Report of the Scientific Committee of the Spanish Agency for Consumer Affairs, Food Safety and Nutrition (AECOSAN) on the risk of the use of seeds of *Mucuna pruriens* in craft products

Section of Consumer Affairs Section

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Abstract

The Scientific Committee of the Spanish Agency for Consumer Affairs, Food Safety and Nutrition (AECOSAN) has assessed the health risks associated with the use of *Mucuna pruriens* seeds in handicraft products. This report describes the different uses in said handicraft products and the uses of its alleged properties as medicinal plant, in human food, as an antidote for snake bites and as a biomass or vegetation cover. The sociological context of the use of *Mucuna pruriens* is also included in this report. Furthermore, the characteristics that identify *Mucuna pruriens* as a plant species are described along with the pharmacology properties and toxicology properties as described in toxicity studies of a single dose and of repeated doses as well as the risk evaluation of accidental ingestion of the seeds in handicraft products. It is concluded that the LD_{50} value of *Mucuna pruriens* is greater than 2000 mg/kg bw and the NOEL can be identified as 70 mg/kg bw/day (limit dose) drawn from a repeated dose toxicity study in rabbits. A value of TD_{Lo} (lowest published toxic dose, or toxic dose low) of L-dopa in humans has been estimated at 4286 mg/kg bw. The calculated security margin of the consumption of *Mucuna pruriens* seeds is broad in relation to the potential exposure in adults as well as children. However, the risk of accidental exposure to the *Mucuna pruriens* seeds should be considered as it could cause respiratory or digestive occlusion in children, which represents an additional risk. Coming into contact with *Mucuna pruriens* seeds could cause intense itching and contact allergy in all population groups. Children and pregnant women have a higher sensitivity to the ingestion of *Mucuna pruriens* seeds due to their content and the pharmacological action of the L-dopa (levadopa).

Key words

Mucuna pruriens, uses, handicraft, safety, pharmacology, toxicology, sociology.

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Contents

1. Introduction

The Scientific Committee of the Spanish Agency for Consumer Affairs, Food Safety and Nutrition (AECOSAN) presents this report with the objective of issuing a scientific ruling to establish whether the use of the seeds of *Mucuna pruriens* in craft products poses a risk for the health of consumers –users and in particular for the infant population.

The following databases have been consulted given their relevance: PubMed-Medline, SciFinder, ScienceDirect, Web of Knowledge.

1.1 Terms of reference

This ruling is issued at the request of the Spanish Agency for Consumer Affairs, Food Safety and Nutrition (AECOSAN) and considering the General Obligation of Safety considered in the legislation.

Art. 11 of Royal Decree 1/2007, of 16 November, approving the consolidated text of the General Law for the defence of Consumers and Users and other supplementary laws, establishes that "goods … placed on the market must be safe". It goes on to define as safe "goods… which, under normal or reasonably foreseeable conditions of use, including their length, do not pose a risk for the health and safety of persons, or only the minimum risks compatible with the use of the good or service and considered acceptable within a high level of protection of the health and safety of persons". In accordance with Art. 2.c) of Royal Decree 1801/2003, of 26 December, on general product safety, risk means "the possibility that the consumers and users suffer damage to their health or safety, derived from the use, consumption or presence of a product".

Given these premises, the present opinion sets out to establish whether craft products which incorporate seeds of *Mucuna pruriens* are safe and whether the sale of these seeds for this purpose is safe.

2. Known uses

This Scientific Committee considers it necessary to provide a brief description of the different uses of the seeds of *Mucuna pruriens*.

The beneficial properties described in the different uses are only the supposed properties described in the scientific literature revised. This Scientific Committee believes it necessary to advise that, although these properties of *Mucuna Pruriens* have been published, this fact does not imply, in any way, that these properties have been scientifically validated or recognised by the official governing Agencies, the scientific community or this Scientific Committee of the AECOSAN.

During the search for documentation and information for their analysis, the Scientific Committee found several web pages in which preparations of *Mucuna pruriens* were offered for sale in various concentrations and forms. Some of these web pages, freely accessed via internet, correspond to establishments registered in Spain; others in member countries of the European Union; and others in third countries, although they are also directed at the Spanish market. Moreover, in all of these, the marketing is accompanied by numerous nutrition and health claims.

2.1 Use in craftwork

The seeds of *Mucuna pruriens* have been used in craft products for the production of bracelets, necklaces and trinkets (Benedetti, 2012). The use of the seed as a craft product may be as the final finished product or as a product for domestic manufacture and in turn it can be found as a final manufactured product or as a product marketed loose without any prior heat treatment.

2.2 Use as a medicinal plant

The seeds of *Mucuna pruriens* have been used in traditional medicine for the treatment of Parkinson's disease. The powder of the seeds of *Mucuna pruriens* contains high concentrations of L-Dopa, a direct precursor of the dopamine neurotransmitter; it has been used for many years in the traditional Ayurvedic medicine of India to treat neurodegenerative diseases such as Parkinson's (Manyam et al., 2004a,b). In large quantities (30 g/dose) it has been used in the treatment of Parkinson's disease as an alternative to the L-Dopa/carbidopa medicine (Katzenschalager et al., 2004). It has also been used in the treatment of psychotic patients or in patients with cognitive disorders, and in the treatment of diabetes mellitus and as an antioxidant and hypolipedemic (Sharma et al., 1978; Yadav et al., 2013). It is also used for its supposed properties in the improvement of the quality of semen in infertile men (Shukla et al., 2010).

Although there are numerous papers referring to the use of *Mucuna pruriens* as a medicine, there is limited information about its single dose and repeated dose toxicity.

In the European Union *Mucuna pruriens* is not included in the list of plant substances for its assessment (EMA, 2014). The document DFS 6000 "List of Herbal and Homeopathic Remedies", an internal manual of the HMRC, the UK's tax, payments and customs authority, classifies *Mucuna pruriens* under its synonym of Dolichos pruriens in category "A", recognised as a medicinal product. (https://www.gov.uk/hmrc-internal-manuals/duty-free-spirits/dfs6000).

The European Food Safety Authority (EFSA, 2012) includes it as a whole plant in the Compendium of Botanicals, which identifies substances of possible risk to human health when used in food and food supplements, based on the high L-Dopa content of its seeds, in addition to other biologically active substances (indole alkaloid), derived from tryptamine including N,N-dimethyltryptamine, bufotenin, and 5-metoxy-N,N-dimethyltryptamin (Infante et al., 1990; Misra and Wagner, 2004). Without prejudice to the current legal framework, this compendium does not have legal status and cannot be used in support or as evidence in any disagreement or dispute relating to the legal classification of the products or substances. Its purpose is to provide an aid to risk assessment and management personnel responsible for the safety of specific ingredients in food supplements.

2.3 Use in human food

The seeds of *Mucuna pruriens* are not considered as a food for direct consumption due to their potential toxic effects derived from their composition as detailed in section 3, sub-section "composition" of this report. Nevertheless, in some African countries, they are consumed after heat treatment in times of hunger or food shortages (Onweluzo and Eilitta, 2003).

Mucuna Pruriens and its seeds have been analysed to determine their nutritional quality given the easy access to this legume in certain countries (Bhat et al., 2008; Gallegos, 1999). For this reason, it was assessed as an alternative source of protein and, although the result was not positive for this objective (Onweluzo, 2003), the procedures used for the assessment suggest the possibility of using preparation techniques which may eliminate L-Dopa and other biologically active compounds. It has been confirmed that some heat treatments including boiling increase the safety of the consumption of the seed due to the drastic reduction of the L-Dopa content to values of less than 1% (Mugendia et al., 2010; Teixeira and Cullen Rich, 2003).

In this respect, the seed or derivatives of *Mucuna pruriens* do not have a history of consumption in the European Union as food; it is not authorised as a "Novel Food"; nor is it registered at national level as a food supplement; as mentioned above, it is included in the "European Compendium of Botanicals" (EFSA, 2012); and moreover, the nutritional and health claims used have not been validated. In addition, it should be noted that the risks would be even more serious as these are products intended directly for human consumption.

2.4 Use as an antidote to snake bites

In Nigeria, the seeds of *Mucuna pruriens* are used in folk medicine as an antidote in the treatment of snake bites (*Echis carinatus, Naja naja*) (Soares et al., 2005).

2.5 Use as biomass or plant cover

Its possible agro-ecological interest has established that it is used as biomass (Villareal Romero et al., 2014) or as plant cover for fallow (Berlingeri et al., 2008).

2.6 Sociological context

The seeds of *Mucuna pruriens* have been used in craft products. This use of the legume has been analysed from the perspective of the development of less-favoured areas. Craftwork is a tool of great value for encouraging the inclusion of indigenous groups in economic activities and also as an element for boosting the cultural wealth which gives them identity and allows them to integrate in society (Gallegos Téllez Rojo, 1999; Benedetti, 2012).

3. Botanical classiication and characteristics of *Mucuna pruriens*

Mucuna pruriens (L.) DC (sin. *Dolichos pruriens*) is a tropical legume from the *Fabaceae* family, belonging to the *Mucuna genus*, known as "velvet bean", "cowitch", "cowage", "ox-eye bean", "cattle bean", "chiporazo", "chiporro", "fogaraté", "kapikachu", "pica", "picapica", "frijol terciopelo", "nescafe", "grano del mar", "kratzbohnen", "konch", ·yerepe (Yoruba)", and "atmagupta". Mucuna pruriens was described by (L.) DC. And published in Prodromus Systematis Naturalis Regni Vegetabilis 2: 405, 1825.

The genus *Mucuna* includes approximately 100 species of liana and shrubs found throughout the tropical regions of the world. *Mucuna pruriens* is native to India and Southeast Asia, but is now found widely distributed throughout the tropics. There are four botanical varieties of

Mucuna pruriens; *Mucuna pruriens var. utilis* is the cultivated variety which does not cause irritation, *Mucuna pruriens var. pruriens* ("pica pica") has urticating hairs that contain the irritant mucunain, *Mucuna pruriens var. hirsuta*, from India, and *Mucuna pruriens var. sericophylla*, from the Philippines.

Mucuna pruriens is a vigorous climber with vines of up to 60 feet (18 m) in length, although there are also varieties of short liana. The leaves are trifoliate, with leaflets of 2 to 5 inches (5 to 12 cm) wide and 3 to 6 inches (7 to 15 cm) long. The white or purple flowers are self-pollinating and found in racemes of up to 12 inches (32 cm) long. The pods are produced in groups of 10 to 14, measure from 0.5 to 1 inch (1 to 2 cm) wide and 1.5 to 5 inches (4 to 13 cm) long, and are covered with fine white or light brown hairs. Each pod contains 3 to 7 seeds, which are 0.3 to 0.5 inches (0.8 to 1.3 cm) wide and 0.4 to 0.8 inches (1 to 1.9 cm) long. The seeds may be black, white, reddish, brown or dappled and have a raised thread. (Bryan, 2011).

(Left) Illustration by Miss S.A. Drake (fl. 1820s-1840s), in volume 24 of the Botanical Register (1838), edited by John Lindley.

Certain variations in the colours and patterns of the seeds of different varieties of *Mucuna*. The raised thread is clearly visible and is the point at which the seed is joined to the pod. **Fuente:** Bryan, 2011.

3.1 Composition

Mucuna pruriens is similar in composition to other species of the genus *Mucuna.* From a nutritional point of view with a majority content of proteins and carbohydrates (humidity (%) 4.64 ± 0.10; protein (%) 37.5 ± 0.27; carbohydrates (%) 44.9 ± 0.25; ash (%) 3.24 ± 0.16; and fat 9.65 ± 0). As regards the amino acids, it has a similar profile to that of other species of *Mucuna* sp., although with a higher deficit in cysteine and methionine than other species of *Mucuna* and without differences in the rest of the amino acids. It is important to note that the values of amino acids by gram of seed are far higher than those described by the FAO/WHO (1985) as essential requirement values in the diet of children of pre-school or school age (Omohimi et al., 2014). In its composition, it contains phenylalanine, and therefore it has been suggested that its consumption may be dangerous for individuals with phenylketonuria (Adebowale et al., 2005).

With reference to the report requested of the Scientific Committee of the AECOSAN on *Mucuna pruriens*, there are certain biologically active substances present in the composition of *Mucuna pruriens* of greater significance given their potential toxic effect and these are, undoubtedly, the substances which limit its use.

Within these biologically active compounds the majority are described as: total phenols (mainly tannins): 7.75 ± 0.02 g/100 g; trypsin inhibitors 24.2±0.08 g/100 g; saponin 1.46±0.01 g/100 g; phytic acid 1.97±0.01 g/100 g; L-Dopa 4.99± 0.02 g/100 g; raffinose 1.65±0.01 g/100 g; stachyose 1.23±0.02 g/100 g and verbascose 0.93±0.01 g/100 g; all expressed in dry matter (Adebowale et al., 2005). These values may vary according to the varieties of *Mucuna pruriens* and the geographical origin of the plant. In the case of L-Dopa there may be concentrations in the seeds of between 1.25 and 9.16 g/100 g of seed (Ingle, 2003).

It is important to highlight the presence of alkaloids, including 1,2,3,4-tetrahydroisoquinoline (Misra and Wagner, 2004). The studies of the alkaloids were based on their identification and their presence or absence after heat treatment, but not on their quantification.

Apart from the biogenic amines, as they are thermolabile compounds the majority of these amines are inactivated with heat treatment. Mwatseteza and Torto (2010) demonstrate with food technology studies that the cooking of *Mucuna Pruriens* eliminates 26 compounds, mainly polycyclic compounds and alkaloids. But as heat treatment of the seeds intended for use in craftwork is not possible as they would lose the colour and texture required for the craft products, these compounds are active in seeds used for this purpose.

The seeds of *Mucuna pruriens* also contain starches and resins. From a nutritional point of view the starches may be of interest given their energy input and that they are linked to food aspects mainly in under-developed regions. The content in resins is associated with problems of dermal (contact), inhalation and digestive toxicity, and may cause nausea, headaches and dizziness as well as respiratory congestion.

Therefore, to sum up, the principal biologically active compounds (Adebowale et al., 2005; Bhat et al., 2008; Donati et al., 2005; Hope-Onyekwere et al., 2012; Manyam et al., 2004; Misra and Wagner, 2007; Shelly and Arthur, 1985) contained in *Mucuna pruriens* include:

- L-Dopa (L-3,4-dihydroxyphenylalanine). It is the precursor of dopamine, and is the main constituent of the seed.
- Adrenalin and phenylalanine.
- Nicotinic acid.
- Tetrahydroisoquinoline alkaloids (in quantities of 8-24 mg/500 g of dry seed).
- Mucunine, mucunadine, mucunadinine and prurienidine alkaloids.
- Serotonin and its precursor 5-hydroxytryptamine (5-HTP).
- Compounds of tryptamine with sympathomimetic and hallucinatory effects. Dimethyl-tryptamine (0.006%), 5-MeO-dimethyl-tryptamine (0.0025%), and dimethyl-tryptamine oxide (0.003%) are found in very low concentrations in the leaves, although they are not present in the seeds.
- Carboxylesterases, various saponins, anthraquinones, flavonoids, terpenoids, cardiac glycosides and tannins.
- Protease inhibitors.
- Mucunaine protease.
- Inositol (2.1 mg/g), myo-inositol (8.2 mg/g), and agalactiae glycosides (11.4-21.2 mg/g).
- Other bioactive substances including β-sitosterol, glutathione, lecithin, vernolic acid, and gallic acid.
- Dietary minerals in small quantities such as selenium and magnesium.

4. Safety

4.1 Pharmacological data of interest for the safety assessment due to the consumption of seeds of *Mucuna pruriens*

In 1937, L-Dopa was isolated from the seeds of *Mucuna pruriens*, and this is when L-Dopa was first considered for the treatment of Parkinson's disease. (Damodaran, 1937).

Katzenschlager et al. (2004) conducted a double-blind, cross-over clinical study with the aim of determining whether a powder formula of seeds of *Mucuna pruriens* would have the same effect, possessed the same kinetic profile and same tolerance as the standard synthetic L-Dopa compound in patients with active psychosis symptoms, in anti-psychotic treatment or in patients with cognitive disorders. The tested doses of powder of *Mucuna pruriens* were 15 g and 30 g containing 500 and 1000 mg of L-Dopa respectively. This study revealed the pharmacologically active profile of the seed powder of *Mucuna pruriens* at the tested doses of 15 and 30 grams.

In another study, the effect of the extract of *Mucuna pruriens* lyophilised powder was studied given different levels of acute and chronic exposure in animal models, rats and mice, of hyperglycaemia, using different diabetogenic agents (Rathi et al., 2002). These authors observed that the maximum reduction in the blood sugar levels was reached in rats with doses of 200 mg *Mucuna pruriens*/kg bw/day after six weeks of treatment. In mice with chronic diabetes treated with this extract of *Mucuna pruriens*, no significant effect on the glucose plasma levels was observed on days 40, 50 and 60 of the study.

4.2 Toxicology

The presence of autacoids (histamine) has been confirmed in *Macuna pruriens.* This is possibly partly the substances involved in the irritation and oedema processes which are mainly associated with the hairiness of the seeds, but as they are difficult to remove without heat treatment they may trigger allergic reactions (Reginald and Georgewill, 2010). The majority of the studies describe reactions which are not very severe but which are associated with oedemas after prolonged contact.

The flowers and pods covered with hairs are the cause of intense swelling and allergy if placed in contact with the skin. Casual contact with the pod of the plant has been found to cause erythema and pruritic macular lesion, presumably as a result of an immediate hypersensitivity reaction (Anonymous, 1985) where the mucunaine protease is the active pruritic agent (Shell and Arthur, 1955).

The scientific literature contains various toxicity studies conducted on animals used in research with *Mucuna pruriens* (ground, extracts or seeds) and these are described below. It should be noted that these studies have not been carried out in accordance with the current standards of Good Laboratory Practices (GLP), or under the OECD directives. Therefore, the results should be interpreted with some caution when defining measures aimed at establishing a risk/benefit relation in the use of the seeds of *Mucuna pruriens*.

4.2.1 Acute toxicity studies

Shahaji and Parnu (2011) assessed the acute oral toxicity of *Mucuna pruriens* using an ethanolic extract of the whole plant which had a transfer performance of 17% p/p in this extract. The study was conducted on Swiss albino mice of both genders; there was no mortality for a "limit dose" of 2000 mg/kg bw in 0.5 ml of distilled water. The ethanolic extract of the *Mucuna pruriens* plant was considered to be low risk with a LD_{50} (median lethal dose) of more than 2000 mg/kg bw in accordance with the OECD directives for classification.

In another study carried out by oral administration to albino mice (race not specified) of both genders with an extract of leaves of *Mucuna pruriens,* an LD_{50} value was obtained of 10000 mg/kg bw (Akindele y Busayo, 2011); no signs of toxicity were observed in this study and nor was there any mortality, indicating that the extract of leaves of *Mucuna pruriens* administered orally is practically non-toxic.

Khan et al. (2013) described the acute oral toxicity of *Mucuna pruriens* in male mice (race not specified), using single oral doses of 10, 100, and 1000 mg/kg bw with an observation period of up to 24 hours after the administration; in this study, the value of the LD_{50} would be higher at 1000 mg/kg bw given that there was no mortality in the animals. *Mucuna pruriens* was ground to obtain a fine powder which was administered orally using a suspension in carboxymethylcellulose at 0.5%.

In addition, Igbinaduwa and Anoh (2012) studied the acute oral toxicity of extracts of leaves of *Mucuna pruriens* in albino mice (gender and race not specified) at single oral doses of 1000, 2000, 4000, 6000 and 8000 mg/kg bw and in Wistar rats of both genders at oral doses of 6000 and 8000

mg/kg bw. Both species were kept under observation for 14 days for possible clinical signs of changes in behaviour, toxicity and mortality. During the 14-day observation period there were no changes in the behaviour or mortality at the maximum oral dose of 8000 mg/kg bw for both animal species. This value confirms that the extracts of *Mucuna pruriens* are practically non-toxic

4.2.2 Repeated dose toxicity studies

Maxwell and Yusuf (2010) assessed the repeated dose oral toxicity (28 days) in Wistar rats (both genders) of seeds of *Macuna pruriens* in which these were included in the diet in the form of flour (raw and cooked) at levels of 10%, 20% and 50%, equivalent to an intake of 2 g/day (10 mg/kg bw/day), 4 g/day (20 mg/kg bw/day), and 10 g/day (50 mg/kg bw/day) of *Macuna pruriens* respectively. The results of this study, which does not comply with the GLP standards or the OECD directives, reveal that there is a significant increase in the hepatic enzymes (aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP)) and total and conjugated bilirubin in serum in the groups treated with doses of 10, 20 and 50 mg/kg bw/day [flour (raw and cooked)]. Following the treatment of the animals, it was observed that the *Macuna pruriens* seed has hepatotoxic potential, an effect which is reduced but not neutralised by cooking the seeds before adding them to the food. These authors suggest that seeds from *Mucuna pruriens* should not be used as food, and that in extreme situations in which their consumption cannot be avoided, they should only be used after cooking and included in small percentages in the diet. In this study, it is not possible to identify a NOAEL based on the modification of the hepatic enzymatic activities. A second repeated dose oral toxicity study (28 days) (which does not comply with the GLP standards or the OECD directives) was carried out on rats (race is not specified) of both genders who were administered an extract of leaves from *Mucuna pruriens* at doses of 50, 100, 200 and 400 mg/kg bw. (Akindele and Busayo, 2011). During the study only a haematological examination was made. At doses of 400 mg/kg bw there was a significant fall in the number of platelets and at doses of 50 and 200 mg/kg bw a significant decrease in the number of neutrophils. In this study, it was not possible to identify a NOAEL based on the significant decrease of the number of platelets and neutrophils.

Recently Omeh et al. (2014) studied the repeated dose oral toxicity (28 days) of seed oil of *Mucuna pruriens* compared to palm oil. For this, male Wistar rates were treated with oral doses of 10 g of *Mucuna pruriens* oil, included in the diet, obtaining similar results to those described by Maxwell and Yusuf (2010), in which there is a statistically significant increase in the number of serum enzymes, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP). An increase of the conjugated and total bilirubin in serum, total proteins, albumin, creatinine and urea is also observed and found to be statistically significant. The histopathological examination of the organs of rats revealed the presence of various lesions, tubular atrophy and medium oedema of the organs of the test group. From this test, it is not possible to identify a NOAEL based on the modification of the hepatic enzymes, bilirubin, total proteins, albumin, creatinine and urea, and the lesions and it is concluded that oil from *Mucuna pruriens* is not safe.

A repeated dose toxicity study lasting 12 weeks (3 months) with oral doses of 5, 10, 20, 30, 40, 50 and 100 mg/kg bw of *Mucuna pruriens* (ethanolic extract of seeds) was conducted on diabetic Wistar rats (induced by an intravenous dose of 120 mg of alloxan monohydrate/kg bw). In this study, the only adverse effect observed was a dose-dependent reduction of the blood sugar levels (Majekodunmi et al., 2011). In addition, Igbinaduwa and Anoh (2012) in a repeated dose study (30 days) (which does not comply with the GLP standard or the OECD directives) revealed that extracts of *Mucuna pruriens* in Wistar rats, of both sexes, administered via gastric catheters in doses of 500, 2000, 6000 and 8000 mg/kg bw/day produces a decrease (not dose dependent) in the serum creatine levels, and no changes in the general behaviour of the animals and their bodyweight (the signs of toxicity were recorded every 7 days until the end of the experiment). Based on the serum creatinine levels it is not possible to identify a NOAEL. The serum creatinine values do not have a behaviour that could be linked to dose or found to be statistically significant. Khan et al. (2013) study the repeated dose toxicity (90 days) of *Mucuna pruriens* in male rabbits (race not specified and GLP standards and OECD directives are not met) at a "dose limit" of 70 mg/kg bw administered orally (*Mucuna pruriens* previously ground to form a powder) in suspension of carboxymethylcelullose at 0.5%. The results indicate that there are no clinical signs of toxicity or mortality. Nor was there any variation in body weight or in the haematological parameters. Based on this data, it is possible to identify a NOEL of 70 mg/kg bw/day.

4.2.3 Toxicity in humans

The bibliography does not have values of NOAEL for L-dopa in humans. In man, the clinical effects of *Mucuna pruriens* on Parkinson's disease have been assessed (Katzenschlager et al., 2004); apart from nausea in two patients treated with doses of 30 g of *Mucuna pruriens*, no other adverse effect was observed, nor were any alterations detected in the clinical biochemistry or in the haematological parameters. Nor were any adverse effects observed on the peripheral dopaminergic system. A toxicity standard value of TD_{Lo} (lowest published toxic dose or toxic dose low) of oral L-Dopa in humans has been established of 4286 mg/kg bw (Cayman Chemical, 2015).

5. Risk assessment

5.1 Assessment of risk from intake

Based on the acute oral toxicity values (LD_{50}) and of repeated dose toxicity it can be concluded that the seeds of *Mucuna pruriens* have a low toxicity level.

The principal risk factor from the oral consumption of seeds of *Mucuna pruriens* is due to the high content in L-Dopa (1.25-9.16 g/100g of seeds) (Ingle, 2003); given the neuropharmacological effects, the most frequent adverse effects include dyskinesias and other types of involuntary movements, nausea, vomiting, psychotic episodes, hallucinations and paranoid ideas. In addition, other minority substances are present in the seeds including N,N-dimethyltryptamine, bufotenin, indole-3-alkylamines and other alkaloids which are substances that are controlled in many countries due to their psychoactive effects at low doses.

To estimate the quantity of L-Dopa in the seeds, its concentration is considered to be in the range of 1.25% to 9.16 % dry matter (mean value of 5%) and its weight between 0.9-1.1 g. In addition, each seed may contain between 12.5-91.6 mg of L-Dopa (mean value 50 mg), concentration which presents pharmacological effects. The dose in the treatment of Parkinson's disease varies between 50-200 mg of L-Dopa administered 3-4 times per day (Brayfield, 2014).

The following table shows the minimum and maximum content of L-dopa in the different parts of the *Mucuna Pruriens* plant.

Table 1. Content of l- dopa in the different parts of *Mucuna pruriens*

Mucuna Pruriens sp.	**L-dopa (% minimum)**	**L-dopa (% maximum)**
Root	0.12	0.16
Stem	0.19	0.31
Leaves	0.17	0.35
Seeds	1.25	9.16
Pericarp	0.09	0.22

Figures taken from Ingle, 2000.

In the case of the seeds and extrapolating their content to the doses of the double-blind cross-over clinical trial carried out by Katzenschlager et al. (2004), a pharmacologically active profile is revealed for the seed powder from *Mucuna pruriens* at the trial doses of 15 and 30 grams (equivalent to 500 and 1000 mg of L-Dopa respectively). It is therefore possible to obtain the intake calculated in number of seeds necessary to observe these effects without increasing the severity of the dyskinesia or other adverse effects at the level of the peripheral dopaminergic system. The following table expresses this calculation in number of seeds.

Table 2. Equivalence of the content of l-dopa to the number of seeds of *Mucuna pruriens*

Mucuna pruriens (seed powder)	L-dopa content in % and in mg per seed of weight of 1 gram	500 mg of L-dopa	1000 mg of L-dopa	1500 mg of L-dopa	2000 mg of L-dopa
Seeds with minimum content OF L-dopa	1.25 % (L-dopa min.) 12.5 mg L-dopa/seed	40 seeds	80 seeds	120 seeds	160 seeds
Seeds with maximum content OF L-dopa	9.16 % (L-dopa max.) 91.6 mg L-dopa / seed	5.4 seeds	10.8 seeds	16.2 seeds	21.6 seeds

Figures taken from Ingle, 2003.

At present, the scientific literature and the summary of product characteristics (SPC) (medicines for human use) which contain L-Dopa, establish a range of 1500 to 2000 mg L-Dopa/person/day as the "maximum tolerable daily dose" for the chronic pharmacological treatment of Parkinson's disease, which could be obtained with the intake of 30-40 seeds containing a mean value of 50 mg of L-Dopa per seed. This figure may be used as a reference for the consumption of L-Dopa resulting from the intake of *Mucuna pruriens*; but it should be remembered that there may be other interactions of a toxic nature due to the effect of other biologically active compounds present in the seeds or when *Mucuna pruriens* is consumed in food supplements or preparations obtained from the whole plant.

All the values mentioned above refer to adults. The safety and efficacy for the paediatric population have not been established and there is insufficient data on the use in children and pregnant women. Therefore, taking the value of "maximum tolerable daily dose" for the chronic pharmacological treatment of Parkinson's disease with neuropharmacological treatment, referred in this case to children and a body weight of 30 kg/child, would result in a "maximum tolerable daily dose" of 643 to 857 mg L-dopa/day. This extrapolation does not consider, due to the lack of scientific data, the possible differences in the toxicological behaviour of L-dopa due to age or gender. Applying the principle of maximum precaution these values should be taken into account for consideration by the risk managers.

For the repeated dose oral toxicity (study over 90 days on rabbits), it was possible to identify a NOEL of 70 mg/kg bw/day ("limit dose"). The principal risk factor from the oral intake of the seeds is due to the high content in L-Dopa, given its pharmacological actions at low doses, in addition to other minority psychoactive substances. Considering the content of L-Dopa (1.2-9.16 %) per seed and of other psychoactive ingredients, it would be necessary to consume an average of 30 seeds to reach the "maximum tolerable daily dose" which presents neuropharmacological effects in adults (1500 mg L-Dopa/person/day) (considering a weight of 70 kg in adults and a mean value of 50 mg of L-Dopa per seed), ranging between 16 and 120 seeds according to the concentration of L-Dopa in the seeds.

The "maximum tolerable daily dose" of L-Dopa/day is not known for children. Taking as a reference the standard toxicological value of the TD_{Lo} for oral L-Dopa in humans of 4286 mg/kg, a safety margin of 200 is obtained in the case of adults and of 85 in children, considering for these doses mean intake values of 21.4 mg/L-Dopa/kg bw (adult weighing 70 kg, equivalent to 1500 mg/L-Dopa/person/day) and 50 mg/L-Dopa/Kg bw (child weighing 30 kg), respectively. Therefore, the continued and/or repeated intake of seeds of *Mucuna pruriens* is considered without risk, as in both cases a safety margin of 30 is exceeded (human variability factor of 10 to which an uncertainty factor of 3 is applied, given that the minimum toxic effect on man is considered).

Based on the available NOEL (70 mg/kg bw/day, "limit dose") and taking into account the consideration of exposure to seeds of *Mucuna pruriens*, a safety margin is obtained of 3 for adults and 1 for children. This is considered low as the value of 100 would not be reached (applying the individual variability factors of 10 and for different species of 10). This NOEL value has been identified from a "limit dose" and might have been higher if a dose-response test had been carried

out. Considering that a standard toxicological value of TD_{Lo} has been published for oral L-Dopa in man, it is considered advisable to take this value into account when calculating the safety margin of the *Mucuna pruriens* seeds, which results in a safety margin of more than 30 for both adults and children, which is considered a broad margin.

In addition to the consumption of the seeds of *Mucuna pruriens*, their use has become popular in recent years in natural products based on medicinal plants, food supplements and alternative medicine for sale in establishments and in particular on Internet with a variety of indications (including alternative treatment for Parkinson's disease, depression, as dietary supplements, energisers, aphrodisiacs, and for digestive disorders). Given the lack of studies on its composition, efficacy and toxicity, and of specific regulations, there is a potential risk in its consumption; by which the consumer may be exposed to natural products other than those referred to and to the additional effect of other active ingredients.

5.2 Assessment of the risk due to handling and use of the seed as a craft product

The handling and use of the seeds of *Mucuna pruriens* as craft products may lead to intense itching and contact allergies, due to the presence of biogenic amines such as histamine and 5-hidroxytryptamine (5-HT) in the composition of the seed and in the hairs on the pods. These effects may be more significant in individuals who are sensitive to *Mucuna pruriens*. It has also been indicated that casual skin contact with the plant pod produces erythema and pruritic macular lesion caused by the mucunain protease (Hoe-Onyekwere, 2012)

In addition, the rubbing of the seed cover against the skin may facilitate the dermal absorption of the biologically active compounds.

The risk resulting from accidental exposure to the seeds through inhalation or ingestion by small children due to the small size and sweet taste must also be considered as this could cause the total or partial obstruction of the respiratory paths or occlusion in the gastrointestinal tract. In the case of seeds from *Mucuna pruriens*, with an average length of 10-19 mm and width of 8-13 mm by 4-6.5 mm thick, this risk remains.

Conclusions

The Scientific Committee of the AECOSAN with respect to the use of seeds of *Mucuna pruriens* in craft products and the possible risk of accidental ingestion, draws the following conclusions:

1. It is not possible to exclude the risk of intense itchiness and contact allergy resulting from the use of the seeds of *Mucuna pruriens* as a craft product. With the scientific data available, it is not possible to calculate this risk factor for its assessment.
2. The intake of the seeds of *Mucuna pruriens* presents low acute oral toxicity (higher than 2000 mg/kg bw in rats), indicating low risk.
3. The safety margin for the intake of the *Mucuna pruriens* seeds, both in accidental and continuous form in adults and in children, is higher than 30, which is considered a broad margin of safety.

4. The accidental intake of seeds of *Mucuna pruriens* does not pose a toxicological risk due to acute and chronic exposure for adults and children due to the use in craft products. Nevertheless, due to the presence of L-Dopa, and other biologically active substances which may in turn have a synergic action, the voluntary intake of seeds of *Mucuna pruriens* in uncontrolled and unassessed conditions is a "risk factor" to be considered for the health of consumers.

Recommendations

The competent regulating authorities are advised to consider the following when adopting the risk management measures they consider opportune:

1. Given their shape, texture, colour, reduced size and sweet flavour, the seeds of *Mucuna pruriens* may be accidentally swallowed by children, leading to possible problems of respiratory or digestive occlusion, especially in children under the age of 3 years. Therefore, in particular for children, the use of the seeds of *Mucuna pruriens* as a component in craft products may be a health concern, given the probability of an accidental respiratory or digestive occlusion which is reasonably foreseeable. Nevertheless, this type of risk is generalised for other legume seeds and products used every day in the domestic environment and within the reach of children in a possible accidental intake. Therefore, this type of craft product should be labelled with specific warnings which include sentences such as "Keep out of reach of children" and/or "This product contains small parts which may be swallowed with the resultant risk of asphyxia for children" or other similar sentences.
2. The effects resulting from the biological activity of the seed may reach the end consumer, either through the sale of the manufactured craft product or through the sale of seeds sold loose. Any risk management measures adopted in this respect must consider the availability of the seed in contexts other than craft markets.
3. In view of the above, the Scientific committee recommends that if the quantitative data for the volume of marketing, ingestion requiring hospital care and/or health warnings due to the voluntary consumption of *Mucuna pruriens* were significant, the risk of the voluntary ingestion of products intended for human consumption which include this seed as the active ingredient should also be assessed; in particular due to its current marketing on Internet, in those cases in which the sale is not governed by a legal status which regulates this sale.

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