



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

Risk assessment of *Argyrea nervosa*

RIVM letter report 2019-0210
W. Chen | L. de Wit-Bos



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Colophon

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Synopsis

Risk assessment of *Argyreia nervosa*

In the Netherlands, seeds from the plant Hawaiian Baby Woodrose (*Argyreia nervosa*) are being sold as a so-called 'legal high' in smart shops and by internet retailers. The use of these seeds is unsafe. They can cause hallucinogenic effects, nausea, vomiting, elevated heart rate, elevated blood pressure, (severe) fatigue and lethargy. These health effects can occur even when the seeds are consumed at the recommended dose. This is the conclusion of a risk assessment performed by RIVM.

Hawaiian Baby Woodrose seeds are sold as raw seeds or in capsules. The raw seeds can be eaten as such, or after being crushed and dissolved in liquid (generally hot water). The seeds of this plant contain the substance lysergic acid amide (LSA), a close analogue to LSD. The seeds are known for their strongly hallucinogenic effects.

Keywords: *Argyreia nervosa*, Hawaiian baby woodrose, food supplement, herbal preparation, Happy Caps, Lysergic Acid Amide, LSA

Publiekssamenvatting

Risicobeoordeling voor *Argyreia nervosa*

In Nederland zijn de zaden van de plant Hawaiian baby woodrose (*Argyreia nervosa*) als roesmiddel te koop in smartshops en via webshops. Het gebruik van deze zaden is niet veilig. Ze kunnen onder andere hallucinaties, misselijkheid, overgeven, verhoogde hartslag, verhoogde bloeddruk, (ernstige) vermoeidheid, en (ernstige) onverschilligheid veroorzaken. Deze gezondheidseffecten kunnen al ontstaan bij de geadviseerde doseringen. Dit blijkt uit een risicobeoordeling van het RIVM.

Hawaiian baby woodrose zaden worden los verkocht of in de vorm van capsules. Ze kunnen direct worden gegeten, of eerst worden vermalen en aangelengd met vloeistof (meestal heet water). In de zaden van deze plant zit de stof lyserginezuuramide (LSA), dat sterk lijkt op LSD. De zaden staan bekend om hun krachtige psychedelische effecten.

Kernwoorden: *Argyreia nervosa*, Hawaïaanse baby woodrose, voedingssupplement, kruidensupplement, Happy Caps, Lyserginezuuramide, LSA

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Summary

In recent years, the National Poisons Information Center (NVIC) received an increasing number of information requests about so-called Happy Caps. Some of these Happy Caps contain seeds of *Argyreia nervosa* (Hawaiian Baby Woodrose). Reported symptoms included nausea, vomiting, agitation, aggression, anxiety, panic, dizziness, dilated pupils, accelerated heartbeat, increased blood pressure and hallucinations. RIVM performed a risk assessment of the use of *A. nervosa* seeds.

In several countries, the use of *A. nervosa* in food supplements is forbidden. *A. nervosa* belongs to the family Convolvulaceae together with other members like *Ipomoea violacea* (Morning Glory) and *Rivea corymbosa* (Ololiuqui). It contains a large number of (ergot) alkaloids, with lysergic acid amide (LSA) and its stereoisomer (iso-LSA) being most prominent. LSA and iso-LSA are generally considered to be the main active compounds in *A. nervosa* seeds. Therefore, the risk assessment focused on studies with these two compounds or whole seeds.

(Food supplements with) *A. nervosa* can be bought on internet as seeds or capsules; an average dose of *A. nervosa* can vary between 2 to 10 seeds (0.2–1 g) or 1 to 2 capsules (containing 75–300 mg seeds). Based on the assumptions that 1 gram seeds contains between 1.7–16 mg LSA + iso-LSA, this roughly results in an exposure to LSA + iso-LSA in the range of 0.35–16 mg (seeds) or 0.13–4.8 mg (capsules). Taken together, this corresponds to 1.9–230 µg/kg bw for an individual weighing 70 kg.

The available toxicological information is limited and no information at all is available on possible long-term, genotoxic, carcinogenic and reproduction or developmental effects of the use of *A. nervosa*. *In vitro* studies suggest that LSA has a preference for serotonergic, dopaminergic and adrenergic receptors. Based on several case reports and human volunteer studies, adverse effects after the use of *A. nervosa* seeds included generally nausea, vomiting, tachycardia, hypertension, mydriasis, agitation, disturbances in orientation, feelings of lethargy and apathy, visual and auditory hallucinations, psychosis and anxiety. These effects were already reported after using the recommended dose (~2–10 seeds). No health based guidance value or no-observed-adverse-effect level (NOAEL) could be derived. As such, no safe level can be derived. An effect level in humans of 10.2 µg/kg bw LSA + iso-LSA was obtained in a human volunteer study.

The estimated exposure to LSA + iso-LSA following what is considered normal use of (food supplements containing) *A. nervosa* seeds is around or higher than this effect level. The use of (food supplements containing) seeds of *A. nervosa* available on the Dutch market therefore poses a safety concern. Effects that may occur when using the food supplements currently on the Dutch market, include amongst others hallucinogenic effects, nausea, vomiting, (severe) fatigue, lethargy,

tachycardia, hypertension. This is also shown in the report by NVIC. In addition, interactions may occur when (food supplements with) *A. nervosa* seeds are used together with other psychoactive compounds, like alcohol or cannabis, or with medicinal products that also act via serotonergic, dopaminergic and adrenergic receptors. Further, the conclusions of the current report may also apply to the use of other LSA-containing plants as or in food supplements.

1 Introduction

1.1 Background

In recent years, the Dutch Poisons Information Center (NVIC) received an increasing number of information requests about so-called Happy Caps. In the last 5 years, in total 41 requests about people who used these Happy Caps and developed poisoning were received by NVIC of which 17 in 2018. Happy Caps are capsules with herbal material, which are sold as products for body and mind. Most information requests concerned Happy Caps Trip-E. These contain seeds (unknown in what form) of *Argyreia nervosa* (Hawaiian Baby Woodrose). Symptoms included nausea, vomiting, agitation, aggression, anxiety, panic, dizziness, dilated pupils, accelerated heartbeat and increased blood pressure. Hallucinations were also reported nine times, indicating serious toxicity. NVIC reported this sharp increase in information requests to the Netherlands Food and Consumer Product Safety Authority (NVWA) (NVIC, 2019). RIVM performed a risk assessment of (food supplements containing) *A. nervosa*. For this risk assessment, the template for the safety assessment of food supplements that was recently developed by RIVM was used (de Wit-Bos et al., 2019).

1.2 Information on existing assessments

No existing toxicological evaluations have been identified for *A. nervosa*.

A. nervosa contains ergot alkaloids, with D-lysergic acid amide (LSA) or ergine and its epimer iso-LSA or isoergine as main active components (see Chapter 3). The European Food Safety Authority (EFSA) has published scientific opinions on ergot alkaloids (2012, 2017), however, they did not include LSA and iso-LSA in their opinion. Some of the ergot alkaloids assessed by EFSA, ergometrine and ergometrinine, do occur in *A. nervosa*, however in lesser amounts than the main active alkaloids LSA and iso-LSA. EFSA derived a group acute reference dose (ARfD) of 1 µg/kg bw and a group tolerable daily intake (TDI) of 0.6 µg/kg bw per day based on a BMDL₁₀¹ of 0.33 mg/kg bw per day for the incidence of tail muscular atrophy in rats fed ergotamine for 13 weeks, for ergot alkaloids (ergometrine, ergotamine, ergosine, ergocristine, ergocryptine, ergocornine and corresponding -inines). The ARfD and TDI were not considered to be applicable for the current assessment of *A. nervosa* since LSA and iso-LSA, the main constituents of *A. nervosa*, were not included in the EFSA opinion.

In 1999, RIVM published an overview of herbal drugs, so-called smart products and eco-drugs, including information about *A. nervosa* (Beltman et al., 1999). This report described amongst others the hallucinogenic and other effects after ingestion of *A. nervosa* seeds. Ingestion of 4-8 seeds result in an LSD²-like state characterized by colourful visions with a mystic experience. Other effects that may occur,

¹ BMDL₁₀ = the lower limit of the 95% confidence interval of the estimated dose leading to a 10% extra risk.

² LSD is the abbreviation of Lysergic acid diethylamide

especially at higher doses, include agitation, tachycardia, hypertension, nausea, vomiting and mydriasis.

1.3 Information on existing legislations

In Belgium, *Ipomoea* spp. are included in list 1 of the Appendix to the Royal Decree of 29 August 1997 meaning that they are considered as dangerous plants that, therefore, may not be used in or as foods (Koninklijk Besluit, 1997). *A. nervosa* is also known as *Ipomoea speciosa* but this synonym is not commonly used.

In Denmark, the use in food of *A. nervosa* is not acceptable because of health concerns, due to the presence of ergot alkaloids in *A. nervosa*, the potency of these alkaloids and the hallucinogenic effect they can cause (Drogelisten; Gry et al., 2011).

In Germany, *A. nervosa* seeds are on list A of the List of Substances of the Competent Federal Government and Federal State Authorities. List A includes substances that are not recommended for use as food or food ingredient due to known risks. *A. nervosa* seeds are on this list due to their psychotropic, highly psychedelic, and effect similar to LSD, because of the presence of ergot alkaloids, especially LSA (BVL, 2014).

The Food Standards Australia New Zealand (FSANZ) included *Argyria nervosa* in schedule 23 of Prohibited plants and fungi as part of the Australian New Zealand Food Standards Code (FSANZ, 2019).

2 Literature search

A search strategy was developed to capture relevant literature for the risk assessment of *A. nervosa*. Search terms were formulated to describe the herb, including its main constituents, to identify references describing toxicity or adverse outcomes and to include animal data as well as human data. The search terms included 'Argyreia nervosa', 'Hawaiian Baby Woodrose', 'Baby Hawaiian Woodrose', 'Elephant creeper', 'LSA', 'ergine', 'lysergic acid amide', 'd-lysergic acid amide', 'd-lysergamide', 'psychoactive', 'hallucinogenic', and 'legal high'. Three databases were searched (Embase, Pubmed, Scopus). Websites such as Google scholar and Google books were also checked. In total, 101 unique references were obtained.

In addition, grey literature was searched using the internet for assessments of *A. nervosa* of other institutes, however, no relevant information was found. The websites of Mansfeld's World Database of Agricultural and Horticultural Crops, the World Checklist of Selected Plant Families (WCSP), and the International Plant Names Index (IPNI) have been accessed to gather information on the identity of *A. nervosa*. The European Pharmacopeia was also searched, but *A. nervosa* is not listed in the European Pharmacopeia.

The obtained references were judged for their relevance based on title/abstract. In addition, the following exclusion criteria were applied:

- Studies solely about the other parts (root, stem, leaf, flower etc.) of *A. nervosa* than the seeds, since this report is focusing on the seeds of *A. nervosa*.
- Studies solely about the effects of a mixture plants.

Reference lists of highly relevant articles were checked to identify possible additional relevant references missed in the literature search. In total 45 references were included in the risk assessment.

3 Description of the product

3.1 Identity and nature of the source material

3.1.1

Botanical (preparation)

Argyreia nervosa, or Hawaiian Baby Woodrose, is a tropical pendulum plant. Its distribution ranges from the Indian subcontinent to Myanmar. *A. nervosa* belongs to the family Convolvulaceae (WCSP, 2019). The Convolvulaceae family is known as the bindweed or morning glory family of plants. Other members are Morning Glory (*Ipomoea violacea*) and Ololiuqui (*Rivea corymbosa*).

Synonyms of *A. nervosa* can be found in table 3.1. *A. nervosa* is a woody climber and its appearance is characterized by silver-coloured and heart-shaped leaves with silky hairs beneath. The flowers are funnel-shaped and violet or lavender-coloured and are structured in clusters. The round fruits are berry-like and contain smooth, brown seeds (Beltman et al., 1999). The seeds are black and are found in the pods of dried flowers. They can only be harvested when the pods are completely dried. Each flower contains 3 to 5 seeds per pod (Ashutosh et al., 2011).

Table 3.1 Information related to the classification of *Argyreia nervosa* (Source: WCSP, 2019; Mansfeld's World Data base of Agricultural and Horticultural Crops, 2019; IPNI, 2019; Beltman et al., 1999; Csurhes, S., 2016; Roux, 2018)

Scientific (Latin) name	Family: <i>Convolvulaceae</i> Species: <i>Argyreia nervosa</i> (Burm.f.) <i>Bojer</i>
Synonyms	<i>Convolvulus nervosus</i> Burm.f. ^a <i>Lettsomia nervosa</i> (Burm.f.) Roxb. <i>Rivea nervosa</i> (Burm.f.) Hallier f. <i>Convolvulus speciosus</i> L.f. <i>Ipomoea speciosa</i> (L.f.) <i>Argyreia speciosa</i> (L.f.) <i>Samudra speciosa</i> (L.f.) <i>Batatas betacea</i> Lindl. <i>Ipomoea valerij</i> Standl. & L.O. Williams
Common names	Hawaiian baby woodrose Baby Hawaiian woodrose Woolly morning glory Silver morning glory Elephant earvine Elephant creeper Elephant's climber Silberkraut Hawaiianische Holzrose <i>Lettsomia nervosa</i> Liane d'Argent
Part used	Seeds, leaves, root, fruits
Geographical origin	Indian subcontinent to Myanmar Introduced to numerous areas worldwide

Growth and harvesting conditions	Prefers tropical and sub-tropical climates. Prefers fertile, moist soil in a protected sunny position. Seed pots should be harvested when thoroughly dry.
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^a Basionym, replaced synonym

Traditionally, *A. nervosa* was used as a rejuvenating drug in the Ayurvedic system of medicines (Joseph et al., 2011) and treatment of, amongst others gonorrhoea, strangury³ and chronic ulcer (Ashutosh et al., 2011). The leaves were used externally in the treatment of ringworm, eczema, itch and other skin diseases. In addition, they were used as local stimulant and rubefacient or to prevent conception (Ashutosh et al., 2011). The root was thought to have immunomodulatory activity and was used for a wide variety of conditions, like anaemia, obesity, diabetes, diseases of the immune system etc. The seeds were used for treatment of anorexia, diabetes and various skin diseases and for their hypotensive, spasmolytic and anti-inflammatory action. Also the fruits were used for treatment of anorexia, diabetes and various skin diseases (Ashutosh et al., 2011). Nowadays, the seeds are used as a popular so-called "legal high". As aforementioned, because only the seeds are used in this respect, no further attention will be paid to the use of the leaves, root or fruits of *A. nervosa*.

3.2 Manufacturing process

3.2.1 Information on the method(s) of manufacture

Seeds are harvested from the dried pods of the flowers of *A. nervosa*. The seeds are sold as such and seeds (unknown in what form) are used in food supplements, singly or in combination with other ingredients.

3.2.2 Information on substances entering the manufacturing process

No entrance of other substances is expected.

3.3 Chemical composition

A large number of constituents have been reported for *A. nervosa* seeds. Table 3.2 provides an overview of these. Some studies analysed the content of commercially available products containing seeds of *A. nervosa*. Results show that the precise alkaloid content of the seeds highly depends on its origin. Hylin & Watson reported that each gram of fresh seeds contains approximately 3 mg of total alkaloids (Hylin & Watson, 1965). Chao & Der Marderosian (1973) found a total alkaloid content of 0.60% dry seed weight. Iso-LSA and LSA were most prominent with relative amounts of 31% and 23% of total alkaloids, respectively. Other ergot alkaloids present included, amongst others, lysergic acid- α -hydroxy ethyl amide (5.8% of total alkaloids) and ergometrine (8.2% of total alkaloids) (Chao & Der Marderosian, 1973). Paulke et al. (2014) studied two different commercially available products and found an LSA, iso-LSA and ergometrine + ergometrine content of respectively 40-42% (27-34 μ g per capsule), 44.5% and 10-11% of total alkaloids in one product (capsules), and in the other

³ Form of dysuria, a painful urination in which the urine is emitted drop by drop due to muscle spasms of the urethra or urinary bladder

product (whole seeds) the contents were 31-67% (3-15 µg per seed), 23.6% and 16-21% of total alkaloids, respectively. In addition, in absolute amounts, the whole seeds contained about 12% of the total alkaloid content of the capsules (Paulke et al., 2014).

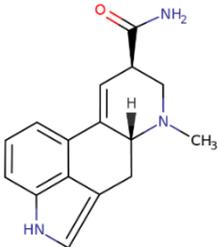
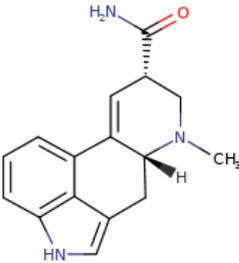
Kremer et al. (2012) analysed 4 batches of *A. nervosa* seeds (10 seeds per batch). Batch 1 and 2 were purchased from online shops from Germany and the Netherlands, respectively, and the other two batches were bought in local stores in Germany. Individual seed were crushed and each seed was analysed separately and the sum of LSA and iso-LSA was determined. Batch 1 had a median concentration of LSA + iso-LSA of 7.76 µg/mg of whole, dried seeds (range 3.75–16.03 µg/mg), batch 4 had a median concentration of 9.28 µg/mg (range 6.05–12.07 µg/mg). Batch 2 and 3 contained only traces of LSA + iso-LSA. In addition, 3 g of seeds from the same supplier as of batch 4 were crushed and homogenised and the LSA + iso-LSA content was 1.73 µg/mg (Kremer et al., 2012). The LSA+iso-LSA content in *A. nervosa* seeds as determined by Kremer et al. (2012) of 1.7-16 mg/g seeds (range) will be used in the exposure and risk assessment since they analysed seeds that are available on the market and they determined the sum of LSA and iso-LSA.

Table 3.2 Constituents of Argyreia seeds (Source: Ashutosh et al., 2011; Chao & Der Marderosian, 1973; Joseph et al., 2011; Paulke et al., 2014, 2015)

Constituents		
agroclavine	isolysergol	Glycerides of:
amino butyric acid	isosetoclavine	alminate acid
argyroside	leucine	behenic acid
caffeic acid	lutein	eicosanoic acid
chanoclavine-I	lysergene	eicosenoic acid
chanoclavine-II	lysergic acid(-α-	heneicosaoic acid
elymoclavine	hydroxy ethyl amide)	linolenic acid
ergine (LSA)	lysine	myristoleic acid
ergometrine	lysergol	myristic acid
ergometrinine	lysergylalanine	nonadecanoic acid
ethyl caffeate	methysergide	oleic acid
festuclavine	methylergometrine	palmitic acid
glutamic acid	molliclavine	stearic acid
glycine	penniclavine	
isoergine (iso-LSA)	phenylalanine	
isoleucine	praline	
isolysergic acid-α-	setoclavine	
hydroxy ethyl amide	tyrosine	

The ergot alkaloid (D-)lysergic acid amide (LSA, also known as ergine), and its epimer iso-LSA are considered to be the main active ingredients of the seeds due to their hallucinogenic properties (see table 3.3). LSA is a close analogue to the synthetic hallucinogen lysergic acid diethylamide (LSD). Since LSA and iso-LSA are considered to be the main active ingredients, the risk assessment will focus on these constituents of *A. nervosa* seeds.

Table 3.3 Active components from *A. nervosa* (Source: ChemID Plus)

Active component	(D-)Lysergic acid amide (LSA)	(D-)isolysergic acid amide (iso-LSA)
Chemical structure		
Systematic name	9,10-Didehydro-6-methyl-ergoline-8beta-carboxamide lysergamide	Ergoline-8-carboxamide-, 9,10-didehydro-6-methyl-, (8alpha)-
CAS No.	478-94-4	2889-26-1
Molecular formula	C16-H17-N3-O	C16-H17-N3-O
Molecular weight	267.3303	267.3303

3.4 Stability

The ratio of LSA:iso-LSA in an extract may vary greatly depending on the storage conditions, light exposure and extraction method (EFSA, 2012). The precise ratio LSA:iso-LSA in food supplements is unknown as it depends on these factors (see also section 3.3).

3.5 Use and use levels

An overview of (food supplements containing) *A. nervosa* seeds available on the Dutch market can be found in table 3.4. The seeds can either be bought as raw seeds or in a capsule (unknown if and how the seeds are processed).

According to the instructions for the use of the raw seeds, the seeds can be eaten as such or after extracting the alkaloids from the seeds. In the latter case, the husk is removed from the seeds after which they are crushed and soaked in hot water. The extract is consumed and according to some instructions the pulp can also be consumed. The average recommended dose of *A. nervosa* varies between 2 and 10 seeds, depending on the person's experience with using this supplement⁴⁵⁶. This equals approximately 0.2 to 1 g seed. For the capsules containing *A. nervosa* seeds a recommended daily dose of 1 to 2 capsules is given⁷⁸.

Some of the web shops list warning phrases for the seeds. The content of these phrases differs. Warning phrases that have been found include: that in case of an overdose it can cause nausea and vomiting, that the product is not intended for children, pregnant women, or breastfeeding women, that it should not be consumed together with alcohol, medicinal products or other stimulates, that it should not be used when having a

⁴ <https://www.dutch-smart.nl/smartshop/lsa-zaden/hawaiian-baby-woodrose-hawaii>

⁵ https://azarius.nl/smartshop/herbs/psychedelic_herbs/hawaiian-baby-woodrose/

⁶ <https://www.zamnesia.nl/lsa-zaden/5277-hawaiian-baby-woodrose-madagascar-argyreia-nervosa-10-zaden.html>

⁷ <https://www.happy-caps.nl/caps/trip-e/>

⁸ <https://www.happy-caps.nl/caps/space-e/>

high blood pressure, cardiovascular disease, or problems with liver, kidney, prostate and/or thyroid, or when familiar with panic attacks, and that it should not be used when using MAO inhibitors or antidepressants, or during heavy exercise⁴⁵⁶⁷.

Table 3.4. Examples of (food supplements containing) A. nervosa available on the Dutch market with recommended daily use and recommended dose.

	Ingredients	Recommended use	Total recommended daily dose
Product 1 ³	Hawaiian baby woodrose seeds	5-10 seeds	Not stated
Product 2 ⁴	Hawaiian baby woodrose Madagascar	2-8 seeds	Not stated
Product 3 ⁵	Hawaiian baby woodrose Madagascar	2-4 seeds	Not stated
Product 4 ⁶	Hawaiian baby woodrose seeds (150 mg), caffeine (20 mg), calcium dioxide, magnesium stearate (capsules)	1-2 capsules	150-300 mg Hawaiian baby woodrose seeds
Product 5 ⁷	Hawaiian baby woodrose (75 mg), L-tryptophan (50 mg), caffeine (40 mg), L-tyrosine (30 mg), theobromine (15 mg), vitamin B6 (10 mg), magnesium stearate, calcium dioxide	1-2 capsules	75-150 mg Hawaiian baby woodrose seeds

4 Exposure: extent and duration

4.1 Exposure from food supplement use

The recommended daily dose of 2-10 seeds (0.2–1 g seeds) or 1-2 capsules (75–300 mg seeds) can be used to give a rough estimate of the exposure to LSA and iso-LSA via consumption of *A. nervosa*. Based on the assumptions that 1 gram seeds contains between 1.7–16 mg LSA + iso-LSA as determined by Kremer et al. (2012), it can be estimated that the exposure to LSA + iso-LSA from consumption of raw seeds is in the range of 0.35–16 mg/day. Based on the same assumption, the estimated exposure to these compounds when using capsules is in the range 0.13–4.8 mg/day. For an individual weighing 70 kg, this corresponds to 4.9–230 µg/kg bw (for raw seeds) and 1.9–69 µg/kg bw (for capsules).

4.2 Possibility of additional/combined human exposure

Other members of the Convolvulaceae family, like *I. violacea* and *R. corymbosa* contain LSA as well, though the content is lower than in *A. nervosa* (Ashutosh et al., 2011). Additional exposure may therefore occur when people consume *A. nervosa* seeds together with seeds from other LSA-containing plants (Juszczak & Swiergiel, 2013). No other food products containing *A. nervosa* or LSA were identified.

4.3 Information on historical use of the ingredient

The seeds of *A. nervosa* have traditionally been used in folk medicine in for example India (Ashutosh et al., 2011). However, no information was found about the dosage of the specific ingredients. No information on the (historical) use of *A. nervosa* (seeds) is available in the European Pharmacopeia, in Hagers Handbuch der Pharmaceutizen Praxis or in the Commission E monographs. A monograph about *A. nervosa* was found in the database of Natural Medicines, where it is stated that oral use is likely unsafe (Natural Medicines, 2017).

5 Toxicological data

5.1 Toxicokinetics

5.1.1 *Absorption, distribution, metabolism, excretion*

During a human study with orally administered seeds of *A. nervosa*, blood and urine samples were obtained. *A. nervosa* seeds (3 g) were crushed and homogenized and analysed by high-performance liquid chromatography coupled to time of flight-mass spectrometry yielded an LSA + iso-LSA content of 1.73 µg/mg (Kremer et al., 2012). Four subjects ingested a seed preparation, corresponding to approximately four seeds (5.88 mg/kg bw, corresponding to an LSA [sum of LSA + iso-LSA] dose of 10.2 µg/kg bw), with a glass of water. Serum and urine samples were collected subsequently at different time intervals. LSA (sum of LSA + iso-LSA) concentrations in the serum samples were in the range of 0.66-1.38 ng/ml 30-40 minutes after ingestion. The highest concentration found was 3.15 ng/mL at 60 minutes after ingestion. In urine, LSA could be found up to 24 hours after ingestion. After 48 hours, no LSA could be detected. The LSA epimer iso-LSA was also detected in serum and urine in varying ratios, and the LSA:iso-LSA ratio varied interindividually and intraindividually at different time points (Paulke et al., 2012).

Disposition of iso-LSA was determined in the liver, brain and plasma of male Sprague-Dawley rats. Iso-LSA was isolated from seeds of *A. nervosa* and purified. After an intraperitoneal injection of 5 mg/kg, peak levels of iso-LSA were measured after 5 minutes in the liver (7.2 µg/g) and after 15 min in the brain (1.2 µg/g) and in the plasma (1.9 µg/mL). After 120 min, 90% of the compound had disappeared from the tissues and plasma. A half-life of 15-30 min was calculated. This study showed that iso-LSA is rapidly absorbed, distributed, and metabolized in rats (Vogel et al., 1972).

5.2 Toxicological data

5.2.1 *Acute toxicity*

In the study of Vogel et al. (1972), described above, also the psychoactive effect of iso-LSA after a single i.p. administration of 1, 5, 10 or 100 mg/kg on behaviour in male Sprague-Dawley rats (n=5-6 per dose group) was studied. The effect of iso-LSA on the conditioned avoidance response (CAR) in rats was determined in a shuttle box. A rat was placed in a box on one side of a barrier and was allowed a 9-sec period of rest prior to an 8-sec period of conditioned stimulus (CS; simultaneous light and buzzer signal). The rat had to leap across the barrier and move to the opposite side of the box to avoid a continuously scrambled, high voltage (0.5-mA) shock administered through the floor of the box. An animal that jumped over the barrier prior to onset of CS was scored a "premature avoidance" (PA). Rats, pretrained to produce consistently a CAR of at least 80% with no premature avoidances nor any significant delay in the actual avoidance movement were used for the behaviour study. At 1 mg/kg, no interference with the CAR was observed. At a dose of 5 mg/kg, rat behaviour was characterised by ptosis, piloerection and ataxia which lasted for approximately 60

minutes. Further, there was a significant decrease in CAR after 15 min followed by a rise to normal after 30 min with no significant occurrence of PA. This corresponded with the iso-LSA levels in the brain: the concentrations of iso-LSA were 0.77 ± 0.13 , 1.21 ± 0.27 and 0.93 ± 0.06 $\mu\text{g/g}$ at 5, 15 and 30 minutes after injection, respectively. Ptosis, piloerection, ataxia, hypersensitivity to handling and marked disorientation occurred at 10 mg/kg. A greater decline in CAR (32% at 15 min, 62% at 30 min and 53% at 45 min) was noted, and a significant number of PA occurred (13% at 15 min, 14% at 30 min, 33% at 45 min and 7% at 60 min). After administration of 100 mg/kg, behaviour was characterised by intense ptosis, hyperexcitability, salivation, loss of clinging response and hyperventilation but there was no paralysis of the limbs. The author suggested that iso-LSA is psychoactive, based on the results and because a decrease in CAR and increase in PA is characteristic for hallucinogenic compounds as hypothesized by Smythies et al. (1969). The close correlation between maximal brain levels of iso-LSA and maximal interference with CAR suggested that iso-LSA is the psychoactive principle (Vogel et al., 1972).

5.2.2 *Short-term and sub-chronic toxicity*

There are no studies available.

5.2.3 *Genotoxicity*

There are no studies available.

5.2.4 *Chronic toxicity and carcinogenicity*

There are no studies available.

5.2.5 *Reproduction and developmental toxicity*

Different extracts of *A. nervosa* seeds were assessed for their sperm-immobilizing potential on human sperm (Sharma et al., 2013). The minimum effective spermicidal concentration of *A. nervosa* seeds (not further specified) that induced instantaneous immobilization of human spermatozoa *in vitro* was 2.34 mg/ml of semen. This was irreversible as evaluated by sperm revival test. Further studies showed that the mechanism appeared to involve sperm plasma membrane disintegration and dissolution of sperm cell acrosomal cap.

5.2.6 *Other studies*

The receptor binding affinities of LSA (purity 99.2%) were studied by Paulke et al. (2013). An *in silico* prediction model was used to screen for serotonin, norepinephrine, dopamine, muscarine, and histamine receptor subtypes as potential targets for LSA, and the results were confirmed by *in vitro* binding assays and compared to LSD. Also for other ergot alkaloids present in *A. nervosa*, namely agroclavine, chanoclavine I+II, elymoclavine, festuclavine, ergometrine + ergometrinine, setoclavine + isosetoclavine, penniclavine and lysergol + isolysergol, the *in silico* prediction model was used to predict their affinity. In the prediction model, LSA and some of the other ergot alkaloids showed generally a preference for binding to serotonergic, dopaminergic and adrenergic receptors but not to muscarinergic or histaminergic receptors. In the *in vitro* binding assays on selected serotonergic, dopaminergic and adrenergic receptor subtypes, LSA and LSD showed comparable receptor preferences with the affinities of LSA

being lower than that of LSD. Not all predicted affinities *in silico* could be confirmed *in vitro* (Paulke et al., 2013).

LSA showed vasoconstrictor activity at bovine lateral saphenous vein and dorsal metatarsal artery. Segments of lateral saphenous vein and dorsal metatarsal artery were trimmed of excessive fat and connective tissues and were placed in buffer. Each tissue section was allowed to equilibrate for 60 min and was exposed to an α -adrenergic agonist solution to assure tissue contractile responsiveness. Cumulative dose-response curves for the selected agonists (phenylephrine, the experimental drug BHT-920, serotonin, *m*-trifluoromethylphenylpiperazine HCl and (\pm)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane HCl) were determined before and after a 30-min preincubation with specific concentrations (10^{-7} , 10^{-6} and 10^{-5} M) of LSA (two or three animals tissues used per agonist). Preincubation of tissues with LSA resulted in partial inhibition of the contractile response of phenylephrine (α 1-adrenergic receptor-selective agonist) and BHT-920 (α 2-adrenergic receptor-selective agonist) ($p < 0.05$), indicating partial agonist or antagonist activity of LSA at these receptors. Studies with selective serotonergic agents indicated that LSA may have predilection for serotonin-2 receptor (5-HT₂). Vasoconstriction in the lateral saphenous vein that was induced by the 5-HT₂ receptor-selective agent DOI ((\pm)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane·HCl) was inhibited ($p < 0.05$) by prior treatment with LSA. The author concluded that LSA acts as a partial agonist or antagonist at adrenergic and serotonergic receptors. As 5-HT₂ receptor is involved with excitatory response in motor neurons, smooth muscle of blood vessels and medication of behaviour response in humans, interacts of LSA with a serotonergic receptor may have impact on a wide variety of biological functions. (Oliver et al., 1993).

5.2.7 Human data

Case reports

Al-Assmar (1999) described a case of Hawaiian Baby Woodrose seed overdose after ingestion of 12 seeds by an 18-year old man (without ingestion of other active substances). He experienced auditory hallucinations, tachycardia (110 beats per minute), hypertension (170/90 mmHg), nausea, vomiting, nystagmus (involuntary, rapid eye movement), diaphoresis, blurred vision and dilated pupils (7 mm). After one month, the patient still complained of flashbacks characterized by auditory hallucinations every time he smoked cigarettes (Al-Assmar, 1999).

A 21-year-old male with a dependency on cannabis and familiar with depressive feelings took *A. nervosa* seeds three days in a row (respectively 4, 3 and 5 seeds) to experience an LSD-like trip. A few hours after he took the 5 seeds, he felt a sudden 'pop in the head' after which he suffered from a marked and persistent right-sided headache. He presented himself being pale and sweating and clearly distressed as he believed he had irreversible brain damage. He had a derealization experience and vigour disturbance with a delusional character. Tachycardia and tachypnoea persisted until the evening of the next day. The headache persisted for several days, while the feeling of distress was completely gone after three weeks. Drug screening in urine and

serum only showed the presence of tetrahydrocannabinol (THC) (Borsutzky et al., 2002).

Gertsch & Wood (2003) reported a case of an 18 year old male with a psychiatric history of polydrug abuse and depression with suicidality. He was submitted into the emergency department approximately 6 hours after ingesting 15 seeds of Hawaiian Baby Woodrose. He also inhaled ether extracted from starter fluid, smoked a small amount of marijuana, ingested dextromethorphan hydrobromide, and took a maintenance dose of paroxetine (20 mg). He was oriented to person but not place or time. He showed erratic and bizarre behaviour, was responding to internal stimuli, admitted to visual hallucinations consisting of a montage of 'colour blotches', symptoms of depression, including suicidal and homicidal ideation, and exhibited a tangential thought process with sporadically nonsensical content. His vital signs indicated sinus tachycardia (119-144 beats) and hypertension (systolic blood pressure: 131-179, diastolic blood pressure: 68-114), and physical examination revealed hyperactive reflexes. Initial laboratory evaluation was unremarkable except for a urine drug screen positive for marijuana only. The patient had polyuria for the first 12 hours after arrival despite a relatively normal fluid intake. He kept hallucinating and behaving in a bizarre fashion. After treatment with risperidone and lorazepam the patient's sensorium began to clear and no suicidal or homicidal ideations were reported by him after several hours. According to the authors, the ingestion of Hawaiian baby woodrose was suspected to be the major cause of the psychotic state because of the number of seeds consumed, the prominence of hallucinations in the clinical situation and the similarity of the clinical situation compared to previous reported intoxications with Hawaiian baby Woodrose. The other ingested substances were not known to cause hallucinations, had a relatively short half-life or were taken in relatively low doses and thus unlikely to be the main cause (Gertsch & Wood, 2003).

A 17-year-old female was submitted after taking 8 seeds of *A. nervosa* with alcohol because she was in an agitated state, frightened and disoriented with respect to time. She also showed significant concentration and attention deficits and gaps in the short and long term memory, rapidly changing mood conditions from euphoria to deep despair, and had delusions and hallucinations. Upon examination, she had normal pupil reflexes, blood pressure was 120:90 mmHg, pulse 74/min, and no warm or dry skin. Neurological tests and laboratory blood screens were both normal. There were no traces of cannabinoids, LSD, stimulantia, cocaine and phenocyclidin found in the urine. The symptoms diminished in the 24 hours after submission (Göpel, Maras, & Schmidt, 2003).

Flodrops et al. (2006) describe a case of acute voluntary intoxication with LSA by a 15-year old female by consuming 8 *A. nervosa* seeds. Clinical examination 2.5 hours after ingestion revealed bilateral mydriasis and a tranquil state which receded within hours. Forty-five minutes after ingestion, the girl had abdominal cramps and vomited. Laboratory tests involving blood count, electrolytes, transaminases, pseudocholinesterase activity, alcohol, benzodiazepines were normal. Urine tested positive for THC (Flodrops et al., 2006).

Legriël et al. (2008) reported on a 39-year-old-man with posterior reversible encephalopathy syndrome (PRES) presenting as convulsive status epilepticus associated with hypertensive encephalopathy after LSA ingestion. PRES is characterized by acute neurologic disorders (including altered mental status, seizure or status epilepticus, headache, visual loss, nausea, and vomiting). The patient had a history of chronic alcohol abuse, smoking, depression and had a seizure 3 years earlier. He was treated with clomipramide 75 mg/day for the last 6 months. The patient experienced several generalized, tonic-clonic seizures. In the hospital, he was presented with a state of altered consciousness with a Glasgow Coma Scale of 11, mental confusion, hyperreflexia, mydriasis, and diaphoresis. His body temperature was 38.4°C, blood pressure 185/130 mmHg, and heart rate 120 beats/min. He was treated with intravenous clonazepam bolus combined with phenobarbital infusion. Laboratory tests showed no metabolic disturbances. Standard toxicology screening tests for ethanol, cocaine, opiates, and benzodiazepines on blood and urine were negative, except for clomipramine. Cerebrospinal fluid analysis and cerebral computed tomography were normal. No cause for the status epilepticus or hypertension was identified. Magnetic resonance imaging (MRI) 24 hours after the end of the seizure showed extensive bilateral high signal predominating in the parietooccipital and posterior-fossa white matter. Three days after admission, physical examination showed mental confusion, headache, and visual hallucinations and hypertension. Seven days later, a repeat MRI was normal. Further urine profiling revealed marked and sustained increases in two specific metabolites of catechol-O-methyltransferase (COMT), normetanephrine and 3-methoxytyramine, indicating strong and simultaneous stimulation of the norepinephrine, dopamine and serotonin systems associated with high COMT-activity. When the patient was sufficiently recovered, he reported taking LSA immediately before the beginning of the seizure, however, the dose was not mentioned. According to the authors, the clinical history, blood and urinary catecholamine levels, and response to treatment strongly suggest that PRES was induced by LSA (Legriël et al., 2008).

Björnstadt et al. (2009) analysed urine of 103 patients of a Swedish emergency department with reported or suspected ingestion of psychoactive plant materials. In 8 patients (7.8%) LSA was suspected to be the cause for intoxication. Three of these patients reported consumption of Hawaiian baby woodrose or Morning Glory and 4 of these reported ingestion of synthetic LSA as powder or blotter (range 0.3–50 mg). For one of these patients it is not specified why LSA was suspected to be the cause for intoxication. This was confirmed by the detection of LSA in urine samples in 2 cases. The symptoms that were reported by these 2 confirmed cases were vomiting, mydriasis and leucocytosis, and lasted for more than 10 hours. The reported ingestion of synthetic LSA could not be verified by detection in urine. To investigate this inconsistency, three synthetic LSA preparations (blotter, liquid, and a chocolate flavoured powder for snorting) were purchased from a website and analysed by the LC-MS/MS multicomponent method. LSA could not be detected in any of them. The authors pointed out that synthetic LSA preparations may not always contain LSA but may contain other designer drugs instead (Björnstad et al., 2009).

Klinke et al. (2010) described two cases of human consumption of seeds from *A. nervosa*, which resulted in one fatality due to falling from a building (male aged 29) and one surviving witness (male aged 25). The seeds were soaked in water for approximately 2.5-3 hours and subsequently ingested. The witness ingested 6 seeds, while it is not clear how many seeds the other person ingested. Shortly thereafter, both males smoked cannabis. Approximately 40 min after ingestion, the witness experienced a sense of wellbeing as well as losing track of time. Approximately 3 hours after ingestion, the other person became severely agitated and jumped out of a window. LSA concentrations were 4.9 µg/L in blood and 1.0 mg/L in urine of the deceased person (collected 13 hours after ingestion) and 1.8 µg/L in blood and 0.50 mg/L in urine of the witness (taken at 9 hours after ingestion). In addition, detectable THC (22 µg/L) and ethanol (0.71 g/L) levels were found in the blood of the deceased but not in the witness. Other constituents originating from the seeds of *A. nervosa*, i.e. ergonovine and lysergic acid α -hydroxyethylamide were identified in the biological samples. Furthermore, two isomers of ergonovine and d-lysergic acid α -hydroxyethylamide were also found in these samples but no iso-LSA. The 2-hydroxy-3-oxo metabolites of LSA and ergonovine were also identified in the urine sample of the deceased (Klinke et al., 2010).

The Swedish Poisons Information Center was consulted in 65 cases (in 34 cases by a hospital) relating to consumption of (suspected) Hawaiian baby wood rose seeds between January 2000 and December 2010. The dose was known in 43 cases and varied between 4-30 seeds. The most common symptoms were nausea/vomiting (n=29), hallucinations (n=14), mydriasis (n=14), tachycardia (n=12), and agitation (n=10). A number of other less common symptoms e.g. diarrhoea, headache, CNS depression, tremor, seizures, leucocytosis and elevated transaminases were noted. Specific anticholinergic symptoms were only found in one case (dry mouth). No relationship between dose and symptoms was reported. Most of the intoxications were mild or moderate and no severe cases occurred (Hultén & Luhr, 2012).

Juszczak & Swiergiel (2013) analysed reports published on a website by Polish drug users who used seeds of *A. nervosa*. Seven reports of the effects induced by *A. nervosa* were registered between 2003 and 2009. All the authors were males; two reported their age (18 and 23 years old). Seeds were eaten (five cases) or swallowed after suspending the ground seeds in non-alcoholic drinks (two cases). In two cases, the seeds were ground before eating and in one case the seeds were held in the mouth until they were easy to chew. In two cases, the subjects mentioned that they removed or attempted to remove the outer shells from seeds. The doses ranged from three to eight seeds. In six cases, the subjects also smoked cannabis and in one case the subject smoked *Leonotis nepetifolia* (Klip Dagga, Lion's Ear). Reported effects included gastrointestinal effects, changes in emotional status, visual and auditory effects. Gastrointestinal effects occurred within 30 minutes, and included nausea (n=4), along with abdominal pain (n=2) and vomiting (n=1). Central nervous system (CNS) effects were reported between 30-120 minutes and lasted for 1.5 hours up to 14 hours. Changes in emotional status included persecutory delusions (n=2), feelings of being looked at and ridiculed (n=2), assuming to have an increased insight (n=2),

euphoria (n=3), happiness (n=2), experience of beauty (n=1), delight (n=1), great mood (n=1), feelings of disdain for other people (n=1), feeling of being trapped (n=1), depressive mood combined with suicidal thought (n=1), feelings of loneliness (n=1), fear and panic (n=1). The visual effects included increased sensitivity to colours (n=3), visual distortions (n=4) and images seen with closed (n=5) or open (n=2) eyes. Auditory effects included hallucinations, increased auditory sensitivity and altered sound perception.

In addition, four reports by three men and one female (aged 19-25 years) were made about the ingestion of the drug "druids fantasy" in 2009 and 2010 (Juszczak & Swiergiel, 2013). This drug is marketed in capsules and is assumed to contain LSA. No subject reported to be taking other drugs, however it is suggested that the product contains more than one ingredient, e.g. also morning glory. Gastrointestinal effects were reported after approximately 60 minutes, including nausea (n=4), abdominal pain (n=1), and vomiting (n=1). Effects on the CNS were reported after 2-4 hours and their duration was between >3.5 - 6.5 hours. Changes in emotional status included happiness (n=1), feeling of love (n=1), euphoria (n=2), experience of beauty (n=2), mental orgasm (n=1), feelings that nothing is a certainty, of futility and helplessness (n=1). In addition, auditory hallucinations (n=1) and visual effects, including increased sensitivity to colours, visual distortions, images seen with closed or open eyes, were reported. Two subjects reported delayed effects like a mild headache and tiredness, and diarrhoea and impaired movements. In all cases, the dose was about 6 capsules. The authors conclude that generally, the effects induced by LSA are variable and subject-specific (Juszczak & Swiergiel, 2013).

Meyer Karre & Heinrich (2014) described an acute ingestion of Hawaiian Baby Woodrose seeds. A 23-year-old Caucasian man presented to the emergency department with an alternation in mental status including agitation and visual hallucinations after an acute ingestion of Hawaiian Baby Woodrose seeds. He was tachycardic (154 beats/min) and hypertensive (152/96 mmHg), and physical examination showed normal-sized, minimally reactive pupils, 2 contusions on his back, and cool extremities. Laboratory tests revealed leukocytosis, an anion gap metabolic acidosis secondary to an elevated lactic acid level (18.1mmol/L), and an elevated creatine kinase level (2330 U/L). He had developed acute kidney injury evidenced by a creatinine level of 1.70 mg/dL, which was thought to be secondary to an electroshock-induced or drug-induced rhabdomyolysis. Urine drug screen was positive for cannabinoids. A head CT scan was normal. Over 24 hours, his acute kidney injury and rhabdomyolysis resolved with hydration and his mental status returned to baseline. He confirmed that he had ingested the Hawaiian baby wood rose seeds, of which his family said it amounted to 30 seeds. Due to the similarities to previous reports of Hawaiian baby woodrose intoxication, hallucinations, hypertension and agitation, it was concluded that the clinical picture was consistent with the effects of Hawaiian baby woodrose seeds and not cannabis (Meyer Karre & Heinrich, 2014).

Ponté & Lapeyre-Mestre (2017) describe 4 cases of unintended psychic effects (leading to hospitalization in 2 cases) caused by the use of LSA, reported to the Toulouse Addictovigilance Centre. These included two

males who ingested Happy Caps Space-E and experienced effects comparable to LSD, and two females who consumed a tea made from *Ipomoea volubilis* seeds and experienced tachycardia, hypertension, mydriasis, disorientation with regard to time and space, incoherent speech and agitation for which hospitalisation was necessary (Ponte & Lapeyre-Mestre, 2017).

Twenty-nine cases of poisoning by *A. nervosa* were reported to the Texas Poison Center Network during 2000-2018. In 15 cases (51.7%) it was consumed as seeds, in 3 cases as beads, pieces or pills and in 11 cases the plant part was unknown. All but one cases concerned oral ingestion. No concomitantly taken other substances were reported in 22 cases (75.9%). In most cases it concerned man (79.3%), and the mean age was 24.4 years (range: 16-53 years). A specific clinical effect was reported in 26 cases (89.7%), including mostly nausea (34.5%), vomiting (24.1%), hallucinations or delusions (24.1%), confusion (13.8%), agitation or irritability (10.3%), mydriasis (13.8%) and tachycardia (24.1%). No deaths were reported (Forrester, 2019).

In the last 5 years, in total 41 information requests about people who used Happy Caps and developed poisoning were received by NVIC of which 17 in 2018. In 27 cases, these Happy Caps contained *A. nervosa*. In addition, in 7 cases LSA-containing seeds were taken for which in 4 cases it was confirmed to be seeds from *A. nervosa*. Ingested amounts varied from 2 to 6 seeds or 1 to 11 capsules. Reported symptoms include nausea, vomiting, agitation, aggression, anxiety, panic, dizziness, dilated pupils, accelerated heartbeat and increased blood pressure. Hallucinations were also reported nine times, indicating serious toxicity. In 14 cases, there were also other substances used concomitantly, like alcohol, cannabis or other drugs (personal communication NVIC, 2019).

Human volunteer studies

Heim, Heimann & Lukács (1968) conducted experiments with increasing doses of LSA (0.04 or 0.09 mg/kg bw), iso-LSA (0.03, 0.06 or 0.07 mg/kg bw), or total alkaloids from the drug Ololiuqui (*Rivea corymbosa*; 0.02, 0.06, 0.08 or 0.10 mg/kg bw) in healthy volunteers. Each dose was tested in one volunteer. Higher doses could not be tested due to expected adverse effects. Ingestion of LSA led to nausea, vomiting, an illness-like state with general fatigue, sweating and dizziness, vision problems, slower movements and speech (a state of lethargy and apathy), beginning approximately 45 minutes after ingestion and becoming more pronounced over the next hours. The volunteer who ingested 0.09 mg/kg bw also suffered from cordial pain and shortness of breath, and a violent unmotivated fear. At the lower dose, the effects were diminished after 3-4 hours while at the higher dose it took until the next day. Ingestion of iso-LSA led first to a sleepy condition, and thereafter feelings of euphoria, paraesthesia and synaesthesia were experienced by the test persons. Later on, also impairment of thinking ability was mentioned. At the highest dose, severe nausea accompanied by a drop in blood pressure, and feelings of being in agony occurred. Ingestion of total alkaloids led to a sleepy condition followed by feelings of euphoria for up to 5-6 hours at a dose of 0.02 mg/kg bw. At higher doses, the vegetative symptoms were more pronounced in the test

persons. At the highest dose of 0.10 mg/kg bw, an increase in blood pressure, pulse rate and a decrease in breath rate occurred and the test person was in agony and showed a strong mydriasis. A total recovery was, according to the test person, achieved after 48 hours. Based on these results, the authors suggest that the vegetative symptoms are probably caused by LSA while iso-LSA leads to impairment of the thinking ability and effects on a persons' conscious (Heim, Heimann & Lukács, 1968). The lowest-observed-adverse-effect-levels (LOAELs) in this study were 0.03 mg/kg bw for iso-LSA, 0.04 mg/kg bw for LSA and 0.02 mg/kg bw for total alkaloids from *R. corymbosa* (the lowest doses tested). However, it must be noted that the purity of the compounds was not given nor were remarks made on the possible epimerisation of the compounds. Therefore, it is not clear if this distinction between the different effects caused by the two epimers can be drawn.

Shawcross (1983) conducted an experiment in which six male volunteers were asked to ingest *A. nervosa* seeds in four sessions, first two seeds and then each session two seeds more, up to 8 seeds (average weight seeds 100 mg) in the final session. Seeds were ground and put into gelatine capsules per two seeds. Doses were 1.77, 2.38, 2.48, 3.15, 3.54, 4.74, 4.96, 5.31, 6.44, 7.02, 7.35 and 9.80 mg/kg bw seeds. For each session a questionnaire with questions concerning the physical and psychic effects were filled out. Nausea and other symptoms in the stomach were often reported, with a time to onset of 10 to 120 minutes. "Speedy" feelings were reported only at the highest two dosages (7.35 and 9.80 mg/kg bw). Only one volunteer reported euphoria at 6.44 mg/kg bw. Psychedelic effects reported at low doses included seeing enhanced colours and visualisation of patterns in both plain and texture surfaces. At the highest three doses, enhanced colours were noted and a woozy feeling.

A study was designed to assess how driving ability is affected by *A. nervosa*. Four healthy drug naive volunteers ingested 5.88 mg/kg bw (corresponding to approximately 4 seeds) of an *A. nervosa* seed preparation with a glass of water on an empty stomach. For the *A. nervosa* seed preparation, 3 g seeds were crushed and homogenized and the sum of LSA+iso-LSA was 1.73 µg/mg. The total LSA + iso-LSA dose was therefore 10.17 µg/kg bw. Thirty minutes after ingestion one participant felt unable to perform any tests due to severe adverse effects, such as (massive) nausea, vomiting, weakness/fatigue and tremor of the hands. One subject had a significant psychological response characterised by aphasia, fits of laughter without any apparent reason, and a psychosis-like state. Another subject exhibited no noticeable abnormalities. A temporarily elevated blood pressure was observed in all individuals. Full recovery of adverse effects occurred within 9 hours after ingestion. The study demonstrates that the ingestion of LSA-containing seeds can lead to severe adverse effects that may require medical treatment. In addition, the variability of adverse effects does not necessarily seem to be related to dose, as all subjects received the same dose per kg bw, which indicated there are large interindividual differences (Kremer et al., 2012). The LOAEL in this study was 10.17 µg/kg bw LSA + iso-LSA, the lowest (only) dose tested.

5.2.8 *Interactions*

No studies were identified studying the interactions between *A. nervosa* seeds and other products. In case reports, it was frequently reported that subjects ingesting seeds of *A. nervosa* also smoked cannabis or drank alcohol which could have led to interactions (Juszczak & Swiergiel, 2013; NVIC, 2019).

5.3 **Derivation of toxicological reference value**

The toxicological information about *A. nervosa*, LSA and iso-LSA is limited. *In vitro* studies suggest that LSA has a preference for serotonergic, dopaminergic and adrenergic receptors. No information regarding short-term toxicity, genotoxicity, chronic toxicity, carcinogenicity or reproduction and developmental toxicity is available for *A. nervosa* and its main active constituents LSA and iso-LSA. Several case reports and some human volunteer studies have been found in literature. Doses reported in these case reports and human volunteer studies ranged from a relatively low amount of 3 seeds, which corresponds to what is considered normal use, up to 15-30 seeds. Adverse effects that were reported included generally nausea, vomiting, tachycardia, hypertension, mydriasis, agitation, disturbances in orientation, feelings of lethargy and apathy, visual and auditory hallucinations, psychosis and anxiety. The occurrence and severity of the effects depended on the alkaloid content of the seeds/products and there were large differences in interindividual susceptibility. Also, in some case studies *A. nervosa* seeds were used in combination with other substances, like alcohol or cannabis which could also influence the severity and type of effects.

It is not possible to establish a health based guidance value due to the limited data available. No no-observed-adverse-effect level (NOAEL) could be derived from the studies available. A LOAEL of 10.2 µg/kg bw was found in the human volunteer study of Kremer et al. (2012). At this exposure level, three of the four human volunteers experienced severe adverse effects like (massive) nausea, vomiting, hypertension, weakness/fatigue, tremor of the hands, aphasia, and a psychosis-like state. Lower doses were not tested in this study. Doses of LSD effective in humans are in the range 25-200 µg p.o. (Passie et al., 2008), or 0.4-2.0 µg/kg bw for a 70-kg person. So the LOAEL for LSA is in the same order of magnitude as the effective doses of LSD. This LOAEL of 10.2 µg/kg bw can be seen as effect level⁹ in humans and will be used in the risk assessment.

⁹ In this risk assessment, an effect level is defined as the lowest dose at which effects have been observed in humans. This does not mean that there are no lower doses at which effect can occur in humans. However, as lower doses have not been investigated no statements can be made about this.

6 Risk assessment

6.1 Risk assessment

A. nervosa cannot be assessed using the presumption of safety approach as no historic use with known exposure levels in large population groups in Europe has been identified. No health-based guidance value could be established for *A. nervosa* and/or its main active ingredients LSA and iso-LSA. No NOAEL could be derived from the studies available. An effect level of 10.2 µg/kg bw could be obtained from the human volunteer study of Kremer et al. (2012).

The estimated exposure to LSA + iso-LSA due to the use of (food supplements containing) *A. nervosa* seeds available on the Dutch market is estimated to be in the range of 1.9–230 µg/kg bw. The estimated exposure is around or higher than the effect level of 10.2 µg/kg bw. The use of (food supplements containing) seeds of *A. nervosa* available on the Dutch market therefore poses a safety concern. Effects that may occur when using the food supplements currently on the Dutch market, include amongst others hallucinogenic effects, nausea, vomiting, fatigue, lethargy, tachycardia, hypertension. This is also shown in the report by NVIC (NVIC, 2019).

6.2 Interactions

As *A. nervosa* seeds contain psychoactive compounds, combined use with other psychoactive compounds may affect the severity and/or duration of the physical and hallucinogenic effects. In case reports, it was frequently reported that subjects ingesting seeds of *A. nervosa* also smoked cannabis or drank alcohol (Juszczak & Swiergiel, 2013; NVIC, 2019). One reason mentioned by users for the concomitant use of cannabis is that it may diminish the nausea caused by *A. nervosa* (Juszczak & Swiergiel, 2013). This may indicate that this is a quite common combination for users.

In addition, as *in vitro* data suggest that LSA may bind to serotonergic, dopaminergic and adrenergic receptors, which is supported by the observed effects in humans, it cannot be ruled out that concomitant use of medicinal products that also act via these receptors may lead to interactions.

6.3 Sensitive/vulnerable groups

Interindividual differences in response to *A. nervosa* have been observed at the same dose, but the reason for these interindividual differences is not yet known.

Vulnerable groups include pregnant women and individuals with a history of liver disorders (Gottlieb, 1973). A reason for this last group was not given, but it may have to do with altered metabolism. Also children are probably more prone to adverse effects due to their still developing body, both physically and mentally.

6.4 Uncertainties

Exposure

The content of the psychoactive compounds in *A. nervosa* seeds varies greatly dependent on the individual plant, time of harvest, environmental conditions, and cultural practices. It has been observed that even in a single batch alkaloid contents can differ significantly (Kremer et al., 2012; Paulke et al., 2014). This hampers a precise estimation of exposure to LSA and iso-LSA when taking (food supplements containing) *A. nervosa* seeds and may therefore lead to an under- or overestimation of an individual's exposure.

In addition, this report focused on LSA and iso-LSA as these are generally considered to be the active compounds of *A. nervosa* seeds. However, the precise role of other (ergot) alkaloids in the (psychedelic) effects of the *A. nervosa* seeds is not clear yet. In case other alkaloids are involved as well, the current rough exposure estimation may be an underestimation of the total exposure to (psycho)active compounds. However, as the LSA + iso-LSA content is highly variable between seeds/batches these exposure estimates must be seen as rough indications. Furthermore, the estimated exposure is according to what is considered normal or recommended use. More than recommended use will lead to even higher exposure to LSA + iso-LSA. Also it must be noted that the effects of *A. nervosa* seeds differ greatly between individuals as also observed in the volunteer study of Kremer et al. It is therefore not possible to derive a safe level nor to predict which precise effects will occur after using (food supplements with) *A. nervosa* seeds.

Toxicity

The toxic effects of *A. nervosa* seeds have not been thoroughly studied. Most evidence for its adverse effects originates from case reports and human volunteer studies after single exposure. This means that the chronic effects are unknown but also that there is no information about genotoxicity or reproduction and developmental toxicity. Also, as in many cases *A. nervosa* seeds are combined with other compounds, which makes it more difficult to distinguish the precise effects of *A. nervosa* and that of other compounds or of the combination of compounds. On the other hand, most effects seen with combined use have also been noticed after use of *A. nervosa* only.

It may also be that, when *A. nervosa* is sold in the form of capsules or pills, other compounds or herbal preparations not declared on the leaflet or package are added to achieve certain effects, as has been observed for synthetic LSA products (Björnstadt et al., 2009). This may lead to more severe or different adverse effects than expected due to interactions or the fact that people are exposed to different compounds not from *A. nervosa*.

7 Conclusions and recommendations

The use of (food supplements with) *A. nervosa* seeds currently available on the Dutch market is not safe and may lead to adverse effects due to the presence of the (psycho)active compounds LSA and iso-LSA. Effects that may occur include amongst others hallucinogenic effects, nausea, vomiting, fatigue, lethargy, tachycardia, hypertension.

This risk assessment focussed on *A. nervosa*. Other plants from the Convolvulaceae family like for example *Rivea corymbosa* and *Ipomoea violacea* also contain LSA and other ergot alkaloids. Case reports of intoxications after the use of these plants are known (e.g. Wilson, 2017). The conclusions of the current report may therefore also apply to the use of other LSA-containing plants as or in food supplements.

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