NEW DIETARY INGREDIENT NOTIFICATION (NDIN)

SAFETY INFORMATION FOR A (b) (4) EXTRACT OF THE DRIED LEAF OF *Mitragyna speciosa* (Korth.) Havil (Rubiaceae)

Submitter: (b) (4) on behalf of American Botanicals Corporation

Date: August 20, 2021

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Regulatory Assessment of New Dietary Ingredient Notification for ABC Kratom Extract and Legality of Product

(b) (4) is submitting this new dietary ingredient notification on behalf of American Botanicals Corporation (ABC or "the Company") because the agency has stated it believes kratom extracts are subject to the new dietary ingredient notification (NDIN) requirements. We respectfully disagree with the agency position. We are submitting this NDIN in the interest of providing the agency with the comprehensive data and information establishing the kratom extract covered by this submission is not subject to the NDIN requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act (FFDCA) because it has been present in the food supply in a form that has not been chemically altered.[1]

The data found in this NDIN demonstrate kratom leaf and products derived from kratom leaves including teas, decoctions and resins have a history of use as food and dietary supplements outside of the United States. The history of use of kratom is extensive. ABC has documented daily use of kratom teas and supplements for well over one hundred years by an extensive number of consumers. Indeed, data from the Thai government issued in 2007 and 2008 document over one million annual users of kratom supplements and teas. We also are providing extensive data and information demonstrating the solvents used to extract the kratom leaf do not result in a chemical alteration of the constituents found in the kratom leaf. Simply, the constituents found in the kratom dietary ingredient covered by this submission have the exact same chemical structure and are the exact same molecule as those found in the kratom teas and kratom leaves that have been used as a dietary supplement and food for over 100 years in Southeast Asia.

Draft Guidance issued by FDA reinforces our position. FDA recognizes history of use as a basis to support the safety of new dietary ingredients when the dietary ingredient is the same as that historically consumed and is consumed at levels consistent with or below historical uses.[2] The data in the NDIN demonstrate the ABC kratom extract contains the same constituents found through consuming kratom teas or chewing kratom leaves. The data also demonstrate the ABC kratom extract is recommended for use well under the levels of historical use. FDA draft guidance does not require toxicology studies when there is an extensive history of use of the substance. ABC, nonetheless, conducted a 90-day toxicity study that further supports the safety at the recommended levels of use of a substantially equivalent kratom extract that was manufactured using a (b) (4) than the kratom extract covered by this NDIN.

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1 FFDCA § 413(a)(1); 21 USC § 350(a)(1).

2 FDA Draft Guidance for Industry, Dietary Supplements: New Dietary Ingredient Notifications and Related Issues, *see, e.g.*, pg. 68 (Aug. 2016) https://www.fda.gov/media/99538/download.

In addition to the extensive history of use, data demonstrating there is no chemical alteration between the kratom extract in this submission and that historically consumed, and the toxicology study supporting safety, the submission addresses other issues that have been raised by FDA such as the anecdotal reports of serious injuries, including deaths, from individuals who purportedly consumed kratom. A review of these reports reveals that in most instances the user was also taking illicit drugs or other substances that are well recognized to be associated with serious adverse health consequences, including death. The anecdotal reports are inconsistent with the extensive history of use of kratom teas in Southeast Asia for over a millennia by millions of users annually. The submission also addresses the concerns that have been expressed with the potential for kratom extracts to be addictive. The data demonstrate that kratom extracts have a low potential for abuse, a low dependence liability, and that there is insufficient evidence of personal harm, adverse health effects, or detriment to the public health when consumed as dietary ingredient.

The data and conclusions provided in the submission are consistent with the 2018 Department of Health & Human Services (HHS) letter to the Drug Enforcement Administration (DEA) recommending that mitragynine and 7-hydroxymitragynine not be scheduled under the Controlled Substances Act (CSA) (either temporarily or permanently) until scientific research can support such an action.[3] The HHS Assistant Secretary for Health makes multiple statements confirming that the available evidence does not support scheduling these substances under the CSA, including:

- I now conclude …that scheduling these chemicals [mitragynine and 7-hydroxymitragynine] would be premature;
- New data suggest that mitragynine does not satisfy the first of the three statutory requisites for Schedule I,[4] irrespective of broader considerations of public health; and
- The level of scientific data and analysis presented by the FDA and available in the literature do not meet the criteria for inclusion of *kratom* or its chemical components in Schedule I of the CSA at this time.

The letter goes on to discuss the need for further analysis, public input, and additional information needed to justify scheduling decisions, if any. Last, the letter unequivocally recognizes the beneficial properties of kratom, stating that there is a "significant risk of immediate adverse public health consequences for potentially millions of users if kratom or its components are included in Schedule I." Some of the significant adverse public health consequences cited in the letter include effects on those suffering from intractable pain, risks

[3] Letter from Brett P. Giroir, M.D., Assistant Secretary for Health, Senior Advisor for Opioid Policy, HHS, to the Honorable Uttam Dhillon, Acting Administrator, DEA (Aug. 16, 2018).

[4] The first criterion requires a finding that the drug or other substance has a high potential for abuse. *See* 21 USC §§ 811(a)(1)(a); 812(b)(1)(A).

with users switching to highly lethal opioids; and a stifling effect on critical research needed on components of kratom (among others).

We recognize that in instances when a dietary ingredient is exempt from the NDIN requirements, the agency maintains the legal authority to deem a dietary supplement adulterated if

(1) it contains a dietary ingredient that presents a significant or unreasonable risk of illness or injury, or
(2) it contains a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not rennet a significant or unreasonable risk of illness or injury.[5]

The FFDCA further specifies that "in any proceeding brought under this paragraph the United States shall bear the burden of proof on each element to show that a dietary supplement is adulterated" and a court shall decide any issue under this paragraph "on a de novo basis."[6] The information in this submission provides for support for the ABC position that FDA would not be able to meet this burden of proof in demonstrating the kratom extract is adulterated regardless of whether it is deemed a dietary ingredient or a new dietary ingredient.

In conclusion, it is our view the kratom extract covered by this submission is exempt from the NDIN requirements under section 413 because it has been present in the food supply for over a hundred years and is in a form that has not been chemically altered. We also are of the view the data and information in this submission provide a compelling case for the safety of this kratom extract based on the extensive history of use of kratom teas and the toxicology study further demonstrating safety. While ABC has a legal basis to support the marketing of its kratom dietary supplement, the Company is committed to transparency and wants the agency to have visibility on the extensive data and information supporting the lawful marketing of the company's kratom extract. We view the kratom extract covered by this submission as being lawfully marketed regardless of the agency response to this submission.

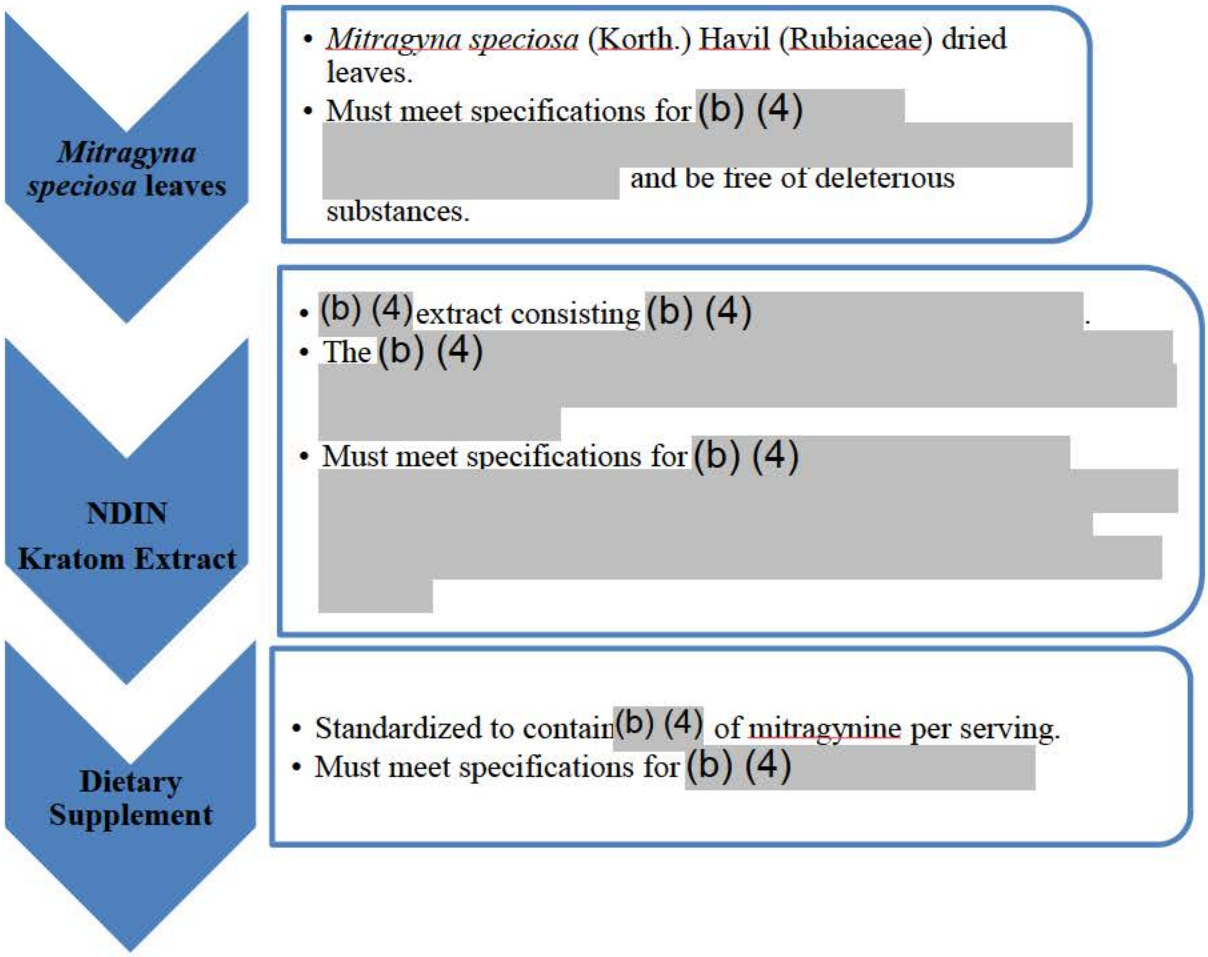
1. Description of Kratom Extract Dietary Ingredient

The notification covers a dietary ingredient that is (b) (4) extract of the dried ground leaf of *Mitragyna speciosa* (Korth.) Havil (Rubiaceae), that consists only of (b) (4) herein and forthwith referred to as "kratom extract".

The term "kratom" is commonly used to refer to the tree, its leaves, and its extracts. The kratom extract will be used (b) (4)

5 FFDCA §§ 402(f)(1)(A),(B); 21 USC §§ 342(f)(1)(A),(B).
6 *Id.* § 402(f)(1); 21 USC § 342(f)(1).

(b) (4) . The extract is prepared as (b) (4) . The dietary ingredient is intended for formulation into dietary supplements that are substantially equivalent to the teas and hot water decoctions prepared from the leaves of *Mitragyna speciosa* traditionally ingested in Southeast Asia for centuries.



1.1 Identity of Botanical Raw Material Used in Manufacture of the Dietary Ingredient

The kratom extract is an extract prepared from the dried leaves of the *Mitragyna speciosa* (Korth.) Havil (Rubiaceae). The term "kratom" is commonly used to refer to the tree, its leaves, and its extracts. *M. speciosa* is a deciduous evergreen tree belonging to the coffee (Rubiaceae) family. It grows well in swampy areas, is native to countries in Southeast Asia, occurs in the wild, primarily in Thailand, Malaysia, Indonesia, and New Guinea, and is also cultivated in these regions. The plant has a long history of use in Southeast Asia and is traditionally used among laborers as an energizer, relaxant, and to relieve stress and/or minor

aches and pain during the workday. The leaves can be chewed or consumed as a tea made from boiling the leaves in water, sometimes with added citrus and sweetener. The leaves are also used in cooking food, such as soup, and chewed.

Botanically *M. speciosa* is taxonomically described as per Mr. G. D. Haviland in the "Revision of Naucleeae", Journal of the Linnean Society, 1897, (Haviland, 1897) as follows:

1. MITRAGYNA SPECIOSA, *Korth.*

Ramuli obtuse angulati. Folia 14 cm. longa, 7 cm. lata, elliptica, abrupte acuminata, basi rotundata vel subcordata, subtus in nervis pubescentia, nervis 15. Petioli 25 mm. Stipulæ 2 cm., lanceolatæ, sparse pubescentes, nervis 9. Pedunculi ternati, 3–5 cm. Bracteæ foliaceæ 4 cm., petiolis 2 cm. Corollæ tubus 5 mm., extra glaber, fauce pilosus; lobi 3 mm., glabri, marginibus revolutis. Stamina reflexa. Stylus 13 mm.; stigma 2 mm. Calycis lobi 5, quatuor breves rotundi, quintus sæpe spathulato-oblongus; tubi pars superior brevis, cupularis. Bracteolæ 4 mm., subglabræ. Receptaculum dense hirsutum. Fructus costæ 10, endocarpiis 4-valvatis.—*M. speciosa*, Korth. Obs. de Naucl. Ind. p. 19 (sine descriptione). *Stephegyne speciosa*, Korth. Verh. Nat. Gesch. Bot. p. 160. *S. parvifolia*, K. Schum. Fl. Kaiser-Wilh.-Land, p. 127. *Nauclea speciosa*, Miq. Fl. Ind. Bat. ii. 140.

Var. (*a*). Folia 15-nervia.—Borneo.

Var. (*b*). Folia 10-nervia.—Ins. Philippinæ; New Guinea.

MALASIA.—Borneo: Banjarmassin (Korthals; Motley, n. 1169). Ins. Philippinæ: Luzon (Vidal, n. 798).

NEW GUINEA.—Kaiser Wilhelmsland (Hollrung, n. 674).

The definition of *M. speciosa* is based on classic scriptures of taxonomy, which do not include differentiation based on "vein color." Brown et al. (2017) acknowledged that *M. speciosa* leaf can be purchased in a wide variety of formats colloquially referred to in a non-botanical manner often likened to "strains", for example Bali, Indo red, Malaysian, Thai green vein, Thai red vein, etc. (Brown et al., 2016; Raffa, 2015). There are only two documented references located in the scientific literature of historical use discussing "vein color." Suwanlert (1975) reported that among traditional Thai users the red and white vein leaves are preferred with the majority favoring a mixture of red and white vein (73%), whereas 17% preferred using red vein, and 10% reported preferring using the white vein kind (Suwanlert, 1975). In a study by Saingam et al. (2013) it was reported that local Thai *M. speciosa* users preferred red vein (Saingam et al., 2013). There is no specification for (b) (4)

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The leaves of *M. speciosa* contain several alkaloids which represent 2% - 3% of the total weight. The alkaloid mitragynine is reported to comprise about 65% - 80% of this 2% - 3% total. Other major alkaloids within the leaf material include paynantheine (8-10%), speciogynine (6-8%) and speciociliatine. Both mitragynine and the Diastereomer (C3 stereoisomer) of mitragynine, speciociliatine, are unique to *Mitragyna speciosa* and diagnostic for identity. Early reports suggest speciociliatine comprises 0.8% to 1% of total alkaloid content of kratom leaf. However, more recent studies using modern instrumentation suggest levels are closer to that of paynantheine and speciogynine in leaf materials. Some *M. speciosa* leaves also contain the alkaloid 7-hydroxymitragynine (0.0 - 0.06% w/w); for the kratom extract, the specifications require this (b) (4)

Not surprisingly, given the plant family origin, the profile of reported effects at lower doses of *Mitragyna speciosa* overlap with those of caffeine. This is consistent with historical use of kratom to increase energy and ability to endure long and demanding occupational demands. Similarly, like caffeine, kratom has long been recognized in South East Asia, and presently reported by many consumers in the US by national surveys, to be used to help increase and/or sustain alertness, concentration, and focus, thereby enhancing occupational performance along with family and social responsibilities (Garcia-Romeu et al., 2020; Grundmann, 2017; Pain News Network, 2021; Singh et al., 2016).

The (b) (4) to those found in the leaves, and the recommended serving size (b) (4) traditionally ingested in a typical serving of kratom leaves or products derived from kratom leaves (tea, decoction, resin) ingested by people in Southeast Asia. However, kratom tea is traditionally ingested throughout the day via multiple doses. Therefore, the (b) (4) . The (b) (4) kratom extract is prepared from *M. speciosa* leaves and materials that meet raw material specifications for identity, purity and content as described in section 1.1.1.

1.1.1 Raw Material Specifications

The dietary ingredient, kratom extract, is prepared from dried leaves of *M. speciosa*. (b) (4) . All raw leaf materials that will be used for the production of the kratom extract are first examined using organoleptic methods to ensure they meet initial raw material specifications. The dry leaf material is analyzed by (b) (4) Only material that

conforms (b) (4), described below, are used in the manufacture of the initial extract.

Material Information:

Binomial name: *Mitragynina speciosa*

Constituents/Plant part: Leaf

Identity:

Physical:

Appearance: (b) (4) Visual

Aroma: (b) (4) Organoleptic

Chemical:

Identification of the characteristic (b) (4) (see Appendix A for method details)

(b) (4)

Purity:

(b) (4)

Pesticides:

Total Microbial Count:

Coliform:

Yeast & Mold:

Salmonella:

E.coli:

S. aureus:

(b) (4)

Content:

Quantification of (b) (4) (see Appendix A for method details)

(b) (4)

1.2 Kratom Extract Manufacture

1.2.1 Raw Material

Mitragyna speciosa (Korth.) Havil (Rubiaceae) leaves meeting the specifications described in Section 1.1.1.

1.2.2 Dietary Ingredient Manufacturing Process

The new dietary ingredient is (b) (4) *Mitragyna speciosa* (Korth.) Havil (Rubiaceae) leaves are used in the manufacture of the dietary ingredient. (b) (4) detailed in Section 1.1.1 above are used in the manufacturing process.

A general description of the manufacturing process is as follows. (b) (4)

(b) (4)

1.2.3 Kratom Extract Specifications

Kratom extract is tested to ensure it meets specifications for (b) (4)
The kratom extract is (b) (4)
The kratom extract is (b) (4)
.

The kratom extract is also evaluated for purity (b) (4)
for pesticides, heavy metal and residual solvents.
The specification for content is (b) (4)

Table 1 describes specific specifications for the kratom extract and the testing method used to establish the specification has been met.

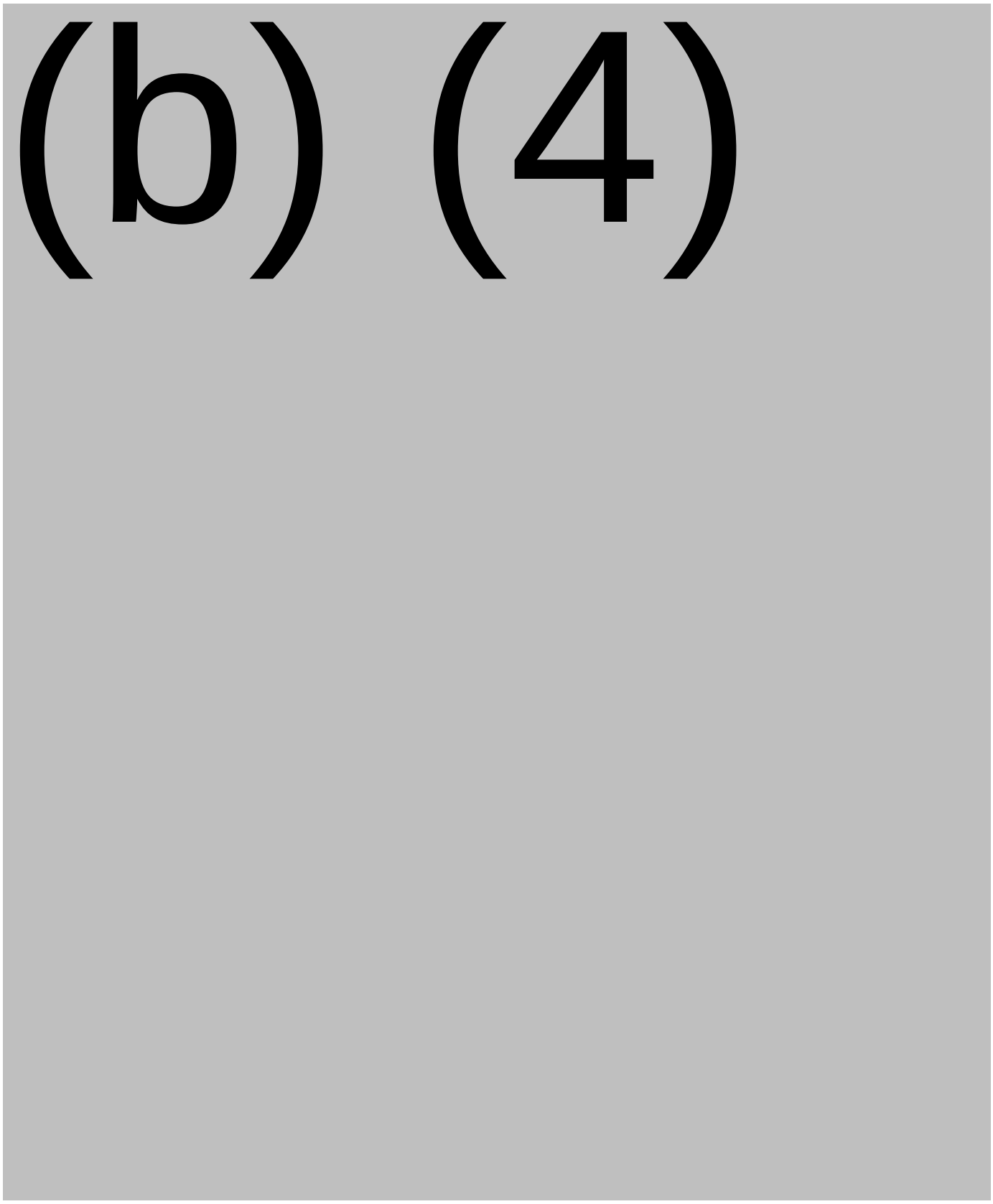
Table 1. Specifications for kratom extract

Specification	Acceptable Level	Testing method
(b) (4)		

Specification	Acceptable Level	Testing method
(b) (4)		

1.2.4 Summary of Specification Methods

Methods used to assess the kratom extract are listed below and provided in Appendices A through H. All methods employed are from authoritative, normative references specifically USP and AOAC Official method of Analysis. The contaminant testing methods are as per pharmacopoeial standards and compliant with USP.



(b) (4)

1.3 Compositional Information on Ingredient

1.3.1 Nutritional profile

Kratom extract is prepared from dried leaves of *M. speciosa*. As with any plant material, (b) (4) . The ratio and amount of the (b) (4) As shown in Table 2 (b) (4)

Table 2. Average Relative Nutritional Composition (%) Kratom Extract Dietary Ingredient and in Kratom leaf

	Kratom Extract	Kratom Leaf
(b) (4)	(b) (4)	

1.3.2 Plant Secondary Metabolite Constituent Verification

Kratom extract is a (b) (4) of *M. speciosa* leaf material. As with any plant material, (b) (4)

Analytical studies comparing the chemical composition of *M. speciosa* leaf materials to the (b) (4) kratom extract were conducted by (b) (4)

1.4 Shelf-Life and Conditions of Storage

The stability of kratom extract was assessed through (b) (4) results are shown in Table 3.

Table 3. Summary of (b) (4) results for the stability study. All results are (b) (4)

(b) (4)

(b) (4) The results are shown in Table 4.

Table 4. Summary of (b) (4) results for the stability study. All results are (b) (4)

(b) (4)

Both the (b) (4) comparisons show (b) (4) .

The results indicate that the sample is (b) (4) .

(b) (4)

The results from the (b) (4)

2. Dietary Supplement Manufacture

The kratom extract dietary ingredient described herein is intended for (b) (4) . These dietary supplements are (b) (4)

2.1 Dietary Supplement Ingredients

2.1.1 Dietary Ingredient

Kratom extract, (b) (4) as described in Section 1.2.3 above.

2.1.2 Other Ingredients

(b) (4)

(b) (4)

Optional ingredients: The finished dietary supplement could also (b) (4)

2.2 Manufacturing Process

The dietary supplement is prepared by (b) (4)

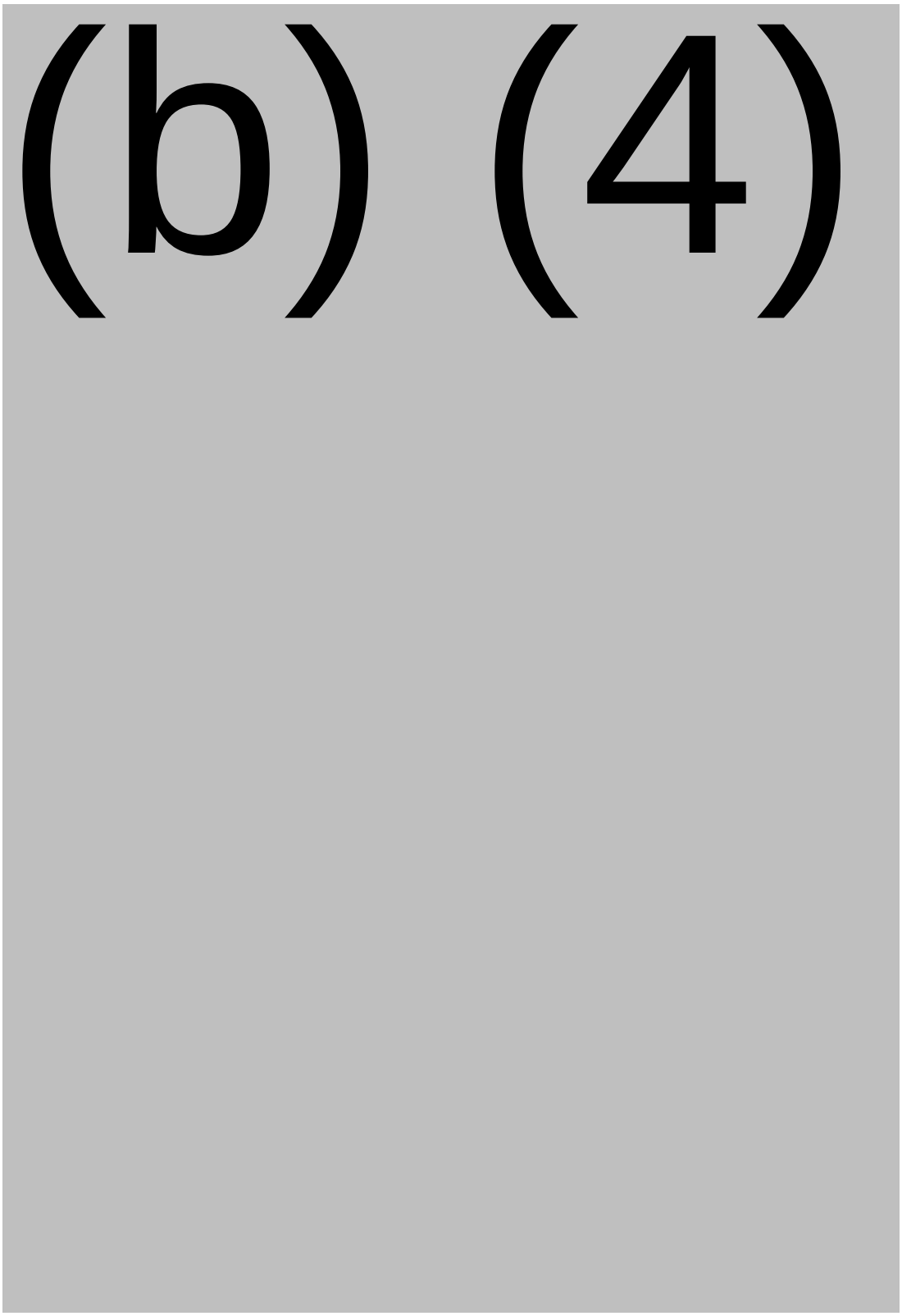
Optional ingredients includ (b) (4)

2.3 Finished Product Specifications

The final dietary supplement will include s(b) (4)

Table 5, below, describes specific specifications for the finished dietary supplement and the testing methods used.

Table 5. Specifications for Dietary Supplements Made from kratom extract



(b) (4)

2.3.1 Methods of Analysis

(b) (4)

2.4 Nutritional Profile

The dietary supplement is (b) (4)

As detailed in Section 1.3.1 above, (b) (4)

To ensure accuracy in labeling, (b) (4)

. As shown in Table 6 below, (b) (4)

The traditional kratom tea was prepared based on literature reports of traditional preparation as shown in Figure 1 in Section 3.1.1, which depicts a flow chart of the process (Farnsworth, 1966; Hassan et al., 2013; Raffa, 2015; Singh et al., 2014; Vicknasingam et al., 2010). In brief, (b) (4)

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When compared to the nutritional profile of a traditionally prepared kratom tea (b) (4)

However, it is noted the dietary supplement (b) (4)

Table 6. Average Relative Nutritional Composition (%) Kratom Extract Dietary Ingredient and in Kratom Leaf

(b) (4)

2.5 Shelf-Life and Conditions of Storage

2.5.1 Shelf-Life and Conditions of Storage

The recommended shelf life of the (b) (4)
(see Section 1.4). The processing (b) (4)

3. History of Use

3.1 Overview and Background

Mitragynina speciosa leaves and products derived from leaves including teas and decoctions have a long history of use in Southeast Asia among Far Eastern cultures (Babu et al., 2008), where the *Mitragyna speciosa* tree is native. Reference to its consumption appear in the scientific literature as early as 1907, when Wray (1907) reported on its consumption in parts of the Malay peninsula, particularly in the region that is now southern Thailand (Wray, 1907).

Wray described several methods of preparation of the leaves, including infusing the dried leaves in hot or boiling water. Multiple reports appear in the literature throughout the 20th and into the 21st century describing leaf or leaf infusion consumption of the leaves or infusions of them. In 1932, Grewel noted the use of kratom by people living in "the Peninsula of Siam" (Thailand) and performed some investigations of the pharmacology on various animal species (Grewal, 1932a) and in humans (Grewal, 1932b). His human experiments used both isolated purified mitragynine acetate and powdered kratom leaves. Further investigations of the pharmacology of mitragynine in animals were conducted by Macko et al. (1972), who also noted the history of use of the plant source by "natives of Siam, Malaya, Borneo, the Philippine Islands and New Guinea." (Macko et al., 1972).

Suwanlert (1975) reported the ongoing consumption of kratom by individuals in Thailand and noted that it had been consumed in Thailand for so long that "the beginning of its use in Thailand cannot be dated." (Suwanlert, 1975). Suwanlert also reported consumption of the fresh or dried leaves of *Mitragyna speciosa* directly or "after having been placed in warm water" and noted that consumers "reason that it helps them to overcome the burden of their hard work and meager existence." (Suwanlert, 1975).

Jansen and Prast (1988) reviewed the history of use of kratom in Southeast Asia, and noted as a report of its consumption by native Malayans as far back as 1836, and repeated the description of methods of consumption reported by Wray (1907), including the drinking of a leaf infusion (Jansen & Prast, 1988; Wray, 1907). Other publications further detail the long history of consumption of kratom. Assanangkornchai et al. (2007) reported that it had been in use "from time immemorial in some Southeast Asian countries (e.g. Malaysia and Myanmar)." (Assanangkornchai et al., 2007). These authors also reported a variety of modes of consumption including "by chewing fresh leaves … grinding up and eating fresh or dried leaves, in cooking and making it into a tea." Vicknasingam et al. (2010) report that "It is a medicinal herb long used in southern Thailand (where it is known as krathom) and the northern states of peninsular Malaysia to increase physical endurance." (Vicknasingam et al., 2010).

Tanguay (2011) reports: "Eating kratom is a tradition that has been practiced for centuries in southern Thailand and up to 70% of the male population in some districts use kratom daily. Indeed, many people in southern Thailand consider chewing kratom similar to drinking coffee." (Tanguay, 2011). Likewise, Adkins (2011) notes that "extracts of this plant have been used for over 100 years in Thailand and Malaysia" and "in small amounts, the leaves of this tree have been utilized by laborers for their stimulant effects and subsequent ability to invigorate workers in harsh conditions." (Adkins et al., 2011). Idayu et al. (2011) state that "*Mitragyna speciosa* Korth leaves have been used for decades … by natives of Malaysia, Thailand and other regions of Southeast Asia." (Idayu et al., 2011). Barceloux (2012) states that consumption of kratom "dates back to at least 1836 as described by Low," and notes that "in 1895, Holmes identified *Mitragyna speciosa* as the source of kratom used by workers." (Barceloux, 2012). Use in Southeast Asian countries since "at least as early as 1836" is also reported by Swogger et al. (Swogger et al., 2015). Warner et al. (2016) report "(h)istorically, kratom has been used by civilizations for many centuries. Cultures located in areas of Southeast Asia have been cultivating and using kratom for several thousand years." (Warner et al., 2016).

It is clear from these many scientific reports that leaves of *Mitragyna speciosa* and water infusions made from them have been used in the diet for hundreds of years, and, therefore, qualify as food under 21 USC 321(f) of the FFDCA.

3.1.1 Description of the Relationship between the Historically Consumed Kratom Materials and Kratom Extract

The dietary ingredient is (b) (4) kratom extract of *Mitragyna speciosa* leaf material. The (b) (4)

(b) (4)

The kratom extract can be (b) (4), such as with traditional teas. The preparation of the dietary supplement is (b) (4) A single traditional serving of *M. speciosa* tea or chewed leaf contains, on average, between 21.7 – 108 mg of mitragynine (Leong Abdullah et al., 2021; Singh et al., 2014; Singh et al., 2018; Singh et al., 2019; Singh et al., 2020; Vicknasingam et al., 2010). The dietary supplement prepared using the kratom extract (b) (4

Decoctions of *Mitragynina speciosa* have a long history of use in Southeast Asia among Far Eastern cultures (Babu et al., 2008) for use as a conventional food and herbal supplement. The leaves can be chewed directly or prepared into a tea. Kratom consumption appears to have started over two decades ago in the United States. Consumption of kratom in the United States grew significantly over the last decade and has now become widespread throughout the country. The most common mode of consumption in the United States is liquids either prepared by consumers or purchased as manufactured products. These liquids are made using both hot and cold water similar to the preparation of tea and coffee. Lemon juice or other acids and sugar, honey, and other flavoring ingredients are often added to facilitate extraction or to improve the taste of the liquids (Gruenwald, 2009; Guimarães et al., 2011; Jones, 1996; Ko, 2006; Shetty et al., 2006; Sõukand et al., 2013; Wu et al., 2011). Kratom teas and hot water decoctions have been traditionally ingested in Southeast Asia (Ahmad & Aziz, 2012; Hassan et al., 2013; Prozialeck et al., 2012; Raffa, 2015; Saingam et al., 2013; Ward et al., 2011; Wray, 1907).

Kratom teas were traditionally prepared by taking several grams of dried or fresh leaves, boiling or steeping them in water for up to an hour before straining with the resulting liquid ingested (Ahmad & Aziz, 2012; Hassan et al., 2013; Kamal et al., 2012; Prozialeck et al., 2012; Ramanathan & Mansor, 2015; Saingam et al., 2013; Wray, 1907). A review of the literature establishes that kratom has been consumed for decades in Southeast Asia. Based on literature reports the following flow chart describes the process of preparing a kratom tea:

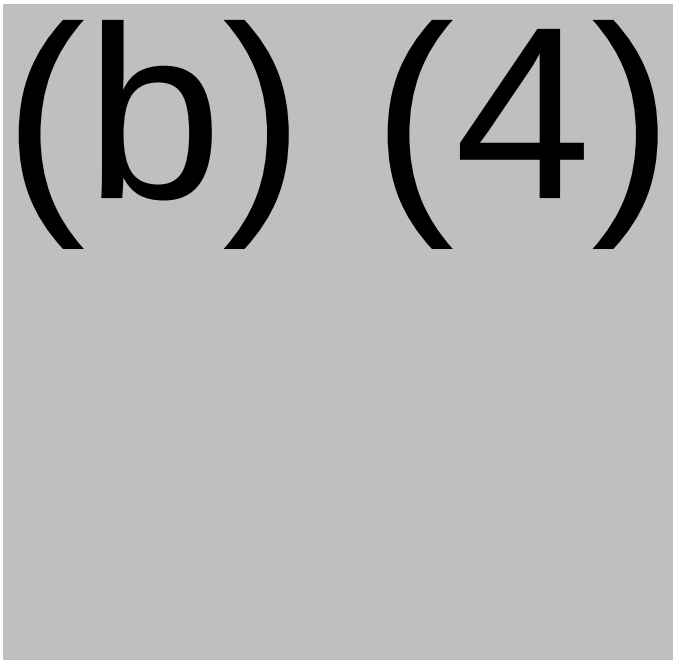


Figure 1. Preparation of a kratom tea

M. speciosa is taxonomically described as per Mr. G. D. Haviland in the "Revision of Naucleeae", *Journal of the Linnean Society*, 1897 (see Section 1.1) (Haviland, 1897). Despite the definition of *M. speciosa* in classic scriptures of taxonomy that do not include differentiation based on "vein color," Suwanlert (1975) reported that among Thai users the red and white veined leaves are traditionally preferred with the majority favoring a mixture of red and white vein (Suwanlert, 1975). In a study by Saingam et al. (2013) it was reported that local Thai *M. speciosa* users preferred the red vein (Saingam et al., 2013). Brown et al. (2017) acknowledged that *M. speciosa* leaf can be purchased in wide variety of formats that are colloquially referred to in a non-botanical manner often likened to "strains", for example Bali, Indo red, Malaysian, Thai green vein, Thai red vein, etc (Brown et al., 2017; Raffa, 2015; Saingam et al., 2013).

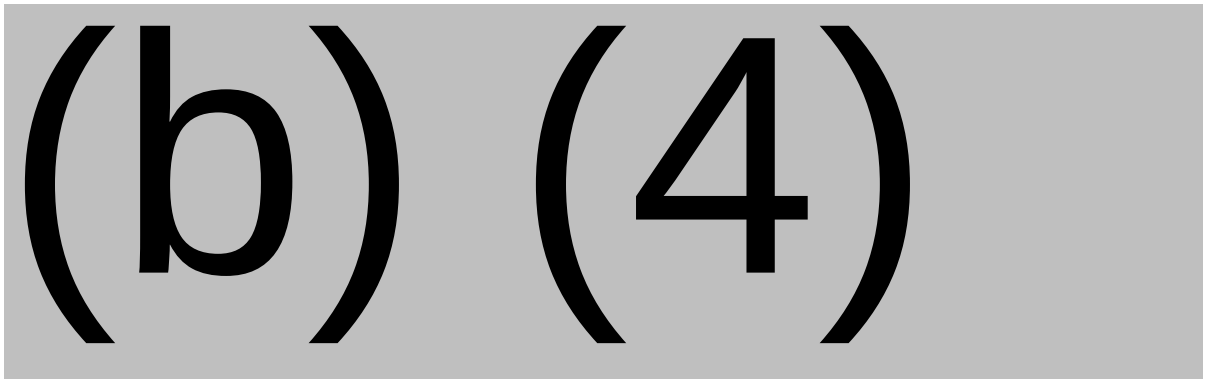


Table 7. Comparison of (b) (4) (See Appendix J)

(b) (4)

Table 8. Comparison of (b) (4) (see Appendix A)

(b) (4)

M. speciosa preparations may employ (b) (4)

The alkaloid content of dried *M. speciosa* leaves ranges from 0.5% – 3% (Hassan et al., 2013; Kruegel & Grundmann, 2018). Of the approximately forty alkaloids identified in the plant, mitragynine has been universally cited as the primary alkaloid constituent in terms of quantity and activity, making up 65% - 80% of the leaf alkaloids. Thus, the amount of mitragynine in dried leaf material ranges from 0.33% – 2.4% in a dry *M. speciosa* leaf. The other reportedly active alkaloid in the plant is 7-hydroxymitragynine, which can make up to two percent of the total leaf alkaloids or up to 0.06 percent of a dry

M. speciosa leaf. The raw materials specifications for (b) (4) (attached as Appendix A).

As described above, mitragynine is the primary chemical alkaloid constituent in kratom. Because of this, several modern studies that examine the relationships between traditional consumption levels of kratom tea with physiological effects have used mitragynine as the main marker compound. Chemical analysis of prepared kratom teas have shown variance in mitragynine levels, both due to inherent biological variance and use fo different analytial methods. Combined, the results from these analyses indicate that a single serving of kratom tea contains between 21.7 – 108.5 mg mitragynine (Leong Abdullah et al., 2021; Singh et al., 2014; Singh et al., 2018; Singh et al., 2019; Singh et al., 2020; Vicknasingam et al., 2010).

Given the importance of this compound, the amount of (b) (4) in the dietary supplement product. The dietary supplement prepared using the kratom dietary ingredient in this notification would contain (b) (4). Hence the level of (b) (4) .(b) (4)).

Although traditional kratom teas are prepared following generally similar procedures as described above, slight variations in some steps would also lead to variance in the final product. For example, the number of leaves used and the time spent boiling the leaf material and steeping would all affect concentration of the chemical constituents. However the relative levels of major constituents would still be expected to remain relatively constant.

As with any product prepared using natural ingredients, the inherent variability of the raw material itself can contribute to the variability of the final product. Such variations are to be expected, yet overall all kratom teas prepared using these processes would share particular characteristics that defines it. These characteristics include organoleptic properties and chemical, biological and physical specifications. By setting specifications

for raw materials and standardizing to a marker compounds, dietary supplement manufacturers are able to produce consistent products made from plant-based dietary ingredients.

The processes used to produce the dietary ingredient and dietary supplement described herein utilizes (b) (4) .
These processes (b) (4)
The precise selection of (b) (4)
Still, some variation among individual constituents would be expected, however by focusing (b) (4)

Traditionally, kratom users would take more than one serving in a day with regular *M. speciosa* users on average consuming two to four servings per day and heavy users consuming five to ten servings per day (Assanangkornchai et al., 2007; Singh et al., 2014; Singh et al., 2019; Singh et al., 2020; Suwanlert, 1975; Vicknasingam et al., 2010). For the dietary ingredient and supplement subject to this notification, it is recommended (b) (4)

3.1.2 Description of Identity Information Verifying the Relationship between Historically Consumed Kratom Materials and Kratom Extract

The dietary ingredient that is the subject of this notification is (b) (4) extract of the dried ground leaf of *Mitragyna speciosa* (Korth.) Havil (Rubiaceae), that consists only of (b) (4) .

The kratom extract is prepared (b) (4)

(b) (4)

3.1.2.1 (b) (4) Profiling by (b) (4)

(b) (4)

Table 9. (b) (4)

Table 9. Relative (b) (4) abundance of a kratom tea sample, kratom extract, and kratom leaf material. Values are (b) (4)

(b) (4)

(b) (4)

(Figures 2 to 5).

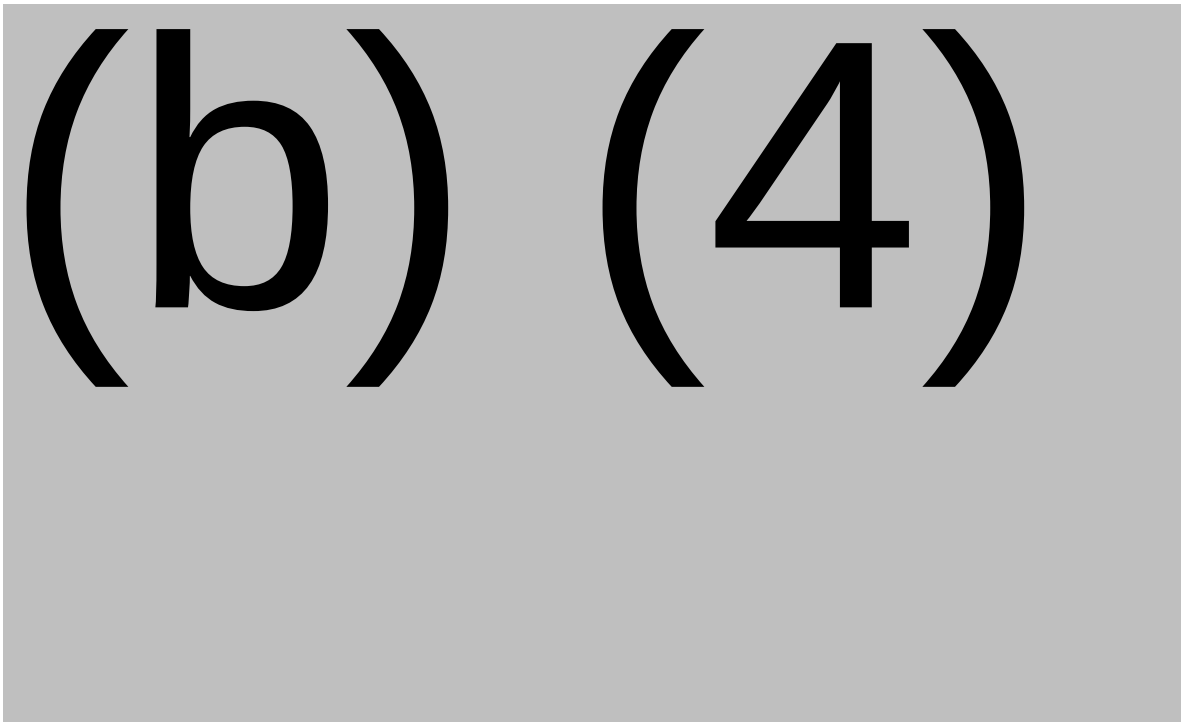


Figure 2. (b) (4) **of a representative kratom leaf sample (black) and a representative sample of the kratom extract (blue).**

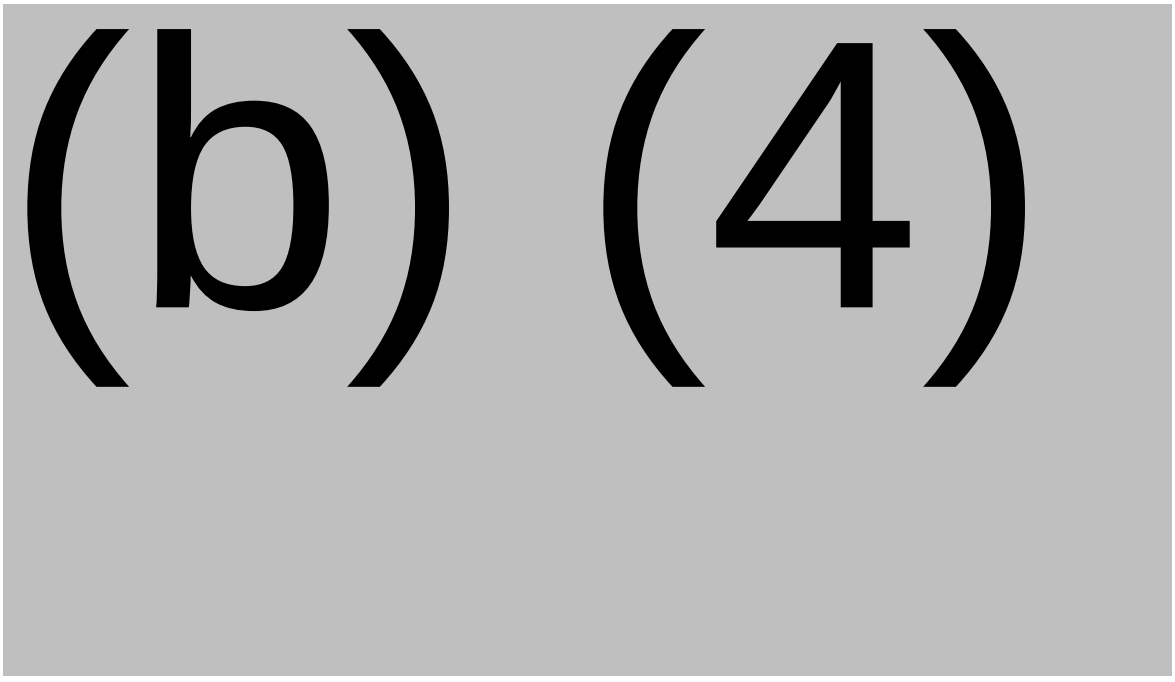


Figure 3. (b) (4) **of a representative kratom leaf sample (black) and a representative sample of the kratom extract (blue) zoomed into the area showing the** (b) (4)

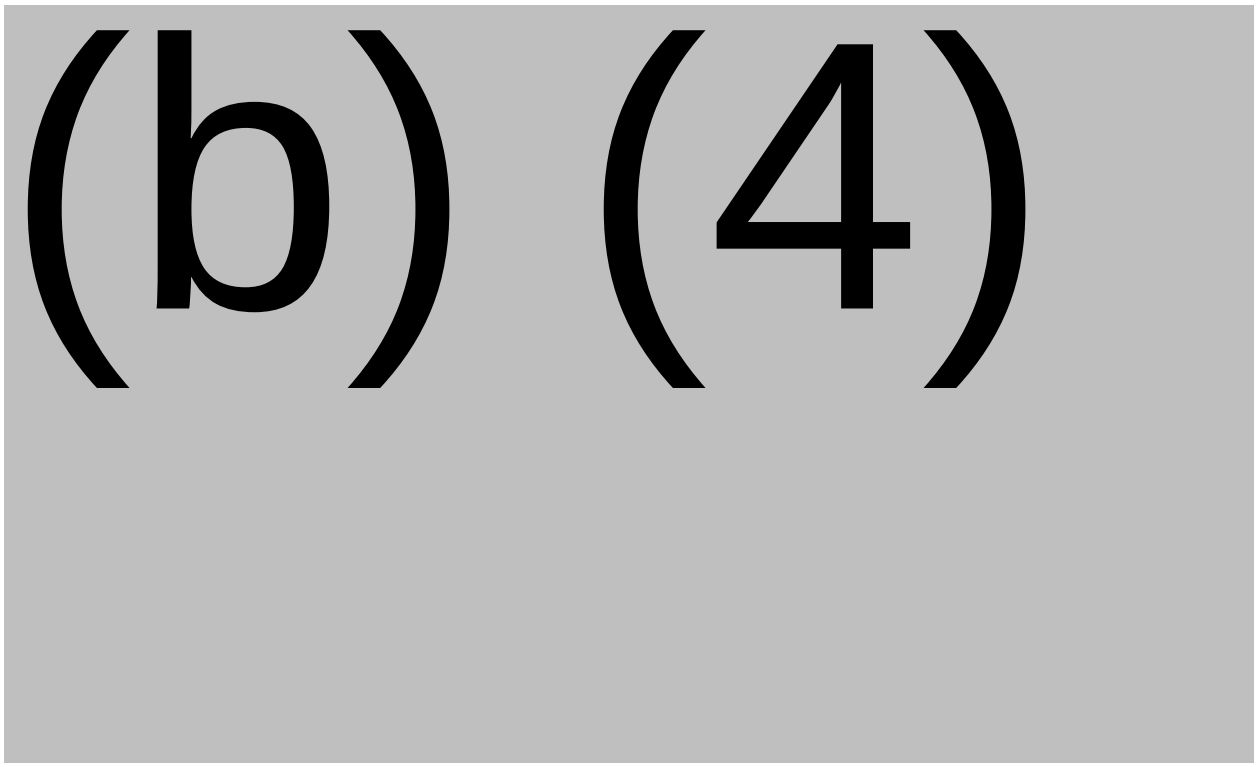


Figure 4. (b) (4) **of a representative traditionally prepared kratom tea sample (blue) and a representative sample of the kratom extract (black).**

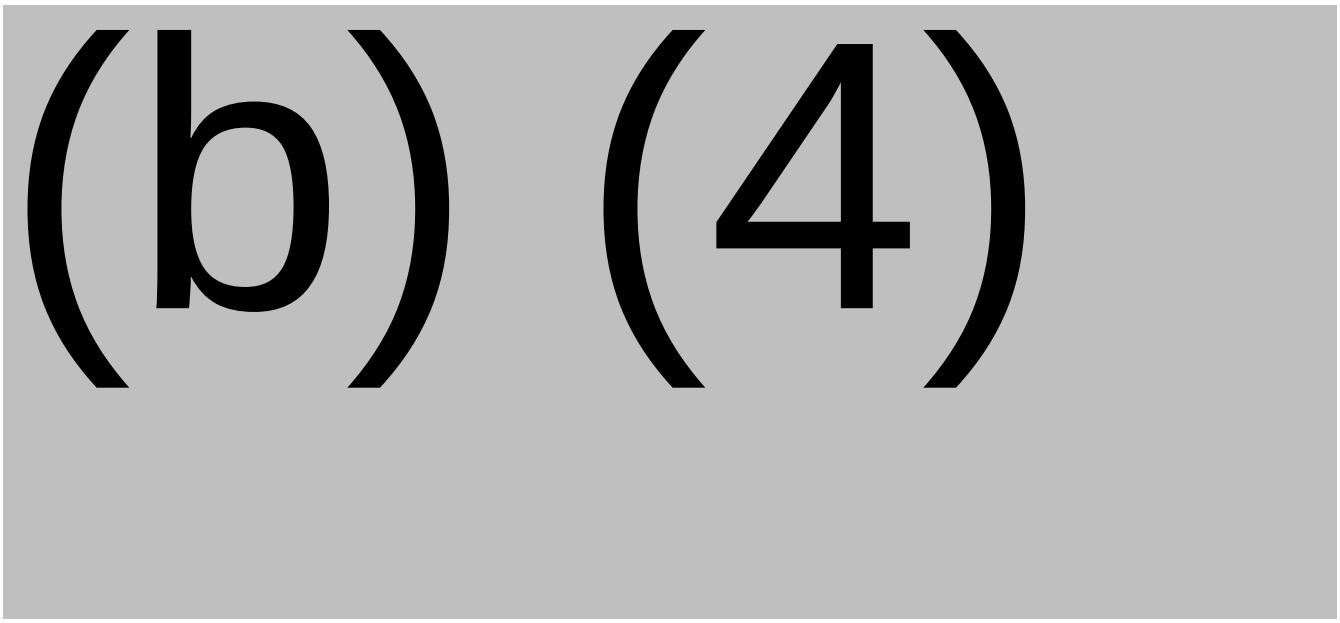
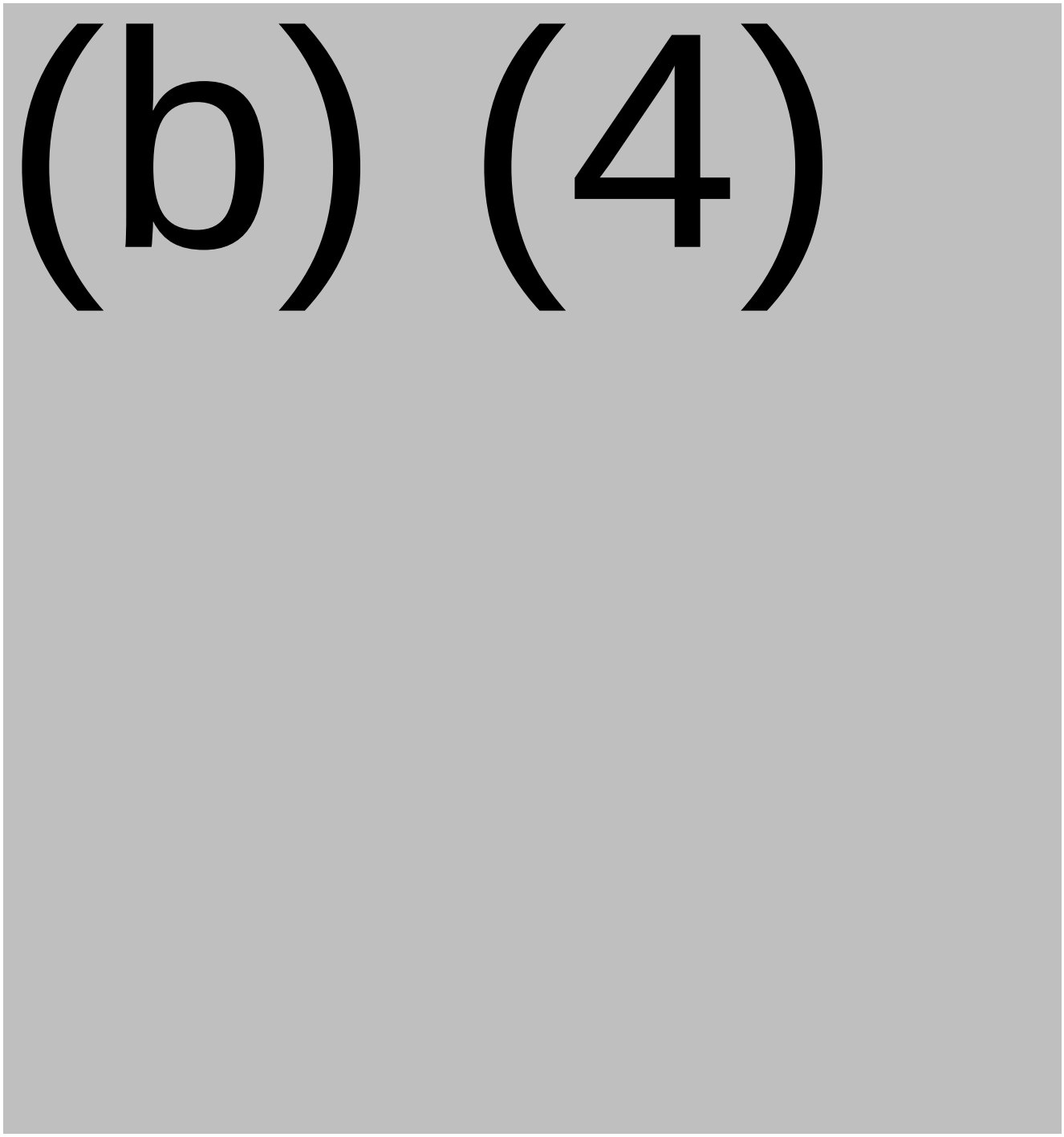


Figure 5. (b) (4) **of a representative traditionally prepared kratom tea sample (blue) and a representative sample of the kratom extract (black) zoomed into the area showing the** (b) (4) **.**



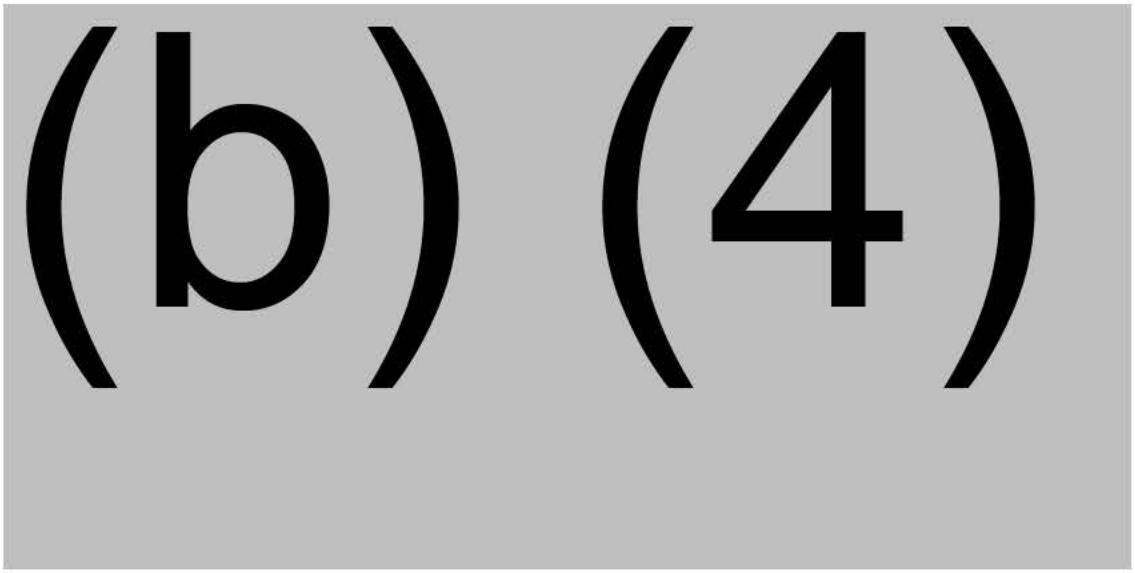


Figure 6. Comparison of the (b) (4) (top) the (b) (4) obtained from the (b) (4) analysis of kratom extract (middle) and the (b) (4) obtained from the (b) (4) analysis of the traditional tea sample (bottom).

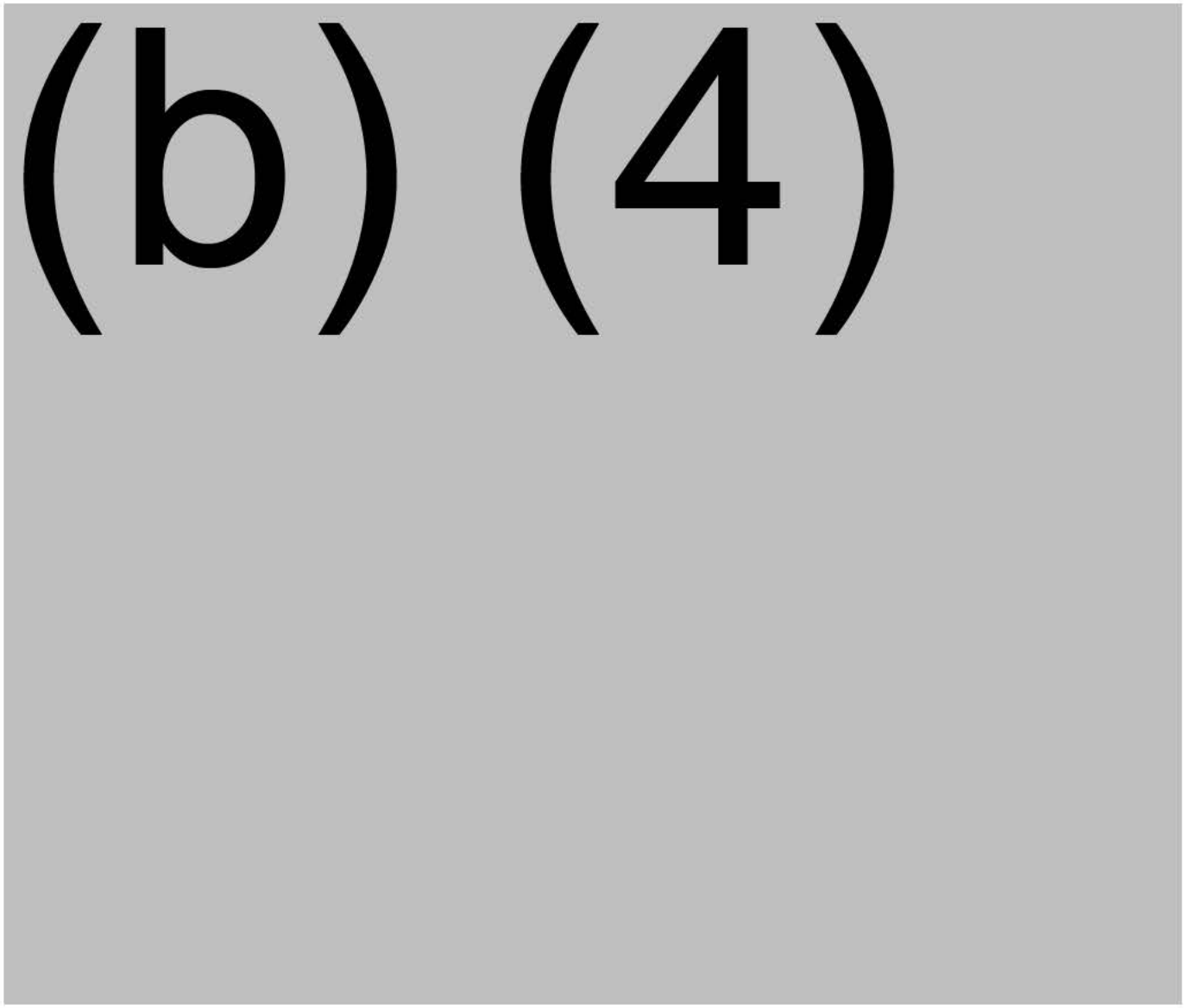


Figure 7. Comparison of the (b) (4) (top) with the spectra for the (b) (4) obtained from the (b) (4) analysis of kratom extract (middle) and the (b) (4) for the (b) (4) obtained from the (b) (4) analysis of traditional kratom tea.

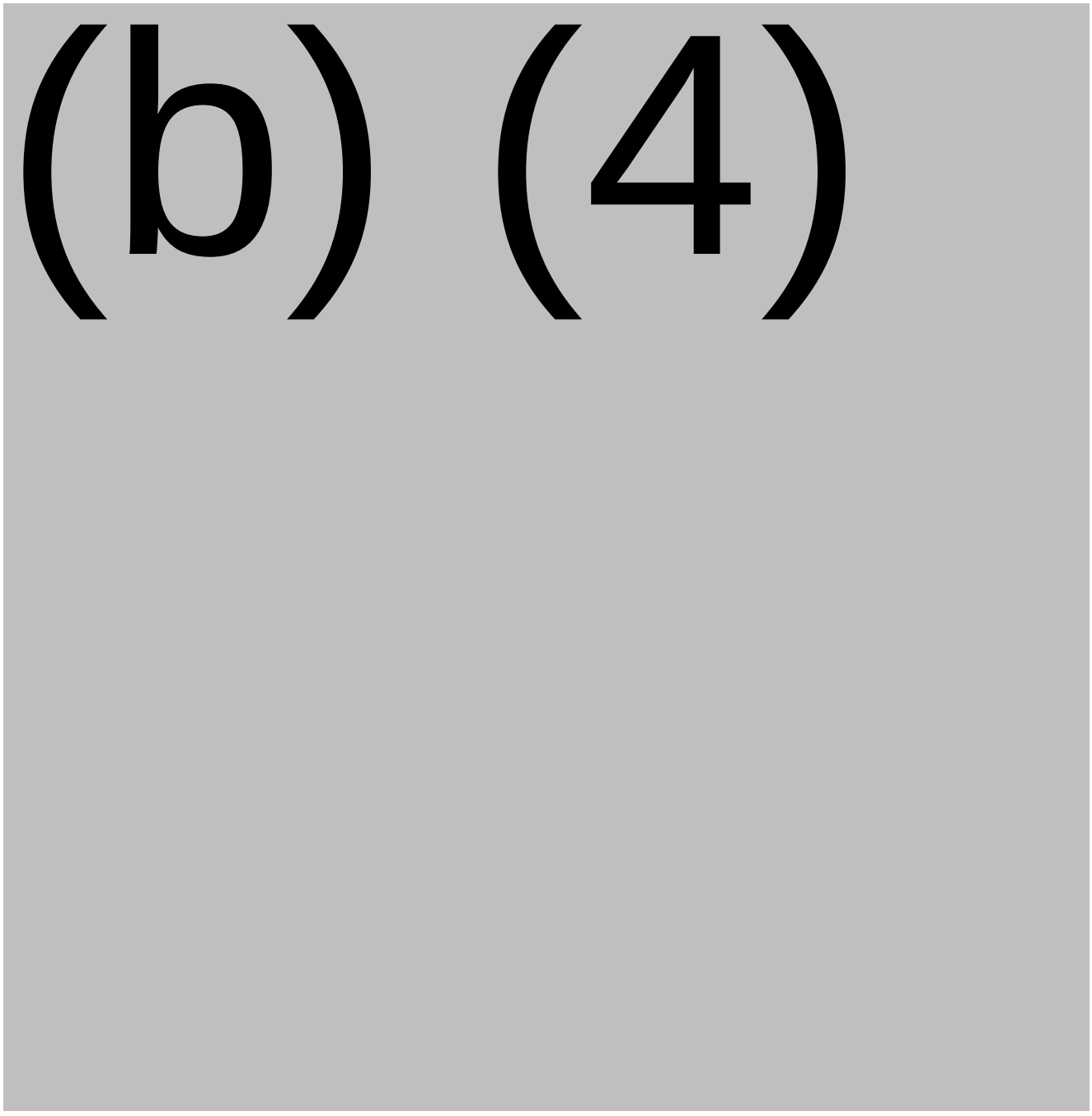


Figure 8. Comparison of the (b) (4) for the (b) (4) obtained from the (b) (4) analysis of the traditional tea sample (top) and kratom extract (bottom).

3.1.2.2 (b) (4) Profiling by (b) (4)

(b) (4)
(see Appendix A). Below are comparisons of the (b) (4)

(b) (4) (Figure 9). (b) (4)

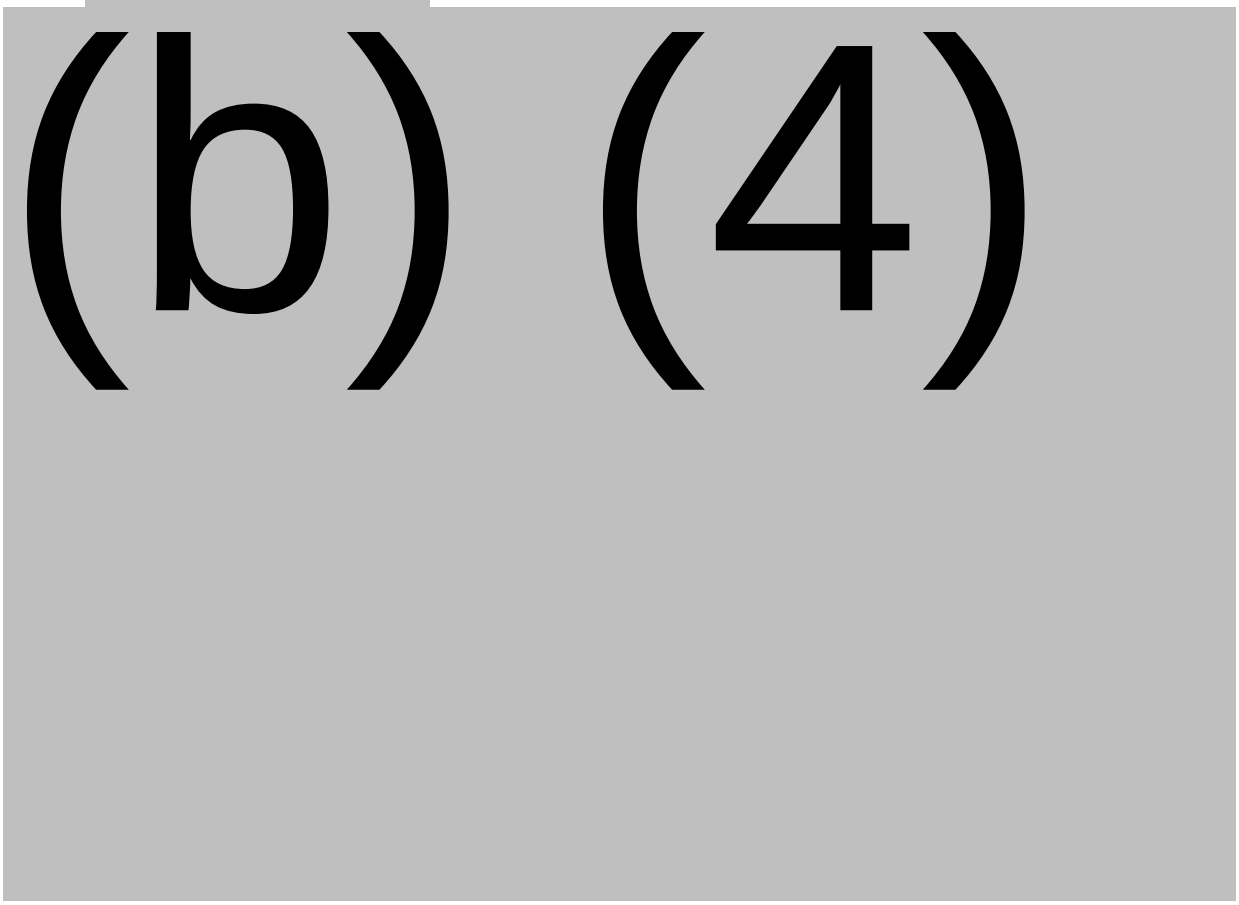
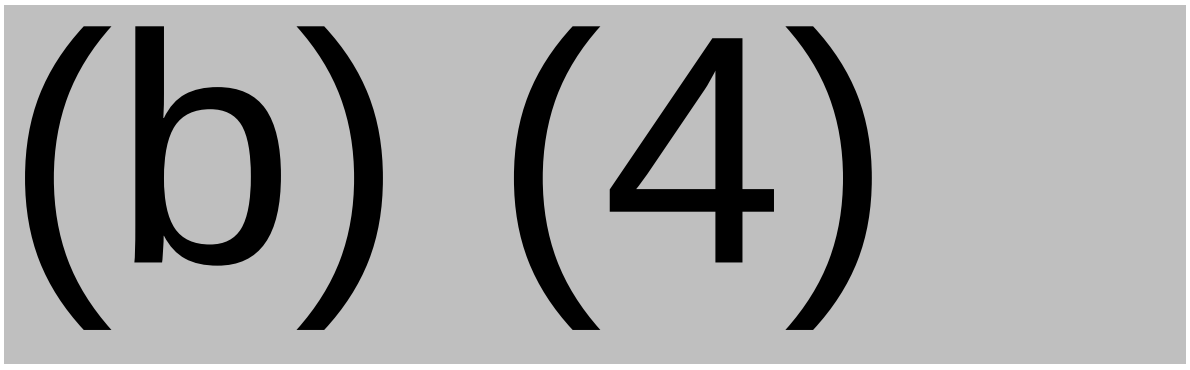


Figure 9. Comparison of (b) (4) obtained from a method for (b) (4) analysis of a representative kratom leaf (top), a representative sample of a traditionally prepared kratom tea (middle) and a representative sample of the kratom extract (bottom).

3.1.2.3 (b) (4) Profiling by (b) (4)



(b) (4)

Table 10. Major (b) (4) **found in M. speciose leaf and kratom extract**

(b) (4)

(b) (4)

3.1.3 History of Use -- Southeast Asia

Kratom has been safely consumed as a dietary supplement and as a folk remedy in Southeast Asia for centuries (Singh et al., 2014; Tanguay, 2011; Veltri & Grundmann, 2019). It is generally orally consumed either by chewing fresh leaves or as a brewed tea. Southeast Asian kratom users typically consume small servings of kratom multiple times per day. Kratom use is especially popular in rural areas, mirroring the plant's geographic availability. Kratom trees are common in the region and leaves could be easily harvested and prepared for consumption by workers or by brewers who then sell the beverages (Saingam et al., 2013; Singh et al., 2016). In Southeast Asia, kratom use is most prevalent in the southern region of Thailand and the northern provinces of Malaysia (Raffa, 2015; Singh et al., 2016).

Historically its use was generally associated with males of older age groups in the rural areas performing manual labor who used kratom to increase their physical endurance and work (Saref et al., 2020; Tanguay, 2011; Veltri & Grundmann, 2019). Over the centuries kratom consumption in these regions has become an integral part of the culture where it is considered a social beverage much as coffee is in other parts of the world:

- "Eating kratom is a tradition that has been practiced for centuries in southern Thailand and up to 70% of the male population in some districts use kratom daily." (Tanguay, 2011)
- "Kratom is chewed in teashops, at certain ceremonies (though this practice is fading) and other informal social events." (Tanguay, 2011)
- "Many of the current users in Thailand and Malaysia who use kratom for improved alertness and its endurance-enhancing effects consider it similar to drinking coffee." (Raffa, 2015)

It has been traditionally used primarily for the following purposes (this list includes conventional food, dietary supplement, and medicinal uses):

Improved alertness and physical endurance:

- "The alkaloids are used in traditional medicine to improve physical stamina" (Stolt et al., 2014)
- "As increase in work efficiency and tolerance to hard work under a scorching sun are also described" (Watanabe et al., 1997)
- "….they reason that it helps them to overcome the burden of their hard work and meager existence" (Suwanlert, 1975)
- "It is a pharmacologically important medicinal herb long used in southern Thailand (where it is known as krathom) and the northern states of peninsular Malaysia to increase physical endurance" (Vicknasingam et al., 2010)
- "Manual laborers use kratom, often or throughout the workday, as effects wear off within a few hours. In small amounts, the leaves of this tree have been utilized by laborers for their stimulant effects and subsequent ability to invigorate workers in harsh conditions." (Adkins et al., 2011)
- "Justifications for the use of kratom by rural workers in Thailand include increased endurance in the hot sun and relief of fatigue from overwork. In this setting, kratom use occurs primarily among adults and the elderly " (Barceloux, 2012)
- "…there are also reports that the leaves are mainly used as a stimulant to enable laborers to endure physical fatigue." (Ahmad & Aziz, 2012)
- "Kratom is chewed while engaging in manual labor and in the comfort of one's own home." (Tanguay, 2011)

- “People use Kratom leaves for their energising and pain relieving effects ...” (Singh et al., 2014).
- “Kratom was used in Thailand and Malaysia by manual laborers to enhance productivity.” (Babu et al., 2008)
- “Its use in Malaysia and Thailand has been primarily for two broad applications: as a stimulant to increase work efficiency, endurance, and tolerance to hot and humid climate conditions for manual laborers and as a medical remedy for a range of symptoms." (Veltri & Grundmann, 2019)

Pain alleviation:

- “The alkaloids are used in traditional medicine to alleviate musculoskeletal pain…” (Stolt et al., 2014)
- “It is a pharmacologically important medicinal herb long used in southern Thailand (where it is known as krathom) and the northern states of peninsular Malaysia …used as a folk remedy for a variety of maladies including fever and pain” (Vicknasingam et al., 2010)
- “People use Kratom leaves for their energizing and pain-relieving effects” (Singh et al., 2014)

Improved blood circulation:

- “Traditionally MS has been used….to improve blood circulation.” (Ahmad & Aziz, 2012)
- “Mitragyna speciosa Korth. Leaves have been used for decades as a traditional medicine to … improve blood circulation by natives of Malaysia, Thailand and other regions of Southeast Asia” (Idayu et al., 2011)

It has also been used traditionally as a folk medicine for treating a variety of other ailments. The leaves have been applied to wounds and used as a vermifuge and local anesthetic, and extracts of the leaves have been used to treat coughs, diarrhea, and musculoskeletal pain (Raffa, 2015).

More recent surveys show that kratom is still used for these reasons (Saingam et al., 2013; Singh et al., 2016). Saingam et al.’s (2013) survey determined kratom had several roles in the Thai local society including serving a means of relaxation and entertainment, having a social function, serving as a source of energy and serving as a herbal medicine (Saingam et al., 2013). More recently, other reasons for kratom use have emerged, such as to reduce dependence and side effects associated with opioid

and methamphetamine use (Singh et al., 2016; Singh et al., 2020; Vicknasingam et al., 2010).

General perception of kratom use in the region is positive with surveys showing that use was perceived to be beneficial to users and accepted by society (Assanangkornchai et al., 2007; Saingam et al., 2013). Assanangkornchai et al. reported their survey results showed that kratom use was perceived to be a personal choice, not disruptive to others and doing more good than harm (Assanangkornchai et al., 2007).

Generally, kratom use in the Southern provinces of Thailand was not viewed as a problem in the region as users had learned how to use kratom safely, the few reported side effects were tolerable and there were no serious medical complications (Assanangkornchai et al., 2007; Saingam et al., 2013). Similarly, in Singh et al.'s (2015) study of regular users in Malaysia, the majority of respondents believed that kratom does not create any social and health risks like other drugs and that users knew how to control its use (Singh et al., 2015). Results from Singh et al.'s (2015) study also demonstrated that social functioning was not impaired among kratom users (Singh et al., 2015).

Estimates of the number of kratom users in Southeast Asia indicate the presence of large number of users. Tanguay (2011) reported that Thai public health surveys in 2007 and 2008 showed that greater than one million adults (1.02 and 1.08 million respectively) self-report as lifetime users, with two patterns of use: 1) chewed leaves or brewed tea for all traditional purposes, and 2) highly concentrated extracts often combined with other substances (e.g. cough syrup with dextromethorphan) intended solely for recreational use (Tanguay, 2011).

Tanguay stated that regardless of use pattern "there is a general consensus among community members and leaders, academics and policymakers, as well as public health and law enforcement representatives in southern Thailand that kratom use and dependence carry little, if any, health risks." (Tanguay, 2011). Using data from a more recent cross-sectional survey Schimmel et al. estimated the number of life-time kratom users to be approximately 9 million (Schimmel et al., 2021; Wonguppa & Kanato, 2017).

3.1.3.1 Serving Sizes and Daily Consumption Rates -- Southeast Asia

There have been several studies that have examined traditional kratom use patterns in Southeast Asia, including serving sizes and daily consumption rates for various uses. In several of these studies, quantitative analysis for mitragynine content have been made on representative single servings obtained in the field. As reported above, these

analyses have shown that a single traditional serving of *M. speciosa* tea or chewed leaf contains, on average, between 21.7 – 108 mg of mitragynine (Leong Abdullah et al., 2021; Singh et al., 2014; Singh et al., 2018; Singh et al., 2019; Singh et al., 2020; Vicknasingam et al., 2010).

Throughout most of Southeast Asia serving sizes remain relatively constant with users simply consuming several servings throughout a given day (Assanangkornchai et al., 2007; Leong Abdullah et al., 2021; Singh et al., 2014; Singh et al., 2018; Singh et al., 2019; Singh et al., 2020; Vicknasingam et al., 2010).

Average "regular users" of kratom will consume between two to four servings per day (Assanangkornchai et al., 2007; Singh et al., 2014; Suwanlert, 1975; Vicknasingam et al., 2010). Using the results from the quantitative analysis of the representative samples the amount of mitragynine consumed by these users would range from (b) (4) mg/day.

Average "heavy users" of kratom will consume anywhere between five to ten servings per day, equating to (b) (4) mg of mitragynine (Assanangkornchai et al., 2007; Singh et al., 2014; Suwanlert, 1975; Vicknasingam et al., 2010). Using the results from the quantitative analysis of the representative samples, the amount of mitragynine consumed by these users would range from (b) (4) mg/day.

In comparison, the dietary ingredient subject to this notification would be used to prepare a (b) (4)

Both the amount of (b) (4)

3.1.4 History of use outside Southeast Asia

Outside Southeast Asia, it is presumed that kratom is still traditionally used in communities with Southeast Asian heritage. For example, in Brazil it has been integrated into the traditional pharmacopeia, after being introduced in the early 1900s by Asian Hindu immigrants (Jorge Riente, Moringa Place, Florida, personal communication).

In North America, kratom usage is still relatively new though growing in popularity, with reports suggesting kratom was first imported into the United States in the 1980s and 1990s (Henningfield et al., 2018; Veltri & Grundmann, 2019). Broader commercial marketing of kratom in the United States increased in the early 2000s and a 2016 survey estimated that approximately 10,000 vendors were selling products in the United States at that time (Henningfield et al., 2018).

The number of kratom users in the United States remains vague with Nicewonder et al. (2019) estimating a range from 3 to 5 million based on survey data and membership information provided by the American Kratom Association (Nicewonder et al., 2019). Schimmel et al. (2020) estimated life-time prevalence of kratom use in the United States to be 1.3% or ~3.3 million adults (Schimmel et al., 2021). Henningfield et al. (2019) gave a much higher estimate of 10 to 16 million users in the United States in 2017, based on recommended dosing and the American Kratom Association kratom tonnage import data for that year (Henningfield et al., 2019).

The reasons for use outside Southeast Asia are generally consistent with the reported traditional uses for kratom in Southeast Asia. Boyer et al. (2007) reports that a cyber-community survey indicates many consumers use undefined kratom products for self-treatment of pain (Boyer et al., 2007) and 91% of the 2798 respondents in Garcia-Romeau et al.'s (2020) survey stated they used kratom to manage pain. Similarly, 68% of the respondents in Grundmann's (2017) survey of 10,000 kratom users reported that they used it for self-treating pain (Grundmann, 2017). In the same survey 66% of the respondents stated they used kratom for emotional or mental support (Grundmann, 2017) whereas Garcia-Romeau et al. (2020) found 67% of users surveyed reported using kratom for stress/anxiety and 65% reported its use for alleviating depression (Garcia-Romeu et al., 2020). Coe et al.'s (2019) online study of consisting of 3024 participants had 48% respondents using kratom to relieve pain, and 22% for anxiety, PTS or depression (Coe et al., 2019).

As with Southeast Asian patterns of use there is subset of kratom users that do so to treat opioid and other drug addiction, though the studies suggest that is true for only a minority of users. Garcia-Romeau et al.'s survey found 40.9% of respondents stating this as a reason for kratom use, whereas in Grundmann's study only 7% of respondents stated they did so because of an illicit drug dependency and 26% of respondents stated they did so for a prescription medicine dependency (Garcia-Romeu et al., 2020; Grundmann, 2017). Similarly only 10% of the respondents in Coe et al.'s (2019) online study stated using kratom to cut down opioid use and/or relieve withdrawal (Coe et al., 2019).

Unlike in Southeast Asia where fresh kratom leaves are easily harvested and prepared, kratom products available in Western markets are obtained through the Internet, herbal stores, tobacco/smoke shops and "head" shops where it is primarily marketed as an herbal supplement used for a variety of conditions (Henningfield et al., 2018; Veltri & Grundmann, 2019). Product on the market may consist of pills or prepared beverages or decoctions containing kratom material (Henningfield et al., 2018; Veltri & Grundmann, 2019).

Most of the commercially available kratom products in North America, however, are in the form of powdered materials that can be dissolved to create a beverage or decoction to be orally consumed (Grundmann, 2017; Henningfield et al., 2018; Veltri & Grundmann, 2019). Preparation details for individual servings, the numbers of servings to be taken and duration of use information provided on the labels of these products can be vague or non-existent resulting in significant variance in the doses and dosages used among kratom consumers.

Grundmann et al.'s survey found an incredibly large range of serving sizes consumed by kratom users in the United States, reporting servings consisting of anywhere from <1 to >8 grams of kratom material and anywhere from 1 to > 48 servings being consumed per week (Grundmann, 2017).

Erowid et al. (2015) summarized data collected by the Erowid Center, a non-profit educational organization that collects information about psychoactive plants and chemicals. Intake estimates for single oral administration and mitragynine content in non-habituated users in North America were provided and summarized in Table 11 (Erowid, 2015).

Table 11. Intake estimates for single oral administration and (b) (4) in non-habituated users in North America.

	(b) (4)	Premium Dried Leaf (g)	Super Premium Dried Leaf (g)	Extract-Enhanced Dried Leaf (g)
Threshold	(b) (4)	2-4	1-2	1-2
Light	(b) (4)	3-5	2-4	1-2
Common	(b) (4)	4-10	3-5	2-3
Strong	(b) (4)	8-15	4-8	3-6

(b) (4)

There has been significant concern with the quality of kratom products on the market. Kratom products available on the marketplace have also been found to be contaminated with pathogenic organisms (Administration, 2018; Dixon et al., 2019; Prevention, 2018; Prozialeck et al., 2020; Yearsley, 2018). There have also been suggestions of products being spiked with endogenous 7-hydroxymitragynine and concerns of high levels of heavy metals in products (Administration, 2019; Lydecker et al., 2016; Prozialeck et al., 2020). One study by Prozialeck et al. (2020) analyzing

kratom products obtained from stores in the suburbs of the Chicago metropolitan area (Prozialeck et al., 2020) found a wide range of mitragynine content among the samples, with significant differences even among samples of the same product (Prozialeck et al., 2020).

Other studies that surveying products on the market and in Kratom raw material have had similar findings (Chear et al., 2021; Flores-Bocanegra et al., 2020; Fowble & Musah, 2019; Griffin et al., 2016; Nacca et al., 2020; Sharma et al., 2019). Prozialeck et al. also reported that all raw leaf products had significant levels of microbial contaminations and heavy metals and although the levels were within acceptable limits set out in guidance for dietary supplements, the wide range observed among the samples, even within samples of the same product, is troubling and suggest that these manufacturers are not following GMP protocols to ensure consistent product quality (Prozialeck et al., 2020).

These reports of quality issues are concerning with respect to the safety of kratom products currently available. Strict adherence to GMPs, implementation of quality control systems and the use of proper labeling are essential to ensuring the production of a safe and consistent product that would be used properly by the consumer. As demonstrated in the sections above, manufacture of the dietary ingredient and dietary supplement subject to this notification will (b) (4)

4. Evidence of Safety

(b) (4)

(b) (4)

4.1 Rising-Dose and Multiple-Dose Tolerance Study of (b) (4) in Rats

The full study report is included in the Appendix K.

4.1.1 Safety Study Type

Rising-dose and multiple dose tolerance study.

4.1.2 Identity Information Verifying the Relationship Between the Test Article (b) (4) and Kratom Extract

(b) (4)

Table 12. (b) (4)

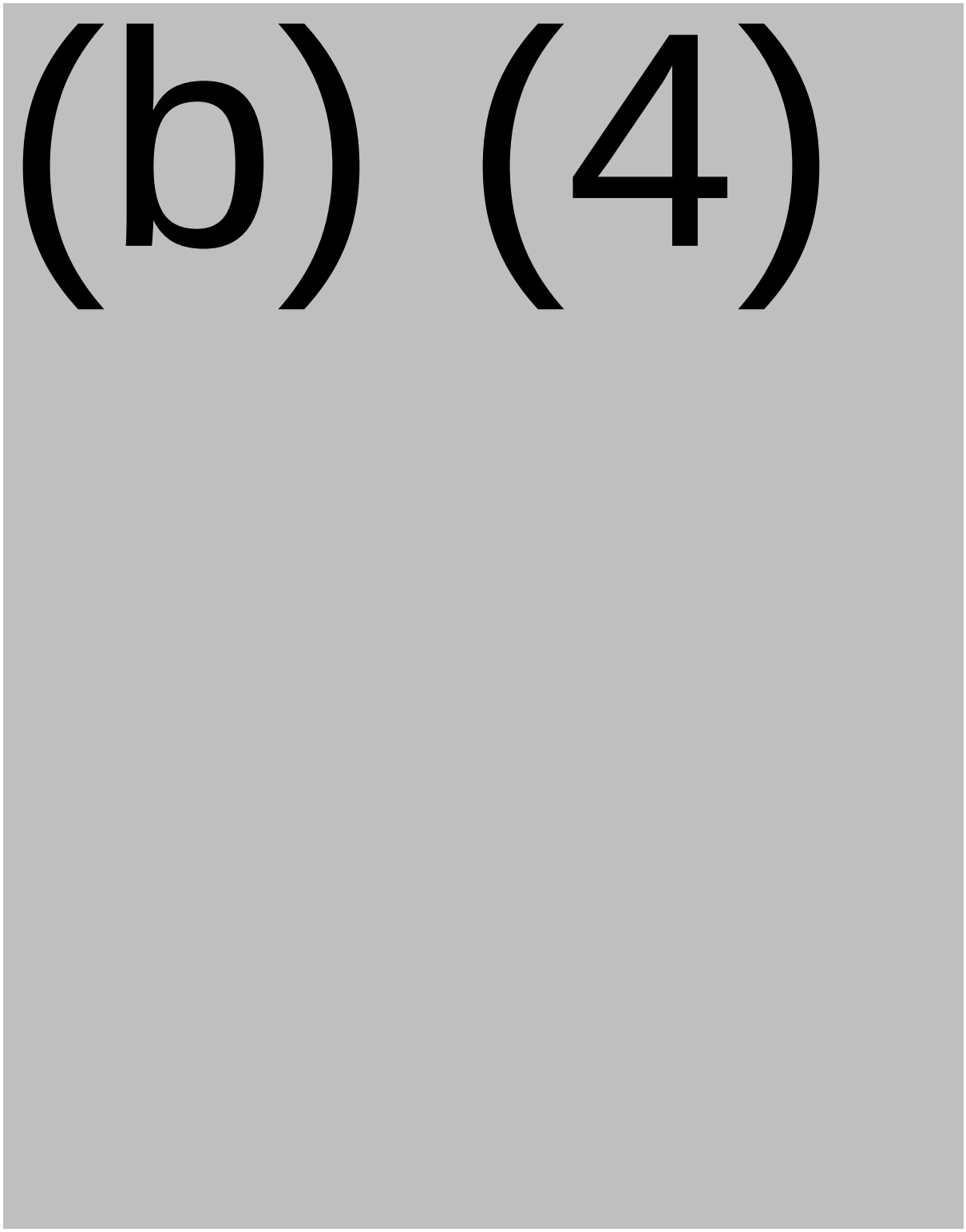


Figure 10. (b) (4)

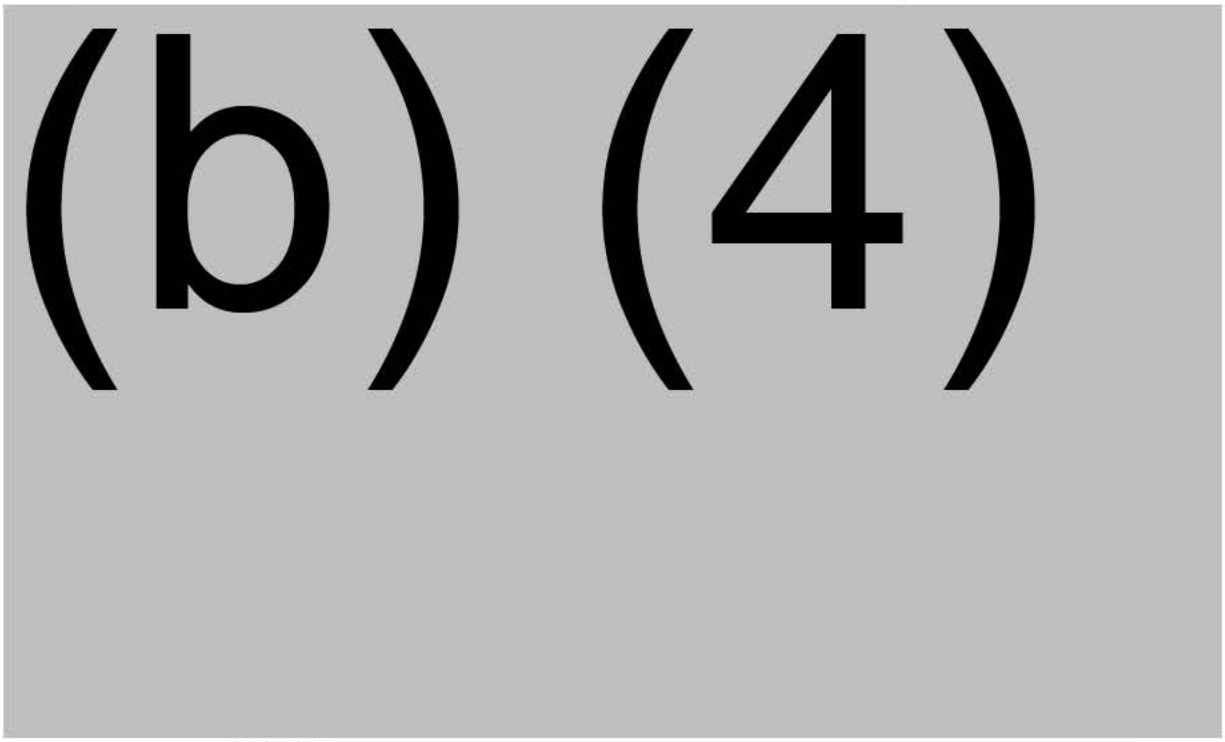


Figure 11. (b) (4)

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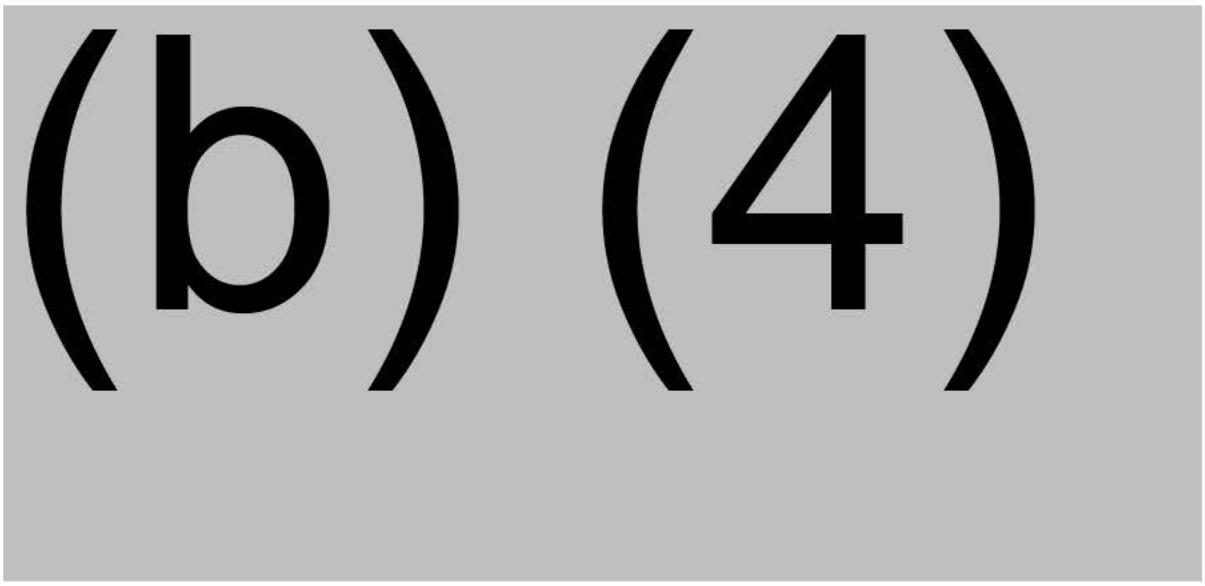


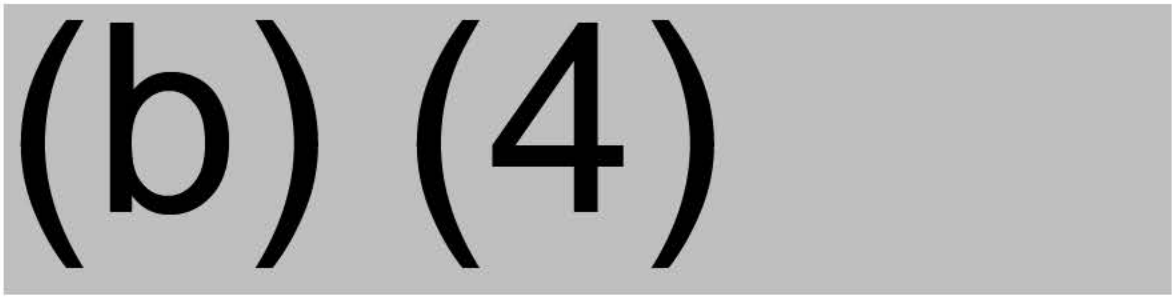
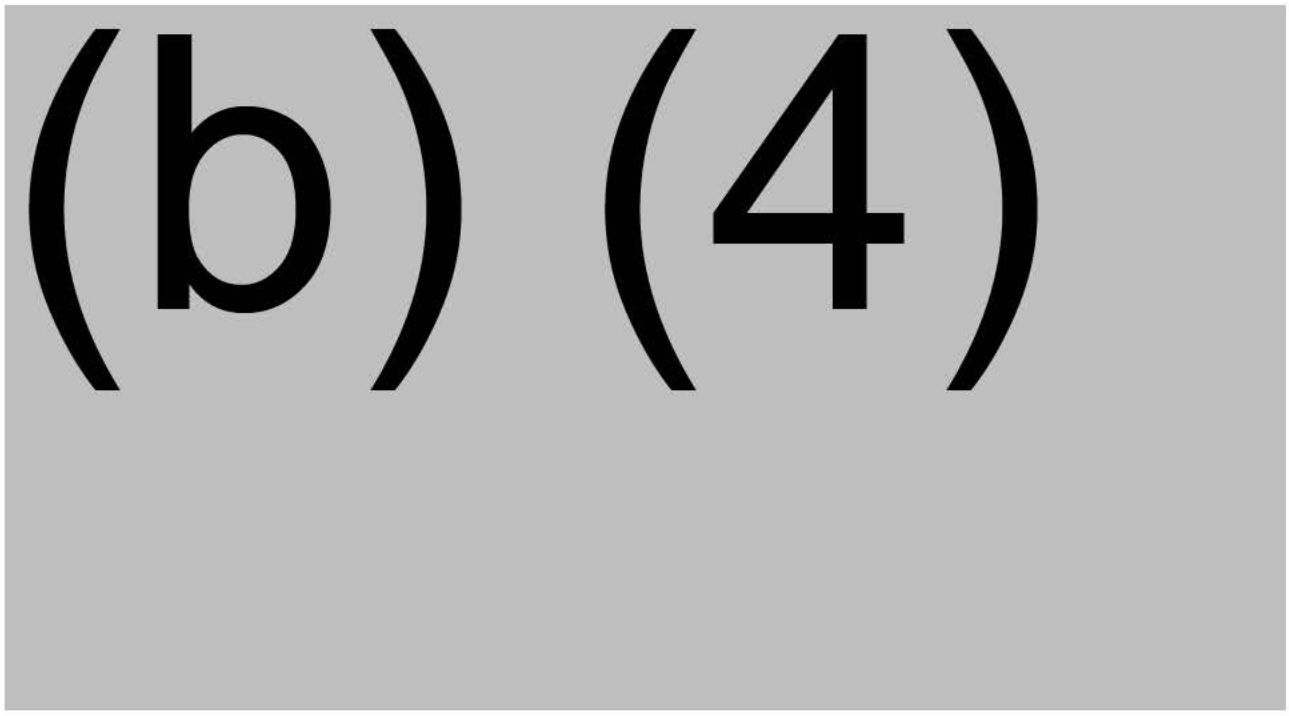
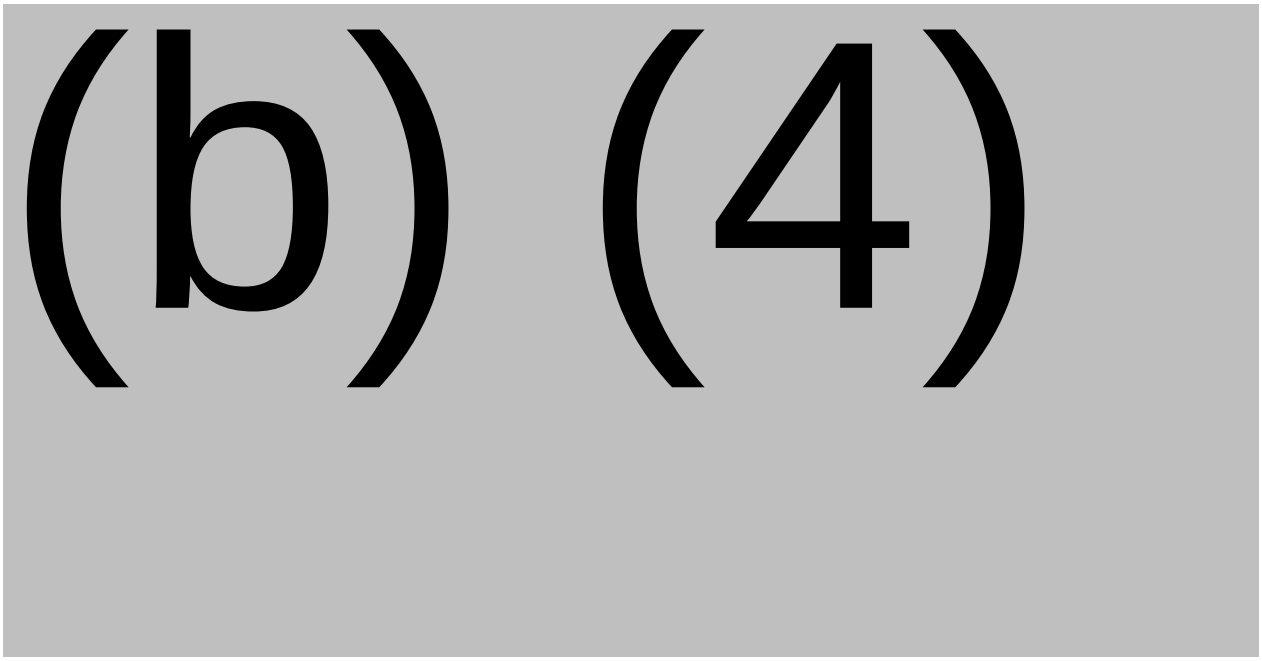


Figure 12. (b) (4)

Table 13. (b) (4)



4.1.3 Discussion of Toxicity and Conclusion



4.2 90-Day Rat Toxicity Study of (b) (4)

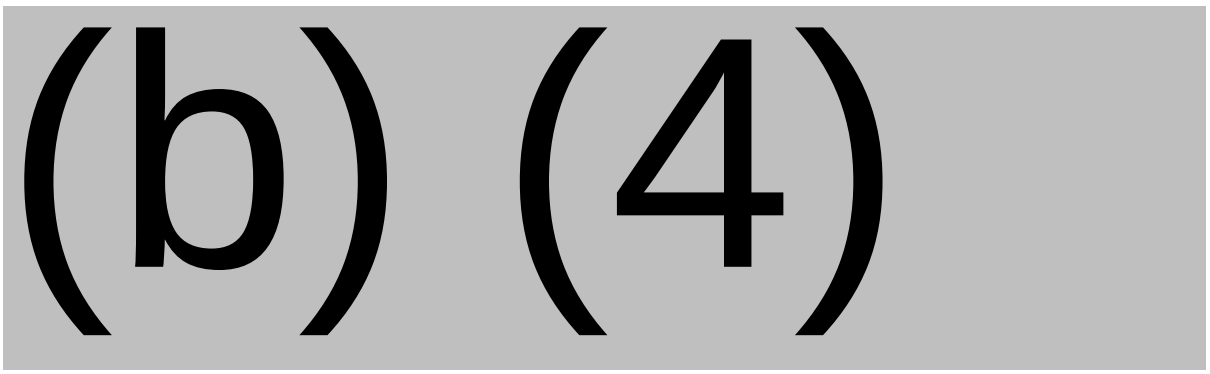
4.2.1 Safety Study Type

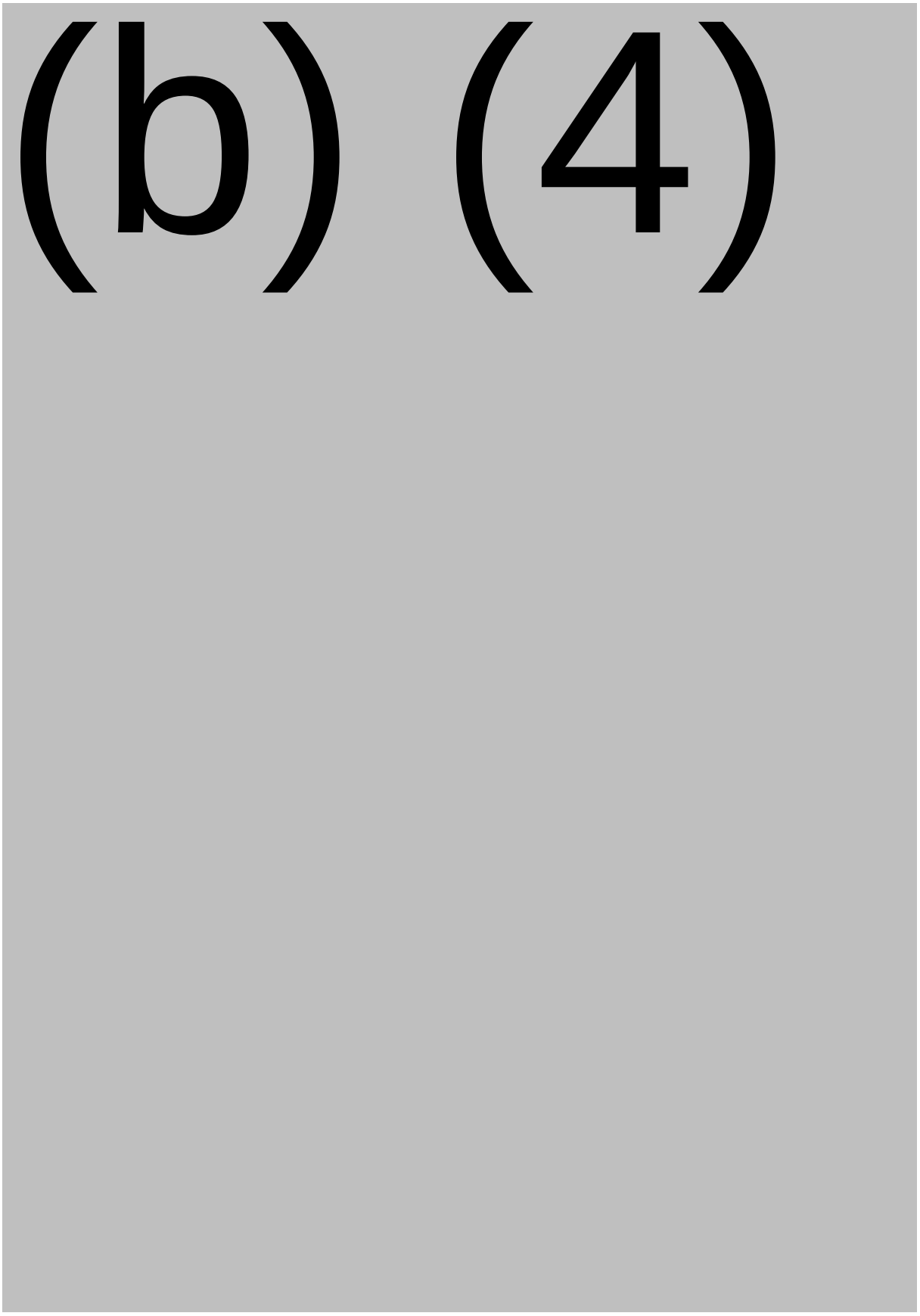
90-Day Rat Toxicity Study

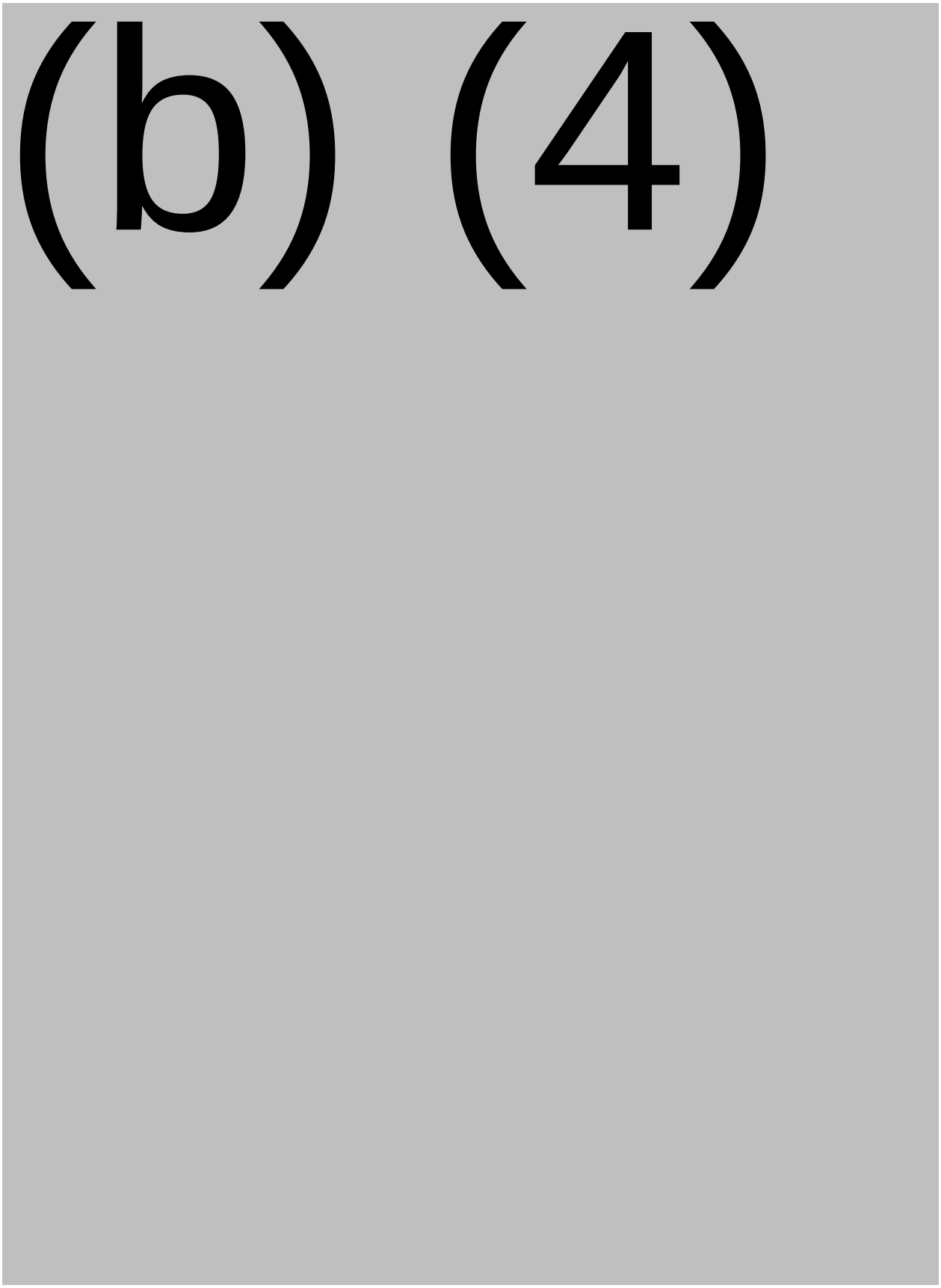
4.2.2 Identity Information Verifying the Relationship between the Test Article and Kratom Extract

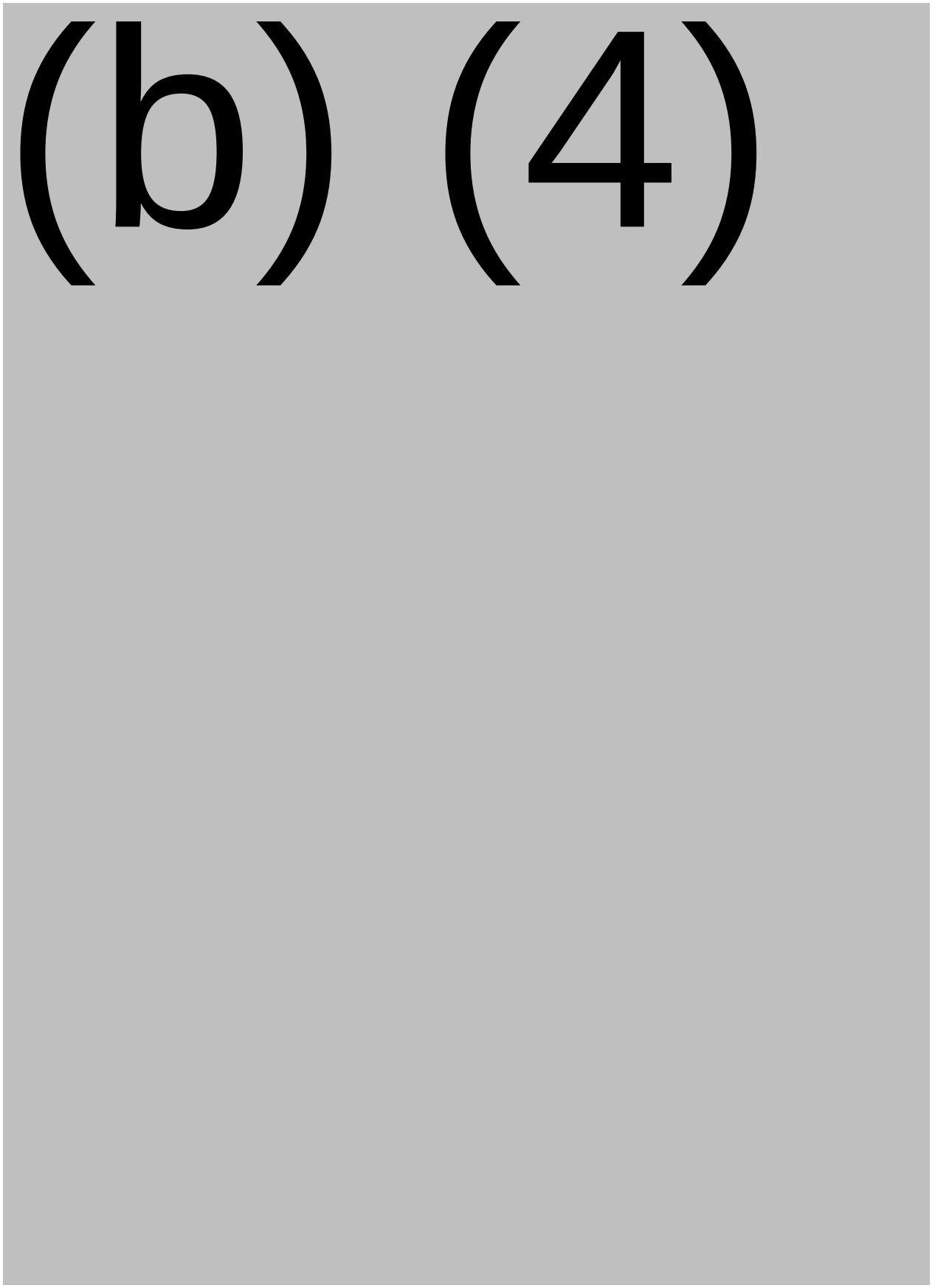
The material used in the study was prepared as per the manufacturing process for an (b) (4) (See Appendix K). The information and data in 4.1.2 confirm the test article (b) (4)

4.2.3 Discussion of Study and Conclusion









(b) (4)

4.3 Peer Review of the 90-Day Feeding Study in Sprague-Dawley Rats Fed Kratom Leaf Extract and Determination of the NOAEL value of the study

(b) (4)

4.4 Other Clinical and Non-Clinical Studies

4.4.1 Human Clinical and Cross-Sectional Studies

Vicknasingam et al. (2020) conducted a small, randomized placebo-controlled double-blind study to assess kratom consumption with pain tolerance (Vicknasingam

et al., 2020). The trial ultimately enrolled 26 kratom users with long histories of daily kratom consumption (Vicknasingam et al., 2020). The paper does not clearly state the dose of kratom administered in the study; the only reference to dosing is that a kratom drink contained mitragynine levels approximating those found in field decoctions (Vicknasingam et al., 2020). Participants consumed three decoction drinks throughout the single study day at 7 am, 10 am and 1 pm. For the study either participants were randomized into groups where only one of the three drinks contained kratom or all three drinks were placebo decoctions (Vicknasingam et al., 2020). The assignment of kratom and placebo drinks consumption sequences was random for all participants and participants and study personnel were blinded about the drinks randomization sequence (Vicknasingam et al., 2020). Pain tolerance was assessed using the cold pressor task, performed on each participant immediately before ingesting each drink and at 1-hour intervals thereafter (Vicknasingam et al., 2020). Withdrawal symptoms were assessed using the Clinical Opioid Withdrawal Scale, administered before each drink and at 120 minute intervals thereafter (Vicknasingam et al., 2020).

No adverse effects were observed in the study and all participants completed all study tasks and procedures without reporting any discomfort or unusual symptoms(Vicknasingam et al., 2020). Participants did not report withdrawal symptoms either using spontaneous self-report or based on assessment of the Clinical Opioid Withdrawal Scale (Vicknasingam et al., 2020). It was noted by the authors that all participants in this study reported long duration and high levels of daily kratom consumption prior to the study. As such, during the study, participants would have experienced kratom discontinuation lasted from between 10 to 20 hours, depending on the randomization arm they were assigned to. Despite this extended discontinuation, none of the participants reported or displayed discomfort, symptoms or signs of potential withdrawal during the study (Vicknasingam et al., 2020). In additional to the safety data, results from this study provided objectively measured evidence supporting the previously reported pain-relieving properties of kratom. Study results demonstrated that the consumption of the kratom decoction demonstrated a substantial and statistically significant increase in pain tolerance as assessed using the cold press task (Vicknasingam et al., 2020).

Trakulsrichai et al.'s (2015) described a small study involving 10 men with a history of consistent heavy kratom use of 6 months-5 years (Trakulsrichai et al., 2015). Participants were divided into five unequal groups and given daily conditioning doses of kratom tea containing 6.25–11.5 mg of mitragynine for 7 days. On day 8, participants were given a single oral dose of kratom tea standardized for mitragynine content (6.25–23 mg). Though predominantly a pharmacokinetics study, the authors did report that there were no adverse events among the subjects. All subjects did

experience increasing blood pressure and heart rate, however onset of this was delayed to 8 hours after drinking kratom, well beyond the Tmax observed in the study, and not attributed to the kratom consumption. The authors stated that further investigation was required (Trakulsrichai et al., 2015).

Published controlled human clinical studies published for kratom products are lacking from the literature. However, there have been several surveys and cross-sectional studies performed which includes adverse effects reported by the participants. This includes a small study published by Grewal in 1932 describing the effects of kratom consumption (Grewal, 1932b). In this study 0.05 g of mitragynine acetate dissolved in 20 mL of distilled water were taken a number of times by five different individuals and three times 0.05 mg followed in 2 hours by another dose of 0.05 g by 2 subjects. The same subjects also took from 0.65 g to 2.6 g of dried powdered kratom leaf materials on a separate day (Grewal, 1932b). Overall symptoms in the subjects after ingestion were relatively mild, with reported feelings of giddiness, lightness of the body, tenseness of muscles and abdominal irritation (Grewal, 1932b). Although there were significant limitations with this study given its size and lack of controls, it does show subjects without any history of kratom ingestion taking substantial doses of the mitragynine and leaf material did not experience any serious adverse effects (Grewal, 1932b).

Generally, the results from the more recent surveys and cross-sectional studies describe findings in a similar vein. A summary of these studies is presented in Appendix R and a more detailed discussion on kratom associated adverse effects is provided in section 4.5 below.

4.4.2 Animal Toxicity Studies

Summaries of published non-clinical kratom toxicity studies are provided in Appendix O and include acute and sub-chronic studies up to 6 weeks in rats and 3 weeks in dogs. Most included purified mitragynine only; a few examined whole plant Kratom extracts (aqueous and methanol). Overall, these data reinforce the safety of kratom extract when consumed according to label directions for use.

The most recent of these studies was Maxwell et al.'s (2020) study on administration of mitragynine in female beagle dogs. Doses administered included a single 5 mg/kg oral dose and a 0.1 mg/kg intravenous dose of mitragynine (Maxwell et al., 2020). The oral dose used in the study is equivalent to the human equivalent dose of 2.8 mg/kg (Maxwell et al., 2020). Thus the oral dose used in this study is(b) (4) that of the kratom NDI's recommended dose for a 60 kg human. No major adverse events were noted with either dose regimes in the study, although all subjects experienced

mild transient sedation immediately after dosing which lasted 2 to 4 hours after the oral dose and up to 1 hour following the intravenous dose. Stress-related frenetic signs were reduced following dosing (Maxwell et al., 2020). No clinically significant changes in vital signs, physical examination or clinical laboratory tests were observed (Maxwell et al., 2020). Blood counts and biochemical parameters were within reference ranges and similar to baseline values (Maxwell et al., 2020). It was concluded that mitragynine administration at these doses was well tolerated (Maxwell et al., 2020).

The rat study of Sabetghadam et al. (2013) was done to an appropriate international standard (OECD), and provides a useful dataset for consideration of the safety for daily intake of kratom extract (Sabetghadam et al., 2013). Sabetghadam et al. (2013) reported a number of differences between the control and dosed groups (i.e., reduced blood neutrophil counts as the most sensitive adverse endpoint, observed after 28 days of ingesting 10 mg/kg pure mitragynine), but concluded that "the study demonstrated that mitragynine is relatively safe at lower sub-chronic doses (1–10 mg/kg) but exhibited toxicity at a highest dose (sub-chronic 28 days: 100 mg/kg). This was confirmed by liver, kidney, and brain histopathological changes, as well as hematological and biochemical changes."(Sabetghadam et al., 2013).

The amount of mitragynine consumed as per the recommended daily intake for a dietary supplement formulated from the (b) (4)

Several uncertainties must be considered when comparing the animal toxicity data with human kratom extract use. First, kratom extract contains (b) (4) For that reason, studies conducted with isolated/purified mitragynine may have only limited applicability to kratom extracts. Second, the relative sensitivity of humans to mitragynine, compared to rats/dogs, is unknown. Finally, study quality issues with the Sabgetghadam et al. (2013) study include hematology and clinical chemistry values in control animals that were higher than typical reference values for that specific rat strain. These uncertainties in the data make it impossible to reliably determine a NOAEL and LOAEL for orally ingested mitragynine in laboratory rodents or humans. These studies do provide a basis through which such calculations can be made and general comparisons made. In the case of the Maxwell study, since it was predominantly a pharmacokinetics study, only 1 dosing level for each route of administration was performed and data to determine affect levels was not available (Maxwell et al., 2020). Still, both studies used doses that were well above the amount of mitragynine (b) (4)

(b) (4) . The results from these studies as well as the other animal studies with toxicity data summarized in Appendix O, provides significant evidence (b) (4)

4.4.3 Pharmacology and Physiology

Manda et al. (2014) evaluated the absorption, distribution, metabolism, and excretion (ADME) properties of mitragynine, 7-hydroxymitragynine and mitraphylline and their effect on major efflux transporter P-glycoprotein using in vitro methods (Manda et al., 2014). (Mitraphylline is a minor alkaloid that is structurally similar to mitragynine.) Major findings were:

> Mitragynine was unstable in simulated gastric fluid with 26% degradation but stable in simulated intestinal fluid and metabolically stable in both human liver microsomes and S9 fractions. 7-Hydroxymitragynine degraded up to 27% in simulated gastric fluid, which could account for its conversion to mitragynine (23%), while only 6% degradation was seen in simulated intestinal fluid. Mitraphylline was stable in simulated gastric fluid but unstable in simulated intestinal fluid (13.6% degradation).
>
> Both mitragynine and 7-hydroxymitragynine showed moderate permeability across Caco-2 and MDR-MDCK monolayers with no significant efflux, indicating moderate intestinal absorption and BBB (blood-brain barrier) penetration, respectively. Mitraphylline was subjected to efflux mediated by P-glycoprotein in both Caco-2 and MDR-MDCK monolayers.
>
> Both mitragynine and 7-hydroxymitragynine inhibited P-glycoprotein with EC50 values of 18.2 ± 3.6 μM and 32.4 ± 1.9 μM, respectively, indicating the possibility of a drug interaction if mitragynine and 7-hydroxymitragynine are co-administered with drugs that are P-glycoprotein substrates.
>
> Both 7-hydroxymitragynine and mitraphylline were metabolized by human liver microsomes with half-lives of 24 and 50 min, respectively. All three compounds exhibited high plasma protein binding (> 90%) determined by equilibrium dialysis.

Trakulsrichai et al.'s 2015 small study involving 10 men with a history of kratom use is the sole published paper focused on the pharmacokinetics study of kratom in humans (Trakulsrichai et al., 2015). Participants were divided into five unequal groups and given daily conditioning doses of kratom tea containing 6.25–11.5 mg of mitragynine for 7 days. On day 8, participants were given a single oral dose of kratom

tea standardized for mitragynine content (6.25–23 mg). During the following 24-hour period, Trakulsrichai et al. (2015) collected and analyzed blood and urine samples at 17 times points (Trakulsrichai et al., 2015). The pharmacokinetics demonstrated linearity and were consistent with an oral two-compartment model (Trakulsrichai et al., 2015). Key pharmacokinetic parameters were a Cmax of 0.105 μg/mL observed at a tmax=0.83±0.35 h and t1/2=23.24±16.07 h. Peak plasma mitragynine concentration appeared to be around 0.4 μg/mL the authors estimated the volume of distribution to be 1.15 L/Kg and the clearance to be 2.97 L/h/kg (Trakulsrichai et al., 2015). Plasma concentrations for most subjects appeared to return to baseline within 5 hours (Trakulsrichai et al., 2015). The authors concluded that mitragynine has a large volume of distribution, and it is mainly distributed out of the circulation following hepatic metabolism. No adverse events were noted, but all subjects had increasing blood pressure and heart rate with onset delayed to 8 hours after drinking kratom (Trakulsrichai et al., 2015).

Trakulrichai noted that their pharmacokinetic results were different than results previously obtained from animal studies and concluded that applying animal data to humans should be used with caution (Trakulsrichai et al., 2015). Traskulsrichai et al. (2015) also noted that a significant limitation of their study was that it was performed on chronic users and thus may not apply for healthy subjects (Trakulsrichai et al., 2015). Ya et al.'s summary of several rat oral pharmacokinetic studies showed that these studies had much higher Cmax (1.06 to 1.76 μg/mL) and longer Tmax (1.26 to 1.83 hours) values compared to Trakulsrichai et al.'s findings, however they noted that the rat studies also demonstrated high variability between studies (de Moraes et al., 2009; Janchawee et al., 2007; Parthasarathy et al., 2010; Ya et al., 2019).

Ya et al. also noted that these higher values could be reflective of the much higher oral doses given to in the rat studies as the 20-50 mg/kg administered in these studies which would equate to 220-550 mg in humans (Ya et al., 2019). Additionally, Ya et al. (2019) also suggested that the simple dissolution in the aqueous media fed to humans without dispensing agents may have allowed for faster absorption in the human studies versus the animal studies (Ya et al., 2019). Ya et al. (2019) concluded that outside of these discrepancies data from pharmacokinetic studies from rats were similar to those in human studies (Ya et al., 2019).

Results from Maxwell et al.'s (2020) pharmacokinetic study in beagle dogs showed generally similar absorption profiles as all Cmax occurred within 2 hours post-dose in all three species (Maxwell et al., 2020). Results from Maxwell et al. (2020)'s study also showed high mitragynine had a large volume of distribution and high clearance in dogs similar to what was observed in the other species in other studies (Maxwell et al., 2020). Maxwell et al. (2020) noted in their study that there was apparent

conversion of mitragynine to 7-hydroxymitragynine in oral study samples, which they attributed to CYP3A-mediated conversion (Maxwell et al., 2020). The metabolite %AUC ratio of 7-hydroxymitragynine to mitragynine was approximately 12.6% (Maxwell et al., 2020).

Evidence of mitragynine metabolism into 7-hydroxymitragynine has also been reported in in vitro metabolism studies (Basiliere & Kerrigan, 2020; Kamble et al., 2019). Given its known activity, the formation of 7-hydroxymitragynine may have pharmacodynamics implications, however these preliminary in vitro studies do not indicate if the metabolic conversion in vitro would produce pharmacodynamically relevant amounts (Basiliere & Kerrigan, 2020; Kamble et al., 2019). General observations from these and other studies would suggest that the amount of 7-hydroxymitragynine produced is very low and further metabolism occurs rather rapidly.

The metabolism studies demonstrated that mitragynine undergoes extensive metabolism into multiple metabolites (Basiliere & Kerrigan, 2020; Kamble et al., 2019). Overall metabolism of mitragynine appears to be predominantly mediated by CYP3A4 enzyme with minor contributions by CYP2D6, CYP2C9 and CYP2C19 (Basiliere & Kerrigan, 2020; Kamble et al., 2019). CYP2C9 and CYP2C18 appear to have minor contributions as well (Basiliere & Kerrigan, 2020; Kamble et al., 2019). Given these metabolic pathways it is clear that inhibition of these enzymes would occur following kratom consumption. Several in vitro studies have shown that mitragynine and other kratom alkaloids inhibit these particular enzyme isoforms (Kamble et al., 2020; Tanna et al., 2021; Todd et al., 2020). Mitragynine has also been shown to be a potent reversible inhibitor of CYP3A (Tanna et al., 2021; Todd et al., 2020). These findings indicate potential herb drug interaction risks with drugs that are substrates for these enzyme isoforms such as the opioids and benzodiazepines (Kamble et al., 2020; Tanna et al., 2021; Todd et al., 2020).

Hassan et al. (2013) provided a review of the reported physiological effects of M. speciosa known at the time (Hassan et al., 2013). The review and references cited therein, described anti-nociceptive, anti-inflammatory and gastrointestinal effects (Hassan et al., 2013). Extracts of various Mitragyna species, including M. speciosa show significant anti-inflammatory effects (Shaik Mossadeq et al., 2009). Research suggests that anti-inflammatory effects could be due to the inhibition of the inflammatory compound prostaglandin as a result of the inhibition of cyclooxygenase (Dongmo et al., 2003).

Animal studies using kratom and its major alkaloids have confirmed analgesic and antinociceptive effects (Hiranita et al., 2019; Raffa, 2015; Shaik Mossadeq et al.,

2009). These properties have contributed to kratom's comparison to the opioids and has raised concerns on its potential for abuse. Significant research has been performed investigating this subject and a detailed discussion on kratom's abuse potential is provided in Appendix Q. In general, research available supports the conclusion that the kratom extract possesses a low potential for abuse.

Henningfield et al., assessed the safety and abuse potential of kratom products in a comprehensive review of publicly available data on the eight factors indicative of the need for control of a substance under the CSA (Henningfield et al., 2018). The analysis ultimately concluded that kratom has a low potential for abuse and a low dependence liability and there is insufficient evidence of personal harm, adverse health effects or detriment to the public health to warrant control under the CSA. This conclusion is consistent with the 2018 Department of Health & Human Services letter to DEA, where the Assistant Secretary for Health stated that "the available evidence does not support mitragynine and 7-hydroxymitragynine being controlled" under the CSA and there is a "significant risk of immediate adverse public health consequences for potentially millions of users if kratom or its components are included in Schedule I." (Department of Health & Human Services, 2018). A detailed summary of the PinneyAssociates report findings and conclusions and the report itself are provided in Appendix P.

Additional studies published since the publication of original report and the sending of the HHS letter further support the conclusions made in those documents. When Takayama et al. confirmed the structures of the major kratom alkaloids including mitragynine, they noted that these alkaloids shared no relevant structural similarities with opiates or opioids (Takayama, 2004; Takayama et al., 2002). Mitragynine and 7-hydroxymitragynine have been shown to be known agonists of mu-, kappa-, and delta opioid receptors (MOR, KOR, and DOR respectively) (Raffa, 2015). It should be noted that although mitragynine and certain mitragynine analogs have high affinity for MOR, it appears that they interact with these receptors in a way that is distinct from opioids, as discussed by Henningfield and other reviews and in vitro studies (Bath et al., 2020; Henningfield et al., 2018; Raffa et al., 2018; Vandeputte et al., 2020; Váradi et al., 2016; Warner et al., 2016).

Narcotic like opioids powerfully activate mu opioid receptors that substantially account for both the intense euphoriant and respiratory depressing effects of narcotic like opioids that have been demonstrated in humans and animal models. In striking contrast, mitragynine produces weaker binding and effects at the mu opioid receptor than prototypic narcotic like opioids, increasingly supporting characterization of mitragynine as a "partial mu" agonist. Pharmacological and other studies on the kratom alkaloids indicate they exert significantly different mechanistic actions than

typical opioids to such an extent that they have been classified as atypical opioids (Bath et al., 2020; Hiranita et al., 2019; Raffa et al., 2018). Specifically, several documented effects of mitragynine have been demonstrated in studies to support its characterization as a partial mu-opioid agonist (Kruegel et al., 2016; Matsumoto et al., 1996; Prozialeck et al., 2020).

Mitragynine has also been shown to be an agonist of alpha-2-adrenergic, dopaminergic, and serotonergic receptors and studies have suggested that these non-opioid mechanisms have a significant role in mediating the alkaloids pharmacological effects further differentiating it from the opioids (Boyer et al., 2008; Hazim et al., 2014; Idayu et al., 2011; Matsumoto et al., 1996). Most recently, Wilson et al. (2020) reported that kratom induces its antinociception through mu opioid receptor agonism and that, unlike typical opioids, this occurs without respiratory depression sedation (Wilson et al., 2020). Váradi et al. (2016) reported that mitragynine actually showed poor affinity at all opioid receptors, whereas 7-hydroxymitragynine showed moderate affinity at the mu opioid receptor and more potency at the delta opioid receptor (Váradi et al., 2016). Váradi et al. (2016) also demonstrated that while mitragynine was a partial agonist at the mu receptor, it was a weak antagonist at the delta and kappa receptors (Váradi et al., 2016).

Furthermore, the kratom alkaloids have been shown to be biased toward G protein signaling and do not recruit β-arrestin to a measurable degree (Kruegel et al., 2016; Váradi et al., 2016). Data suggests that G protein-biased mu opioid receptor agonists may induce less respiratory depression and inhibition of gastrointestinal transit compared to classical opioids (Kruegel & Grundmann, 2018; Siuda et al., 2017).

Results from several animal studies indicate that analgesic effects of mu receptor agonists are G protein mediated and the adverse effects such as constipation, respiratory depression, and tolerance, are mediated by arrestin-3 (Conibear & Kelly, 2019). Given the main Kratom alkaloids apparent G protein bias, these effects may explain the apparently superior side effect profile of kratom compared to classical opioid agonists (Conibear & Kelly, 2019; Obeng et al., 2020; Siuda et al., 2017; Vandeputte et al., 2020).

These differences are important from a safety perspective because they confer the relatively low risk and prevalence of abuse, dependence and serious adverse effects, as have been discussed elsewhere (Henningfield et al., 2018; Raffa, 2015; Warner et al., 2016). As noted above a more in depth discussion on the evidence addressing the abuse potential of kratom is presented in Appendix Q. In summary the available research (b) (4)

(b) (4)

4.5 Adverse Events and Other Evidence of Safety

The safety of the raw material and extracts derived from the leaves of the plant has also been directly assessed through several human and animal studies. Results for several of these studies are summarized below. Overall the studies have concluded that there is relatively low risk associated with the consumption of the plant and its extracts under recommended use. In Ramanathan and Mansor's toxicology review of mitragynine and analogs it was concluded that "To date there have been no reports of fatal overdose of kratom per se. If there are such occurrences, they are probably the result of kratom products contaminated with synthetic adulterants." (Ramanathan & Mansor, 2015). This conclusion has been echoed in several other reviews performed on the plant including Warner et al.'s pharmacological and toxicological review (Warner et al., 2016).

Henningfield et al. assessed the safety and abuse potential of kratom products in a comprehensive review of publicly available data on the eight factors indicative of the need for control of a substance under the CSA (Henningfield et al., 2018). The analysis ultimately concluded that kratom has a low potential for abuse and a low dependence liability and there is insufficient evidence of personal harm, adverse health effects or detriment to the public health to warrant control under the CSA. This conclusion is consistent with the HHS Letter to DEA, where the Assistant Health Secretary stated that "the available evidence does not support mitragynine and 7-hydroxymitragynine being controlled" under the CSA and there is a "significant risk of immediate adverse public health consequences for potentially millions of users if kratom or its components are included in Schedule I." (Department of Health & Human Services, 2018). A detailed summary of the PinneyAssociates report findings and conclusions and the report itself are provided in Appendix P. As noted elsewhere, further discussion on the abuse potential of mitragynine are found in Appendix Q.

With respect to kratom extract, which is (b) (4) extract (b) (4) as described in section 1.1.1. The manufacturing process ensures that (b) (4)

(b) (4) , as shown in section 3.1.2 which establishes the relationship between (b) (4) . Further comparisons between the (b) (4) are found above.

4.5.1 Experience Reports

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) website (European Monitoring Centre for Drugs and Drug Addiction, 2015) described effects following different levels of consumption:

> After taking a few grams of dried leaves, the invigorating effects and euphoria are felt within 10 minutes and last for one to one and a half hours. Kratom users report increased work capacity, alertness, sociability and sometimes heightened sexual desire. Kratom taken in large, sedating doses corresponding to 10–25 g of dried leaves may initially produce sweating, dizziness, nausea and dysphoria but these effects are shortly superseded with calmness, euphoria and a dreamlike state that last for up to six hours.

The EMCDDA also reports regular kratom use may produce dependence, and withdrawal symptoms (including cravings, weakness and lethargy, anxiety, restlessness, rhinorrhea, myalgia, nausea, sweating, muscle pain, jerky movements of the limbs, tremor as well as sleep disturbances), but these are typically mild and diminish within a week (European Monitoring Centre for Drugs and Drug Addiction, 2015). Additional surveys have been conducted among kratom users in the United States. A summary of these studies is shown in Table 14 below and additional testimonials are reviewed in the 8 Factor Assessment of Kratom detailed in Appendix P.

Overall, these surveys show that only a minority of respondents report kratom-related adverse effects. There are few serious adverse effects reported and those few that are reported are likely associated with poly drug use and the use of adulterated products rather than kratom itself (discussed in more detail in Section 4.5.2 and in Appendix S. Discussion on Serious Adverse Events Associated with Kratom). Side effects that are reported are similar to those reported among Southeast Asian users and are relatively benign and short lasting (Coe et al., 2019; Garcia-Romeu et al., 2020; Grundmann, 2017; Smith & Lawson, 2017).

Table 14. Summary of Surveys of Kratom Users in the United States

Author / Year	Sample Size	Negative Effects of Kratom Reported by Users
Grundmann (2017) Drug and Alcohol Dependence (Grundmann, 2017)	N=8,049	(b) (4)
Pain News Network Website (2016) (Pain News Network, 2021)	N=6,150	
Garcia-Romeu, Dunn, & Griffiths (2020); (Garcia-Romeu et al., 2020)	N=2798	
Henningfield et al. American College of Neuropsychopharma-cology Annual Meeting Dec. 6, 2017 (Henningfield et al., 2017; Hogan Lovells & PinneyAssociates, 2016)	N=2,867	
American Kratom Association Testimonials (2016); Hogan, Lovells, & PinneyAssociates filing to FDA	N=173	

Author / Year	Sample Size	Negative Effects of Kratom Reported by Users
Covvey, et al. Prevalence and characteristics of self-reported kratom use in a representative US general population sample. (Covvey et al., 2020)	N=1,842	(b) (4)
Swogger et al. Experiences of Kratom users: A qualitative analysis. (Swogger et al., 2015)	N=161	(b) (4)
Coe et al. Kratom as a substitute for opioids: Results from an online study. (Coe et al., 2019)	N=3024	(b) (4)
Smith and Lawson. Prevalence and motivations for kratom use in a residential treatment program. (Smith & Lawson, 2017)	N=500	(b) (4)
Nicewonder et al. Distinct kratom user populations across the United States: A regional analysi based on an online survey. (Nicewonder et al., 2019)	N=8049	(b) (4)

4.5.2 Serious Adverse Events Associated with Kratom

As reported in several surveys and retroactive studies, there is a subset of kratom users who use kratom to help these individuals deal with drug withdrawal symptoms (Coe et al., 2019; Garcia-Romeu et al., 2020; Grundmann, 2017; Grundmann et al., 2021; Nicewonder et al., 2019; Smith & Lawson, 2017; Swogger et al., 2015). Not surprisingly, this subset of kratom users is at high risk of serious adverse health consequences during their use of opioids, narcotics, and other controlled substances that are associated with severe adverse effects including death. The scientific literature includes reports linking kratom consumption to serious adverse health consequences. A detailed evaluation and analysis of the literature however, reveals that in almost all instances the serious adverse events occurred in individuals that had substances in their systems that are widely recognized as causing serious injury and death. In the remaining cases, missing details and a lack of definitive information does not allow for the conclusion of kratom consumption being the sole cause of the adverse event being reported. This is consistent with the 2018 HHS letter to DEA that stated "there is still debate among reputable scientists over whether kratom by itself is associated with fatal overdoses." (Department of Health & Human Services, 2018).

Singh et al. (2016) notes that despite the high use of kratom in Southeast Asia, reports of serious adverse events are lacking in the region (Singh et al., 2016). Singh et al., (2016) review found only one study from Thailand that documented cases of kratom poisoning and diverse withdrawal symptoms among users, and in this study most of the respondents who did report poisoning and withdrawal symptoms were found to be also under the influence of other illicit drugs (Singh et al., 2016). Singh et al.'s comprehensive review also noted that the main side effects reported in the literature for those users with over a year of regular consumption as loss of weight, dehydration, constipation and hyper pigmentation (Singh et al., 2016). Longer-term users also report lethargy and tiredness (Singh et al., 2016).

Reviews by Singh and others report that severe side effects linked with kratom use are virtually unknown in Southeast Asia and those that are reported are typically associated with co-ingestion of other substances, particularly amphetamines and other stimulants (Davidson et al., 2021; Raffa, 2015; Singh et al., 2016). Overall, there have been few serious adverse events reported in Southeast Asia associated with Kratom consumption. For perspective, kratom use is quite high in Southeast Asia, as demonstrated by Tanguay's conservative estimates of > 1 million regular adult users and Schimmel's more recent estimate of > 8 million users in Thailand alone (Schimmel et al., 2021; Tanguay, 2011; Wonguppa & Kanato, 2017).

In contrast to the lack of reports from Southeast Asia, reports of kratom-associated serious adverse events have emerged in the Western nations. Still, the total number of kratom users in the United States has been estimated to be between 2 to 16 million by different researchers (Covvey et al., 2020; Henningfield et al., 2019; Nicewonder et al., 2019; Schimmel et al., 2021). As such, the <2000 confirmed adverse event reports associated with kratom ingestion between 2010 and 2017 make up only a very small fraction of the total users (Anwar et al., 2016; Post et al., 2019). Furthermore, review of scientific literature, as discussed in more detail in Appendix S, indicates that many of these cases are associated with exposure to other substances with known adverse effects.

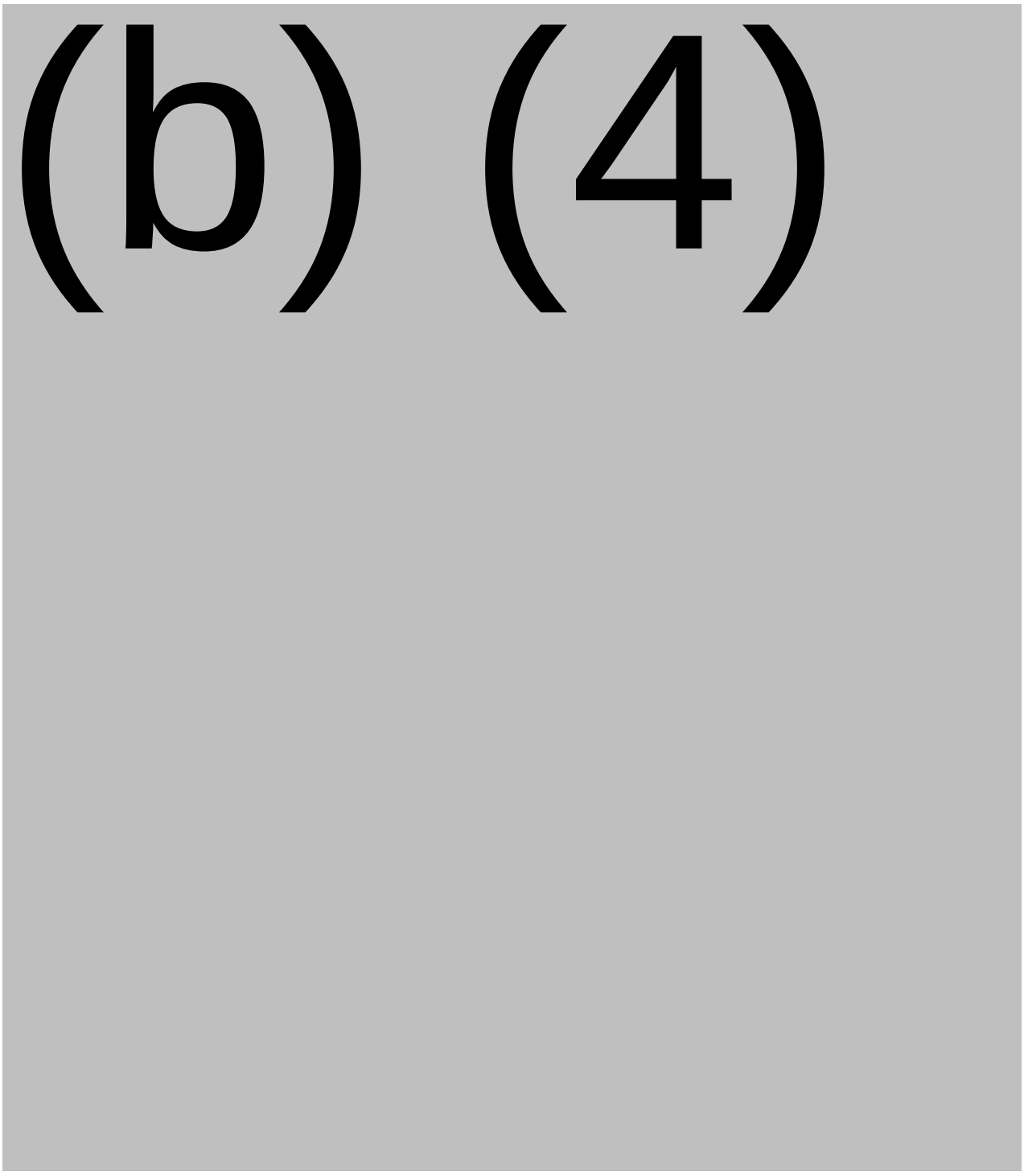
Singh et al. (2016) concluded in their comprehensive literature review, that while reports of kratom toxicity and mortality have emerged in the West, many of the cases have involved individuals who had abused other substances along with kratom or had histories of alcohol dependence or heroin abuse (Singh et al., 2016). Similarly, Ramanathan and Mansor's toxicology review of mitragynine and analogs concluded that "To date there have been no reports of fatal overdose of kratom per se. If there are such occurrences, they are probably the result of kratom products contaminated with synthetic adulterants." (Ramanathan & Mansor, 2015). This conclusion has been echoed in several other reviews performed on the plant including reviews and assessments published by Warner et al. and Henningfield et al. (Henningfield et al., 2018; Warner et al., 2016). As described in a more detailed discussion in Appendix S, the available scientific literature shows that kratom-associated serious adverse events have been predominantly linked to co-use with other drugs and/or consumption of adulterated products.

Overall, the general conclusion obtained from a review of the available scientific data is that kratom has a relatively benign risk profile with only a minority of respondents indicating adverse effects, withdrawal symptoms or problematic use. The totality of the evidence shows that serious adverse events are only reported among a very minor proportion of kratom users with the vast majority of these confirmed to be associated with co-use with other drugs and/or consumption of adulterated products.

5. Labeled Intended Conditions of Use (Route of Administration, Serving Size, Frequency of Use, and Duration of Use)

Dietary supplements containing the dietary ingredient kratom extract are intended to be used by adults over the age of 18. The finished dietary supplement will be (b) (4) . The recommended serving will be (b) (4)

(b) (4) The label will also contain numerous other warnings and directions for use. Below, we highlight each of the statements that will appear on the label (IN ALL CAPITAL LETTERS AND IN BOLD) and provide the reasons for including those statements on the label of the dietary supplement.



(b) (4)

6. Basis for Concluding the Safety of the Dietary Ingredient in the Dietary Supplement

6.1 Kratom Extract Is Safe on the Basis of the Extensive History of Use of Kratom Teas and Supplements

In its draft guidance on the submission of new dietary ingredient notifications, FDA recognizes the safety of dietary ingredients can be established by a "history of safe" use and that the history "could be from the United States or another country, as long as the substance was consumed as a food, dietary supplement, or, in the case of foreign history of use, category of product comparable to a dietary supplement in the U.S." (U.S. Department of Health and Human Services, 2016). FDA further recognizes substantiation for a history of safe use requires data demonstrating the similarities in composition of the historically consumed article and the dietary ingredient. FDA also requests data on the (a) dose per serving and total daily intake, (b) duration of use, (c) frequency of intake, and (d) any other information that describes the conditions of use of the historically consumed material. FDA concludes, "for these data to demonstrate a history of safe use, the intake level for the historically consumed article should be the same as or higher than the anticipated intake level of the NDI in the dietary supplement, based on the conditions of use described in the NDI notification."

The data in this notification establish kratom teas have been safely consumed in Southeast Asia as a conventional tea and that kratom leaves have been chewed and used as a supplement for centuries. The information in this notification also establish a sizable number of humans reporting use of kratom, with over one million Thai residents reporting use in 2007 and 2008. The data also establish the (b) (4) found in these conventionally brewed teas and consumed through chewing the kratom leaves are the same as those found in kratom extract. With regard to usage data, the data demonstrate the average user in Southeast Asia would consume between (b) (4) per day, with heavy users reporting between (b) (4) per day. The historical uses involve chronic daily use that could extend over a lifetime. The dietary ingredient in this notification is intended to be used (b) (4) Moreover, while kratom teas and kratom leaves are consumed

daily, the dietary supplement is labeled for (b) (4)

6.2 The History of Use is Corroborated by Animal Toxicity Data and the Determination of the No-Observed-Adverse-Effect-Level (NOAEL) or Lowest-Observed Adverse Effect Level (LOAEL)

Sabetghadam et al. (2013b) reported reduced blood platelet counts as the most sensitive adverse endpoint observed after 28 days of ingesting 1 mg/kg pure mitragynine, but that finding seems to be an artifact of an unusually high platelet count in the control animals. Also the test material in that study is (b) (4)

Furthermore the rising-dose and multiple dose tolerance study performed on the (b) (4) material determined no evident clinical signs and only a slight effect on weight gain at a single day dose of (b) (4) . It is noted that the multiple dose tolerance study did find that (b) (4)

(b) (4)

.

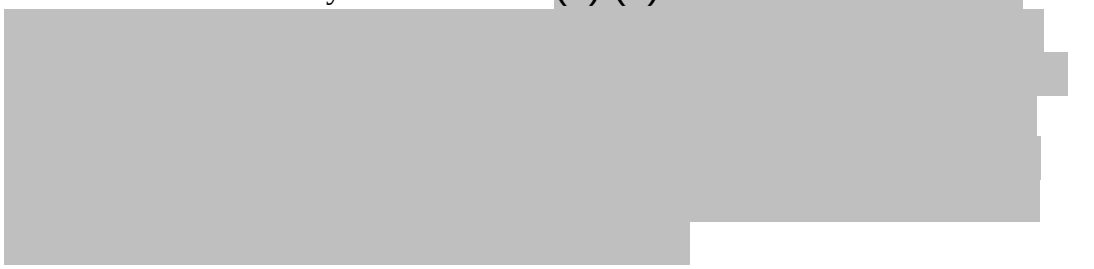
6.3 Response to Agency

Following the New Dietary Ingredient Notification American Botanical Corp. submitted on December 21, 2017, the Agency issued a letter citing concerns with the submission. In the interest of thoroughness, we have responded to each of the issues identified by the Agency in Appendix T, including citations to where the issues are addressed in the current NDIN.

6.4 Safety Narrative and Conclusion

Kratom has been safely consumed as a conventional food and consumed as a tea, dietary supplement, and folk remedy in Southeast Asia for centuries. Kratom consumption is common in Southeast Asia and is reported to be quite high, with

likely over 1 million regular consumers in Thailand alone. The data demonstrate the kratom extract covered by this submission (b) (4)

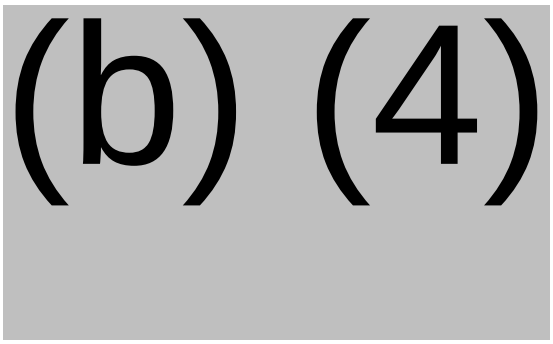


The type of adverse events are similar to those that would be expected for other plant extracts such coffees and teas and other lawfully marketed dietary supplements such as St. John's Wart, Valerian, and Kava Kava. With respect to reports of withdrawal, it is the case that daily high dosage consumption of kratom can lead to the state, common in many if not most daily coffee drinkers in the US, that abrupt cessation will be accompanied by transient symptoms of withdrawal that are readily self-managed, tolerable and resolve within a few days.

The reports in the literature of serious adverse events associated with kratom consumption need to be placed in the proper context. It is well recognized that kratom extracts are commonly consumed by individuals who have a history of using illegal drugs and that kratom extracts have been included as an ingredient in a "cocktail" that includes illegal drugs. Globally, fewer than 100 serious adverse events appear to have been published associated with kratom consumption, and a careful review of the case reports indicates that in almost all cases, other substances consumed by the individual are likely responsible. The data in the notification and summarized in detail in the attached Pinney Associates report establishes kratom extracts have a low potential for abuse, a low dependence liability, and there is insufficient evidence of personal harm, adverse health effects, or detriment to the public health. This is consistent with the 2018 HHS letter to DEA concluding that data suggests that mitragynine does not satisfy the statutory requirement for scheduling to demonstrate that kratom has a high potential for abuse.

The data in this notification, therefore, demonstrate the dietary ingredient will be consumed at (b) (4)

Submitted by:



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