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

Risk assessment of herbal preparations containing *Tabernanthe iboga*

RIVM letter report 2024-0030
W. Chen

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Synopsis

Risk assessment of herbal preparations containing *Tabernanthe iboga*

In the Netherlands, products with extracts of the herb *Tabernanthe iboga* are mainly sold online. They are sometimes used as a drug withdrawal aid, but also as a mind-altering product. The Ministry of Health, Welfare and Sport has asked RIVM to assess the safety of this herbal preparation.

RIVM has investigated whether products containing *Tabernanthe iboga* are harmful to health. Based on this investigation, RIVM advises consumers not to use herbal preparations containing *Tabernanthe iboga*.

The main side effect is disturbance of the heart rhythm. In the worst case, people can die from this. Worldwide, dozens of deaths have been reported after using this herb, including some cases in the Netherlands.

Other adverse effects commonly occurring are nausea, vomiting, or more serious: acute psychosis, seizures, and hallucinations. These effects can already arise at levels commonly used.

Keywords: ibogaine, noribogaine, psychoactive substance, safety

Publiekssamenvatting

Risicobeoordeling van kruidenpreparaten met *Tabernanthe iboga*

In Nederland worden producten met extracten van het kruid *Tabernanthe iboga* vooral online verkocht. Ze worden soms gebruikt als hulpmiddel om af te kicken van drugs, maar ook als geestverruimend middel. Het ministerie van VWS heeft het RIVM gevraagd om de veiligheid van dit kruidenpreparaat te beoordelen.

Het RIVM heeft hiervoor onderzocht of producten met *Tabernanthe iboga* schadelijk zijn voor de gezondheid. Op basis daarvan adviseert het RIVM consumenten geen kruidenpreparaten met *Tabernanthe iboga* te gebruiken.

De belangrijkste bijwerking is verstoring van het hartritme. In het ernstigste geval kunnen mensen hieraan overlijden. Wereldwijd, zijn tientallen doden gemeld na het gebruik van dit kruid, waaronder enkele gevallen in Nederland.

Andere schadelijke effecten die vaak voorkomen zijn misselijkheid, overgeven, of ernstiger: acute psychoses, epileptische aanvallen en hallucinaties. Deze effecten kunnen al ontstaan bij de algemeen gebruikte hoeveelheden.

Kernwoorden: ibogaine, noribogaine, psychoactieve stof, veiligheid

Contents

Summary

Introduction

In December 2020, the Minister for Medical Care and Sport of the Ministry of Health, Welfare and Sport (VWS) announced actions to better regulate food supplements and herbal preparations in the Netherlands, thereby facilitating enforcement. One of those actions is to expand the list included in the Herbal Preparations Decree of the Dutch Commodities Act with substances/botanicals that are either forbidden or restricted (i.e. subject to a maximum level) in food supplements or herbal preparations. In order to determine whether a substance or botanical needs to be included in this list, a risk assessment is warranted. The selection of substances and botanicals chosen for risk assessment was based on the prerequisite that the substances/botanicals are sold on the Dutch market and (widely) used in the Netherlands and that there are indications for possible health risks, e.g. Rapid Alert System for Food and Feed (RASFF) reports, from enforcement institutes. The current assessment is about herbal preparations containing *Tabernanthe iboga* (iboga).

T. iboga is used as a herbal preparation for amongst others its hallucinogenic effects. The main active constituent of *T. iboga* is ibogaine.

Currently, in the Netherlands, there are no specific restrictions for the use of *T. iboga* in herbal preparations included in the Herbal Preparations Decree of the Dutch Commodities Act[1] or the Opium Act[2]. *T. iboga* and ibogaine are not registered as medicines in the Netherlands[3] and hence the use as a medicinal product is not allowed.

Previous evaluations

No existing toxicological evaluations have been identified for *T. iboga*.

Products on the Dutch market

Products containing *T. iboga* or ibogaine are not sold as regular food supplements in the Netherlands. Some information can be found online on its use during 'iboga-ceremonies' and on microdosing of *T. iboga*. It is also (illegally) used in the treatment of drug addiction, sometimes with fatal outcomes, which has led to a couple of court cases in the Netherlands[4].

Exposure

When used for its hallucinogenic effects or to treat addiction, i.e. the most common uses, exposures to ibogaine reported in literature ranged from approximately 1 to 30 mg/kg bw (for a 70-kg individual) (Alper et al., 1999; Alper, Lotsof, & Kaplan, 2008; Fernandez & Fernandez, 2001;

[1] https://wetten.overheid.nl/BWBR0001969/2018-11-17, Accessed August, 2022.
[2] https://wetten.overheid.nl/BWBR0001941/2022-07-01/0. Accessed August 12, 2022.
[3] Home | Geneesmiddeleninformatiebank | College ter Beoordeling van Geneesmiddelen. Accessed August 15, 2022.
[4] https://www.om.nl/zoeken?trefwoord=ibogaine&search-submit=. Accessed August 12, 2022..

Lotsof & Wachtel, 2002; Mash et al., 2001; Schenberg et al., 2014). Therefore, this dosage range is considered as common use levels. In clinical studies, investigated exposures ranged from 0.3 to ~55 mg/kg bw.

Biological data

- After oral ingestion, ibogaine is rapidly and almost completely absorbed. Ibogaine and its metabolites can be excreted via urine and feces. Due to their high lipophilicity, they can cross the blood-brain barrier and distribute in brain and fat tissues.
- Oral median lethal doses (LD_{50} values) for ibogaine of 263 mg/kg bw (in mice) and 327 mg/kg bw (in rats) were reported, as well as an oral LD_{50} value of 630 mg/kg bw for noribogaine in mice (Kubiliene et al., 2008).
- A few short-term toxicity studies are available, but these only focused on neurotoxicity. A systematic review and meta-analysis showed that ibogaine caused motor impairment in animals after oral and intraperitoneal administration, whereas cerebral cell loss was only observed after intraperitoneal administration (Belgers et al., 2016)
- No studies on genotoxicity, chronic toxicity and carcinogenicity, and reproductive and developmental toxicity are available for *T. iboga* or ibogaine.
- No animal studies on the cardiac toxicity of *T. iboga* or ibogaine were identified. Shi et al. (2021) derived $BMDL_{10}$[5] values for ibogaine and its metabolite noribogaine for cardiotoxicity in human based on *in vitro* data and kinetic modelling. (Shi et al., 2021). However, due to various uncertainties, the $BMDL_{10}$ values are not used as point of departure (POD) in the current report.
- The Dutch National Poisons Information Center (NVIC) received 14 information requests on poisoning with *T. iboga*/ibogaine in the period 2010-2022. Symptoms reported were related to the gastrointestinal system, nervous system, respiratory system and cardiac system.
- In total 58 case reports after ingestion of *T. iboga* or ibogaine were identified in the literature. Doses reported in these case reports ranged from 4.5 to 100 mg/kg bw ibogaine. The majority of the cases described people with substance abuse. Sudden death was reported in 34 cases. This occurred even at the lowest dose of 4.5 mg/kg bw. Adverse effects on the heart were reported including long QT/QTc (an extended interval between the heart contracting and relaxing), Torsade de Pointes (a type of ventricular tachycardia) and ventricular fibrillation. Other adverse effects included nausea, vomiting, acute psychotic episodes, seizures, ataxia (impaired coordination), hallucinations, hallucinogen persisting perception disorder, behavioral alternations, drop in the level of consciousness and suicide attempts.
- A clinical study in healthy volunteers with a dose of 20 mg ibogaine (0.3 mg/kg bw based on a body weight of 70 kg) resulted in reports of nausea, gastrointestinal symptoms (unspecified) and dizziness. In clinical studies in subjects with

[5] $BMDL_{10}$ = The 95% lower confidence limit of the benchmark dose.

opioid or cocaine use disorder, nausea, vomiting, ataxia of gait, sensory and perceptual changes, bradycardia (lower heart rate) and clinically relevant QTc prolongation were reported in doses from 8-12 mg/kg bw onwards and in the dose range 25-55 mg/kg bw one participant died.

- Two clinical studies with noribogaine were reported with an oral dose range of 3-60 mg in healthy male volunteers and 60-180 mg in subjects with opioid use disorder. No statistically significant adverse effects (including QTc prolongation) were reported in healthy volunteers. In subjects with opioid use disorder, noribogaine caused nausea, headache, visual impairment and dose- and concentration-dependent QTc prolongation, which reached clinically concerning levels at 120 and 180 mg (Glue et al., 2015a; Glue et al., 2016).

No safe use level

It was investigated whether the presumption of safety could be applied to *T. iboga*. Botanical preparations for which an adequate body of knowledge exists, can benefit from a presumption of safety without any need for further testing (EFSA, 2009; EFSA, 2014). Since several cases are reported in which the use of the root of *T. iboga* or its main active component ibogaine has led to severe adverse effects including death, no presumption of safety can be applied.

Toxicological studies with *T. iboga*, ibogaine and noribogaine are limited. No information regarding chronic toxicity, genotoxicity, carcinogenicity or reproduction and developmental toxicity is available for ibogaine and its metabolite noribogaine. Some short-term toxicity studies are available, but these focused on neurotoxicity and did not cover all endpoints. Therefore, it is not possible to derive a health-based guidance value (HBGV).

Based on the effects reported in humans, nausea, gastrointestinal symptoms (unspecified) and dizziness may occur at low dose levels (0.3 mg/kg bw ibogaine). At higher dose levels (from 4.5 mg/kg bw onwards), also ataxia of gait, sensory and perceptual changes, bradycardia (lower heart rate), clinically relevant QTc prolongation and death were reported. These doses can be seen as effect levels and are used in the risk assessment.

Risk assessment

Ibogaine exposure typically ranges from 1 to 30 mg/kg bw for its common uses, namely hallucinogenic effects and addiction treatment. When compared to the reported effect levels, severe adverse effects affecting the cardiovascular system, including QTc prolongation and Torsade de Pointes (TdPs), as well as adverse effects on the gastrointestinal and the neurological system may occur at these dose levels. Additionally, in this dose range numerous deaths were reported in the case reports. Hence, we conclude that the use of *T. iboga* is not safe.

Conclusions and recommendations

The use of products containing *T. iboga* or ibogaine and its metabolite noribogaine, at common use levels can lead to acute adverse health effects. *T. iboga* is cardiotoxic and can cause prolonged QT/QTc intervals and TdPs, which can result in severe heart rhythm disturbances and death. Also, adverse effects on the gastrointestinal system (such as nausea and vomiting) as well as neurotoxic effects (such as psychosis, seizures, hallucinations and behavioural alterations) can occur.

Based on the acute adverse health effects, RIVM advises consumers to not use (herbal preparations containing) *T. iboga* or (nor)ibogaine.

This risk assessment focussed on *T. iboga*. However, ibogaine is also present in *T. manii* and, in small quantities, in *Tabernaemontana crassa* (*Tabernaemontana* is a closely related genus of *Tabernanthe*). The conclusions of the current report may therefore also apply to the use of other ibogaine-containing plants.

1 Introduction

1.1 Background

In December 2020, the Minister for Medical Care and Sport of the Ministry of Health, Welfare and Sport (VWS) announced the actions that would be taken to better regulate food supplements and herbal preparations in the Netherlands, thereby facilitating enforcement. One of those actions is to expand the list included in the Herbal Preparations Decree of the Dutch Commodities Act[6] with substances/botanicals that are either forbidden or restricted (i.e. subject to a maximum level) in food supplements or herbal preparations (van Ark, 2020). In order to determine whether a substance or botanical needs to be included in this list, a risk assessment is warranted. The selection of substances and botanicals chosen for risk assessment was based on the prerequisite that the substances/botanicals were sold on the Dutch market and (widely) used in the Netherlands and that there were indications for possible health risks, e.g. Rapid Alert System for Food and Feed (RASFF) reports from enforcement institutes. The current assessment is about herbal preparations containing *Tabernanthe iboga* (iboga).

Tabernanthe iboga (*T. iboga*) is available on the Dutch market as a herbal preparation for amongst others its hallucinogenic effects. It is also (illegally) used in the treatment of drug addiction, sometimes with fatal outcomes, which has led to a couple of court cases in the Netherlands[7]. The main active constituent of *T. iboga* is ibogaine.

1.2 Information on existing assessments

No toxicological evaluations have been identified for *T. iboga*.

T. iboga has not been evaluated by the Committee on Herbal Medicinal Products (HPMC) of the European Medicines Agency (EMA).

T. iboga is listed in EFSA's Compendium of Botanicals, which reports botanicals with naturally occurring substances of possible concern for human health but has no legal or regulatory force. Ibogaine is mentioned as the substance of concern in *T. iboga*[8].

1.3 Information on existing legislations

Currently, in the Netherlands, there are no specific restrictions for the use of *T. iboga* in herbal preparations included in the Herbal Preparations Decree of the Dutch Commodities Act[3] or the Opium Act[9].

T. iboga and ibogaine are not registered as medicines in the Netherlands[10] and hence the use as a medicinal product is not allowed.

[6] https://wetten.overheid.nl/BWBR0012174/2020-07-01. Accessed August 12, 2022.
[7] https://www.om.nl/zoeken?trefwoord=ibogaine&search-submit=. Accessed August 12, 2022.
[8] https://www.efsa.europa.eu/en/data-report/compendium-botanicals. Accessed February 20, 2023.
[9] https://wetten.overheid.nl/BWBR0001941/2022-07-01/0. Accessed August 12, 2022.
[10] Home | Geneesmiddeleninformatiebank | College ter Beoordeling van Geneesmiddelen. Accessed August 15, 2022.

Many countries have added ibogaine to their acts restricting controlled drugs and substances and a few countries have legitimized the use of ibogaine for medical reasons.

2 Literature search

The risk assessment for herbal preparations containing *T. iboga* was conducted using the template for the safety assessment of plant food supplements as a basis (de Wit-Bos et al., 2019).

A search strategy was developed to capture relevant literature for the risk assessment of *T. iboga*. Search terms were formulated to describe the herb, including its main constituent, to identify references describing toxicity and kinetics or adverse outcomes and to include animal data as well as human data. The search terms included '*T. iboga*', 'Iboga', 'Ibogaine', 'noribogaine', 'toxicity' and 'IBO'. Three databases were searched (Embase, Pubmed, Scopus). Websites such as Google scholar and Google books were also checked. In total, 226 unique references were obtained.

In addition, grey literature was searched using the internet for assessments of *T. iboga* 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, 2021), and the International Plant Names Index (IPNI) have been accessed to gather information on the identity of *T. iboga*. The European Pharmacopeia, ESCOP monographs, Commission E monographs and WHO monographs were also searched, but *T. iboga* was not listed. A monograph about *T. iboga* was found in the database of Natural Medicines (Natural Medicines, 2021).

The obtained references were judged for their relevance based on title/abstract. Reference lists of highly relevant articles and reviews were checked to identify possible additional relevant references missed in the literature search. In total 108 references were included in the risk assessment.

3 Description of the herbal products

3.1 Identity and nature of the source material

3.1.1 *Botanical (preparation)*

T. iboga is a perennial rainforest shrub native to west Africa. It is an evergreen bush indigenous to Gabon, the Democratic Republic of Congo, and the Republic of Congo, and it is cultivated across West Africa. *T. iboga* belongs to the *Apocynacae* family (WCSP, 2021).

On an erect and branching stem, *T. iboga* bears dark green, narrow leaves and clusters of white tubular flowers, as well as yellow-orange fruits that resemble olives (Duke, 2002). Normally growing to a height of 2 m, iboga may eventually grow into a small tree up to 10 m tall, given the right conditions. The flowers are yellowish-white or pink and followed by a fruit, orange at maturity, that may be either globose or fusiform. Its yellow-fleshed roots contain a number of indole alkaloids, most notably ibogaine, which is found in the highest concentration in the root barks (Hofmann & Schultes, 1980). It has various common names e.g., 'bitter grass', 'leaf of god' and 'thie-pelakano' (Table 1).

Table 1 Information related to the classification of T. iboga (Sources: (WCSP, 2021)

Scientific (Latin) name	Family: *Apocynacae* Species: *Tabernanthe iboga* Baillon
Common names	Bitter grass Iboga Leaf of God Thie-pelakano lopundja (Zaire) lopundu (Zaire) mokundji (Zaire)
Part used	Roots, leaves, latex
Geographical origin	Native to tropical forests, it is cultivated across West Africa
Growth and harvesting conditions	Prefers moist soil in partial shade

3.2 Manufacturing process

3.2.1 *Information on the method(s) of manufacture*

The root bark is the most valued and used part of the plant, as it contains the highest concentration of ibogaine. Iboga root bark is generally dried and sold as thin strips, or ground into powder (Underwood, Bright & Les Lancaster, 2021).

The alkaloids can be extracted from the root bark relatively easily via an acid/base extraction. Even weak acids such as acetic acid are strong enough to convert iboga alkaloids into salts. Extraction of alkaloids from *T. iboga* root bark by only diluted vinegar and ammonia was described by Jenks (Jenks, 2002).

Ibogaine can also be synthesized. Total synthesis of ibogaine was first described in a US patent in 1957 (Janot & Goutarel, 1957), and a detailed paper on its complete synthesis in 1966 (Büchi et al., 1966). They prepared both ibogamine and 12-methoxy ibogamine (ibogaine) in the form of their racemates, starting with nicotinamide and proceeding through a 13-step sequence involving an isoquinuclidone intermediate. The most standardized formulation available from commercial laboratories is pure crystalline ibogaine hydrochloride (HCl), typically produced by semi-synthesis from voacangine or from nicotinamide using a multi-step process (Maciulaitis et al., 2008)

The form of ibogaine used most often in the clinical setting (see also 5.2.7) is ibogaine HCl with a purity of 95 to 98% (Massariello, 2014).

3.2.2 *Information on substances entering the manufacturing process*
No additional information on substances entering the manufacturing process is available.

3.3 Chemical composition

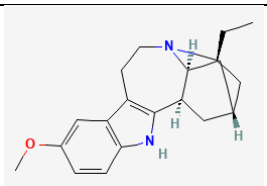
The active compounds in the root, root bark, stem bark, leaves and seeds of *T. iboga* are indole alkaloids. About 20 indole alkaloids have been identified so far. The highest concentrations (approximately 6%) occur in the root bark of *T. iboga* (Rätsch, 2004). The overall iboga alkaloid composition of *T. iboga* alkaloid extracts may range from 15% to 50%. The three principal iboga alkaloids being ibogaine (~ 80%), ibogaline (~ 15%), and ibogamine (~ 5%) (Jenks, 2002). Other compounds found in *T. iboga* include coronaridine, tabersonine, vincadifformine, pandoline, epi-pandoline in leaves and voacangine and alkaloids in seeds (Mahop et al., 2004).

Research has focused largely on the pharmacology of ibogaine since it is the most abundant alkaloid in *T. iboga* and is used to treat addiction (Cameron et al., 2021). It differs from the other alkaloids in its class by the presence of a methoxy group (Table 2) (Mahop et al., 2004).

Ibogaine is present in all plant parts except the seeds. The concentrations of ibogaine reported by Heckelman were root 1.27%, root-bark 2-6%, stems 1.95% and leaves 0.35% (Heckelman et al., 1996).

The current risk assessment will focus on ibogaine as the main active alkaloid in *T. iboga*. Since ibogaine is metabolized to the major and active metabolite noribogaine (see 5.1), related toxicokinetic and toxicological information over noribogaine is mentioned in the risk assessment as well.

Table 2 Chemical composition of the main active alkaloid from T. iboga, ibogaine (Source: (Pubchem))

Active component	Ibogaine
Chemical structure	
Systematic name	(1R,15R,17S,18S)-17-ethyl-7-methoxy-3,13-diazapentacyclo[13.3.1.02,10.04,9.013,18]nonadeca-2(10),4(9),5,7-tetraene
Synonyms	DEA No. 7260 7-Ethyl-6,6beta,7,8,9,10,12,13-octahydro-2-methoxy-6,9-methano-5H-pyrido(1',2':1,2)azepino(5,4-b)indole UNII-3S814I130U Endabuse 12-Methoxyibogamine (-)-Ibogaine
CAS No.	83-74-9
Molecular formula	$C_{20}H_{26}N_2O$
Molecular weight	310.4 g/mol

3.4 Stability

Ibogaine is heat- and light-sensitive and can spontaneously oxidize in solution, giving iboluteine and ibochine (Popik & Skolnick, 1999).

3.5 Use and use levels

Products containing ibogaine are not sold as regular food supplements. Some information about use of ibogaine can be found via Dutch websites on iboga ceremonies[11] and microdosing (as shown in Table 3). One website states that ”the ceremonies are held in the middle of Netherlands over 5 days and the group size varies between 6 and 10 participants”. No information on the doses used is provided.

Iboga root bark is sold online[12] with the description “In African traditional medicine and rituals, chewing the yellow-colored root or bark is used to cause hallucinations and near-death symptoms, resulting in some deaths.” Microdosing[13] with the bark of the iboga root or with a tincture is mentioned on another website[14]. This website recommends to use about 400 to 500 mg root bark of *T. iboga* every four days against addiction or as an antidepressant.

[11] The Origin Iboga Ceremony | The Origin. Accessed 13 August, 2022.
[12] https://www.medsconsulting.com/nl/product/ibogaine/iboga-wortelschors/, accessed 13 August 2022.
[13] Microdosing involves taking very small doses of some popular psychedelic hallucinogens or other drugs. These very small doses are not enough to produce a “trip” or the hallucinations often associated with these drugs (https://www.medicalnewstoday.com/articles/microdosing).
[14] Iboga microdosing microdosing.nl. Accessed August 12, 2022.

It is also (illegally) used in the treatment of drug addiction, sometimes with fatal outcomes, which has led to a couple of court cases in the Netherlands[15]. In several cases reported to the Netherlands National Poisons Information Center (Annex I), patients got ibogaine treatments in alternative rehabilitation centers in the Netherlands, however, the rehab centers cannot be found directly online. Some "naturopaths" in the Netherlands used ibogaine in the treatment of drug addicts. For instance, in IJzendijke in Zeeland, an Iboga farm was found in 2017[16]. In 2021, a blogger described his/her experience doing an Iboga flood dose in the Netherlands without mentioning the name of the retreat[17].

Table 3 Examples of (products containing) T. iboga available on the Dutch market with recommended use, if available.

	Ingredients	**Recommended use**	**Reference**
Iboga ceremony	Iboga	Not stated	The Origin | Program
Iboga	Iboga root bark	400 mg to 500 mg root bark of the iboga plant is used every 4 days	Iboga microdosing microdosing.nl
Iboga	Iboga root bark	Not stated	Iboga Wortelschors
Iboga Tincture	Iboga total alkaloid (TA) extract	One drop contains 0.58 mg of iboga TA extract, not exceed one drop per day	Tabernanthe iboga (Iboga) | State of Mind

[15] https://www.om.nl/zoeken?trefwoord=ibogaine&search-submit=. Accessed August 12, 2022.
[16] Supreme Court: ibogaine healer rightly convicted (kwakzalverij.nl). Accessed August 12, 2022.
[17] My experience doing an Iboga flood dose in the Netherlands : RationalPsychonaut (reddit.com)

4 Exposure: extent and duration

4.1 Exposure from herbal preparation use

Exposure to ibogaine when used for its hallucinogenic effects or to treat addiction reported in literature ranged from approximately 1 to 30 mg/kg bw (for a 70-kg individual) (Alper et al., 1999; Alper, Lotsof & Kaplan, 2008; Fernandez & Fernandez, 2001; Lotsof & Wachtel, 2002; Mash et al., 2001; Schenberg et al., 2014).

The use of ibogaine in the treatment of addiction, more specifically the treatment of opioid and cocaine addiction, has been and is still investigated in clinical studies. The exposure to ibogaine in clinical studies ranged from 0.3 to ~55 mg/kg bw (see also 5.2.7).

4.2 Possibility of additional/combined human exposure

Ibogaine is also present in *Tabernanthe manii* and, in small quantities, in *Tabernaemontana crassa* (*Tabernaemontana* is a closely related genus of Tabernanthe) (Cousins & Huffman, 2002). Additional exposure from other sources than herbal preparations is highly unlikely. No other food products containing ibogaine were identified.

4.3 Information on historical use of the ingredient

Traditionally, *T. iboga* root was used in lower doses as a neurostimulant to reduce fatigue and for treating infertility (Neuwinger, 1996; Clark & Sunderland, 2004; Fernandez, 1982), and in higher doses as a sacrament in spiritual initiation ceremonies (Doblin, Doyle, & Mojeiko, 2003).

No information on the (historical) use of *T. iboga* is available in the European Pharmacopeia[18], in Hagers Handbuch der Pharmaceutizen Praxis[19] or in the Commission E monographs[20]. A monograph about *T. iboga* was found in the database of Natural Medicines (Natural Medicines, 2021), where it is stated that oral use of ibogaine has been associated with cases of arrhythmia, psychological disturbance, and (sudden) death[21].

[18] https://pheur.edqm.eu/home, Accessed August 12, 2022.
[19] Reuss, W. (2013). Hagers handbuch der pharmazeutischen praxis (Vol. 1). Springer-Verlag.
[20] https://www.elsevier.com/books/the-complete-german-commission-e-monographs/blumenthal/978-0-9655555-0-0 Accessed August 12, 2022.
[21] https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements/professional.aspx?productid=440, Accessed April 11, 2023.

5 Biological data

5.1 Toxicokinetics

5.1.1 *Absorption, distribution, metabolism, excretion*

After ingestion of single doses of 500-1000 mg, maximum plasma levels of ibogaine are reached after 0.5-4 hours (T_{max}) with a free maximum plasma concentration (C_{max}) of approximately 1 µg/mL (Koenig and Hilber, 2015, Mash et al., 2000). The majority of ibogaine (>90%) is eliminated after 24 hours and the plasma half-life ($t_{½}$) amounted to 2–7 hours (Koenig & Hilber, 2015; Mash et al., 1998; Mash et al., 2001). Ibogaine undergoes extensive metabolism and is primarily metabolized into the biologically active metabolite noribogaine (12-hydroxyibogamine) in the liver and the gut wall, mostly by CYP2D6 and to a lesser extent by CYP2C9 and CYP3A4 (Figure 1; Mash et al., 1998; Koenig & Hilber, 2015). After ibogaine ingestion, high circulating noribogaine levels were observed (dependent on the CYP2D6 phenotype, see below), and these did not significantly decline after 24 hours (Mash et al., 1998, Mash et al., 2001). One of the pathways noribogaine is cleared by, is via glucuronidation as noribogaine glucuronide (Figure 1; Glue et al., 2015b; Glue et al., 2015a; Glue et al., 2016).

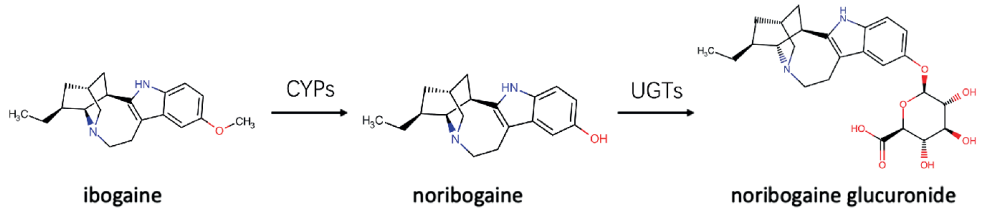


Figure 1 Metabolization of ibogaine to noribogaine by P450 cytochromes (CYPs) and subsequent conversion of noribogaine to noribogaine glucuronide by glucuronosyltransferases (UGTs) (Taken from Shi et al., 2021).

Plasma concentrations of ibogaine and noribogaine are influenced by polymorphisms in the CYP2D6 enzyme (Yip & Deng, 2016). Depending on whether a particular isoenzyme is present or absent, individuals can be classified as extensive or poor metabolizers (Alper, 2001); this has effect on the pharmacokinetic parameters of ibogaine and noribogaine as can be observed in Table 4 by the statistically significant differences in C_{max}, $t_{1/2}$ and area under the curve (AUC) (Mash et al., 2001).

The plasma-protein binding of ibogaine in human plasma was found to be 65% by Koenig et al. (2013), and 96% by Shi et al. (2021). Both used an equilibrium dialysis method. The differences may be explained by the fact that plasma protein binding could be influenced by the level of α1-acid glycoprotein[22] in plasma, which has striking differences among populations (Smith & Waters, 2019). For noribogaine, Shi et al. found a plasma-protein binding of 74% (Shi et al., 2021).

[22] α-1-acid glycoprotein is considered as one of the most relevant plasma proteins in terms of drug binding (Mehvar, 2005)

Table 4 Pharmacokinetic parameters of ibogaine and noribogaine in human extensive and poor metabolizers (CYP2D6) (taken from: Mash, Kovera & Pablo, 2001)

	*Extensive Metabolizers	**Poor Metabolizers
Ibogaine		
t_{max}, hr	1.70 ± 0.15	2.50 ± 1.04
C_{max}, ng/ml	737 ± 76	896 ± 166
AUC_{0-24}hr, ng.hr/ml	3936 ± 556	11471 ± 414
$t_{1/2}$, hr	7.45 ± 0.81	***NQ
Noribogaine		
t_{max}, hr	6.17 ± 0.85	3.17 ± 1.36
C_{max}, ng/ml	949 ± 67	105 ± 30
AUC_{0-24}hr, ng.hr/ml	14705 ± 1024	3648 ± 435
$t_{1/2}$, hr	NQ	NQ

*N = 24 (10 mg/kg), i.e. 16 males and 8 females
** N = 3, i.e. 3 males (10 mg/kg)
*** NQ = not quantifiable

Ibogaine and noribogaine are highly lipophilic which leads to high concentrations of these compounds in brain and fat tissue. A post-mortem analysis of a person who died from iboga poisoning revealed particularly high concentrations of ibogaine and noribogaine in liver, spleen, lung and brain (Mash et al., 2001). Similar distribution results were confirmed by Kontrimavičiūtė et al., 2006. Post-mortem quantitation of ibogaine and noribogaine in tissues (heart, liver, kidney, prostate, lung, brain, spleen, and muscle), bile, and stomach contents after a fatal poisoning with root bark from *T. iboga* revealed the highest concentrations in spleen, liver, brain, and lung. The tissue/subclavian blood concentration ratios averaged 1.78, 3.75, 1.16, and 4.64 for ibogaine and 0.83, 2.43, 0.90, and 2.69 for noribogaine for spleen, liver, brain, and lung, respectively. Very low concentrations of the two alkaloids were found in the prostate tissue. Both ibogaine and noribogaine are secreted in the bile and urine, in which also high concentrations were observed. The results demonstrate a widespread distribution of ibogaine and noribogaine throughout the body (Kontrimavičiūtė et al., 2006).

When noribogaine is orally administered in doses of 0, 3, 10, 30 or 60 mg per person to healthy drug-free male volunteers aged between 18 and 55 years (n=3-6 per dose group), noribogaine was rapidly absorbed, with a mean T_{max} of 2–3 hours. C_{max} and AUC rose in a linear relationship with dose. When looking at the individual plasma concentration-time profiles fluctuations that suggest the possibility of enterohepatic recirculation were observed in some individuals. The elimination of noribogaine was slow with mean $t_{1/2}$ values ranging from 28 to 49 hours across dose groups. The volume of distribution was substantial (ranging from 1417 to 3086 L across dose groups). In the 30 mg and 60 mg dose groups, noribogaine was excreted unchanged in absolute amounts of 1.16 mg and 0.82 mg, respectively, via urine in 24 hours, representing 3.9% and 1.4% of the doses administered. Noribogaine glucuronide plasma levels reached their maximum

approximately 3-4 hours after administration of noribogaine, and displayed a slow elimination with estimated mean $t_{1/2}$ values of 21-23 hours. The ratio between the C_{max} and $AUC_{0-\infty}$ of noribogaine glucuronide and the C_{max} and $AUC_{0-\infty}$ of noribogaine was 3-4% (Glue et al., 2015a).

5.2 Toxicological data

5.2.1 *Acute toxicity*

To investigate the oral acute toxicity of ibogaine, groups of four mice (gender not specified) received a dose of 100, 300, 400 or 500 mg/kg bw ibogaine or vehicle (saline) intragastrically (Kubiliene et al., 2008). Upon administration of ibogaine at doses of 400 and 500 mg/kg bw, all mice died. Three out of four mice died in the group that received 300 mg/kg bw. No deaths were observed in the lowest dose group, and an oral median lethal dose (LD_{50}) value of 263 mg/kg bw was determined by the authors for ibogaine (Kubiliene et al., 2008).

To investigate the oral acute toxicity of noribogaine, groups of four mice (gender not specified) were administered 300, 500, 700 or 900 mg/kg bw noribogaine or vehicle (saline) by gavage. Noribogaine at doses up to 500 mg/kg bw had no effect on the survival of the mice. Three of the four mice in the dose group of 700 mg/kg bw died, and all mice died after receiving 900 mg/kg bw. The LD_{50} value of noribogaine was calculated by the authors to be 630 mg/kg bw (Kubiliene et al., 2008).

In rats, an oral LD_{50} value of ibogaine of 327 mg/kg bw has been reported. LD_{50} values after intraperitoneal administration have been reported in guinea pigs (82 mg/kg bw) and rats (145 mg/kg bw) (as cited by (Kubiliene et al., 2008))[23].

5.2.2 *Short-term and sub-chronic toxicity*

Studies of short-term and sub-chronic toxicity only focused on neurotoxicity and are therefore mentioned in 5.2.6.1 (neurotoxicity).

5.2.3 *Genotoxicity*

No studies were identified.

5.2.4 *Chronic toxicity and carcinogenicity*

No studies were identified.

5.2.5 *Reproduction and developmental toxicity*

No studies were identified.

5.2.6 *Other studies*

5.2.6.1 Neurotoxicity

Oral studies

Bading-Taika et al. (2018) conducted a study to determine the effects of *T. iboga* root bark water extract in the feed on cognitive function of mice. Male C57BL/6J mice (8 weeks of age) were randomly assigned into 4 groups of 12 animals, namely: Group 1, LFD (low-fat diet) normal control; Group 2, HFD (high-fat-diet) control; Group 3, HFD + low-dose iboga (0.83 mg ibogaine/kg bw per day); and Group 4, HFD + high-dose iboga (2.07 mg ibogaine/kg bw per day). The mouse doses of 0.83 and

[23] Original information sources cannot be found.

2.07 mg/kg bw are equivalent to human doses of 4.7 mg/day and 12 mg/day for a 70-kg person by allometric scaling of dose. The animals were exposed for ten weeks. HFD mice were tested three days before sacrifice for cognitive performance using a water maze method. Mice were first trained for one day to locate a clear platform that was submerged below the water surface and had a visual flag. This was followed by two days of hidden training (using the platform without flag). On day 4, the mice were tested for spatial memory retention during a probe trial, in which the platform was removed completely from the maze. This was again followed by two additional visual trials. Hidden trials analysis showed that there was an overall improvement of spatial learning and memory in the control and low dose iboga group but not in the high dose iboga group (p=0.55, no statistically significant differences). Probe trail analysis showed statistically significant differences due to iboga treatment. The high dose iboga group swam on average further away from the location where the platform was located during the training. The authors concluded based on the water maze trial results that the high-dose iboga extract may be harmful and impair spatial learning and memory, as compared to mice receiving only a HFD (Bading-Taika et al., 2018).

Routine histopathological evaluation did not show neuropathological damage in African green monkeys (vervets) administered repeated doses of 25 mg/kg bw ibogaine orally (Mash, 1995).

Three male and three female cynomolgus monkeys, aged about two years, were instrumented with electroencephalographic (EEG) telemetry transmitters. Each monkey received noribogaine hydrochloride orally at two dosages (160 and 320 mg/kg bw) and the control (vehicle) were administrated orally in a dose escalation design. Animals had a wash-out period of at least seven days between each treatment. The effects on behaviour and on the EEG were assessed. The EEG was recorded continuously from at least 24-h prior to dosing to at least 24-h post-dosing. Pentylenetetrazol (PTZ, administered intravenously at dose levels of 38-65 mg/kg bw) served as a positive control for inducing seizures. EEG evidence of seizure or EEG signals known to be early indicators of increased seizure risk (e.g., abrupt waves, atypical synchronization, shifts to high-frequency patterns) were not linked to noribogaine administration at either of the doses tested. Noribogaine was linked to a minor decrease in activity, increased scratching, licking, and chewing, emesis, partial anorexia (i.e. decreased appetite), as well as to some degree of poor coordination and other clinical signs at both dose levels. A single monkey displayed short myoclonic movements that increased in frequency at the high dose but did not generalize, cluster, or appear to be associated with EEG abnormalities. EEG patterns were within normal limits following administration of noribogaine at doses up to 320 mg/kg bw with concurrent clinical signs and resolved by the end of the monitoring period (Authier et al., 2016).

Intraperitoneal studies
Popik and Wróbel (2001) performed a study to determine if anxiety could be identified in male Albino Swiss mice (26-32 g) following an intraperitoneal administration of 10 (n=10), 20 (n=10) or 40 mg/kg bw (n=9) of ibogaine hydrochloride. An elevated plus maze was used to

study anxiety in mice. The maze consisted of two open arms and two enclosed arms. The arms extended from a central platform. Ibogaine was administered 30 minutes before the test that lasted 5 minutes. Mice were tested in an order counterbalanced for the treatment condition. Mice were placed on the central platform, and the time spent on each of the four arms as well as the number of entries into the arms was manually recorded. The results showed that ibogaine statistically significantly reduced the percentage of open arm time (in the 20 and 40 mg/kg bw group) and the percentage of open arm entries (in 40 mg/kg bw group). Mean locomotor activity (closed arm entries) was not affected by the treatment. According to the authors the results indicate that ibogaine increased anxiety (Popik & Wróbel, 2001).

Effects of ibogaine on cerebellar Purkinje cells in male Fischer 344 rats were studied by Helsley et al. (1997). Ibogaine (10 mg/kg bw) was intraperitoneally administered to a group of six rats every other day for 60 days while the control group received an equivalent volume of saline (1 mL/kg). Forty-eight hours after the last treatment, brains were removed and the cerebellum was separated. Purkinje cell number were determined using the optical dissector/fractionator technique. No statistically significant differences in Purkinje cell number were observed between the ibogaine and control group (Helsley et al., 1997).

O'Hearn & Molliver (1993) discovered that intraperitoneal administration of ibogaine to rats caused microglia and astrocyte activation in the cerebellar vermis, which can activate the inferior olivary nucleus and cause excitotoxic Purkinje cell degeneration. In their study, Sprague-Dawley rats (males, 175-200 g, n=50) were treated with a single dose of ibogaine (100 mg/kg bw). The cerebellum of the rats was examined for morphologic evidence of neuronal damage. The authors concluded that administration of ibogaine had selective neurotoxic effects which lead to degeneration of a subset of Purkinje cells in the cerebellar vermis (O'Hearn & Molliver, 1993).

In 1996, Molinari, Maisonneuve & Glick re-examined cerebellar responses at this dose level and at a lower dose. In total 36 female Sprague-Dawley rats (250–275 g) received ibogaine at a single dose of 40 mg/kg bw, a single dose of 100 mg/kg bw or three doses of 100 mg/kg bw, one per day for three consecutive days, or received no injections or a single intraperitoneal injection of 4 ml/kg saline (number of animals per group not stated). The animals were sacrificed 7, 21, or 26 days after the final injection and Purkinje cell degeneration and enhanced glial cell activity were evaluated. Every rat treated with the high dose of ibogaine (100 mg/kg bw or 3 × 100 mg/kg bw) displayed clear evidence of Purkinje cell degeneration. The degeneration consistently occurred in the intermediate and lateral cerebellum, as well as the vermis. Purkinje cells in lobules 5 and 6 were particularly susceptible. This finding suggests that any long-term motor deficits produced by ibogaine-induced degeneration would probably affect the head and upper extremity since purkinje cells responsive to stimulation of the forelimb and face are concentrated in the vermis and intermediate portions of lobules 5 and 6. In contrast, rats treated with 40 mg/kg bw displayed no degeneration above the level seen in controls (Molinari, Maisonneuve & Glick, 1996).

Review
Belgers et al. (2016) performed a systematic review and meta-analysis on (amongst others) the toxic effects of ibogaine (administered orally or intraperitoneally) on motor function, cerebellar cell loss and cardiac rhythm. Because dosing regimens varied considerably among studies, the authors grouped studies into low, medium and high dose studies, corresponding with 0–40 mg/kg bw, 40–80 mg kg/bw and >80 mg/kg bw ibogaine, respectively. Eight studies were found on toxic effects of ibogaine on motor functioning, but three studies were excluded since the original data could not be retrieved. In the five other studies, in total 10 independent comparisons with continuous outcome measures and 6 with dichotomous outcome measures were reported on the effect of ibogaine on motor functioning. Eight comparisons used rats, and the other eight used mice (male animals in all cases). All measurements were obtained within 24 hours after administration (route not described). Both the continuous and dichotomous outcome measures showed that the administration of ibogaine caused motor impairment. There was no difference in the occurrence of motor symptoms after ibogaine between different dosing regimens, however, subgroups on dosages of >80 mg/kg bw were too small to analyze as well as the subgroup of medium dosage in the group of dichotomous measurements. Eleven studies reported on toxic effects of ibogaine on cerebellar cell loss, but one study was excluded because the original data could not be retrieved. In total 28 comparisons were reported on the effects of ibogaine administration on cerebellar degeneration. Both the continuous and dichotomous outcome measures showed that administration of ibogaine causes cerebellar cell loss. The effect of ibogaine on cerebral cell loss was only observed after intraperitoneal administration, but not after oral administration. No studies were found on cardiac rhythm. The results showed that ibogaine causes acute motor impairment in animals, even at low dosages and high intraperitoneal doses of ibogaine were associated with reduced cerebellar cell counts (Belgers et al., 2016).

5.2.6.2 *Cardiotoxicity*
Cardiac effects of ibogaine could be related to reported fatalities after ibogaine ingestion and intoxications (see 5.2.7), however, no animal studies addressed this issue.

Shi et al. (2021) used a new approach methodology (NAM) to predict the potential cardiotoxicity of ibogaine and its metabolite noribogaine in humans. In brief, they first quantified the *in vitro* cardiotoxicity of both compounds by measuring the extracellular field potential duration prolongation corrected for beat rate (FPDc) in human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) using a multi-electrode array (MEA) technique. This serves as a surrogate for QTc prolongation *in vivo*. The resulting data was combined with *in vitro* biokinetic data obtained from *in vitro* liver microsomal incubations, Caco-2 transport studies, and *in silico* modelling and used in a physiologically-based kinetic (PBK) modeling-based reverse dosimetry approach. Using the PBK model, the *in vitro* concentration-response curves were translated to *in vivo* dose-response curves for QTc prolongation and compared to clinical human QTc prolongation data. A toxic equivalence (TEQ) approach assuming dose-addition was applied to combine the cardiotoxicity of ibogaine and noribogaine. BMD analysis

was performed and point of departures were derived. The predicted $BMDL_{10}$ values were 94.2 mg for noribogaine (1.35 mg/kg bw for a 70-kg person) and 108 mg for ibogaine (1.54 mg/kg bw for a 70-kg person). From the clinical study of Glue et al. (2016), Shi et al. (2021) derived a $BMDL_{10}$ of 163 mg for noribogaine (1.99 mg/kg bw for 81.9-kg person).

The BMDL as predicted by Shi et al. is not used in the current report. Reasons for this have, amongst others, to do with the BMD analysis and the method used to derive the toxic equivalence factors (TEFs). In the various kinetic (PBK) extrapolations, no uncertainty or variability seems to be included which has consequences for the interpretation of the results. Human variability and (parameter) uncertainty should be considered to make statements for a sensitive human with a sufficient certainty. Also, the dose-response analysis could not be judged as the actual dose-response analysis results were not provided. For example, the BMDU[24] should also have been given to judge the uncertainty in the dose-response. For the derivation of the TEFs, the BMDL data from the *in vitro* concentration-response data were used whereas the BMD should have been used and also no confidence interval around the TEF has been given.

5.2.7 *Human data*

5.2.7.1 Cases reported to Dutch National Poisons Information Center (NVIC)

The Dutch National Poisons Information Center (NVIC) is the knowledge center for clinical toxicology in the Netherlands. NVIC searched their database in the time range of January 1st 2010 to May 22th 2022. In total, 14 cases were found related to T. iboga/ibogaine (as shown in Annex I. There were no duplications with cases listed in Annex II.

Professionals can call the NVIC for advices in case of poisonings. It should be noted that in the Netherlands there is no obligation to report poisonings. This means that not all poisonings are reported to the NVIC. The information presented in Annex I was collected during the phone calls with the professionals fairly quickly after the exposure. It is possible that additional symptoms developed later, and were not reported to the NVIC. In 8 out of the 14 cases, *T. iboga*/ibogaine was used for withdrawal from heroin, cocaine, cigarette or unknown drugs. The doses were unclear for most of the cases. Seven cases reported dose ranges between 1.4 mg to 20 g *T. iboga* without specifying the percentage of active compounds. Only in one case an estimated ibogaine dose was provided (25-50 mg).

Symptoms that have been reported include digestive system effects such as diarrhea, nausea, vomiting and abdominal pain; nervous system effects such as altered consciousness, coma, agitation, aggression, disorientation, psychosis, convulsions and tremors/myoclonus; respiratory system effects like shortness of breath and hyperventilation; and circulatory system effects including arrhythmias and changes in electrocardiogram.

[24] BMDU = The 95% upper confidence limit of the benchmark dose.

5.2.7.2 Case reports from literature

Annex II gives an overview of case reports from the literature in which adverse events were associated with the oral use of *T. iboga* products. These included in total 58 cases, with 42 males and 16 females aged between 22 and 63 years. In total 34 sudden deaths (26 males and 8 females) were reported from 1990 to 2021. The majority of the cases (49/58) involved drug addicts searching for treatment of their addiction. In addition, there were six cases in which *T. iboga* products were taken for a spiritual experience and three cases with unknown reason. The *T. iboga* products used included powdered root bark, extracts and capsules with ibogaine or ibogaine HCL. Dose information was not always available. The reported doses varied greatly from 4.5 mg/kg bw to ~100 mg/kg bw of ibogaine. The time to sudden death or onset of the adverse events also varied greatly. The adverse effects occurred within a few minutes to 48 hours after a single exposure, and sudden death occurred after 1.5 to 76 hours.

Most of the adverse effects reported were effects of ibogaine on the nervous and (blood) circulatory systems. Nervous system effects reported included seizures, acute psychotic episodes, close-eyed visions, visual memories, mania, irritability, grandiose delusions, rapid tangential speech, aggressive behavior, little to no sleep, emotional lability, hallucinations, impulsivity, psychomotor agitation, consciousness alternation, acute panic, persisting perception disorder (HPPD), ataxia, unspecified pain and panic, worsening distractibility, grandiosity, racing thoughts, and suicidal ideation. Circulatory system effects included prolonged QT interval, tachycardia (VT), Torsade de Pointes (TdP) arrhythmias, fibrillation (VF), pause-dependent polymorphic ventricular tachycardia and bradycardia. Nausea, vomiting and diarrhea were the most reported digestive system effects and there was also one case reporting apnoea. In most of the cases, patients were hospitalized and treated for 9 hours to 9 days before discharge. Two patients were admitted to the intensive care unit and discharged later.

It was hypothesized that the sudden deaths in humans were related to cardiac arrhythmias (Koenig & Hilber, 2015). These are most probably caused by the ability of ibogaine to induce a QT interval prolongation, which is known to enhance the risk for a life-threatening abnormal heart rhythm called TdP arrhythmia. The 15 cases of QTc prolongation are summarized in Table 5.

Table 5 Summary of case reports showing QTc prolongation upon oral intake of ibogaine

Reference	Reason for ibogaine use	Sex	Dose (mg/day)[a]	Baseline QTc (ms)[b]	Post QTc (ms)	QTc (% to baseline)
Hoelen, Spiering & Valk (2009)	Alcohol addiction	Female	525[c]	411	616	149.9
Paling et al. (2012)	Alcohol addiction	Female	525	411	616	149.9
Pleskovic et al. (2012)	NR	Male	600	405	460	113.6
Knuijver et al. (2018)	Opioid addiction	Male	700	420	516	122.9
Wilson, Millar & Matieschyn (2021)	Polydrug use	Female	725-1850	411	512	124.6
Henstra et al. (2017)	Heroin addiction	Female	1400	411	647	130.2
Grogan et al. (2019)	Cocaine and heroin addiction	Female	2000	411	788	191.7
Vlaanderen et al. (2014)	NR	Male	2400	405	663	163.7
Meisner, Wilcox & Richards (2016)	Heroin addition	Male	4000	405	588	145.2
Steinberg & Deyell (2018)	Opioid addiction	Male	5600	405	714	176.3
Asua (2013)	Heroin addiction	Male	7000	405	600	148.1
Hildyard et al. (2016)	Heroin addiction	Male	7000	405	730	182.5
Paling et al. (2012)	Heroin addiction	Male	NR	405	700	172.8
Paling et al. (2012)	Heroin addiction	Female	NR	411	480	116.8
Shawn et al. (2012)	Opioid addiction	Male	NR	NR	NR	NR

[a] internet-purchased ibogaine with unknown purity; [b] Baseline was assumed to be 405 and 411 milliseconds (ms) for male and female respectively, given that no baseline information was reported (Wedam et al., 2007); [c] a dose of 3500 mg ibogaine was corrected for the reported purity of 15%. NR = not reported

In 1997, the European Committee for Proprietary Medicinal Products suggested as upper limit for a QT interval 450 milliseconds (ms) for men and 470 ms for women (CPMP, 1997). A QT interval of at least 500 ms generally has been shown to correlate with a higher risk of TdP[25] (Moss et al., 1991; Bednar et al., 2001). Table 5 showed that QTc prolongation (% to baseline) was not dose-related, and large variation in QTc prolongation at similar reported oral doses could be observed. This may be related to the individuals' health condition (most persons were addicts), diverse demographic characteristics and/or potential other QTc prolonging risk factors, which were not well-documented (Shi et al., 2021).

Noteworthy is that the ibogaine-ascribed deaths occurred between 1.5–76 hours after the intake (Annex II). Considering that ibogaine has a half-life of only 4–7 hours in human plasma (see Table 4), the occurrence of fatalities due to cardiac toxicity 24–76 hours after drug ingestion may be due to ibogaine's long-lived metabolite noribogaine rather than ibogaine itself (Koenig & Hilber, 2015). Other aspects that could have played a role in the ibogaine-ascribed deaths include the concomitant use of other drugs and underlying systemic diseases affecting the heart. For example, the risk of death from opioid overdose is linked to ventricular hypertrophy and atherosclerotic disease (Darke, Kaye & Duflou, 2006), both of which were contributory variables in this case series and are linked to a history of methamphetamine and cocaine use (Knuepfer, 2003; Kaye et al., 2007). The presence of advanced preexisting medical comorbidities in this series of fatalities appears to be a more general association between systemic disease and the risk of fatal overdose (Alper, Stajić & Gill, 2012). Together with the general uncertainty around the exact used dose, it is difficult to make a direct link between the dose of ibogaine and fatality.

5.2.7.3 Clinical studies

Clinical studies investigating the use of ibogaine are listed in Annex III. Six clinical trials were reported for ibogaine (Glue et al., 2015b; Davis et al., 2017; Noller, Frampton & Yazar-Klosinski, 2018; Brown & Alper, 2018; Mash et al., 2018; Knuijver et al., 2021; Forsyth et al., 2016). One study was conducted in healthy volunteers at an oral dose of 20 mg (0.3 mg/kg bw for a 70-kg individual) (Glue et al., 2015b; Forsyth et al., 2016) and five in opioid- or cocaine-dependent individuals at oral doses ranging between 8 to ~55 mg/kg bw.

In healthy volunteers, adverse effects reported after a dose of 20 mg ibogaine included nausea, gastrointestinal symptoms (unspecified) and dizziness which were more often reported after concomitant treatment with paroxetine (metabolite is an inhibitor of CYP2D6) and these resolved without intervention.
In individuals with an opioid use disorder, clinically relevant reversible QTc prolongation was reported at a dose of 10 mg/kg bw in addition to other transient adverse effects including bradycardia, ataxia and psychedelic effects of ibogaine (Knuijver et al., 2021). Knuijver et al. reported that clinically relevant QTc prolongation also occurred in patients without pre-existing cardiac abnormalities, which warranted

[25] There is no established threshold below which prolongation of the QT interval is considered free of proarrhythmic risk.

treatment with magnesium. Hence they concluded that the use of ibogaine outside a well-controlled clinical setting with strict cardiac monitoring should be avoided. In another study in subjects with an opioid or cocaine use disorder, nausea, vomiting, ataxia of gait and sensory and perceptual changes were reported after a dose of 8-12 mg/kg bw. In one study a participant died after ingestion of 25-55[26] mg/kg bw ibogaine very likely related to ibogaine ingestion and most probably related to cardiac arrhythmia.

Also two studies for noribogaine (Glue et al., 2015a; Glue et al., 2016), one in healthy volunteers at an oral doses ranging from 3 to 60 mg and one in opioid addicts at oral doses ranging from 60 to 180 mg, were reported.
In healthy volunteers, no statistically significant adverse effects (including QTc prolongation) were reported at doses up to 60 mg (Glue et al., 2015a). In opioid addicts, noribogaine caused statistically significant and dose-dependent QTc prolongation, which reached clinically concerning levels in the 120 and 180 mg groups according to the authors (Glue et al., 2016). Other adverse events included headache, visual impairment and nausea. Shi et al. (2021) derived a $BMDL_{10}$ for QTc prolongation of 163 mg for subjects with an average body weight of 81.9 kg (corresponding to 1.99 mg/kg bw) for noribogaine based on this clinical study (Shi et al., 2021).

Three ongoing clinical trials were found in ClinicalTrials.gov[27], a database of the U.S. National Library of privately and publicly funded clinical studies conducted around the world. One study is performed in human healthy volunteers[28], one study in patients in a methadone program[29] and one study in alcohol addicts[30]. These trials will be finalized in the course of 2023.

5.2.8 *Interactions*

No studies were identified studying the interactions between *T. iboga* and other products. Case reports show that ibogaine is widely used by addicts who often have a long history of substances abuse. Alcohol, heroin, cocaine, benzodiazepines and methadone are among the abused substances, frequently also combinations thereof. When addicts use ibogaine, other substances (both prescribed and illicit) can also be present in the patient's blood plasma (Annex II). Several substances of abuse, such as alcohol (Rossinen et al., 1999), cocaine (O'Leary, 2001), and methadone (Kuryshev, Kirsch & Brown, 2010; Mujtaba, Romero & Taub, 2013) have also been linked to hERG channel inhibition and/or QT interval prolonging in the heart. Thus ibogaine's QT prolonging effect, and hence the risk of TdP arrhythmias, will be increased if meaningful amounts of these substances are still present in the plasma when ibogaine is administered. More attention needs to be paid to methadone due to its extremely long plasma half-life (15–55 hours) (Brown et al., 2004).

[26] Precise dose not given
[27] https://clinicaltrials.gov/, accessed 12 August, 2022.
[28] https://clinicaltrials.gov/ct2/show/NCT05029401?term=Ibogaine&cntry=GB&draw=2&rank=1, accessed 13 August, 2022.
[29] https://www.clinicaltrials.gov/ct2/show/NCT04003948, accessed 13 August, 2022.
[30] https://clinicaltrials.gov/ct2/show/NCT03380728, accessed 13 August, 2022.

Impairment of the drug's metabolism is another option for drug-drug interactions. The enzymatic transformation of CYP2D6 can be easily influenced by medications that metabolize in the same way, resulting in system saturation, or by direct interactions between the drug and the metabolizing enzyme. As a result, it is likely that relevant plasma levels of certain medications will affect the toxicokinetics of ibogaine. An example is pre-treatment with the CYP2D6 inhibitor paroxetine that led to higher plasma levels of ibogaine in this group compared to placebo (Glue et al., 2015). It is however not completely clear what the consequences are for the cardiotoxic risk. Both ibogaine and noribogaine are considered to be able to induce QTc prolongation. However, some suggested that noribogaine has a lower potency (Knuijver et al., 2021). If that is the case, poor metabolizers would have higher risk on developing cardiotoxicity. On the other hand, the plasma half-life of noribogaine is much longer (28-49 hours) than that of ibogaine (2-7 hours), thereby adding to the risk of a persistent QTc prolongation (Knuijver et al., 2021; Ona et al., 2021).

5.3 Derivation of toxicological reference value

The toxicological information about *T. iboga*, iboga and noribogaine is limited. No information regarding chronic toxicity, genotoxicity, carcinogenicity or reproduction and developmental toxicity is available for ibogaine and its metabolite noribogaine. Some short-term toxicity studies are available, but these focused on neurotoxicity and/or cerebral cell loss and did not cover all endpoints. A systemic review and meta-analysis showed that ibogaine caused motor impairment in animals after oral and intraperitoneal administration, whereas cerebral cell loss was only observed after intraperitoneal administration (Belgers et al., 2016).

A clinical study in healthy volunteers with a dose of 20 mg ibogaine (0.3 mg/kg bw based on a body weight of 70 kg) resulted in reports of nausea, gastrointestinal symptoms (unspecified) and dizziness, that were more often reported after concomitant exposure to a CYP2D6 inhibitor. In the clinical studies in subjects with opioid or cocaine use disorder, nausea, vomiting, ataxia of gait, sensory and perceptual changes, bradycardia and clinically relevant QTc prolongation were reported from the dose range 8 to 12 mg/kg bw and in the dose range 25-55 mg/kg bw one participant died.

In the case reports obtained from literature and NVIC a wide range of adverse effects including fatalities have been reported. The estimated doses is in the case reports ranged from 4.5 – 100 mg/kg bw. Death was reported from doses of 4.5 mg/kg bw onwards. Other reported adverse effects were related to the nervous and circulatory systems as well as to the digestive and respiratory system. These effects included amongst other acute psychotic episodes, mania, aggressive behavior, prolonged QT interval on the electrocardiogram, tachycardia and fibrillation.

Taken together, based on the absence of toxicological data on several endpoints and the reported adverse effects at all reported dose levels/exposures, it is not possible to derive a health-based guidance value (HBGV).

Based on the effects reported in humans, nausea, gastrointestinal symptoms (unspecified) and dizziness may occur at low dose levels (0.3 mg/kg bw ibogaine). At higher dose levels (from 4.5 mg/kg bw onwards), also ataxia of gait, sensory and perceptual changes, bradycardia (lower heart rate), clinically relevant QTc prolongation and death were reported. These doses can be seen as effect levels and are used in the risk assessment.

6 Risk assessment

6.1 Risk assessment

As a first step in the risk assessment, it was investigated whether the presumption of safety can be applied to *T. iboga*. Botanical preparations for which an adequate body of knowledge exists, can benefit from a presumption of safety without any need for further testing (EFSA, 2009; EFSA, 2014). This generally means that when there is a history of safe use and the intended use of the botanical preparation in food supplements does not exceed the historical levels of intake, the intended use in food supplements is assumed to be safe.
Since several cases are reported in which the use of the root of *T. iboga* or its main active component ibogaine has led to severe adverse effects including death, no presumption of safety can be applied.

Ibogaine exposure typically ranges from 1 to 30 mg/kg bw for its common uses, namely hallucinogenic effects and addiction treatment. When compared to the effect levels, severe adverse effects affecting the cardiovascular system, including QTc prolongation and TdPs, as well as adverse effects on the gastrointestinal and the neurological system may occur at these dose levels. Additionally, in this dose range numerous deaths were reported in the case reports. Hence, we conclude that the use of *T. iboga* is not safe.

6.2 Interactions

The interaction between ibogaine and other medications or drugs is a reason for concern, as a large percentage of the population that uses ibogaine are people with substance use disorders (Alper, 2001; Popik & Skolnick, 1999).

Additionally, substrates or inhibitors of cytochrome P450 (CYP) liver isoforms, mainly CYP2D6, could hamper the effective O-demethylation of ibogaine, resulting in higher plasma levels of ibogaine and prolonged exposure (Glue et al., 2015). Ibogaine is an inhibitor of the efflux transporter P-glycoprotein[31] (P-gp) and can therefore increase the plasma levels of substrates of P-gp. The use of *T. iboga* or ibogaine should be avoided when taking substrates of P-gp (Tournier et al., 2010).

6.3 Sensitive/vulnerable groups

Lotsof & Wachtel (2002) described exclusion criteria for addiction treatment with ibogaine. These criteria can be assumed as criteria for sensitive or vulnerable groups. These include: active neurological or psychiatric disorders, such as cerebellar dysfunction, psychosis, bipolar illness, major depression, organic brain disease or dementia, significant heart disease or a history of myocardial infarction, disease of the gastrointestinal system, liver or kidneys, or abnormal condition which

[31] P-gp is a member of the large ATP-binding cassette (ABC) family of proteins Ambudkar, Suresh V, Kimchi-Sarfaty, Chava, Sauna, Zuben E & Gottesman, Michael M 2003. P-glycoprotein: from genomics to mechanism. *Oncogene,* 22**,** 7468-7485.

compromises a function of these systems and could result in a possibility of altered metabolism or excretion of ibogaine (Lotsof & Wachtel, 2002).

It needs to the noted that this is not an exhaustive list. Existing differences in CYP2D6 phenotype lead to differences in first-pass effect and hence in bioavailability and elimination of ibogaine and the exposure to noribogaine across individuals. Therefore, extensive and ultra-rapid metabolizers have higher levels of noribogaine and lower levels of ibogaine in their plasma than poor metabolizers. Poor metabolizers have higher plasma levels of ibogaine and lower plasma levels of noribogaine than extensive metabolizers (Mash et al., 2015, see also 5.1.1). Currently, it is however not completely clear what the consequences are for the cardiotoxic risk (see also 5.2.8).

Even though there is no conclusive explanation till now for causes of the fatalities, there are indications that the interaction of opioids and ibogaine potentiates opioid toxicity (Alper, 2001; Popik and Skolnick, 1999), which makes people with substance abuse a vulnerable group.

6.4 Uncertainties

There is uncertainty in the estimated exposure to ibogaine when is it used outside a clinical setting (like for example in the case reports). When purchasing ibogaine, extracted from *T. iboga*, online, the purity may vary substantially with estimations for the total alkaloid content ranging from 15 to 50% (Alper, Stajić & Gill, 2012).

The toxic effects of *T. iboga* have not been thoroughly studied and information was limited. Most evidence for its adverse effects originates from case reports and human volunteer studies after single doses of *T. iboga*. This means that the chronic effects are unknown and no conclusions can be drawn about possible genotoxicity, carcinogenicity or reproduction and developmental toxicity of *T. iboga*, ibogaine or noribogaine due to lack of information. Also, it should be noted that most case studies and clinical studies were performed in substance addicts, only few data are available from healthy volunteers.

7 Conclusions and recommendations

The use of products containing *T. iboga* or ibogaine and its metabolite noribogaine, at common use levels can lead to acute adverse health effects. *T. iboga* is cardiotoxic and can cause prolonged QT/QTc intervals and Torsade de Pointes, which can result in severe heart rhythm disturbances and death. Also, adverse effects on the gastrointestinal system (such as nausea and vomiting) as well as neurotoxic effects (such as psychosis, seizures, hallucinations and behavioural alterations) can occur.

Based on the acute adverse health effects, RIVM advises consumers to not use (herbal preparations containing) *T.iboga* or (nor)ibogaine.

This risk assessment focussed on *T. iboga*. However, ibogaine is also present in *T. manii* and, in small quantities, in *Tabernaemontana crassa* (*Tabernaemontana* is a closely related genus of *Tabernanthe*). The conclusions of the current report may therefore also apply to the use of other ibogaine-containing plants.

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Annex I Cases reported to the Netherlands National Poisons Information Center in the period January 2010 – May 2022[a]

Year	Age	Sex	Reason	Location of use	Dosage	Co-ingestion	Symptoms
2019	35	Male	Mind-altering effect	At home	Unknown amount of powder dissolved in water. Took 1 sip of this.	-	Psychosis, confusion, agitation, rhabdomyolysis (possibly due to agitation and struggle with police)
2019	28	Female	Not clear	Public space	Unclear: There was a thermos of ginger tea. Possibly Ibogaine, possibly Rapé, or something else.	Olanzapine, omeprazole, possibly Rapé	Unconsciousness / fluctuating consciousness, soporous
2019	Adult, age unknown	Male	Withdrawal (unknown from which drug)	Unknown	600 mg plant material (supposed to contain 25-50 mg active ingredient ibogaine)	-	Tachycardia (may not be correlated with intake due to congenital cardiomyopathy)
2016	44	Female	Withdrawal (heroin)	Alternative rehab center	900 mg Iboga	-	Muscle cramps, tremors, bradycardia, hypotension, hyperthermia, arrhythmias
2015	25	Male	Withdrawal (weed)	At home	2 grams eaten and 2 grams boiled in water and drunk	-	Agitation, palpitations, shortness of breath
2015	53	Male	Mind-altering effect + withdrawal (unknown from which drug)	Alternative rehab center	3 x 2 grams in powder form	-	Diarrhea, chattering teeth, burning sensation behind sternum, hyperventilation
2015	35	Male	Unknown	Unknown	20 grams over 2 days	-	Psychosis (probably started 0.5/1 day after last use and may have

Year	Age	Sex	Reason	Location of use	Dosage	Co-ingestion	Symptoms
							been over 2 days). No cardiac effects
2014	Adult, age unknown	Male	Withdrawal (cigarettes)	Alternative rehab center	Unknown	-	Generalized convulsions, resembling tetanus (whole body cramps), pain
2014	35	Male	Withdrawal (cocaine)	Alternative rehab center	"A few grams" spread over 2 days	Possibly also a treatment with kambo-frog-poison	Tremors/myoclonias, "felt like fainting", ECG changes, fell down the stairs
2014	27	Male	Withdrawal (amphetamine)/ possible suicide attempt	At home (found on the street)	500 pills from a tube marked "Iboga 30" (obtained online)	-	Sopor, aggression
2014	45	Female	Withdrawal (heroin)	At home	1.4 mg over 12 hours (obtained online)	-	Palpitations, bradycardia, tachycardia, QT prolongation (670 msec), ventricular fibrillation (resuscitation setting), 3x Torsade des pointes. At a later time also withdrawal symptoms including motor restlessness
2013	Adult, age unknown	Female	Unknown	At home	Unknown (obtained online)	-	Nausea, vomiting
2013	Adult, age unknown	Female	Unknown	Unknown	Unknown	-	Vomiting, abdominal pain, disorientation (possible appendicitis)
2011	26	Male	Unknown	Unknown	2400 mg in 1.5 hours (in 400 mg capsules). Obtained from an alternative practitioner (female)	-	Vomiting, ventricular fibrillation (resuscitation setting setting), QT time prolongation, (prolonged) coma

[a] Information provided by the NVIC.

Annex II Overview of reported cases of adverse effects after *T. Iboga* use in literature (NR: Not reported; AE: Adverse event)

Reference	**Gender Age**	**Context and motivation of use**	**Presenting Symptoms**	**Information on the dose**	**Time to onset of AEs**	**Medical history**	**Medical examination, blood tests, serology**	**Official cause of death /Treatment**
Alper et al. (2012)	F, 44	1990 Psychological/ spiritual	Sudden death	Ibogaine HCl 300 mg (c. 4.5 mg/kg bw)	4 h	Hypertension; prior left ventricular myocardial infarct, marked 3-vessel coronary artery atherosclerosis Inverted T waves noted on EKG 3 months prior to death	Ibogaine Blood: 0.24 mg/L Liver: 0.17 mg/kg, Kidney: 0.3 mg/kg Other toxicology: negative	Acute heart failure (autopsy)
Alper et al. (2012)	F, 24	1993 Opioid detoxification	Sudden death	Ibogaine HCl 29 mg/kg bw	19 h	Charred tin foil found in room	Ibogaine Morphine: ‘‘trace’’ Noribogaine	Undetermined; (autopsy)
Alper et al. (2012)	M, 36	1999 Opioid detoxification, cocaine dependence	Sudden death	Ibogaine HCl; estimated 16–20 mg/kg bw	8-9 h	Depression, adverse life events prior to treatment; decedent was aware of dangers of use of cocaine or heroin	Ibogaine Benzoylecgonine Opiates Morphine	Acute intoxication due to the combined effects of opiates, cocaine, and ibogaine (autopsy)

Reference	Gender Age	Context and motivation of use	Presenting Symptoms	Information on the dose	Time to onset of AEs	Medical history	Medical examination, blood tests, serology	Official cause of death /Treatment
						concurrently with ibogaine		
Alper et al. (2012)	M, 40	2000 Opioid detoxification	Sudden death	*T. iboga* alkaloid extract; 6 g administered over circa 6 h	40 h	Hepatitis C with liver fibrosis, pulmonary and cerebral edema	Ibogaine Noribogaine Ibogamine Other toxicology: negative	Fatal reaction to *T. iboga* preparation. Contributing condition: Hepatitis C (autopsy)
Alper et al. (2012)	F, 35	2002 Psychological / spiritual	Sudden death	Ibogaine HCl 500 mg (circa 8 mg/ kg bw)	1.5 h	Childhood heart surgery congenital, moderate coronary artery atherosclerosis	Unknown	Heart failure / intoxication (autopsy)
Alper et al. (2012)	M, 32	2003 Opioid detoxification (self-administered by opiate abuser)	Sudden death	Bag of brown powder at scene that tested positive for ibogaine	Unknown	Moderate coronary artery atherosclerotic stenosis. History of opiate abuse	Iboagine Benzoylecgonine Methadone Nordiazepam	Ibogaine intoxication. Contributing conditions: atherosclerotic cardiovascular disease, cocaine use (autopsy)
Alper et al. (2012)	M, 54	2003 Opioid detoxification, alcohol dependence	Sudden death	Ibogaine HCl 13 mg/kg bw	60 h	Obesity, chronic alcoholism, smoker	Unknown	Pulmonary Thromboembolism (death certificate)

Reference	Gender Age	Context and motivation of use	Presenting Symptoms	Information on the dose	Time to onset of AEs	Medical history	Medical examination, blood tests, serology	Official cause of death /Treatment
Alper et al. (2012)	M, 45	2004 Opioid detoxification, alcohol dependence	Sudden death	Ibogaine HCl 15 mg/kg bw	20 h	Chronic alcoholism, obesity, cardiac pacemaker	Unknown	Acute hemorrhagic pancreatitis. Contributing conditions: Chronic alcoholism, obesity, opiate pain medication dependency (autopsy)
Alper et al. (2012)	F, 48	2005 Opioid detoxification	Sudden death	Ibogaine HCl 14 mg/kg bw	2 days	Prior gastric bypass surgery, Fibromyalgia, benzodiazepine dependence	Ibogaine Diazepam Oxazepam Temazepam (trace)	Sudden cardiac death due to acute myocardial infarct due to acute coronary syndrome. Contributing conditions: Fibromyalgia chronic pain medication dependency (autopsy)
Alper et al. (2012)	M, 43	2005 Opioid detoxification, alcohol dependence	Sudden death	Ibogaine HCl, dose unknown	27 h	Dilated cardiomyopathy, coronary artery atherosclerosis, pulmonary	Ibogaine Diazepam Trimethobenzamide Benzoylecgonine	Valvular heart disease. Contributing conditions: Dilated

Reference	Gender Age	Context and motivation of use	Presenting Symptoms	Information on the dose	Time to onset of AEs	Medical history	Medical examination, blood tests, serology	Official cause of death /Treatment
						edema Hepatitis B	Ibogamine ibogaline	Cardiomyopathy (autopsy)
Alper et al. (2012)	M, 51	2005 Opioid detoxification, methampheta mine and alcohol dependence	Sudden death	Ibogaine HCl 12 mg/kg bw	24 h	Not performed	Unknown	Cardiorespiratory arrest due to acute myocardial infarction (death certificate, clinical diagnosis of attending physician)
Alper et al. (2012)	M, 38	2006 Opioid detoxification	Sudden death	Ibogaine HCl 13 mg/kg bw	12 h	Cutaneous abscesses, hepatitis	Ibogaine: unknown Cocaine and morphine metabolites	Pulmonary thromboembolism (death certificate)
Alper et al. (2012)	M, 48	2006 Unknown	Sudden death	18 "soup-spoons" of a mixture of powdered *T. iboga* root bark and sweetened condensed milk over 10 h	53 h	Pulmonary edema. Buprenorphine Tablets, substance abuse	Ibogaine Noribogaine Ibogamine Other toxicology: negative	Acute ibogaine intoxication (autopsy)
Alper et al. (2012)	M, 28	2006 Opioid detoxification	Sudden death	*T.iboga* alkaloid extract, 7.5 grams over	76 h	Choroid plexus papilloma involving hippocampus	Ibogaine, cannabinoid concentrations	Not conclusive regarding proximal cause of death.

Reference	Gender Age	Context and motivation of use	Presenting Symptoms	Information on the dose	Time to onset of AEs	Medical history	Medical examination, blood tests, serology	Official cause of death /Treatment
				circa 18 h		with hypoxic damage to hippocampus. Large duodenal ulcer with accumulation of blood in duodenum	reportedly ''low.'' Negative for other drugs of abuse and ethanol	'Toxicological cause not likely' (autopsy)
Alper et al. (2012)	M, 30	2006 Opioid detoxification	Sudden death	Ibogaine HCl 17 mg/kg bw (1.75 g) Single dose	8 h	Not performed	Not tested	'Cardio-respiratory collapse secondary to drug related illness' (death certificate)
Alper et al. (2012)	M, 27	2006 Unknown	Sudden death	Powdered root bark (7.2% ibogaine, 0.6% ibogamine).	≤20 h	History of dependence on crack cocaine, benzodiazepines and alcohol	Ibogaine Methadone Diazepam Oxazepam Temazepam Ibogamine	Drug overdose due to ibogaine, methadone, diazepam, and temazepam (autopsy)
Alper et al. (2012)	M, 45	2006 Opioid detoxification	Sudden death	Ibogaine HCl 22 mg/kg bw	8-12 h	Hepatic steatosis	Ibogaine Diazepam Fentanyl Norfentanyl	Mixed drug intoxication (autopsy)
Alper et al. (2012)	M, 33	2007 Opioid detoxification crack cocaine dependence	Sudden death	Ibogaine HCl 11 mg/kg bw	6.5 h	Family history of pulmonary thromboembolism	Not tested	Pulmonary thromboembolism (death certificate)

Reference	Gender Age	Context and motivation of use	Presenting Symptoms	Information on the dose	Time to onset of AEs	Medical history	Medical examination, blood tests, serology	Official cause of death /Treatment
Alper et al. (2012)	M, 41	2007 Opioid detoxification cocaine dependence	Sudden death	Ibogaine HCl 13 mg/kg bw (1080 mg)	6 h	Cardiac hypertrophy Triglycerides: 397 mg / dL	Not tested	Fatal arrhythmia during drug addiction treatment with cardiac hypertrophy (autopsy)
Papadodima et al. (2013)	M, 52	Addiction treatment	Sudden death	Unknown	12-24 h	Hypokalemia and hypomagnesemia, 20-year alcoholism, atherosclerosis, liver cirrhosis	Ibogaine	Cardiac, ibogaine-related death 40-45% occlusion of coronary arteries was observed (moderate atherosclerosis), liver cirrhosis and heavy fatty infiltration (autopsy)
Mazoyer et al. (2013)	M, 27	Addiction treatment	Sudden death	Unknown Claimed by witness group: A teaspoon of iboga powder, however, concentration measurement indicated larger quantities been used	12 h	Multiple substance addiction, no cardiac pathology	Ibogaine ibogamine diazepam nordiazepam oxazepam temazepam EDDP no methadone >48 h	No underlying cardiac or pulmonary pathology was detected (autopsy).

Reference	Gender Age	Context and motivation of use	Presenting Symptoms	Information on the dose	Time to onset of AEs	Medical history	Medical examination, blood tests, serology	Official cause of death /Treatment
Jalal, Daher & Hilu (2013)	M, 25	Addiction treatment	Sudden death	2.5 g of ibogaine over 3 hours	48 h	heroin addiction, supraventricular tachycardia	Toxicology results confirmed that Ibogaine was the ingested substance	Multi - organ failure.
Meisner, Wilcox & Richards (2016)	M, 40	Home. Treatment of heroin dependence	Sudden death	4 g ibogaine (unknown presentation; internet supplier); Analysis not performed	Unknown	History of heroin dependence	Serum drug screening positive for opioids and negative for other drugs.	Cardiopulmonary death, family declined post-mortem examination.
Aćimović et al. (2021)	M, 27	Addiction treatment	Sudden death	A powder labeled *T. iboga* bought online	5-12 hours	Drugs abuse	Ibogaine: noribogaine as its main active metabolite and other metabolites (ibogaline and ibogamine), morphine and codeine	Cause and manner of death were not established.
Myeboga (2018)	F, 60	unknown	Sudden death	unknown	unknown	15 years methadone use and a history of HEP B and a thyroid condition	NR	Exact details of the cause of death have not been released.

Reference	Gender Age	Context and motivation of use	Presenting Symptoms	Information on the dose	Time to onset of AEs	Medical history	Medical examination, blood tests, serology	Official cause of death /Treatment
Black (2011)	F, 32	Spiritual ceremony	Sudden death	unknown	unknown	no prior history of drug-taking	NR	Died from cardiac arrest associated with iboga according to the pathologist
Stewart (2015)	F, 45	Addition treatment	Sudden death	Four doses of ibogaine on the first day of treatment and received last dose following day at 7 am	unknown, but around 32 h based on GP's records	Drug addict since teenager. At the time of her death, taking morphine	NR	NR
Amundsen (2015)	F, 42	Addiction treatment	Sudden death	Two-day treatments, doses not reported	Found dead the third day at 6 am	history of addiction to a range of drugs, latterly heroin	Ibogaine capsules were found near the body	use of ibogaine and myocardial infarction.
Cheer (2015)	M, 33	Addiction treatment	Sudden death	Got two doses of ibogaine, amount not reported	Found dead 20 minutes after taking valium on second treatment day	methamphetamine addiction, had an undiagnosed heart problem	Post-mortem samples indicated the presence of ibogaine in the blood, urine, stomach and bile specimens	Heart problem probably contributed to cardiac arrest
Gummin (2017)	M, 26	Addiction treatment	Sudden death	unknown	Day 14	history of polysubstance abuse, dependence on oxycodone	No autopsy was conducted	NR

Reference	Gender Age	Context and motivation of use	Presenting Symptoms	Information on the dose	Time to onset of AEs	Medical history	Medical examination, blood tests, serology	Official cause of death /Treatment
Corkery (2018)	M, 36	Addiction treatment	Sudden death	Got single dose ibogaine at about 21:00, amount not reported	~18h Found dead about 15:00 the other day	opioid dependence	Ibogaine in blood, urine, washing up bowl containing vomit 35 mg ibogaine	ibogaine and opiate intoxication
Corkery (2018)	M, 50s	Addiction treatment	Sudden death	unknown	unknown	Alcoholic, used heroin (route unknown), and dependent on diazepam	Post-mortem toxicology positive for ibogaine, noribogaine, unspecified tryptamine, oxycodone and mirtazapine	toxic effects of drugs (including iboga and heroin) and alcohol
Corkery (2018)	M, 53,	Addiction treatment	Sudden death	unknown	unknown	heroin addiction	acetone—blood 3mg/dL, urine 95mg/dL, ibogaine in blood, morphine and cocaine in urine	acetone and ibogaine overdose
Carr (2017)	M, 36	Addiction treatment	Sudden death	unknown	unknown	heroin addict	Post-mortem toxicology indicates the ingestion of morphine/heroin in the hours prior to death,	cardiac arrest, combined effects of morphine and ibogaine intoxication

Reference	Gender Age	Context and motivation of use	Presenting Symptoms	Information on the dose	Time to onset of AEs	Medical history	Medical examination, blood tests, serology	Official cause of death /Treatment
							ibogaine detected in urine	
Hoelen, Spiering & Valk (2009)	F, 31	Alcohol addiction	Long QT, VT	A single dose of 3.5 g of ibogaine 15% (7.5 mg/kg bw)	Unknown	Alcohol addiction	No alcohol, no other drugs	QT interval normalized at 42 hours after presentation
Houenou et al. (2011)	M, 26	Spiritual	Acute psychotic episodes	Unknown	Unknown	Intermittent hallucinations and persecutory delusions	Not performed	Treatment with olanzapine (10 mg/d) and sedative medication
Paling et al. (2012)	M, 49	Anti-addictive	Long QT, TdP	Unknown	Unknown	Heroin addiction, hyperthyroidism	Traces of opioids in urine	NR
Paling et al. (2012)	F, 31	Treatment-resistant alcohol dependence	Nausea Long QT, TdP (torsade de pointes)	A single dose of 3.5 g of ibogaine 15% (7.5 mg/kg bw)	Unknown	Alcohol addiction	No other medication	NR
Paling et al. (2012)	F, 43	Treatment heroin and benzodiazepines addiction	Long QT	Unknown	Unknown	Heroin/benzodiazepin addiction, on methadone	Opioids in urine, blood samples showed potentially lethal ibogaine levels (0.37 mg/ml)	Injected with flumazenil (Anexate) and naloxone

Reference	Gender Age	Context and motivation of use	Presenting Symptoms	Information on the dose	Time to onset of AEs	Medical history	Medical examination, blood tests, serology	Official cause of death /Treatment
Pleskovic et al. (2012)	M, 33	Cocaine, heroin and methadone abstinence	Long QT, ventricular fi brillation (VF)	A single 600 mg dose of ibogaine (8.6 mg/kg- bw)	30 minutes	Cocaine, heroin and methadone addiction	Ibogaine, Noribogaine and methadone in blood	NR
Shawn et al. (2012)	M, 63	Opioid detoxification	Long QT, VT, TdP	4 doses of ibogaine (10.5 mg/kg per dose) and tabernanthe bark root extract (14 mg/kg bw per dose)	3 h	Opioid abuse	Short-acting opioids	2 g of intravenous magnesium and was admitted to the critical care unit
Ausa et al. (2013)	M, young	Soothe the symptoms of heroin withdrawal	Long QT, VT, TdP	7 g of ibogaine (100 mg/kg bw)	Unknown	No family history of heart disease	Unremarkable	i.v.magnesium, epinephrine, and isoprenaline
Vlaanderen et al. (2014)	M, 26	For spiritual experience	Seizures, long QT, VT, VF	2400 mg ibogaine (34 mg/kg bw)	<5 h	Healthy	Benzodiazepines and ibogaine	Anti-epileptics (phenytoin, valproic acid and levetiracetam)
Breuer et al. (2015)	M, 22	Spiritual cleansing at home with family members.	Visual memories nausea vomiting seizer	Two portions within 5 mins, cumulative dose 38 g (Iboga root bark; internet supplier);	1 hour	No history of acute or chronic illnesses. No concomitant medication or drug abuse.	Presence of ibogaine and noribogaine in hair samples; presence of noribogaine in urine sample.	Midazolam (i.v.unknown dose) and levetiracetam (1 g).

Reference	Gender Age	Context and motivation of use	Presenting Symptoms	Information on the dose	Time to onset of AEs	Medical history	Medical examination, blood tests, serology	Official cause of death /Treatment
				Analysis not performed.				
Marta et al. (2015)	Case 1 M, 36	Treatment of an opioid use relapse	Mania, Irritability, grandiose delusions, rapid tangential speech, and aggressive behavior	Unknown	Unknown	Depression, ADHD, maniac symptoms and polysubstance dependence. Medications used: divalproex ER. 1,000 mg, risperidone 2 mg, and quetiapine 200 mg, daily.	Urine drug screening positive for benzodiazepines	Intervention at residential chemical dependency treatment (divalproex 1 g, risperidone 2 mg, quetiapine 200 mg daily); Intervention at ED (divalproex 1.5 g daily, risperidone 2 mg, atomoxetine 80 mg).
Marta et al. (2015)	Case 2 F, 35	Treatment of an opioid use relapse	Little to no sleep, aggression, impulsivity, psychomotor agitation, irritability, emotional lability, hallucinations, pres-sured and tangential speech	Unknown	Unknown	History of opioid dependence	Toxicology positive for methadone at first intervention; toxicology positive for methadone, opioids, and benzodiazepines at second intervention.	Quetiapine, risperidone, and olanzapine at unknown doses

Reference	Gender Age	Context and motivation of use	Presenting Symptoms	Information on the dose	Time to onset of AEs	Medical history	Medical examination, blood tests, serology	Official cause of death /Treatment
Marta et al. (2015)	Case 3 M, 40	Spiritual reasons.	Worsening distractibility, irritability, grandi-osity, motional lability,decreased need for sleep, racing thoughts, and suicidalideation	Unknown	Unknown	Without history of acute or chronic illness	Urine drug screening positive for cannabinoids (admitted to having used an unknown quantity of psilocybin mushrooms days after ibogaine).	Involuntary hospitalization for 6 days but refused all treatments offered.
O'Connell et al. (2014)	M, 33	Home Treatment of heroin dependence	Nausea, vomiting, altered mental status, and gait instability	3.8 g ibogaine (8 capsules over a few hours; internet supplier); ibogaine quantity in capsule confirmed	7.5 h	History of heroin dependence and good health status	Ibogaine was detected in both urine and serum samples.	Discharged from ED after 24 h without treatment
Hildyard et al. (2016)	M, 39	Treatment of heroin dependence	Seizure QT prolongation and pause-dependent polymorphic	7 g ibogaine (unknown presentation; internet supplier).	5 h	History of heroin addiction	Not performed	Electrical cardioversion, i.v. magnesium 2 g, atropine 1 mg, and isoproterenol 2.5 µg per minute.

Reference	Gender Age	Context and motivation of use	Presenting Symptoms	Information on the dose	Time to onset of AEs	Medical history	Medical examination, blood tests, serology	Official cause of death /Treatment
			ventricular tachycardia (VT)					
Henstra et al. (2017)	F, 46	Home. Treatment of drug dependence	Prolonged QTc-interval Torsades des Pointes (TdP)	1.4 g ibogaine (repeated ingestion over 12 h, capsules; internet supplier; Analysis not performed.	A few hours	With history of heroin, cannabis, alcohol, and cocaine dependence. No medical history of cardiovascular disease.	Urine drug screening negative. LC-MS/MS confirmed the presence of ibogaine and noribogaine.	Isoproterenol (unknown dose), pacemaker, i.v. sodium and magnesium.
Wilkins et al. (2017)	F, 47	Home with support service and remote monitoring, detoxification of methadone	NR	Repeated low doses ranging from 150 to 600 mg of ibogaine HCL; Purity confirmed through unknown method	Unknown	History of heroin dependence and HCV, history of cannabis, heroin, amphetamine, and ethanol use.	Not performed	Use of a single dose of diazepam (2 mg) after the first session. After the other sessions use of oral cannabis oil.
Steinberg & Deyell (2018)	M, 61	Holistic, naturopathic clinic. Blunt opioid addiction symptoms	Heavy vomiting and diarrhea, significant alteration of his level of consciousnes	5.6 g (65-70 mg/kg bw)(capsules; without medical prescription	6-12h	Chronic cervico-lumbar pain syndrome. History of depression, mild hypertension, and dyslipidemia	Lab screening negative for cointoxication	ED and ICU intervention (defibrillation, i.v. supplementation).

Reference	Gender Age	Context and motivation of use	Presenting Symptoms	Information on the dose	Time to onset of AEs	Medical history	Medical examination, blood tests, serology	Official cause of death /Treatment
			s, QT prolongation	and supervision); Analysis not performed.				
Barsuglia (2018)	M, 31	A 4-day program at an ibogaine clinic (Mexico) with medical screening and monitoring, treatment of alcohol use disorder	Ataxia, vomiting, acute panic, experienced close-eyed visions	1550 mg (17.9 mg/kg bw) of ibogaine HCl with the first three doses ((500, 500, 300mg)) given in 30 min and the fourth (250 mg) 3h after the prior.	4.5 h	ADHD, PTSD, depressed mood and alcohol use disorder.	Urine alcohol toxicology results negative upon arrival.	Administration of 500 mL of intravenous saline for hydration, 1 ampule of magnesium sulfate, and ranitidine 50 mg for nausea prior to the first dose of ibogaine.
Knuijver et al. (2018)	M, 31	Treat opioid use disorder	QTc prolongation , hallucinogen persisting perception disorder (HPPD)	Single dose of IBO hydrochloride (HCl) (100% purified, 10 mg/kg bw: 700 mg)	48 h	With opioid use disorder, history of heroin dependence.	Urine drug screening negative.	EMDR therapy
Grogan et al. (2019)	F, 34	Home, self-withdraw from opioids.	Hallucinations, four to five seizure-	2 g (ibogaine powder; internet supplier); LC-	Shortly after ingestion	Medical history significant for heroin use disorder	Urine drug screening positive for cannabinoids,	Intervention at ED and ICU for 4 days, and 5 additional days in an inpatient

Reference	Gender Age	Context and motivation of use	Presenting Symptoms	Information on the dose	Time to onset of AEs	Medical history	Medical examination, blood tests, serology	Official cause of death /Treatment
			like episodes with altered mental status, clenching teeth, and extension of arms, apneic	QTOF/MS confirmed the presence of ibogaine, quantitative analysis could not be performed.	of the ibogaine		cocaine, and opioids.	psychiatric unit. Treatment included intubation and i.v. magnesium sulfate.
Matamoros-Castillo et al. (2019)	M, 31	Home, withdraw from codeine and alprazolam	Feeling of unsteadiness and unspecified fear that onset a panic attack, behavioral alterations and a drop in the level of consciousness.	Unknown; Analysis not performed.	Few minutes	With history of anxiety and muscular pain, used codeine as auto-medication	Urine drug screening negative.	Intervention in ED (olanzapine 20 mg); Intervention in psychiatric ward (rehydration and forced diuresis through fluid therapy).
Wilson, Millar, & Matieschyn (2021)	M, 35	Case series Two different clinics at Vancouver area. Case 1: treatment of	Case 1: NM	Case 1: ibogaine/ibog a doses not informed.	Unknown	Case 1: 5-year history of opioid use disorder secondary to chronic pain.	Not performed	Case 1: 10 mg diazepam between treatments to help the patient sleep and an antiemetic (not specified).

Reference	Gender Age	Context and motivation of use	Presenting Symptoms	Information on the dose	Time to onset of AEs	Medical history	Medical examination, blood tests, serology	Official cause of death /Treatment
		opioid dependence.						
Wilson, Millar, & Matieschyn (2021)	F, 34	Case 2: treatment of polydrug use.	Case 2: QTc prolongation and bradycardia	Case 2: *T. iboga* (containing 725 – 1850 mg of ibogaine per ceremony) Unclear analysis	Unknown	Case 2: with history of cocaine, heroin, fentanyl, and crystal methamphetamine use, and prescribed opioids.	Not performed	Case 2: Self-administration of 25 mg of quetiapine orally before first ibogaine session. Intervention in ED (i.v. fluids and zopiclone). Discharged 9 hours later.

Annex III Overview of clinical studies with ibogaine and noribogaine

Reference	Dose	Duration	Study population	No. of participants	Adverse events (AEs)
Glue et al. (2015b) Forsyth et al. (2016)	20 mg (corresponding to 0.3 mg/kg bw) ibogaine in combination with concomitant treatment with paroxetine (of which metabolite inhibits CYP2D6) or placebo	Single dose	Healthy male or sterilized female volunteers, aged between 20 and 40 years, and drug- and medication-free	21 participants	No stimulating effects were observed and no other adverse effects were mentioned (Forsyth et al., 2016). In total 7 AEs were reported after dosing with ibogaine, the most common adverse events were nausea (5 reports, all paroxetine), gastro-intestinal symptoms (3 reports, 2 paroxetine), and dizziness (3 reports, 2 paroxetine). Most AEs were of mild severity and resolved without intervention prior to study completion. No reports of hallucinations or any perceptual changes (Glue et al., 2015b).
Davis et al. (2017)	15 mg/kg bw ± 5 mg/kg bw ibogaine HCl Observational study	One week	male and female opioid users, 18-60 years old	88 participants	Most reported AEs: Participants reported on experienced acute subjective effects of ibogaine. 'I saw visions or visuals' and 'I experienced physical discomfort' were most frequently reported.
Mash et al. (2018)	8–12 mg/kg bw ibogaine HCl in gel caps under open-label	Single dose	Subjects met DSM-IV criteria for opioid or cocaine dependence and	191 participants (men= 144; women= 47)	Nausea and vomiting and ataxia of gait were most common AEs observed shortly after drug administration. Sensory and

Reference	Dose	Duration	Study population	No. of participants	Adverse events (AEs)
	conditions		demonstrated active use with positive urine screens, average age for opioid abusers: 35.8 ± 9.9 years for cocaine abusers: 36.1 ± 9.1 years.		perceptual changes, including active visualizations, were reported. No serious AEs occurred but several cases of orthostatic hypotension and bradycardia were observed in cocaine dependent subjects but not in opioid abusers due to volume depletion.
Knuijver et al. (2021)	10 mg/kg bw ibogaine-HCl (purity 98-102%), orally in a yoghurt mixture, pre-treated with 20 mg of metoclopramide	Single dose	Males or females 20–60 years of age, a wish for detoxification and abstinence of opioids and prior treatment failure	14 participants	Reported AEs included mild bradycardia and decrease in blood pressure during first 12 hours, vomiting (n=2), ataxia with in ability to walk, wakeful dreaming and reliving memories. Fifty percent of subjects reached a QTc of over 500 ms during the observation period. In six out of 14 subjects prolongation above 450 ms lasted beyond 24 hours after ingestion of ibogaine. No torsades des pointes were observed.
Noller, Frampton & Yazar-Klosinski (2018)	25-55 mg/kg bw ibogaine (purity 98.5%) given in multiple doses over 24-96 hours	Multiple doses during 24-96 hours.	Opioid users, 28-47 years	15 participants (50% male, 50% female)	One participant died during treatment, very likely related to ibogaine ingestion and most probably related to cardiac arrhythmia.
Brown & Alper (2018)	Ibogaine HCl Initial dose: 3 mg/kg bw (purity 94%)	Multiple doses during 2 days	Patients with DSM-IV Opioid Dependence, average age 29.0 ± 9.0 years	30 subjects (25 males, 5 females)	No clinically significant cardiovascular or other medical events occurred in this study.

Reference	Dose	Duration	Study population	No. of participants	Adverse events (AEs)
	Flood dose 2-12 hours later: typically 12 mg/kg bw sometimes followed by booster dose 1-16 hours later: 3 to 5 mg/kg bw Additionally, five subjects received crude extract of *T. iboga* root bark (total alkaloid 15-25% of which 25-50% ibogaine)				
Glue et al. (2015a)	3, 10, 30, or 60 mg noribogaine capsules or matching placebo	Single dose	Healthy drug-free male volunteers, aged between 18 and 55 years	36 participants, 4 cohorts (n=6 per noribogaine group, n=3 per placebo group)	In total, 13 AEs reported by 7 participants. Most common AEs were headache (4 reports) and epistaxis (2 reports) but were not statistically significantly different between placebo and dose groups. No QTcF values >500 milliseconds were observed at any time. All AEs were of mild or moderate intensity, and all resolved prior to study completion.
Glue et al. (2016)	60, 120, or 180 mg noribogaine HCl	single dose	Patients seeking to discontinue methadone opioid substitution	27 patients (21 male and 6 female), (n=6 per noribogaine group and n=3	In total, 78 AEs were reported by 22 participants. Most common were visual impairment, headache and nausea, with a higher number of reports of visual impairment at 120

Reference	Dose	Duration	Study population	No. of participants	Adverse events (AEs)
			treatment (OST) who had been switched to morphine during the previous week, age ≥18	per placebo group)	and 180 mg compared to placebo. No hallucinations reported, no deaths. Noribogaine caused statistically significant dose-dependent QTc prolongation, which reached clinically concerning levels at 120 and 180 mg. In addition, generally small observed effects on heart rate and PR interval across dosing groups with no clear dose-related trends.

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