increase metabolism (Roelen et al., 2016; Roelen et al., 2017; Verputten et al., 2018; Roelen et al., 2019; van Riel et al., 2020). These substances stimulate the sympathetic nervous system, producing an adrenaline-like effect. Figure 4 presents an overview of the substances that are mentioned most frequently in questions to the NVIC concerning stimulating sports/slimming products. The information referred to often comes from the label, but sometimes it is derived from verbal communication by the user (anamnesis) or found in subsequent analysis. Between 2015 and 2019, the NVIC received several questions from users of these substances who experienced serious health problems such as nausea, vomiting, agitation, dizziness, increased blood pressure, increased heart rate and chest pain. In addition, between 2015 and 2019 the NVIC, in collaboration with RIVM, analysed 44 samples of stimulant supplements for active ingredients. One or more pharmacologically active substances were found in 38 of these samples. Twenty-five samples contained caffeine. Of those, 13 also contained another substance, such as 1,3-DMAA (Roelen et al., 2016; Roelen et al., 2017; Verputten et al., 2018; Roelen et al., 2019; van Riel et al., 2020). In 2019, the number of reports involving caffeine ingestion increased. The most common complaints after caffeine intake were (persistent) vomiting, nausea, restlessness, tremors and tachycardia (increased heart rate) (van Riel et al., 2020).

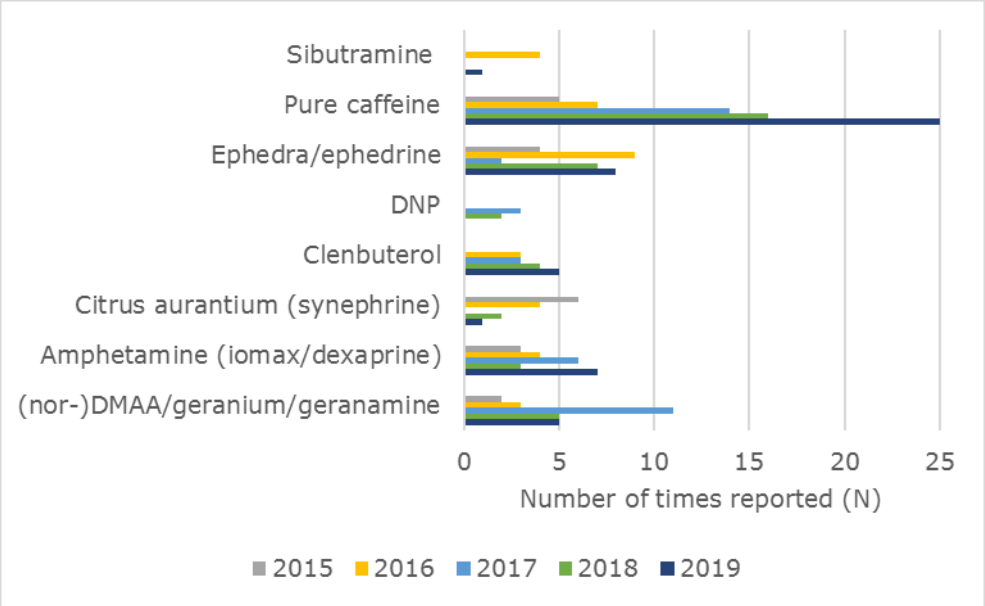

Figure 4. *Overview of the number of reports for the substances that are mentioned most frequently in notifications to the NVIC in the category of stimulating sports/slimming products.*

Complaints submitted to the Netherlands Pharmacovigilance Centre
Besides receiving complaints about adverse effects of medicines and vaccines, the Netherlands Pharmacovigilance Centre (Lareb) also deals with complaints about adverse effects of herbal preparations, vitamins, supplements and other health products that are not registered medicines. Lareb shares these anonymised complaints with the NVWA. Lareb received 103 notifications in 2015, 102 in 2016, 128 in 2017, 196 in 2018 and 165 in 2019 (Lareb, 2016;2017;2019;2020). The majority of complaints concern (multi)vitamin preparations, most frequently in connection with vitamin B6 and neuropathic symptoms. The other complaints can be grouped according to preparations with fermented red rice (red yeast rice) containing lovastatin-like monacolin K, melatonin, valerian, phyto-oestrogens, St. John's wort and others. In 2016, Lareb received 3 complaints about 3 slimming products from the same brand. RIVM analysed 2 of those products and found sibutramine and phenolphtalein in 1. No pharmacologically active substances were found in the other product (Lareb, 2017).

Hazard characterisation
The NVWA analyses (Annex I), the RASFF notifications (Annex II) and the information from the NVIC (Figure 4) and Lareb show that many different substances are found in food supplements. As it is not possible to carry out a risk assessment for all substances, the Special Food & Drink Products domain has provided a list of 12 substances that are regularly found in food supplements but are not regulated by law:

- DMAA (1,3-dimethylamylamine)
- DMBA (1,3-dimethylbutylamine; nor-DMAA)
- DMHA (1,5-dimethylhexylamine; octodrine)
- BMPEA (β-methylphenethylamine)
- PEA (phenethylamine)
- N,N-DMPEA (N,N-dimethylphenethylamine)
- Halostachine

- Higenamine
- Hordenine
- Icariin
- Isopropyloctopamine
- Methylsynephrine

In the list of ingredients of a food supplement, the above substances appear under various different names. Annex III presents an overview of the synonyms found. Annex IV summarises the available information on kinetics and dynamics for each substance.

Health-based guidance value
A risk assessment compares the level of exposure with a health-based guidance value, derived from toxicological data for the substance concerned. When the exposure exceeds this toxicological value, users may be at risk. In the ideal situation, BuRO compares the actual level of exposure with an available health-based guidance value (e.g. an acute reference dose[26] or an acceptable daily intake[27] established by EFSA, JECFA or another scientific institute). Otherwise, BuRO can establish a health-based guidance value itself or request one on the basis of toxicological studies of sufficient quality. Health-based guidance values are not established for substances that are genotoxic and carcinogenic. In those cases, an MOE (Margin of Exposure) approach is applied (EFSA, 2005). The MOE approach is also suitable when the toxicity information available is not sufficient to establish a health-based guidance value. The required MOE depends, among other things, on the quality of the data on which it is based. The greater the uncertainty, the higher the MOE.

In many cases, in the risk assessment of a pharmacologically active substance in a food supplement no health-based guidance value is available nor can such a value be derived from toxicological information. In such cases, it is impossible to perform a risk assessment comparing the exposure with a health-based guidance value based on toxicological information. However, there may be other information that can still give an indication of the possible risks to consumers. This could include information from answers to the following questions:
- Is the substance naturally present in a foodstuff (which may give indications of its historical safe use)?
- Has the substance been used as (an ingredient in) a medicine?
- Are there any studies in which the substance produced adverse effects after oral ingestion by humans or animals?
- Is there any other information that might point to potential possible risks for consumers (e.g. case reports)?

Information on historical safe use as a foodstuff does not necessarily indicate that a substance is safe to use in a food supplement. Whether it is depends, among other things, on the concentration in which it is used. The use of supplements containing concentrated green tea extracts was found to produce adverse effects

[26] Acute Reference Dose (ARfD) is an estimate of the amount of a substance in food or drinking water that a person is able to ingest within a 24-hour period without any appreciable health risk.
[27] Acceptable Daily Intake (ADI) is an estimate of the amount of a substance that a person is able to ingest daily, for the rest of their lives, without any appreciable health risk.

in the liver, while drinking green tea showed no adverse effects at all (Dekant et al., 2017; Navarro et al., 2017; Galli et al., 2019).

The above information can provide insight into the lowest examined concentration of a substance at which (adverse) effects occur in humans or animals after oral ingestion. This is known as an effect level. In this case, the outcome of the risk assessment is difficult to interpret. If the effect level is exceeded, (adverse) health effects cannot be ruled out. However, if the effect level is not exceeded, this does not necessarily mean that no such effects will occur. Because information is lacking, further research is required to make any firm statement.

In some cases, little or no information will be available to indicate the potential risks to consumers. In these cases, read-across or the Threshold of Toxicological Concern (TTC) approach could be applied. 'Read-across' is an approach in which information that is available on the potential effects of a substance is used to estimate the potential effects of a similar substance for which information is lacking. The TTC approach provides generic thresholds for chronic exposure in humans, which are established by grouping experimental toxicity data from animal bioassays. These TTC thresholds are such that the likelihood of adverse effects at exposures below these thresholds is considered to be low. The TTC approach distinguishes between different substance classes (Table 4).

Table 4. *TTC values - substances classification (EFSA Scientific Committee, 2019).*

Classification	**Description**	**TTC value (µg/kg body-weight/day)**
Potential DNA-reactive mutagens and/or carcinogens		0.0025
Organophosphates and carbamates		0.3
Cramer Class III	Substances with chemical structures that permit no strong initial presumption of safety or may even suggest significant toxicity or have reactive functional groups	1.5
Cramer Class II	Substances which possess structures which are less innocuous than Class I substances, but do not contain structural features suggestive of toxicity such as those of Class III	9.0
Cramer Class I	Substances with simple chemical structures and for which efficient modes of metabolism exist, suggesting a low order of oral toxicity	30

EFSA mentions software tools such as Toxtree or Derek that allow the structure of a chemical compound to be analysed using the TTC approach (EFSA & WHO, 2016; EFSA Scientific Committee, 2019). In addition, the TTC value can be calculated by answering various questions relating to the structure of a substance (Appendix A EFSA, 2016).

When the exposure does not exceed the TTC value, the risk of (adverse) health effects is small. However, if the TTC value is exceeded, that does not necessarily mean that (adverse) effects will occur. In such cases, further research will be required. So there is a grey area between a TTC value and the effect level (Figure 5).

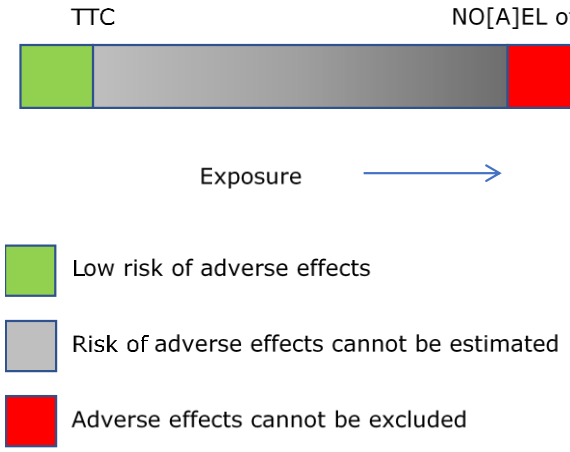

Figure 5. Estimation of health risks for substances for which the toxicological dataset is insufficient to establish a health-based exposure limit (RIVM, 2020d).

EFSA, JECFA nor any other scientific institution have assessed the toxicological data available for DMAA, DMBA, DMHA, BMPEA, PEA, N,N-DMPEA, halostachine, higenamine, hordenine, icariin, isopropyloctopamine and methylsynephrine and therefore have not established health-based guidance values. Both BuRO and FO have assessed the available toxicological data for these substances, but they were unable to establish health-based guidance values because no good-quality dose-effect studies with humans or animals are available. Only for hordenine did BuRO establish a health-based exposure limit (but FO did not). For the other substances, there is other information that may give an indication of the concentration values that pose a risk to consumers. This is explained in further detail below for each of these substances. BuRO does not comment on a possible novel food status or the concentration at which a substance has a significant pharmacological therapeutic effect (i.e. medicine by administration).

DMAA

Naturally present in foodstuffs?
DMAA is believed to be present in geranium oil as a mixture of optical isomers. However, there is no scientific evidence to support this. DMAA can be synthetically prepared (BuRO, 2012; RIVM, 2018).

Used as a medicine?
DMAA was patented in 1942 by Eli Lilly & CO and developed as a medicine for relieving nasal congestion. This application of DMAA was discontinued around 1970 (RIVM, 2010;2011; BuRO, 2012; RIVM, 2018).

Studies with people or animals
In the early 1950s, 4 hours after eating a light breakfast, 5 volunteers took 3 mg of DMAA (hydrochloride) per kg with 200 ml of water. Forty-five minutes to 1 hour after ingestion, their blood pressure rose, the difference between systolic and diastolic blood pressure increased and their heart rate fell. The volunteers complained of goose bumps and dry mouth, among other things (Marsh et al., 1951).

In a double-blind placebo-controlled study, 10 healthy volunteers, for 5 consecutive days, took 1 capsule a day containing 250 mg of caffeine, 50 mg of DMAA, 75 mg of DMAA, 250 mg of caffeine + 50 mg of DMAA, or 250 mg of caffeine + 75 mg of DMAA. The researchers found a statistically significant increase in systolic blood pressure in the volunteers who had taken 75 mg of DMAA (≤10%) or 75 mg of DMAA + caffeine (≤17%) compared to caffeine intake alone. Also, systolic blood pressure increased significantly in volunteers taking 75 mg of DMAA + caffeine (≤14%) compared to those taking 50 mg of DMAA alone (Bloomer et al., 2011a).

In another study, the same researchers examined the effect of DMAA on sports performance. On each of 4 test days, 60 minutes before the start of a 10 km run, 12 healthy trained volunteers took a placebo, 4 mg/kg of caffeine, 1 mg/kg of DMAA or a combination of the latter two. The authors observed a significant increase in heart rate (approximately 12 bpm) 5 minutes after completion of a round of exercise after taking caffeine + DMAA compared to taking DMAA alone. At the same moment after exercise, the heart rate after taking placebo did not differ significantly from that following the intake of caffeine, DMAA or caffeine + DMAA. Five minutes following exercise, the researchers also observed a significant increase in systolic blood pressure in the volunteers who had taken caffeine (141±4 mm Hg) or DMAA (147±4 mm Hg) compared to placebo (126±3 mm Hg) or a combination of DMAA and caffeine (126±3 mm Hg). Diastolic blood pressure also increased significantly after taking DMAA (66±3 mm Hg) compared with caffeine + DMAA (61±2 mm Hg), but not compared with placebo (Bloomer et al., 2011b).

Eight healthy volunteers each took a single capsule containing 25 mg of DMAA. Because 1 volunteer had a very high blood DMAA level that could not be explained, the authors decided not to include this volunteer's data in the analysis. In the end, the data of 7 volunteers were analysed. No significant increase or decrease in blood pressure or heart rate was observed. The heart rate increased from 61.0±3.2 bpm to 69.1±2.9 bpm(Schilling et al., 2013).

The same researchers then examined the effect of long-term intake of DMAA in combination with caffeine in a randomised double-blind study. For a period of 12 weeks, 50 healthy male volunteers took a placebo, 250 mg of caffeine, 50 mg of DMAA or a combination of the latter two. In the first week, the volunteers took one 25 mg capsule a day to get used to the practice. From week 2, the volunteers took 2 capsules a day until the end of the study after 12 weeks. None of the

parameters studied (including resting respiratory rate, blood pressure and electrocardiogram) showed any significant differences. After taking DMAA alone, the heart rate increased by 5 beats per minute (start of study versus end of study) (Bloomer et al., 2013).

In 2012, several studies were published on the effects of the DMAA-containing supplements Jack3d and OxyElite Pro in humans. The same group of researchers was also involved in the studies described above. These studies were co-financed by the manufacturer of the supplements and conducted by the same group of researchers (Farney et al., 2012; McCarthy et al., 2012a; McCarthy et al., 2012b; Whitehead et al., 2012). None of the studies analysed or reported on the composition of the supplements taken, nor did they indicate whether the participants were familiar with the use of the supplements. Another researcher analysed the supplements Jack3d and OxyElite Pro, which contain 142±25 and 31±5 mg of DMAA per serving, respectively (Zhang et al., 2012c). It is not clear whether the DMAA content in Jack3d and OxyElite Pro is standardised. The content may vary, therefore, from one supplement or batch to another.

In 1 double-blind study, 32 healthy and fit adults (16 men and 16 women) took OxyElite Pro or a placebo for 8 weeks (McCarthy et al., 2012a). The subjects were asked to take the recommended dosage of the supplement (1 or 2 capsules per day). Of the 16 subjects in the supplement group, 11 took 2 capsules (approximately 62 mg of DMAA per day) and the other 5 took 1 capsule per day (approximately 31 mg of DMAA per day). These latter 5 subjects reported nervousness and insomnia following the intake of 2 capsules. Compared to the baseline measurement, the supplement intake resulted in a significant reduction in body weight, BMI and abdominal circumference, a significantly increased resting heart rate (from 63 bpm to 69 bpm) and a significant increase in total cholesterol (from 147 mg/dl to 156 mg/dl). The results do not distinguish between participants who took 1 capsule and those who took 2.

In 1 double-blind crossover study, 12 healthy and fit adults (6 men and 6 women) took 2 capsules of the supplement OxyElite Pro or placebo on 2 different days (McCarthy et al., 2012b). Two capsules of OxyElite Pro correspond to an intake of approximately 62 mg of DMAA. Before taking the capsules, the subjects' blood pressure and heart rate were measured, and blood and breath samples were taken. The same parameters were determined again 30, 60, 90 and 120 minutes after ingestion. The subjects were not physically active during the experiment. Compared to the baseline measurement, taking the capsules with DMAA resulted in significantly increased blood plasma concentrations of glycerol (from 8 µg/ml to 12 µg/ml) and free fatty acids (from 0.5 mmol/l to 0.9 mmol/l) and a significantly increased metabolism (from 33 to 39 kilocalories per 30 minutes). In addition, the intake also resulted in a significant increase in blood pressure (systolic from 103 mm Hg to 118 mm Hg; diastolic from 60 mm Hg to 67 mm Hg) and heart rate (from 66 bpm to 70 bpm).

In one study, 6 healthy and fit adults (4 men and 2 women) took the supplement OxyElite Pro (Farney et al., 2012). Seven other healthy and fit adults (men) took the supplement Jack3d. The subjects took 2 capsules of the supplements a day for 14 days. This corresponds to an intake of 62 mg of DMAA (OxyElite Pro) or 284

mg of DMAA (Jack3d). There was no control group (placebo group) in this study. Various parameters were sampled up to 2 hours after intake on the first day and at the end of the 14-day period. Compared to the baseline measurement, systolic blood pressure decreased significantly (from 115 mm Hg to 110 mm Hg) within 2 hours of taking OxyElite Pro.

For a period of 10 weeks, 25 healthy and fit men took 1 to 3 capsules of placebo or the supplement Jack3d (containing approximately 142 mg of DMAA per capsule) about 30 minutes before the start of a workout. They did not take the capsules on non-workout days. On average, they had a work-out on 4 days a week. Blood pressure increased, but not significantly, in the supplement group (6 mm Hg for systolic blood pressure) (Whitehead et al., 2012).

Other information
Several case reports in the literature describe adverse effects such as cerebral haemorrhage, neurological effects, necrotising myopathy (muscle wasting), cardiac arrest, acute liver failure or even death after taking supplements that contained DMAA. Generally, the exact dosage is not known but the supplements are often reported to have been taken according to the instructions for use. In some patients, a blood analysis detected the presence of DMAA in combination with other substances such as caffeine. In 2 publications, the DMAA content of the supplement was determined and found to range from 50 mg to 278 mg per capsule/tablet (RIVM, 2018).

Dunn systematically reviewed the existing evidence for acute and chronic effects of DMAA. Of 842 potentially relevant articles identified, only 16 articles (8 case reports and 8 experimental studies) met the criteria for inclusion in the review. Based on the case reports, the author concluded that DMAA intake can potentially cause seriously adverse effects but that some of these effects are reversible once DMAA intake is stopped. Based on the experimental studies, the author concluded that DMAA intake leads to an increase in blood pressure, while noting that the studies were characterised by a suboptimal design, lack of power and the absence of generalisable results outside the laboratory (Dunn, 2017).

DMAA is on the World Anti-Doping Agency (WADA) list of banned substances (WADA, 2019).

Conclusion
FO concludes that an oral intake of 4 mg of DMAA produces sympathicomimetic[28] effects (RIVM, 2018). Based on the FO assessment, the BuRO advice of 2012 and the above findings, BuRO concludes that no new information is available that would change the conclusion of its advice of 2012. An oral dose of 4 mg is the lowest dose of DMAA expected to produce an effect (dilation of the bronchi). BuRO does not consider the temporary dilation of the bronchi to be an adverse effect. Estimated daily doses of DMAA orally from 30 mg upwards can cause serious adverse effects (increased blood pressure and heart rate).

[28] Stimulation of the sympathetic (autonomous) nervous system. The sympathetic nervous system is involuntary and maintains the body's vital functions.

DMBA

Naturally present in foodstuffs?
There is no convincing evidence that DMBA has ever been extracted from a plant (Cohen et al., 2015a).

Used as a medicine?
No medicinal product is or has been registered with DMBA as an active ingredient.

Studies with people or animals
There are no studies that examine the effects of DMBA after oral ingestion in humans or animals.

Other information
Cohen et al. describe a supplement named 'Unstoppable' that was found to contain DMBA without this being declared on the label. In 3 cases, adverse effects such as agitation, inability to sit still and sharpened focus have been reported after taking the supplement (Cohen et al., 2015a).

DMBA is on WADA's list of prohibited substances (WADA, 2019).

Conclusion
Based on the above information, BuRO is unable to provide an indication of a dose of DMBA that produces (adverse) effects. Such an indication can be provided, however, using the read-across approach. In line with FO (RIVM, 2018), BuRO concludes that read-across with DMAA is possible because:

1. the chemical structure of DMBA is similar to that of DMAA;
2. DMBA has the same biological properties as DMAA (sympathomimetic effect).

The conclusions drawn for DMAA also apply to DMBA until new information becomes available.

DMHA

Naturally present in foodstuffs?
Several studies suggest that DMHA occurs naturally in various species of plants, algae and fish. However, convincing evidence is lacking (RIVM, 2018).

Used as a medicine?
In the 1940s and 1950s, the US Food and Drug Administration approved a medicinal application of DMHA on two occasions: twice as an inhaler for the treatment of, among other things, bronchitis. Between the early 1960s and the mid-2000s, DMHA was sold in Europe, but not in the Netherlands, as an active ingredient in multi-ingredient tablets (dose between 8.2 and 33 mg). These tablets were advertised for the treatment of hypotension and asthma, among others (Cohen et al., 2018).

Studies with people or animals
In an animal study, 9 rats were administered DMHA orally (100 mg/kg body weight) for 30 days. After each administration, the rats showed symptoms related to depression, followed by goose bumps and restlessness. On average, the weight of the rats increased by 38 grams. Six other rats were administered 75 mg/kg bw

orally for 30 days. In these rats, mild symptoms of depression were observed, and an average 49-gram increase in bodyweight (Fellows, 1947).

In 4 healthy male volunteers, an increase in systolic (20-25 mm Hg) and diastolic (8-12 mm Hg) blood pressure was observed 3 to 6 quarters of an hour after single oral intake of 4 mg/kg bw per day. This effect lasted for 2 to 3 hours. The symptoms reported by the volunteers after taking 4 mg/kg bw included stomach ache, dry mouth, goose bumps and warm skin. No effects were observed at intakes of 1 and 2 mg/kg bw (Marsh & Herring, 1951).

Other information
DMHA is on WADA's list of prohibited substances (WADA, 2019).

Conclusion
The above data give a very limited indication of the lowest DMHA concentration that might cause (adverse) effects. That is why read-across is applied, as with DMBA. In line with FO (RIVM, 2018), BuRO concludes that read-across with DMAA is possible because DMAA and DMHA have both been used as medicines for the treatment of respiratory disease and possibly hypotension with doses in the same range. The conclusions drawn for DMAA also apply to DMHA, until new information becomes available.

BMPEA

Naturally present in foodstuffs?
BMPEA is a synthetically produced amine (RIVM, 2020d).

Used as a medicine?
No medicinal product is or has been registered with BMPEA as an active ingredient.

Studies with people or animals
No studies are available that have examined the effects of BMPEA after oral ingestion in humans or animals.

Other information
The literature describes 1 case in which a female athlete suffered a cerebral haemorrhage after taking a food supplement containing 290 mg of BMPEA. Half an hour after taking the supplement, the athlete developed symptoms including numbness and clumsiness in her left hand. She recovered within a few days (Cohen et al., 2015b).

BMPEA (‘phenethylamine and its derivatives’) is on WADA's list of prohibited substances (WADA, 2019).

Conclusion
FO concludes that no health-based guidance value and no effect level can be established for BMPEA (RIVM, 2020d). Based on the FO assessment and the above findings, BuRO concludes that it is not possible to give an indication of a minimum dose at which (adverse) effects occur after oral intake. Based on a qualitative read-across, BuRO, in line with FO, concludes that given its structural similarity to amphetamine, BMPEA can be expected to produce similar stimulant effects. Quantitative read-across for BMPEA is not possible because insufficient *in vitro*

and *in vivo* data are available to comment on the *in vivo* human potency of PEA, BMPEA and N,N-DMPEA and the other phenetylamine derivatives compared with amphetamine and with adrenaline, the natural ligand of the adrenergic receptors (RIVM, 2020d).

In order to still give an indication of a dose that involves a low risk of adverse health effects, FO has, at the request of BuRO, applied the TTC approach. According to computer models (Toxtree v2.6.13 and Derek Knowledgebase 2018), BMPEA falls into Cramer Class III. This corresponds to a TTC value of 90 µg/day for a 60 kg adult (RIVM, 2020d).

PEA

Naturally present in foodstuffs?

PEA is a biogenic amine found in foodstuffs. Biogenic amines can be toxic when ingested in large quantities, producing symptoms such as headache (Jansen et al., 2003; Millichap & Yee, 2003). The PEA content in foodstuffs varies. Pastore et al. determined that the PEA content in chocolate was below the detection limit (3 mg/kg) (Pastore et al., 2005). Other researchers found PEA levels in chocolate between 0.22 mg/kg and 22.0 mg/kg (Baker et al., 1987) or between 0.2 mg/kg and 0.4 mg/kg depending on the origin of the chocolate (Granvogl et al., 2006). Landete et al. determined the level of PEA in wine to be between 0.1 mg/kg and 1.8 mg/kg (Landete et al., 2007). The PEA content in cheese is between 6.1 and 11.3 mg/kg (Baker et al., 1987) or higher than 100 mg/kg (Rauscher-Gabernig et al., 2010). PEA has also been found in eggs (in the egg white) at levels between 25 mg/kg and 38 mg/kg (Figueiredo et al., 2013).

The above means that consumers are exposed to PEA not only through supplements, but also through foodstuffs (background exposure). Table 5 presents an overview of the amount of PEA ingested by a consumer when consuming chocolate, wine, cheese and egg white. The table is based on the 95th percentile of the consumption distribution and on the highest PEA concentrations found in the literature.

Table 5. *Overview of exposure to PEA from chocolate, wine, cheese and egg white.*

		P95 consumption (grams per day)[1]		**PEA intake (mg per day)**	
Product	**PEA content (mg/kg)**	**All days**	**Consumption days**	**All days**	**Consumption days**
Chocolate	22	50	100	1.1	2.2
Wine	1.8[2]	271	520	0.5	0.9
Cheese	100	98	126	9.8	12.6
Egg white	38	36[3]	90	1.4	3.4

[1]Data taken from the Dutch National Food Consumption Survey (VCP) 2012-2016; Dutch population aged 19-79 (statline.rivm.nl).

[2]Based on the assumption that 1.8 mg/l of wine corresponds to 1.8 mg/kg.

[3]Based on the assumption that an egg consists of 2/3 egg white and 1/3 yolk. P95 all days 54.5 g/day and P95 consumption days 135 g/day.

Used as a medicine?
No medicinal product with PEA as an active ingredient is or has been registered.

Studies with people or animals
In one study, 27 healthy volunteers took part in a placebo-controlled double-blind trial (Luthy & Schlatter, 1983). The volunteers took 25 mg of histamine, 25 mg of tyramine and 5 mg of PEA in apple juice (2 dl) at 2 different points in time. In addition, a placebo consisting of a glass of apple juice (2 dl) without any added substances was taken 6 times. After consuming a glass of apple juice, the volunteers filled in a questionnaire to record any effects that occurred within 20 hours. About a quarter of the 27 volunteers reported effects such as dizziness, sweating, mild headache and nausea after taking 2 x 5 mg of PEA. In a second part of the study, 4 volunteers who indicated sensitivity to PEA took 5 mg of PEA in apple juice (2 dl) or a placebo once at 3 different points in time. This resulted in 12 observations per group. Of the 12 observations in the PEA group, 5 included headache, while in the placebo group headache was reported twice.

Other information
Rauscher-Gabernig et al. proposed a 'maximum tolerable level' of 25 mg/kg for cheese and fish, 50 mg/kg for fermented sausages and chocolate, 70 mg/kg for soy sauce and other liquid flavourings, and 1 mg/l for alcoholic drinks, based on the above study and the P95 consumption pattern for the Austrian population (Rauscher-Gabernig et al., 2010).

PEA ('phenethylamine and its derivatives') is on WADA's list of prohibited substances (WADA, 2019).

Conclusion
FO concludes that no health-based guidance value for PEA can be established. FO considers a single intake of 5 mg of PEA to be the effect level (RIVM, 2020d). In a limited study, the intake of apple juice containing 5 mg of PEA was found to produce adverse effects (dizziness, sweating, mild headache and nausea) in a small number of participants. FO then concludes, after applying the TTC approach, that PEA falls into Cramer Class III. This corresponds to a TTC value of 90 µg/day for a 60 kg adult. The dosage that involves a low risk of adverse health effects (RIVM, 2020d).

According to BuRO, using TTC for PEA is overly conservative. PEA occurs naturally in foodstuffs. The intake of PEA through food is in the order of several milligrams per day (Table 5). This is the same order of magnitude as in the study described above with PEA in apple juice (5 mg). The number of participants in that study was small and the effects were self-reported. This has led BuRO to conclude that the intake of 5 mg of PEA from a supplement per day involves a low risk of adverse effects.

N,N-DMPEA

Naturally present in foodstuffs?
There are no indications that N,N-DMPEA has a natural origin.

Used as a medicine?
No medicinal product with N,N-DMPEA as an active ingredient is or has been registered.

Studies with people or animals
The effects of oral intake of N,N-DMPEA as a food supplement have not been studied in humans or animals.

Other information
In 2008, WHO concluded that ingestion of N,N-DMPEA as a flavouring in the quantities in which it is present in food poses no health risk. In Europe, this concerned a daily dose of 0.0002 µg/kg body weight (WHO, 2008). This is equivalent to 0.012 µg of N,N-DMPEA per day in a 60 kg adult.

N,N-DMPEA ('phenethylamine and its derivatives') is on WADA's list of prohibited substances (WADA, 2019).

Conclusion
FO concludes that no health-based guidance value and no effect level can be established for N,N-DMPEA (RIVM, 2020d). Based on the FO assessment and the above findings, BuRO concludes that it is not possible to give an indication of a minimum dosage at which (adverse) effects occur after oral intake. Based on a qualitative read-across, BuRO, in line with FO, concludes that given its structural similarity to amphetamine, N,N-DMPEA can be expected to produce similar stimulant effects. Quantitative read-across is not possible for N,N-DMPEA because insufficient *in vitro* and *in vivo* data are available to comment on the *in vivo* human potency of PEA, BMPEA and N,N-DMPEA, and the other phenetylamine derivatives compared with amphetamine and with adrenaline, the natural ligand of the adrenergic receptors (RIVM, 2020d).

In order to still give an indication of a dose at which there is a low risk of adverse health effects, FO has, at the request of BuRO, applied the TTC approach. According to computer models (Toxtree v2.6.13 and Derek Knowledgebase 2018), N,N-DMPEA falls into Cramer Class III. This is equivalent to a TTC value of 90 µg/day for a 60 kg adult (RIVM, 2020d). At exposure levels below this TTC value, the risk of adverse effects is low. If the exposure is higher, no statement can be made.

Halostachine

Naturally present in foodstuffs?
Halostachine occurs naturally but can also be manufactured synthetically and/or formed in the human body when phenylethanolamine is converted to N-methylphenylethanolamine by the enzyme N-methyltransferase (RIVM, 2020e).

Used as a medicine?
No medicinal product is or has been registered that contains halostachine as an active ingredient.

Studies with people or animals
The effects of oral intake of halostachine have been examined in 1 study with humans. No animal studies have been conducted.

No effect on blood pressure was observed after oral intake of 50 mg of halostachine by 5 men with nasal congestion. After administration of a 1% halostachine solution in the same men, their nasal mucosa contracted causing the

nasal cavity to dilate (Chen et al., 1929; RIVM, 2020e). The authors do not specify how the halostachine solution was administered. Most likely it was sprayed directly into the nose.

Conclusion
FO concludes that no health-based guidance value and no effect level can be established for halostachine (RIVM, 2020e). Based on the FO assessment and the above findings, BuRO concludes that it is not possible to give an indication of a minimum dose at which (adverse) effects occur after oral intake. BuRO also concludes, in line with FO, that it is not possible to apply quantitative read-across. Insufficient *in vitro* and *in vivo* data are available to comment on the *in vivo* human potency of halostachine compared with amphetamine and with adrenaline, the natural ligand of the adrenergic receptors (RIVM, 2020e).

In order to still give an indication of a dose that involves a low risk of adverse health effects, FO has, at the request of BuRO, applied the TTC approach. According to computer models (Toxtree v2.6.13 and Derek Knowledgebase 2018), halostachine falls into Cramer Class III. This is equivalent to a TTC value of 90 µg/day for a 60 kg adult (RIVM, 2020e). At exposure levels below this TTC value, the risk of adverse effects is low. If the exposure is higher, no statement can be made.

Higenamine

Naturally present in foodstuffs?
Higenamine occurs naturally but can also be manufactured synthetically (RIVM, 2020f).

Used as a medicine?
No medicinal product with higenamine as an active ingredient is or has been registered.

Studies with people or animals
Clinical trials have been conducted in China on the efficacy of higenamine in the treatment of various heart conditions. In studies involving 14 to 68 patients, higenamine was administered intravenously in doses ranging from 2.5 mg to 5 mg. In all studies an increase in heart rate was observed, but the effects on blood pressure were variable (Cohen et al., 2019). Reported side effects included shortness of breath, palpitations, dizziness, headaches and chest tightness (Cohen et al., 2019; RIVM, 2020f). Zhang et al. have written a review on the potential of higenamine as a medicine. The authors conclude that higenamine may have a valuable therapeutic effect in various conditions. However, since the underlying mechanisms remain unclear, the safety and efficacy of this substance have not been demonstrated (Zhang et al., 2017).

In a double-blind placebo-controlled trial, 16 healthy and fit volunteers (8 men and 8 women) received a single oral dose of placebo or of a supplement consisting of a combination of higenamine, yohimbe and caffeine (270 mg). The article does not describe how much higenamine or yohimbe the supplement contained. The authors conclude that the supplement increases the heart rate (by 3 bpm) and systolic blood pressure (by 12 mm Hg). Because the supplement consists of a combination of substances, it is not possible to determine the individual

contribution of each of those substances to the observed effects (Lee et al., 2013b).

In another placebo-controlled study by the same group of authors, 48 healthy men took a placebo or 1 of 3 available supplements, orally. One supplement (in the form of a capsule) contained higenamine (50 mg), caffeine (125 mg) or a combination of higenamine (50 mg), caffeine (125 mg) and yohimbe (3.5 mg). For 8 weeks, the volunteers took 1 to 3 capsules a day. Before the start of the study and after 4 and 8 weeks, morning blood and urine samples were taken and heart rate, blood pressure and respiratory rate were measured. These tests were done after the volunteers had been fasting for at least 10 hours. They were not allowed to take a capsule on test days (Bloomer et al., 2015b; RIVM, 2020f). Since the half-life of higenamine (several minutes) is much shorter than the time elapsed between the last higenamine intake and the measurements, FO concludes that it is unlikely that effects of higenamine were observed in this study (RIVM, 2020f).

A case report describes a 22-year-old man who developed rhabdomyolysis (breakdown of muscle tissue) and possibly compartment syndrome (increased tissue pressure within a compartment – in this case muscles) after taking (150% of the recommended daily dose of) a supplement containing an unknown quantity of higenamine. The man took the supplement before exercising. He had fully recovered after 4 months (Jeter et al., 2015a).

Other information
Higenamine is on WADA's list of prohibited substances (WADA, 2019).

Conclusion
FO concludes that no health-based guidance value and no effect level can be established for higenamine (RIVM, 2020f). Based on the FO assessment and the above findings, BuRO concludes that it is not possible to give an indication of a minimum dose that involves (adverse) effects following oral intake of higenamine. In line with FO, BuRO also concludes that it is not possible to apply quantitative read across. Insufficient *in vitro* and *in vivo* data are available to comment on the *in vivo* human potency of higenamine compared with amphetamine and with adrenaline, the natural ligand of the adrenergic receptors. Both amphetamine and adrenaline are structurally related to higenamine (RIVM, 2020f).

In order to still give an indication of a dose that involves a low risk of adverse health effects, FO has, at the request of BuRO, applied the TTC approach. An analysis using the computer models Toxtree v2.6.13 and Derek Knowledgebase 2018 showed that the structure of higenamine may give rise to genotoxic properties. Hence, the TTC value is 0.15 µg/day for a 60 kg adult (RIVM, 2020f). At exposure levels below this TTC value, the risk of adverse effects is low. If the exposure is higher, no statement can be made.

Hordenine

Naturally present in foodstuffs?
Hordenine occurs naturally in foodstuffs made from barley, such as beer. Hordenine has also been detected in *Ginkgo biloba* extracts (RIVM, 2020a). Sommer et al. found a hordenine content in beer of between 1.05 and 6.32 mg/l (Sommer et al., 2019). This means that consumers are exposed to hordenine not

only through supplements, but also through food. The 2012-2016 Dutch National Food Consumption Survey (VCP) shows that Dutch people consume 700 grams (all reported days in VCP) of beer per day (P95). Assuming that beer contains about 6 mg/kg of hordenine and consumers consume 700 grams of beer, each consumer takes in 4 mg of hordenine per day.

Used as a medicine?
Hordenine has not been used as an active substance in a medicinal product.

Studies with people or animals
At the end of the 19th century, a researcher ingested 100 mg of hordenine but observed no obvious effects except slight drowsiness (Heffter, 1894).

Goelz et al. fed meadow voles (*Microtus pennsylvanicus*, N=10 per group) hordenine sulphate at concentrations of 0, 0.15, 0.31 or 0.62% of the feed for 21 days (Goelz et al., 1980). This is equivalent to 0, 123, 255 or 509 mg/kg bw per day (RIVM, 2020a). No clinical signs of illness or mortality were observed in any of the groups that had been exposed to hordenine. Neither was any effect observed on the quantity of food intake or weight of the mice. However, in all dose groups, effects on the kidneys were observed, such as damage to the proximal tubule (Goelz et al., 1980). FO concludes that the LOAEL from this study was 123 mg/kg bw/day (RIVM, 2020a).

In another study, groups of 2 sheep each were given a single dose of 10, 20, 40, 80 or 160 mg/kg bw of hordenine (intravenously) or 200, 400 or 800 mg/kg bw (orally). There were no sheep that did not receive any hordenine (i.e. there was no control group). For 24 hours, the animals were observed for the development of clinical effects. The researchers found a NOAEL of 10 mg/kg bw (intravenous) or 400 mg/kg bw (oral). At an oral dose of 800 mg/kg bw, similar but milder effects were observed compared with an intravenous dose of 160 mg/kg bw. These effects included paralysis and disturbances in balance and movement coordination (Bourke et al., 1988a).

Conclusion
FO concludes that no health-based guidance value and no effect level can be established for hordenine. FO subsequently applied the TTC approach. Analysis of hordenine using the computer model Derek showed that the structure of this substance gives rise to possible genotoxic properties. As a result, the TTC value for hordenine is 0.15 µg/day for a 60 kg adult (RIVM, 2020a).

According to BuRO, the TTC approach for hordenine is overly conservative. Hordenine occurs naturally in foodstuffs. Even though it is just 1 study, BuRO does not consider it appropriate to disregard the data from the study by Goelz et al. with meadow voles. Based on that study, FO arrived at a LOAEL of 123 mg/kg bw per day. Using this same LOAEL, BuRO established a provisional ADI of 0.039 mg/kg bw per day (=39 µg/kg bw per day). This is equivalent to a daily dose of 2,340 µg for a 60 kg adult. For this purpose, BuRO first adjusted the LOAEL for the difference in body weight between humans and meadow voles (123 x $(0.025/60)^{0.25}$ = 17.6 mg/kg bw) based on allometric scaling and then applied a safety factor of 450 (a factor 2.5 for interspecies differences, a factor 10 for

intraspecies differences, a factor 6 for the translation of a subacute study to a chronic situation and a factor 3 for using a LOAEL instead of a NOAEL) (17.6/450 = 0.039 mg/kg bw) (ECHA, 2012).

Icariin

Naturally present in foodstuffs?

Icariin is naturally present in plants of the species *Epimedium*, such as horny goat weed or ying yang huo (Ono et al., 1991).

Used as a medicine?

In traditional Chinese medicine, extracts from these plants are used for aphrodisiac effects, anti-inflammatory effects and health promotion (Zhang et al., 2014b). They are also used to stimulate erectile function (Makarova et al., 2007).

Studies with people or animals

There have been no studies with humans or animals focusing on possible adverse health effects of exposure to icariin. However, a number of studies did focus on potential positive effects on the heart, osteogenesis, reproduction and the brain (Table 6), among others, after oral intake of icariin.

Ten depressed adult patients diagnosed with bipolar disorder and alcohol addiction participated in an 8-week study. In week 3, the patients who had presented only marginal improvement of their depression compared with the start of the study or who still consumed alcohol took 100 to 200 mg of icariin (horney goat weed supplement) per day. In week 6, that dosage was raised to a maximum of 300 mg of icariin per day for patients who continued to present only marginal improvement of their depression or still consumed alcohol. Three patients were lost to follow-up and did not complete the study. After 8 weeks, the scores for depression and anxiety had fallen significantly. Alcohol consumption levels had also fallen. Side effects reported for this study include vivid dreams, enhanced libido, constipation, diarrhoea, headache and hyperactivity (Xiao et al., 2016).

In a 2-year study, postmenopausal women took 4 capsules of a food supplement (N=43) or placebo (N=42) a day. In total, the 4 supplement capsules contained 60 mg of icariin, 15 mg of daidzein and 3 mg of genistein. In addition, all participants were given 300 mg of calcium a day. The researchers found that the treated women showed no decline in bone mineral density after 12 weeks and after 24 months, while they did observe a decline in the placebo group. No adverse effects were reported (Zhang et al., 2007).

Table 6. *Overview of the effects of oral administration of icariin to laboratory animals (table continued on the following pages).*

Impact	Dose	Type	Reference
Reduced amyloid-β deposition and increased microglia activation	100 mg/kg/day for 10 days	Mouse	(Zhang et al., 2014e)
Reduced amyloid-β deposition and reduced cognitive symptoms	10 or 40 mg/kg twice daily for 23 days	Rat	(Li et al., 2015d)

Impact	Dose	Type	Reference
Reduced depression-like symptoms after chronic stress	30 or 60 mg/kg for four weeks	Rat	(Pan et al., 2010; Pan et al., 2013)
Reduced depression-like symptoms after chronic stress	20 or 40 mg/kg/day for 35 days	Rat	(Wei et al., 2016a)
	60 mg/kg/day for 21 days	Rat	(Gong et al., 2016)
	20 or 40 mg/kg/day for 35 days	Rat	(Liu et al., 2015a)
	15, 30 or 60 mg/kg/day for 5 weeks	Rat	(Pan et al., 2007)
	35 or 70 mg/kg/day for 6 weeks	Rat	(Pan et al., 2006)
Improved learning, memory and cognitive functions	0, 30, 60 or 120 mg/kg/day for 3 months	Rat	(Xu et al., 2009)
	75 or 150 mg/kg/day for 15 weeks	Mouse	(He et al., 2010)
	30 or 120 mg/kg/day for 17 days	Rat	(Guo et al., 2010)
	60 mg/kg/day for 3 months	Mouse	(Li et al., 2015a)
	30 or 60 mg/kg twice daily for 4 months	Mouse	(Jin et al., 2014)
	50 µmol/kg/day for 8 days	Mouse	(Urano & Tohda, 2010)
	20 mg/kg/day for 3 months	Rat	(Wu et al., 2012a)
	60 mg/kg/day for 4 months	Rat	(Li et al., 2010a)

Impact	Dose	Type	Reference
Improved learning, memory and cognitive functions	17.5 and 35 mg/kg/day for 21 days	Mouse	(Pan et al., 2005)
Protection against excitotoxicity by ibotenic acid	20 or 40 mg/kg, twice daily for 20 days	Mouse	(Zong et al., 2016)
Protection from the toxic effects of aluminium	60 or 120 mg/kg/day for 3 months	Rat	(Luo et al., 2007)

Following oral administration of icariin (10 to 60 mg/kg bw) for 3 to 12 weeks, cardiovascular effects were observed in studies with rats, mice and rabbits. These effects include reduced infarct size and inflammation of the heart in ischaemia, reduced cardiac abnormalities in hypertensive rats, reduced blood pressure, reduced arteriosclerosis and reduced thrombosis (Hu et al., 2016b; Wang et al., 2016d; Qian et al., 2017; RIVM, 2020c).

Oral administration of icariin (20 to 100 mg/kg bw; ranging from a single dose to daily doses for 8 weeks) in mice was found to have anti-inflammatory effects in brain and spinal cord inflammation, airway inflammation and lymph node inflammation (Xu et al., 2010; Li et al., 2014c; Shen et al., 2015; Wei et al., 2015b; RIVM, 2020c). In addition, single oral doses of 30 to 90 mg/kg bw had an inhibitory effect on intestinal inflammation in rats (Wang et al., 2016c; RIVM, 2020c).

Following oral administration of icariin (25 mg/kg for 20-21 days) in arthritic mice, a reduction in the effects of arthritis was observed (Sun et al., 2013; Chi et al., 2014; RIVM, 2020c).

Oral administration of icariin to ovariectomised rats (5, 25 and 125 mg/kg bw) for 12 weeks increased bone mineral density (Nian et al., 2009). Similar effects were seen in rabbits (oral intake of 2.5 mg/kg bw for 2 to 4 weeks) (Wei et al., 2011). Oral administration of icariin to ovariectomized rats (125 mg/kg bw; 6 times a week) for 12 weeks reduced bone degradation (Li et al., 2014b). Similar effects were seen in mice (oral intake of 0.1 or 0.3 mg of icariin/g bw in combination with titanium particles per day for 2 weeks or 250 mg of icariin/kg bw per day for 60 days) (Shao et al., 2015; Hu et al., 2017). Oral administration of icariin to rats (2.5 mg/kg bw per day) for 3 weeks reduced tooth decay (Wang et al., 2012).

Male rats were administered 0, 50, 100 or 200 mg icariin/kg bw per day orally for 35 consecutive days. At a dose of 100 mg/kg bw per day, the sperm count increased significantly. At doses of 50 and 100 mg/kg bw, a significantly increased testosterone level was observed (Chen et al., 2014).

Oral exposure of mice with colorectal cancer to icariin (40 mg/kg bw per day) for 3 weeks reduced tumour size (Zhang et al., 2014c).

Conclusion
FO concludes that no health-based guidance value and no effect level can be established for icariin (RIVM, 2020c). Based on the FO assessment, the above findings and information from Annex IV, BuRO concludes that animal studies as

well as *in vitro* and *in vivo* studies point to possible beneficial effects of icariin on various clinical pictures. There are no studies that have examined the toxic effects of icariin. It is not possible to give an indication of a minimum dose at which (adverse) effects occur following oral intake of icariin.

In line with FO, BuRO also concludes that it is not possible to apply quantitative read across. Insufficient *in vitro* and *in vivo* data are available to comment on the *in vivo* potency of icariin in humans compared with structurally related substances (RIVM, 2020c).

In order to still give an indication of a dose that involves a low risk of adverse health effects, FO has, at the request of BuRO, applied the TTC approach. Analysis using the computer models Toxtree v2.6.13 and Derek Knowledgebase 2018 revealed that the structure of icariin may give rise to genotoxic properties. Hence, the TTC value is 0.15 µg/day for a 60 kg adult (RIVM, 2020c). At exposure levels below this TTC value, the risk of adverse effects is low. If the exposure is higher, no statement can be made.

Isopropyloctopamine

Naturally present in foodstuffs?
Isopropyloctopamine is synthetically manufactured from natural compounds and is chemically related to octopamine and synephrine (RIVM, 2020g).

Used as a medicine?
No medicinal product with isopropyloctopamine as an active ingredient is or has been registered.

Studies with people or animals
After intravenous administration of isopropyloctopamine (500 µg/min; 15 mg) to 5 volunteers for 30 minutes, an increase in heart rate was observed but no effect on blood pressure. An increase in plasma free fatty acids was also observed. Prior to the experiment, the volunteers had been treated with a beta-adrenergic blocker, propranolol (Pilkington et al., 1966). FO concludes that it is unknown which oral dose results in a similar concentration in blood. It is likely to be greater than 15 mg as 100% absorption is considered unlikely (RIVM, 2020g).

Other information
Between May 2012 and October 2013, the NVIC received 26 reports of possible poisoning incidents following intake of a supplement called Dexaprine. Intake varied from half a tablet once only to 1 or more tablets over a longer period (to a maximum of 46 tablets). Most symptoms, such as nausea, vomiting, sweating, agitation, tachycardia, chest pain and palpitations, occurred 1 hour after taking 1 tablet or less. One case of cardiac arrest was reported in a person who had taken half a tablet. Analysis of 4 tablets showed that they contained a mixture of different substances such as synephrine (46-86 mg), isopropyloctopamine (19-39 mg), methylsynephrine (1-5 mg), yohimbe (2-5 mg), caffeine (175-355 mg) and theophylline (53-101 mg) (Venhuis et al., 2014). Other researchers found that the Dexaprine supplement contained 40 to 60 mg of isopropyloctopamine (Bovee et al., 2016). It is likely that this dose contributed to the adverse reactions reported to the NVIC, because it is in the same range as the dose considered effective by a manufacturer. The FDA rejected a notification request for a supplement (maximum intake 80 mg daily) containing isopropyloctopamine (SSPF, 2004).

Conclusion
FO concludes that no health-based guidance value and no effect level can be established for isopropyloctopamine (RIVM, 2020g). Based on the FO assessment and the above findings, BuRO concludes that it is not possible to give an indication of a minimum dose at which (adverse) effects occur after oral intake. Based on a qualitative read across, BuRO, in line with FO, concludes that given its structural similarity to amphetamine, isopropyloctopamine can be expected to produce similar stimulant effects. Quantitative read-across for isopropyloctopamine is not possible because insufficient *in vitro* and *in vivo* data are available to assess the *in vivo* human potency of isopropyloctopamine compared with amphetamine and with adrenaline, the natural ligand of the adrenergic receptors (RIVM, 2020g).

In order to still give an indication of a dose that involves a low risk of adverse health effects, FO has, at the request of BuRO, applied the TTC approach. According to computer models (Toxtree v2.6.13 and Derek Knowledgebase 2018), isopropyloctopamine falls into Cramer Class III. This is equivalent to a TTC value of 90 µg/day for a 60 kg adult (RIVM, 2020g). At exposure levels below this TTC value, the risk of adverse effects is low. If the exposure is higher, no statement can be made.

Methylsynephrine

Naturally present in foodstuffs?
There are no indications that methylsynephrine has a natural origin.

Used as a medicine?
Methylsynephrine was prescribed in Germany, among other countries, as a medication for the treatment of hypotension in doses of 16, 20, 32 or 40 mg (Cohen et al., 2017).

Studies with people or animals
In 1 study, 10 children with orthostatic hypotension took a single dose of approximately 20 mg of methylsynephrine. During the 10 minutes after ingestion, various physiological parameters were measured while the children were lying on a tipping table at an angle of 65°. These children then took 20 mg of methylsynephrine 3 times a day for 2 and for 4 weeks. It was found that methylsynephrine, during orthostatic stress, induced a significant increase in pulse pressure, cardiac output, stroke volume and systolic ejection rate with reduced peripheral vascular resistance. The authors did not represent the changes in parameters in absolute terms, but in percentage terms (Hoffmann et al., 1987).

In one study, 30 patients with orthostatic hypotension were treated with methylsynephrine (32 mg/day) for 2 weeks. Thirty patients received a placebo. After treatment, blood pressure was found to have increased significantly by 48% during the tilt-table test (Schellong test), from 126 +/- 21 mm Hg x min to 187 +/- 39 mm Hg x min. In patients who had received a placebo, blood pressure increased by 20%. The Schellong test is a test in which people lie horizontally on a table and are strapped down for safety. The table is then tilted almost completely upright. This makes it possible to measure orthostatic changes in blood pressure (Pohl & Kriech, 1991).

Kauert et al. (1988) studied the effect of a single oral dose (120 mg) of methylsynephrine on heart rate and mean arterial blood pressure in 8 healthy volunteers (Kauert et al., 1988a). Both parameters remained unchanged. However, systolic and diastolic blood pressure increased by 14% and 9% respectively. The researchers also found a positive inotropic effect (increase in muscle contraction strength), with the left ventricular fraction shortened by 21%.

In a randomised double-blind study, 10 healthy volunteers took 3 capsules of a supplement called Meltdown® or placebo. The supplement contained a mix of substances, including 20 mg of methylsynephrine. Whether methylsynephrine is responsible for the observed effects is unknown. For 3 subsequent hours, heart rate, blood pressure and oxygen uptake were measured. During those 3 hours, oxygen uptake, energy expenditure, heart rate and blood pressure were significantly higher compared with the placebo group. In addition, the volunteers who had taken Meltdown were found to be more stressed and confused compared with the placebo group (Hoffman et al., 2009). In another randomised double-blind study, 20 healthy and fit volunteers took a single capsule of the Meltdown® supplement or a placebo. Ingestion of the supplement caused an increase in plasma adrenaline, noradrenaline, glycerol and free fatty acids after 90 minutes. In addition, increased blood pressure and heart rate were found in the volunteers who had taken the supplement (Bloomer et al., 2009a). In a similar type of study conducted by the same researchers, 10 fit male subjects took either the supplement or a placebo. The researchers concluded that ingestion of the supplement resulted in an acute increase in the plasma concentration of norepinephrine and of lipolysis markers. No change in haemodynamic parameters was observed (Bloomer et al., 2009b).

Other information
Between May 2012 and October 2013, the NVIC received 26 reports of possible poisoning incidents following intake of a supplement called Dexaprine. Intake varied from half a tablet once only to 1 or more tablets over a longer period (to a maximum of 46 tablets). Most symptoms, such as nausea, vomiting, sweating, agitation, tachycardia, chest pain and palpitations, occurred 1 hour after taking 1 tablet or less. One case of cardiac arrest was in a person who had taken half a tablet. Analysis of 4 tablets showed that they contained a mixture of different substances such as synephrine (46-86 mg), isopropyloctopamine (19-39 mg), methylsynephrine (1-5 mg), yohimbe (2-5 mg), caffeine (175-355 mg) and theophylline (53-101 mg) (Venhuis et al., 2014).

Methylsynephrine is on WADA's list of prohibited substances (WADA, 2019).

Conclusion
FO concludes that no health-based guidance value for methylsynephrine can be established. According to FO, effect levels are a single intake of 20 mg or repeated intakes of 32 mg (RIVM, 2020b). BuRO is of the opinion that an effect on the blood pressure of patients with orthostatic hypotension cannot be regarded as an effect level for healthy consumers. The effects of these intake levels in healthy consumers is unknown.

In order to obtain an indication of the dose which involves a low risk of adverse effects, FO, commissioned by BuRO, applied the TTC approach. According to

computer models (Toxtree v2.6.13 and Derek Knowledgebase 2018), methylsynephrine falls into Cramer Class III. This is equivalent to a TTC value of 90 µg/day for a 60 kg adult (RIVM, 2020b). At exposure levels below this TTC value, the risk of adverse effects is low. If the exposure is higher, no statement can be made.

Summary of health-based guidance values
Table 7 lists the daily doses of DMAA, DMBA, DMHA, BMPEA, PEA, N,N-DMPEA, halostachine, higenamine, hordenine, icariin, isopropyloctopamine and methylsynephrine that involve a low risk of adverse health effects.

***Table 7**. Overview of the daily doses (µg/day) of DMAA, DMBA, DMHA, BMPEA, PEA, N,N-DMPEA, halostachine, higenamine, hordenine, icariin, isopropyloctopamine and methylsynephrine that involve a low risk of adverse health effects and/or where adverse effects cannot be excluded.*

Substance	**Daily dose (µg/day) with a low risk of adverse effects**	**Substantiation**
DMAA	4,000	BuRO advice, 2012
DMBA	4,000	Read-across
DMHA	4,000	Read-across
BMPEA	90	TTC approach
PEA	5,000	Comparison with intake through food
N,N-DMPEA	90	TTC approach
Halostachine	90	TTC approach
Higenamine	0.15	TTC approach
Hordenine	2,340	ADI, comparison with intake through food
Icariin	0.15	TTC approach
Isopropyloctopamine	90	TTC approach
Methylsynephrine	90	TTC approach

Synergy & Interactions
Supplements consist of a mixture of different substances which potentially enhance each other's effects. In general, it can be concluded that the effects of the stimulants described above on heart rate, cardiac contraction and blood pressure can increase when they are used in combination with substances that have similar stimulating effects (e.g. synephrine, yohimbine, caffeine etc.) (RIVM, 2018;2020d;2020e;2020f;2020g;2020b).

The stimulating effect of DMAA, DMHA and DMBA will increase when these substances are combined with other sympathicomimetics (substances that stimulate the sympathetic nervous system) and adrenergic substances. Combined intake of aliphatic amines, such as DMAA, and monoamine oxidase (MAO) inhibitors, such as caffeine, can lead to a hypertensive crisis[29] because the combined use accelerates the development of stimulant effects (RIVM, 2018).

[29] A severe increase in blood pressure, usually >220 mm Hg systolic and/or 120 mm Hg diastolic requiring immediate reduction of the elevated blood pressure.

BMPEA, PEA, N,N-DMPEA and halostachine are metabolised by MAO enzymes. These enzymes ensure that monoaminergic neurotransmitters such as serotonin, (nor)adrenaline and dopamine are broken down. Neurotransmitters play a role in regulating blood pressure, mood and motor function, among other things. Interactions may occur with medicines that inhibit these enzymes (e.g. some antidepressants or medication against Parkinson's disease) (RIVM, 2020d;2020e).

BMPEA, N,N-DMPEA and higenamine have an inhibitory effect on certain cytochrome P450 enzymes (CYP2D6 and CYP3A4). Most cytochrome P450 enzymes are responsible for the metabolism of exogenous substances. The plasma concentration of medicines converted by these enzymes could be affected by the concomitant use of BMPEA, N,N-DMPEA and higenamine. This may have an impact on the efficacy of the medicines especially when the therapeutic window is narrow[30] (RIVM, 2020d;2020f).

In humans, icariin is largely converted to icariside II by intestinal flora before it is absorbed. This is why medications that affect the intestinal flora (e.g. antibiotics) can indirectly influence the conversion of icariin to icariside II (RIVM, 2020c).

Exposure
Annex V provides an overview of the mean, median, minimum and maximum daily doses of the supplements sampled by the NVWA (N=502) between October 2013 and December 2019. Of these supplements, 314 contain one or more pharmacologically active substances. The daily dose is determined by multiplying the concentration of a substance found in a supplement by the desired daily intake according to the label. It was not possible to calculate daily doses for all substances because not all samples were quantified or because instructions for use data were lacking. Also, in some cases the daily dose was calculated on the basis of a very small number of samples. See Table 8 for an overview specifically for DMAA, DMBA, DMHA, PEA, BMPEA, N,N-DMPEA, halostachine, higenamine, hordenine, icariin, isopropyloctopamine and methylsynephrine.

[30] The therapeutic window of a medicine is the concentration in which the medicine must be present to have a therapeutic but non-toxic effect. Higher concentrations often lead to adverse effects, while lower concentrations usually do not produce the desired effect.

Table 8. *Overview of the mean, median, minimum and maximum daily doses (µg/day) and the daily doses that involve a low risk of adverse effects from oral intake of DMAA, DMBA, DMHA, BMPEA, PEA, N,N-DMPEA, halostachine, higenamine, hordenine, icariin, isopropyloctopamine and methylsynephrine.*

Substance		Daily dose (µg/day)				
	Number (N)	Mean	Median	Minimum	Maximum	Low risk of adverse effects
DMAA	14	60,400	62,300	0.1	143,400	4,000
DMBA	8	133,200	57,100	51,500	286,000	4,000
DMHA*	0					4,000
BMPEA	10 (9)**	139,200	136,500	115,500	162,000	90
PEA	16	12,200	9	1	127,700	5,000
N,N-DMPEA*	0					90
Halostachine	1	34,000	34,000	34,000	34,000	90
Higenamine	32 (27)	31,200	14,300	0.01	90,700	0.15
Hordenine	23 (19)	83,200	24,600	25	668,600	2,340
Icariin	31 (29)	29,900	40	0.02	402,900	0.15
Isopropyl-octopamine	1	140,000	140,000	140,000	140,000	90
Methylsynephrine	17 (15)	56,700	63,000	3	137,800	90

* No data available.

** The number in brackets represents the actual number of detections for which the substance content has been quantified and dosage information was available to determine the daily dose.

Risk Assessment

Table 8 also lists the doses that involve a low risk of effects. The mean and maximum daily doses of all the substances listed in Table 8 exceed the daily dose that involves a low risk of adverse effects. This also applies to the median daily dose for all substances, except PEA. As regards the minimum daily dose, DMBA, BMPEA, halostachine and isopropyloctopamine exceed the daily dose which involves a low risk of adverse effects.

Sensitive groups

Several groups of consumers may run an elevated risk when taking food supplements containing the substances described in this advice. These are 'sensitive groups'. In a general sense, this concerns children and pregnant and lactating women. More specifically, this concerns athletes and other users who deliberately take these supplements to benefit from their stimulating effects. They face an elevated risk because strenuous physical exercise may amplify the effects on the cardiovascular system. Consumers who already have an elevated blood pressure or heart rate are also at extra risk, such as consumers with

cardiovascular disease or obesity (RIVM, 2018;2020d;2020e;2020f;2020g;2020b). Although MAO inhibitors are prescribed less and less frequently, consumers taking these drugs have an elevated risk of adverse effects after taking supplements containing BMPEA, PEA and N,N-DMPEA. Both the medicines and the supplements have an influence on MAO enzymes (RIVM, 2020d).

References

Aasen AJ, Culvenor CCJ, Finnie EP, Kellock AW & SMith LW, 1969. Alkaloids as a possible cause of ryegrass staggers in grazing livestock. Aust. J. Agric. Res, 20, 71-86.

Ambrosio C, Molinari P, Fanelli F, Chuman Y, Sbraccia M, Ugur O & Costa T, 2005. Different structural requirements for the constitutive and the agonist-induced activities of the beta2-adrenergic receptor. J Biol Chem, 280 (25), 23464-23474. Beschikbaar online: https://doi.org/10.1074/jbc.M502901200

An X, Long C, Deng X, Tang A, Xie J, Chen L & Wang Z, 2017. Higenamine inhibits apoptosis and maintains survival of gastric smooth muscle cells in diabetic gastroparesis rat model via activating the beta2-AR/PI3K/AKT pathway. Biomed Pharmacother, 95, 1710-1717. Beschikbaar online: https://doi.org/10.1016/j.biopha.2017.08.112

Anderson WG, 1983. The sympathomimetic activity of N-isopropyloctopamine in vitro. J Pharmacol Exp Ther, 225 (3), 553-558. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/6306210

Anwar MA, Ford WR, Broadley KJ & Herbert AA, 2012. Vasoconstrictor and vasodilator responses to tryptamine of rat-isolated perfused mesentery: comparison with tyramine and beta-phenylethylamine. Br J Pharmacol, 165 (7), 2191-2202. Beschikbaar online: https://doi.org/10.1111/j.1476-5381.2011.01706.x

Baba S, Kuroda Y & Horie M, 1986. Studies on drug metabolism by use of isotopes. XXVIII--Biological isotope effect for deuterated ephedrine. Biomed Environ Mass Spectrom, 13 (3), 137-140. Beschikbaar online: https://www.ncbi.nlm.nih.gov/pubmed/2938654

Babusyte A, Kotthoff M, Fiedler J & Krautwurst D, 2013. Biogenic amines activate blood leukocytes via trace amine-associated receptors TAAR1 and TAAR2. J Leukoc Biol, 93 (3), 387-394. Beschikbaar online: https://doi.org/10.1189/jlb.0912433

Bai G, Yang Y, Shi Q, Liu Z, Zhang Q & Zhu YY, 2008. Identification of higenamine in Radix Aconiti Lateralis Preparata as a beta2-adrenergic receptor agonist1. Acta Pharmacol Sin, 29 (10), 1187-1194. Beschikbaar online: https://doi.org/10.1111/j.1745-7254.2008.00859.x

Bailey BA, Philips SR & Boulton AA, 1987. In vivo release of endogenous dopamine, 5-hydroxytryptamine and some of their metabolites from rat caudate nucleus by phenylethylamine. Neurochem Res, 12 (2), 173-178. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/2437473

Baker GB, Wong JT, Coutts RT & Pasutto FM, 1987. Simultaneous extraction and quantitation of several bioactive amines in cheese and chocolate. J Chromatogr, 392, 317-331. Beschikbaar online: https://doi.org/10.1016/s0021-9673(01)94276-1

Bakhle YS & Youdim MB, 1979. The metabolism of 5-hydroxytryptamine and beta-phenylethylamine in perfused rat lung and in vitro. Br J Pharmacol, 65 (1), 147-154. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/32944

Bannour M, Lachenmeier DW, Straub I, Kohl-Himmelseher M, Khadhri A, Aschi-Smiti S, Kuballa T & Belgacem H, 2016. Evaluation of Calligonum azel Maire, a North African desert plant, for its nutritional potential as a sustainable food and feed. Food Res Int, 89 (Pt 1), 558-564. Beschikbaar online: https://doi.org/10.1016/j.foodres.2016.09.004

Barger G & Dale HH, 1910. Chemical structure and sympathomimetic action of amines. J. Physiol, 41, 19-59. Beschikbaar online: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1513032/pdf/jphysiol02555-0025.pdf

Barr GA, Gibbons JL & Bridger WH, 1979. A comparison of the effects of acute and subacute administration of beta-phenylethylamine and d-amphetamine on mouse killing behavior of rats. Pharmacol Biochem Behav, 11 (4), 419-422. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/574970

Barroso N & Rodriguez M, 1996. Action of beta-phenylethylamine and related amines on nigrostriatal dopamine neurotransmission. Eur J Pharmacol, 297 (3), 195-203. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/8666050

Barwell CJ, Basma AN, Lafi MA & Leake LD, 1989. Deamination of hordenine by monoamine oxidase and its action on vasa deferentia of the rat. J Pharm Pharmacol, 41 (6), 421-423. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/2570842

Ben-Harari RR & Bakhle YS, 1980. Uptake of beta-phenylethylamine in rat isolated lung. Biochem Pharmacol, 29 (4), 489-494. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/7370046

Benkirane S, Arbilla S & Langer SZ, 1986. Phenylethylamine-induced release of noradrenaline fails to stimulate alpha 1-adrenoceptors modulating [3H]-acetylcholine release in rat atria, but activates alpha 2-adrenoceptors modulating [3H]-serotonin release in the hippocampus. Naunyn Schmiedebergs Arch Pharmacol, 334 (2), 149-155. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/3024030

Berkov S, Bastida J, Sidjimova B, Viladomat F & Codina C, 2011. Alkaloid diversity in Galanthus elwesii and Galanthus nivalis. Chem Biodivers, 8 (1), 115-130. Beschikbaar online: https://doi.org/10.1002/cbdv.200900380

Berkov S, Pavlov A, Georgiev V, Weber J, Bley T, Viladomat F, Bastida J & Codina C, 2010. Changes in apolar metabolites during in vitro organogenesis of Pancratium maritimum. Plant Physiol Biochem, 48 (10-11), 827-835. Beschikbaar online: https://doi.org/10.1016/j.plaphy.2010.07.002

Berry MD, 2004. Mammalian central nervous system trace amines. Pharmacologic amphetamines, physiologic neuromodulators. J Neurochem, 90 (2), 257-271. Beschikbaar online: https://doi.org/10.1111/j.1471-4159.2004.02501.x

Biesterbos J, Eland J, Van De Koppel S & Van Hunsel F, 2017. Ask patient for details about supplement and drug combination. Food supplement next to medication: Pay attention to the interactions. Pharmaceutisch Weekblad, 152 (27-28), 12-13. Beschikbaar online: https://www.scopus.com/inward/record.uri?eid=2-s2.0-85025135538&partnerID=40&md5=54ffa6449f826a2072364a33a0eab2a2

Biesterbos JWH, Sijm DTHM, van Dam R & Mol HGJ, 2019. A health risk for consumers: the presence of adulterated food supplements in the Netherlands. Food Addit Contam Part A Chem Anal Control Expo Risk Assess, 1-16. Beschikbaar online: https://doi.org/10.1080/19440049.2019.1633020

Bloomer RJ, Canale RE, Blankenship MM, Hammond KG, Fisher-Wellman KH & Schilling BK, 2009a. Effect of the dietary supplement Meltdown on catecholamine secretion, markers of lipolysis, and metabolic rate in men and women: a randomized, placebo controlled, cross-over study. Lipids

Health Dis, 8, 32. Beschikbaar online: https://doi.org/10.1186/1476-511X-8-32

Bloomer RJ, Farney TM, Harvey IC & Alleman RJ, 2013. Safety profile of caffeine and 1,3-dimethylamylamine supplementation in healthy men. Hum Exp Toxicol, 32 (11), 1126-1136. Beschikbaar online: https://doi.org/10.1177/0960327113475680

Bloomer RJ, Fisher-Wellman KH, Hammond KG, Schilling BK, Weber AA & Cole BJ, 2009b. Dietary supplement increases plasma norepinephrine, lipolysis, and metabolic rate in resistance trained men. J Int Soc Sports Nutr, 6, 4. Beschikbaar online: https://doi.org/10.1186/1550-2783-6-4

Bloomer RJ, Harvey IC, Farney TM, Bell ZW & Canale RE, 2011a. Effects of 1,3-dimethylamylamine and caffeine alone or in combination on heart rate and blood pressure in healthy men and women. The Physician and sportsmedicine, 39 (3), 111-120. Beschikbaar online: https://doi.org/10.3810/psm.2011.09.1927

Bloomer RJ, McCarthy CG, Farney TM & Harvey IC, 2011b. Effect of Caffeine and 1,3-Dimethylamylamine on Exercise Performance and Blood Markers of Lipolysis and Oxidative Stress in Trained Men and Women. Journal of Caffeine Research, 1 (3), 169-177. Beschikbaar online: https://doi.org/10.1089/jcr.2011.0019

Bloomer RJ, Schriefer JM & Gunnels TA, 2015a. Clinical safety assessment of oral higenamine supplementation in healthy, young men. Hum Exp Toxicol, 34 (10), 935-945. Beschikbaar online: https://doi.org/10.1177/0960327114565490

Bloomer RJ, Schriefer JM & Gunnels TA, 2015b. Clinical safety assessment of oral higenamine supplementation in healthy, young men. Human & Experimental Toxicology, 34 (10), 935-945. Beschikbaar online: https://doi.org/10.1177/0960327114565490

Borowsky B, Adham N, Jones KA, Raddatz R, Artymyshyn R, Ogozalek KL, Durkin MM, Lakhlani PP, Bonini JA, Pathirana S, Boyle N, Pu X, Kouranova E, Lichtblau H, Ochoa FY, Branchek TA & Gerald C, 2001. Trace amines: identification of a family of mammalian G protein-coupled receptors. Proc Natl Acad Sci U S A, 98 (16), 8966-8971. Beschikbaar online: https://doi.org/10.1073/pnas.151105198

Bourke CA, Carrigan MJ & Dixon RJ, 1988a. Experimental evidence that tryptamine alkaloids do not cause Phalaris aquatica sudden death syndrome in sheep. Australian Veterinary Journal, 65 (7), 218-220. Beschikbaar online: https://doi.org/doi:10.1111/j.1751-0813.1988.tb14462.x

Bourke CA, Carrigan MJ & Dixon RJ, 1988b. Experimental evidence that tryptamine alkaloids do not cause Phalaris aquatica sudden death syndrome in sheep. Aust Vet J, 65 (7), 218-220. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/3421887

Bovee TF, Mol HG, Bienenmann-Ploum ME, Heskamp HH, Van Bruchem GD, Van Ginkel LA, Kooijman M, Lasaroms JJ, Van Dam R & Hoogenboom RL, 2016. Dietary supplement for energy and reduced appetite containing the beta-agonist isopropyloctopamine leads to heart problems and hospitalisations. Food Addit Contam Part A Chem Anal Control Expo Risk Assess, 33 (5), 749-759. Beschikbaar online: https://doi.org/10.1080/19440049.2016.1167965

Bunzow JR, Sonders MS, Arttamangkul S, Harrison LM, Zhang G, Quigley DI, Darland T, Suchland KL, Pasumamula S, Kennedy JL, Olson SB, Magenis

RE, Amara SG & Grandy DK, 2001. Amphetamine, 3,4-methylenedioxymethamphetamine, lysergic acid diethylamide, and metabolites of the catecholamine neurotransmitters are agonists of a rat trace amine receptor. Mol Pharmacol, 60 (6), 1181-1188. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/11723224

Burdock GA, 2016. Fenaroli's Handbook of Flavor Ingredients. 6th, CRC Press, 499 pp.

BuRO, 2012. Advies over de riscobeoordeling van 1,3 dimethylamylamine (DMAA) in voedingssupplementen. Bureau Risicobeoordeling & onderzoeksprogrammering; Nederlandse Voedsel- en Warenautoriteit, Utrecht.

Bush LP & Jeffreys JA, 1975. Isolation and separation of tall fescue and ryegrass alkaloids. J Chromatogr, 111 (1), 165-170. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/1158998

Caldwell J, 1976. The metabolism of amphetamines in mammals. Drug Metab Rev, 5 (2), 219-280. Beschikbaar online: https://doi.org/10.3109/03602537609029979

Calvert R, Vohra S, Ferguson M & Wiesenfeld P, 2015. A beating heart cell model to predict cardiotoxicity: effects of the dietary supplement ingredients higenamine, phenylethylamine, ephedrine and caffeine. Food Chem Toxicol, 78, 207-213. Beschikbaar online: https://doi.org/10.1016/j.fct.2015.01.022

Camus L, 1906a. L'hordénine, son degré de toxicité, symptomes de l'intoxication. Compt. Rend., 142, 110-113.

Camus L, 1906b. Action de sulfate d'hordenine sur circulation. Compt. Rend., 142 (237-239).

Cao H, Ke Y, Zhang Y, Zhang CJ, Qian W & Zhang GL, 2012. Icariin stimulates MC3T3-E1 cell proliferation and differentiation through up-regulation of bone morphogenetic protein-2. Int J Mol Med, 29 (3), 435-439. Beschikbaar online: https://doi.org/10.3892/ijmm.2011.845

Cashin CH, 1972. Effect of sympathomimetic drugs in eliciting hypertensive responses to reserpine in the rat, after pretreatment with monoamineoxidase inhibitors. Br J Pharmacol, 44 (2), 203-209. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/4668590

Chang KC, Chong WS & Lee IJ, 1994. Different pharmacological characteristics of structurally similar benzylisoquinoline analogs, papaverine, higenamine, and GS 389, on isolated rat aorta and heart. Can J Physiol Pharmacol, 72 (4), 327-334. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/7922863

Chang YC, Chang FR, Khalil AT, Hsieh PW & Wu YC, 2003. Cytotoxic benzophenanthridine and benzylisoquinoline alkaloids from Argemone mexicana. Z Naturforsch C, 58 (7-8), 521-526. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/12939038

Chen KK, Wu C-K & Henriksen E, 1929. Relationship between the pharmacological action and the chemical constitution and configuration of the optical isomers of ephedrine and related compounds. Journal of Pharmacology and Experimental Therapeutics, 36 (3), 363-400. Beschikbaar online: http://jpet.aspetjournals.org/content/jpet/36/3/363.full.pdf

Chen M, Hao J, Yang Q & Li G, 2014. Effects of icariin on reproductive functions in male rats. Molecules, 19 (7), 9502-9514. Beschikbaar online: https://doi.org/10.3390/molecules19079502

Chen S, Jiang H, Cao Y, Wang Y, Hu Z, Zhu Z & Chai Y, 2016a. Drug target identification using network analysis: Taking active components in Sini decoction as an example. Sci Rep, 6, 24245. Beschikbaar online: https://doi.org/10.1038/srep24245

Chen WF, Wu L, Du ZR, Chen L, Xu AL, Chen XH, Teng JJ & Wong MS, 2017. Neuroprotective properties of icariin in MPTP-induced mouse model of Parkinson's disease: Involvement of PI3K/Akt and MEK/ERK signaling pathways. Phytomedicine, 25, 93-99. Beschikbaar online: https://doi.org/10.1016/j.phymed.2016.12.017

Chen Y, Han S, Huang X, Ni J & He X, 2016b. The Protective Effect of Icariin on Mitochondrial Transport and Distribution in Primary Hippocampal Neurons from 3x Tg-AD Mice. Int J Mol Sci, 17 (2). Beschikbaar online: https://doi.org/10.3390/ijms17020163

Chen Y, Sun T, Wu J, Kalionis B, Zhang C, Yuan D, Huang J, Cai W, Fang H & Xia S, 2015. Icariin intervenes in cardiac inflammaging through upregulation of SIRT6 enzyme activity and inhibition of the NF-kappa B pathway. Biomed Res Int, 2015, 895976. Beschikbaar online: https://doi.org/10.1155/2015/895976

Chen YL, Zhuang XD, Xu ZW, Lu LH, Guo HL, Wu WK & Liao XX, 2013. Higenamine Combined with [6]-Gingerol Suppresses Doxorubicin-Triggered Oxidative Stress and Apoptosis in Cardiomyocytes via Upregulation of PI3K/Akt Pathway. Evid Based Complement Alternat Med, 2013, 970490. Beschikbaar online: https://doi.org/10.1155/2013/970490

Cheng S, Qiu F, Wang S & He J, 2007. HPLC analysis and pharmacokinetics of icariin in rats. J Sep Sci, 30 (9), 1307-1312. Beschikbaar online: https://doi.org/10.1002/jssc.200600313

Cheng T, Zhang Y, Zhang T, Lu L, Ding Y & Zhao Y, 2015. Comparative Pharmacokinetics Study of Icariin and Icariside II in Rats. Molecules, 20 (12), 21274-21286. Beschikbaar online: https://doi.org/10.3390/molecules201219763

Chi L, Gao W, Shu X & Lu X, 2014. A natural flavonoid glucoside, icariin, regulates Th17 and alleviates rheumatoid arthritis in a murine model. Mediators Inflamm, 2014, 392062. Beschikbaar online: https://doi.org/10.1155/2014/392062

Chung BH, Kim JD, Kim CK, Kim JH, Won MH, Lee HS, Dong MS, Ha KS, Kwon YG & Kim YM, 2008. Icariin stimulates angiogenesis by activating the MEK/ERK- and PI3K/Akt/eNOS-dependent signal pathways in human endothelial cells. Biochem Biophys Res Commun, 376 (2), 404-408. Beschikbaar online: https://doi.org/10.1016/j.bbrc.2008.09.001

Cohen PA, Avula B, Venhuis B, Travis JC, Wang YH & Khan IA, 2017. Pharmaceutical doses of the banned stimulant oxilofrine found in dietary supplements sold in the USA. Drug Test Anal, 9 (1), 135-142. Beschikbaar online: https://doi.org/10.1002/dta.1976

Cohen PA, Travis JC, Keizers PHJ, Boyer FE & Venhuis BJ, 2019. The stimulant higenamine in weight loss and sports supplements. Clin Toxicol (Phila), 57 (2), 125-130. Beschikbaar online: https://doi.org/10.1080/15563650.2018.1497171

Cohen PA, Travis JC, Keizers PHJ, Deuster P & Venhuis BJ, 2018. Four experimental stimulants found in sports and weight loss supplements: 2-amino-6-methylheptane (octodrine), 1,4-dimethylamylamine (1,4-DMAA), 1,3-dimethylamylamine (1,3-DMAA) and 1,3-dimethylbutylamine (1,3-

DMBA). Clin Toxicol (Phila), 56 (6), 421-426. Beschikbaar online: https://doi.org/10.1080/15563650.2017.1398328

Cohen PA, Travis JC & Venhuis BJ, 2015a. A synthetic stimulant never tested in humans, 1,3-dimethylbutylamine (DMBA), is identified in multiple dietary supplements. Drug Test Anal, 7 (1), 83-87. Beschikbaar online: https://doi.org/10.1002/dta.1735

Cohen PA, Zeijlon R, Nardin R, Keizers PH & Venhuis B, 2015b. Hemorrhagic Stroke Probably Caused by Exercise Combined With a Sports Supplement Containing beta-Methylphenyl-ethylamine (BMPEA): A Case Report. Ann Intern Med, 162 (12), 879-880. Beschikbaar online: https://doi.org/10.7326/L15-5101

Cooper SJ & Dourish CT, 1984. Hypodipsia, stereotypy and hyperactivity induced by beta-phenylethylamine in the water-deprived rat. Pharmacol Biochem Behav, 20 (1), 1-7. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/6538044

Cui Z, Sheng Z, Yan X, Cao Z & Tang K, 2016. In Silico Insight into Potential Anti-Alzheimer's Disease Mechanisms of Icariin. Int J Mol Sci, 17 (1). Beschikbaar online: https://doi.org/10.3390/ijms17010113

Daly JW, Creveling CR & Witkop B, 1966. The chemorelease of norepinephrine from mouse hearts. Structure-activity relationships. I. Sympathomimetic and related amines. J Med Chem, 9 (3), 273-280. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/5960887

Dekant W, Fujii K, Shibata E, Morita O & Shimotoyodome A, 2017. Safety assessment of green tea based beverages and dried green tea extracts as nutritional supplements. Toxicol Lett, 277, 104-108. Beschikbaar online: https://doi.org/10.1016/j.toxlet.2017.06.008

Deng GF, Wang DL, Meng MX, Hu F & Yao TW, 2009. Simultaneous determination of notoginsenoside R1, ginsenoside Rg1, Re, Rb1 and icariin in rat plasma by ultra-performance liquid chromatography-tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci, 877 (22), 2113-2122. Beschikbaar online: https://doi.org/10.1016/j.jchromb.2009.06.003

Denham BE, 2017. When contaminated dietary supplements cause positive drug tests: methylhexaneamine as a doping agent in sport. International Journal of Sport Policy and Politics, 9 (4), 677-689. Beschikbaar online: https://doi.org/10.1080/19406940.2017.1348963

Denno KM & Sadler TW, 1990. Phenylalanine and its metabolites induce embryopathies in mouse embryos in culture. Teratology, 42 (5), 565-570. Beschikbaar online: https://doi.org/10.1002/tera.1420420513

Derelanko MJ, 1990. Gastric mucosal protection with beta-phenylethylamine (PEA) and other sympathomimetic amines against absolute ethanol in the rat. Dig Dis Sci, 35 (6), 769-773. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/2344811

Di S, Fan C, Yang Y, Jiang S, Liang M, Wu G, Wang B, Xin Z, Hu W, Zhu Y, Li W, Zhou Y, Li X & Yan X, 2015. Activation of endoplasmic reticulum stress is involved in the activity of icariin against human lung adenocarcinoma cells. Apoptosis, 20 (9), 1229-1241. Beschikbaar online: https://doi.org/10.1007/s10495-015-1142-0

Ding L, Liang XG, Hu Y, Zhu DY & Lou YJ, 2008. Involvement of p38MAPK and reactive oxygen species in icariin-induced cardiomyocyte differentiation of murine embryonic stem cells in vitro. Stem Cells Dev, 17 (4), 751-760. Beschikbaar online: https://doi.org/10.1089/scd.2007.0206

Ding L, Liang XG, Zhu DY & Lou YJ, 2007. Icariin promotes expression of PGC-1alpha, PPARalpha, and NRF-1 during cardiomyocyte differentiation of murine embryonic stem cells in vitro. Acta Pharmacol Sin, 28 (10), 1541-1549. Beschikbaar online: https://doi.org/10.1111/j.1745-7254.2007.00648.x

Dominiak P, Kees F, Welzel D & Grobecker H, 1992. Cardiovascular parameters and catecholamines in volunteers during passive orthostasis. Influence of antihypotensive drugs. Arzneimittelforschung, 42 (5), 637-642. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/1530677

Dourish CT, 1981. Behavioural effects of acute and chronic beta-phenylethylamine administration in the rat: evidence for the involvement of 5-hydroxytryptamine. Neuropharmacology, 20 (11), 1067-1072. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/7322283

Dourish CT, 1982. An observational analysis of the behavioural effects of beta-phenylethylamine in isolated and grouped mice. Prog Neuropsychopharmacol Biol Psychiatry, 6 (2), 143-158. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/7202236

Dourish CT, 1985. Local application of beta-phenylethylamine to the caudate nucleus of the rat elicits locomotor stimulation. Pharmacol Biochem Behav, 22 (1), 159-162. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/3975242

Dourish CT & Cooper SJ, 1983. Pharmacology of beta-phenylethylamine-induced seizures in mice. Prog Neuropsychopharmacol Biol Psychiatry, 7 (4-6), 787-790. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/6141619

Du Yan-rong LF, Ri-yi., Xu., Yan., Zhang., Meng., Ouyang., Hong-li. & Jing., 2007. Tolerability of higenamine hydrochloride in healthy volunteers
Chin. J. Clin. Pharm, 23 (4), 258-260.

Duan W, Chen J, Wu Y, Zhang Y & Xu Y, 2016. Protective effect of higenamine ameliorates collagen-induced arthritis through heme oxygenase-1 and PI3K/Akt/Nrf-2 signaling pathways. Exp Ther Med, 12 (5), 3107-3112. Beschikbaar online: https://doi.org/10.3892/etm.2016.3730

Duiven E & Koert W, 2020. Dopingmiddelen in sportsupplementen. Sport & Geneeskunde, 1. Beschikbaar online: https://www.willemkoert.nl/archief/images2/dopingmiddelen-in-sportsupplementen.pdf

Dunn M, 2017. Have prohibition policies made the wrong decision? A critical review of studies investigating the effects of DMAA. Int J Drug Policy, 40, 26-34. Beschikbaar online: https://doi.org/10.1016/j.drugpo.2016.10.005

Durden DA, Philips SR & Boulton AA, 1973. Identification and distribution of beta-phenylethylamine in the rat. Can J Biochem, 51 (7), 995-1002. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/4725364

Dyck LE & Boulton AA, 1989. Effects of beta-phenylethylamine on polyphosphoinositide turnover in rat cerebral cortex. Neurochem Res, 14 (1), 63-67. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/2540445

Dzoljic MR, Bruinvels J & Bonta IL, 1977. Desynchronization of electrical activity in rats induced by deprenyl--an inhibitor of monoamine oxidase B--and relationship with selective increase of dopamine and beta-phenylethylamine. J Neural Transm, 40 (1), 1-12. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/833580

ECHA, 2012. Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health. European Chemicals Agency. Beschikbaar online: https://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf

EFSA, 2005. 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. EFSA Journal, 3 (10), 282. Beschikbaar online: https://doi.org/10.2903/j.efsa.2005.282

EFSA & WHO, 2016. Review of the Threshold of Toxicological Concern (TTC) approach and development of new TTC decision tree. EFSA Supporting Publications, 13 (3), 1006E. Beschikbaar online: https://doi.org/10.2903/sp.efsa.2016.EN-1006

EFSA Scientific Committee, 2019. Guidance on the use of the Threshold of Toxicological Concern approach in food safety assessment. EFSA Journal, 17 (6), e05708. Beschikbaar online: https://doi.org/10.2903/j.efsa.2019.5708

Eichner S, Maguire M, Shea LA & Fete MG, 2016. Banned and discouraged-use ingredients found in weight loss supplements. J Am Pharm Assoc (2003), 56 (5), 538-543. Beschikbaar online: https://doi.org/10.1016/j.japh.2016.03.013

Fan C, Yang Y, Liu Y, Jiang S, Di S, Hu W, Ma Z, Li T, Zhu Y, Xin Z, Wu G, Han J, Li X & Yan X, 2016. Icariin displays anticancer activity against human esophageal cancer cells via regulating endoplasmic reticulum stress-mediated apoptotic signaling. Sci Rep, 6, 21145. Beschikbaar online: https://doi.org/10.1038/srep21145

Fan JJ, Cao LG, Wu T, Wang DX, Jin D, Jiang S, Zhang ZY, Bi L & Pei GX, 2011. The dose-effect of icariin on the proliferation and osteogenic differentiation of human bone mesenchymal stem cells. Molecules, 16 (12), 10123-10133. Beschikbaar online: https://doi.org/10.3390/molecules161210123

Farney TM, McCarthy CG, Canale RE, Allman RJ, Jr. & Bloomer RJ, 2012. Hemodynamic and hematologic profile of healthy adults ingesting dietary supplements containing 1,3-dimethylamylamine and caffeine. Nutrition and metabolic insights, 5, 1-12. Beschikbaar online: https://doi.org/10.4137/nmi.S8568

Fellows EJ, 1947. The pharmacology of 2-amino-6-methylheptane. J Pharmacol Exp Ther, 90 (4), 351-358.

Feng R, Feng L, Yuan Z, Wang D, Wang F, Tan B, Han S, Li T, Li D & Han Y, 2013. Icariin protects against glucocorticoid-induced osteoporosis in vitro and prevents glucocorticoid-induced osteocyte apoptosis in vivo. Cell Biochem Biophys, 67 (1), 189-197. Beschikbaar online: https://doi.org/10.1007/s12013-013-9533-8

Feng S, Jiang J, Hu P, Zhang JY, Liu T, Zhao Q & Li BL, 2012. A phase I study on pharmacokinetics and pharmacodynamics of higenamine in healthy Chinese subjects. Acta Pharmacol Sin, 33 (11), 1353-1358. Beschikbaar online: https://doi.org/10.1038/aps.2012.114

Figueiredo TC, Viegas RP, Lara LJ, Baiao NC, Souza MR, Heneine LG & Cancado SV, 2013. Bioactive amines and internal quality of commercial eggs. Poult Sci, 92 (5), 1376-1384. Beschikbaar online: https://doi.org/10.3382/ps.2012-02735

Finberg JP & Gillman K, 2011. Selective inhibitors of monoamine oxidase type B and the "cheese effect". Int Rev Neurobiol, 100, 169-190. Beschikbaar online: https://doi.org/10.1016/B978-0-12-386467-3.00009-1

Fischer W, Neubert RH & Brandsch M, 2010. Transport of phenylethylamine at intestinal epithelial (Caco-2) cells: mechanism and substrate specificity. Eur J Pharm Biopharm, 74 (2), 281-289. Beschikbaar online: https://doi.org/10.1016/j.ejpb.2009.11.014

Frank M, Weckman TJ, Wood T, Woods WE, Tai CL, Chang SL, Ewing A, Blake JW & Tobin T, 1990. Hordenine: pharmacology, pharmacokinetics and behavioural effects in the horse. Equine Vet J, 22 (6), 437-441. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/2269269

Galli CL, Walker NJ, Oberlies NH, Roe AL, Edwards J, Fitzpatrick S, Griffiths JC, Hayes AW, Mahony C, Marsman DS & O'Keeffe L, 2019. Development of a consensus approach for botanical safety evaluation - A roundtable report. Toxicol Lett, 314, 10-17. Beschikbaar online: https://doi.org/10.1016/j.toxlet.2019.05.008

Glennon RA, Naiman NA, Pierson ME, Smith JD, Ismaiel AM, Titeler M & Lyon RA, 1989. N-(phthalimidoalkyl) derivatives of serotonergic agents: a common interaction at 5-HT1A serotonin binding sites? J Med Chem, 32 (8), 1921-1926. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/2754715

Goelz MF, Rothenbacher H, Wiggins JP, Kendall WA & Hershberger TV, 1980. Some hematological and histopathological effects of the alkaloids gramine and hordenine on meadow voles (Microtus pennsylvanicus). Toxicology, 18 (2), 125-131. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/7020159

Gong MJ, Han B, Wang SM, Liang SW & Zou ZJ, 2016. Icariin reverses corticosterone-induced depression-like behavior, decrease in hippocampal brain-derived neurotrophic factor (BDNF) and metabolic network disturbances revealed by NMR-based metabonomics in rats. J Pharm Biomed Anal, 123, 63-73. Beschikbaar online: https://doi.org/10.1016/j.jpba.2016.02.001

Goudie AJ & Buckland C, 1982. Serotonin receptor blockade potentiates behavioural effects of beta-phenylethylamine. Neuropharmacology, 21 (12), 1267-1272. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/7155309

Graham BE & Cartland GG, 1944. Some comparative pharmacological actions of beta-hydroxy and methoxy phenyl-n-propylamines. Journal of Pharmacology and Experimental Therapeutics, 81 (4), 360-367.

Granvogl M, Bugan S & Schieberle P, 2006. Formation of amines and aldehydes from parent amino acids during thermal processing of cocoa and model systems: new insights into pathways of the strecker reaction. J Agric Food Chem, 54 (5), 1730-1739. Beschikbaar online: https://doi.org/10.1021/jf0525939

Greenshaw AJ & Dourish CT, 1984. Differential aversive stimulus properties of beta-phenylethylamine and of d-amphetamine. Psychopharmacology (Berl), 82 (3), 189-193. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/6425899

Greenshaw AJ, Sanger DJ & Blackman DE, 1985. Effects of d-amphetamine and of beta-phenylethylamine on fixed interval responding maintained by self-regulated lateral hypothalamic stimulation in rats. Pharmacol Biochem Behav, 23 (4), 519-523. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/4070329

Grobecker HF & Kees F, 1993. Pharmacokinetic parameters and haemodynamic actions of midodrine in young volunteers. Int Angiol, 12 (2), 119-124. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/7690382

Gu ZF, Zhang ZT, Wang JY & Xu BB, 2017. Icariin exerts inhibitory effects on the growth and metastasis of KYSE70 human esophageal carcinoma cells via PI3K/AKT and STAT3 pathways. Environ Toxicol Pharmacol, 54, 7-13. Beschikbaar online: https://doi.org/10.1016/j.etap.2017.06.004

Guo J, Li F, Wu Q, Gong Q, Lu Y & Shi J, 2010. Protective effects of icariin on brain dysfunction induced by lipopolysaccharide in rats. Phytomedicine, 17 (12), 950-955. Beschikbaar online: https://doi.org/10.1016/j.phymed.2010.03.007

Guven KC, Percot A & Sezik E, 2010. Alkaloids in marine algae. Mar Drugs, 8 (2), 269-284. Beschikbaar online: https://doi.org/10.3390/md8020269

Ha YM, Kim MY, Park MK, Lee YS, Kim YM, Kim HJ, Lee JH & Chang KC, 2012. Higenamine reduces HMGB1 during hypoxia-induced brain injury by induction of heme oxygenase-1 through PI3K/Akt/Nrf-2 signal pathways. Apoptosis, 17 (5), 463-474. Beschikbaar online: https://doi.org/10.1007/s10495-011-0688-8

Halldin C, Bjurling P, Stalnacke CG, Jossan SS, Oreland L & Langstrom B, 1989. 11C-labelling of dimethylphenethylamine in two different positions and biodistribution studies. Int J Rad Appl Instrum A, 40 (7), 557-560. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/2551855

Han Y, Jung HW & Park YK, 2015. Effects of Icariin on insulin resistance via the activation of AMPK pathway in C2C12 mouse muscle cells. Eur J Pharmacol, 758, 60-63. Beschikbaar online: https://doi.org/10.1016/j.ejphar.2015.03.059

Han YY, Song MY, Hwang MS, Hwang JH, Park YK & Jung HW, 2016. Epimedium koreanum Nakai and its main constituent icariin suppress lipid accumulation during adipocyte differentiation of 3T3-L1 preadipocytes. Chin J Nat Med, 14 (9), 671-676. Beschikbaar online: https://doi.org/10.1016/S1875-5364(16)30079-6

Hannan CJ, Jr., 1986. beta-phenylethylamine effect on brain and blood catechol-O-methyltransferase activity. Pharmacol Biochem Behav, 24 (4), 1141-1146. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/3714772

Hapke HJ & Strathmann W, 1995. [Pharmacological effects of hordenine]. Dtsch Tierarztl Wochenschr, 102 (6), 228-232. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/8582256

Hartung M & Munch J, 1931. The preparation and pharmacodynamic activity of four isomeric phenylpropylamines. J Am Chem Soc., (53:), 1875–1879.

Hawthorn MH, Broadley KJ & Gibbon CJ, 1985. Examination of the bronchoconstrictor response of guinea-pig isolated lung to beta-phenylethylamine. Gen Pharmacol, 16 (4), 371-378. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/4043715

He XL, Zhou WQ, Bi MG & Du GH, 2010. Neuroprotective effects of icariin on memory impairment and neurochemical deficits in senescence-accelerated mouse prone 8 (SAMP8) mice. Brain Res, 1334, 73-83. Beschikbaar online: https://doi.org/10.1016/j.brainres.2010.03.084

Heffter A, 1894. Ueber Pellote. Ein Beitrag zur pharmakologischen Kenntnis der Cacteen. Arch. exp. Path. Pharmakol., 34, 65-86.

Hoffman JR, Kang J, Ratamess NA, Rashti SL, Tranchina CP & Faigenbaum AD, 2009. Thermogenic effect of an acute ingestion of a weight loss

supplement. J Int Soc Sports Nutr, 6, 1. Beschikbaar online: https://doi.org/10.1186/1550-2783-6-1

Hoffmann W, Lindinger A & Larbig-Bottcher U, 1987. Modification of cardiovascular dynamics in orthostatic dysregulation in childhood by oxilofrin. Klinische Padiatrie, 199 (5), 343-347. Beschikbaar online: https://doi.org/10.1055/s-2008-1026816

Hossain M, Wickramasekara RN & Carvelli L, 2014. beta-Phenylethylamine requires the dopamine transporter to increase extracellular dopamine in Caenorhabditis elegans dopaminergic neurons. Neurochem Int, 73, 27-31. Beschikbaar online: https://doi.org/10.1016/j.neuint.2013.10.010

Howard JL, Pollard GT, Rohrbach KW & Harto NE, 1976. Effect of beta-phenylethylamine and d-amphetamine on electrical self-stimulation of brain. Pharmacol Biochem Behav, 5 (6), 661-664. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/139616

Hsieh TP, Sheu SY, Sun JS & Chen MH, 2011. Icariin inhibits osteoclast differentiation and bone resorption by suppression of MAPKs/NF-kappaB regulated HIF-1alpha and PGE(2) synthesis. Phytomedicine, 18 (2-3), 176-185. Beschikbaar online: https://doi.org/10.1016/j.phymed.2010.04.003

Hsieh TP, Sheu SY, Sun JS, Chen MH & Liu MH, 2010. Icariin isolated from Epimedium pubescens regulates osteoblasts anabolism through BMP-2, SMAD4, and Cbfa1 expression. Phytomedicine, 17 (6), 414-423. Beschikbaar online: https://doi.org/10.1016/j.phymed.2009.08.007

Hu J, Mao Z, He S, Zhan Y, Ning R, Liu W, Yan B & Yang J, 2017. Icariin protects against glucocorticoid induced osteoporosis, increases the expression of the bone enhancer DEC1 and modulates the PI3K/Akt/GSK3beta/beta-catenin integrated signaling pathway. Biochem Pharmacol, 136, 109-121. Beschikbaar online: https://doi.org/10.1016/j.bcp.2017.04.010

Hu Y, Liu K, Yan M, Zhang Y, Wang Y & Ren L, 2016a. Icariin inhibits oxidized low-density lipoprotein-induced proliferation of vascular smooth muscle cells by suppressing activation of extracellular signal-regulated kinase 1/2 and expression of proliferating cell nuclear antigen. Mol Med Rep, 13 (3), 2899-2903. Beschikbaar online: https://doi.org/10.3892/mmr.2016.4813

Hu Y, Sun B, Liu K, Yan M, Zhang Y, Miao C & Ren L, 2016b. Icariin Attenuates High-cholesterol Diet Induced Atherosclerosis in Rats by Inhibition of Inflammatory Response and p38 MAPK Signaling Pathway. Inflammation, 39 (1), 228-236. Beschikbaar online: https://doi.org/10.1007/s10753-015-0242-x

Huang JH, Cai WJ, Zhang XM & Shen ZY, 2014a. Icariin promotes self-renewal of neural stem cells: an involvement of extracellular regulated kinase signaling pathway. Chin J Integr Med, 20 (2), 107-115. Beschikbaar online: https://doi.org/10.1007/s11655-013-1583-7

Huang Z, He L, Huang D, Lei S & Gao J, 2015. Icariin protects rats against 5/6 nephrectomy-induced chronic kidney failure by increasing the number of renal stem cells. BMC Complement Altern Med, 15, 378. Beschikbaar online: https://doi.org/10.1186/s12906-015-0909-8

Huang ZS, Xiao HJ, Qi T, Hu ZM, Li H, Chen DL, Xu YL & Chen J, 2014b. Antioxidative protective effect of icariin on the FeSO4/H 2O 2-damaged human sperm based on confocal raman micro-spectroscopy. J Huazhong Univ Sci Technolog Med Sci, 34 (5), 755-760. Beschikbaar online: https://doi.org/10.1007/s11596-014-1348-3

HvJ-EU, 2009. Zaak C-140/07 Hecht-Pharma GmbH tegen Staatliches Gewerbeaufsichtsamt Lüneburg (verzoek van het Bundesverwaltungsgericht om een prejudiciële beslissing) „Richtlijn 2001/83/EG – Artikelen 1, punt 2, en 2, lid 2 – Begrip ‚geneesmiddel naar werking' – Product waarvan hoedanigheid van geneesmiddel naar werking niet is vastgesteld – Inaanmerkingneming van mengverhouding van werkzame stoffen". Hof van Justitie van de Europese Unie. Beschikbaar online: https://eur-lex.europa.eu/legal-content/NL/TXT/HTML/?uri=CELEX:62007CJ0140&from=en

HvJ-EU, 2014. „Geneesmiddelen voor menselijk gebruik — Richtlijn 2001/83/EG — Werkingssfeer — Uitlegging van het begrip ‚geneesmiddel' — Draagwijdte van het criterium van geschiktheid om fysiologische functies te wijzigen — Producten op basis van aromatische planten en cannabinoïden — Daarvan uitgesloten" In de gevoegde zaken C-358/13 en C-181/14, betreffende verzoeken om een prejudiciële beslissing krachtens artikel 267 VWEU, ingediend door het Bundesgerichtshof (Duitsland) bij beslissingen van 28 mei 2013 en 8 april 2014, ingekomen bij het Hof respectievelijk op 27 juni 2013 en 14 april 2014, in de strafzaken tegen Markus D. (C-358/13) en G. (C-181/14). Het Hof van Justitie van de Europese Unie. Beschikbaar online: https://eur-lex.europa.eu/legal-content/NL/TXT/PDF/?uri=CELEX:62013CJ0358&from=EN

Inoue O, Tominaga T, Yamasaki T & Kinemuchi H, 1984. A new method for in vivo measurement of brain monoamine oxidase activity. Prog Neuropsychopharmacol Biol Psychiatry, 8 (3), 385-395. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/6435178

Inoue O, Tominaga T, Yamasaki T & Kinemuchi H, 1985. Radioactive N,N-dimethylphenylethylamine: a selective radiotracer for in vivo measurement of monoamine oxidase-B activity in the brain. J Neurochem, 44 (1), 210-216. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/3917289

Inwang EE, Mosnaim AD & Sabelli HC, 1973. Isolation and characterization of phenylethylamine and phenylethanolamine from human brain. J Neurochem, 20 (5), 1469-1473. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/4716838

Ishida K, Murata M, Katagiri N, Ishikawa M, Abe K, Kato M, Utsunomiya I & Taguchi K, 2005a. Effects of beta-phenylethylamine on dopaminergic neurons of the ventral tegmental area in the rat: a combined electrophysiological and microdialysis study. J Pharmacol Exp Ther, 314 (2), 916-922. Beschikbaar online: https://doi.org/10.1124/jpet.105.084764

Ishida K, Murata M, Kato M, Utsunomiya I, Hoshi K & Taguchi K, 2005b. Beta-phenylethylamine stimulates striatal acetylcholine release through activation of the AMPA glutamatergic pathway. Biol Pharm Bull, 28 (9), 1626-1629. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/16141528

Iwatsuki N, Amaha K & Koga Y, 1982. Biphasic change in human peripheral vascular resistance produced by carnigen. Tohoku J Exp Med, 138 (1), 81-85. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/7147235

Jackson DM, 1975. The effect of beta-phenylethylamine on temperature in mice and its possible mechanisms of action. Arzneimittelforschung, 25 (5), 776-780. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/1242322

Jacquot C & Rapin JR, 1980. [Presynaptic adrenergic mechanisms of action of oxilofrin]. Arzneimittelforschung, 30 (5), 776-779. Beschikbaar online: https://www.ncbi.nlm.nih.gov/pubmed/7190419

Jacquot C, Rapin JR & Cohen Y, 1980. [Effects of oxilofrine on the release and storage of noradrenaline in cardiac sections of the rat (author's transl)]. Arzneimittelforschung, 30 (6), 946-948. Beschikbaar online: https://www.ncbi.nlm.nih.gov/pubmed/7191269

Jansen SC, van Dusseldorp M, Bottema KC & Dubois AE, 2003. Intolerance to dietary biogenic amines: a review. Ann Allergy Asthma Immunol, 91 (3), 233-240; quiz 241-232, 296. Beschikbaar online: https://doi.org/10.1016/s1081-1206(10)63523-5

Janssen PA, Leysen JE, Megens AA & Awouters FH, 1999. Does phenylethylamine act as an endogenous amphetamine in some patients? Int J Neuropsychopharmacol, 2 (3), 229-240. Beschikbaar online: https://doi.org/10.1017/S1461145799001522

Jarrott B & Picken GM, 1975. Cardiac adenylate cyclase. I. Preparation and characterisation of a subcellular fraction containing catecholamine-sensitive adenylate cyclase. J Mol Cell Cardiol, 7 (9), 685-695. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/171422

Jeter J, Dezee KJ & Kennedy L, 2015a. A Case of Paraspinal Muscle Rhabdomyolysis in a 22-Year-Old Male After Ingesting a Supplement Containing Higenamine. Military Medicine, 180 (7), E847-E849. Beschikbaar online: https://doi.org/10.7205/milmed-d-14-00647

Jeter J, DeZee KJ & Kennedy L, 2015b. A Case of Paraspinal Muscle Rhabdomyolysis in a 22-Year-Old Male After Ingesting a Supplement Containing Higenamine. Mil Med, 180 (7), e847-849. Beschikbaar online: https://doi.org/10.7205/MILMED-D-14-00647

Jia C, Liu H, Li M, Wu Z & Feng X, 2014. Effects of icariin on cytokine-induced ankylosing spondylitis with fibroblastic osteogenesis and its molecular mechanism. Int J Clin Exp Pathol, 7 (12), 9104-9109. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/25674296

Jin F, Gong QH, Xu YS, Wang LN, Jin H, Li F, Li LS, Ma YM & Shi JS, 2014. Icariin, a phosphodiesterase-5 inhibitor, improves learning and memory in APP/PS1 transgenic mice by stimulation of NO/cGMP signalling. Int J Neuropsychopharmacol, 17 (6), 871-881. Beschikbaar online: https://doi.org/10.1017/S1461145713001533

Jin MS, Shi S, Zhang Y, Yan Y, Sun XD, Liu W & Liu HW, 2010. Icariin-mediated differentiation of mouse adipose-derived stem cells into cardiomyocytes. Mol Cell Biochem, 344 (1-2), 1-9. Beschikbaar online: https://doi.org/10.1007/s11010-010-0523-5

Kam SC, Do JM, Choi JH, Jeon BT, Roh GS, Chang KC & Hyun JS, 2012. The relaxation effect and mechanism of action of higenamine in the rat corpus cavernosum. Int J Impot Res, 24 (2), 77-83. Beschikbaar online: https://doi.org/10.1038/ijir.2011.48

Kang YJ, Lee YS, Lee GW, Lee DH, Ryu JC, Yun-Choi HS & Chang KC, 1999. Inhibition of activation of nuclear factor kappaB is responsible for inhibition of inducible nitric oxide synthase expression by higenamine, an active component of aconite root. J Pharmacol Exp Ther, 291 (1), 314-320. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/10490919

Karoum F, Chuang LW & Wyatt RJ, 1981. Presence and distribution of phenylethylamine in the rat spinal cord. Brain Res, 225 (2), 442-445. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/7306800

Kashiwada Y, Aoshima A, Ikeshiro Y, Chen YP, Furukawa H, Itoigawa M, Fujioka T, Mihashi K, Cosentino LM, Morris-Natschke SL & Lee KH, 2005. Anti-HIV benzylisoquinoline alkaloids and flavonoids from the leaves of Nelumbo nucifera, and structure-activity correlations with related alkaloids. Bioorg Med Chem, 13 (2), 443-448. Beschikbaar online: https://doi.org/10.1016/j.bmc.2004.10.020

Kato E, Inagaki Y & Kawabata J, 2015. Higenamine 4'-O-beta-d-glucoside in the lotus plumule induces glucose uptake of L6 cells through beta2-adrenergic receptor. Bioorg Med Chem, 23 (13), 3317-3321. Beschikbaar online: https://doi.org/10.1016/j.bmc.2015.04.054

Kato E, Kimura S & Kawabata J, 2017. Ability of higenamine and related compounds to enhance glucose uptake in L6 cells. Bioorg Med Chem. Beschikbaar online: https://doi.org/10.1016/j.bmc.2017.10.011

Kato M, Ishida K, Chuma T, Abe K, Shigenaga T, Taguchi K & Miyatake T, 2001. beta-Phenylethylamine modulates acetylcholine release in the rat striatum: involvement of a dopamine D(2) receptor mechanism. Eur J Pharmacol, 418 (1-2), 65-71. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/11334866

Katritch V, Reynolds KA, Cherezov V, Hanson MA, Roth CB, Yeager M & Abagyan R, 2009. Analysis of full and partial agonists binding to beta2-adrenergic receptor suggests a role of transmembrane helix V in agonist-specific conformational changes. J Mol Recognit, 22 (4), 307-318. Beschikbaar online: https://doi.org/10.1002/jmr.949

Kauert G, Angermann C, Lex H & Spes C, 1988a. Clinical pharmacokinetics after a single oral dose of oxilofrine. Int J Clin Pharmacol Res, 8 (5), 307-314. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/3229871

Kauert G, Herrle I & Schoppek B, 1988b. Detection of oxilofrine in plasma and urine by high-performance liquid chromatography with electrochemical detection and comparison with gas chromatography-mass spectrometry. J Chromatogr, 428 (2), 291-300. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/3215932

Ke Z, Liu J, Xu P, Gao A, Wang L & Ji L, 2015. The Cardioprotective Effect of Icariin on Ischemia-Reperfusion Injury in Isolated Rat Heart: Potential Involvement of the PI3K-Akt Signaling Pathway. Cardiovasc Ther, 33 (3), 134-140. Beschikbaar online: https://doi.org/10.1111/1755-5922.12121

Kim B, Byun BY & Mah JH, 2012. Biogenic amine formation and bacterial contribution in Natto products. Food Chem, 135 (3), 2005-2011. Beschikbaar online: https://doi.org/10.1016/j.foodchem.2012.06.091

Kim NH, Pham NB, Quinn RJ & Kwon HJ, 2010. R-(-)-beta-O-methylsynephrine, a natural product, inhibits VEGF-induced angiogenesis in vitro and in vivo. Biochem Biophys Res Commun, 399 (1), 20-23. Beschikbaar online: https://doi.org/10.1016/j.bbrc.2010.07.025

Kim NH, Pham NB, Quinn RJ, Shim JS, Cho H, Cho SM, Park SW, Kim JH, Seok SH, Oh JW & Kwon HJ, 2015. The Small Molecule R-(-)-beta-O-Methylsynephrine Binds to Nucleoporin 153 kDa and Inhibits Angiogenesis. Int J Biol Sci, 11 (9), 1088-1099. Beschikbaar online: https://doi.org/10.7150/ijbs.10603

Kim SC, Lee JH, Kim MH, Lee JA, Kim YB, Jung E, Kim YS, Lee J & Park D, 2013. Hordenine, a single compound produced during barley germination, inhibits melanogenesis in human melanocytes. Food Chem, 141 (1), 174-181. Beschikbaar online: https://doi.org/10.1016/j.foodchem.2013.03.017

Kimura I, Chui LH, Fujitani K, Kikuchi T & Kimura M, 1989. Inotropic effects of (+/-)-higenamine and its chemically related components, (+)-R-coclaurine and (+)-S-reticuline, contained in the traditional sino-Japanese medicines "bushi" and "shin-i" in isolated guinea pig papillary muscle. Jpn J Pharmacol, 50 (1), 75-78. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/2724702

Kimura I, Islam MA & Kimura M, 1996. Potentiation by higenamine of the aconitine-induced positive chronotropic effect in isolated right atria of mice: the effects of cholera toxin, forskolin and pertussis toxin. Biol Pharm Bull, 19 (8), 1032-1037. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/8874810

Kimura I, Makino M, Takamura Y, Islam MA & Kimura M, 1994. Positive chronotropic and inotropic effects of higenamine and its enhancing action on the aconitine-induced tachyarrhythmia in isolated murine atria. Jpn J Pharmacol, 66 (1), 75-80. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/7861670

Kittams DW & Vidaver GA, 1969. Inhibition by beta-phenylethylamine and similar compounds of glycine transport by pigeon red cells. Biochim Biophys Acta, 173 (3), 540-547. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/5769645

Kleinau G, Pratzka J, Nurnberg D, Gruters A, Fuhrer-Sakel D, Krude H, Kohrle J, Schoneberg T & Biebermann H, 2011. Differential modulation of Beta-adrenergic receptor signaling by trace amine-associated receptor 1 agonists. PLoS One, 6 (10), e27073. Beschikbaar online: https://doi.org/10.1371/journal.pone.0027073

Knoll J, Miklya I, Knoll B, Marko R & Racz D, 1996. Phenylethylamine and tyramine are mixed-acting sympathomimetic amines in the brain. Life Sci, 58 (23), 2101-2114. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/8649195

Koizumi H, Yu J, Hashimoto R, Ouchi Y & Okabe T, 2010. Involvement of androgen receptor in nitric oxide production induced by icariin in human umbilical vein endothelial cells. FEBS Lett, 584 (11), 2440-2444. Beschikbaar online: https://doi.org/10.1016/j.febslet.2010.04.049

Konczol A, Rendes K, Dekany M, Muller J, Riethmuller E & Balogh GT, 2016. Blood-brain barrier specific permeability assay reveals N-methylated tyramine derivatives in standardised leaf extracts and herbal products of Ginkgo biloba. J Pharm Biomed Anal, 131, 167-174. Beschikbaar online: https://doi.org/10.1016/j.jpba.2016.08.032

Kong L, Liu J, Wang J, Luo Q, Zhang H, Liu B, Xu F, Pang Q, Liu Y & Dong J, 2015. Icariin inhibits TNF-alpha/IFN-gamma induced inflammatory response via inhibition of the substance P and p38-MAPK signaling pathway in human keratinocytes. Int Immunopharmacol, 29 (2), 401-407. Beschikbaar online: https://doi.org/10.1016/j.intimp.2015.10.023

Kosa E, Marcilhac-Flouriot A, Fache MP & Siaud P, 2000. Effects of beta-phenylethylamine on the hypothalamo-pituitary-adrenal axis in the male rat. Pharmacol Biochem Behav, 67 (3), 527-535. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/11164083

Kraemer T & Maurer HH, 2002. Toxicokinetics of amphetamines: metabolism and toxicokinetic data of designer drugs, amphetamine, methamphetamine, and their N-alkyl derivatives. Ther Drug Monit, 24 (2), 277-289. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/11897973

Landete JM, Pardo I & Ferrer S, 2007. Tyramine and phenylethylamine production among lactic acid bacteria isolated from wine. Int J Food Microbiol, 115 (3), 364-368. Beschikbaar online: https://doi.org/10.1016/j.ijfoodmicro.2006.10.051

Lands AM, 1952. The cardiovascular actions 1-(3-aminophenyl)-2-aminoethanol and related compounds. J Pharmacol Exp Ther, 104 (4), 474-477. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/14918070

Lands AM & Grant JI, 1952. The vasopressor action and toxicity of cyclohexylethylamine derivatives. J Pharmacol Exp Ther, 106 (3), 341-345. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/13000630

Lareb, 2016. Meldingen van bijwerkingen van warenwetmiddelen rapportage 2015. Bijwerkingencentrum Lareb.

Lareb, 2017. Overzicht NVWA meldingen 2016. Bijwerkingencentrum Lareb.

Lareb, 2019. Overzicht NVWA meldingen 2018. Bijwerkingencentrum Lareb.

Lareb, 2020. Overzicht meldingen Warenwet producten 2019. Bijwerkingencentrum Lareb.

Le AW, Shan L, Wang ZH, Dai XY, Xiao TH & Zuo R, 2015. Effects of icariin on the expression of ER, VEGF, and KDR in the endometrial cells of thin endometrium. Genet Mol Res, 14 (3), 11250-11258. Beschikbaar online: https://doi.org/10.4238/2015.September.22.19

Lee HY, Lee JS, Kim EJ, Han JW, Lee HW, Kang YJ & Chang KC, 1999. Inhibition of lipopolysaccharide-induced inducible nitric oxide (iNOS) mRNA expression and nitric oxide production by higenamine in murine peritoneal macrophages. Arch Pharm Res, 22 (1), 55-59. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/10071960

Lee SR, Schriefer JM, Gunnels TA, Harvey IC & Bloomer RJ, 2013a. Acute oral intake of a higenamine-based dietary supplement increases circulating free fatty acids and energy expenditure in human subjects. Lipids Health Dis, 12, 148. Beschikbaar online: https://doi.org/10.1186/1476-511X-12-148

Lee SR, Schriefer JM, Gunnels TA, Harvey IC & Bloomer RJ, 2013b. Acute oral intake of a higenamine-based dietary supplement increases circulating free fatty acids and energy expenditure in human subjects. Lipids in Health and Disease, 12, 8. Beschikbaar online: https://doi.org/10.1186/1476-511x-12-148

Lee YS, Kang YJ, Kim HJ, Park MK, Seo HG, Lee JH, Yun-Choi HS & Chang KC, 2006. Higenamine reduces apoptotic cell death by induction of heme oxygenase-1 in rat myocardial ischemia-reperfusion injury. Apoptosis, 11 (7), 1091-1100. Beschikbaar online: https://doi.org/10.1007/s10495-006-7110-y

Lewin AH, Navarro HA & Mascarella SW, 2008. Structure-activity correlations for beta-phenethylamines at human trace amine receptor 1. Bioorg Med Chem, 16 (15), 7415-7423. Beschikbaar online: https://doi.org/10.1016/j.bmc.2008.06.009

Lewis RJ, 1996. Sax's Dangerous Properties of Industrial Materials. 9th ed, Van Nostrand Reinhold, New York, 2624 pp.

Li B, Duan X, Xu C, Wu J, Liu B, Du Y, Luo Q, Jin H, Gong W & Dong J, 2014a. Icariin attenuates glucocorticoid insensitivity mediated by repeated psychosocial stress on an ovalbumin-induced murine model of asthma. Int Immunopharmacol, 19 (2), 381-390. Beschikbaar online: https://doi.org/10.1016/j.intimp.2014.01.009

Li D, Yuan T, Zhang X, Xiao Y, Wang R, Fan Y & Zhang X, 2012. Icariin: a potential promoting compound for cartilage tissue engineering. Osteoarthritis Cartilage, 20 (12), 1647-1656. Beschikbaar online: https://doi.org/10.1016/j.joca.2012.08.009

Li F, Dong HX, Gong QH, Wu Q, Jin F & Shi JS, 2015a. Icariin decreases both APP and Abeta levels and increases neurogenesis in the brain of Tg2576 mice. Neuroscience, 304, 29-35. Beschikbaar online: https://doi.org/10.1016/j.neuroscience.2015.06.010

Li F, Gao B, Dong H, Shi J & Fang D, 2015b. Icariin induces synoviolin expression through NFE2L1 to protect neurons from ER stress-induced apoptosis. PLoS One, 10 (3), e0119955. Beschikbaar online: https://doi.org/10.1371/journal.pone.0119955

Li F, Gong QH, Wu Q, Lu YF & Shi JS, 2010a. Icariin isolated from Epimedium brevicornum Maxim attenuates learning and memory deficits induced by d-galactose in rats. Pharmacol Biochem Behav, 96 (3), 301-305. Beschikbaar online: https://doi.org/10.1016/j.pbb.2010.05.021

Li GW, Xu Z, Chang SX, Nian H, Wang XY & Qin LD, 2014b. Icariin prevents ovariectomy-induced bone loss and lowers marrow adipogenesis. Menopause, 21 (9), 1007-1016. Beschikbaar online: https://doi.org/10.1097/GME.0000000000000201

Li J, Jiang K & Zhao F, 2015c. Icariin regulates the proliferation and apoptosis of human ovarian cancer cells through microRNA-21 by targeting PTEN, RECK and Bcl-2. Oncol Rep, 33 (6), 2829-2836. Beschikbaar online: https://doi.org/10.3892/or.2015.3891

Li L, Peng L, Miao J, Qiu Y, Zhou Y, Gao X, Xu Y, Shi Z, Shao D & Ma Z, 2011a. Icariin induces the expression of toll-like receptor 9 in ana-1 murine macrophages. Phytother Res, 25 (11), 1732-1735. Beschikbaar online: https://doi.org/10.1002/ptr.3514

Li L, Sun J, Xu C, Zhang H, Wu J, Liu B & Dong J, 2014c. Icariin ameliorates cigarette smoke induced inflammatory responses via suppression of NF-kappaB and modulation of GR in vivo and in vitro. PLoS One, 9 (8), e102345. Beschikbaar online: https://doi.org/10.1371/journal.pone.0102345

Li M, Zhang ND, Wang Y, Han T, Jiang YP, Rahman K, Qin LP, Xin HL & Zhang QY, 2016a. Coordinate regulatory osteogenesis effects of icariin, timosaponin B II and ferulic acid from traditional Chinese medicine formulas on UMR-106 osteoblastic cells and osteoblasts in neonatal rat calvaria cultures. J Ethnopharmacol, 185, 120-131. Beschikbaar online: https://doi.org/10.1016/j.jep.2016.03.023

Li S, Dong P, Wang J, Zhang J, Gu J, Wu X, Wu W, Fei X, Zhang Z, Wang Y, Quan Z & Liu Y, 2010b. Icariin, a natural flavonol glycoside, induces apoptosis in human hepatoma SMMC-7721 cells via a ROS/JNK-dependent mitochondrial pathway. Cancer Lett, 298 (2), 222-230. Beschikbaar online: https://doi.org/10.1016/j.canlet.2010.07.009

Li W, Wang L, Chu X, Cui H & Bian Y, 2017. Icariin combined with human umbilical cord mesenchymal stem cells significantly improve the impaired kidney function in chronic renal failure. Mol Cell Biochem, 428 (1-2), 203-212. Beschikbaar online: https://doi.org/10.1007/s11010-016-2930-8

Li WW, Gao XM, Wang XM, Guo H & Zhang BL, 2011b. Icariin inhibits hydrogen peroxide-induced toxicity through inhibition of phosphorylation of JNK/p38 MAPK and p53 activity. Mutat Res, 708 (1-2), 1-10. Beschikbaar online: https://doi.org/10.1016/j.mrfmmm.2010.12.017

Li WX, Deng YY, Li F, Liu B, Liu HY, Shi JS & Gong QH, 2015d. Icariin, a major constituent of flavonoids from Epimedium brevicornum, protects against cognitive deficits induced by chronic brain hypoperfusion via its anti-amyloidogenic effect in rats. Pharmacol Biochem Behav, 138, 40-48. Beschikbaar online: https://doi.org/10.1016/j.pbb.2015.09.001

Li XA, Ho YS, Chen L & Hsiao WL, 2016b. The Protective Effects of Icariin against the Homocysteine-Induced Neurotoxicity in the Primary Embryonic Cultures of Rat Cortical Neurons. Molecules, 21 (11). Beschikbaar online: https://doi.org/10.3390/molecules21111557

Li Y, Duan J, Guo T, Xie W, Yan S, Li B, Zhou Y & Chen Y, 2009. In vivo pharmacokinetics comparisons of icariin, emodin and psoralen from gan-kang granules and extracts of herba Epimedii, Nepal dock root, Ficus hirta yahl. J Ethnopharmacol, 124 (3), 522-529. Beschikbaar online: https://doi.org/10.1016/j.jep.2009.05.008

Li Y, Jiang J, He Y, Jiang R, Liu J, Fan Z & Cheng Y, 2014d. Icariin combined with breviscapine improves the erectile function of spontaneously hypertensive rats. J Sex Med, 11 (9), 2143-2152. Beschikbaar online: https://doi.org/10.1111/jsm.12614

Li YC, Ding XS, Li HM & Zhang C, 2013. Icariin attenuates high glucose-induced type IV collagen and fibronectin accumulation in glomerular mesangial cells by inhibiting transforming growth factor-beta production and signalling through G protein-coupled oestrogen receptor 1. Clin Exp Pharmacol Physiol, 40 (9), 635-643. Beschikbaar online: https://doi.org/10.1111/1440-1681.12143

Li Z, Cheung FS, Zheng J, Chan T, Zhu L & Zhou F, 2014e. Interaction of the bioactive flavonol, icariin, with the essential human solute carrier transporters. J Biochem Mol Toxicol, 28 (2), 91-97. Beschikbaar online: https://doi.org/10.1002/jbt.21540

Liang CS & Sprecher D, 1979. Cardiovascular actions of beta-phenylethylamine. Am J Physiol, 236 (4), H592-595. Beschikbaar online: https://doi.org/10.1152/ajpheart.1979.236.4.H592

Liang SR, Bi JW, Guo ZL, Bai Y & Hu Z, 2014. Protective effect of icariin on kidney in 5/6 nephrectomized rats and its mechanism. Genet Mol Res, 13 (3), 6466-6471. Beschikbaar online: https://doi.org/10.4238/2014.August.25.10

Liang W, Lin M, Li X, Li C, Gao B, Gan H, Yang Z, Lin X, Liao L & Yang M, 2012. Icariin promotes bone formation via the BMP-2/Smad4 signal transduction pathway in the hFOB 1.19 human osteoblastic cell line. Int J Mol Med, 30 (4), 889-895. Beschikbaar online: https://doi.org/10.3892/ijmm.2012.1079

Liang X, Hong D, Huang Y, Rao Y, Ma K, Huang M, Zhang X, Lou Y & Zhao Q, 2015. Icariin promotes expression of junctophilin 2 and Ca2+ related function during cardiomyocyte differentiation of murine embryonic stem cells. Pharmazie, 70 (12), 804-809. Beschikbaar online: https://www.ncbi.nlm.nih.gov/pubmed/26817278

Liapakis G, Chan WC, Papadokostaki M & Javitch JA, 2004. Synergistic contributions of the functional groups of epinephrine to its affinity and efficacy at the beta2 adrenergic receptor. Mol Pharmacol, 65 (5), 1181-1190. Beschikbaar online: https://doi.org/10.1124/mol.65.5.1181

Lin J & Cashman JR, 1997. N-oxygenation of phenethylamine to the trans-oxime by adult human liver flavin-containing monooxygenase and retroreduction of phenethylamine hydroxylamine by human liver microsomes. J

Pharmacol Exp Ther, 282 (3), 1269-1279. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/9316835

Liu B, Xu C, Wu X, Liu F, Du Y, Sun J, Tao J & Dong J, 2015a. Icariin exerts an antidepressant effect in an unpredictable chronic mild stress model of depression in rats and is associated with the regulation of hippocampal neuroinflammation. Neuroscience, 294, 193-205. Beschikbaar online: https://doi.org/10.1016/j.neuroscience.2015.02.053

Liu B, Zhang H, Xu C, Yang G, Tao J, Huang J, Wu J, Duan X, Cao Y & Dong J, 2011. Neuroprotective effects of icariin on corticosterone-induced apoptosis in primary cultured rat hippocampal neurons. Brain Res, 1375, 59-67. Beschikbaar online: https://doi.org/10.1016/j.brainres.2010.12.053

Liu C, Zhu C, Wang G, Xu R & Zhu Y, 2015b. Higenamine regulates Nrf2-HO-1-Hmgb1 axis and attenuates intestinal ischemia-reperfusion injury in mice. Inflamm Res, 64 (6), 395-403. Beschikbaar online: https://doi.org/10.1007/s00011-015-0817-x

Liu MH, Sun JS, Tsai SW, Sheu SY & Chen MH, 2010. Icariin protects murine chondrocytes from lipopolysaccharide-induced inflammatory responses and extracellular matrix degradation. Nutr Res, 30 (1), 57-65. Beschikbaar online: https://doi.org/10.1016/j.nutres.2009.10.020

Liu W, Sato Y, Hosoda Y, Hirasawa K & Hanai H, 2000. Effects of higenamine on regulation of ion transport in guinea pig distal colon. Jpn J Pharmacol, 84 (3), 244-251. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/11138724

Liu XJ, Wagner HN, Jr. & Tao S, 1983. Measurement of effects of the Chinese herbal medicine higenamine on left ventricular function using a cardiac probe. Eur J Nucl Med, 8 (6), 233-236. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/6873101

Liu Y, Huang L, Hao B, Li H, Zhu S, Wang Q, Li R, Xu Y & Zhang X, 2017. Use of an Osteoblast Overload Damage Model to Probe the Effect of Icariin on the Proliferation, Differentiation and Mineralization of MC3T3-E1 Cells through the Wnt/beta-Catenin Signalling Pathway. Cell Physiol Biochem, 41 (4), 1605-1615. Beschikbaar online: https://doi.org/10.1159/000470896

Liu Y & Santillo MF, 2016. Cytochrome P450 2D6 and 3A4 enzyme inhibition by amine stimulants in dietary supplements. Drug Test Anal, 8 (3-4), 307-310. Beschikbaar online: https://doi.org/10.1002/dta.1863

Liu ZQ, 2006. Icariin: a special antioxidant to protect linoleic acid against free-radical-induced peroxidation in micelles. J Phys Chem A, 110 (19), 6372-6378. Beschikbaar online: https://doi.org/10.1021/jp053998z

Liu ZQ, Luo XY, Sun YX, Wu W, Liu CM, Liu ZQ & Liu SY, 2004. The antioxidative effect of icariin in human erythrocytes against free-radical-induced haemolysis. J Pharm Pharmacol, 56 (12), 1557-1562. Beschikbaar online: https://doi.org/10.1211/0022357044869

Lo CF & Chen CM, 1994. Determination of higenamine in plasma and urine by high-performance liquid chromatography with electrochemical detection. J Chromatogr B Biomed Appl, 655 (1), 33-39. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/8061831

Lo CF & Chen CM, 1996. Pharmacokinetics of higenamine in rabbits. Biopharm Drug Dispos, 17 (9), 791-803. Beschikbaar online: https://doi.org/10.1002/(SICI)1099-081X(199612)17:9<791::AID-BDD993>3.0.CO;2-T

Lo CF & Chen CM, 1997. Acute toxicity of higenamine in mice. Planta Med, 63 (1), 95-96. Beschikbaar online: https://doi.org/10.1055/s-2006-957619

Lu YF, Xu YY, Jin F, Wu Q, Shi JS & Liu J, 2014. Icariin is a PPARalpha activator inducing lipid metabolic gene expression in mice. Molecules, 19 (11), 18179-18191. Beschikbaar online: https://doi.org/10.3390/molecules191118179

Luo Y, Nie J, Gong QH, Lu YF, Wu Q & Shi JS, 2007. Protective effects of icariin against learning and memory deficits induced by aluminium in rats. Clin Exp Pharmacol Physiol, 34 (8), 792-795. Beschikbaar online: https://doi.org/10.1111/j.1440-1681.2007.04647.x

Luthy J & Schlatter C, 1983. Biogenic amines in food: effects of histamine, tyramine and phenylethylamine in the human. Zeitschrift fur Lebensmittel-Untersuchung und -Forschung, 177 (6), 439-443. Beschikbaar online: https://doi.org/10.1007/bf01409672

Lv XC, Bi LJ, Jiang Y & Wang X, 2013. Effects of icariin on the alkline phosphatase activity of human periodontal ligament cells inhibited by lipopolysaccharide. Mol Med Rep, 8 (5), 1411-1415. Beschikbaar online: https://doi.org/10.3892/mmr.2013.1677

Lynnes T, Horne SM & Pruss BM, 2014. ss-Phenylethylamine as a novel nutrient treatment to reduce bacterial contamination due to Escherichia coli O157:H7 on beef meat. Meat Sci, 96 (1), 165-171. Beschikbaar online: https://doi.org/10.1016/j.meatsci.2013.06.030

Ma G, Bavadekar SA, Schaneberg BT, Khan IA & Feller DR, 2010. Effects of synephrine and beta-phenethylamine on human alpha-adrenoceptor subtypes. Planta Med, 76 (10), 981-986. Beschikbaar online: https://doi.org/10.1055/s-0029-1240884

Ma HP, Ma XN, Ge BF, Zhen P, Zhou J, Gao YH, Xian CJ & Chen KM, 2014. Icariin attenuates hypoxia-induced oxidative stress and apoptosis in osteoblasts and preserves their osteogenic differentiation potential in vitro. Cell Prolif, 47 (6), 527-539. Beschikbaar online: https://doi.org/10.1111/cpr.12147

Ma HP, Ming LG, Ge BF, Zhai YK, Song P, Xian CJ & Chen KM, 2011. Icariin is more potent than genistein in promoting osteoblast differentiation and mineralization in vitro. J Cell Biochem, 112 (3), 916-923. Beschikbaar online: https://doi.org/10.1002/jcb.23007

Ma J, Wang S, Huang X, Geng P, Wen C, Zhou Y, Yu L & Wang X, 2015. Validated UPLC-MS/MS method for determination of hordenine in rat plasma and its application to pharmacokinetic study. J Pharm Biomed Anal, 111, 131-137. Beschikbaar online: https://doi.org/10.1016/j.jpba.2015.03.032

Makarova MN, Pozharitskaya ON, Shikov AN, Tesakova SV, Makarov VG & Tikhonov VP, 2007. Effect of lipid-based suspension of Epimedium koreanum Nakai extract on sexual behavior in rats. J Ethnopharmacol, 114 (3), 412-416. Beschikbaar online: https://doi.org/10.1016/j.jep.2007.08.021

Mangino MM & Scanlan RA, 1984. Rapid formation of N-nitrosodimethylamine from gramine, a naturally occurring precursor in barley malt. IARC Sci Publ, (57), 337-346. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/6533024

Marsh DF & Herring DA, 1951. The comparative pharmacology of the hydroxy and methyl derivatives of 6-methyl-2-heptylamine. J Pharmacol Exp Ther, 103 (2), 178-186. Beschikbaar online: http://jpet.aspetjournals.org/content/103/2/178.long

Marsh DF, Howard A & Herring DA, 1951. The comparative pharmacology of the isomeric nitrogen methyl substituted heptylamines. J Pharmacol Exp Ther, 103 (3), 325-329.

McCarthy CG, Canale RE, Alleman RJ, Jr., Reed JP & Bloomer RJ, 2012a. Biochemical and anthropometric effects of a weight loss dietary supplement in healthy men and women. Nutrition and metabolic insights, 5, 13-22. Beschikbaar online: https://doi.org/10.4137/nmi.S8566

McCarthy CG, Farney TM, Canale RE, Alleman RJ, Jr. & Bloomer RJ, 2012b. A finished dietary supplement stimulates lipolysis and metabolic rate in young men and women. Nutrition and metabolic insights, 5, 23-31. Beschikbaar online: https://doi.org/10.4137/nmi.S8567

McCulloch J & Harper AM, 1979. Factors influencing the response of the cerebral circulation to phenylethylamine. Neurology, 29 (2), 201-207. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/219389

McLaughlin JL, 1969. Cactus alkaloids. VI. Identification of hordenine and N--methyltyramine in Ariocarpus fissuratus varieties fissuratus and lloydii. Lloydia, 32 (3), 392-394. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/5361626

Meng X, Pei H & Lan C, 2015. Icariin Exerts Protective Effect Against Myocardial Ischemia/Reperfusion Injury in Rats. Cell Biochem Biophys, 73 (1), 229-235. Beschikbaar online: https://doi.org/10.1007/s12013-015-0669-6

Mercader J, Wanecq E, Chen J & Carpene C, 2011. Isopropylnorsynephrine is a stronger lipolytic agent in human adipocytes than synephrine and other amines present in Citrus aurantium. J Physiol Biochem, 67 (3), 443-452. Beschikbaar online: https://doi.org/10.1007/s13105-011-0078-2

Miller GM, Verrico CD, Jassen A, Konar M, Yang H, Panas H, Bahn M, Johnson R & Madras BK, 2005. Primate trace amine receptor 1 modulation by the dopamine transporter. J Pharmacol Exp Ther, 313 (3), 983-994. Beschikbaar online: https://doi.org/10.1124/jpet.105.084459

Millichap JG & Yee MM, 2003. The diet factor in pediatric and adolescent migraine. Pediatr Neurol, 28 (1), 9-15. Beschikbaar online: https://doi.org/10.1016/s0887-8994(02)00466-6

Minami H, Dubouzet E, Iwasa K & Sato F, 2007. Functional analysis of norcoclaurine synthase in Coptis japonica. J Biol Chem, 282 (9), 6274-6282. Beschikbaar online: https://doi.org/10.1074/jbc.M608933200

Mo ZT, Li WN, Zhai YR & Gao SY, 2017. The effects of icariin on the expression of HIF-1alpha, HSP-60 and HSP-70 in PC12 cells suffered from oxygen-glucose deprivation-induced injury. Pharm Biol, 55 (1), 848-852. Beschikbaar online: https://doi.org/10.1080/13880209.2017.1281968

Mok SK, Chen WF, Lai WP, Leung PC, Wang XL, Yao XS & Wong MS, 2010. Icariin protects against bone loss induced by oestrogen deficiency and activates oestrogen receptor-dependent osteoblastic functions in UMR 106 cells. Br J Pharmacol, 159 (4), 939-949. Beschikbaar online: https://doi.org/10.1111/j.1476-5381.2009.00593.x

Mosnaim AD, Callaghan OH, Hudzik T & Wolf ME, 2013. Rat brain-uptake index for phenylethylamine and various monomethylated derivatives. Neurochem Res, 38 (4), 842-846. Beschikbaar online: https://doi.org/10.1007/s11064-013-0988-1

Mosnaim AD, Hudzik T & Wolf ME, 2014. Analgesic effects of beta-phenylethylamine and various methylated derivatives in mice. Neurochem Res, 39 (9), 1675-1680. Beschikbaar online: https://doi.org/10.1007/s11064-014-1354-7

Mosnaim AD, Hudzik T & Wolf ME, 2015. Behavioral effects of beta-phenylethylamine and various monomethylated and monohalogenated analogs in mice are mediated by catecholaminergic mechanisms. Am J Ther, 22 (6), 412-422. Beschikbaar online: https://doi.org/10.1097/MJT.0000000000000337

Murata M, Katagiri N, Ishida K, Abe K, Ishikawa M, Utsunomiya I, Hoshi K, Miyamoto K & Taguchi K, 2009. Effect of beta-phenylethylamine on extracellular concentrations of dopamine in the nucleus accumbens and prefrontal cortex. Brain Res, 1269, 40-46. Beschikbaar online: https://doi.org/10.1016/j.brainres.2009.03.002

Nakamura M, Ishii A & Nakahara D, 1998. Characterization of beta-phenylethylamine-induced monoamine release in rat nucleus accumbens: a microdialysis study. Eur J Pharmacol, 349 (2-3), 163-169. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/9671094

Nan Y, Zhang X, Yang G, Xie J, Lu Z, Wang W, Ni X, Cao X, Ma J & Wang Z, 2014. Icariin stimulates the proliferation of rat Sertoli cells in an ERK1/2-dependent manner in vitro. Andrologia, 46 (1), 9-16. Beschikbaar online: https://doi.org/10.1111/and.12035

Narang D, Kerr PM, Lunn SE, Beaudry R, Sigurdson J, Lalies MD, Hudson AL, Light PE, Holt A & Plane F, 2014. Modulation of resistance artery tone by the trace amine beta-phenylethylamine: dual indirect sympathomimetic and alpha1-adrenoceptor blocking actions. J Pharmacol Exp Ther, 351 (1), 164-171. Beschikbaar online: https://doi.org/10.1124/jpet.114.216523

Navarro VJ, Khan I, Bjornsson E, Seeff LB, Serrano J & Hoofnagle JH, 2017. Liver injury from herbal and dietary supplements. Hepatology, 65 (1), 363-373. Beschikbaar online: https://doi.org/10.1002/hep.28813

Nelson BC, Putzbach K, Sharpless KE & Sander LC, 2007. Mass spectrometric determination of the predominant adrenergic protoalkaloids in bitter orange (Citrus aurantium). J Agric Food Chem, 55 (24), 9769-9775. Beschikbaar online: https://doi.org/10.1021/jf072030s

Nian H, Ma MH, Nian SS & Xu LL, 2009. Antiosteoporotic activity of icariin in ovariectomized rats. Phytomedicine, 16 (4), 320-326. Beschikbaar online: https://doi.org/10.1016/j.phymed.2008.12.006

Nie J, Luo Y, Huang XN, Gong QH, Wu Q & Shi JS, 2010. Icariin inhibits beta-amyloid peptide segment 25-35 induced expression of beta-secretase in rat hippocampus. Eur J Pharmacol, 626 (2-3), 213-218. Beschikbaar online: https://doi.org/10.1016/j.ejphar.2009.09.039

Ning H, Xin ZC, Lin G, Banie L, Lue TF & Lin CS, 2006. Effects of icariin on phosphodiesterase-5 activity in vitro and cyclic guanosine monophosphate level in cavernous smooth muscle cells. Urology, 68 (6), 1350-1354. Beschikbaar online: https://doi.org/10.1016/j.urology.2006.09.031

Nojima H, Okazaki M & Kimura I, 2000. Counter effects of higenamine and coryneine, components of aconite root, on acetylcholine release from motor nerve terminal in mice. J Asian Nat Prod Res, 2 (3), 195-203. Beschikbaar online: https://doi.org/10.1080/10286020008039911

NVWA, 2017. Voedingssupplementen met farmacologisch actieve stoffen Nederlandse Voedsel- en Warenautoriteit, Utrecht. Beschikbaar online: https://www.nvwa.nl/documenten/consument/eten-drinken-roken/supplementen-en-preparaten/publicaties/onderzoek-voedingssupplementen-met-farmacologisch-actieve-stoffen

Oldendorf WH, 1971. Brain uptake of radiolabeled amino acids, amines, and hexoses after arterial injection. Am J Physiol, 221 (6), 1629-1639. Beschikbaar online: https://doi.org/10.1152/ajplegacy.1971.221.6.1629

Ono H, Ito H & Fukuda H, 1991. 2-phenylethylamine and methamphetamine enhance the spinal monosynaptic reflex by releasing noradrenaline from the terminals of descending fibers. Jpn J Pharmacol, 55 (3), 359-366. Beschikbaar online: https://www.jstage.jst.go.jp/article/jphs1951/55/3/55_3_359/_pdf

Paetsch PR, Baker GB & Greenshaw AJ, 1993. Induction of functional down-regulation of beta-adrenoceptors in rats by 2-phenylethylamine. J Pharm Sci, 82 (1), 22-24. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/8381487

Paetsch PR & Greenshaw AJ, 1993. 2-Phenylethylamine-induced changes in catecholamine receptor density: implications for antidepressant drug action. Neurochem Res, 18 (9), 1015-1022. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/7901780

Pan Y, Hong Y, Zhang QY & Kong LD, 2013. Impaired hypothalamic insulin signaling in CUMS rats: restored by icariin and fluoxetine through inhibiting CRF system. Psychoneuroendocrinology, 38 (1), 122-134. Beschikbaar online: https://doi.org/10.1016/j.psyneuen.2012.05.007

Pan Y, Kong L, Xia X, Zhang W, Xia Z & Jiang F, 2005. Antidepressant-like effect of icariin and its possible mechanism in mice. Pharmacol Biochem Behav, 82 (4), 686-694. Beschikbaar online: https://doi.org/10.1016/j.pbb.2005.11.010

Pan Y, Kong LD, Li YC, Xia X, Kung HF & Jiang FX, 2007. Icariin from Epimedium brevicornum attenuates chronic mild stress-induced behavioral and neuroendocrinological alterations in male Wistar rats. Pharmacol Biochem Behav, 87 (1), 130-140. Beschikbaar online: https://doi.org/10.1016/j.pbb.2007.04.009

Pan Y, Wang FM, Qiang LQ, Zhang DM & Kong LD, 2010. Icariin attenuates chronic mild stress-induced dysregulation of the LHPA stress circuit in rats. Psychoneuroendocrinology, 35 (2), 272-283. Beschikbaar online: https://doi.org/10.1016/j.psyneuen.2009.06.020

Pan Y, Zhang WY, Xia X & Kong LD, 2006. Effects of icariin on hypothalamic-pituitary-adrenal axis action and cytokine levels in stressed Sprague-Dawley rats. Biol Pharm Bull, 29 (12), 2399-2403. Beschikbaar online: https://www.ncbi.nlm.nih.gov/pubmed/17142971

Park CW, Chang KC & Lim JK, 1984. Effects of higenamine on isolated heart adrenoceptor of rabbit. Arch Int Pharmacodyn Ther, 267 (2), 279-288. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/6712361

Park H, Ha J, Koo JY, Park J & Park SB, 2017. Label-free target identification using in-gel fluorescence difference via thermal stability shift. Chem Sci, 8 (2), 1127-1133. Beschikbaar online: https://doi.org/10.1039/c6sc03238a

Park JE, Kang YJ, Park MK, Lee YS, Kim HJ, Seo HG, Lee JH, Hye Sook YC, Shin JS, Lee HW, Ahn SK & Chang KC, 2006. Enantiomers of higenamine inhibit LPS-induced iNOS in a macrophage cell line and improve the survival of mice with experimental endotoxemia. Int Immunopharmacol, 6 (2), 226-233. Beschikbaar online: https://doi.org/10.1016/j.intimp.2005.08.007

Pastore P, Favaro G, Badocco D, Tapparo A, Cavalli S & Saccani G, 2005. Determination of biogenic amines in chocolate by ion chromatographic separation and pulsed integrated amperometric detection with implemented wave-form at Au disposable electrode. J Chromatogr A, 1098

(1-2), 111-115. Beschikbaar online: https://doi.org/10.1016/j.chroma.2005.08.065

Paterson IA, 1993. The potentiation of cortical neuron responses to noradrenaline by 2-phenylethylamine is independent of endogenous noradrenaline. Neurochem Res, 18 (12), 1329-1336. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/8272197

Paterson IA, Juorio AV & Boulton AA, 1990. 2-Phenylethylamine: a modulator of catecholamine transmission in the mammalian central nervous system? J Neurochem, 55 (6), 1827-1837. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/2172461

Pawar RS & Grundel E, 2017. Overview of regulation of dietary supplements in the USA and issues of adulteration with phenethylamines (PEAs). Drug Test Anal, 9 (3), 500-517. Beschikbaar online: https://doi.org/10.1002/dta.1980

Pei Z, Zhang F, Niu Z & Shi S, 2013. Effect of icariin on cell proliferation and the expression of bone resorption/formation-related markers in human periodontal ligament cells. Mol Med Rep, 8 (5), 1499-1504. Beschikbaar online: https://doi.org/10.3892/mmr.2013.1696

Pellati F & Benvenuti S, 2007. Chromatographic and electrophoretic methods for the analysis of phenethylamine [corrected] alkaloids in Citrus aurantium. J Chromatogr A, 1161 (1-2), 71-88. Beschikbaar online: https://doi.org/10.1016/j.chroma.2007.05.097

Philips SR, 1986. In vivo release of endogenous dopamine from rat caudate nucleus by beta-phenylethylamine and alpha,alpha,-dideutero-beta-phenylethylamine. Life Sci, 39 (25), 2395-2400. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/3796200

Pilkington TR, Lowe RD, Foster R, Robinson BF & Antonis A, 1966. Effect of sympathomimetic compounds with beta-adrenergic effects on plasma free fatty acids in man. J Lipid Res, 7 (1), 73-76.

Pohl K & Kriech W, 1991. Therapy of orthostatic disorders of cardiovascular regulation. Placebo controlled double-blind study with oxilofrine. Fortschr Med, 109 (33), 685-688. Beschikbaar online: <Go to ISI>://MEDLINE:1769643

Praman S, Mulvany MJ, Williams DE, Andersen RJ & Jansakul C, 2012. Hypotensive and cardio-chronotropic constituents of Tinospora crispa and mechanisms of action on the cardiovascular system in anesthetized rats. J Ethnopharmacol, 140 (1), 166-178. Beschikbaar online: https://doi.org/10.1016/j.jep.2012.01.006

Praman S, Mulvany MJ, Williams DE, Andersen RJ & Jansakul C, 2013. Crude extract and purified components isolated from the stems of Tinospora crispa exhibit positive inotropic effects on the isolated left atrium of rats. J Ethnopharmacol, 149 (1), 123-132. Beschikbaar online: https://doi.org/10.1016/j.jep.2013.06.010

Pyo MK, Kim JM, Jin JL, Chang KC, Lee DH & Yun-Choi HS, 2007. Effects of higenamine and its 1-naphthyl analogs, YS-49 and YS-51, on platelet TXA2 synthesis and aggregation. Thromb Res, 120 (1), 81-86. Beschikbaar online: https://doi.org/10.1016/j.thromres.2006.07.006

Qian Q, Li SL, Sun E, Zhang KR, Tan XB, Wei YJ, Fan HW, Cui L & Jia XB, 2012. Metabolite profiles of icariin in rat plasma by ultra-fast liquid chromatography coupled to triple-quadrupole/time-of-flight mass spectrometry. J Pharm Biomed Anal, 66, 392-398. Beschikbaar online: https://doi.org/10.1016/j.jpba.2012.03.053

Qian ZQ, Wang YW, Li YL, Li YQ, Ling Z & Yang DL, 2017. Icariin prevents hypertension-induced cardiomyocyte apoptosis through the mitochondrial apoptotic pathway. Biomed Pharmacother, 88, 823-831. Beschikbaar online: https://doi.org/10.1016/j.biopha.2017.01.147

Rapin JR & Jacquot C, 1980. [Effects of oxilofrine on the activity of the sympathetic nervous system (author's transl)]. Arzneimittelforschung, 30 (7), 1077-1079. Beschikbaar online: https://www.ncbi.nlm.nih.gov/pubmed/6106499

Rauscher-Gabernig E, Grossgut R, Bauer F & Paulsen P, 2010. Phenylethylamine in foods: concentrations and development of maximum tolerable levels. Wiener Tierarztliche Monatsschrift, 97 (9-10), 242-252. Beschikbaar online: <Go to ISI>://WOS:000283187500005

RIVM, 2010. Geranamine advies; VW2009-0003. Rijksinstituut voor Volksgezondheid en Milieu, Bilthoven.

RIVM, 2011. Geranamine - orale werkzaamheid. Rijksinstituut voor Volksgezondheid en Milieu, Bilthoven.

RIVM, 2018. Factsheet DMAA, DMBA and DMHA in supplements. Front Office Voedsel- en Productveiligheid, Bilthoven. Beschikbaar online: https://www.rivm.nl/documenten/fact-sheet-dmaa-dmba-dmhafinal20180129anon

RIVM, 2020a. Beoordeling van hordenine. Front Office Voedsel- en Productveiligheid, Bilthoven. Beschikbaar online: https://www.rivm.nl/documenten/fo-beoordeling-hordeninedefinitief20200410anonpdf

RIVM, 2020b. Beoordeling van methylsynefrine. Front Office Voedsel- en Productveiligheid, Bilthoven. Beschikbaar online: https://www.rivm.nl/documenten/fo-beoordeling-methylsynefrinedefinitief20200401anonpdf

RIVM, 2020c. Beoordeling van icariin. Front Office Voedsel- en Productveiligheid, Bilthoven. Beschikbaar online: https://www.rivm.nl/documenten/fo-beoordeling-icariinedefinitief20200401anonpdf

RIVM, 2020d. Beoordeling van beta-fenethylamine (FEA), beta-methylfenethylamine (BMFEA) en N-beta-dimethylfenethylamine (N,N-DMFEA). Front Office Voedsel- en Productveiligheid, Bilthoven. Beschikbaar online: https://www.rivm.nl/documenten/fo-beoordeling-feasdefinitief20200401anonpdf

RIVM, 2020e. Beoordeling van halostachine. Front Office Voedsel- en Productveiligheid, Bilthoven. Beschikbaar online: https://www.rivm.nl/documenten/fo-beoordeling-halostachinedefinitief20200410anonpdf

RIVM, 2020f. Beoordeling van higenamine. Front Office Voedsel- en Productveiligheid, Bilthoven. Beschikbaar online: https://www.rivm.nl/documenten/fo-beoordeling-higenaminedefinitief20200401anonpdf

RIVM, 2020g. Beoordeling van isopropyloctopamine. Front Office Voedsel- en Productveiligheid, Bilthoven. Beschikbaar online: https://www.rivm.nl/documenten/fo-beoordeling-isopropyloctopaminedefinitief20200410anonpdf

Rocha T, Amaral JS & Oliveira M, 2016. Adulteration of Dietary Supplements by the Illegal Addition of Synthetic Drugs: A Review. Comprehensive Reviews in Food Science and Food Safety, 15 (1), 43-62. Beschikbaar online: https://doi.org/10.1111/1541-4337.12173

Rodriguez M & Barroso N, 1995. beta-Phenylethylamine regulation of dopaminergic nigrostriatal cell activity. Brain Res, 703 (1-2), 201-204. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/8719633

Roelen CCJ, van Riel AJHP & de Vries I, 2016. Overzicht NVIC-meldingen over voedingssupplementen in 2015. Nationaal Vergiftigingen Informatie Centrum, Utrecht.

Roelen CCJ, Verputten PM, van Riel AJHP & de Vries I, 2017. Overzicht NVIC-meldingen over voedingssupplementen in 2016. Nationaal Vergiftigingen Informatie Centrum, Utrecht.

Roelen CCJ, Verputten PM, van Riel AJHP, de Vries I & de Lange DW, 2019. Overzicht NVIC-meldingen over voedingssupplementen in 2018. Nationaal Vergiftigingen Informatie Centrum, Utrecht.

Roth JA & Gillis CN, 1974. Deamination of beta-phenylethylamine by monoamine oxidase--inhibition by imipramine. Biochem Pharmacol, 23 (18), 2537-2545. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/4412708

Saavedra JM, 1974. Enzymatic isotopic assay for and presence of beta-phenylethylamine in brain. J Neurochem, 22 (2), 211-216. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/4364337

Saavedra JM & Axelrod J, 1973. Demonstration and distribution of phenylethanolamine in brain and other tissues. Proc Natl Acad Sci U S A, 70 (3), 769-772. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/4268476

Sabelli HC, Mosnaim AD, Vazquez AJ, Giardina WJ, Borison RL & Pedemonte WA, 1976. Biochemical plasticity of synaptic transmission: a critical review of Dale's Principle. Biol Psychiatry, 11 (4), 481-524. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/9160

Safratowich BD, Hossain M, Bianchi L & Carvelli L, 2014. Amphetamine potentiates the effects of beta-phenylethylamine through activation of an amine-gated chloride channel. J Neurosci, 34 (13), 4686-4691. Beschikbaar online: https://doi.org/10.1523/JNEUROSCI.3100-13.2014

Sander LC, Putzbach K, Nelson BC, Rimmer CA, Bedner M, Thomas JB, Porter BJ, Wood LJ, Schantz MM, Murphy KE, Sharpless KE, Wise SA, Yen JH, Siitonen PH, Evans RL, Nguyen Pho A, Roman MC & Betz JM, 2008. Certification of standard reference materials containing bitter orange. Anal Bioanal Chem, 391 (6), 2023-2034. Beschikbaar online: https://doi.org/10.1007/s00216-008-2074-0

Sashidhara KV, Singh SP & Shukla PK, 2009. Antimicrobial evaluation of clerodane diterpenes from Polyalthia longifolia var. pendula. Nat Prod Commun, 4 (3), 327-330. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/19413108

Sato S, Tamura A, Kitagawa S & Koshiro A, 1997. A kinetic analysis of the effects of beta-phenylethylamine on the concentrations of dopamine and its metabolites in the rat striatum. J Pharm Sci, 86 (4), 487-496. Beschikbaar online: https://doi.org/10.1021/js960192p

Schepers RJ, Oyler JM, Joseph RE, Jr., Cone EJ, Moolchan ET & Huestis MA, 2003. Methamphetamine and amphetamine pharmacokinetics in oral fluid and plasma after controlled oral methamphetamine administration to human volunteers. Clin Chem, 49 (1), 121-132. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/12507968

Schilling BK, Hammond KG, Bloomer RJ, Presley CS & Yates CR, 2013. Physiological and pharmacokinetic effects of oral 1,3-dimethylamylamine

administration in men. BMC Pharmacol Toxicol, 14, 52. Beschikbaar online: https://doi.org/10.1186/2050-6511-14-52

Schluesener JK & Schluesener H, 2014. Plant polyphenols in the treatment of age-associated diseases: revealing the pleiotropic effects of icariin by network analysis. Mol Nutr Food Res, 58 (1), 49-60. Beschikbaar online: https://doi.org/10.1002/mnfr.201300409

Servillo L, Castaldo D, Giovane A, Casale R, D'Onofrio N, Cautela D & Balestrieri ML, 2017. Tyramine Pathways in Citrus Plant Defense: Glycoconjugates of Tyramine and Its N-Methylated Derivatives. J Agric Food Chem, 65 (4), 892-899. Beschikbaar online: https://doi.org/10.1021/acs.jafc.6b04423

Sha D, Li L, Ye L, Liu R & Xu Y, 2009. Icariin inhibits neurotoxicity of beta-amyloid by upregulating cocaine-regulated and amphetamine-regulated transcripts. Neuroreport, 20 (17), 1564-1567. Beschikbaar online: https://doi.org/10.1097/WNR.0b013e328332d345

Shannon HE, Cone EJ & Yousefnejad D, 1981. Physiologic effects and plasma kinetics of phenylethanolamine and its N-methyl homolog in the dog. J Pharmacol Exp Ther, 217 (2), 379-385. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/7229979

Shannon HE, Cone EJ & Yousefnejad D, 1982. Physiologic effects and plasma kinetics of beta-phenylethylamine and its N-methyl homolog in the dog. J Pharmacol Exp Ther, 223 (1), 190-196. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/7120117

Shannon HE & Degregorio CM, 1982. Self-administration of the endogenous trace amines beta-phenylethylamine, N-methyl phenylethylamine and phenylethanolamine in dogs. J Pharmacol Exp Ther, 222 (1), 52-60. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/7201021

Shao H, Shen J, Wang M, Cui J, Wang Y, Zhu S, Zhang W, Yang H, Xu Y & Geng D, 2015. Icariin protects against titanium particle-induced osteolysis and inflammatory response in a mouse calvarial model. Biomaterials, 60, 92-99. Beschikbaar online: https://doi.org/10.1016/j.biomaterials.2015.04.048

Shen R, Deng W, Li C & Zeng G, 2015. A natural flavonoid glucoside icariin inhibits Th1 and Th17 cell differentiation and ameliorates experimental autoimmune encephalomyelitis. Int Immunopharmacol, 24 (2), 224-231. Beschikbaar online: https://doi.org/10.1016/j.intimp.2014.12.015

Shi DB, Li XX, Zheng HT, Li DW, Cai GX, Peng JJ, Gu WL, Guan ZQ, Xu Y & Cai SJ, 2014. Icariin-mediated inhibition of NF-kappaB activity enhances the in vitro and in vivo antitumour effect of 5-fluorouracil in colorectal cancer. Cell Biochem Biophys, 69 (3), 523-530. Beschikbaar online: https://doi.org/10.1007/s12013-014-9827-5

Shimosato K, Tomita M & Ijiri I, 1986. Urinary excretion of p-hydroxylated methamphetamine metabolites in man. I. A method for determination by high-performance liquid chromatography-electrochemistry. Arch Toxicol, 59 (3), 135-140. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/3813878

Shin JS, Yun-Choi HS, Kim EI & Lee MK, 1999. Inhibitory effects of higenamine on dopamine content in PC12 cells. Planta Med, 65 (5), 452-455. Beschikbaar online: https://doi.org/10.1055/s-2006-960810

Shindel AW, Xin ZC, Lin G, Fandel TM, Huang YC, Banie L, Breyer BN, Garcia MM, Lin CS & Lue TF, 2010. Erectogenic and neurotrophic effects of icariin, a purified extract of horny goat weed (Epimedium spp.) in vitro and in vivo.

J Sex Med, 7 (4 Pt 1), 1518-1528. Beschikbaar online: https://doi.org/10.1111/j.1743-6109.2009.01699.x

Shinotoh H, Inoue O, Suzuki K, Yamasaki T, Iyo M, Hashimoto K, Tominaga T, Itoh T, Tateno Y & Ikehira H, 1987. Kinetics of [11C]N,N-dimethylphenylethylamine in mice and humans: potential for measurement of brain MAO-B activity. J Nucl Med, 28 (6), 1006-1011. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/3495646

Sloviter RS, Connor JD & Drust EG, 1980. Serotonergic properties of beta-phenethylamine in rats. Neuropharmacology, 19 (11), 1071-1074. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/6449675

Smith TA, 1977. Phenethylamine and related compounds in plants. Phytochemistry, 16 (1), 9-18.

Sommer T, Dlugash G, Hübner H, Gmeiner P & Pischetsrieder M, 2019. Monitoring of the dopamine D2 receptor agonists hordenine and N-methyltyramine during the brewing process and in commercial beer samples. Food Chemistry, 276, 745-753. Beschikbaar online: https://doi.org/10.1016/j.foodchem.2018.10.067

Sommer T, Göen T, Budnik N & Pischetsrieder M, 2020. Absorption, Biokinetics, and Metabolism of the Dopamine D2 Receptor Agonist Hordenine (N, N-Dimethyltyramine) after Beer Consumption in Humans. Journal of Agricultural and Food Chemistry, 68 (7), 1998-2006. Beschikbaar online: https://doi.org/10.1021/acs.jafc.9b06029

Sommer T, Hubner H, El Kerdawy A, Gmeiner P, Pischetsrieder M & Clark T, 2017. Identification of the Beer Component Hordenine as Food-Derived Dopamine D2 Receptor Agonist by Virtual Screening a 3D Compound Database. Sci Rep, 7, 44201. Beschikbaar online: https://doi.org/10.1038/srep44201

Song L, Zhao J, Zhang X, Li H & Zhou Y, 2013. Icariin induces osteoblast proliferation, differentiation and mineralization through estrogen receptor-mediated ERK and JNK signal activation. Eur J Pharmacol, 714 (1-3), 15-22. Beschikbaar online: https://doi.org/10.1016/j.ejphar.2013.05.039

Song YH, Cai H, Gu N, Qian CF, Cao SP & Zhao ZM, 2011. Icariin attenuates cardiac remodelling through down-regulating myocardial apoptosis and matrix metalloproteinase activity in rats with congestive heart failure. J Pharm Pharmacol, 63 (4), 541-549. Beschikbaar online: https://doi.org/10.1111/j.2042-7158.2010.01241.x

Song YH, Cai H, Zhao ZM, Chang WJ, Gu N, Cao SP & Wu ML, 2016a. Icariin attenuated oxidative stress induced-cardiac apoptosis by mitochondria protection and ERK activation. Biomed Pharmacother, 83, 1089-1094. Beschikbaar online: https://doi.org/10.1016/j.biopha.2016.08.016

Song YX, Miao JY, Qiang M, He RQ, Wang XM & Li WW, 2016b. Icariin protects SH-SY5Y cells from formaldehyde-induced injury through suppression of Tau phosphorylation. Chin J Integr Med, 22 (6), 430-437. Beschikbaar online: https://doi.org/10.1007/s11655-015-2116-3

Sotnikova TD, Budygin EA, Jones SR, Dykstra LA, Caron MG & Gainetdinov RR, 2004. Dopamine transporter-dependent and -independent actions of trace amine beta-phenylethylamine. J Neurochem, 91 (2), 362-373. Beschikbaar online: https://doi.org/10.1111/j.1471-4159.2004.02721.x

SSPF, 2004. Premarket notification for a new dietary ingredient: betaphrine. Syntech (SSPF) International, Inc. Beschikbaar online: https://www.regulations.gov/document?D=FDA-2005-S-0518-0010

Staack RF, Fehn J & Maurer HH, 2003. New designer drug p-methoxymethamphetamine: studies on its metabolism and toxicological detection in urine using gas chromatography-mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci, 789 (1), 27-41. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/12726841

Stoff DM & Gale K, 1981. beta-Phenylethylamine reversal of chlorpromazine-induced activation of striatal tyrosine hydroxylase and catalepsy. Brain Res, 211 (2), 492-496. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/6113030

Su YS, Fan ZX, Xiao SE, Lin BJ, Miao Y, Hu ZQ & Liu H, 2017. Icariin promotes mouse hair follicle growth by increasing insulin-like growth factor 1 expression in dermal papillary cells. Clin Exp Dermatol, 42 (3), 287-294. Beschikbaar online: https://doi.org/10.1111/ced.13043

Sun E, Xu F, Qian Q, Cui L, Tan X & Jia X, 2016. Metabolite Profiles of Icariin in Rat Feces, Bile and Urine by Ultraperformance Liquid-Chromatography/Quadrupole-Time-of-Flight Mass Spectrometry. J Chromatogr Sci, 54 (2), 158-164. Beschikbaar online: https://doi.org/10.1093/chromsci/bmv121

Sun P, Liu Y, Deng X, Yu C, Dai N, Yuan X, Chen L, Yu S, Si W, Wang X, Wu D, Liu S & Pang H, 2013. An inhibitor of cathepsin K, icariin suppresses cartilage and bone degradation in mice of collagen-induced arthritis. Phytomedicine, 20 (11), 975-979. Beschikbaar online: https://doi.org/10.1016/j.phymed.2013.04.019

Sun X, Sun X, Jin X, Zhang X, Liu C, Lei L, Jin L & Liu H, 2011. Icariin induces mouse embryonic stem cell differentiation into beating functional cardiomyocytes. Mol Cell Biochem, 349 (1-2), 117-123. Beschikbaar online: https://doi.org/10.1007/s11010-010-0666-4

Sun ZB, Wang JW, Xiao H, Zhang QS, Kan WS, Mo FB, Hu S & Ye SN, 2015. Icariin may benefit the mesenchymal stem cells of patients with steroid-associated osteonecrosis by ABCB1-promoter demethylation: a preliminary study. Osteoporos Int, 26 (1), 187-197. Beschikbaar online: https://doi.org/10.1007/s00198-014-2809-z

Suzuki O, Katsumata Y & Oya M, 1981. Oxidation of beta-phenylethylamine by both types of monoamine oxidase: examination of enzymes in brain and liver mitochondria of eight species. J Neurochem, 36 (3), 1298-1301. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/7205271

Suzuki O, Katsumata Y, Oya M & Matsumoto T, 1979. Oxidation of phenylethanolamine and octopamine by type A and type B monoamine oxidase. Effect of substrate concentration. Biochem Pharmacol, 28 (15), 2327-2332. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/387041

Suzuki O, Oya M & Katsumata Y, 1980. Characterization of N-methylphenylethylamine and N-methylphenylethanolamine as substrates for type A and type B monoamine oxidase. Biochem Pharmacol, 29 (19), 2663-2667. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/6775642

Symeva YI, 1941. The pharmacology of the new alkaloid halostachine. Farmakologiya i Toksikologiya, 4, 45-51.

Szabo A, Billett E & Turner J, 2001. Phenylethylamine, a possible link to the antidepressant effects of exercise? Br J Sports Med, 35 (5), 342-343. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/11579070

Tiago Guimaraes J & Soares-da-Silva P, 2000. Unusual pattern of beta-phenylethylamine deamination in the rat heart. Neurobiology (Bp), 8 (1), 109-118. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/11008882

Tsukiyama M, Ueki T, Yasuda Y, Kikuchi H, Akaishi T, Okumura H & Abe K, 2009. Beta2-adrenoceptor-mediated tracheal relaxation induced by higenamine from Nandina domestica Thunberg. Planta Med, 75 (13), 1393-1399. Beschikbaar online: https://doi.org/10.1055/s-0029-1185743

Ueki T, Akaishi T, Okumura H, Morioka T & Abe K, 2011. Biphasic tracheal relaxation induced by higenamine and nantenine from Nandina domestica Thunberg. J Pharmacol Sci, 115 (2), 254-257. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/21282929

Ukponmwan OE, van der Poel-Heisterkamp AL, Haffmans J & Dzoljic M, 1983. MAO-B inhibitor deprenyl and beta-phenylethylamine potentiate [D-ALA2]-Met-enkephalinamide-induced seizures. Naunyn Schmiedebergs Arch Pharmacol, 322 (1), 38-41. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/6405286

Urano T & Tohda C, 2010. Icariin improves memory impairment in Alzheimer's disease model mice (5xFAD) and attenuates amyloid beta-induced neurite atrophy. Phytother Res, 24 (11), 1658-1663. Beschikbaar online: https://doi.org/10.1002/ptr.3183

van Riel AJHP, Verputten PM, Roelen CCJ, de Vries I & de Lange DW, 2020. Overzicht NVIC-meldingen over voedingssupplementen in 2019. Nationaal Vergiftigingen Informatie Centrum, Utrecht.

Vanderwolf CH, Robinson TE & Pappas BA, 1980. Monoamine replacement after reserpine: catecholaminergic agonists restore motor activity but phenylethylamine restores atropine-resistant neocortical low voltage fast activity. Brain Res, 202 (1), 65-77. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/6968619

Venhuis B, Keizers P, van Riel A & de Kaste D, 2014. A cocktail of synthetic stimulants found in a dietary supplement associated with serious adverse events. Drug Test Anal, 6 (6), 578-581. Beschikbaar online: https://doi.org/10.1002/dta.1664

Verho M, Malerczyk V, Kauert G & Lorenz H, 1988. Dose linearity and relative bioavailability testing of oxilofrine, a sympathicomimetic drug, in healthy volunteers. Int J Clin Pharmacol Res, 8 (3), 211-215. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/3403107

Verputten PM, Roelen CCJ, van Riel AJHP & de Vries I, 2018. Overzicht NVIC-meldingen over voedingssupplementen in 2017. Nationaal Vergiftigingen Informatie Centrum, Utrecht.

Vevelstad M, Oiestad EL, Nerem E, Arnestad M & Bogen IL, 2017. Studies on Para-Methoxymethamphetamine (PMMA) Metabolite Pattern and Influence of CYP2D6 Genetics in Human Liver Microsomes and Authentic Samples from Fatal PMMA Intoxications. Drug Metab Dispos, 45 (12), 1326-1335. Beschikbaar online: https://doi.org/10.1124/dmd.117.077263

WADA, 2019. PROHIBITED LIST JANUARY 2020 World Anti Doping Agency. Beschikbaar online: https://www.wada-ama.org/sites/default/files/wada_2020_english_prohibited_list_0.pdf

Wainscott DB, Little SP, Yin T, Tu Y, Rocco VP, He JX & Nelson DL, 2007. Pharmacologic characterization of the cloned human trace amine-associated receptor1 (TAAR1) and evidence for species differences with

the rat TAAR1. J Pharmacol Exp Ther, 320 (1), 475-485. Beschikbaar online: https://doi.org/10.1124/jpet.106.112532

Wainwright T, Slack PT & Long DE, 1982. N-nitrosodimethylamine precursors in malt. IARC Sci Publ, (41), 71-80. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/6183201

Wang F, Liu Z, Lin S, Lu H & Xu J, 2012. Icariin enhances the healing of rapid palatal expansion induced root resorption in rats. Phytomedicine, 19 (11), 1035-1041. Beschikbaar online: https://doi.org/10.1016/j.phymed.2012.06.001

Wang J, Tao Y, Ping Z, Zhang W, Hu X, Wang Y, Wang L, Shi J, Wu X, Yang H, Xu Y & Geng D, 2016a. Icariin attenuates titanium-particle inhibition of bone formation by activating the Wnt/beta-catenin signaling pathway in vivo and in vitro. Sci Rep, 6, 23827. Beschikbaar online: https://doi.org/10.1038/srep23827

Wang L, Zhang L, Chen ZB, Wu JY, Zhang X & Xu Y, 2009. Icariin enhances neuronal survival after oxygen and glucose deprivation by increasing SIRT1. Eur J Pharmacol, 609 (1-3), 40-44. Beschikbaar online: https://doi.org/10.1016/j.ejphar.2009.03.033

Wang P, Zhang F, He Q, Wang J, Shiu HT, Shu Y, Tsang WP, Liang S, Zhao K & Wan C, 2016b. Flavonoid Compound Icariin Activates Hypoxia Inducible Factor-1alpha in Chondrocytes and Promotes Articular Cartilage Repair. PLoS One, 11 (2), e0148372. Beschikbaar online: https://doi.org/10.1371/journal.pone.0148372

Wang Q, Hao J, Pu J, Zhao L, Lu Z, Hu J, Yu Q, Wang Y, Xie Y & Li G, 2011. Icariin induces apoptosis in mouse MLTC-10 Leydig tumor cells through activation of the mitochondrial pathway and down-regulation of the expression of piwil4. Int J Oncol, 39 (4), 973-980. Beschikbaar online: https://doi.org/10.3892/ijo.2011.1086

Wang QS, Wang GF, Zhou J, Gao LN & Cui YL, 2016c. Colon targeted oral drug delivery system based on alginate-chitosan microspheres loaded with icariin in the treatment of ulcerative colitis. Int J Pharm, 515 (1-2), 176-185. Beschikbaar online: https://doi.org/10.1016/j.ijpharm.2016.10.002

Wang X, Li J, Qian L, Zang XF, Zhang SY, Wang XY, Jin JL, Zhu XL, Zhang XB, Wang ZY & Xu Y, 2013. Icariin promotes histone acetylation and attenuates post-stroke cognitive impairment in the central cholinergic circuits of mice. Neuroscience, 236, 281-288. Beschikbaar online: https://doi.org/10.1016/j.neuroscience.2012.12.074

Wang Y, Dong H, Zhu M, Ou Y, Zhang J, Luo H, Luo R, Wu J, Mao M, Liu X, Zhang J & Wei L, 2010. Icariin exterts negative effects on human gastric cancer cell invasion and migration by vasodilator-stimulated phosphoprotein via Rac1 pathway. Eur J Pharmacol, 635 (1-3), 40-48. Beschikbaar online: https://doi.org/10.1016/j.ejphar.2010.03.017

Wang Y, Wang YS, Song SL, Liang H & Ji AG, 2016d. Icariin inhibits atherosclerosis progress in Apoe null mice by downregulating CX3CR1 in macrophage. Biochem Biophys Res Commun, 470 (4), 845-850. Beschikbaar online: https://doi.org/10.1016/j.bbrc.2016.01.118

Wang YK & Huang ZQ, 2005. Protective effects of icariin on human umbilical vein endothelial cell injury induced by H2O2 in vitro. Pharmacol Res, 52 (2), 174-182. Beschikbaar online: https://doi.org/10.1016/j.phrs.2005.02.023

Wang Z, Yang L, Xia Y, Guo C & Kong L, 2015a. Icariin enhances cytotoxicity of doxorubicin in human multidrug-resistant osteosarcoma cells by inhibition of ABCB1 and down-regulation of the PI3K/Akt pathway. Biol Pharm Bull,

38 (2), 277-284. Beschikbaar online: https://doi.org/10.1248/bpb.b14-00663

Wang Z, Zhang H, Dai L, Song T, Li P, Liu Y & Wang L, 2015b. Arsenic Trioxide and Icariin Show Synergistic Anti-leukemic Activity. Cell Biochem Biophys, 73 (1), 213-219. Beschikbaar online: https://doi.org/10.1007/s12013-015-0660-2

Wang ZM, Song N & Ren YL, 2015c. Anti-proliferative and cytoskeleton-disruptive effects of icariin on HepG2 cells. Mol Med Rep, 12 (5), 6815-6820. Beschikbaar online: https://doi.org/10.3892/mmr.2015.4282

Wei H, Wu H, Yu W, Yan X & Zhang X, 2015a. Shenfu decoction as adjuvant therapy for improving quality of life and hepatic dysfunction in patients with symptomatic chronic heart failure. J Ethnopharmacol, 169, 347-355. Beschikbaar online: https://doi.org/10.1016/j.jep.2015.04.016

Wei H, Zili L, Yuanlu C, Biao Y, Cheng L, Xiaoxia W, Yang L & Xing W, 2011. Effect of icariin on bone formation during distraction osteogenesis in the rabbit mandible. Int J Oral Maxillofac Surg, 40 (4), 413-418. Beschikbaar online: https://doi.org/10.1016/j.ijom.2010.10.015

Wei K, Xu Y, Zhao Z, Wu X, Du Y, Sun J, Yi T, Dong J & Liu B, 2016a. Icariin alters the expression of glucocorticoid receptor, FKBP5 and SGK1 in rat brains following exposure to chronic mild stress. Int J Mol Med, 38 (1), 337-344. Beschikbaar online: https://doi.org/10.3892/ijmm.2016.2591

Wei Q, Zhang J, Hong G, Chen Z, Deng W, He W & Chen MH, 2016b. Icariin promotes osteogenic differentiation of rat bone marrow stromal cells by activating the ERalpha-Wnt/beta-catenin signaling pathway. Biomed Pharmacother, 84, 931-939. Beschikbaar online: https://doi.org/10.1016/j.biopha.2016.09.107

Wei Y, Liu B, Sun J, Lv Y, Luo Q, Liu F & Dong J, 2015b. Regulation of Th17/Treg function contributes to the attenuation of chronic airway inflammation by icariin in ovalbumin-induced murine asthma model. Immunobiology, 220 (6), 789-797. Beschikbaar online: https://doi.org/10.1016/j.imbio.2014.12.015

Wenkeova J, Kuhn E & Wenke M, 1975. Adrenergic lipolysis in human adipose tissue in vitro. Eur J Pharmacol, 30 (1), 49-55. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/235437

Wheaton TA & Stewart I, 1970. The distribution of tyramine, N-methyltyramine, hordenine, octopamine, and synephrine in higher plants. Lloydia, 33 (2), 244-254. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/5495514

Whitehead PN, Schilling BK, Farney TM & Bloomer RJ, 2012. Impact of a dietary supplement containing 1,3-dimethylamylamine on blood pressure and bloodborne markers of health: a 10-week intervention study. Nutrition and metabolic insights, 5, 33-39. Beschikbaar online: https://doi.org/10.4137/nmi.S8885

WHO, 2008. Evaluation of certain food additives. Sixty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives. World Health Organization. Beschikbaar online: https://apps.who.int/iris/bitstream/handle/10665/44062/WHO_TRS_952_eng.pdf?sequence=1&isAllowed=y

Wo Y, Zhu D, Yu Y & Lou Y, 2008. Involvement of NF-kappaB and AP-1 activation in icariin promoted cardiac differentiation of mouse embryonic stem cells. Eur J Pharmacol, 586 (1-3), 59-66. Beschikbaar online: https://doi.org/10.1016/j.ejphar.2008.02.080

Wong KK, Lo CF & Chen CM, 1997. Endothelium-dependent higenamine-induced aortic relaxation in isolated rat aorta. Planta Med, 63 (2), 130-132. Beschikbaar online: https://doi.org/10.1055/s-2006-957628

Wu B, Chen Y, Huang J, Ning Y, Bian Q, Shan Y, Cai W, Zhang X & Shen Z, 2012a. Icariin improves cognitive deficits and activates quiescent neural stem cells in aging rats. J Ethnopharmacol, 142 (3), 746-753. Beschikbaar online: https://doi.org/10.1016/j.jep.2012.05.056

Wu H, Kim M & Han J, 2016a. Icariin Metabolism by Human Intestinal Microflora. Molecules, 21 (9). Beschikbaar online: https://doi.org/10.3390/molecules21091158

Wu J, Du J, Xu C, Le J, Xu Y, Liu B & Dong J, 2011. Icariin attenuates social defeat-induced down-regulation of glucocorticoid receptor in mice. Pharmacol Biochem Behav, 98 (2), 273-278. Beschikbaar online: https://doi.org/10.1016/j.pbb.2011.01.008

Wu J, Zhou J, Chen X, Fortenbery N, Eksioglu EA, Wei S & Dong J, 2012b. Attenuation of LPS-induced inflammation by ICT, a derivate of icariin, via inhibition of the CD14/TLR4 signaling pathway in human monocytes. Int Immunopharmacol, 12 (1), 74-79. Beschikbaar online: https://doi.org/10.1016/j.intimp.2011.10.015

Wu MP, Zhang YS, Zhou QM, Xiong J, Dong YR & Yan C, 2016b. Higenamine protects ischemia/reperfusion induced cardiac injury and myocyte apoptosis through activation of beta2-AR/PI3K/AKT signaling pathway. Pharmacol Res, 104, 115-123. Beschikbaar online: https://doi.org/10.1016/j.phrs.2015.12.032

Wu PH & Boulton AA, 1975. Metabolism distribution, and disappearance of injected beta-phenylethylamine in the rat. Can J Biochem, 53 (1), 42-50. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/1120290

Wu Y, Xia L, Zhou Y, Xu Y & Jiang X, 2015. Icariin induces osteogenic differentiation of bone mesenchymal stem cells in a MAPK-dependent manner. Cell Prolif, 48 (3), 375-384. Beschikbaar online: https://doi.org/10.1111/cpr.12185

Wu YT, Lin CW, Lin LC, Chiu AW, Chen KK & Tsai TH, 2010. Analysis of biliary excretion of icariin in rats. J Agric Food Chem, 58 (18), 9905-9911. Beschikbaar online: https://doi.org/10.1021/jf101987j

Xiao-Hong D, Chang-Qin X, Jian-Hua H, Wen-Jiang Z & Bing S, 2013. Icariin delays homocysteine-induced endothelial cellular senescence involving activation of the PI3K/AKT-eNOS signaling pathway. Pharm Biol, 51 (4), 433-440. Beschikbaar online: https://doi.org/10.3109/13880209.2012.738332

Xiao H, Wignall N & Brown ES, 2016. An open-label pilot study of icariin for co-morbid bipolar and alcohol use disorder. Am J Drug Alcohol Abuse, 42 (2), 162-167. Beschikbaar online: https://doi.org/10.3109/00952990.2015.1114118

Xiao HB, Liu ZK, Lu XY, Deng CN & Luo ZF, 2015. Icariin regulates PRMT/ADMA/DDAH pathway to improve endothelial function. Pharmacol Rep, 67 (6), 1147-1154. Beschikbaar online: https://doi.org/10.1016/j.pharep.2015.04.017

Xie Z & Miller GM, 2008. Beta-phenylethylamine alters monoamine transporter function via trace amine-associated receptor 1: implication for modulatory roles of trace amines in brain. J Pharmacol Exp Ther, 325 (2), 617-628. Beschikbaar online: https://doi.org/10.1124/jpet.107.134247

Xin H, Zhou F, Liu T, Li GY, Liu J, Gao ZZ, Bai GY, Lu H & Xin ZC, 2012. Icariin ameliorates streptozotocin-induced diabetic retinopathy in vitro and in vivo. Int J Mol Sci, 13 (1), 866-878. Beschikbaar online: https://doi.org/10.3390/ijms13010866

Xiong D, Deng Y, Huang B, Yin C, Liu B, Shi J & Gong Q, 2016. Icariin attenuates cerebral ischemia-reperfusion injury through inhibition of inflammatory response mediated by NF-kappaB, PPARalpha and PPARgamma in rats. Int Immunopharmacol, 30, 157-162. Beschikbaar online: https://doi.org/10.1016/j.intimp.2015.11.035

Xiong W, Chen Y, Wang Y & Liu J, 2014. Roles of the antioxidant properties of icariin and its phosphorylated derivative in the protection against duck virus hepatitis. BMC Vet Res, 10, 226. Beschikbaar online: https://doi.org/10.1186/s12917-014-0226-3

Xu AL, Jiang MC, Chen XH & Chen WF, 2016. Icariin protects against MPP(+)-induced neurotoxicity in MES23.5 cells. Sheng Li Xue Bao, 68 (5), 585-591. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/27778023

Xu CQ, Liu BJ, Wu JF, Xu YC, Duan XH, Cao YX & Dong JC, 2010. Icariin attenuates LPS-induced acute inflammatory responses: involvement of PI3K/Akt and NF-kappaB signaling pathway. Eur J Pharmacol, 642 (1-3), 146-153. Beschikbaar online: https://doi.org/10.1016/j.ejphar.2010.05.012

Xu HB & Huang ZQ, 2007a. Icariin enhances endothelial nitric-oxide synthase expression on human endothelial cells in vitro. Vascul Pharmacol, 47 (1), 18-24. Beschikbaar online: https://doi.org/10.1016/j.vph.2007.03.002

Xu HB & Huang ZQ, 2007b. Vasorelaxant effects of icariin on isolated canine coronary artery. J Cardiovasc Pharmacol, 49 (4), 207-213. Beschikbaar online: https://doi.org/10.1097/FJC.0b013e3180325abe

Xu J & Yan R, 2017. Determination of the Metabolite of Ephedrine, 4-Hydroxyephedrine, by LC-MS-MS in Rat Urine and Its Application in Excretion Profiles After Oral Administration of Ephedra sinica Stapf and Processing Ephedra sinica Stapf. J Chromatogr Sci, 55 (2), 162-165. Beschikbaar online: https://doi.org/10.1093/chromsci/bmw165

Xu RX, Wu Q, Luo Y, Gong QH, Yu LM, Huang XN, Sun AS & Shi JS, 2009. Protective effects of icariin on cognitive deficits induced by chronic cerebral hypoperfusion in rats. Clin Exp Pharmacol Physiol, 36 (8), 810-815. Beschikbaar online: https://doi.org/10.1111/j.1440-1681.2009.05149.x

Xu S, Yu J, Zhan J, Yang L, Guo L & Xu Y, 2017a. Pharmacokinetics, Tissue Distribution, and Metabolism Study of Icariin in Rat. Biomed Res Int, 2017, 4684962. Beschikbaar online: https://doi.org/10.1155/2017/4684962

Xu Y, Xin H, Wu Y, Guan R, Lei H, Fu X, Xin Z & Yang Y, 2017b. Effect of icariin in combination with daily sildenafil on penile atrophy and erectile dysfunction in a rat model of bilateral cavernous nerves injury. Andrology, 5 (3), 598-605. Beschikbaar online: https://doi.org/10.1111/andr.12341

Yamada S, Harano M & Tanaka M, 1998. Antagonistic effects of beta-phenylethylamine on quinpirole- and (-)-sulpiride-induced changes in evoked dopamine release from rat striatal slices. Eur J Pharmacol, 343 (2-3), 145-150. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/9570461

Yang H, Yan L, Qian P, Duan H, Wu J, Li B & Wang S, 2015a. Icariin inhibits foam cell formation by down-regulating the expression of CD36 and up-

regulating the expression of SR-BI. J Cell Biochem, 116 (4), 580-588. Beschikbaar online: https://doi.org/10.1002/jcb.25009

Yang HY & Neff NH, 1973. Beta-phenylethylamine: a specific substrate for type B monoamine oxidase of brain. J Pharmacol Exp Ther, 187 (2), 365-371. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/4748552

Yang L, Lu D, Guo J, Meng X, Zhang G & Wang F, 2013. Icariin from Epimedium brevicornum Maxim promotes the biosynthesis of estrogen by aromatase (CYP19). J Ethnopharmacol, 145 (3), 715-721. Beschikbaar online: https://doi.org/10.1016/j.jep.2012.11.031

Yang L, Wang Y, Guo H & Guo M, 2015b. Synergistic Anti-Cancer Effects of Icariin and Temozolomide in Glioblastoma. Cell Biochem Biophys, 71 (3), 1379-1385. Beschikbaar online: https://doi.org/10.1007/s12013-014-0360-3

Yang L, Yu Z, Qu H & Li M, 2014. Comparative effects of hispidulin, genistein, and icariin with estrogen on bone tissue in ovariectomized rats. Cell Biochem Biophys, 70 (1), 485-490. Beschikbaar online: https://doi.org/10.1007/s12013-014-9945-0

Yang P, Guan YQ, Li YL, Zhang L, Zhang L & Li L, 2016. Icariin promotes cell proliferation and regulates gene expression in human neural stem cells in vitro. Mol Med Rep, 14 (2), 1316-1322. Beschikbaar online: https://doi.org/10.3892/mmr.2016.5377

Yao X, Parnot C, Deupi X, Ratnala VR, Swaminath G, Farrens D & Kobilka B, 2006. Coupling ligand structure to specific conformational switches in the beta2-adrenoceptor. Nat Chem Biol, 2 (8), 417-422. Beschikbaar online: https://doi.org/10.1038/nchembio801

Ye C, Zhang W, Wang S, Jiang S, Yu Y, Chen E, Xue D, Chen J & He R, 2016. Icariin Promotes Tendon-Bone Healing during Repair of Rotator Cuff Tears: A Biomechanical and Histological Study. Int J Mol Sci, 17 (11). Beschikbaar online: https://doi.org/10.3390/ijms17111780

Ye Y, Chou GX, Wang H, Chu JH & Yu ZL, 2010. Flavonoids, apigenin and icariin exert potent melanogenic activities in murine B16 melanoma cells. Phytomedicine, 18 (1), 32-35. Beschikbaar online: https://doi.org/10.1016/j.phymed.2010.06.004

Ye Y, Jing X, Li N, Wu Y, Li B & Xu T, 2017. Icariin promotes proliferation and osteogenic differentiation of rat adipose-derived stem cells by activating the RhoA-TAZ signaling pathway. Biomed Pharmacother, 88, 384-394. Beschikbaar online: https://doi.org/10.1016/j.biopha.2017.01.075

Yen ST, Li MH, Hsu CT, Lee TL & Cheng JT, 1998. Stimulatory effect of octopamine on beta 3-adrenoceptors to lower the uptake of [14C]-deoxy-D-glucose into rat adipocytes in vitro. J Auton Pharmacol, 18 (1), 13-19. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/9728321

Yokoo Y, Kohda H, Kusumoto A, Naoki H, Matsumoto N, Amachi T, Suwa Y, Fukazawa H, Ishida H, Tsuji K & Nukaya H, 1999. Isolation from beer and structural determination of a potent stimulant of gastrin release. Alcohol Alcohol, 34 (2), 161-168. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/10344776

Youdim MB & Finberg JP, 1991. New directions in monoamine oxidase A and B selective inhibitors and substrates. Biochem Pharmacol, 41 (2), 155-162. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/1989626

Yu F, Kong L & Wang S, 2013. Influence of racemic higenamine on the sinus node. Exp Ther Med, 5 (2), 591-595. Beschikbaar online: https://doi.org/10.3892/etm.2012.813

Yu GR, Wang BY, Zheng DS, Huang MX, Gu BK, Chen YL, Shang M, Jin ZJ & Cheng TO, 1985. Effect of higenamine on action potential of ventricular myocardial cells. J Electrocardiol, 18 (1), 97-103. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/3973525

Yun-Choi HS, Pyo MK, Chang KC & Lee DH, 2002. The effects of higenamine on LPS-induced experimental disseminated intravascular coagulation (DIC) in rats. Planta Med, 68 (4), 326-329. Beschikbaar online: https://doi.org/10.1055/s-2002-26741

Yun-Choi HS, Pyo MK, Park KM, Chang KC & Lee DH, 2001. Anti-thrombotic effects of higenamine. Planta Med, 67 (7), 619-622. Beschikbaar online: https://doi.org/10.1055/s-2001-17361

Zeng KW, Fu H, Liu GX & Wang XM, 2010a. Icariin attenuates lipopolysaccharide-induced microglial activation and resultant death of neurons by inhibiting TAK1/IKK/NF-kappaB and JNK/p38 MAPK pathways. Int Immunopharmacol, 10 (6), 668-678. Beschikbaar online: https://doi.org/10.1016/j.intimp.2010.03.010

Zeng KW, Ko H, Yang HO & Wang XM, 2010b. Icariin attenuates beta-amyloid-induced neurotoxicity by inhibition of tau protein hyperphosphorylation in PC12 cells. Neuropharmacology, 59 (6), 542-550. Beschikbaar online: https://doi.org/10.1016/j.neuropharm.2010.07.020

Zeng L, Wang W, Rong XF, Zhong Y, Jia P, Zhou GQ & Li RH, 2014. Chondroprotective effects and multi-target mechanisms of Icariin in IL-1 beta-induced human SW 1353 chondrosarcoma cells and a rat osteoarthritis model. Int Immunopharmacol, 18 (1), 175-181. Beschikbaar online: https://doi.org/10.1016/j.intimp.2013.11.021

Zhai M, He L, Ju X, Shao L, Li G, Zhang Y, Liu Y & Zhao H, 2015. Icariin Acts as a Potential Agent for Preventing Cardiac Ischemia/Reperfusion Injury. Cell Biochem Biophys, 72 (2), 589-597. Beschikbaar online: https://doi.org/10.1007/s12013-014-0506-3

Zhai YK, Guo XY, Ge BF, Zhen P, Ma XN, Zhou J, Ma HP, Xian CJ & Chen KM, 2014. Icariin stimulates the osteogenic differentiation of rat bone marrow stromal cells via activating the PI3K-AKT-eNOS-NO-cGMP-PKG. Bone, 66, 189-198. Beschikbaar online: https://doi.org/10.1016/j.bone.2014.06.016

Zhang DC, Liu JL, Ding YB, Xia JG & Chen GY, 2013a. Icariin potentiates the antitumor activity of gemcitabine in gallbladder cancer by suppressing NF-kappaB. Acta Pharmacol Sin, 34 (2), 301-308. Beschikbaar online: https://doi.org/10.1038/aps.2012.162

Zhang F, Li ZL, Xu XM, Hu Y, Yao JH, Xu W, Jing HR, Wang S, Ning SL & Tian XF, 2015a. Protective effects of icariin-mediated SIRT1/FOXO3 signaling pathway on intestinal ischemia/reperfusion-induced acute lung injury. Mol Med Rep, 11 (1), 269-276. Beschikbaar online: https://doi.org/10.3892/mmr.2014.2679

Zhang G, Qin L & Shi Y, 2007. Epimedium-derived phytoestrogen flavonoids exert beneficial effect on preventing bone loss in late postmenopausal women: a 24-month randomized, double-blind and placebo-controlled trial. J Bone Miner Res, 22 (7), 1072-1079. Beschikbaar online: https://doi.org/10.1359/jbmr.070405

Zhang H, Liu B, Wu J, Xu C, Tao J, Duan X, Cao Y & Dong J, 2012a. Icariin inhibits corticosterone-induced apoptosis in hypothalamic neurons via the PI3-K/Akt signaling pathway. Mol Med Rep, 6 (5), 967-972. Beschikbaar online: https://doi.org/10.3892/mmr.2012.1041

Zhang J, Li Y, Sun J, Liu C & Zhang D, 2011. Synergistic or antagonistic effect of MTE plus TF or icariin from Epimedium koreanum on the proliferation and differentiation of primary osteoblasts in vitro. Biol Trace Elem Res, 143 (3), 1746-1757. Beschikbaar online: https://doi.org/10.1007/s12011-011-8987-z

Zhang L, Huang S, Chen Y, Wang Z, Li E & Xu Y, 2010. Icariin inhibits hydrogen peroxide-mediated cytotoxicity by up-regulating sirtuin type 1-dependent catalase and peroxiredoxin. Basic Clin Pharmacol Toxicol, 107 (5), 899-905. Beschikbaar online: https://doi.org/10.1111/j.1742-7843.2010.00595.x

Zhang L, Shen C, Chu J, Zhang R, Li Y & Li L, 2014a. Icariin decreases the expression of APP and BACE-1 and reduces the beta-amyloid burden in an APP transgenic mouse model of Alzheimer's disease. Int J Biol Sci, 10 (2), 181-191. Beschikbaar online: https://doi.org/10.7150/ijbs.6232

Zhang L, Zhang X, Li KF, Li DX, Xiao YM, Fan YJ & Zhang XD, 2012b. Icariin promotes extracellular matrix synthesis and gene expression of chondrocytes in vitro. Phytother Res, 26 (9), 1385-1392. Beschikbaar online: https://doi.org/10.1002/ptr.3733

Zhang M, Liu J, Guo W, Liu X, Liu S & Yin H, 2016. Icariin regulates systemic iron metabolism by increasing hepatic hepcidin expression through Stat3 and Smad1/5/8 signaling. Int J Mol Med, 37 (5), 1379-1388. Beschikbaar online: https://doi.org/10.3892/ijmm.2016.2545

Zhang N, Lian Z, Peng X, Li Z & Zhu H, 2017. Applications of Higenamine in pharmacology and medicine. J Ethnopharmacol, 196, 242-252. Beschikbaar online: https://doi.org/10.1016/j.jep.2016.12.033

Zhang Q, Li H, Wang S, Liu M, Feng Y & Wang X, 2013b. Icariin protects rat cardiac H9c2 cells from apoptosis by inhibiting endoplasmic reticulum stress. Int J Mol Sci, 14 (9), 17845-17860. Beschikbaar online: https://doi.org/10.3390/ijms140917845

Zhang SQ, Cai WJ, Huang JH, Wu B, Xia SJ, Chen XL, Zhang XM & Shen ZY, 2015b. Icariin, a natural flavonol glycoside, extends healthspan in mice. Exp Gerontol, 69, 226-235. Beschikbaar online: https://doi.org/10.1016/j.exger.2015.06.020

Zhang WP, Bai XJ, Zheng XP, Xie XL & Yuan ZY, 2013c. Icariin attenuates the enhanced prothrombotic state in atherosclerotic rabbits independently of its lipid-lowering effects. Planta Med, 79 (9), 731-736. Beschikbaar online: https://doi.org/10.1055/s-0032-1328551

Zhang X, Liu T, Huang Y, Wismeijer D & Liu Y, 2014b. Icariin: does it have an osteoinductive potential for bone tissue engineering? Phytother Res, 28 (4), 498-509. Beschikbaar online: https://doi.org/10.1002/ptr.5027

Zhang Y, Wei Y, Zhu Z, Gong W, Liu X, Hou Q, Sun Y, Chai J, Zou L & Zhou T, 2014c. Icariin enhances radiosensitivity of colorectal cancer cells by suppressing NF-kappaB activity. Cell Biochem Biophys, 69 (2), 303-310. Beschikbaar online: https://doi.org/10.1007/s12013-013-9799-x

Zhang Y, Woods RM, Breitbach ZS & Armstrong DW, 2012c. 1,3-Dimethylamylamine (DMAA) in supplements and geranium products: natural or synthetic? Drug Test Anal, 4 (12), 986-990. Beschikbaar online: https://doi.org/10.1002/dta.1368

Zhang Z, Li M, Wang Y, Wu J & Li J, 2014d. Higenamine promotes M2 macrophage activation and reduces Hmgb1 production through HO-1 induction in a murine model of spinal cord injury. Int Immunopharmacol, 23 (2), 681-687. Beschikbaar online: https://doi.org/10.1016/j.intimp.2014.10.022

Zhang ZY, Li C, Zug C & Schluesener HJ, 2014e. Icariin ameliorates neuropathological changes, TGF-beta1 accumulation and behavioral deficits in a mouse model of cerebral amyloidosis. PLoS One, 9 (8), e104616. Beschikbaar online: https://doi.org/10.1371/journal.pone.0104616

Zhao J, Ohba S, Shinkai M, Chung UI & Nagamune T, 2008. Icariin induces osteogenic differentiation in vitro in a BMP- and Runx2-dependent manner. Biochem Biophys Res Commun, 369 (2), 444-448. Beschikbaar online: https://doi.org/10.1016/j.bbrc.2008.02.054

Zheng Ying-Li ZZ, Bao-ling., Chen., Ke., Wang., Li-ming., Xue., Li., Fang., De-liang. & Gu., 2004. Determination of higenamine in plasma by HPLC-ECD and study on its pharmacokinetics. Chin. Pharm. J., 39 (11), 848-850.

Zhou H, Yuan Y, Liu Y, Ni J, Deng W, Bian ZY, Dai J & Tang QZ, 2015. Icariin protects H9c2 cardiomyocytes from lipopolysaccharideinduced injury via inhibition of the reactive oxygen speciesdependent cJun Nterminal kinases/nuclear factor-kappaB pathway. Mol Med Rep, 11 (6), 4327-4332. Beschikbaar online: https://doi.org/10.3892/mmr.2015.3289

Zhou L, Huang Y, Zhang Y, Zhao Q, Zheng B, Lou Y & Zhu D, 2013. mGluR5 stimulating Homer-PIKE formation initiates icariin induced cardiomyogenesis of mouse embryonic stem cells by activating reactive oxygen species. Exp Cell Res, 319 (10), 1505-1514. Beschikbaar online: https://doi.org/10.1016/j.yexcr.2013.03.017

Zhou L, Zheng B, Tang L, Huang Y & Zhu D, 2014. Involvement of PIKE in icariin induced cardiomyocyte differentiation from murine embryonic stem cells. Pharmazie, 69 (3), 198-202. Beschikbaar online: http://www.ncbi.nlm.nih.gov/pubmed/24716409

Zhou Yuanpeng JJ, 1992. The experimental and clinical study of higenamine pharmacology and clinics of Chinese Materia. . Medica, 8 (3), 43-46.

Zhu D, Qu L, Zhang X & Lou Y, 2005. Icariin-mediated modulation of cell cycle and p53 during cardiomyocyte differentiation in embryonic stem cells. Eur J Pharmacol, 514 (2-3), 99-110. Beschikbaar online: https://doi.org/10.1016/j.ejphar.2005.03.031

Zhu DY, Cui R, Zhang YY, Li H, Zhou LM & Lou YJ, 2011. Involvement of ubiquitin-proteasome system in icariin-induced cardiomyocyte differentiation of embryonic stem cells using two-dimensional gel electrophoresis. J Cell Biochem, 112 (11), 3343-3353. Beschikbaar online: https://doi.org/10.1002/jcb.23264

Zhu HR, Wang ZY, Zhu XL, Wu XX, Li EG & Xu Y, 2010. Icariin protects against brain injury by enhancing SIRT1-dependent PGC-1alpha expression in experimental stroke. Neuropharmacology, 59 (1-2), 70-76. Beschikbaar online: https://doi.org/10.1016/j.neuropharm.2010.03.017

Zong N, Li F, Deng Y, Shi J, Jin F & Gong Q, 2016. Icariin, a major constituent from Epimedium brevicornum, attenuates ibotenic acid-induced excitotoxicity in rat hippocampus. Behav Brain Res, 313, 111-119. Beschikbaar online: https://doi.org/10.1016/j.bbr.2016.06.055

Annex I - Overview of substances found in food supplements sampled by the NVWA

The table below presents a complete overview of the number of times an individual substance was found in a food supplement sampled by the NVWA between October 2013 and December 2019.

***Table 9**. Overview of the number of times that an individual substance was found in a food supplement sampled by the NVWA between October 2013 and December 2019 (table continued on the following pages).*

Substance	**2013 (N=71)**	**2014 (N=71)**	**2015 (N=201)**	**2016 (N=160)**	**2017 (N=76)**	**2018 (N=25)**	**2019 (N=17)**	**Total**
Agmatine	0	0	1	0	0	0	0	1
Amphetamine	0	0	1	0	0	0	0	1
Aminotadalafil	0	0	0	2	0	0	1	3
Aristolochic acid I	0	0	0	1	0	0	0	1
Aristolochic acid II	0	0	0	0	0	0	0	0
Atropine	1	1	0	1	0	0	0	3
Baicalein	0	0	1	0	0	0	0	1
Benzylsibutramine	0	0	3	1	0	6	0	10
BMPEA (β-methylphenethylamine)	0	0	10	0	0	0	0	10
Caffeine	0	0	10	50	43	4	7	114
Capsaicin	0	0	3	0	0	0	0	3
Cathinon	0	0	2	0	0	0	0	2
Chlorogenic acid	0	0	12	0	0	0	0	12
Chromium picolinate	0	0	6	0	0	0	0	6
Corynanthine/Rauwolfscine	1	0	0	0	0	0	0	1
Dapoxetine	0	0	1	0	0	0	0	1
Desmethyl-sibutramine	0	0	3	0	0	0	0	3
Diclofenac	0	0	1	0	0	0	0	1
DMAA (1,3-dimethylamylamine)	4	7	0	3	0	0	0	14
DMAE (dimethylaminoethanol)	0	0	0	0	1	0	0	1
DMBA (1,3-dimethylbutylamine)	0	3	0	5	0	0	0	8
(DMHA) (1,5-dimethylhexylamine)	0	0	1	0	0	0	0	1
Ephedrine	2	3	7	3	0	0	0	15
Evodiamine	0	0	1	0	0	0	0	1

Substance	**2013 (N=71)**	**2014 (N=71)**	**2015 (N=201)**	**2016 (N=160)**	**2017 (N=76)**	**2018 (N=25)**	**2019 (N=17)**	**Total**
PEA (phenethylamine)	0	0	12	4	0	0	0	16
Phenolphthalein	1	1	1	5	5	3	0	16
Phentermine	0	0	0	0	0	0	0	0
Fluoxetine	1	0	1	1	1	0	0	4
Forskolin	0	0	2	0	0	0	0	2
Halostachine	0	0	0	1	0	0	0	1
Heliotrine	1	0	2	1	0	0	0	4
Higenamine	4	10	6	12	0	0	0	32
Hordenine	0	3	0	13	3	0	4	23
Icariin	3	7	13	6	0	0	2	31
Isopropyloctopamine	0	0	0	1	0	0	0	1
Kavain	0	1	0	1	0	0	0	2
Kynurenine	0	0	1	0	0	0	0	1
Lorcaserin	1	0	5	0	0	0	0	6
Lycopsamine	0	0	0	2	1	0	0	3
Methamphetamine	0	0	1	0	0	0	0	1
Methylsynephrine	0	0	13	4	0	0	0	17
Monocrotaline	1	0	0	2	0	0	0	3
Monocrotaline N-oxide	0	0	0	1	0	0	0	1
N-Isopropyl-octopamine	0	0	1	0	0	0	0	1
Norepinephrine	0	0	1	0	0	0	0	1
Octopamine	5	1	0	3	0	3	0	12
Unknown m/z 288	0	0	1	0	0	0	0	1
Unknown m/z 331	0	0	1	0	0	0	0	1
Unknown m/z 375	0	0	1	0	0	0	0	1
Unknown m/z 407	0	0	1	0	0	0	0	1
Unknown m/z 411	0	0	1	0	0	0	0	1
Unknown m/z 419	0	0	4	0	0	0	0	4
Unknown m/z 427	0	0	1	0	0	0	0	1
Oxyfedrine	0	0	2	0	0	0	0	2
Piperine	0	0	9	0	0	0	0	9
Podophyllotoxin	2	0	0	0	0	0	0	2
Propadin	0	0	3	0	0	0	0	3
Rimonabant	0	0	1	0	0	0	0	1
Rutecarpine	0	0	1	0	0	0	0	1
Scopolamine	0	1	0	0	0	0	0	1
Senecionine-NO	0	1	0	0	0	0	0	1
Seneciphylline-NO	0	1	0	0	0	0	0	1
Sibutramine	3	1	4	8	9	1	0	26
Sildenafil	8	8	18	2	5	0	1	42
Strychnine	0	0	1	1	0	0	0	2
Sulbutiamine	0	0	1	0	0	0	0	1
Synephrine	15	11	4	21	8	0	2	61

Substance	**2013 (N=71)**	**2014 (N=71)**	**2015 (N=201)**	**2016 (N=160)**	**2017 (N=76)**	**2018 (N=25)**	**2019 (N=17)**	**Total**
Tadalafil	1	1	1	0	0	5	0	8
THC (Tetrahydrocannabidiol)	2	0	1	0	0	0	0	3
Theobromine	0	0	1	0	0	0	0	1
Theophylline	0	0	2	0	0	0	0	2
Thiodimethylsildenafil	0	0	2	0	0	0	0	2
Thiohomosildenafil	4	2	0	0	0	0	0	6
Thiosildenafil	4	2	14	0	0	1	0	21
Vonedrine	0	0	1	0	0	0	0	1
Wogoniside	0	0	1	0	0	0	0	1
Yohimbe	7	6	2	5	0	2	0	22

Annex II - Overview of detected substances in RASFF notifications

The table below presents a complete overview of the number of times an individual substance was mentioned in RASFF notifications (N=280) involving the Netherlands regarding chemical substances in food supplements between 2015 and 2019.

***Table 10**. Overview of the number of times an individual substance was mentioned in RASFF notifications involving the Netherlands regarding chemical substances in food supplements between 2015 and 2019 (table continued on the following pages).*

Substance	**2015 (N=32)**	**2016 (N=143)**	**2017 (N=99)**	**2018 (N=70)**	**2019 (N=67)**	**Total**
3,3'-diindolylmethane		1	1			2
3,5-diiodothyronine		1				1
4-(4'-hydroxyphenyl)butane-2-one	1					1
5 HTP (5-hydroxytryptophan)				1		1
Acacia Rigidula		3	9			12
Acetyl-L-carnitine		1				1
Adansonia digitata					1	1
Aegeline	4					4
Aflatoxins		1				1
Agmatine sulphate	4	15	19	1	1	40
Alpha lipoic acid			1			1
Alpha GPC (L-alpha glyceryl phosphorylcholine)				2		2
Aluminium			1	1		2
Amphetamine		1				1
Annona muricata					1	1
Antraquinone			1			1
Arginine nitrate			1			1
Argyreia nervosa					1	1
Arsenic					1	1
Artemisia annua					1	1
Atropine		1				1
Bauhinia pupurea			1			1
Benzo(a)pyrene		2	3	5		10
Berberine		1				1
Black cohosh	1					1
BMPEA (β-methylphenethylamine)		3				3
Boron citrate		1				1
Brahmi			1			1
Caffeine	1	10	3	4	3	21
Canavalia gladiata		1				1

Substance	**2015 (N=32)**	**2016 (N=143)**	**2017 (N=99)**	**2018 (N=70)**	**2019 (N=67)**	**Total**
Cassia Nomame		1				1
CBD (Cannabidiol)				1	19	20
Chili pepper extract		1				1
Chlorpropham			1			1
Chlorate				1	1	2
Chromium chelate		3				3
Cirsium Oligophyllum			1			1
Citrulline aspartate		2				2
Coleus forskohlii		1				1
Creatine nitrate		4	1			5
DMAA (1,3-dimethylamylamine)		5	2			7
DMBA (1,3-dimethylbutylamine)		6				6
DMHA (1,5-dimethylhexylamine)		1	1			2
DNP (2,4-dinitrophenol)	1				2	3
E 104		1				1
Ephedra		1	1			2
EGCG (Epigallocatechin gallate)					1	1
Epimedium	1		5	7	1	14
Evodia rutaecarpa		1				1
Evodiamine			1			1
PEA (phenethylamine)		7				7
Velvet bean	1					1
Gamma-aminobutyric acid	1			1		2
Garcinia cambodia				2		2
Gingko biloba		1				1
Ginkgolide A		1				1
Glycine betaine		1				1
Halostachine		1				1
Higenamine		2				2
Hoodia Gordonii			7			7
Hordenine		5				5
Isopropyloctopamine		1				1
Iodine			1			1
Jojoba seed			1			1
Potassium chelate		1				1
Copper chelate		2				2
Mercury	3	1	1	1		6
l-Arginine l-pyroglutamate		1				1
Lead	2	2	2	2		8
Lycium barbarum					1	1
Lycopene			1			1
Magnesium					1	1
Magnesium chelate		1				1

Substance	**2015 (N=32)**	**2016 (N=143)**	**2017 (N=99)**	**2018 (N=70)**	**2019 (N=67)**	**Total**
Magnesium creatine chelate		1				1
Manganese chelate		1				1
Melatonin				1		1
Molybdenum chelate		2				2
Mucuna pruriens		1		1	1	3
N,N-dimethyl-2-phenylpropan-1-amine		1				1
N,N-DMPEA (N-β-dimethylphenethylamine)		2				2
N-carbamylglutamate		1				1
Nicotinic acid	1	3	1	1		6
N-methyltyramine		1				1
N-nicotinoyl-GABA		1				1
Ocimum tenuiflorum				1		1
Oxilofrine		3				3
PAHs (Polycyclic Aromatic Hydrocarbons)			4	5	3	12
Parasitic loranthus		1				1
PAs (Pyrrolizidine alkaloids)					6	6
Paulownia extract		1				1
Perchlorate				1		1
Polygonum cuspidatum		1		1		2
Propargite			1			1
Propionyl-L-Carnitine		1				1
Psoralea corylifolia		1				1
Rauwolfia vomitoria		1		1		2
Salvia hispanica				1		1
SARMs (selective androgen receptor modulator)					1	1
Sceletium tortuosum		1				1
Sheep placenta extract	1					1
Selaginella tamariscina		2				2
Selenium chelate		3				3
Senna	1					1
Sildenafil		1	1	3	2	7
Siraitia grosvenorii			1			1
Solanum nigrum				2		2
Sophora japonica		1				1
Sulphite				4	1	5
Synephrine		8	1	1		10
Tetradecylthioacetic acid		1				1
THC (Tetrahydrocannabidiol)		1		1	11	13
Theacrine			1			1
Thermopsis lanceolata		1				1
Thiono analogue of sildenafil			1	1		2
Tongkat ali	1	1	1		1	4

Substance	**2015 (N=32)**	**2016 (N=143)**	**2017 (N=99)**	**2018 (N=70)**	**2019 (N=67)**	**Total**
Tribulus alatus	1					1
Tribulus terrestris		1				1
Vanadyl sulphate			1	1		2
Vardenafil			1			1
Vinpocetine			2			2
Vitamin A			2	1	1	4
Vitamin B6	5	1	5	6		17
Vitamin E	1		1	2		4
Yohimbe	1	1	5	2	1	10
Zeolite				1	1	2
Zinc			3	3	3	9
Zinc chelate		1				1

Annex III - Synonyms list

The table below lists synonyms and/or trivial names of BMPEA, DMAA, DMBA, DMHA, PEA, halostachine, higenamine, hordenine, icariin, isopropyloctopamine, N,N-DMPEA and methylsynephrine.

***Table 11**. Overview of synonyms and/or trivial names of BMPEA, DMAA, DMBA, DMHA, PEA, halostachine, higenamine, hordenine, icariin, isopropyloctopamine, N,N-DMPEA and methylsynephrine (table continued on the next page).*

Substance	Synonym or trivial name
BMPEA	1-amino-2-phenylpropane 2-phenylpropylamine Acacia Rigidula Alpha-benzylethylamine Beta-methylbenzene-ethanolamine Beta-methylphenetylamine R-beta-methylphenetylamine β-methylphenetylamine
DMAA	2-amino-4-methylhexane 1,3-dimethylpentylamine 1,3-dimethylamylamine 1,3-dimethylpentylamine Floradrene Forthan Forthane Geranamine Geranium extract Methylhexaneamine 4-methyl-2-hexaneamine 4-methyl-2-hexylamine
DMBA	AMP 4-AMP AMP Citrate 4-AMP Citrate Amperall 2-amino-4-methylpentane 2-amino-4-methylpentane citrate 4-amino-2-pentanamine 4-amino methylpentane citrate 4-amino-2-methylpentane citrate 1,3-dimethylbutylamine 4-methyl-2-pentanamine Pentergy Nor-DMAA
DMHA	2-amino-6-methylheptane 1,5-dimethylhexylamine 6-methyl-2-heptanamine 6-methyl-2-heptylamine Octodrine

Substance	Synonym or trivial name
PEA	1-amino-2-phenylethane 2-phenethylamine 2-phenylethan-1-amine 2-phenylethylamine Phenethylamine β-phenylethylamine
Halo-stachine	N-methylphenylethanolamine (R)-(-)-α-[(methylamino)methyl]-benzenemethanol 1-hydroxy-1-phenyl-2-methylaminoethane α-(methylaminomethyl)benzyl alcohol 2-methylamino-1-phenylethanol
Higena-mine	Norcoclaurin 1-[(4-hydroxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinoline-6,7-diol Demethylcoclaurine
Hordenine	4-(2-dimethylaminoethyl)phenol N,N-dimethyltyramine Peyocactin Anhaline
Icariin	Iearilіne Epimedium extract 1.3-((6-deoxymannopyranosyl)oxy)-7-(glucopyranosyloxy)-5-hydroxy-2-(4-methoxyphenyl)-8-(3-methyl-2-butenyl)-4H-1-benzopyran-4-one
Isopropyl-octopamine	Betaphrin Isopropylnorsynephrine Deterenol
N,N-DMPEA	N,N-dimethyl-2-phenylethan-1-amine N,N-DMPEA N,N-dimethyl-2-phenylethanamine N,N-beta-dimethylphenylethylamine
Methyl-synephrine	Oxilofrine Hydroxyephrine Oxyephrine 1-(4-hydroxyphenyl)-2-methylamin-propanol (4-HMP) Suprifen Carnigen

Annex IV – Toxicology

Approach
BuRO asked the Front Office for Food and Product Safety (FO) to prepare a fact sheet for DMAA, DMBA and DMHA with information on the following aspects:
- trivial names or synonyms
- (toxico)kinetics (absorption, distribution, metabolism and excretion)
- (toxico)dynamics
- interactions with other substances

In addition, BuRO asked FO to establish, if possible, a health-based guidance value for these substances.

BuRO asked the Department of Pharmacology & Toxicology of Maastricht University to prepare fact sheets for BMPEA, PEA, N,N-DMPEA, halostachine, higenamine, hordenine, icariin, isopropyloctopamine and methylsynephrine, focusing specifically on the following aspects:
- trivial names or synonyms
- (toxico)kinetics (absorption, distribution, metabolism and excretion)
- (toxico)dynamics
- interactions with other substances

Information for the fact sheets was collected from Pubmed, Medline, Embase and the Hazardous Substances Data Bank (HSDB), based on substance name and synonyms. Toxline was searched using the CAS number. Articles dealing with the detection of the substance in question were not considered. Table 12 provides an overview of the total number of publications found by UM for the substance in question and the number of publications that contained relevant information ((toxico)kinetics, (toxico)dynamics and interactions).

Table 12. *Overview of the number of publications found by UM and the number of relevant publications.*

Substance	Publications found (N)	Relevant publications (N)
BMPEA	29	15
PEA	141	105
N,N-DMPEA	21	14
Halostachine	14	13
Higenamine	108	53
Hordenine	78	29
Icariin	295	180
Isopropyloctopamine	14	9
Methylsynephrine	42	23

The remainder of this annex presents the available information for each substance. With respect to DMAA, DMBA and DMHA, a brief summary of the FO assessment is presented. For details, please refer to the underlying references. For the other substances, the full fact sheet as prepared by UM is presented.

BMPEA
BMPEA, β-methylphenethylamine is an organic compound in the phenetylamine class. BFPEA was synthesised in the 1930s as a replacement for the drug amphetamine, of which it is an isomer (Figure 6). Due to its structural similarities to amphetamine, BMPEA is estimated to have similar physiological effects (Eichner et al., 2016). Like amphetamine, BMPEA probably acts as an indirect sympathomimetic that can activate α- and β-adrenergic receptors. In addition, BMPEA is an agonist of the TAAR1 receptor. TAAR1 plays an important role in the regulation of neurotransmission in dopaminergic, noradrenalinergic and serotonergic neurons of the central nervous system.

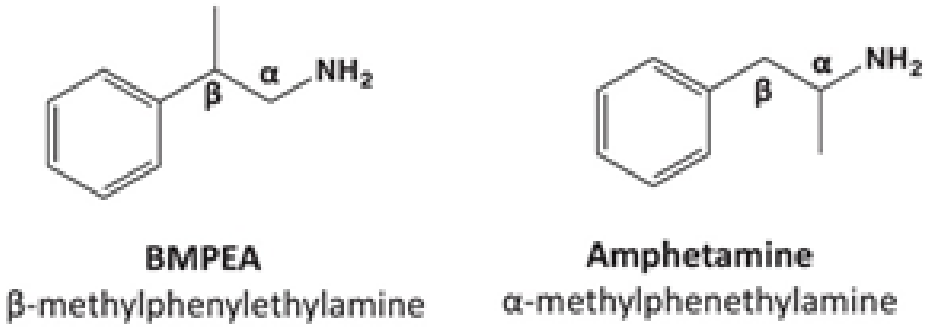

Figure 6. *Chemical structures of BMPEA and amphetamine.*

Kinetics
There are few, if any, studies available on the kinetics of BMPEA. As a food supplement, BMPEA is taken orally. Mosnaim et al. (2013) have shown in rats that BMPEA is metabolised by MAO and can cross the blood-brain barrier (Mosnaim et al., 2013).

However, we do have information about the toxicokinetics of amphetamine, and it is likely that BMPEA has a similar kinetic pathway. After oral intake in humans, amphetamine is rapidly absorbed in the intestines (Schepers et al., 2003). Amphetamine reaches peak concentration in plasma after approximately 1 to 3 hours. The plasma half-life is 11.25 hours. Amphetamine is mainly found in high concentrations in the kidneys, lungs and cerebrospinal fluid. Approximately 5% to 30% of amphetamine intake is normally excreted unchanged in urine (Shimosato et al., 1986).

The metabolism of amphetamine involves several steps (Kraemer & Maurer, 2002). First, amphetamine is hydrolysed by cytochrome P450 into 4-hydroxyamphetamine, or into alpha-hydroxyamphetamine, which is also known as norephedrine. Both substances are biologically active and can contribute to drug effects (Caldwell, 1976). Both are further oxidised to 4-hydroxyhedrine. Alpha-hydroxyamphetamine is then deaminated to phenylacetone, which is eventually converted to and excreted as benzoic acid and hippuric acid (Caldwell, 1976).

Dynamics
Hartung et al. (1931) showed that BMPEA was orally active and had anti-hypotensive effects after oral and intravenous administration of 1 mg/kg bw in dogs (Hartung & Munch, 1931). The same study showed a minimum lethal dose of

500 mg/kg in rats (subcutaneous administration) and 50 mg/kg in rabbits (intravenous administration).

Graham et al. (1944) found increased blood pressure and heart rate after intravenous administration of 20 mg of BMPEA in dogs (Graham & Cartland, 1944). This effect was equivalent to 30% of the potency of amphetamine. They also observed bronchodilation in isolated lungs of rabbits after administration of 20 mg BMPEA, which was two times greater than the effect of amphetamine.

Mosnaim et al. (2013) found that BMPEA, after intravenous administration of 100 µg, was able to diffuse across the blood-brain barrier in rats treated with the monoamine oxidase (MAO) inhibitor pargyline (Mosnaim et al., 2013).

Mosnaim et al. (2015) found that intraperitoneal administration of 15 and 75 mg/kg of BMPEA in mice led to increased locomotor activity, hyperexcitation and increased fighting behaviour (Mosnaim et al., 2015).

In an *in vitro* study in sAV12-664 cells, BMPEA was shown to be an agonist of the TAAR1 receptor (Wainscott et al., 2007).

Liu et al. (2016) studied the effects of BMPEA on the activity of CYP2D6 and CYP3A4 (Liu & Santillo, 2016). They found that BMPEA inhibited CYP2D6 activity with an IC_{50} of 2 µM. 100 µM of BMPEA inhibited CYP3A4 activity by 36.5%. This could be enough to alter the effects of medicines metabolised by these 2 enzymes.

Cohen et al. (2015) described one case from 2014 where BMPEA was associated with cerebral haemorrhage in a 53-year-old Swedish athlete. The athlete had taken a food supplement containing 290 mg of BMPEA (which was not labelled as such) before exercise and had no other medical history. Half an hour after taking the supplement, the first symptoms appeared in the form of numbness and clumsiness in her left hand (Cohen et al., 2015b). The athlete recovered and was discharged from hospital after 5 days.

DMAA

The text below is a brief summary of the FO assessment. For a complete overview, see (RIVM, 2018).

DMAA (1,3-dimethylamylamine) is a simple aliphatic amine that is synthesised but is also thought to be naturally present in geranium oil. Until 1970, DMAA was used as a medicine to relieve nasal congestion, with an inhaled dose of 0.6 mg of DMAA or more being considered pharmacotherapeutically effective. Below is a brief overview of the available substance-specific information. For more details, please refer to the BuRO advice from 2012 and the FO assessment from 2018 (BuRO, 2012; RIVM, 2018).

Kinetics

After oral intake, DMAA is absorbed relatively slowly. Its half-life is 24 hours. Most of the DMAA is then excreted unchanged in urine. The oral efficacy of DMAA depends on concurrent medication (e.g. monoamine oxidase inhibitors) and nutrients. Caffeine is a known (weak) monoamine oxidase inhibitor. The simultaneous use of caffeine and DMAA may cause the side effects of DMAA to occur at a lower dose. *In vitro*, DMAA inhibits the enzymes CYP2D6 and CYP3A4.

Dynamics

No information is available from animal studies on chronic toxicity, genotoxicity, carcinogenicity and reproductive toxicity following exposure to DMAA. After intraperitoneal administration of DMAA in mice, an LD_{50} of 185 mg/kg bw was found.

Pharmacological effects on the lungs (bronchodilation) and nasal mucosa can be expected to occur after a single oral dose of approximately 4-15 mg. Pharmacological effects on the heart can be expected after a single oral dose of from about 50-75 mg. Pharmacological effects on blood pressure are expected after a single oral dose from about 100 mg. Due to the long half-life, there is a risk that repeated doses within 24-36 hours could result in cumulative pharmacological effects.

Several case studies describe the occurrence of adverse effects after ingestion of supplements containing DMAA, including cerebral haemorrhage, neurological effects, cardiac arrest, acute liver failure and death. Many of those supplements also contained other substances, such as caffeine, and were taken just before strenuous exercise.

DMBA

The text below is a brief summary of the FO assessment. For a complete overview, see (RIVM, 2018).

DMBA (1,3-dimethylbutylamine; nor-DMAA; AMP) is a simple synthetic aliphatic amine. Researchers claim that DMBA also exists as a natural constituent of tea or of the plant *Coreopsis tinctoria*. The evidence for this is not particularly strong. DMBA has never been registered as an active substance in a medicinal product. Below is a brief overview of the available substance-specific information. For more details, please refer to the 2018 FO assessment (RIVM, 2018).

Kinetics

In vitro, DMBA inhibits the enzymes CYP2D6 and CYP3A4. DMAA is at least 15 times more potent than DMBA.

Dynamics

No information from animal studies is available on acute toxicity, chronic toxicity, genotoxicity, carcinogenicity and reproductive toxicity after exposure to DMBA. Neither have any studies on these effects in humans been found.

One case report lists the following effects after ingestion of DMBA: agitation, difficulty sitting still and sharpened focus.

DMHA

The text below is a brief summary of the FO assessment. For a complete overview, see (RIVM, 2018).

DMHA (1,5-dimethylhexylamine; octodrine) is a simple synthetic aliphatic amine. Several studies suggest that DMHA also occurs naturally in various species of plants, algae and fish. However, there is no convincing evidence for this. In Europe (though not in the Netherlands), DMHA was sold as an active ingredient of multi-ingredient tablets (with a dosage between 8.2 and 33 mg). In addition, DMHA was used to treat hypotension. Below is a brief overview of the available substance-specific information. For more details, please refer to the 2018 FO assessment (RIVM, 2018).

Kinetics

Maximum serum concentrations of DMHA were reached 2 hours after ingestion.

Dynamics

Acute toxicity of DMHA following intraperitoneal exposure has been studied in mice, rats, rabbits and guinea pigs. In all these animal species, tremors, convulsions and eventual death occurred at doses of 40-75 mg/kg bw (mice), 30-60 mg/kg bw (rats), 50-100 mg/kg bw (rabbits) or 25-100 mg/kg bw (guinea pigs). Rats showed depression symptoms after being administered 100 mg of DMHA per kg body weight orally for 30 days.

No information is available from animal studies on chronic toxicity, genotoxicity, carcinogenicity and reproductive toxicity following exposure to DMHA.

In 4 volunteers, ingestion of DMHA (4 mg/kg) led to a 20-25 mm Hg increase in systolic blood pressure during the subsequent 2 to 3 hours. Reported effects were abdominal pain, dry mouth, goose bumps, urination, sweating, reduced blood volume in the finger and forced sighing. No measurable effects occurred at doses of 1 or 2 mg/kg.

PEA
Phenethylamine (PEA) is a natural alkaloid and amine and is synthesised in various organisms, including humans, plants and various algae and bacteria (Smith, 1977; Berry, 2004; Guven et al., 2010; Kim et al., 2012). In the human body, PEA is synthesised from the amino acid L-phenylalanine (Janssen et al., 1999; Berry, 2004) through decarboxylation of the amino acid by the aromatic amino acid decarboxylase (AADC). PEA has been detected in the brain of humans and other mammals. This is because PEA has the ability to cross the blood-brain barrier. In the brain of rats, mice and rabbits, endogenous amounts of PEA have been found between 1.0-2.1 ng/g (rats), 1.0-1.76 ng/g (mice) and 0.44 ng/g (rabbits) (Berry, 2004). PEA can also be synthesised in fungi and bacteria and occurs naturally in plants of the *Leguminosae* family.

In addition to the synthesis of PEA in our bodies, it is also present in certain food products, such as chocolate and eggs (Granvogl et al., 2006; Figueiredo et al., 2013). In eggs, amounts of 38.0 mg/kg of PEA have been detected in egg white and 1.02 mg/kg of PEA in yolks. These quantities depend on the age of the chickens and the duration and temperature of storage. Pastore et al. (2005) showed that the amounts of PEA in chocolate were below the detection limit of 3 mg/kg of PEA for chocolate (Pastore et al., 2005).

PEA acts as a neurotransmitter in the bodies of humans and animals (Sabelli et al., 1976). It consists of a benzene ring to which a chain of two carbon atoms is attached. This structure is also known as the phenethylamine backbone. Due to this backbone, PEA is the basis for a chemical class of substances such as catecholamines and trace amines, which are monoamine modulators of the nervous system. Examples of trace amines are octopamine, synephrine, adrenaline and tyramine. Many of these substances, such as amphetamine and ephedrine, are psychoactive. Chemically, PEA is very similar to amphetamine (Figure 7). Methylation of the second carbon atom of the carbon chain of PEA leads to the formation of amphetamine or to beta-methylphenethylamine, depending on the site of the methylation. Based on the structural similarity to amphetamine, the pharmacological effects are also expected to be similar. For example, PEA, like amphetamine, probably acts as an indirect sympathomimetic. PEA can also activate the TAAR1 and TAAR2 receptors (Borowsky et al., 2001).

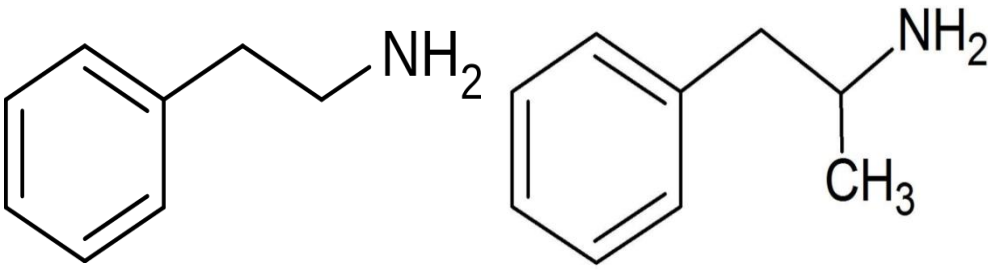

Figure 7. *Chemical structures of PEA (left) and amphetamine (right).*

Kinetics
Fischer et al. (2010) investigated the intestinal transport of PEA in human epithelial intestinal cells (CaCo-2) (Fischer et al., 2010). The uptake of radiolabelled PEA in these cells was sodium independent. The uptake was also saturable, with the following kinetic parameters: Km 2.6 mM and Vmax 96.2

nmol/min per milligram of protein. Phenelzine, tranylcypromine, amphetamine, methadone, chlorphenamine, diphenhydramine and promethazine were all found to inhibit the uptake of PEA.

Ben-Harari and Bakhle (1980) studied the uptake and metabolism of PEA in isolated lungs of rats (Ben-Harari & Bakhle, 1980), and found that the metabolism of PEA (50 µM) was inhibited by several factors: cold, anoxia, glucose deficiency, sodium deficiency and MAO inhibitors.

Karoum et al. (1981) showed that PEA was present in different parts of the central nervous system (Karoum et al., 1981). For example, 114-238 pg/mg protein was found to be present in the dorsal and ventral horns of the cervical spinal cord; in the zona intermedia and the dorsal and ventral horns of the lumbar cord. PEA was also found in the nucleus caudatus (218 pg/mg) and the cerebellum (73 pg/mg).

Oldendorf (1971) found a brain uptake index of 67% in rats administered 0.346 mM ^{14}C of labelled PEA intravenously (Oldendorf, 1971). The rats died shortly after administration of PEA, leading the authors to conclude that PEA diffused through the blood-brain barrier.

Shannon et al. (1982) studied the kinetics of PEA (5.6, 10.0 and 17.5 mg/kg, administered intravenously) in 5 dogs (Shannon et al., 1982). After administration of PEA, plasma levels dropped quite rapidly. The kinetics can be described using a one-compartment model. The half-life was found to increase from 6.1 minutes at the lowest dose to 16 minutes at the highest.

Durden et al. (1973) examined the distribution of PEA in rats (Durden et al., 1973). They administered radiolabelled PEA to male rats, and then measured the amount of PEA in various organs. The brain was found to contain 1.8 ng/g of PEA. In the heart, kidneys, liver, lungs and spleen quantities of 5.7, 20.5, 2.0, 4.0 and 4.7 ng/g were found, respectively.

Sato et al. (1997) studied the kinetics of PEA in rats (Sato et al., 1997). The plasma concentration of PEA can be described using a two-compartment model with non-linear elimination. After administration of PEA, dopamine in the rat brain increased rapidly while the concentration of DOPAC, a metabolite of the neurotransmitter dopamine, decreased.

Paterson et al. (1990) showed that PEA is mainly present in dopaminergic neurons of rats. Here the rate of synthesis of PEA is equal to that of dopamine (Paterson et al., 1990). However, the concentrations in the striatal neurons were lower than for dopamine. This is due to the rapid conversion of PEA by monoamine oxidase B (MAO-B).

Janssen et al. (1999) described the kinetics of PEA in the brain. PEA is formed by decarboxylation of phenylalanine (Janssen et al., 1999). In the brain, PEA is rapidly metabolised by MAO. PEA has a higher affinity for MAO-B than for MAO-A. In the brain of mice, PEA was found to have a half-life of half a minute, which is due to its very rapid degradation by MAO-B.

Yang and Neff (1973) found that PEA is present in the brain of rats and is metabolised there by MAO-B (Yang & Neff, 1973). After the rats were killed, the

brains were removed and the mitochondria isolated. These mitochondria were then used to test whether PEA was metabolised by MAO.

Saavedra (1974) found 1.5 ng/g of PEA in the brain of rats (Saavedra, 1974). When the rats received phenylalanine, the quantity of PEA increased. Following administration of an MAO-inhibitor, the quantity of PEA in the brain increased 40-fold. A 400-fold increase in the amount of PEA in the brain was found after combined administration of both an MAO inhibitor and phenylalanine. This increase was inhibited by administration of the decarboxylase inhibitor NSD-1055.

Mosnaim et al. (2013) found that an intravenous dose of 100 µg of PEA was able to diffuse across the blood-brain barrier in rats treated with the MAO inhibitor pargyline (Mosnaim et al., 2013).

Bahkle and Youdim (1979) studied the metabolism of PEA in the lungs of rats (Bakhle & Youdim, 1979). They found an PEA Km value of 54 micrograms for MAO in the perfused lungs. *In vitro*, however, they found an PEA Km value of 330 micrograms for MAO-A and 28 micrograms for MAO-B.

Suzuki et al. (1981) found that PEA in a low concentration (10 µM) was metabolised by MAO-B in both the brain and the liver of 8 different species (human, rat, mouse, guinea pig, chicken, rabbit, pig and cattle) (Suzuki et al., 1981). In a concentration of 1000 µM, PEA was metabolised in some species by both MAO-B and MAO-A. In human liver and brain, rat liver and brain, mouse brain, guinea pig liver and brain and bovine brain, PEA in high concentrations was metabolised by both forms of MAO. In chickens and rabbits, it was still metabolised specifically by MAO-B.

Paetsch et al. (1993) demonstrated that PEA is a metabolite of the MAO inhibitor phenelzine (Paetsch & Greenshaw, 1993). They studied this in the brain of rats.

Lin et al. (1997) showed that PEA is oxidised by the human enzyme flavin monooxygenase (FMO) and by human liver microsomes (Lin & Cashman, 1997).

Roth et al. (1974) demonstrated that PEA in isolated mitochondria from rabbit lungs and brain was metabolised by MAO, forming phenylacetic acid, among others (Roth & Gillis, 1974). Addition of the antidepressant imipramine (100 µM) inhibited 70% of the metabolism of PEA.

Saavedra et al. (1973) found that phenylethanolamine was present in several organs in rats, including the brain and heart (Saavedra & Axelrod, 1973). When PEA (50 mg/kg; intraperitoneal) was administered to the rats, the amount of phenylethanolamine in the brain was found to increase from 6 ng/g to 22 ng/g. When dopamine B-hydroxylase was administered together with PEA however, this amount did not increase. This shows that this enzyme is capable of converting PEA into phenylethanolamine.

Guimaraes and Soares-da-Silva (2000) found that in the rat brain, PEA is specifically metabolised by MAO-B (Tiago Guimaraes & Soares-da-Silva, 2000). as the metabolism was inhibited by lazabemide. In the heart, however, PEA was metabolised by MAO-A, as its metabolism was inhibited by the MAO-A inhibitor Ro 41-1049.

Wu and Boulton (1975) found that when radiolabelled PEA was administered intravenously, it was oxidised quite rapidly to phenylacetic acid (Wu & Boulton, 1975). When pargyline (an MAO inhibitor) was also injected, the PEA was found unchanged in several tissues, including the brain. Small amounts of tyramine and octopamine were also found.

Inwang et al. (1973) showed that in the human brain both PEA and its metabolite phenylethanolamine are present (Inwang et al., 1973).

Szabo et al. (2001) examined the amount of phenylacetic acid in the urine of 20 healthy athletes (Szabo et al., 2001). The athletes had to run on a treadmill for 30 minutes at 70% of their maximum heart rate. Twenty-four hours after exercise, in 18 out of 20 cases the amount of phenylacetic acid in the urine was found to have increased by 77%. The concentration of phenylacetic acid is a measure of the amount of PEA in the human body.

Dynamics
In a placebo-controlled double-blind study (Luthy & Schlatter, 1983), 27 healthy volunteers took 2 x 25 mg of histamine, 2 x 25 mg of tyramine and 2 x 5 mg of PEA in apple juice (2 dl). In addition, the volunteers took 6 times a placebo (a glass of apple juice (2 dl) without any added substances). After consuming the apple juice, the volunteers filled in a questionnaire to record any effects that occurred within 20 hours. In a second part of the study, 4 volunteers who indicated sensitivity to PEA were given a single dose of 5 mg of PEA in apple juice (2 dl). Three volunteers took a placebo. Out of the 27 volunteers, 3 reported effects such as dizziness, sweating, mild headache and nausea after taking 5 mg of PEA.

Some animal studies have shown that PEA can cause serotonin behaviour syndrome. This condition, which results from the use of medicines that increase the amount of serotonin, can cause symptoms such as agitation, tremors, sweating, diarrhoea and increased body temperature. Reducing endogenous serotonin levels did not help to prevent the behaviour syndrome in rats (Sloviter et al., 1980). However, the serotonin receptor antagonists methysergide and mianserin did block these effects.

Dourish and Cooper (1983) found that intravenous administration of 125-200 mg/kg of PEA in mice caused strokes (Dourish & Cooper, 1983). Pretreatment with the benzodiazepines diazepam, chlordiazepoxide, midazolam and clonazepam reduced these strokes. Injection with the GABA transaminase inhibitor aminooxyacetic acid, which increases the level of GABA, also reduced the effects of PEA.

Shannon et al. (1982) found that PEA (5.6, 10 and 17.5 mg/kg; administered intravenously) caused dilation of the pupils, tachycardia and increased body temperature (Shannon et al., 1982).

Furthermore, different toxicity values have been published for PEA based on different toxicity studies. For example, LD_{50} values of 320 mg/kg (subcutaneous),

100 mg/kg (intravenous) and 39 mg/kg (intracervical) have been described for rats (Lewis, 1996).

Denno et al. (1990) found that PEA (0.01-10 mM) had toxic effects, with neural tube damage being detected and even embryo-lethal effects in mouse embryos (Denno & Sadler, 1990).

Various neuronal effects of PEA have been demonstrated in animal studies. For example, PEA appears to have amphetamine-like effects, mainly reducing neuronal activity and increasing the release of various neurotransmitters (such as dopamine and acetylcholine). Table 13 summarises the various neuronal effects.

***Table 13**: The neuronal effects of PEA.*

Effect	Dose	Mode of administration	Species	Reference
Enhanced neuronal response	1 µM	Intravenous and iontophoretic	Rat	(Paterson, 1993)
	0.3-1 mg/kg	Intravenous	Rat	(Ono et al., 1991)
Increased dopamine release	1.75-29.16 mg/kg	Intravenous	Rat	(Barroso & Rodriguez, 1996)
	10-100 mg/kg	Intraperitoneal	Mouse	(Sotnikova et al., 2004)
	500 µM	Intracerebral	Rat	(Bailey et al., 1987)
	1-100 µM	Intracerebral	Rat	(Nakamura et al., 1998)
	12.5-25 mg/kg	Intraperitoneal	Rat	(Murata et al., 2009)
	25 mg/kg	Intracardial	Rat	(Philips, 1986)
Reduced neuronal responses	1-5 mg/kg	Intravenous	Rat	(Ishida et al., 2005a)
	0.4-3.4 mg/kg	Intravenous	Rat	(Rodriguez & Barroso, 1995)
	80 mg/kg	Intraperitoneal	Rat	(Vanderwolf et al., 1980)
Increase in tyramine and metabolite release	50 mg/kg	Subcutaneous	Mouse	(Nakamura et al., 1998)
Reduced brain activity	1-40 mg/kg	Intraperitoneal	Rat	(Howard et al., 1976)
Increased acetylcholine release	25-50 mg/kg	Intraperitoneal	Rat	(Kato et al., 2001)
	12.5-25 mg/kg	Intraperitoneal	Rat	(Ishida et al., 2005b)
Decrease Catechol-o-methyltransferase activity	50 mg/kg	Intravenous	Gerbils	(Hannan, 1986)

Several animal studies have also been conducted into the effects of PEA on behaviour. The main findings were that PEA stimulated locomotor activity and fighting behaviour. In higher doses, it even induced serotonin syndrome. Table 14 provides a summary of the behavioural effects of PEA.

Table 14: *The behavioural effects of PEA.*

Effect	**Dose**	**Mode of administra-tion**	**Species**	**Reference**
Increased locomotor activity, hyperexcitability, fighting behaviour, jumping and vocalisation	15 and 75 mg/kg	Intraperitoneal	Mouse	(Mosnaim et al., 2015)
Increased locomotor activity	200-300 µg	Intracerebral	Rat	(Dourish, 1985)
	50 mg/kg	Intravenous	Mouse	(Dourish, 1982)
Serotonin syndrome	50 mg/kg	Intraperitoneal	Rat	(Dourish, 1981)
	20-60 mg/kg	Intraperitoneal	Rat	(Goudie & Buckland, 1982)
Reduction of aggressive behaviour towards mice	16-32 mg/kg	-	Rat	(Barr et al., 1979)
Hyperthermia	100 mg/kg	Intraperitoneal	Mouse	(Jackson, 1975)
Increased self-administration (addictive effect)	6.0-36.0 µmol/kg/injection	Intravenous	Dog	(Shannon & Degregorio, 1982)
Reduced water consumption	2.125-50 mg/kg	Intravenous	Rat	(Cooper & Dourish, 1984)
Involuntary contractions of submandibular muscle and peak electro-corticograph activity	20-100 µg	Intravenous	Rat, under anaesthetic	(Ukponmwan et al., 1983)
Reduced response to electrical stimulation of the hypothalamus	1.25-50 mg/kg	Intraperitoneal	Rat	(Greenshaw et al., 1985)
Reduced intake of saccharin	100 mg/kg	Intraperitoneal	Rat	(Greenshaw & Dourish, 1984)

Several studies have been done showing cardiovascular effects of PEA such as reduced heart rate and cardiac output, increased blood pressure and increased peripheral resistance. In addition to an increase in catecholamine release, alpha and beta receptors also play a role in these effects. See Table15 for a summary of the cardiovascular effects of PEA.

Table15: *The cardiovascular effects of PEA.*

Effect	**Dose**	**Mode of administration**	**Species**	**Reference**
Decreased heart rate, tachycardia, bradycardia, increased pupil diameter and body temperature	5.6-17.5 mg/kg	Intravenous	Dog	(Shannon et al., 1982)
Decrease in cerebral blood flow and cerebral oxygen consumption	2 mM/kg/min	Intravenous	Baboon	(McCulloch & Harper, 1979)
Decreased sensitivity of beta receptors	10 mg/kg/day	Intravenous	Rat	(Paetsch et al., 1993)
Increased blood pressure caused by increased release of catecholamines (due to PEA in combination with MAO inhibitor)	0.1 mg/kg	Intravenous	Rat	(Cashin, 1972)
Increased blood pressure and peripheral resistance; reduced heart rate	0.0625-0.5 mg/kg	Intravenous	Dog	(Liang & Sprecher, 1979)
Desynchronisation of electrocorticography	75 mg/kg	Intraperitoneal	Rat	(Dzoljic et al., 1977)

Several studies have examined effects of PEA other than the neuronal, behavioural and cardiovascular effects mentioned above. These studies are briefly described below. Mosnaim et al. (2014) found that PEA (from 6 mg/kg; administered intraperitoneally) provided analgesic effects in mice (Mosnaim et al., 2014). This was measured by measuring the time of response to a thermal stimulus. When PEA was administered, this time increased.

Kosa et al. (2000) studied the effects of PEA (50 mg/kg/day; administered intraperitoneally for 10 days) on the hypothalamic-pituitary-adrenal (HPA) axis in rats (Kosa et al., 2000). PEA caused an increased release of corticotrophin releasing hormone (CRH), an increased mRNA expression of CRH and increased plasma levels of adreno-corticotrophin hormone. The researchers concluded that PEA stimulates the HPA axis.

Derelanko (1990) found that PEA (50 and 100 mg/kg; administered orally) reduced the severity of alcohol-induced damage in the stomach of rats (Derelanko, 1990).

Stoff and Gale (1981) found that PEA (75 mg/kg) inhibited chlorpromazine-stimulated tyrosine hydroxylase activity by 50% (Stoff & Gale, 1981). At a dose of 150 mg/kg of PEA, activation of the enzyme by chlorpromazine was inhibited by 100%. PEA was 10 times less potent than amphetamine in this regard.

Safratowich et al. (2014) studied the effects of PEA in *Caenorhabditis elegans* (Safratowich et al., 2014). The researchers found that PEA activated the dopamine transporter and the amine-activated chloride channel LGC-55.

In addition to *in vivo* animal studies, the effects of PEA have also been examined in several *in vitro* studies. These effects are summarised in Table16.

Table16: *The effects of PEA studied in vitro (table continued on the next page)*

Effect	**Concentration**	**Cell type/tissue**	**Reference**
Activation of TAAR1 receptor, allosteric inhibitor of beta-adrenergic receptors	10 mM	Human embryonic kidney cells (HEK293)	(Kleinau et al., 2011)
Activation of TAAR1 and uptake of PEA by the dopamine transporter	10 nM – 1 µM	HEK293 cells	(Bunzow et al., 2001; Miller et al., 2005; Babusyte et al., 2013)
Vasoconstriction, increased release of noradrenaline	1–30 µM	Mesenteric blood vessels from rats	(Narang et al., 2014)
Vasodilation of blood vessels pretreated with phenylephrine	0,1 nM-3 µM	Mesenteric blood vessels from rats	(Anwar et al., 2012)
Reduced uptake and increased release of neurotransmitters by activation of TAAR1	0,1-1 µM	Synaptosomes from monkey and mouse brains	(Xie & Miller, 2008)
Increased release of noradrenaline, dopamine and serotonin and contraction of resistance arteries	0.2-0.9 µg/ml	Pulmonary arteries and resistance arteries of rabbits	(Knoll et al., 1996)
Increased noradrenaline release	3-100 µM	Atrial sections from rats	(Benkirane et al., 1986)

Effect	Concentration	Cell type/tissue	Reference
Increased dopamine release	100 µM	Kidney cells and neuronal cells from *C. Elegans*	(Hossain et al., 2014)
Activation and inactivation of alpha receptors (IC_{50} of 7.25 and 8.5 for alpha-1 and alpha-2)	Activation: 500 µM	HEK293 cells and Chinese ovarian cells isolated from hamsters (CHO)	(Ma et al., 2010)
Reduction of *E. Coli* bacteria on steak	1.5-150 mg/ml	Steak	(Lynnes et al., 2014)
Inhibition of glycine transport	Ki: ,.35 mM	Red blood cells from pigeons	(Kittams & Vidaver, 1969)
Bronchoconstriction	1 µM-100 mM	Lung tissue from guinea pigs	(Hawthorn et al., 1985)
Stimulation of inositol phosphate production	1 µM-100 mM	Cortical sections from rats	(Dyck & Boulton, 1989)
Inhibition of quinpirole-induced reduction of dopamine	0-1 µM	Striatum from rats	(Yamada et al., 1998)

N,N-DMPEA
N,N-DMPEA (N-beta-dimethylphenetylamine) is a substance in the phenetylamine class. It is an alkaloid that was first isolated from an orchid (*Eria jarensis*). N,N-DMPEA is mainly used as flavouring in cereals, cheese, fish and meat (Burdock, 2016). Structurally, N,N-DMPEA very similar to amphetamine (Figure 8). However, compared to amphetamine, it contains 2 methyl groups at a different site in the molecule. As a result, its pharmacological properties are expected to differ as well. The extra methyl groups make a molecule more lipophilic, making it easier for it to cross the blood-brain barrier. Amphetamine is an agonist of the TAAR1 receptor. N,N-DMPEA is also expected to be an agonist of the TAAR1 receptor, which may result in stimulating effects. For this reason, it is also used in supplements for bodybuilders. There are several supplements on the market that contain *Eria jarensis* as an ingredient. These supplements therefore contain, among other things, N,N-DMPEA.

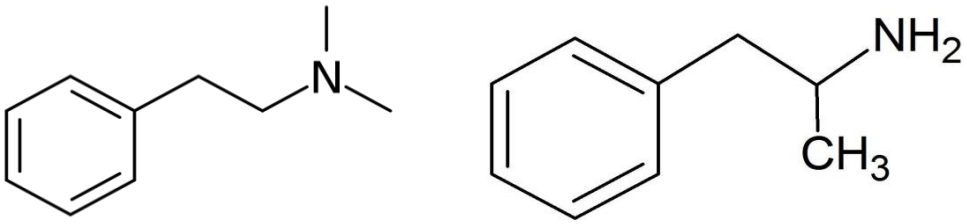

Figure 8. *Chemical structures of N,N-DMPEA (left) and amphetamine (right).*

Kinetics
Shinotoh et al. (1987) studied the kinetics of radiolabelled N,N-DMPEA in mice and humans (Shinotoh et al., 1987). In mice, N,N-DMPEA was administered intravenously and was rapidly absorbed into various organs (mainly kidneys, brain and lungs). A peak was seen in the brain 1 minute after injection. The researchers found that N,N-DMPEA was metabolised by monoamine oxidase B (MAO-B). After administration of an MAO-B inhibitor, radioactivity remained elevated for more than 60 minutes. There was also a rapid increase in the human brain within 4-6 minutes of intravenous administration.

Haalldin et al. (1989) also studied the kinetics of N,N-DMPEA in monkeys (Halldin et al., 1989). Following intravenous administration, they observed a peak in the monkeys' brain within 3-5 minutes, which then fell to zero within 60 minutes.

Inoue et al. (1985) found that N,N-DMPEA is a substrate for MAO-B in the brain of mice in both *in vitro* and *in vivo* studies (Inoue et al., 1985). After administration of the MAO-B inhibitor 1-deprenyl, less of the radioactive metabolite dimethylamine was formed. However, when the MAO-A inhibitor clorgyline was added, this effect was not visible.

Dynamics
Liu et al. (2016) studied the effects of N,N-DMPEA on the activity of CYP2D6 and CYP3A4 (Liu & Santillo, 2016). They found that N,N-DMPEA inhibited CYP2D6 activity with an IC_{50} of 5.9 µM. 100 µM of N,N-DMPEA further inhibited CYP3A4 activity by 29.8%. As such, it could alter the effects of medicines metabolised by these 2 enzymes.

Lewin et al. (2008) found that N,N-DMPEA binds to the TAAR1 receptor in RD-HGA16 cells. These are Chinese ovarian cells from hamsters transfected with human TAAR1 receptor (Lewin et al., 2008). However, it had a much lower affinity than N,N-DMPEA (EC_{50}: 100 µM compared with 129 nM).

Glennon et al. (1989) studied the binding capacity of N,N-DMPEA to the serotonin receptor (5-HT 1A receptor) in rat striatal membranes (Glennon et al., 1989). They measured the receptor's ability to move radiolabelled DPAT and found that N,N-DMPEA was able to bind to the receptor.

One case is known where supplementation with a supplement containing N,N-DMPEA led to a brain haemorrhage in a Swedish female athlete (Cohen et al., 2015b). Forty-five minutes after starting training, she experienced numbness and clamminess in her left hand. She ended up in hospital with a brain haemorrhage. In addition to N,N-DMPEA, the supplement also contained PEA, BMPEA and caffeine.

In 2008, the World Health Organisation (WHO) conducted a study on the safety of flavourings (WHO, 2008). WHO concluded that ingestion of N,N-DMPEA as a flavouring in the quantities in which it is present in food poses no health risk. This equated to a daily dose of 0.0002 µg/kg body weight (in Europe).

Halostachine
Halostachine is a natural substance belonging to the group of alkaloids. It is present in *Halostachys caspica*, an Asian shrub (Symeva, 1941). Extracts of this shrub are used as ingredients in food supplements. In addition, halostachine is present in *Lolium perenne* and *Festuca arundinacea* (Aasen et al., 1969; Bush & Jeffreys, 1975). Halostachine can be synthesised from acetophenone or benzene and formed in the human body by the conversion of phenylethanolamine to n-methylphenylethanolamine by the enzyme N-methyltransferase (Saavedra & Axelrod, 1973).

On the basis of its structure, it can be concluded that halostachine is very closely related to synephrine (Figure 9). Compared with halostachine, synephrine has an additional hydroxyl group attached to the benzene ring. As a result, its affinity and effectiveness for adrenergic receptors will be slightly different. For example, the affinity and effectiveness of synephrine for beta-2 adrenergic receptors are somewhat higher than those of halostachine. On the basis of structural similarity, halostachine is expected to share functional properties with synephrine.
For example, halostachine is known to be a beta-adrenergic agonist, like synephrine (Ambrosio et al., 2005; Katritch et al., 2009). Both substances appear unable to fully activate the beta-2 adrenergic receptor, making them partial agonists (Liapakis et al., 2004). The researchers showed that halostachine had a similar affinity and effectiveness for the beta-2 adrenergic receptor as synephrine. When 2 hydroxyl groups were added to halostachine (producing adrenaline), the substance changed from a partial to a full agonist for the beta-2 adrenergic receptor. In addition to beta-adrenergic receptors, halostachine is also able to activate alpha-adrenergic receptors. This can lead to increased blood pressure, among other things.

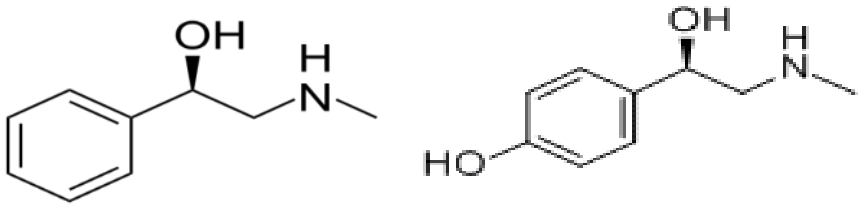

Figure 9. *Chemical structures of halostachine (left) and synephrine (right).*

Kinetics
The kinetics of halostachine in humans has not been studied. Shannon et al. (1981) did study the pharmacokinetics of halostachine in dogs (Shannon et al., 1981). After intravenous administration, halostachine was found to be metabolised by monoamine oxidase (MAO). The pharmacokinetics is described by a bi-exponential function with a half-life of approximately 30-60 minutes.

Suzuki et al. (1980) found that halostachine is a substrate for monoamine oxidase B (MAO-B) (Suzuki et al., 1980). In mitochondria isolated from rat brain, it was found that in a concentration of 10 µM halostachine was a substrate specific for MAO-B, whereas in higher concentrations (100 and 1000 µM) it was also bound by MAO-A.

Inoue et al. (1984) found that halostachine was metabolised by MAO-B (Inoue et al., 1984). Following intravenous administration of radiolabelled C_{14} halostachine, an MAO-B inhibitor inhibited the conversion of the halostachine.

Dynamics
Lands and Grant reported an LD_{50} of 44 mg/kg when halostachine was administered intravenously in mice. Intraperitoneal administration resulted in an LD_{50} of 144 mg/kg (Lands & Grant, 1952). In another study, these researchers found an LD_{50} of 490 mg/kg in mice following intraperitoneal administration (Lands, 1952).

Chen et al. (1929) found a minimum lethal dose of 100 mg/kg (administered intravenously) in rabbits (Chen et al., 1929).

Barger and Dale (1910) studied the blood pressure effects of halostachine in cats and compared them with the blood pressure effects of phenylethanolamine (Barger & Dale, 1910). They found that halostachine (administered intravenously) increased blood pressure in a similar degree to phenylethanolamine.

Chen et al. (1929) found that intravenous administration of 1 mg (equivalent to 6 mM) of halostachine increased blood pressure by 26 mm Hg in cats (Chen et al., 1929). This effect was found to equal 50% of the effect of phenylethanolamine in the same dose. The researchers further found that a drop of halostachine (0.05 mol/l) in the eye of rabbits could cause dilation of the pupil. This effect was 5 times stronger than that of phenylethanolamine in the same dose.

Lands and Grant (1952) found that intravenous administration of 0.41 mg/kg in dogs produced an increase in blood pressure of 38 mm Hg (Lands, 1952; Lands & Grant, 1952). They compared this effect with that of ephedrine, and found that the hypertensive effect of halostachine was 0.5% of the hypertensive effect of ephedrine (in the same dose).

Aasen et al. (1969) studied the effects of halostachine in sheep and guinea pigs (Aasen et al., 1969). They found that intravenous administration of halostachine (30 mg/kg) led to dilation of the pupils. Further increase of the dose to 100 mg/kg induced a state of arousal/excitement. In guinea pigs, intraperitoneal administration of 30 mg/kg led to restlessness. Increasing the dose to 100 mg/kg led to an increase in heart rate and respiration rate, muscle tremors, pupil dilation, an increase in saliva production and hair standing on end.

Shannon et al. (1981) studied the effects of intravenous administration of halostachine (6-18 mg/kg) in dogs (Shannon et al., 1981), and found that halostachine induced dilation of the pupils. Other effects found were a decrease in heart rate (the higher the dose, the smaller the effect), a decrease in body temperature, hair standing on end and increased saliva production. The authors conclude that pupil dilation is a consequence of alpha receptor activation.

Liapakis et al. (2004) studied the affinity of halostachine for the beta2-adrenergic receptor in human embryonic kidney cells (HEK293) (Liapakis et al., 2004). The affinity was measured on the basis of adenylyl cyclase activation, in which cAMP is formed. Halostachine was found to be a partial agonist for these receptors, with

an efficacy equal to 19% of that of adrenaline (-log EC50 was 4.73 versus 7.00 for adrenaline). The efficacy of halostachine was similar to that of synephrine.

Yao et al. (2006) found that halostachine is a weak partial agonist for the beta-2 adrenergic receptor (Yao et al., 2006). They studied this using fluorescent spectroscopy, examining the ability to activate the beta-2 adrenergic receptor. Halostachine was found to induce a response that was 50% of the response of isoproterenol.

Halostachine is a substrate for MAO (Suzuki et al., 1980; Inoue et al., 1984). This implies that interactions may occur between halostachine and MAO inhibitors, with potentially negative effects.

Higenamine

Higenamine (Figure 10), also known as norcoclaurin, is a compound that occurs naturally in several Asian plant species, including *Nandina domestica* (mainly in the fruit) (Tsukiyama et al., 2009; Ueki et al., 2011), *Nelumbo Nucifera* (mainly in the seeds) (Kashiwada et al., 2005), Argemone mexicana (Chang et al., 2003), *Magnolia salicifolia* (Kimura et al., 1989), *Aconitum carmichaelii* (mainly in the root) (Bai et al., 2008), *Tinospora crispa* (Praman et al., 2012) and *Coptis japonica* (Minami et al., 2007). Higenamine is found in relatively high concentrations in the fruit of *Nandina domestica Thunberg* of the *Berberidaceae* family. Higenamine is a benzyltetrahydroisoquinoline. It has a molecular weight of 237.31 g/mol. Derived from various Asian plants, higenamine has been part of traditional Chinese medicine for centuries. Extracts of Aconite (*Aconitum carmichaelii*) were commonly used as a traditional medicine to combat fever, asthma and high blood pressure, among others.

Higenamine is mainly known as an ingredient in food supplements, in which it is mainly used as a fat burner. A distinction can be made between the natural and synthetic forms of higenamine. No studies have yet been conducted that compare the safety of these two forms. In the world of professional sports, higenamine has been banned by the World Anti-Doping Agency (WADA).

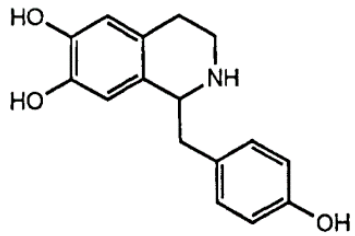

Figure 10. *Chemical structure of higenamine.*

Kinetics

Feng et al. (2012) conducted a study with healthy Chinese volunteers who received continuous intravenous higenamine injection at gradually increasing doses of 0.4 to 4 µg/kg/min. Each dose was administered for 3 minutes (Feng et al., 2012). Peak plasma concentrations ranged from 15.1 to 44 ng/ml. A half-life of 0.133 hours was found, while the Area Under the Curve (AUC) was 5.39 ng/h/ml. Total clearance was 249 L/h, with 9.3% of administered higenamine recovered in urine within 8 hours. The pharmacokinetics of higenamine is described using a two-compartment model with non-linear clearance.

Lo et al. (1996) conducted a similar study in rabbits, in which higenamine was administered intravenously or orally in food (Lo & Chen, 1996). The plasma higenamine concentrations dropped quite rapidly, with a half-life of 22 minutes. The higher the dose administered, the greater the AUC, while the percentage of unchanged higenamine excreted in the urine remained constant. Total body clearance, mean time of higenamine presence in the body, volume of distribution and urinary excretion faction were 127.7 mL min-1 kg-1, 9.28 min, 1.44 kg-1, and 5.48% respectively (Lo & Chen, 1994). The percentage of protein-bound higenamine in plasma was 54.8% after intravenous administration. After oral administration, higenamine was rapidly absorbed, reaching peak concentration within 10 minutes. It is noteworthy that 2 groups of rabbits could be distinguished

in terms of plasma concentration-time curves, Cmax, degree of absorption and excretion differed between the 2 groups. AUC and urinary excretion were 21.86 and 2.84% versus 20.19 and 5.50% respectively for the 2 groups. These differences can probably be explained by differences in absorption and metabolism. For example, the enzyme glucuronidase probably plays a major role in this. Differences in the activity of this enzyme can therefore cause differences in metabolism (Lo & Chen, 1996).

Zheng Ying-li et al. (2004) conducted a pharmacokinetic study in dogs (Zheng Ying-Li et al., 2004). After intravenous administration of a single dose of 10 mg/kg, they found a half-life of 8.6 minutes, a clearance of 0.13 L/min/kg and an AUC of 0.076 mg/min/L. Also in dogs, the pharmacokinetics of higenamine is described using a two-compartment model.

Dynamics
In mice, an LD_{50} of 300 mg (p.o.), 3.35 mg (i.p.) and 58.9 mg (i.v.) was found. (Zhou Yuanpeng, 1992; Zhang et al., 2017).

Lo and Chen (1996) studied the effects of higenamine on 240 mice. An LD_{50} of 50 mg/kg body weight was found for intravenous administration. Following intravenous administration of 60 mg/kg body weight, most mice died. However, following oral administration of higenamine in a dose of 2.0 g/kg body weight, all mice survived (Lo & Chen, 1997).

In histopathological examinations in dogs, after i.v. administration of 10 µg/kg body weight for 14 days no changes were seen in the liver, kidneys, heart, lungs, brain, electrocardiogram or heart rate. In rats, the same functions were studied after i.p. administration of 30 mg/kg bw for 30 days, where no effects were found either. Nor were any mutagenic effects found in rats or teratogenic effects in mice and rabbits (Zhang et al., 2017).

A human study into the tolerability of higenamine showed that i.v. administration of higenamine at 22.5 µg/kg bw did not produce any adverse effects in healthy individuals nor in cardiac patients (Du Yan-rong et al., 2007; Zhang et al., 2017). In this study, the researchers measured blood pressure and heart rate and looked at electrocardiography. The main side effect that occurred was dizziness (in 16% of cases). One person complained of nausea. However, other studies report side effects such as dry mouth, chest pain and headaches.

A recent study included 48 healthy volunteers who took higenamine orally with or without caffeine. The volunteers took 1 to 3 capsules of 50 mg higenamine per day. The average body weight in this group was 89 kg. Administration of higenamine for 8 weeks was found to have no significant effects on heart rate, blood pressure, liver enzymes, lipid content and urine, as measured by a complete urinalysis (Bloomer et al., 2015a).

Another study examined the pharmacokinetic and pharmacodynamic effects of intravenous administration of higenamine (0.5 to 4.0 µg/kg bw) (Feng et al., 2012). In 10 subjects, no effects were found on heart rate and blood pressure. The only side effect mentioned was dizziness.

Jeter et al. (2015) describe a case of a 22-year-old man who developed rhabdomyolysis and compartment syndrome after taking a supplement containing higenamine (JACK3D micro). Rhabdomyolysis is a painful and life-threatening disease in which the muscles are broken down (Jeter et al., 2015b). The man experienced more pain than usual. Two days later, the pain was so severe that he called the emergency room. No kidney damage was detected. The pain persisted for 3 months, after which it diminished and finally disappeared.

Liu and Santillo (2016) found that higenamine is a strong inhibitor of the enzyme CYP2D6 (with an IC_{50} of 0.14 ± 0.01 µM) (Liu & Santillo, 2016). It also inhibited CYP3A4 at high concentration (100 µM). Both these enzymes are involved in the metabolism of many different medicines, with potential interactions between substrates of both enzymes and higenamine.

Several *in vitro* and *in vivo* studies have found pharmacological effects of higenamine. Higenamine is a beta-1 and beta-2 receptor agonist. Stimulation of beta-1 receptors can increase the heart rate and cardiac contraction. Stimulation of beta-2 receptors can lead to bronchodilation through relaxation of smooth muscle cells in the trachea, increased aortic dilation and relaxation of the corpus cavernosum in the penis. Furthermore, several studies show that higenamine inhibits platelet aggregation, has antioxidant and anti-inflammatory activity as well as a protective effect under ischaemic conditions. Finally, some studies show that higenamine inhibits acetylcholine release in motor neurons. Here, too, the beta receptors play an important role. Table 17 presents a summary of the potential clinical effects of higenamine.

Table 17. *(Potential) clinical use of higenamine (table continued on the next page).*

Disease	**Subject/dose**	**Proposed mechanism**	**Reference**
Coronary artery disease	Humans, 22.5 µg/kg, i.v.	Positive chronotropic and ionotropic effect	(Feng et al., 2012)
Bradyarrhytmia	Humans, 2.5 mg/kg, i.v.	Slow channel activation AV nodal conduction improvement Improve function of the sinus node Heart rate increase	(Liu et al., 1983)
Heart failure	Guinea pig, 10 µg/kg, i.v.	Positive ionotropic effect Vascular dilatation	(Zhang et al., 2017)
Ischemia-reperfusion injury	Rat, 1-10 mg/kg, i.p.	Antioxidant effect Anti-apoptosis Reduced platelet aggregation Vascular dilatation	(Lee et al., 2006; Liu et al., 2015b; Wu et al., 2015)

Disease	Subject/dose	Proposed mechanism	Reference
Disseminated intravascular coagulation	Rat, 10-50 mg/kg, p.o.	Positive ionotropic effect Anti-thrombosis Relaxation of smooth muscle cells Inhibition of iNOS and NO	(Yun-Choi et al., 2001; Yun-Choi et al., 2002; Pyo et al., 2007)
Sepsis	Dog, 0.42 mg/kg, i.v. Mouse, 10-20 mg/kg, i.p. Rat, 50 mg/kg, i.p.	Inhibition of platelet aggregation Positive ionotropic effect Vasodilation	(Kang et al., 1999; Park et al., 2006; Zhang et al., 2017)
Erectile dysfunction	Rat, 0.5-2 µg/kg, i.v.	Relaxation of corpus cavernosum	(Kam et al., 2012)
Spinal cord injury	Mouse, 5-15 mg/kg, i.p.	Stimulation of locomotor function Stimulation M2 macrophage activation	(Zhang et al., 2014d)
Arthritis	Rat, 30 mg/kg, i.p.	Radical scavenging Inhibition of lipid peroxidation	(Zhang et al., 2017)
Bronchoconstriction diseases	Guinea pig, 2 mg/kg, i.p.	Relaxation of airways	(Tsukiyama et al., 2009; Ueki et al., 2011)

Liu et al. (1983) administered an intravenous injection of higenamine 2.5 mg in 100 ml solution at an infusion rate of 15-25 µg/min for 10-60 minutes to 15 patients with cardiac disease (Liu et al., 1983), resulting in an increase in left ventricular ejection fraction and heart rate from 45% to 63%.

Lee et al. (2013) studied the effects of oral intake of a food supplement containing both higenamine and caffeine in 16 healthy volunteers (Lee et al., 2013a). The supplement was found to stimulate energy consumption and fat burning. In addition, an increased heart rate (by 3 beats per minute, on average) and increased blood pressure (by about 12 mm Hg) were found. However, based on the literature, it was concluded that it was mostly caffeine, rather than higenamine, that produced these effects.

Feng et al. (2012) found that after administration of 22.5 µg/kg bw of higenamine, the heart rate increased rapidly (Feng et al., 2012). The maximum increase was by 76 beats per minute. Thirty minutes after higenamine administration, blood pressure was found to have returned to its pre-administration level. Moreover, hardly any side effects were seen.

Wei et al. (2015) studied the effects of a water extract of shenfu decoction as adjuvant therapy in 40 patients with chronic heart failure (Wei et al., 2015a). This extract was taken orally and contained, among other substances, higenamine and ginsenosides. The shenfu contained 10 grams of an extract of aconite root, which contains higenamine. The treatment improved the patients' quality of life and repaired liver damage.

Vascular and tracheal effects

Praman et al. (2012) found that higenamine reduced blood pressure and increased heart rate in rats (Praman et al., 2012). They isolated higenamine from a *Tinospora crispa* extract, traditionally used in Thai and Indonesian medicine for, among other things, the treatment of high blood pressure, and gave it intravenously to the rats in doses of 0.001-0.3 mg/kg bw. This effect could be inhibited by the beta-1 selective blocker atenol and the beta-2 selective blocker ICI-118,551 (Praman et al., 2013).

Liu et al. (2015) found that higenamine (10 mg/kg, i.p.) reduced intestinal ischaemia-reperfusion injury in mice by increasing HO-1 protein levels and activity and as a result of decreased inflammatory cytokine expression (Liu et al., 2015b).

Wu et al. (2015) found that higenamine (10 mg/kg, i.p.) in mice reduced the size of myocardial infarction (Wu et al., 2016b).

Kam et al. studied the effects of higenamine in rats (Kam et al., 2012). Intravenous administration of low doses (0.0005 mg/kg to 0.002 mg/kg bw) produced no changes in either blood pressure or heart rate. A dose of 10 µM induced a 92.5% relaxation of the corpus cavernosum. Propanolol was able to inhibit this relaxation. This means that here too the effects of higenamine are induced via the beta-2 receptor. The effects of higenamine may be enhanced when it is combined with phosphodiesterase-5 (PDE-5) inhibitors.

Yu et al. (2013) studied the effects of racemic higenamine on 40 rabbits, half of which had a damaged sinus node. Intravenous administration of 0.04 mg/kg led to an improvement in sinus-atrial and atrioventricular conduction (Yu et al., 2013).

Kimura et al. showed that higenamine has in *vivo* and *in vitro* inotropic and chronotropic effects (Kimura et al., 1989; Kimura et al., 1994). Higenamine increased the heart rate and the force of contraction of the heart in a concentration-dependent manner. These effects were determined on isolated atria from mice and were caused by activation of the beta-1 adrenergic receptors. The beta-1 blocker propanolol was able to block these effects, whereas the beta-2 blocker butoxamine was not (Kimura et al., 1996).

Chang et al. (1994) showed that higenamine increased both heart rate and isometric tension and cAMP levels in rat hearts (Chang et al., 1994). In addition, higenamine (3 µM) relaxed rat aortic rings contracted with phenylephrine, with greater potency than papverine and GS 389, two other benzylisoquinoline compounds.

Tsukiyama et al. (2009) showed that higenamine is a beta-2 adrenergic agonist. In an *in vitro* study, the authors made an extract of *Nandina* and measured its

affinity for the beta-2 adrenergic receptor in tracheal cells. The extract, containing 49% higenamine, was found to have an EC_{50} value of 47.6 ng/ml for the receptors (Tsukiyama et al., 2009). In isolation, higenamine had an EC_{50} value of 23.33 ng/ml. Synthetic higenamine was found to have a slightly higher EC_{50} value than higenamine extracted from *Nandina*.

Park et al. (1984) found the same positive ionotropic effects of higenamine on isolated hearts of rabbits (Park et al., 1984). The beta-blocker propanolol blocked these effects.

Yu et al. (1985) studied the effects of higenamine on the action potential of ventricular myocardial cells from pig hearts (Yu et al., 1985). The anatomy and function of these cells appear to be similar to those in humans. Higenamine was found to increase the amplitude and duration of the plateau phase of the heart. These effects could be inhibited by administration of manganese, a blocker of the slow channels. Higenamine was also able to reactivate the inactivated sodium channels. It was concluded that higenamine can activate the slow channels leading to an increase of inflow into the slow channels. This suggests that *in vivo* higenamine may counteract decreased heart rate (bradycardia).

Wong et al. (1997) conducted an *in vitro* study with isolated rat aortas to determine the concentration dependence of the vasodilatory effects of higenamine (Wong et al., 1997). Higenamine-induced vasodilation could only be partially blocked by beta-receptor blocker propranolol. The vasodilatory effects were endothelium-dependent.

In addition to relaxation of the blood vessels, higenamine also plays a role in the relaxation of the trachea. Bai et al. (2008) showed that higenamine-induced relaxation of the trachea was concentration-dependent (Bai et al., 2008). Even concentrations as low as 1 nM were found to stimulate relaxation.
Again, propanolol was able to block the effects of higenamine. Tsukiyama et al. (2009) reported that the beta-2 receptors are involved in these effects of higenamine on the trachea (Tsukiyama et al., 2009). Addition of the beta-2 selective antagonist IC 118,551 competitively inhibited the effects of higenamine. The beta-2 receptors thus play an important role in the higenamine-induced relaxation of tracheal smooth muscle.

Ueki et al. (2011) found that higenamine in isolated guinea pig tracheas induced bronchodilation through stimulation of the beta-2 receptor (Ueki et al., 2011). Calvert et al. (2015) found that higenamine (31.3 ng/ml or 313 ng/ml) increased the number of beats per minute in a beating human cardiomyocyte cell line. Combined addition of caffeine and higenamine had a greater effect (Calvert et al., 2015).

Anti-thrombotic effects
In vivo, an anti-thrombotic effect was also found in mouse and rat thrombosis models after oral intake of a higenamine concentration of 50-100 mg/kg bw. This study found an increased recovery rate after acute thrombosis. A similar effect was found in a rat model of diffuse intravascular coagulation after oral administration of 10-50 mg/kg bw of higenamine (Yun-Choi et al., 2001; Yun-Choi et al., 2002).

Yunchoi et al. (2001) showed that higenamine had an inhibitory effect on platelet aggregation induced by adenosine diphosphate (ADP), collagen and adrenaline in humans and rats (Yun-Choi et al., 2001). The effects were greatest on adrenaline-induced aggregation.

Pyo et al. (2007) showed that in blood taken from rats and humans, higenamine had an anti-platelet aggregation effect through inhibition of arachidonic acid (Pyo et al., 2007). The researchers found an IC_{50} of 140 µM and established a direct effect of higenamine on TA receptors. These are the receptors to which the metabolite of arachidonic acid, thromboxane A2, binds to induce platelet aggregation. Given the IC_{50} of 2,990 µM, the bond was rather weak.

Anti-oxidative effects

Lee et al. (2006) showed that higenamine (1 mg/kg, 5 mg/kg and 10 mg/kg) inhibited the oxidation of cytochrome C by peroxynitrite (Lee et al., 2006). Furthermore, the authors found that *in vivo* administration of higenamine (5 mg/kg and 10 mg/kg bw, intravenous bolus injection) in rats reduced the release of caspase-3 activity and increased the ratio of bcl-2/bax expression (Lee et al., 2006). Higenamine increased the expression of bcl-2 and HO-1 as well as HO enzyme activity in a concentration-dependent manner. These effects were important in protecting against ischaemia/reperfusion-induced damage.

Ha et al. (2012) found that higenamine is further able to protect cardiomyocytes from oxidative stress induced by H_2O_2 through the reduction of reactive oxygen radicals and stimulation of antioxidant systems (hemeoxygenase-1 (HO-1) activity) (Ha et al., 2012).

Wu et al. (2015) found that higenamine has anti-apoptotic effects through stimulation of the β2-AR/PI3K/AKT signalling pathway via the beta-2 adrenergic receptor (Wu et al., 2016b). They found that PI3K inhibitors and beta-2 antagonist inhibited the anti-apoptotic effects of higenamine.

Chen et al. (2013) found that higenamine protected cardiomyocytes from the toxic effects of doxorubicin by activating the PI3K/Akt signalling pathway (Chen et al., 2013).

Anti-inflammatory effects

Zhang et al. (2014) found that higenamine (10 mg/kg intraperitoneal) induced inhibition of Cd4+ expression, CD8 on T lymphocytes, inhibition of Ly6 G+ neutrophils and CD11b+ macrophages in mice (Zhang et al., 2014d). In addition, higenamine stimulated the expression of IL-4, IL-10 and stimulated M2 macrophage activation. These results show that higenamine also has a clear immunomodulatory effect.

Park et al. (2006) found that administration of 10 mg/kg of S-higenamine led to a decrease in serum NO concentration from 88 µM to 28 µM (Park et al., 2006). (-68%). R-higenamine required a higher dose (20 mg/kg) to achieve the same effect. These are downstream effects resulting from a reduction of iNOS activity due to inhibition of NF-κB and decrease of serum NO levels by higenamine.

Kang et al. (1999) found that higenamine in a dose of 10 mg/kg increased the survival rate of rats exposed to lipopolysaccharide (LPS), a substance used to induce inflammation.

Higenamine also has anti-inflammatory effects. Kang et al. found that higenamine inhibited NO production and iNOS expression in LPS and IFNγ-stimulated macrophages by inhibiting NFκB pathway activation (Kang et al., 1999).

Park et al. (2006) found an IC_{50} value of 53.4 µM of higenamine for the inhibition of LPS-induced nitrite accumulation in macrophages (Park et al., 2006).

Chen et al. (2016) found that higenamine could bind directly to TNFa and thereby prevent TNFa-induced cell death in L929 cells (Chen et al., 2016a).

Lee et al. (1999) found that higenamine in peritoneal macrophages isolated from mice inhibited lipopolysaccharide-induced expression of iNOS and thus has anti-inflammatory effects (Lee et al., 1999).

Other effects

Ha et al. (2012) found that intraperitoneal administration of higenamine reduced the size of cerebral infarction and prevented mortality in MCAO rats, which is a rat model for cerebral infarction (Ha et al., 2012). 10 mg/kg was found to significantly reduce infarct size. This suggests that higenamine has a protective effect under ischaemic conditions.

An et al. (2017) studied the effects of higenamine (10 mg/kg bw, i.v.) in a rat model of diabetes gastroparesis (An et al., 2017). Higenamine not only inhibited apoptosis, but also improved stomach-emptying ability in these rats. In addition, it was found to stimulate proliferation of the smooth muscle cells in the stomach. The researchers concluded that activation of the β2-AR/PI3K/AKT pathway plays an important role in these effects.

Duan et al. (2016) found that higenamine (10 mg/kg) reduced disease progression in a mouse model of arthritis (Duan et al., 2016). It also reduced inflammatory reactions, oxidative damage and caspase-3/9 activation. Furthermore, higenamine stimulated HO-1 protein expression and the PI3K/Akt/Nrf-2 signalling pathway.

Nojima et al. (1999) showed that higenamine at a concentration of 10 µM stimulated the release of acetylcholine in motor neuronal cells isolated from mice (Nojima et al., 2000). This effect was blocked by propanolol, a beta-adrenergic receptor antagonist. Higher concentrations (30-100 µM) inhibited the release of acetylcholine in stimulated motor neurons. This suggests a peak efficacy concentration of 10-30 µM for higenamine.

Shin et al. (1999) determined the effects of higenamine on dopamine concentrations in PC12 neuronal cells (Shin et al., 1999). At a concentration of 20 mM, higenamine reduced dopamine concentrations by 52%. The IC_{50} was 18.2 mM. This inhibition may be explained by inhibition of tyrosine hydroxylase, which converts L-DOPA to dopamine.

Kato et al. (2017) found that higenamine stimulated glucose uptake in L6 cells (skeletal muscle cells) via the beta-2 adrenergic receptor (Kato et al., 2015; Kato et al., 2017).

Liu and Santillo (2016) found that *in vitro*, higenamine is a strong inhibitor of the enzyme CYP2D6 (with an IC_{50} of 0.14 ± 0.01 µM) (Liu & Santillo, 2016). It also inhibited CYP3A4 at high concentration (100 µM).

Liu et al. (2000) found that higenamine inhibited sodium uptake and stimulated potassium and calcium secretion in the distal colon of guinea pigs (Liu et al., 2000). These effects were blocked by beta-2 receptor blocker ICI-118,551.

Hordenine

Hordenine is an alkaloid compound belonging to the phenetylamine class and is also known as N,N-dimethyltyramine (Hapke & Strathmann, 1995). It occurs naturally in various plant species that are used as animal feed. In addition, hordenine is present in bitter orange (Nelson et al., 2007; Pellati & Benvenuti, 2007; Sander et al., 2008), barley (Wainwright et al., 1982; Mangino & Scanlan, 1984), snowdrops (Berkov et al., 2011), certain cacti (McLaughlin, 1969; Wheaton & Stewart, 1970) and the plants *Pancratium maritimum* (Berkov et al., 2010), *Polyalthia oblongofolia* (Sashidhara et al., 2009) and *Calligonum azel Maire* (Bannour et al., 2016). Hordenine is also present in plants of the Citrus genus (Servillo et al., 2017). The presence of hordenine in Ginkgo Biloba extracts has recently been demonstrated (Konczol et al., 2016).

Hordenine is chemically related to tyramine and N-methyltyramine. The claimed central nervous system stimulant effect and weight are probably caused by the adrenergic activity of hordenine. It is also suggested that hordenine may activate TAAR1 receptors (Bunzow et al., 2001).

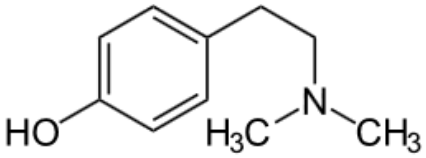

Figure 11. *Chemical structure of hordenine.*

Kinetics

After intravenous administration of 2 mg/kg bw in horses, a maximum plasma value of 1 µg/ml was achieved. This value then decreased in a bi-exponential manner. The alpha phase had a half-life of 3 minutes, and the subsequent beta phase had a half-life of 35 minutes. Total urine concentrations of hordenine (free and bound) peaked at 400 µg/ml. After 24 hours, the urine concentration had returned to normal values (Frank et al., 1990). Oral administration of 2 mg/kg bw produced a maximum plasma value of 0.15 µg/ml 1 hour after administration. This value then decreased in a multi-exponential manner. The total urine concentration (free and bound) after oral administration was 200 µg/ml. After 8 hours, all hordenine had disappeared from the urine. Hordenine is absorbed very slowly from the intestines. As a result, plasma levels remain low and the authors conclude that the oral intake of hordenine is unlikely to produce any pharmacological effect.

Ma et al. (2015) investigated the kinetics of hordenine in rats. Rats were given hordenine orally (15 mg/kg bw) or intravenously (5 mg/kg bw). The bioavailability of hordenine was 66.2% (Ma et al., 2015).

Hordenine is largely deaminated by monoamine oxidase B (MAO-B) (Barwell et al., 1989). Barwell et al. found that hordenine was a selective substrate for MAO-B (derived from rat livers) with a Km of 479 µM and a Vmax of 128 nM/mg protein/h. In addition, a small part is also metabolised by MAO-A.

Four healthy volunteers ingested a hordenine concentration of 0.075 mg/kg bw by drinking beer. After 0-60 minutes, a maximum plasma concentration of 12.0-17.3 nM of unbound hordenine was found. Half-life in plasma was 52.7-66.4 minutes for unbound hordenine and about 60-80 minutes longer for hordenine sulphate and hordenine glucuronide. Urinary excretion peaked 2-3.5 hours after ingestion (Sommer et al., 2020).

Dynamics
In mice and rats, after intra-peritoneal administration an LD_{50} >100 mg/kg was found (Finberg & Gillman, 2011).

There are also some very old studies (from 1906) by Camus on the toxicity of hordenine in different animals. After administration of a parenteral dose, effects such as vomiting, respiratory problems, cramps and paralysis were observed, eventually leading to death (Camus, 1906a). Intravenous administration of several hundred mg of hordenine in dogs and rabbits caused an increase in blood pressure and changes in cardiac rhythm and the strength of cardiac contraction. Oral administration did not produce such effects (Camus, 1906b). Minimum lethal doses were found of 300 mg/kg bw in dogs (intravenous), 2000 mg/kg bw in dogs (oral), 250 mg/kg bw in rabbits (intravenous), 300 mg/kg bw in guinea pigs (intravenous), 2000 mg/kg bw in guinea pigs (subcutaneous) and 1000 mg/kg bw in rats (subcutaneous).

Heffter studied the effect of hordenine on a 2.8 kg cat, administering 0.3 g subcutaneously. He observed no effects except that the cat vomited. After 45 minutes the cat behaved completely normal again. However, when he gave hordenine to frogs, paralysis of the nervous system occurred (Heffter, 1894).

In 1990, Frank et al. studied the effects of intravenous administration of 2 mg/kg bw of hordenine in 10 horses (Frank et al., 1990). Immediately after administration, the horses showed the flehmen response, which is a particular way of smelling when a horse curls its upper lip and stretches its neck to pick up a scent. This lasted for about 60 seconds. Furthermore, they observed that after administration, respiratory problems occurred, with a substantial increase in the respiratory rate (by 250%). They also observed a doubling of the heart rate and increased sweating while the basal body temperature remained unchanged. Within 30 minutes of administration, all symptoms had disappeared. Moreover, these effects were not observed after oral administration.

Goelz et al. (1980) studied the effects of hordenine on mice. They administered hordenine via the feed (in molar equivalents of 0, 0.15, 0.31 or 0.62% of the feed) and observed no clinical morbidity or mortality effects. However, they did detect kidney injury in these mice, with glucose present in the urine (Goelz et al., 1980).

Hapke et al. (1995) found positive ionotropic effects of hordenine on the heart in dogs and rats, observing an increase in cardiac contraction strength, increased blood pressure and increased peripheral blood volumes (Hapke & Strathmann, 1995). They also did experiments with isolated organs and found that hordenine had an indirect adrenergic effect (through the release of noradrenaline). This indirect effect of hordenine has been the subject of further research. For example, Daly et al. concluded that 10 mg of hordenine sulphate had no effect on the

release of noradrenaline. This is in contrast to tyramine and N-methyltyramine, which did show this effect (Daly et al., 1966).

Bourke et al. (1988) studied the effects of hordenine in sheep and found that 20 mg/kg bw (i.v.) and 800 mg/kg bw (p.o.) were the lowest doses (LOAEL) of hordenine that caused clinical signs, such as leg paralysis and tail twitch. The higher the doses, the more prolonged and intense the symptoms (Bourke et al., 1988b).

Barwell et al. (1989) studied the pharmacokinetics and some dynamic effects of hordenine. In contrast to tyramine, hordenine did not cause contraction of the isolated rat vas deferens. However, hordenine (25 µM) did enhance the effect of maximal doses of noradrenaline and also inhibited the effect of tyramine. It was concluded that hordenine inhibits the reuptake of adrenaline in the vas deferens (Barwell et al., 1989).

In 1999, hordenine was found to be capable of stimulating gastrin release in rats. 83 nmol/kg stimulated a release of approximately 60% compared to N-methyltyramine-treated rats where the release was maximal (100%). These effects were similar to those of N-methyltyramine (Yokoo et al., 1999).

Bunzow et al. showed that hordenine (1µM) stimulates cyclic AMP via the rat trace amine receptor (TAAR1) in human embryonic kidney cells (HEK293). Compared to hordenine, tyramine had a higher potency for this effect (Bunzow et al., 2001).

Kim et al. (2013) studied the effects of hordenine on human melanocytes. They found that hordenine (0-100 µM) suppressed melangonese by inhibiting intracellular cAMP synthesis (Kim et al., 2013).

Park et al. (2016) found that hordenine stimulated protein translation in HEK293 cells by binding to nucleophosmin, a protein involved in the regulation of this translation (Park et al., 2017).

Sommer et al. (2017) reports that hordenine is an agonist for dopamine D2 receptors. These receptors play a role in food intake and reward systems (Sommer et al., 2017). In the brain, dopamine acts as a reward signal through activation of the dopamine receptors. The effect of hordenine on this receptor was comparable to that of dopamine (76%).

Konczol et al. (2016) found in an *in vitro* blood-brain barrier model that hordenine from Ginkgo Biloba extracts was able to cross this barrier (Konczol et al., 2016).

Icariin
Icariin is a chemical from the group of flavonoids. It is classified as a prenylated flavonoid glycoside, which is a subclass of the flavonoids. Icariin is a derivative of kaempferol-3,7-O-diglucoside. It is naturally present in plants of the *Epimedium* species, such as horny goat weed or ying yang huo (Ono et al., 1991). In traditional Chinese medicine, extracts from these plants are used for their aphrodisiac, anti-inflammatory and health-promoting effects. (Zhang et al., 2014b). For example, they are used to stimulate erection (Makarova et al., 2007). Icariin is also used to combat osteoporosis, blood pressure and bronchitis.

Based on its structure, it can be concluded that icariin is related to kaempferol, with which it also shares functional properties. Icariin contains a glucosyl group at the C-3 position, a rhamnosyl group at the C-7 position, a methoxyl group at the C-4 position and a prenyl group at the C-8 position. Icariin is known to be a weak phosphodiesterase-5 (PDE-5) inhibitor. In addition, icariin is described in the literature as having antioxidant activity, anti-depressant and anti-Alzheimer effects, stimulating nitric oxide (NO) production and having testosterone-like effects. In addition, it is suggested that icariin has anti-cancer effects.

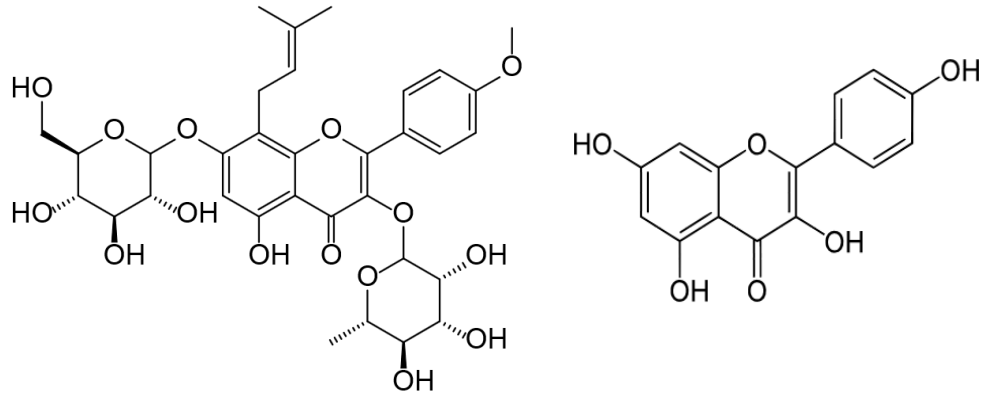

Figure 12. *Chemical structures of icariin (left) and kaempferol (right).*

Kinetics
The pharmacokinetics of icariin has been researched in several studies. Icariin is converted quite quickly after (oral) intake and has a relatively short half-life in the blood. In addition, many different metabolites of icariin have been found.

Xu et al. (2017) studied the pharmacokinetics of icariin after a single oral intake of an extract of *Herba Epimedii* (42 mg/g icariin) in rats (Xu et al., 2017a). After half an hour, a peak concentration (Cmax= ± 80 ng/mL) of icariin was found in the blood. The half-life was 3.1 hours. After about 6 hours, no icariin was detectable in the plasma. The researchers also studied the metabolism of icariin by administering either 20 mg/kg (intramuscular) or 50 mg/kg (oral) to rats. A total of 11 different metabolites were found in the faeces of the rats (10 metabolites after oral intake, 9 after intramuscular administration).

Deng et al. (2009) detected icariin in the plasma of rats after oral intake of Qihuotongqiao pills (Deng et al., 2009). These pills contain, among other substances, the *E. epimedii* extract and are intended for the treatment of Alzheimer's disease.

Li et al. (2009) studied the pharmacokinetic parameters of icariin in rats after ingestion of Gan-Kang granules, a traditional Chinese medicine containing the extracts of 8 different Chinese herbs (Li et al., 2009). The concentration of icariin in the plasma was measured at various times. At approximately 1.56-2 hours after ingestion, the icariin concentration peaked at 3.5 µg/ml. After 24 hours, icariin was almost undetectable.

Wu et al. (2010) studied the distribution of icariin in rats (Wu et al., 2010). After intravenous administration of 10 mg/kg and 20 mg/kg of icariin, it was found to have a half-life in the plasma of 7 and 8 minutes, respectively. The main excretion route was through bile. In bile, icariin had a half-life of 27 minutes (10 mg/kg) and 29 minutes (20 mg/kg). The Cmax values in bile were 91.9 µg/ml and 161.2 µg/ml.

Cheng et al. (2007) studied the pharmacokinetics of icariin in rats (Cheng et al., 2007). After an intravenous injection of 10 mg/kg of icariin, they found a half-life of 0.562 hours, a clearance of 20.1 L/kg/hour and an AUC0 of 8.73 µg*hour/ml.

Cheng et al. (2015) studied the pharmacokinetic parameters of icariin after oral and intravenous administration in rats (Cheng et al., 2015). After oral administration, 91.2% of the icariin was converted to icariside II, compared with only 0.4% after intravenous administration. Moreover, after oral administration the Cmax for icariside II was 3.8 times higher than that of icariin, whereas the Cmax for icariside II was only 12.1% of icariin after intravenous administration.

Sun et al. (2016) studied the metabolic profile of icariin in the faeces, bile and urine of rats after oral administration of 100 mg/kg (Sun et al., 2016). A total of 17 metabolites of icariin were found in the samples. Icariin appears to be metabolised through several reactions, including desugarisation, dehydrogenation, hydroxylation, demethylation and glucuronidation.

Wu et al. (2016) found that icariin is converted to icariside II quite rapidly, before absorption, by the human microflora (mainly the 3 bacteria *Streptococcus sp.* (MRG-ICA-B), *Enterococcus sp.* (MRG-ICA-E), and *Blautia sp.* (MRG-PMF-1), which had been isolated (Wu et al., 2016a). Within a day, all the icariin in the medium was converted to icariside II.

Qian et al. (2012) studied the metabolic profile of icariin after oral administration in rats of 120 mg/kg (Qian et al., 2012). After 60 minutes, 19 different metabolites were detected in the plasma: icariside I, icaritiin, desmethylicaritin and its isomer, icaritin-3-O-gluA, icaritin-7-O-gluA, icariside II and its isomer, icaritin-3,7-di-O-gluA, 1,3-isoprene alcohol icaritin and its isomer, 1,3-isoprene alcohol icariside II, allylic alcohol icaritin and its isomer, 1,3-isoprene icariside II and icaritin-3-O-rha-7-O-gluA.

Dynamics
Xiao et al. (2016) studied the effect of icariin supplementation (300 mg/day) for 8 weeks on 10 people with bipolar disorder, who were depressed and had an alcohol addiction at the time of the study (Xiao et al., 2016). After 8 weeks, there was a significant reduction in several depression scores (HAMD, HAMA and QID-SR). In addition, alcohol use had fallen and no subjects had dropped out due to side effects. Possible side effects mentioned were increased libido, diarrhoea,

headache, insomnia, dry mouth and nervousness. However, these side effects were mentioned only once.

Zhang et al. (2007) conducted a randomised, double-blind, placebo-controlled study into the effect of a flavonoid extract (60 mg of icariin, 15 mg of daidzein and 3 mg of genistein) from the plant *Epimedium* on bone mineral density in 85 healthy menopausal women (Zhang et al., 2007). The extract was administered once daily for 24 months, during which time the women also had to take 300 mg of calcium a day. After 12 months of administration of the extract, mineral density was already found to be higher compared to the placebo treatment. This was measured in the lumbar spine and the femoral neck. No effect was found on plasma oestrogen levels.

Zhang et al. (2015) examined the effects of icariin on mice (Zhang et al., 2015b). Icariin (0.02% in the feed) prolonged the life of the mice by 8%. In addition, icariin improved the behavioural characteristics as tested in the Morris water maze test and improved the physical activity of the mice. In addition, icariin was found to increase the mineral density of the bones. Furthermore, icariin decreased the expression of γ-H2AX and of several genes (23 out of 26 genes studied) related to DNA damage. Finally, icariin was found to increase the expression of superoxide dismutase (SOD) and decrease malonaldehyde (MDA) levels in the liver. The researchers concluded that icariin improved general health characteristics in the mice.

Anti-inflammation

Several animal studies show that icariin has anti-inflammatory effects. These effects have been measured in animals with pneumonia, arthritis and colitis, among others, and are summarised in Table 18.

Table 18: *The anti-inflammatory effects of icariin as demonstrated in animal studies.*

Effect	Dose	Mode of administration	Species	Reference
Reduced inflammatory response in the lungs	20-100 mg/kg	Intragastric, oral	Mouse	(Xu et al., 2010; Li et al., 2014c; Wei et al., 2015b)
Reduced inflammatory response and arthritis score	25 mg/kg	Oral	Mouse	(Chi et al., 2014)
	35 mg/kg	Oral	Mouse	(Sun et al., 2013)
	20 µM	Intravenous	Rat	(Zeng et al., 2014)
Improved clinical score of experimental autoimmune encephalomyelitis and reduced inflammation in lymph nodes	25 mg/kg	Oral	Mouse	(Shen et al., 2015)
Reduced inflammatory response in the colon	30-90 mg/kg	Oral	Rat	(Wang et al., 2016c)

Several *in vitro* studies show that icariin also has (anti-)inflammatory effects. For example, icariin decreased the viability of macrophages (Li et al., 2011a), and reduced the production of several inflammatory markers (TNF-α, IL-6, IL-8, IL-1β,MCP-1 and NF-κB) and the production of inflammatory cells (Th17 cells and monocytes) (Wu et al., 2012b; Chi et al., 2014; Kong et al., 2015). Reduced gene expression levels of these markers and reduced activation of the MAPK signalling pathway were also found.

Icariin also has anti-oxidative effects. For example, several *in vitro* studies show that icariin protects cells from the harmful effects of reactive oxygen radicals and lipid peroxidation (Liu, 2006; Huang et al., 2014b). As a result, icariin prevented cell death in different cell types (endothelial cells and erythrocytes) (Liu et al., 2004; Wang & Huang, 2005). It was also found to increase the expression of the antioxidant enzyme superoxide dismutase.

<u>Osteogenesis</u>
Horny goat weed is used in traditional Chinese medicine against osteoporosis, among other things. The effects of icariin in this field have been examined in several animal studies. Icariin appears to counteract the degradation of bones and even stimulate their mineralisation. In this context, various different parameters have been measured (such as alkaline phosphatase activity and the expression of various osteogenic markers). This has been researched in several studies, which are summarised in Table 19.

***Table 19**. The anti-osteoporosis effects of icariin as demonstrated in animal studies.*

Effect	Dose	Mode of administration	Species	Reference
Increased bone mineral density	20 mg/kg/day for 12 weeks	Intragastric	Rat	(Yang et al., 2014)
	5-125 mg/kg/day for 12 weeks	Oral	Rat	(Nian et al., 2009)
	2.5 mg/kg/day for 4 weeks	Oral	Rabbit	(Wei et al., 2011)
Decreased bone degradation	125 mg/kg/day for 12 weeks	Oral	Rat	(Li et al., 2014b)
	0.1-0.3 mg/g/day for 2 weeks	Oral	Mouse	(Shao et al., 2015)
	250 mg/kg/day for 60 days	Oral	Mouse	(Hu et al., 2017)
Increased bone mass, decreased apoptosis of bone cells and increased alkaline phosphatase activity	5-125 mg/kg/day for 12 weeks	Intragastric	Rat	(Feng et al., 2013)
	0.125 mg/g	Intragastric	Rat	(Ye et al., 2016)
Reduced tooth decay	2.5 mg/kg/day for 3 weeks	Oral	Rat	(Wang et al., 2012)

As well as the various *in vivo* studies, many *in vitro* studies have been conducted on the osteogenic effects of icariin. For an overview of these studies, see Table 200.

***Table 20.** The osteogenic effects of icariin as demonstrated in in vitro studies (table continued on the following pages).*

Effect	Concentration	Cell type	Reference
Stimulation of osteogenesis and expression of osteogenic markers and reduction of oxidative stress	0.1 nM – 10 μM	Mesenchymal stem cells isolated from the femur of patients with osteonecrosis	(Sun et al., 2015)
	10 nM-0.1 mM	Bone marrow stromal cells from rats	(Zhai et al., 2014)

Effect	Concentration	Cell type	Reference
Stimulation of proliferation, osteogenic differentiation, mineralisation and expression of osteogenic markers	10 nM – 1 µM	Stem cells isolated from rat adipose tissue	(Ye et al., 2017)
	1 pM-1 µM	Osteoblasts from rats	(Zhao et al., 2008; Mok et al., 2010; Zhang et al., 2011)
	0-100 nM	Osteoblasts from mice	(Cao et al., 2012; Song et al., 2013)
	0.1 µM	Osteoblasts from rats	(Liu et al., 2017)
	0.1 µM	Bone marrow stromal cells	(Wu et al., 2015; Wei et al., 2016b)
Increased mineralisation, increased viability, expression of osteogenic markers and increased alkaline phosphatase activity	0-1 µM	Human osteoblasts	(Liang et al., 2012)
	1-10 µM	Osteoblasts from rats	(Ma et al., 2011; Ma et al., 2014)
	25 µg/ml, 50 µg/ml and 100 µg/ml	Cytokine-treated fibroblasts from patients with ankylosing spondylitis	(Jia et al., 2014)
Counteracting the inhibitory effects of titanium on mesenchymal stem cell differentiation	0.1-10 nM	Mesenchymal stem cells	(Wang et al., 2016a)
Synergistic effects on osteoblast proliferation, alkaline phosphatase activity and the mineralisation process	Icariin (0,001 nM) ferulic acid (100 nM) timosaponin B (10 nM)	Osteoblasts from rats	(Li et al., 2016a)
Decreased proliferation and differentiation of osteoclasts and stimulation of osteoblast proliferation and differentiation	1 nM-1 µM	Osteoblasts and osteoclasts	(Hsieh et al., 2010; Hsieh et al., 2011)

Effect	Concentration	Cell type	Reference
Stimulating the proliferation and differentiation of mesenchymal stem cells isolated from human bones	1 nM- 1 µM	Mesenchymal stem cells isolated from human bones	(Fan et al., 2011)
Stimulation of proliferation of human periodontal ligament cells and increase of osteogenic markers	0.001-1 µg/ml	Human periodontal ligament cells	(Pei et al., 2013)

In addition to its osteogenic effects, icariin stimulates chondrocyte proliferation, extracellular matrix production (glycosaminoglycans and collagen) in cells and the gene expression of chondrogenic markers (such as aggrecan, sox9 and collagen type II) (Li et al., 2012; Zhang et al., 2012b; Wang et al., 2016b). In addition, icariin protected chondrocytes from lipopylsaccharide (LPS) induced cell death (Liu et al., 2010).

Reproduction

Horny goat weed is also used in traditional Chinese medicine to treat erectile dysfunction and reproductive disorders. The effects of icariin in this field have been studied in 3 animal studies and are shown in Table 21.

Table 21. *The reproductive effects of icariin as demonstrated in animal studies.*

Effect	Dose	Mode of administration	Species	Reference
Increase in sperm cell count	100 mg/kg	Oral	Rat	(Chen et al., 2014)
Increased pressure in the corpus cavernosum	1.5 mg/kg	Intragastric	Rat	(Xu et al., 2017b)
	1-10 mg/kg/day for 4 weeks	Intragastric	Rat	(Shindel et al., 2010)

In vitro studies show that extracts of *Epimedium brevicornum Maxim*, of which icariin is the main component, stimulate the synthesis of oestrogen (Yang et al., 2013). Isolated icariin also appears to have this effect. In addition, icariin increased the protein expression of the oestrogen receptor, VEGF and kinase insert domain receptor (KDR) in endometrial cells (Le et al., 2015). Icariin also inhibits the activity of phosphodiesterase-5 (PDE-5) in smooth muscle cells isolated from the cavernosum (Ning et al., 2006; Li et al., 2014d).

Neurological effects

Many different animal studies have been done on the neurological effects of icariin, as it has been suggested that horny goat weed helps in the treatment of Alzheimer's disease and depression. Table 22 provides a summary of the neurological effects of icariin.

Table 22. *The neurological effects of icariin as demonstrated in animal studies (table continued on the following pages).*

Effect	**Dose**	**Mode of administration**	**Species**	**Reference**
Reduced amyloid-β deposition and increased microglia activation	100 mg/kg/day for 10 days	Oral	Mouse	(Zhang et al., 2014e)
Reduced amyloid-β deposition and reduced cognitive symptoms	10-40 mg/kg twice daily for 23 days	Oral	Rat	(Li et al., 2015d)
Reduced depression-like symptoms following chronic stress	30-60 mg/kg for 4 weeks	Oral	Rat	(Pan et al., 2010; Pan et al., 2013)
	20-40 mg/kg/day for 35 days	Oral	Rat	(Wei et al., 2016a)
	60 mg/kg/day for 21 days	Oral	Rat	(Gong et al., 2016)
	20-40 mg/kg/day for 35 days	Oral	Rat	(Liu et al., 2015a)
	25-50 mg/kg/day for 28 days	Intragastric	Mouse	(Wu et al., 2011)
	15, 30 and 60 mg/kg/day for 5 weeks	Oral	Rat	(Pan et al., 2007)
	35 and 70 mg/kg/day for 6 weeks	Oral	Rat	(Pan et al., 2006)

Effect	**Dose**	**Mode of administra-tion**	**Species**	**Reference**
Improved learning and memory	0-120 mg/kg/day for 3 months	Oral	Rat	(Xu et al., 2009)
	75-150 mg/kg/day for 15 weeks	Oral	Mouse	(He et al., 2010)
	30-120 mg/kg/day for 17 days	Oral	Rat	(Guo et al., 2010)
	60 mg/kg/day for 3 months	Oral	Mouse	(Li et al., 2015a)
	30-100 µmol/kg/day for 6 months	Intragastric	Mouse	(Zhang et al., 2014a)
	30-60 mg/kg twice daily for 4 months	Oral	Mouse	(Jin et al., 2014)
	30-120 mg/kg/day for 14 days	Intragastric	Rat	(Nie et al., 2010)
	50 µmol/kg/day for 8 days	Oral	Mouse	(Urano & Tohda, 2010)
Reduction of infarct size and reduced oedema formation in the brain	50-200 mg/kg/day for 7 days	Intragastric	Mouse	(Zhu et al., 2010)
Improved cognitive functions	30-120 mg/kg	Intragastric	Mouse	(Wang et al., 2013)
	20 mg/kg/day for 3 months	Oral	Rat	(Wu et al., 2012a)
	60 mg/kg/day for 4 months	Oral	Rat	(Li et al., 2010a)

Effect	Dose	Mode of administration	Species	Reference
Improved cognitive functions	17.5 and 35 mg/kg/day for 21 days	Oral	Mouse	(Pan et al., 2005)
Protection against excitotoxicity by ibotenic acid	20-40 mg/kg twice daily for 20 days	Oral	Mouse	(Zong et al., 2016)
Protection from the toxic effects of aluminium	60 and 120 mg/kg/day for 3 months	Oral	Rat	(Luo et al., 2007)
Improvement in the amount of dopamine in the neurons and protection against the loss of neurons	50-200 mg/kg	Intragastric	Mouse	(Chen et al., 2017)

The neurological effects studied *in vitro* are summarised in Table 23.

Table 23. *The neurological effects of icariin as demonstrated in in vitro studies (table continued on the next page).*

Effect	Concentration	Cell type	Reference
Stimulation of neuronal stem cell proliferation and differentiation	10-200 nM	Neuronal stem cells	(Huang et al., 2014a)
	0.1-10 μM	Neuronal stem cells	(Yang et al., 2016)
Protection against MPP toxicity	0.0001-0.1 μM	Neuronal (MES23.5) cells	(Xu et al., 2016)
Inhibition of the apoptotic effects of corticosterone	0-1 μM	Neuronal cells isolated from rat hypothalamus	(Liu et al., 2011; Zhang et al., 2012a)
Stimulation of mitochondrial motility and the length and size of mitochondria in neurons. Reduced expression of Aβ and phosphorylated Tau	20 μM	Hippocampal cells isolated from Alzheimer's mice	(Chen et al., 2016b)
Protection against toxicity of formaldehyde	1-10 μM	Neuroblastoma cells (SH-SY5Y)	(Song et al., 2016b)

Effect	Concentration	Cell type	Reference
Reduction of cell death by Aβ(25-35) through inhibition of Tau protein	0-20 µM	PC12 cells	(Zeng et al., 2010b)
	0-320 µg/ml	Cortical neuronal cells	(Sha et al., 2009)
Protection against toxicity of H_2O_2	200-800 µM	Neuronal cells	(Li et al., 2011b)
	0.15-9.6 µM		(Zhang et al., 2010)
Repair of the cytoskeleton after homocysteine damage	0-10 µM	Cortical neuronal cells	(Li et al., 2016b)
Protection against I/R damage	0-9.6 µM	Neuronal cells	(Wang et al., 2009)
Protection against cell death by LPS	0-50 µM	Microglia	(Zeng et al., 2010a)
Stimulation of protein and mRNA expression of synoviolin	0-10 µM	Neuroblastoma cells	(Li et al., 2015b)

Anti-cancer

Two animal studies have been conducted into the potential anti-cancer effects of icariin.

Zhang et al. (2014) investigated the effects of icariin on radiotherapy in mice with colorectal cancer (Zhang et al., 2014c). Icariin (40 mg/kg) reduced tumour volume in these mice, both when given alone and in combination with radiotherapy.

Zhang et al. (2013) found that icariin (40 mg/kg/day, administered intraperitoneally for 2 weeks) enhanced the effects of the anti-tumour drug gemcitabine (Zhang et al., 2013a). In combination with gemcitabine, icariin significantly reduced the tumour size in the gall bladder of the mice. The tumour was smaller than in treatment with gemcitabine alone.

The potential anti-cancer effects of icariin have been the subject of many *in vitro* studies. Icariin has anti-proliferative and pro-apoptotic effects in several cancer cell lines. Table 24 presents a summary of the results found.

Table 24. *The anti-cancer effects of icariin as demonstrated in in vitro studies.*

Effect	Concentration	Cell type	Reference
Inhibition of proliferation and stimulation of apoptosis in combination with temozolomide	0-20 μM	Glioblastoma cells	(Yang et al., 2015b)
Inhibition of proliferation and stimulation of apoptosis in combination with radiotherapy	0-80 μM	HCT116 and HT29 cells, two colon cancer cell lines	(Zhang et al., 2014c)
Inhibition of proliferation and stimulation of apoptosis	0-80 μM	Human osteosarcoma doxorubicin-resistant cell line MG-63/DOX	(Wang et al., 2015a)
	0-40 μM	Human hepatoma cells	(Li et al., 2010b)
	0-100 μg/ml	Leydig tumour cells from mice	(Wang et al., 2011)
	40-160 μg/mL	Gallbladder carcinoma cells	(Zhang et al., 2013a)
	0-100 μM	Lung carcinoma cells (A549)	(Di et al., 2015)
	0-80 μM	Esophageal carcinoma cells	(Fan et al., 2016)
	0-20 μM	Acute leukaemia cells	(Wang et al., 2015b)
	0-100 μM	Oesophageal cancer (KYSE70) cells	(Gu et al., 2017)
	0-100 μM	Human ovarian cancer cells (A2780)	(Li et al., 2015c)
Increased tyrosinase activity	EC_{50}: 1.01 μM	B16 melanoma cells	(Ye et al., 2010)
Inhibition of proliferation and stimulation of apoptosis in combination with 5-fluorouracil (5-FU)	0-80 μM	Colorectal cancer cells	(Shi et al., 2014)
Inhibition of migration and invasion	20 - 200 μg/ml	Human stomach cancer cells	(Wang et al., 2010)

Cardiovascular effects

Table 25 shows the cardiovascular effects of icariin as described in various animal studies. Icariin has been shown to have a number of beneficial effects on the cardiovascular system, including reducing infarct size, lowering blood pressure and heart rate and reducing blood cholesterol levels.

Table 25. *The cardiovascular effects of icariin as demonstrated in animal studies.*

Effect	**Dose**	**Mode of administration**	**Species**	**Reference**
Reduction of infarct size of the heart and reduction of inflammation in the heart	10 mg/kg	Intraperitoneal	Rat	(Meng et al., 2015; Zhai et al., 2015)
	10-30 mg/kg twice daily for 3 days	Intragastric	Rat	(Xiong et al., 2016)
	5-10 µmol/L	Intravenous	Rat	(Ke et al., 2015)
Reduction of atherosclerotic lesions	30-60 mg/kg/day for 10 weeks	Oral	Mouse	(Wang et al., 2016d)
Improved remodelling of the heart and reduced blood pressure	20-40 mg/kg twice daily for 12 weeks	Oral	Rat	(Qian et al., 2017)
Lowering of plasma cholesterol levels and inhibition of platelet aggregation	5 mg/kg/day for 8 weeks	Intragastric	Rabbit	(Zhang et al., 2013c)
	30-60 mg/kg/d for 4 weeks	Oral	Rat	(Hu et al., 2016b)
Decreased heart rate, left ventricular diastolic blood pressure and left ventricular weight	10-40 mg/kg/day for 8 weeks	Intragastric	Rat	(Song et al., 2011)

In vitro, icariin has been demonstrated to have various different effects on (the development of) cells from the cardiovascular system. Many studies show that the primary effect of icariin is the differentiation of embryonic stem cells into cardiomyocytes (Zhu et al., 2005; Ding et al., 2008; Wo et al., 2008; Jin et al., 2010; Sun et al., 2011; Zhu et al., 2011; Zhou et al., 2013; Zhou et al., 2014; Liang et al., 2015). These cardiomyocytes contain the structure and function of healthy heart cells, with essential proteins (such as myosin light chain-1v (MLC1v), atrial natriuretic polypeptide (ANP), α-actin, troponin T and cardiac troponin I (cTnI)) being well expressed (Ding et al., 2007).

In addition, studies have demonstrated that icariin protected cardiomyocytes from the toxic effects of H_2O_2 (Song et al., 2016a) and stimulated the enzyme activity of histone deacetylase SIRT6 in mouse hearts (Chen et al., 2015), and that it caused relaxation of coronary arteries from dogs (Xu & Huang, 2007b), reduced apoptosis in heart cells (Zhang et al., 2013b) and stimulated angiogenesis in human endothelial cells (Chung et al., 2008).

Other effects

In addition to the various different effects (as described above), some animal studies have been conducted into other types of effects of icariin. These studies are described below. See Table 26 for an overview of these effects.

Table 26. *The other effects of icariin as demonstrated in animal studies (table continued on the next page).*

Effect	**Dose**	**Mode of administra-tion**	**Species**	**Reference**
Reduction of airway hypersensitivity	10-100 mg/kg	Oral	Mouse	(Li et al., 2014a)
Protection against I/R damage in lungs	60 mg/kg/ day for 3 days	Intragastric	Rat	(Zhang et al., 2015a)
Reduction of liver damage	31.25 mg/kg	Intramuscular	Duck	(Xiong et al., 2014)
Reduction of protein in urine and cell death in kidneys after nephrectomy	20-40 mg/kg/ day for 12 weeks	Intragastric	Rat	(Liang et al., 2014)
Less kidney damage after nephrectomy	40 mg/kg/ day for 8 weeks	Intragastric	Rat	(Huang et al., 2015)

Effect	Dose	Mode of administration	Species	Reference
Increased fatty acid oxidation in the liver	0-400 mg/kg/ day for 5 days	Oral	Mouse	(Lu et al., 2014)
Reduced production of reactive oxygen radicals	10-30 mg/kg	Intragastric	Mouse	(Xiao et al., 2015)
Reduced retinopathy in diabetes	0.5 mg/kg/ day for 12 weeks	Intragastric	Rat	(Xin et al., 2012)
Accelerated hair growth cycle	50 mg/kg	Intragastric	Mouse	(Su et al., 2017)
Increased body weight and improved renal function after transplantation of icariin-treated human umbilical mesenchymal cells (HuMSCs) in rats with renal failure	-	-	Rat	(Li et al., 2017)

For an overview of the other effects found in *in vitro* studies, see Table 27. These effects mainly consist in proliferative and differentiation effects on different cell types.

Table 27. *The other effects of icariin as demonstrated in in vitro studies (table continued on the next page).*

Effect	Concentration	Cell type	Reference
Inhibition of proliferation	10 nM-100 µM	HepG2 cells	(Wang et al., 2015c)
	0-40 µM	Smooth muscle cells	(Hu et al., 2016a)
Stimulation of proliferation		Sertoli cells	(Nan et al., 2014)
	10 nM – 1 µM	Human peridontal ligament cells	(Lv et al., 2013)
Stimulation of phosphorylation of eNOS, Akt and ERK	0.1 µM	Human endothelial cells (HUVECs)	(Koizumi et al., 2010)
Reduced differentiation	0-200 µM	Pre-adipocytes to adipocytes	(Han et al., 2016)

Effect	Concentration	Cell type	Reference
Inhibition of organic anion transport polypeptides (OATPs) 1B3 and 2B1	IC_{50}: 3.0 and 6.4 µM	Human embryonic kidney cells (HEK293)	(Li et al., 2014e)
Stimulation of adiponectin production	50 and 100 µM	Skeletal muscle cells from mice (C2C12)	(Han et al., 2015)
Reduced ageing of the cells and reactive oxygen radicals	0-5 µM	Human endothelial cells (HUVECs)	(Xiao-Hong et al., 2013)
Reduction of apoptosis by oxygen deprivation	0.1-10 µM	PC12 cells	(Mo et al., 2017)
Stimulation of hepcidin expression, a key protein in iron homeostasis	5-50 µM	Hepatocytes	(Zhang et al., 2016)
Inhibition of foam cell formation from macrophages	0-20 µM	Macrophages	(Yang et al., 2015a)
Reduced accumulation of collagen and fibronectin in the cells and decreased TGF-β production	10 nM-0.1 mM	Human and rat mesangial cells	(Li et al., 2013)
Stimulation of nitric oxide production	0.1-10 µM	Human endothelial cells (HUVECs)	(Xu & Huang, 2007a)

Network analysis

Schluesener and Schluesener (2014) performed a network analysis to determine the pleitropic effects of icariin (Schluesener & Schluesener, 2014). They found that icariin interacts with several pathways, including PDE, TGF-β, MAPK, PPAR, NOS, IGF and sirtuin. This led the researchers to conclude that icariin could potentially be an important agent against a variety of age-related diseases, such as depression, diabetes and osteoporosis.

Cui et al. (2016) examined the anti-Alzheimer effects of icariin in a network analysis (Cui et al., 2016). The analysis shows that potential effect mechanisms are reduction of hyperphosphorylation of tau proteins, anti-inflammatory effects and regulation of Ca^{2+} homeostasis.

Zhou et al. (2015) studied the anti-inflammatory effects of icariin in cardiomyocytes from rats exposed to lipopolysaccharide (LPS) (Zhou et al., 2015). Icariin (0.1-10 µM) decreased the increased mRNA expression of TNF-α, IL-1β and IL-6 induced by LPS. In addition, icariin inhibited the production of reactive oxygen radicals and blocked the phosphorylation of JNK and NF-κB.

Isopropyloctopamine

Isopropyloctopamine is chemically very similar to octopamine and synephrine (Figure 13). However, it contains an isopropyl group which accounts for its different functional properties compared to octopamine. Octopamine is a highly specific agonist for the beta-3 adrenergic receptor (Yen et al., 1998). It does not activate any of the other adrenergic receptors. Because isopropyloctopamine contains an isopropyl group, its receptor dynamics are different compared with octopamine and synephrine. Unlike octopamine and synephrine, isopropyloctopamine is also able to activate beta-1 and beta-2 adrenergic receptors (Anderson, 1983).

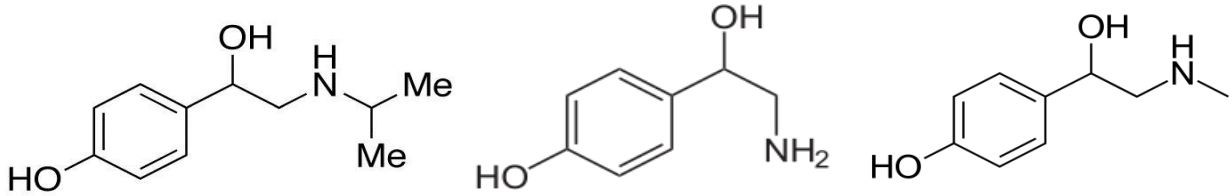

Figure 13. *Chemical structures of isopropyloctopamine (left), octopamine (centre) and p-synephrine (right).*

Kinetics

There are no known studies describing the kinetics of isopropyloctopamine. However, given its structural similarity to octopamine, a similar metabolic pathway is presumed. Octopamine is metabolised by the monoamine oxidase enzymes A and B (MAO A and MAO B) (Suzuki et al., 1979; Youdim & Finberg, 1991).

Dynamics

Mercader et al. (2011) studied the fat burning capacity of isopropyloctopamine on human adipocytes and compared it with the effect of synephrine, octopamine, tyramine and isoprenaline (Mercader et al., 2011). Like isopropyloctopamine, all of these substances occur naturally in *Citrus aurantium*. Isopropyloctopamine was found to be clearly lipolytic. 1 µg/ml induced a response that equalled 60% of the maximum effect of isoprenaline, a recognised lipolytic agent. The other substances studied (such as synephrine) were clearly less potent.

Anderson (1983) examined the sympathomimetic effects of isopropyloctopamine in an in vitro study (Anderson, 1983). He isolated the atria and trachea from guinea pigs and aortas from rabbits. In both guinea pig atria and trachea, isopropyloctopamine was found to have both beta-1 and beta-2 adrenergic activity. EC_{50} values (in M) for the different tissues found: 4.11×10^{-7} for the left atrium (isoproterenol: 2.57×10^{-9}), 1.44×10^{-6} for the right atria (isoproterenol: 6.82×10^{-9}) and 8.37×10^{-8} for the trachea (isoproterenol: 1.89×10^{-8}). Isopropyloctopamine was thus shown to be much less potent in receptor activation than isoproterenol. Addition of the beta-blocker propanolol led to a rightward shift of the concentration-response curve, demonstrating that the effects of isopropyloctopamine are beta-receptor mediated. Moreover, the effects of isopropyloctopamine persisted after washout.

Picken and Jarrott (1975) found that 100 µM of isopropyloctopamine induced a 21% increase in cAMP concentration by activation of the beta-2 receptors in rat hearts (Jarrott & Picken, 1975).

Wenkeová et al. (1975) found that isopropyloctopamine induced 40% of the response of isoproterenol to the release of free fatty acids and glycerol in a medium containing albumin. This was studied in human adipose tissue (Wenkeova et al., 1975).

Bovee et al. (2016) examined a food supplement associated by the Dutch authorities with 11 reported adverse events in 2013 (Bovee et al., 2016). These events were mainly heart problems. In 1 case, use of this supplement even led to cardiac arrest. In the UK, a 20-year-old woman died from an overdose of this supplement. The NVWA banned this supplement because it was found to contain yohimbe alkaloids, which are banned. However, this did not explain the cause of the symptoms. The researchers in this study found that the supplement also contained large amounts of the beta-3 adrenergic agonist N-isopropyloctopamine, which in high doses is associated with heart problems. In 3 different biosensor assays (ELISA, radiolabelled binding assay and a new imaging assay), they additionally detected beta-2 adrenergic activity for isopropyloctopamine.

Venhuis et al. (2014) examined the food supplements Dexaprine and Dexaprine XR, which are marketed as energy boosters for athletes and people who want to lose weight (Venhuis et al., 2014). In recent years, these supplements have been associated with serious adverse effects. Between May 2012 and October 2013, the National Poisons Information Centre (NVIC) received 26 reports of toxicity following ingestion of dexaprine. In 11 of these cases, only 1 pill had been taken. An hour after intake, side effects occurred included nausea, vomiting, excessive sweating, agitation, tachycardia, chest pain and palpitations. There is 1 known case of cardiac arrest after taking half a pill. The researchers found that these supplements contained, among other things, isopropyloctopamine.

Methylsynephrine

Methylsynephrine was originally synthesised to treat low blood pressure (Pohl & Kriech, 1991). It is chemically very similar to synephrine and ephedrine. However, unlike synephrine, methylsynephrine is entirely synthetic. Although methylsynephrine is claimed to be naturally present in *Citrus aurantium*, it has never been shown that this is actually the case (Pawar & Grundel, 2017). The difference between the two substances is the addition of a methyl group to the amine group, resulting in potential differences in the receptor dynamics of the two substances. Methylsynephrine activates both alpha and beta adrenergic receptors. The structure and effects of methylsynephrine are similar to those of synephrine and ephedrine, 2 of the most active alkaloids (Figure 14).

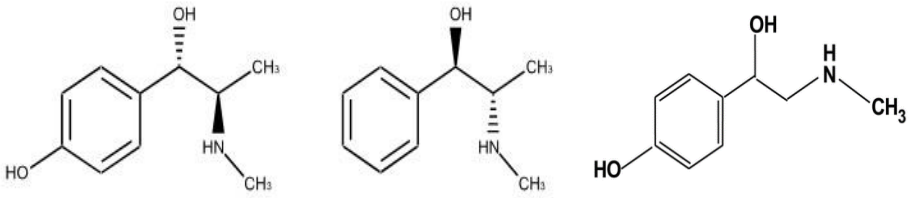

Figure 14. *The chemical structure of methylsynephrine (left), ephedrine (centre) and p-synephrine (right).*

Kinetics

Verho et al. (1988) studied the bioavailability of methylsynephrine in 12 healthy volunteers (Verho et al., 1988). The volunteers received a single oral dose of 16, 32 or 64 mg and their plasma methylsynephrine levels were monitored for 24 hours. Cmax values were 11.4, 31.4 and 122.9 ng/ml respectively for the different doses. These concentrations were found between 0.7 and 1.7 hours after intake. The Cmax values increased rapidly at increasing concentrations, implying a saturated first-pass metabolism. In the end, 50% of the doses given was found in the urine. No other side effects were reported.

Kauert et al. (1988) also studied the pharmacokinetics of methylsynephrine in 8 healthy volunteers (Kauert et al., 1988a; Kauert et al., 1988b). The volunteers received an oral dose of 120 mg after which their plasma methylsynephrine levels were measured. The authors observed reabsorption of methylsynephrine in the liver. After 2-3 hours, a second methylsynephrine peak occurred.

Vevelstad et al. (2017) studied how para-methoxymetamphetamine (PMMA) is metabolised in humans (Vevelstad et al., 2017). They examined this in human liver microsomes and in blood. After PMMA metabolism, the researchers also found low levels of methylsynephrine. They also detected low levels of methylsynephrine in the samples of fatal PMMA intoxications.

Stack et al. (2003) investigated the metabolism of p-methoxy-methamphetamine (80 mg/kg) in rats and identified methylsynephrine as one of the metabolites formed (Staack et al., 2003).

Xu et al. (2017) found a peak in the concentration of methylsynephrine in the urine of rats approximately 10 minutes after administration of oral extracts of *Ephedra sinica Stapf* (Xu & Yan, 2017). *Ephedra sinica Stapf* (Ma Huang) is a common medicinal herb in traditional Chinese medicine and contains ephedrine.

Baba et al. (1986) studied the metabolism of ephedrine. In rats, ephedrine was found to be partially metabolised into p-hydroxyfeedrine (=methylsynephrine) (Baba et al., 1986). This metabolic route was also found in humans.

Dynamics
In one study, 30 patients with orthostatic hypotension were treated with methylsynephrine (32 mg/day) for 2 weeks. Thirty patients received a placebo. After treatment, in the tilt-table test (Schellong test) blood pressure was found to have increased significantly, from 126 +/- 21 mm Hg x min to 187 +/- 39 mm Hg x min (+48%). In patients who received a placebo, blood pressure increased by 20% (Pohl & Kriech, 1991). The Schellong test is a test in which people lie horizontally on a table and are strapped down for safety. The table is then tilted almost completely upright. This makes it possible to measure orthostatic changes in blood pressure.

Kauert et al. (1988) studied the effect of a single oral dose (120 mg) of methylsynephrine on heart rate and mean arterial blood pressure in 8 healthy volunteers (Kauert et al., 1988a). Both values remained unchanged. However, systolic and diastolic blood pressure increased by 13% and 9% respectively. The researchers also found a positive inotropic effect, with the left ventricular fraction shortened by 21%.

Grobecker and Kees (1993) studied the effect of i.v. methylsynephrine (20 mg) in volunteers undergoing a tilt study to measure the effects on orthostatic blood pressure drop (Dominiak et al., 1992; Grobecker & Kees, 1993). Methylsynephrine had no effect on heart rate or blood pressure. However, it did increase the ejection fraction of the heart, stroke volume and cardiac index.

Hoffmann S, et al. (1987) studied the anti-hypotensive effects of methylsynephrine in 10 children with clinical dysregulation of orthostatic blood pressure (Hoffmann et al., 1987). The children were given a single acute dose of 20 mg orally and 20 mg chronically 3 times a day for 4 weeks. Methylsynephrine was found to induce an increase in pulse pressure, cardiac output, stroke volume and systolic ejection rate with reduced peripheral vascular resistance during orthostatic stress. The authors concluded that these effects resulted from activation of the alpha and beta adrenergic receptors.

Iwatsuki et al. (1982) studied the effect of carnigen (methylsynephrine) on vascular resistance in 11 individuals (Iwatsuki et al., 1982). Administration of 2 ml of carnigen into the subjects' bypasses led to an initial 9% decrease in blood pressure, followed by a significant 13% increase after 5 minutes.

Bloomer et al. (2009) found that a supplement called Meltdown, which includes methylsynephrine, increased plasma adrenaline, noradrenaline, glycerol and free fatty acid levels in healthy volunteers after 90 minutes (Bloomer et al., 2009a). In addition, they found increased blood pressure and increased heart rate after intake of the supplement. In a similar study, the same researchers measured the same parameters for 6 hours (Bloomer et al., 2009b). Again, after 6 hours the parameters were all higher compared to the placebo group. In addition, they found a 13.5% increase in calories burned. After 6 hours, heart rate and systolic and diastolic blood pressure were also higher compared to the placebo group.

Hoffman et al. (2009) studied the effect of 3 capsules of the supplement Meltdown in 10 healthy volunteers (Hoffman et al., 2009), measuring heart rate, blood pressure and oxygen intake over a period of 3 hours. During those 3 hours, oxygen uptake, energy expenditure, heart rate and blood pressure were all significantly higher compared with the placebo-treated volunteers. In addition, the volunteers who had taken the Meltdown supplement showed symptoms of confusion.

Kim et al. (2015) studied the anti-angiogenic effects of methylsynephrine in 2 animal models: seahorses and mice (Kim et al., 2015). In both models, methylsynephrine (20 uM, administered intravitrally) was found to inhibit angiogenesis. Methylsynephrine inhibited binding to the mRNA binding domain of nucleoporin 153. Depletion of this nucleoporin was found to be involved in the anti-angiogenic effects.

Kim et al. (2010) analysed the effect of methylsynephrine on angiogenesis *in vivo* in chicken embryos (Kim et al., 2010). After treating the embryos for 2 days (1 µg/egg), capillary formation was found to be inhibited by 67%.

Jacquot et al. (1980) found that methylsynephrine (10 uM) stimulated the release of noradrenaline from ventricular sections of the rat heart (Jacquot et al., 1980). A dose of 50 µM stimulated a 30% release. They also found that methylsynephrine inhibited the storage of noradrenaline.
In another study, the same researchers found that methylsynephrine is stored in the heart of rats in the same way as noradrenaline (Jacquot & Rapin, 1980). They also found that methylsynephrine had a high affinity for the storage vesicles of noradrenaline, where stimulation induces noradrenaline release.

Rapin et al. (1980) studied the effects of methylsynephrine on the sympathetic nervous system of rats (Rapin & Jacquot, 1980). They isolated the hearts and found that methylsynephrine (1.5 uM) inhibited the storage of noradrenaline in the heart and stimulated its release.

Kim et al. (2010) studied the anti-angiogenic effects of methylsynephrine in *in vitro* and *in vivo* settings (Kim et al., 2010). In the presence of vascular endothelial growth factor (VEGF), human umbilical vein endothelial cells (HUVECs) form a network of tubes. Methylsynephrine (10 µM and 20 µM) inhibited VEGF-induced vascular tube formation of HUVECs.

Venhuis et al. (2014) examined the food supplements Dexaprine and Dexaprine XR, which are marketed as energy boosters for athletes and people wanting to lose weight (Venhuis et al., 2014). These supplements have been associated with serious adverse effects in recent years. Between May 2012 and October 2013, the National Poisons Information Centre (NVIC) received 26 reports of toxicity following ingestion of dexaprine. In 11 of these cases, only 1 pill had been swallowed. An hour after intake, side effects occurred included nausea, vomiting, excessive sweating, agitation, tachycardia, chest pain and palpitations. There is 1 known case of cardiac arrest after taking half a pill. The researchers found that these supplements contained methylsynephrine (Venhuis et al., 2014). However, the amounts of synephrine, and isopropyloctopamine were much higher.

Annex V - Results of NVWA samples

Office for Risk Assessment & Research

Date
9 November 2021

Our reference
TRCVWA/2021/5480

The table below presents an overview of the mean, median, minimum and maximum daily doses of NVWA-sampled supplements (N=502) in the period between October 2013 and December 2019. Of these supplements, 314 contain one or more pharmacologically active substances. The daily dose is determined by multiplying the concentration of a substance found in a supplement by the desired daily intake according to the label. It was not possible to calculate daily doses for every substance because not all samples were quantified or because data on the prescription for use were lacking. Also, in some cases the daily dose was calculated on the basis of a very small number of samples.

***Table 28**. Overview of the mean, median, minimum and maximum daily doses **(mg/day**) of NVWA-sampled supplements in the period between October 2013 and December 2019 (table continued on the next page).*

Substance	**N**	**Dose (mg/day)**			
		Mean	**Median**	**Minimum**	**Maximum**
Aminotadalafil	3	2.7	0.006	0.006	8.2
Aristolochic acid I	1	0.00006	0.00006	0.00006	0.00006
Atropine	3	0.0006	0.0007	0.0001	0.001
Benzylsibutramine	10 (2)*	1.5	1.5	0.0006	3.0
BMPEA	**10 (9)**	**139.2**	**136.5**	**115.5**	**162.0**
Caffeine	114 (83)	191.7	125.0	0.01	1940.0
Corynanthine/Rauwolfscine	1	0.0007	0.0007	0.0007	0.0007
Dapoxetine	1	58.1	58.1	58.1	58.1
DMAA	**14**	**60.4**	**62.3**	**0.0001**	**143.4**
DMAE	1	67.8	67.8	67.8	67.8
DMBA	**8**	**133.2**	**57.1**	**51.5**	**286.0**
Ephedrine	15 (11)	0.6	0.003	0.00004	5.9
PEA	**16**	**12.2**	**0.009**	**0.001**	**127.7**
Phenolphthalein	16 (15)	40.4	4.1	0.00004	250.0
Fluoxetine	4	5.2	5.0	0.6	10.0
Halostachine	**1**	**34.0**	**34.0**	**34.0**	**34.0**
Heliotrine	4	0.002	0.002	0.0005	0.004
Higenamine	**32 (27)**	**31.2**	**14.3**	**0.000009**	**90.7**
Hordenine	**23 (19)**	**83.2**	**24.6**	**0.03**	**668.6**
Icariin	**31 (29)**	**29.9**	**0.04**	**0.00002**	**402.9**
Isopropyloctopamine	**1**	**140.0**	**140.0**	**140.0**	**140.0**
Kavain	2	0.0002	0.0002	0.0002	0.0003
Lorcaserin	6 (5)	14.2	14.3	13.5	15.0
Lycopsamine	3	0.0002	0.0002	0.00009	0.0002
Methylsynephrine	**17 (15)**	**56.7**	**63.0**	**0.003**	**137.8**
Monocrotaline	3	0.0001	0.00008	0.00003	0.0002
Monocrotaline N-oxide	1	0.0002	0.0002	0.0002	0.0002
Octopamine	12	18.5	0.1	0.006	83.9
Podophyllotoxin	2	0.0001	0.0001	0.0001	0.0001
Scopolamine	1	0.0001	0.0001	0.0001	0.0001

Substance	N	Dose (mg/day)			
		Mean	Median	Minimum	Maximum
Senecionine-NO	1	0.0002	0.0002	0.0002	0.0002
Seneciphylline-NO	1	0.00003	0.00003	0.00003	0.00003
Sibutramine	26 (21)	14.6	15.0	0.001	40.0
Sildenafil	42	46.8	24.8	0.02	135.0
Strychnine	2	0.003	0.003	0.0001	0.005
Synephrine	61 (60)	23.0	11.7	0.0001	226.0
Tadalafil	8 (3)	12.2	9.0	0.5	27.0
THC (tetrahydrocannabidiol)	3	0.0005	0.0005	0.0004	0.0006
Thiodimethylsildenafil	2	24.4	24.4	0.1	48.8
Thiohomosildenafil	6 (2)	0.1	0.1	0.09	0.1
Thiosildenafil	21 (17)	30.5	36.0	0.3	76.4
Yohimbe	22 (19)	1.8	0.005	0.00005	13.4

* The number in brackets represents the actual number of detections for which the substance content has been quantified and dosage information was available to determine the daily dose.