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Risk assessment of synephrine

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This investigation has been performed by order and for the account of VWS and NVWA.

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Synopsis

Risk assessment of synephrine

Synephrine is a substance that occurs naturally in citrus fruits, particularly in bitter orange (*Citrus aurantium*). It is added to food supplements for weight loss or to improve sports performance. The use of synephrine has increased since ephedrine, a related substance, was prohibited. Ephedrine is prohibited because it may have adverse effects on health.

At present, there is no legislation in the Netherlands which limits the amount of synephrine in food supplements. A maximum permitted amount may be desirable, however, because adverse effects cannot be excluded. This has been demonstrated by a risk assessment conducted by RIVM. Due to insufficient data on the safety of synephrine, no safe dose can currently be derived. In particular, data on the effects of chronic exposure are lacking. It may be possible that an (indicative) maximum safe amount of synephrine in food supplements could be determined based on the intake from a normal diet.

It is known that synephrine can increase blood pressure. In addition, other adverse effects are reported on the cardiovascular system by people who have used preparations containing synephrine. This aspect is particularly relevant because people who are overweight, the target group for weight loss products, are particularly at risk from cardiovascular diseases. Synephrine may also interact with various other drugs, affecting their efficacy. In addition, the effects of synephrine can be magnified when combined with caffeine and/or physical activity.

Keywords: p synephrine, oxedrine, *Citrus aurantium*, food supplements, botanicals

Publiekssamenvatting

Risicobeoordeling van synefrine

Synefrine is een stof die van nature voorkomt in citrusvruchten en vooral in bittersinaasappel (*Citrus aurantium*). Deze stof wordt toegevoegd aan voedingssupplementen om af te vallen of sportprestaties te verbeteren. Synefrine wordt steeds vaker gebruikt sinds de verwante stof efedrine is verboden. Efedrine is verboden omdat het schadelijk kan zijn voor de gezondheid.

Op dit moment bestaat er in Nederland geen wetgeving voor de maximaal toegestane hoeveelheid synefrine in voedingssupplementen. Dat is wel gewenst omdat bij gebruik van synefrine ongewenste effecten niet kunnen worden uitgesloten. Dit blijkt uit een risicobeoordeling die het RIVM heeft uitgevoerd. Doordat onvoldoende gegevens beschikbaar zijn over de veiligheid van synefrine, kan op dit moment echter geen veilige dosering bepaald worden. Vooral gegevens over effecten na langdurig gebruik ontbreken nog. Mogelijk kan wel een (indicatieve) maximaal toegestane hoeveelheid synefrine in voedingssupplementen worden vastgesteld op basis van de hoeveelheid die wordt ingenomen via de normale voeding.

Bekend is wel dat synefrine de bloeddruk kan verhogen. Daarnaast zijn er andere schadelijke effecten op het hart- en vaatstelsel gerapporteerd nadat mensen preparaten hadden gebruikt die synefrine bevatten. Dit aspect is vooral relevant omdat mensen met overgewicht, de doelgroep voor middelen om af te vallen, een hoger risico hebben op hart- en vaatziekten. Ook kan synefrine mogelijk de werking van diverse geneesmiddelen beïnvloeden. De effecten van synefrine kunnen bovendien worden versterkt in combinatie met cafeïne en/of lichamelijke activiteit.

Kernwoorden: p-synefrine, oxedrine, *Citrus aurantium*, voedingssupplementen, kruidenpreparaten

Contents

Summary

Synephrine is a constituent of *Citrus spp,* such as *Citrus aurantium* (*C. aurantium,* bitter orange), and is structurally similar to adrenaline and ephedrine. Since the ban on ephedrine/ephedra in herbal preparations/food supplements in 2014 due to its adverse effects on human health, synephrine is increasingly being used as a substitute for ephedrine in food supplements for weight loss and food supplements for athletes (energizing, muscle-enhancing agents), often in combination with caffeine (among other ingredients).

In recent years, RIVM and other scientific bodies have performed several risk assessments on synephrine and *C. aurantium*. In view of the revision of the Dutch Herbal Products Decree of the Commodities Act, the Dutch Ministry of Health, Welfare and Sport (VWS) asked RIVM to update the risk assessment for synephrine. In addition, VWS is considering initiating the procedure to ultimately place synephrine on Annex III of Regulation (EC) No 1925/2006. In this report, the information taken from previous risk assessments conducted by RIVM on synephrine has been merged and updated. An overview of risk assessments conducted by other scientific bodies is also provided, as is an overview of the current legislation in several countries. The results of an analysis of synephrine in several food supplements and herbal teas are included as well.

The toxicological data on synephrine are limited; data on chronic toxicity in particular are lacking. It is therefore not possible to derive a health-based guidance value for synephrine. Synephrine-containing preparations have the effect of increasing blood pressure and can increase the occurrence of cardiovascular disorders. The target group for weight-loss products has an increased risk of suffering the adverse cardiovascular effects associated with synephrine. In addition, because synephrine inhibits cytochrome P450 3A4, interactions with several medicines cannot be excluded. In view of the above, adverse effects from the ingestion of food supplements containing *C. aurantium*/synephrine cannot be excluded. It is stressed that the effects of *p*-synephrine taken in combination with caffeine and/or physical activity may be increased. Furthermore, food supplements in some cases may contain not only *p*-synephrine, but also the more potent *m*-synephrine (phenylephrine, this substance is not naturally occurring in *C. aurantium*).

In absence of a health-based guidance value, a maximum limit for *p*-synephrine in dietary supplements might be based on the amount of *p*-synephrine consumed via the regular diet, since *p*-synephrine is present in frequently used citrus fruits. The intake estimates of BfR (Germany) and ANSES (France) described in this report could be used for this purpose, since it is assumed that there is not much difference in the consumption of foods containing synephrine in these countries and in the Netherlands. A maximum limit for synephrine should be combined with labelling requirements and possibly with requirements for caffeine and/or *m*-synephrine levels.

1 Introduction

Synephrine is a constituent of *Citrus* spp (including sweet orange, lemon and mandarin). The highest quantities of synephrine are found in *C. aurantium* (bitter orange). Synephrine is associated with weight reduction. Synephrine is structurally similar to adrenaline (also called epinephrine) and ephedrine (1). Since the ban on ephedrine/ephedra in herbal preparations/food supplements due to adverse effects on human health, synephrine is increasingly being used as a substitute for ephedrine in herbal preparations, often in combination with caffeine (among other ingredients). Synephrine is used in weight-loss products and food supplements for athletes (energizing, muscle-enhancing agents). The use of *C. aurantium* in food supplements is different from its traditional use as an agent for the treatment of digestive problems and to stimulate the appetite and gastric secretion (2).

There are six possible isomers of synephrine; three depending on the position of the phenolic hydroxyl group (*para*, *meta*, *ortho*; see Figure 1*)*, and two optical isomers for each of them.

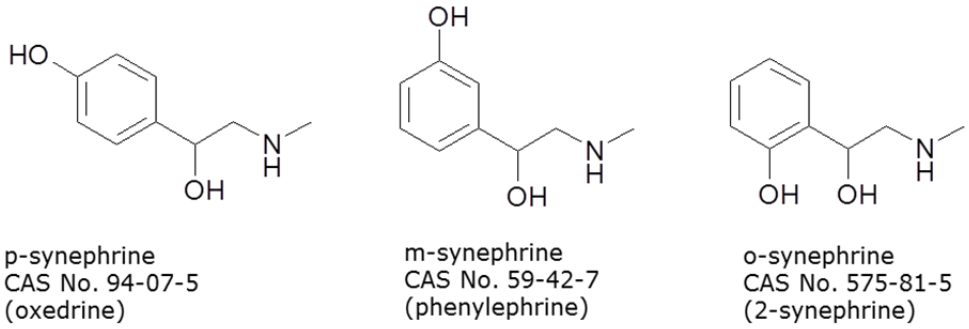

Figure 1. Chemical structures of different synephrine isomers

p-Synephrine (also known as oxedrine), and particularly its R-(-)-enantiomer, occurs naturally in *C. aurantium* and other citrus fruits (1, 3, 4). However, both *p*-synephrine and *m*-synephrine (also known as the drug phenylephrine) have in some cases been found in herbal preparations containing *C. aurantium*. The European Food Safety Authority (EFSA) indicates that it is unlikely that the (+)-*p*-synephrine isomer or *m*-synephrine in food supplements originates from *C. aurantium* and hence their presence in food supplements containing *C. aurantium* extract is an indication of adulteration (1, 5).

Currently, there are no medicinal products with *p*-synephrine registered in the Netherlands or at the European level (6, 7). *m*-Synephrine is present in twelve registered medicinal products in the Netherlands and all of these are solutions for injection, eye drops or ophthalmic preparations (6). It is also present in one medicinal product authorized at the European level (7). Medicinal products containing p-synephrine (oxedrine) are registered in several other European countries, including France, Germany, Austria, Hungary, Switzerland and Italy (8). *p*-Synephrine and *m*-synephrine are not considered to be prohibited

substances by the World Anti-Doping Agency, but have been included in their monitoring programme since 2009. The purpose of the monitoring is to detect potential patterns of abuse in sports (9). With respect to food supplements, there are several proposals for health claims on *C. aurantium* in the European Union that have to be reviewed by EFSA. These health claims refer to digestion, sleep/relaxation, breathing and the metabolism of fat/weight control. These applications have not yet been reviewed by EFSA because the whole group of botanicals awaits the start of the review.

RIVM performed several risk assessments on synephrine and *C. aurantium* that were commissioned by the Netherlands Food and Consumer Product Safety Authority (NVWA) (10-12). The most recent risk assessment conducted by RIVM was performed in 2011 at the request of the NVWA after a RASFF[1] alert regarding a food supplement containing, amongst other ingredients, synephrine (RIVM, 2011). In addition, in 2012 a literature study was performed by RIVM for the Dutch Health Care Inspectorate (IGZ) on the working mechanism, activity and effectiveness of synephrine on weight loss (13). In 2015, a background document was written on synephrine for the Dutch Ministry of Health, Welfare and Sport (VWS) that described, amongst other things, the legislation on synephrine and *C. aurantium* in food supplements in several countries and conclusions drawn from previous risk assessments by RIVM and other scientific bodies (14).

VWS is revising the Herbal Products Decree of the Commodities Act and is intending to put *C. aurantium* and/or synephrine on the list of herbs and/or herbal substances that are not allowed in herbal preparations. In addition, VWS is considering initiating the procedure to ultimately place synephrine on Annex III of Regulation (EC) No 1925/2006. This Regulation regulates the addition of vitamins, minerals and certain other substances (a substance other than a vitamin or a mineral that has a nutritional or physiological effect) to foods. Annex III of this Regulation contains a list of 'other substances' whose use in foods is prohibited, restricted or under Community scrutiny. Towards this aim, VWS requested RIVM to update the risk assessment for synephrine.

In the current report, information from previous risk assessments on synephrine has been merged and updated. In order to extend the information used in the 2011 risk assessment, a new literature search was performed. This search was conducted using the search engines SCOPUS, PubMed, TOXLINE and Google Scholar, together with the following key words: 'synephrine' OR 'Citrus aurantium' OR 'oxedrine'. The focus was on articles published between 2011 and 2016, since the latest evaluation of synephrine (RIVM, 2011), included data gathered up to 2011. New studies on (only) *m*-synephrine were not taken into account because it is now known that *C. aurantium* contains only *p*-synephrine. In the remainder of the document, the particular isomer of synephrine that has been used is indicated where possible. If the isomer is not indicated in the reference cited, then 'synephrine' has been used.

[1] The Rapid Alert System for Food and Feed (RASFF) was put in place to provide food and feed control authorities within the EU with an effective tool to exchange information about measures taken responding to serious risks detected in relation to food or feed. https://ec.europa.eu/food/safety/rasff_en

2 Pharmacological mechanism and kinetics

2.1 Pharmacological mechanism

Synephrine is a sympathetic adrenergic agonist that stimulates both *α* adrenoreceptors and *β* adrenoreceptors, such as noradrenaline (norepinephrine). These receptors are involved in vasoconstriction and vasodilation, respectively. Each isomer of synephrine has its own adrenergic agonist capacity. Both *p*-synephrine and *m*-synephrine are sympathetic adrenergic agonists. *p*-Synephrine is a much weaker adrenergic agonist than *m*-synephrine. *p*-Synephrine acts mainly via the β3 adrenoceptor, while *m*-synephrine acts via α, β1 and β2 adrenoceptors. Activation of β3 adrenoceptors results in increased fat burning/lipolysis, activation of α, β1 and β2 adrenoceptors results in an increased heart rate and blood pressure (1, 15). The effect of synephrine on weight loss is increased in combination with caffeine. The theory for weight reduction is that β3 agonists influence body weight and fat mass, whereas β1 and β2 agonists influence the cardiovascular system. Many weight-loss products base their mode of action on the β3 agonistic effect, such as the effect of ephedrine. The effect on weight reduction is enhanced in combination with caffeine. This is the supposed working mechanism of combination preparations that contain synephrine and caffeine. Synephrine and caffeine produce catecholamines that affect lipolysis. The human body has a natural defense mechanism against weight loss; it has negative feedback mechanisms that stop lipolysis. These feedback mechanisms may be inhibited by caffeine (16-18).

2.2 Kinetics

The oral absorption of *p*-synephrine in humans is rapid and complete, with maximum plasma concentrations reached after one to two hours. Following oral administration of 6 mg of ^{3}H-*p*-synephrine (361 µCi), approximately 80% was excreted in the urine within 24 hours. Only 2.5% of the dose was excreted as synephrine. The major metabolite in the urine was deaminated *p*-hydroxy-mandelic acid (~53%). Based on a comparison of urine data after oral and IV administration, the oral biovailability of *p*-synephrine was low. The biological half-life of *p*-synephrine was about two hours (19). Compared with ephedrine, *p*-synephrine is poorly soluble in fat. As a result, passage across the blood-brain barrier is low (20).

When *m*-synephrine (R-(-)-*m*-synephrine) was administered orally to humans (six tablets of 5 mg in eight hours), it was mainly excreted as metabolites in urine: unconjugated m-hydroxymandelic acid (MHMA, 30%), *m*-hydroxyphenylglycol (MHPG) sulphate (6%), *m*-synephrine sulphate (47%) and *m*-synephrine glucuronide (12%). After inhalation of *m*-synephrine (three times in each nostril every three hours for nine hours; total dose equivalent to 10, 24 or 34 mg) these metabolites were observed in amounts of 24%, 6%, 56% and 4%, respectively, in urine (21). After intraperitoneal injection in rats, *m*-synephrine was excreted as 5% unconjugated MHMA, 33% MHPG sulphate, 7% unconjugated *m*-synephrine and *m*-synephrine conjugates (9%; 4% as the glucuronide and 5% as the sulphate) in urine (22).

C. aurantium juice is a strong inhibitor of the enzyme cytochrome P450 3A4. This enzyme is involved in the biotransformation of many drugs. As a result, intake of *C. aurantium* may result in increased blood concentrations of several drugs and thus increase the toxicity of the drugs. This is particularly relevant for drugs with a narrow therapeutic window (2, 23).

Interaction between synephrine and monoamine oxidase (MAO) inhibitors has been reported. The simultaneous intake of MAO inhibitors and synephrine results in an increased synephrine concentration, which may result in cardiotoxicity (23).

3 Toxicology

3.1 Animal and in vitro data

3.1.1 Acute toxicity

In a mouse study, an LD_{50} of approximately 24 g/kg bw was observed for synephrine isolated from Calamansi (*Citrus microcarpa*) (24).
In another study, an LD_{50} for mice of 71 g/kg bw was mentioned for the herb, corresponding to 177 mg/kg of synephrine (at a synephrine content of 0.25%) (25).

In an acute oral toxicity study in rats, 'gasping' and salivation were observed at dosages ranging from 150 mg of *p*-synephrine/kg bw onwards, and a decrease in locomotor activity, piloerection and exophthalmos were observed at doses of 300 mg/kg or higher. The effects were reversible and occurred for 3-4 hours after administration. The oral LD_{50} was above 2,000 mg/kg, the highest dose tested (26).

Synephrine acetonide resulted in anesthetized rats and guinea pigs in transient hypertension and tachycardia, mediated via α and β adrenergic receptors, respectively (27).

Single administration of essential oil from *C. aurantium* peel (0.5 and 1.0 g/kg bw) by gavage to male mice resulted in an increased latency period of tonic seizures. The highest dose resulted in increased hypnotic and anxiolytic activity. Subcutaneous administration of *p*-synephrine (700-1,500 mg/kg bw) to mice resulted in convulsion and effects on the sense organs and respiration. Oral administration of *p*-synephrine (0.3-1.0 mg/kg lg) resulted in increased body temperature in mice (as summarized in (28)).

3.1.2 Short-term toxicity

Mice

Groups of nine male mice received 400, 2,000, or 4,000 mg of *C. aurantium* extract/kg bw, or 30 or 300 mg of *p*-synephrine/kg bw via a stomach tube for 28 days. The animals were observed twice daily and their body weight was measured daily. At the end of the study, various biochemical and haematological parameters were measured in the plasma and various organs were weighed and examined macroscopically. Furthermore, various biomarkers for oxidative stress were studied. The increase in body weight was significantly reduced in the two *p*-synephrine groups. In addition, glutathione peroxidase was significantly reduced in all dose groups, with the exception of the 4,000 mg of *C. aurantium* extract/kg bw group, and glutathione was significantly increased in the 4,000 mg of *C. aurantium* extract/kg bw group and in both *p*-synephrine groups (29).

Repeated oral administration of a herbal mixture with ~10% *C. aurantium* peel for 13 weeks at doses of 125 to 2,500 mg/kg bw did not show toxicological changes in mice (28).

Rats
In an oral study, rats were administered 2.5 – 20 mg/kg bw of two *C. aurantium* extracts (4% and 6% synephrine, respectively) for seven days. Mortality (dose-related) and changes in electrocardiogram (ECG; ventricular arrhythmias with enlargement of QRS complex, dose-related) were observed in all groups (30).

In a 15-day gavage study with rats, mortality and effects on the heart (ventricular arrhythmia and prolonged QRS) were observed (as summarized in (28)).

In a study with rats fed a 0.1% synephrine-containing feed for 14 days, a slight decrease was observed in some blood lipid values (phospholipids, triglycerides, total cholesterol). Also, a slight increase in HDL-cholesterol was observed (31).

In a study with portal hypertensive rats, the hemodynamic effect of an 8-day administration of synephrine by gavage (1 mg/kg bw per 12 hours) was studied. Compared with the control group, the following effects were observed: reduction in portal venous pressure (~ −12%), portal blood flow tributary (~ −20%) and cardiac index (~ −15%), while an increase was observed in mean arterial pressure (~ 17%), systemic vascular resistance (~ 38%) and portal vascular resistance (~ 57%) (32).

Rats were given a *C. aurantium* extract in their diet for 79 days in concentrations corresponding to 0, 0.1, 0.4, 2.2 and 11 mg of synephrine/kg bw per day. There were no dose-related effects on body weight or organ/tissue weights. In the highest dose group, the weight of the heart, the spleen and the perirenal fat was significantly lower than in the control group, but not when compared to the lowest dose group. There were no histopathological abnormalities observed in the heart. Adrenaline and dopamine concentrations were significantly elevated in the plasma and in the urine (only adrenaline) of the highest dose group (33).

In a study of Takebayashi *et al.* (2006), rats were given *C. aurantium* extract in their diet for 44-45 days, alone or in combination with caffeine. The dosages corresponded to about 3 mg/kg bw of synephrine and approximately 5 mg/kg bw of caffeine per day. No significant differences were observed in food intake, body weight gain and organ weights. The levels of epinephrine, norepinephrine and dopamine were not significantly different compared to the control group. In addition, no histopathological changes in the heart were observed (34).

As part of the National Toxicology Program, Hansen *et al*. (2012) evaluated the potential effects of synephrine and/or bitter orange's extract on the cardiovascular system of rats, with or without the co-administration of caffeine (35). Female Sprague-Dawley rats were given one of two different commercially available extracts of *C. aurantium* orally by gavage (6% synephrine and almost purified 95% synephrine, respectively) for 28 consecutive days. The final doses of synephrine applied for each extract were 10 and 50 mg/kg bw/day. The results revealed an increase in the systolic blood pressure (maximum increase of 6.4 mm Hg, seen at 4h post-treatment) with the higher dose of 50 mg/kg bw/day for both of the extracts. Diastolic blood pressure

recordings appeared elevated only with the high dose of the 6% extract. The 6% extract induced a more pronounced effect, suggesting that ingredients[2] other than synephrine may either contribute to the overall effect or alter the potency of synephrine, leading ultimately to an increased response. The 6% extract increased the heart rate at the high dose group for four hours after dosing, whereas the 95% extract increased the heart rate only at the low dose group, for eight hours. The QT intervals were not influenced by the treatment. Co-administration with 25 mg of caffeine exacerbated the aforementioned effects.

In a later study of the same group and with a similar design, the same extracts were given daily for 28 days to female Sprague-Dawley rats at the same doses. The animals performed a 30-minute physical exercise, three times per week, 10 minutes after dosing (36). Both dose levels of each extract increased the systolic and diastolic blood pressure, when compared to the vehicle control for up to eight hours. The maximum increase for the systolic pressure was 7.5 mm Hg at four hours after administration, while for diastolic pressure 6 mm Hg at eight hours after administration. The heart rate was not influenced by the treatment. The results indicate that physical activity increases the potency of synephrine. In addition, the exerted effects were again more prominent in the presence of caffeine. It should be noted that in both articles the authors mentioned that synephrine did not seem to influence the body weights of the animals.

In another study, a ten-day treatment of male obese Sprague-Dawley rats with a commercially obtained *C. aurantium* extract (6% synephrine content, dosed: 5.6 mg of extract/kg bw/day) produced a significant increase in heart rate, 24 hours post treatment. Administration of the botanical extract did not impact feeding patterns or body weights (37).

3.1.3 Genotoxicity

Synephrine (20-3,600 µg/mL) was negative in an in-vitro gene mutation assay (L5178Y mouse lymphoma assay) (38).

3.1.4 Reproductive/developmental toxicity

In a study on reproductive and teratological effects, rats were injected intramuscularly with 55 or 110 mg/kg bw of synephrine daily on days 7-16 of gestation. A decrease in implantations and viable fetuses and a delayed cranial and thoracic ossification were observed (based on summary in (28)).

In a teratogenicity study in which rats were orally administered a *C. aurantium* extract on days 3 - 20 of gestation, no adverse effects were observed on fetal development (doses up to 100 mg of synephrine/kg bw or 50 mg of synephrine/kg bw plus 25 mg of caffeine/kg bw). However, a decrease in the body weight of the dams was observed at 50 mg of synephrine + 25 mg of caffeine/kg bw and in the group receiving only 25 mg of caffeine (39).

[2] HPLC/MS and GC/MA analysis showed the presence of hordenine, octopamine and tyramine: 6% extract 0.63%, 0.1% and 0.09%, respectively, and 95% extract, 0.05%, 0.39% and 0.02%, respectively.

C. aurantium and *p*-synephrine did not result in a significant oestrogenic or anti-oestrogenic effect in an 'uterotrophy' test in rats. However, a decrease in the weight of the adrenals was observed (40). *p*-Synephrine can influence steroidogenesis in bovine luteal cells via β adrenergic receptors (41).

In a study with Sertoli cell cultures taken from 19-day-old rats, the aromatization of testosterone was studied. With a concentration of 10^{-5} M of *p*-synephrine, a stimulating effect was observed in which α and β-2 receptors were involved. Adrenergic agonists therefore may play a role in the development and function of the testes (42).

3.1.5 Others

From an *in vivo* and an *in vitro* study with rats on the antidepressant-like effects of *p*-synephrine stereoisomers (concentration range 0.3-10 mg/kg bw, oral administration), it was concluded that S-(+)-*p*-synephrine has a more effective antidepressant activity than R-(-)-*p*-synephrine (21).

Immune toxicity was tested with an extract of the peel of *C. aurantium* fruit and of unripe fruit. Oral administration of the extract of the peel to mice resulted in a decrease in the viability of splenocytes and thymocytes in mice. Oral administration of extracts of the unripe fruits resulted in inhibition of Type I allergenicity reactions in rats (as summarized in (28)).

In addition to several studies described above, NTP (2004) reported effects of synephrine on several systems (without further details), among which were cardiovascular effects (effects on blood pressure, cardiovascular toxicity and adrenergic activity) in humans, rats, guinea pigs, cats and dogs, neurological effects and effects on cell growth and enzymes (CYP3A) (28).

3.2 Human data

3.2.1 Clinical trials

In a study involving 12 healthy volunteers, *p*-synephrine was administered intravenously (4 mg/min). A significant increase in systolic and mean arterial blood pressure was observed, whereas diastolic blood pressure and heart rate remained unchanged. The "cardiac index" increased and the peripheral vascular resistance decreased significantly (43).

In a clinical trial (adults and children), the effects of synthetic synephrine on different types of shock were investigated. Cardio tonic and diuretic effects were observed. The coronary flow and renal arterial flow were increased. The negative effects were small (21).

In a human study on the effects of a herbal preparation for weight loss containing synephrine/caffeine (17, 44), nine overweight adults used a preparation containing 975 mg of *C. aurantium* (58.5 mg synephrine), 528 mg of caffeine and 900 mg of St John's Wort (3% hypericum) for six weeks. No negative effects were reported. However, no frequent haemodynamic monitoring was performed (17, 45).

Penzak et al. (2001) observed no effect on blood pressure and heart rate in normotensive adults that ingested 8 ounces of *C. aurantium* juice

(corresponding with 13-14 mg synephrine), followed by a repeat ingestion eight hours later (46).

No effect was found on the cardiovascular system after a single oral dose of 50 mg of *p*-synephrine in a double-blinded, randomized, placebo-controlled protocol with 10 subjects per treatment group. However, resting metabolic rate was increased, as compared with the placebo group (15).

In a randomized, placebo-controlled, crossover, double-blind designed study conducted in young adults that were provided with a supplement containing 13 mg of *p*-synephrine and 176 mg of caffeine at all three meals during a single day, no effect on heart rate and blood pressure was observed (47).

In a study involving healthy volunteers who were given 18 mg of synephrine per day in the form of a food supplement based on, amongst other things, *C. aurantium* or that received 60 mg of *m*-synephrine per day for eight weeks, no significant reduction of body weight was observed. At the beginning of the treatment, an increased resting metabolic rate was observed, but this effect disappeared in the course of eight weeks. Based on laboratory tests, electrocardiograms and physical testing, no adverse effects were observed, i.e. no harmful side effects, no increase in blood pressure or heart rate, and no evidence of toxicity (48).

In a double-blind, placebo-controlled crossover study, 10 young adults were given single doses of 21 mg of synephrine and 304 mg of caffeine or a placebo during rest, and one hour before moderate exercise lasting half an hour. No significant adverse effects occurred. However, diastolic blood pressure and glucose levels after exercise were increased after supplement use. In addition, the effort expended was experienced as less severe by the volunteers. Heart rate, systolic blood pressure and body temperature were not different compared to the placebo (49).

In a prospective, randomized, double-blind, placebo-controlled crossover study, 15 young, healthy adult subjects received either a single dose of a 900 mg food supplement extract standardized to 6% synephrine (~54 mg), or matching placebo, with a one week washout period. An increase in the systolic and diastolic blood pressure and the heart rate were observed for five hours after exposure (50).

A single dose of 49 mg of *p*-synephrine in the form of bitter orange extract was given to 18 healthy volunteers in a double-blinded, placebo-controlled cross-over study in order to examine potential cardiovascular effects. The heart rate, blood pressure, electrocardiograms and several blood parameters were determined at various time points up to eight hours after administration. A small, yet significant decrease in diastolic blood pressure was observed one hour after administration of the substance. No other significant effects were detected (51).

In a double-blinded, placebo-controlled study involving 75 healthy individuals (15 males and 60 females), Kaats et al. reported no significant changes in the systolic and diastolic blood pressure, nor in several blood

chemistry parameters, after oral treatment with capsules containing *p*-synephrine. The participants were instructed to consume the provided capsules containing *p*-synephrine on a daily basis for 60 consecutive days. Subjects were instructed to take two capsules before breakfast and two capsules at 3:00–4:00 PM daily. The dose of *p*-synephrine per capsule was either 24.4 mg (Group B) or 24.6 mg (Group A), in a form of bitter orange extract (commercial name: Advantra Z). Four capsules corresponded to ~98 mg per day in total. In group A, synephrine was co-administered with hesperidin and naringin. Measurements of the different parameters for this assessment were only recorded at the start and end of the experiment. A small, yet still significant increase in heart rate was seen only in group A, in which p-synephrine was combined with hesperidin and naringin, but not in group B, in which *p*-synephrine was given alone. The authors of the publication regarded this effect as irrelevant with respect to its clinical importance (52).

No studies are available in which healthy volunteers are exposed to synephrine for a period longer than eight weeks.

3.2.2 Case studies

Several case studies are described in the literature in which the effects observed were associated with synephrine. In many cases, however, effects were observed after the intake of synephrine-containing combination preparations, containing caffeine and/or willow bark/salicine, amongst other ingredients. The effects observed can therefore simply not be attributed to synephrine, but rather often to the combination of synephrine and caffeine and willow bark/salicine. Below, a selection of case studies is described.

An ischemic stroke associated with use of a *p*-synephrine-containing supplement was reported in a 38-year-old man (45, 53). A case of exercise-induced syncope was reported in a 22-year-old healthy woman one hour after intake of a food supplement (amount not reported) for weight loss. Prolongation of QT was diagnosed. The weight-loss preparation contained both synephrine and caffeine (54).

A 55-year-old woman, who took a multicomponent food supplement for weight loss for the past year, had an acute myocardial infection. This preparation for weight loss contained 300 mg of *C. aurantium*, 30 mg of guaranine and 30 mg of green tea, amongst other ingredients. She did not have a history of hypertension, coronary disease or hyperlipidemia (obesity). She smoked and reported a high level of caffeine use (23).

A 21-year-old woman was checked into the hospital emergency room with disturbed consciousness and a seizure. The clinical examination revealed increased blood pressure and heart rate, prolonged QT and apical ballooning of the left heart ventricle (apical ballooning syndrome-ABS). The woman had been consuming different food supplements containing synephrine and caffeine over the preceding week for weight-loss purposes. Her condition was stabilized and after 10 days in hospital she was discharged to return home (55).

In a review of data taken from selected European and Brazilian poison centres, *C. aurantium* was found to be one of the ten most often

reported herbs associated with adverse effects after consumption of botanical food supplements (56). A confirmed or probable causal relationship between consumption and observed adversity was established based on the WHO causality assessment criteria (57). Nonetheless, in the cases described, *C. aurantium* was not consumed alone, but rather in combination with other botanicals in the same product, which made the interpretation of data difficult.

Also, in two other cases identified in the literature, it was not possible to clarify whether the observed effects were associated with the consumption of synephrine, since more than one substance with potential effects on the cardiovascular system and/or sympathomimetic action were consumed (e.g. 1,3-dimethylamylamine, xilofrine, deterenol, yohimbine, caffeine, theophylline, etc.) (58, 59).

4 Evaluations by other scientific bodies

4.1 EFSA

C. aurantium has been used in 2009 as a case study by the EFSA Scientific Cooperation (ESCO) Working Group on botanicals and botanical preparations. EFSA concluded that for the traditional food uses of bitter orange, there is no presumed safety concern. But EFSA indicated that, for the safety assessment of the use of bitter orange preparations with a *p*-synephrine content above 6%, additional data are required, including data on ADME (absorption, distribution, metabolism, excretion), genotoxicity, long-term toxicity and developmental toxicity (1).

In 2014, EFSA evaluated the suitability of the Qualified Presumption of Safety (QPS) approach for a number of botanicals, including *C. aurantium.* EFSA concluded that *p*-synephrine is a threshold substance, but one with no health-based guidance value currently in place, due to insufficient toxicity data (60). The long history of the use of *p*-synephrine, which is present in traditional foods (such as mandarin), has not shown any harmful effects. EFSA indicated that it should be underlined, however, that the absence of evidence for any adverse effect cannot be taken as evidence for the absence of adverse effect(s). Considering the doses showing a pharmacological effect in humans and the levels of exposure resulting from the traditional use of *C. aurantium* preparations, there is a biological plausibility for an adverse health effect, although it has not been picked up by historical data. EFSA proposed two options for the assessment of *C. aurantium* extracts. If the assessment is based on the absence of adverse effects seen with the traditional use, then dried hydro-alcoholic extracts of the dried immature fruit and the dried peel of the immature/mature fruits could be assigned the QPS status, provided that the use is restricted to intakes which are not significantly higher than the intake from the traditional diet. In the event it is decided to ignore the long history of use, given the likelihood of undetected long-term effects of exposure to *C. aurantium*, dried hydro-alcoholic extracts of the dried immature fruit and the dried peel of the immature/mature fruits shall be ruled out from the QPS status (60).

In 2015, EFSA evaluated the safety of caffeine. The evaluation also covered possible interactions between caffeine and *p*-synephrine, as well as the safety of food products containing these two substances. No conclusions could be drawn by EFSA, however, because the question of whether or not *p*-synephrine modifies the acute cardiovascular effects of single doses of caffeine or the long-term effects of caffeine on the cardiovascular system has not been adequately investigated in humans (5).

4.2 BfR

In 2012, the German Federal Institute for Risk Assessment (BfR) performed a risk assessment on sports/weight-loss products containing synephrine and caffeine on the German market. BfR did not derive a health-based guidance value for synephrine, but recommended that quantities of synephrine in sports/weight-loss products should not exceed 6.7 mg/day. This quantity represents the intake via conventional foods

(such as bitter oranges), with maximum contents of synephrine for average consumers. This would ensure, even for frequent consumers, an overall intake of synephrine from the conventional diet and from supplements that does not exceed 25.7 mg. BfR also noted that synephrine together with caffeine might induce synergistic effects, as it is well known that caffeine interacts with sympathomimetic compounds. Therefore, BfR proposes that the following labelling requirements be introduced for combination preparations of synephrine and caffeine (61):

- can lead to increased blood pressure and heart rate, therefore not suitable for people with hypertension, obesity and other cardiovascular disorders.
- consult a physician when used in combination with medicines.
- be careful when used in combination with intensive effort.
- not intended for pregnant and lactating women, nor for children.

4.3 ANSES

In 2014, the French Agency for Food, Environmental and Occupational Health and Safety (ANSES) investigated the risks of food supplements containing synephrine or ingredients from *Citrus spp* fruits containing *p*-synephrine. This risk analysis was based on published literature (animal studies, clinical studies, as well as case studies) and case reports within the nutrivigilance scheme (3). Based on the available data, ANSES "considers that it is not possible to establish a maximum permissible dose of *p*-synephrine in food supplements due to the lack of exploitable data from literature". ANSES considers food supplements that lead to a daily intake of *p*-synephrine higher than 20 mg/day (the 95th percentile of dietary synephrine consumption in the French population) to be unsuitable for sale to consumers.

Furthermore, ANSES recommends that the combination of *p*-synephrine with caffeine or any other substances that have cardiovascular effects should be avoided, and "strongly advises against the consumption of *p*-synephrine by populations that have a higher risk of adverse effects (people receiving chronic treatment, particularly for hypertension, heart disease or depression), by pregnant or breastfeeding women, or by children and adolescents" (3).

In addition, ANSES highlights the possible potentiation of *p*-synephrine when used in combination with physical exercise, as shown in a rat study (Hansen *et al*., 2013, described in further detail in paragraph 3.1.2). In another study involving human volunteers (Haller *et al*., 2008, as referenced in ANSES, 2014), *p*-synephrine together with caffeine before exhaustive exercise did not allow a proper decrease of the diastolic blood pressure, as normally seen following physical exercise. This effect in hypotension after exercise is considered as one of the beneficial effects of exercise and is correlated with sympathomimetic activity. Given the fact that supplements containing *p*-synephrine are used for weight loss and/or its ergogenic potential, it is expected that people will possibly combine them with physical exercise. The need to generate long-term data for clarification of such effects is noted (3).

4.4 FSANZ

In 2015, Food Standards Australia New Zealand (FSANZ) performed an analytical survey to investigate whether food products intended for weight loss on the Australian market contained any pharmaceuticals. Of the 36 products included in the test, two contained *C. aurantium.* A risk assessment was performed on foods containing *p*-synephrine at the measured levels. FSANZ noted that many products containing *p*-synephrine also contained other ingredients, such as caffeine, but those other ingredients were not taken into account in the risk assessment.

FSANZ executed a literature study on bitter orange and *p*-synephrine (oxedrine) to assess the hazard of bitter orange and *p*-synephrine. Based on animal toxicity studies (including Kaats *et al*. (2013) described in further detail in paragraph 3.2.1), case reports and clinical studies, they concluded that "the weight of evidence from clinical studies conducted on bitter orange extracts of known oxedrine content indicates minimal concerns for potential adverse effects. Ingestion of bitter orange extract resulting in oxedrine doses approaching 100 mg per day for 60 days, the highest dose tested in published clinical studies, was not associated with adverse effects".

As a second step, FSANZ conducted an exposure assessment based on dietary exposure to citrus fruits and their products, as well as weight-loss products. The dietary exposure for mean consumers was estimated to be 0.5-14 mg per day for Australia and 0.7-11 mg per day for New Zealand. The dietary exposure for high consumers (90^{th} percentile) was estimated to be 1.3-35 mg per day for Australia and 2.5-26 mg per day for New Zealand. In the survey on weight-loss products, two products contained *p*-synephrine. When taken at the recommended daily dose stated on the product labels, this would result in a *p*-synephrine intake of 13 or 39 mg per day, respectively. If this comes on top of the dietary exposure, this could lead to a dose of 74 mg per day.

In the risk characterization, FSANZ concluded that dietary exposure and exposure from weight-loss products together "would not be expected to result in a total dietary exposure exceeding 98 mg/day, a dose that resulted in no effects in a double-blind, placebo-controlled clinical trial lasting 60 days". As a conclusion, FSANZ stated that the highest *p*-synephrine level found in this analytical survey "does not indicate a public health and safety concern" (62).

4.5 Health Canada

In November 2011, Health Canada published a health risk assessment on synephrine, octopamine and caffeine. It was concluded that 1 to 50 mg of *p*-synephrine per day – and up to 40 mg of *p*-synephrine in combination with a maximum of 320 mg of caffeine per day – for healthy adults is not likely to cause any adverse health consequences (63).

5 Legislation

This chapter provides an overview of the legislation regulating *p*-synephrine and *C. aurantium* in food supplements and other food products in various countries.

5.1 The Netherlands

5.1.1 Advice Group Status Determination

Synephrine has been discussed in the Advice Group on Status Determination. The Advice Group consists of members from IGZ, NVWA, VWS, CBG, the Central Committee on Research Involving Human Subjects (CCMO) and RIVM, and gives advice on the legal status of products on the borderline between food (commodities), medicines and medical devices, among other things. The Advice Group recommended that products with synephrine should be considered as commodities, with the note that commodities should be safe. No final decision has yet been taken by IGZ and NVWA on the status of these products.

This opinion is based on the following conclusion: synephrine indeed induces a pharmacological effect, but there are no data on the efficacy of synephrine alone. There are no human studies available that have investigated the effects of synephrine alone on weight loss. There are insufficient data to provide a lower limit for efficacy. In addition, on the basis of the available data, no safe dose can be determined. Products that contain synephrine, therefore, cannot be regarded as medicinal products, but should be regarded as commodities (64).

5.1.2 Draft amendment Commodities Act for Herbal Preparations

In the most recent version of the draft amendment of the Commodities Act for Herbal Preparations (discussed in the Regular Commodities Act Consultation Group [Regulier Overleg Warenwet, ROW])" of April 2, 2014) it is proposed that herbal preparations may not contain synephrine or derivatives thereof. Furthermore, *C. aurantium* (bitter orange) was added to the list of plants that cannot be used in herbal preparations. However, it is stated that the ban on synephrine and *C. aurantium* applies only to food supplements and therefore not to other herbal preparations/food.

5.2 Belgium

In Belgium, *C. aurantium* has been placed on list 3 of the Royal Decree of 29 August 1997 (consolidated version of January 2017)(65). List 3 contains plants that are allowed in food supplements and, for some of these plants, maximum amounts are laid down per daily portion.
For food supplements to which preparations of the fruit of *C. aurantium* have been added, the intake of the recommended daily dose should not lead to an intake of more than 20 mg of *p*-synephrine. Analyses should show that the preparation does not contain detectable amounts of *m*-synephrine. In addition, the label of the food supplements must contain the following warnings:

- Do not use during pregnancy or breastfeeding;
- Not to be used by persons who are being treated for hypertension;
- Not to be used by children under 12 years;
- If signs of restlessness or nervousness appear, stop taking the product.

5.3 Germany

BfR recommends that the amount of synephrine which may be ingested through food supplements should be limited to a maximum amount of 6.7 mg/day (the average daily intake from food) and proposes a number of labelling requirements (see paragraph 4.2) (61). It is not clear whether or how this is included in legislation in Germany.

5.4 Sweden

C. aurantium is on the list (VOLM) of plants and plant components which may not be used in food. An assessment is only performed for extracts with high levels of synephrine (not further specified)(66).
Items that contain a daily dose ≥ 160 mg of synephrine are considered a medicinal product (67).

5.5 Denmark

C. aurantium is placed on the Drogelisten in Denmark, pointing out that concentrated extracts (not further specified) of synephrine are not acceptable (68).

5.6 Finland

The Finnish Food Safety Authority EVIRA holds the view that food supplements containing a combination of synephrine and caffeine can pose a serious health risk to the consumer and should not be marketed as such. Such supplements have therefore been withdrawn from the market in Finland. In a press release, EVIRA stated that such supplements also may not be marketed in Denmark and Sweden (69).

5.7 Canada

Food supplements
In November 2011, Health Canada established a limit of 50 mg of *p*-synephrine or up to 40 mg of *p*-synephrine in combination with 320 mg of caffeine in food supplements, in combination with the following risk phrases:

- Contraindicated for children, during pregnancy and during breastfeeding.
- Do not use in combination with drugs that can have an effect on blood pressure (both hypertensive and anti-hypertensive), thyroid medication, sympathomimetics or monoamine oxidase inhibitors

For supplements containing higher levels, additional product-specific risk assessments are needed. Products with a recommended daily dose of up to 50 mg of *p*-synephrine/day, or a combination of up to 40 mg of *p*-synephrine content in combination with 320 mg of caffeine, and that contain the required warning phrases, are classified as a Type III health

risk: " a situation in which the use of or exposure to a product is not likely [emphasis added] to cause any adverse health consequences". Products that contain higher concentrations or that do not have the required warning phrases are classified as a Type II health risk: "a situation in which use of or exposure to a product may cause temporary adverse consequences or where the possibility of serious adverse health consequences is remote" (63).

C. aurantium as a flavour enhancer

For the use of synephrine as a flavour enhancer in products intended for oral intake, it applies that no "risk information" is necessary for products that provide ≤5 mg of synephrine + octopamine as a daily dose. Risk information is required for products providing a total of 5.1 -50 mg of synephrine + octopamine as a daily dose. Authorized products providing a daily dose of <40 mg/day of *p*-synephrine + 320 mg/day or less of caffeine are considered safe, provided appropriate risk statements are available on the product labels (70).

6 Analysis of synephrine in food supplements and herbal teas

Samples of food supplements and herbal teas were analysed by RIKILT – Wageningen University & Research using a method developed in 2010 for the determination of plant toxins, including *p*-synephrine. This method is based on liquid chromatography with mass spectrometric detection (LC-high resolution MS, LC-MS/MS). From 2010-2012, samples of herbal tea, food supplements and Traditional Chinese Medicines (TCMs) were purchased by RIKILT in shops (some on the Internet) in the Netherlands and analysed. From 2013 onwards, samples of herbal preparations were taken by the NVWA and analysed by RIKILT. The research initially focused on regulated plant toxins (pyrrolizidine alkaloids, yohimbe alkaloids, aristolochic acids), other bioactive substances including *p*-synephrine, and the presence of prohibited plants from the Herbal Preparations Decree of the Dutch Commodities Act. Gradually, the scope was enlarged with other natural and non-natural bioactives, including synthetic adulterants (pharmaceuticals).

The NVWA samples are herbal food supplements with emphasis on products sold as a performance enhancer, sexual enhancer or weight-loss product. *p*-Synephrine was found in a large proportion of these samples. In many samples analysed, caffeine was (also) present, often in high amounts. Caffeine levels were not quantified. Appendix 1 summarizes the available analytical data. *p*-Synephrine was found in all three subcategories (herbal tea, food supplements and TCMs).

In total, 20% of the 335 samples investigated contained *p*-synephrine. It should be noted that the numbers of samples of herbal tea and TCMs were limited and most food supplements were taken selectively by NVWA on the basis of specific claims (performance enhancer, sexual enhancer, weight-loss products).

The amounts in positive samples of herbal tea ranged from 0.4 to 25 mg/kg (in tea as bought, so the dried herbal mixture). The values in TCMs ranged from 0.04 to 3.7 mg/kg. In positive food supplement samples, the amounts varied widely, from 0.02 to 81,000 mg/kg. On the basis of the (maximum) daily dose indicated on the product labels, the corresponding intake of *p*-synephrine could be calculated for 51 of the 56 food supplements in which *p*-synephrine was found. For 17 of these supplements, the dosage was (much) lower than 1 mg/day. In the other 39 cases, the dosage varied from 1.6 to 65 mg/day. For 19 supplements, the dosage was higher than 20 mg/day (the maximum daily dose in Belgium). Appendix 2 shows the composition of these products according to the label. In almost all of these products, *C. aurantium* or synephrine was indicated on the label, usually without an amount

7 Discussion and conclusions

7.1 Hazard characterization

The database for the evaluation of synephrine is limited. Only a small number of studies are available, focused mainly on working mechanism and metabolism/kinetics. For the endpoints of chronic exposure, carcinogenicity, cytotoxicity and tumour initiation/promotion, (almost) no data are available. Since slimming agents are generally taken over a long period of time, at least chronic toxicity data are essential.

From the limited literature, it can be concluded that synthetic synephrine and an extract of C. aurantium have a comparable working mechanism. Since synephrine is considered as a sympathicomimetic with both α and β adrenergic effects, comparable to ephedrine, an increase in blood pressure is an effect that can be attributed to synephrine, as well as effects on the cardiovascular system (arrhythmia, seizures, prolongation QT). Although the amount of data is limited and not fully consistent, possibly due to differences in the composition of the supplement used (C. aurantium or synephrine), a synephrine-induced increase in blood pressure has been observed in humans, rats and dogs. Very likely, there is a lower limit for the efficacy of synephrine (considering the mode of action via adrenoceptors, the effects of both *m*-synephrine and *p*-synephrine will only occur when a threshold is reached). However, based on the literature available, this lower limit cannot be derived. The observed effects of synephrine on blood pressure can increase the risk of cardiovascular diseases, especially in individuals with an existing cardiovascular disease. It should be kept in mind that high blood pressure often occurs in people with obesity, the target group for weight-loss products. Athletes are also a risk group, as the cardiovascular system is exerted by extreme effort. As a consequence, the target groups have an increased risk of adverse effects. In addition, weight-loss products are commonly used over a longer period, whereas no toxicity data are available after long-term exposure. In addition, apart from the occurrence of cardiovascular effects, C. aurantium/synephrine has an inhibitory effect on CYP3A4, which can result in altered plasma concentrations and, consequently, an altered effect from several medicines. Synephrine can also interact with monooxidase inhibitors, resulting in an increase of the synephrine concentration in the blood and an increased risk of cardiotoxicity.

In conclusion, it is not possible to derive a health-based guidance value for synephrine, and the occurrence of adverse effects from the ingestion of food supplements cannot be excluded, since

a. toxicity data after long-term intake are lacking,
b. synephrine can increase blood pressure and cardiovascular disorders were reported after intake of synephrine-containing preparations,
c. there is an increased risk of adverse effects in the target population for synephrine-containing products,
d. interactions between synephrine and possibly a variety of medicines may occur.

Caffeine intake results in increased plasma levels of epinephrine and norepinephrine, increased blood pressure and an increase in heart rate. In view of the effects that may occur on the cardiovascular system after the intake of synephrine and caffeine separately, it is expected that these effects especially will be enhanced when taking preparations that combine synephrine with caffeine, due to the additive and/or synergistic effect of these substances.

7.2 Presence of synephrine in herbal preparations

The analyses of RIKILT show that *p*-synephrine was found in 20% of the 335 samples examined (herbal tea, TCMs and food supplements), with the highest levels found in food supplements. It should be noted that the numbers of samples of herbal tea and TCMs were limited and most food supplements were taken selectively by NVWA on the basis of specific claims (performance enhancer, sexual enhancer, weight-loss products).

On the basis of the (maximum) daily dose indicated on the product labels, the corresponding intake of *p*-synephrine could be calculated for 51 of the 56 food supplements in which p-synephrine was found. For 17 of these supplements, the intake of *p*-synephrine was (much) lower than 1 mg/day. In the other 39 cases, the intake varied from 1.6 to 65 mg/day. For 18 supplements, the intake of *p*-synephrine was higher than 20 mg/day (the maximum daily dose in Belgium).

In almost all of these products, *C. aurantium* or synephrine was indicated on the label/product leaflet, usually without an amount. In these cases, it concerns deliberate addition of *C. aurantium* and/or *p*-synephrine as such, rather than contamination. In the supplements with lower levels of *p*-synephrine, it is currently not known in how many *C. aurantium*/synephrine has been added on purpose or is due to contamination.

7.3 Exposure

No exposure data are available on the intake of dietary or supplemental synephrine in the Dutch population. French consumption data showed that the dietary *p*-synephrine intakes "are 6.2 mg/day on average and 20.0 mg/day at the 95th percentile for the maximum levels" (ANSES, 2014). German consumption data revealed that the dietary synephrine intakes are 0.88-6.73 mg per day for average consumers and 6.62-25.82 mg per day for high consumers (BfR, 2012). It is expected that the dietary intake of synephrine for the Dutch population will be in the same range as the intake of the French and German populations. It should be noted that this is the synephrine intake via regular food products containing synephrine, such as citrus fruits, juices, jam and marmalade. Any intake of synephrine via food supplements comes on top of the regular dietary intake.

7.4 Legislation

The most recent draft amendment of the Dutch Commodities Act for Herbal preparations proposes a ban on the use of *C. aurantium* and synephrine (and derivates of synephrine) in food supplements. In several countries described in this report, the use of *C. aurantium* and synephrine in food supplements is allowed, provided that a number of

requirements are met. These requirements include maximum levels of synephrine, the absence of *m*-synephrine (phenylephrine, this substance does not naturally occur in *C. aurantium*), the absence or maximum levels of caffeine, and labelling requirements.

7.5 Concluding remarks

The toxicological data on synephrine are limited. Data on chronic toxicity, in particular, are lacking. It is therefore not possible to derive a health-based guidance value for synephrine. Synephrine-containing preparations have the effect of increasing blood pressure and can increase the occurrence of cardiovascular disorders. In particular, the target group for products containing synephrine has an increased risk of suffering the adverse effects described for synephrine. In addition, because synephrine inhibits cytochrome P450 3A4, interactions with several medicines cannot be excluded. In view of the above, the occurrence of adverse effects from the ingestion of food supplements that contain C. aurantium/synephrine cannot be excluded. It is stressed that the effects of *p*-synephrine in combination with caffeine and/or physical activity may be increased. Furthermore, food supplements may not only contain *p*-synephrine, but also the more potent *m*-synephrine.

In the absence of a health-based guidance value, a maximum limit for synephrine in dietary supplements might be based on the amount of synephrine consumed via the regular diet, since synephrine is present in frequently consumed citrus fruits. The intake estimations of Germany and France could be used for this purpose, since it is expected that there is not much difference in the consumption of foods that contain synephrine in these countries and their consumption in the Netherlands. A maximum limit for synephrine should be combined with labelling requirements and possibly with requirements with regard to caffeine and/or *m*-synephrine levels.

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Appendix 1. Overview of levels of synephrine in traditional Chinese medicines (TCMs), herbal tea and food supplements analyzed by RIKILT in 2010-2016.

Year	Health claim	Synephrine	
		mg/kg	mg/day*
TCM (11 samples, 4 positive)			
2010	No specific claim	0.058	n.d.
2010	No specific claim	3.7	n.d.
2011	No specific claim	0.037	n.d.
2011	No specific claim	14	n.d.
Herbal tea (16 samples, 6 positive)			
2011	No specific claim	2.1	n.d.
2012	No specific claim	0.46	n.d.
2012	No specific claim	6.9	n.d.
2012	No specific claim	25	n.d.
2012	No specific claim	14	n.d.
2012	No specific claim	0.42	n.d.
Food supplements (308 samples, 56 positive)			
2010	No specific claim	2.9	n.d.
2010	No specific claim	0.17	n.d.
2012	No specific claim	0.07	n.d.
2012	No specific claim	0.015	n.d.
2012	No specific claim	0.024	n.d.
2013	Sexual enhancer	81,000	65
2013	Sexual enhancer	29	0.052
2013	Performance enhancer	1.5	0.006
2013	Sexual enhancer	50,000	38
2013	Weight loss	4.1	0.011
2013	Sexual enhancer	9.8	0.013
2013	Sexual enhancer	2.2	0.0028
2013	Weight loss	2.0	0.0056
2013	Weight loss	1.4	0.028
2013	Weight loss	8,500	17
2013	Sexual enhancer	8,400	21
2013	No specific claim	3,800	57
2013	Weight loss	210	0.93
2013	Sexual enhancer	0.23	0.00012
2013	Sexual enhancer	10	0.015
2014	No specific claim	1,500	2.0

Year	Health claim	Synephrine	
		mg/kg	mg/day*
2014	No specific claim	0.44	0.0010
2014	No specific claim	100	0.20
2014	No specific claim	0.55	0.0005
2014	Sexual enhancer	0.9	0.0046
2014	Weight loss	3	0.0079
2014	No specific claim	3,400	51
2014	No specific claim	790	12
2014	No specific claim	810	12
2014	Sexual enhancer	19,000	11
2014	Performance enhancer	0.47	0.0028
2015	Sexual enhancer	2.6	0.0021
2015	General health	81	0.12
2015	Sexual enhancer	4.8	0.0039
2015	Weight loss	33,000	45
2016	Weight loss	8,000	20
2016	Work out	2,100	21
2016	Weight loss	6,600	22
2016	No specific claim	1,200	2.3
2016	No specific claim	500	4.8
2016	No specific claim	15,000	34
2016	No specific claim	2.3	0.0058
2016	No specific claim	8,600	22
2016	No specific claim	142	0.36
2016	No specific claim	61,000	226
2016	No specific claim	1,400	13
2016	No specific claim	550	0.85
2016	No specific claim	280	1.6
2016	No specific claim	5.8	0.0018
2016	No specific claim	4,200	26
2016	Work out	5,000	56
2016	Work out	5,400	60
2016	Work out	5,600	63
2016	Work out	5,600	63
2016	Work out	5,700	64
2016	Work out	5,300	59

n.d. = not determined.
* based on the maximum daily dose as indicated on the product label.

Appendix 2. Label information for food supplements from Appendix 1 with a daily dose > 1 mg.

Year	Claim	Daily dose synephrine (mg/day)	Label information
2014	No specific claim	2.0	**citrus aurantium,** vitis vinifera, vaccinium corybosum, rubus fruticosus; [560 mg salvestrols per 2 capsules]
2014	Sexual enhancer	11	Gynostemma Pentaphyllum, Lepidium Meyenii Walp, **Citrus Aurantium Extract**, Ilex Paraguarensis, Oyster Crassostrea Gigas, Vitamin E, Vitamin B12, Vitamin B3, Vitamin B1 and gelatin.
2014	No specific claim	12	cola nitida, paulinia cupana, **citrus aurantium** 6%, dextro, 375 mg ascorbixc acid, glycyrrhiza 25%, 375 mg potassium, phenylalanine, oleum mentha, 74 mg niacin
2014	No specific claim	12	phenylalanine aroma, paulinia cupana, **citrus aurantium** 6%, 375 mg potassium, glycyrhiza 25%, 75 mg dextro, niacin
2013	Weight loss	17	flax seed oil (280 mg); green tea extract camillia sinencis (100 mg); **citrus aurantium** (100 mg); l-carnitine (20 mg); vitamin B3 nicotinamide (18 mg); vitamin B6 (pyridoxine 2 mg)
2013	Enhance performance	21	**citrus aurantium**; phenylalanine; tyrosine; caffeine (200 mg); carcinia cambogia (60% HCA: hydroxycitric acid); green tea extract (epigallocatechin gallate (EGCG)); bitter melon; taraxacum officinale; hesperidin; inositol; **citrus fruit extract** (naringin); quercetin; resveratrol; alpha lipoic acid; bioperine (piper nigrum extract)
2013	Sexual enhancer	38	Vit B1 (1.4 mg); Vit B2 (1.6 mg); niacine (Vit B3 36 mg); Vit B5 (6 mg); Vit B6 (10 mg); Vit B12 (0.003 mg); l-tyrosine (25 mg); l-taurine (150 mg); plant extracts 223 mg; contains caffeine and **synephrine** (from **bitter orange**)
2014	No specific claim	51	*Mitragyna speciosa* extract

Year	Claim	Daily dose synephrine (mg/day)	Label information
2013	No specific claim	57	*Mitragyna speciosa* extract
2013	Sexual enhancer	65	Vit B1 (1.4 mg); Vit B2 (1.6 mg); niacin (Vit B3 18 mg); Vit B5 (6 mg); Vit B6 (10 mg); Vit B12 (0.003 mg); ascorbic acid (Vit C 10 mg); l-tyrosine (20 mg); l-phenylalanine (20 mg); l-glutamine (20 mg); l-pyroglutamine (10 mg); l-arginine (25 mg); Vit B15 (22.5 mg); plant extracts 225 mg en 285 mg, contains caffeine and **synephrine** [per capsule]
2015	Weight loss	45	Green coffee bean (Coffea arabica); Rhodiola Rosea; **Citrus Aurantium**, Moringa mix (Leaf Powder, Seed Cake, Fruit powder); BioPerene; Caffeine
2016	Weight loss	20	**citrus aurantium 100 mg**; Caffeine Anhydrous 100 mg; Coleus Forskohlii(root) 50 mg; Guggulsterones Z&E 1:1 10 mg; Piper Nigrum 2.5 mg
2016	Work out	21	Vitamin B3 - 12.5 mg; Vitamin B12 - 1,000 mg; L-Citrulline - 4,000 mg; L-Taurine - 2,000 mg; N-Acetyl L-Tyrosine - 750 mg; Choline Bitartrate - 500 mg; Higenamine Hydrochloride - 50 mg; Hordenine Hydrochloride - 50 mg; Halostachine Hydrochloride - 50 mg; **Synephrine Hydrochloride - 30 mg**; Caffeine Anhydrous; Dicaffeine Malate; Theobromine; Caffeine; Yerba Mate Extract; Guarana Extract; Green Coffee Bean Extract; Gotu Kola Extract; 400 mg caffeine/serving
2016	Weight loss	22	caffeine anhydrous; hordenine; **synephrine HCl**; Yohimbine HCl; Rauwolscine
2016	No specific claim	2.3	Extract of green tea leaves; water-free caffeine; nettle extract; ginger root extract; extract of black tea leaves; green coffee extract (powder); **bitter orange-extract**; Yerba mate extract; cayenne pepper extract; extract of the fruit of black pepper; capsule (gelatin; titaniumdioxide). Contains polyphenols; caffeine; gingerol; synephrin; capsaicin

Year	Claim	Daily dose synephrine (mg/day)	Label information
2016	No specific claim	4.8	Per 2 tablets: Vitamin C 90 mg; Folate 2160mcg; Vitamin B12 54mcg; Zinc: 18 mg; L-carnitine complex; Taurine; rosemary leaf extract (50% ursolic acid) AstraGin; San-qi Ginseng root and Astragalus root; Caffeine anhydrous; **bitter orange citrus aurantium extract** (providing synephrine) Purenergy caffeine-p Teropure cocrystal; Norcoclaurine
2016	No specific claim	34	Per capsule: Niacin 10 mg; vitamin B6 5 mg; Vitamin B12 25 mcg; Caffeine Anhydrous 160 mg; N-Acetyl-L-Tyrosine 150 mg; Toothed clubmoss (whole plant) 2.5 mg; Cranberry fruit extract 100 mg; iFAS50 62.5 mg; Amla fruit extract 37.5 mg; **Citrus aurantium 33.33mg**; Red pepper (2% capsaicinoids) 15 mg
2016	No specific claim	22	Per 3 capsules: Chrome 11.5 µg; Caffeine 220mg; Revex-16 complex 2,165 mg; **Citrus aurantium extract (4% synephrine) 500 mg**; L-Phenylalanine; L-Tyrosine; Dried Caffeine 200 mg; Garcinia cambogia extract (60% Hydroxy citric acid) 200 mg; Green tea extract (min 50% polyphenoles) 200 mg; Bitter melon extract (min 10% charantin) 100 mg; Taraxacum extract (min 20% flavonoids) 100 mg; Hesperidine (93%) 50 mg; Inositol 50 mg; Naringin 93% 50 mg; Quercetin dihydrate 84% 50 mg; Resveratol extract 50 mg; Alpha lipoic acid 10 mg; Bioperine (>95% piperine) 5 mg; Chromium picolinate 100 µg
2016	No specific claim	0.36	per 3 capsules: **Citrus aurantium 450mg**; Green tea (95% extract) 300 mg; Caffein anhydrous 300 mg; L-Tyrosine 200 mg; L-Theanine 150 mg; Raspberry ketones 150 mg; Cayenne Pepper 150 mg; Bioperine 5 mg; Chromium picolinate 1 mg

Year	Claim	Daily dose synephrine (mg/day)	Label information
2016	No specific claim	226	Per capsule: Chromium 20 mcg; Garcinia cambogia extract 67 mg; Caffein 67 mg; Green tea extract 40 mg; **Citrus Aurantium extract 40 mg**; Grapefruit extract 33 mg; Guarana seed extract 33 mg; L-Camitin 30mg; Ginger root extract 30 mg; Cayenne pepper extract 15 mg; black pepper extract (95% piperine) 2.5 mg
2016	No specific claim	13	Per 2 tablets: Vitamin C 90 mg; Folate 2,160 mcg; Vitamin B12 54 mcg; Zinc: 18 mg; L-carnitine complex; Taurine; rosemary leaf extract (50% ursolic acid) AstraGin; San-qi Ginseng root and Astragalus root; Caffein anhydrous; **bitter orange citrus aurantium extract** (providing synephrine) Purenergy caffeine-p Teropure cocrystal; Norcoclaurine
2016	No specific claim	0.85	per 2 capsules: Narangine 600mg; Caffeine anhydrous 300 mg; Hesperidine (40%) 250 mg; **Synephrine HCL (99%pure) 50 mg**; Capsicum Annuum 20 mg; Piper Nigrum 20 mg
2016	No specific claim	26	Contents per 2 capsules: Caffein 300 mg; **aurantium extract (6% synephrine) 334 mg;** Green tea extract (standardized for 98% polyphenols) 200 mg; Yerba Mate extract 300 mg; Bioperine (95% piperine) 5 mg; Nicotinic acid (Niacin) 25 mg; 1,3 dimethylamaylamine 12.5 mg
2016	Work out	56	per 11.2 gram:citrulline malate 4, 000 mg, creatine monohydrate 2,000 mg, N-Acetyl-L-Tyrosine 750 mg, gamma-aminobutyric acid 500 mg, caffeine 450 mg, 2-aminoisoheptane 75 mg, higenamine 75 mg, hordenine 75 mg, **synephine HCL 75 mg**, niacinamide 30 mg, bioperine 10 mg

Year	Claim	Daily dose synephrine (mg/day)	Label information
2016	Work out	60	per 11.2 gram: citrulline malate 4,000 mg, creatine monohydrate 2,000 mg, N-Acetyl-L-Tyrosine 750 mg, caffeine 450 mg, 2-aminoisoheptane 75 mg, **citrus aurantium 75 mg**, higenamine 75 mg, hordenine 75 mg, niacinamide 30 mg, arcofuel 10 mg, bioperine 10 mg
2016	Work out	63	per 11.2 gram: citrulline malate 4,000 mg, creatine monohydrate 2,000 mg, N-Acetyl-L-Tyrosine 750 mg, caffeine 450 mg, 2-aminoisoheptane 75 mg, **citrus aurantium 75 mg**, higenamine 75 mg, hordenine 75 mg, niacinamide 30 mg, arcofuel 10 mg, bioperine 10 mg
2016	Work out	63	Per 11.2 gram: citrulline malate 4,000 mg, creatine monohydrate 2,000 mg, N-Acetyl-L-Tyrosine 750 mg, caffeine 450 mg, 2-aminoisoheptane 75 mg, **citrus aurantium 75 mg**, higenamine 75 mg, hordenine 75 mg, niacinamide 30 mg, arcofuel 10 mg, bioperine 10 mg
2016	Work out	64	per 11.2 gram: citrulline malate 4,000 mg, creatine monohydrate 2,000 mg, N-Acetyl-L-Tyrosine 750 mg, caffeine 450 mg, 2-aminoisoheptane 75 mg, **citrus aurantium 75 mg**, higenamine 75 mg, hordenine 75 mg, niacinamide 30 mg, arcofuel 10 mg, bioperine 10 mg
2016	Work out	59	per 11.2 gram: citrulline malate 4,000 mg, creatine monohydrate 2,000 mg, N-Acetyl-L-Tyrosine 750 mg, gamma-aminobutyric acid 500 mg, caffeine 450 mg, 2-aminoisoheptane 75 mg, higenamine 75 mg, hordenine 75 mg, **synephrine HCL 75 mg**, niacinamide 30 mg, bioperine 10 mg

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