NEW DIETARY INGREDIENT (NDI) SAFETY INFORMATION

Mitragyna speciosa leaf extract standardized to 75 ± 3.5% mitragynine on a dried weight basis

1. New Dietary Ingredient Identity Information (Recommended)

1.1. Description of the identity of the NDI

1.1.1. Identity of the New Dietary Ingredient (NDI): *Mitragyna speciosa* leaf extract standardized to 75 ± 3.5% mitragynine on a dried weight basis

1.1.2. Botanical Name: *Mitragyna speciosa* (Korth.) Havil.

1.1.3. Part of Plant Used: Leaves

1.1.4. Botanical Description: Mitragyna speciosa, commonly known in the United States as kratom, is a tropical evergreen tree belonging to the Rubiaceae family. Kratom is native to Southeast Asia, particularly Thailand, Malaysia, and Indonesia. Kratom trees can grow up to 30 meters in height. The leaves of the kratom tree are elliptical and glossy with a dark green color when mature. Kratom trees have deep yellow flowers that grow in clusters of over 100 florets[1].

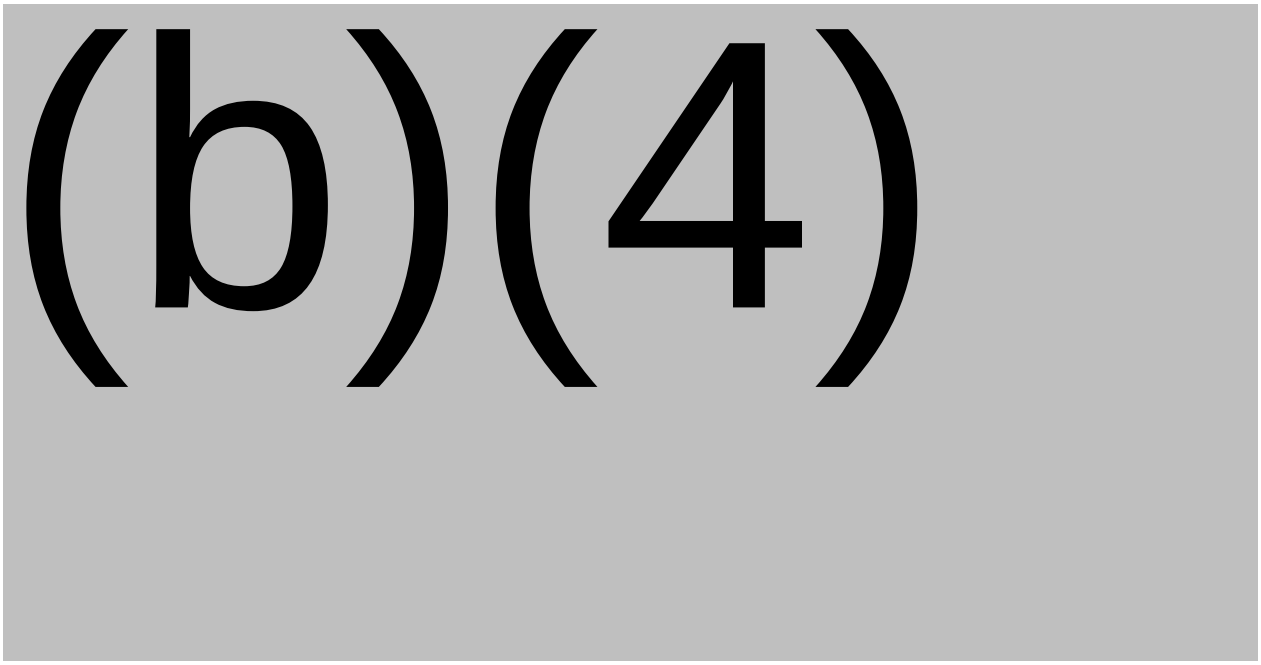
1.1.5. Concentration of the Active Ingredient: 75 ± 3.5% mitragynine on a dried weight by weight (w/w) basis

1.2. Description of the evidence verifying the identity of the NDI

1.2.1. Botanical raw material: The identity of the botanical raw material (*Mitragyna speciosa*) used to manufacture the *Mitragyna speciosa* leaf extract standardized to 75% mitragynine is confirmed as detailed below:

1.2.1.1. The leaves of the kratom tree contain over 50 monoterpene indole and oxindole alkaloids, but the alkaloid mitragynine is unique to *M. speciosa* [2]. Other species of *Mitragyna* include *M. hirsuta*, *M. diversifolia*, *M. rotundifolia,* and *M. parvifolia* in which the most abundant compound found is either mitraphylline or

mitraciliatine, but no other species of *Mitragyna* produce mitragynine[3]. As such, the identity of the raw material used to produce the *Mitragyna speciosa* extract standardized to 75% mitragynine is confirmed by the presence of the alkaloid mitragynine in the leaf material. The specification for the *Mitragyna speciosa* raw material is (b)(4) .



1.3. NDI Identity Conclusion

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This process produces an extract of *Mitragyna speciosa* standardized to be comprised of 75 ± 3.5% mitragynine. The process is described in detail below with the finished product specifications and in-process quality control measures undertaken to ensure the consistency and validity of the finished product.

2. NDI manufacture

2.1. Raw materials

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(b)(4)

Table 2.1.A Raw Material and Processing Aids Used in the Manufacturing

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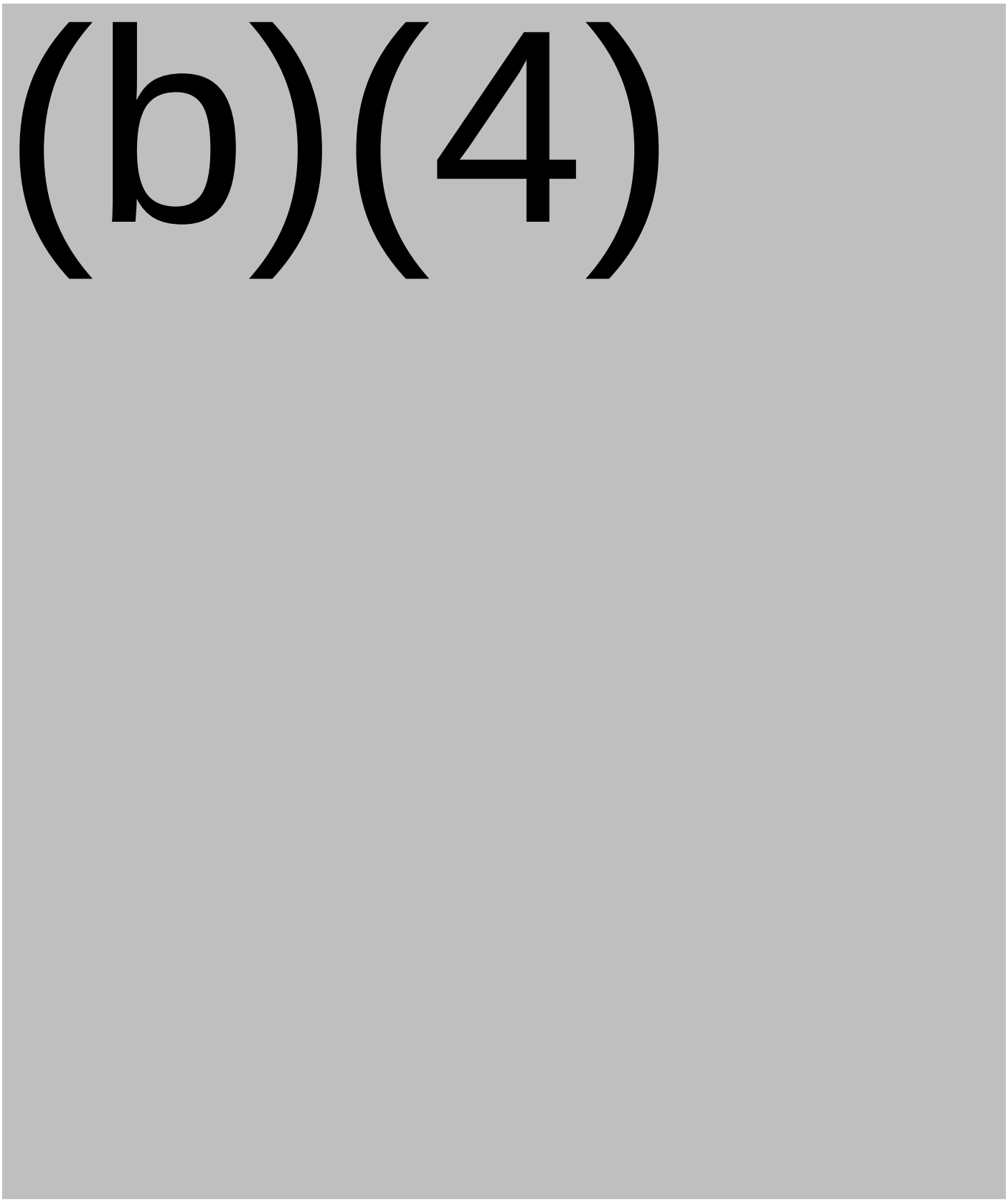
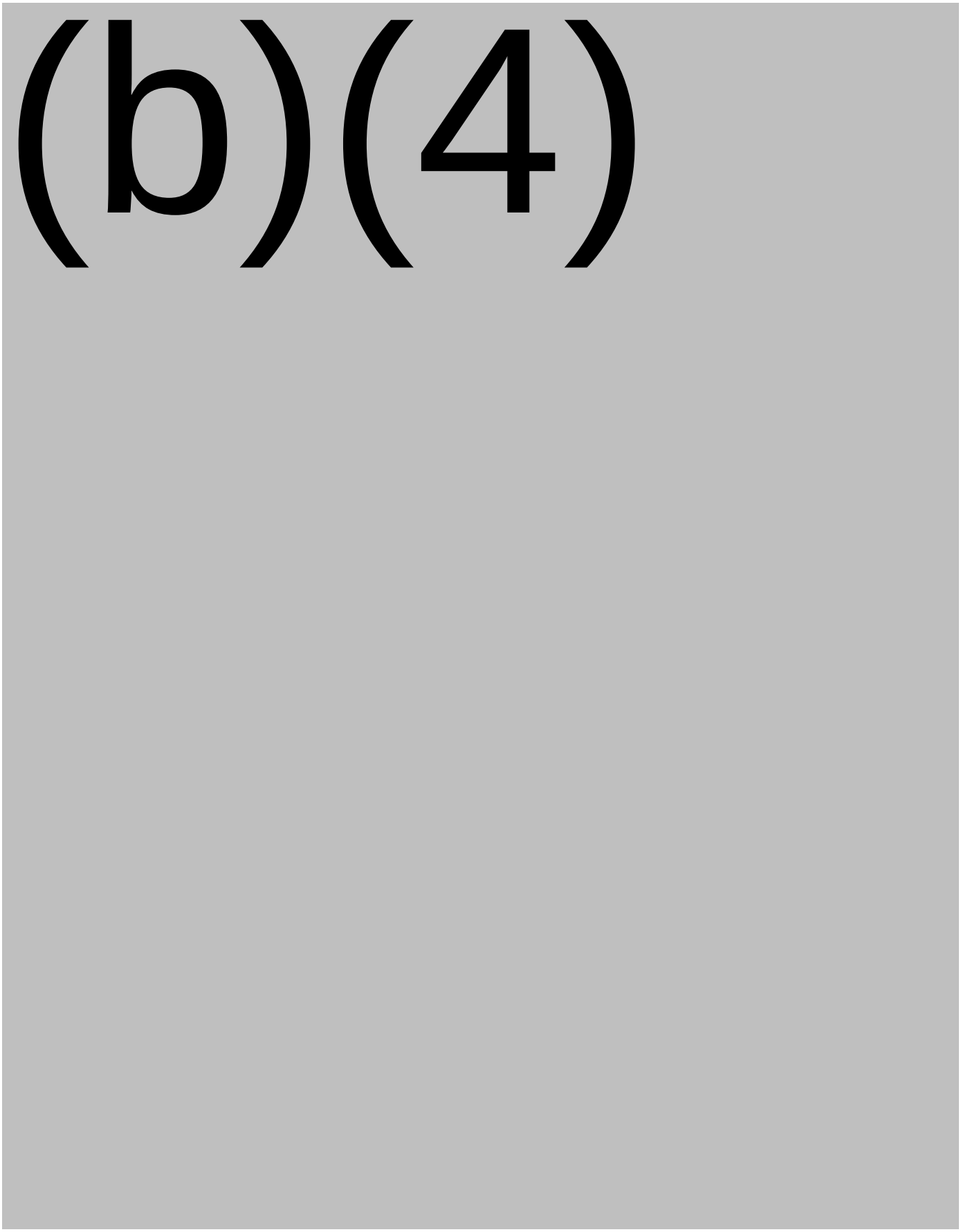
2.2. Formulation ingredients

(b)(4)

2.3. Manufacturing process

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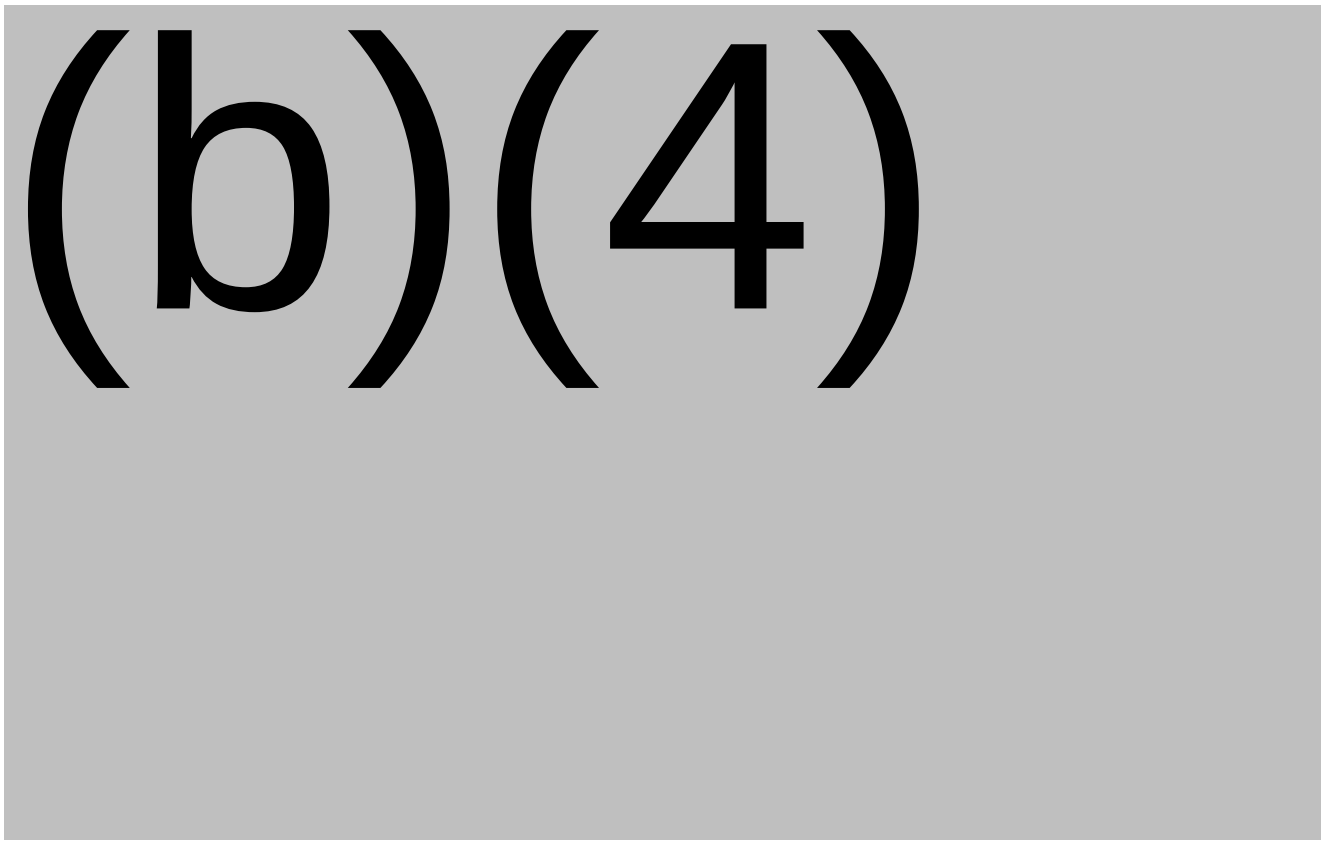
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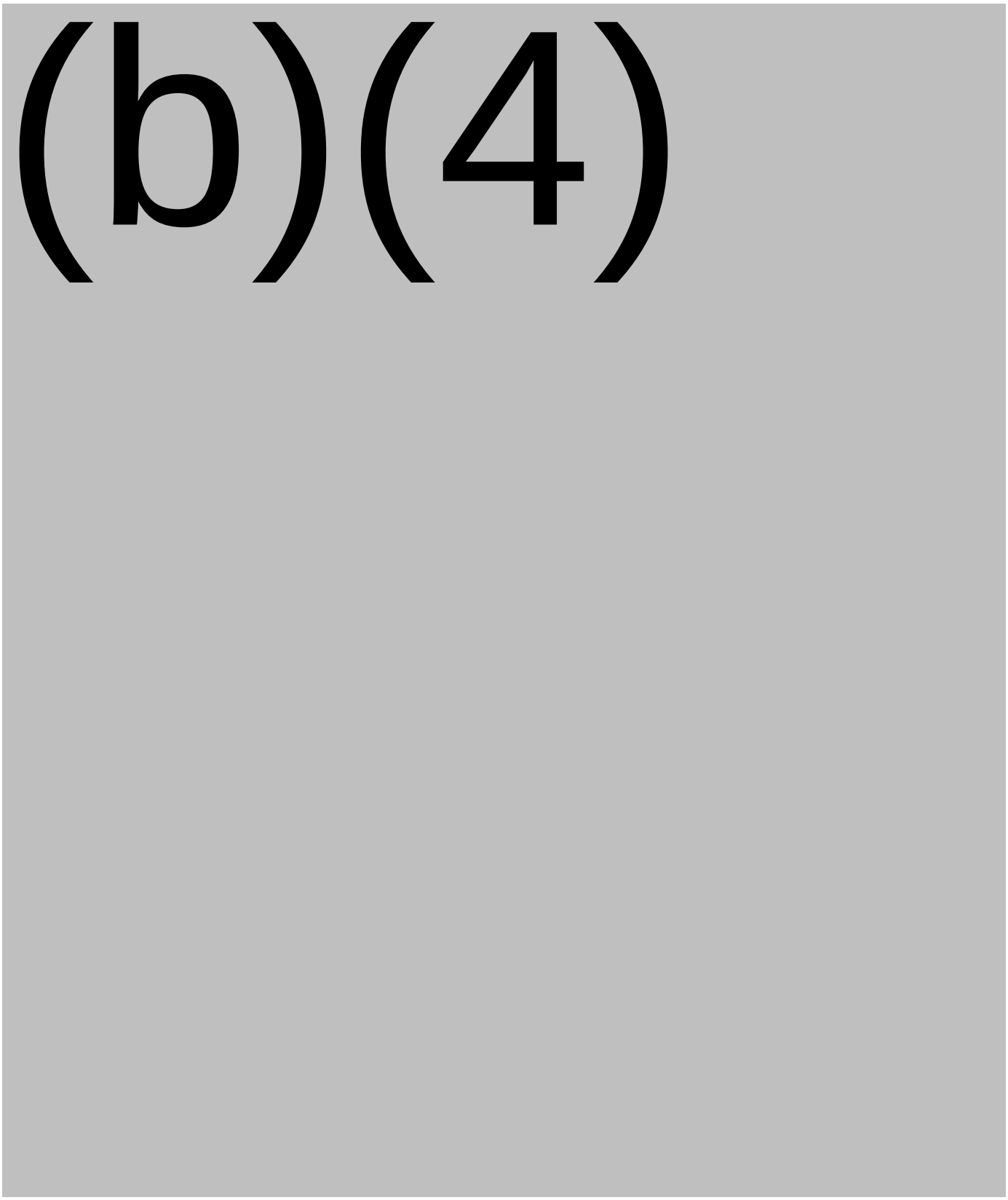
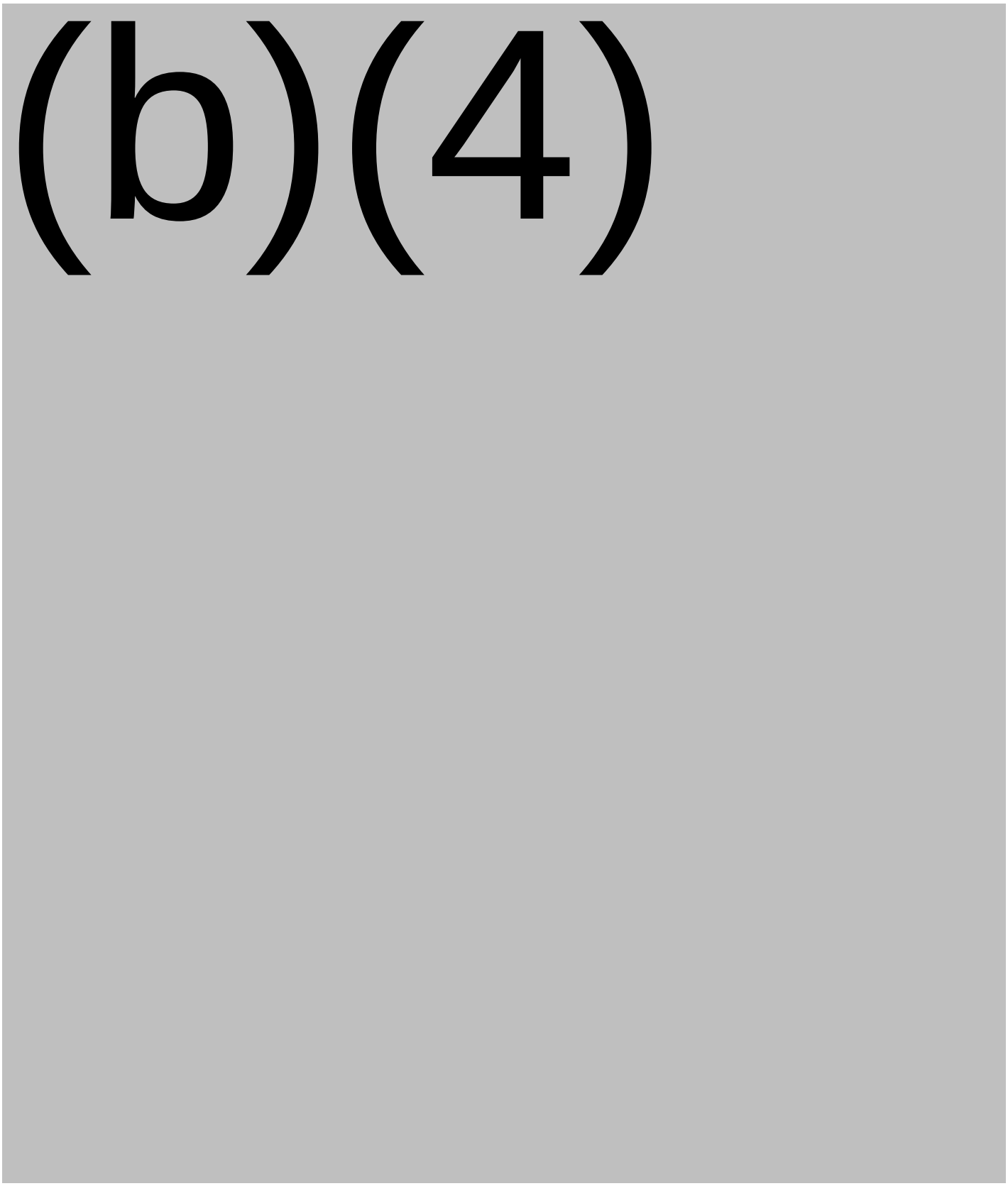
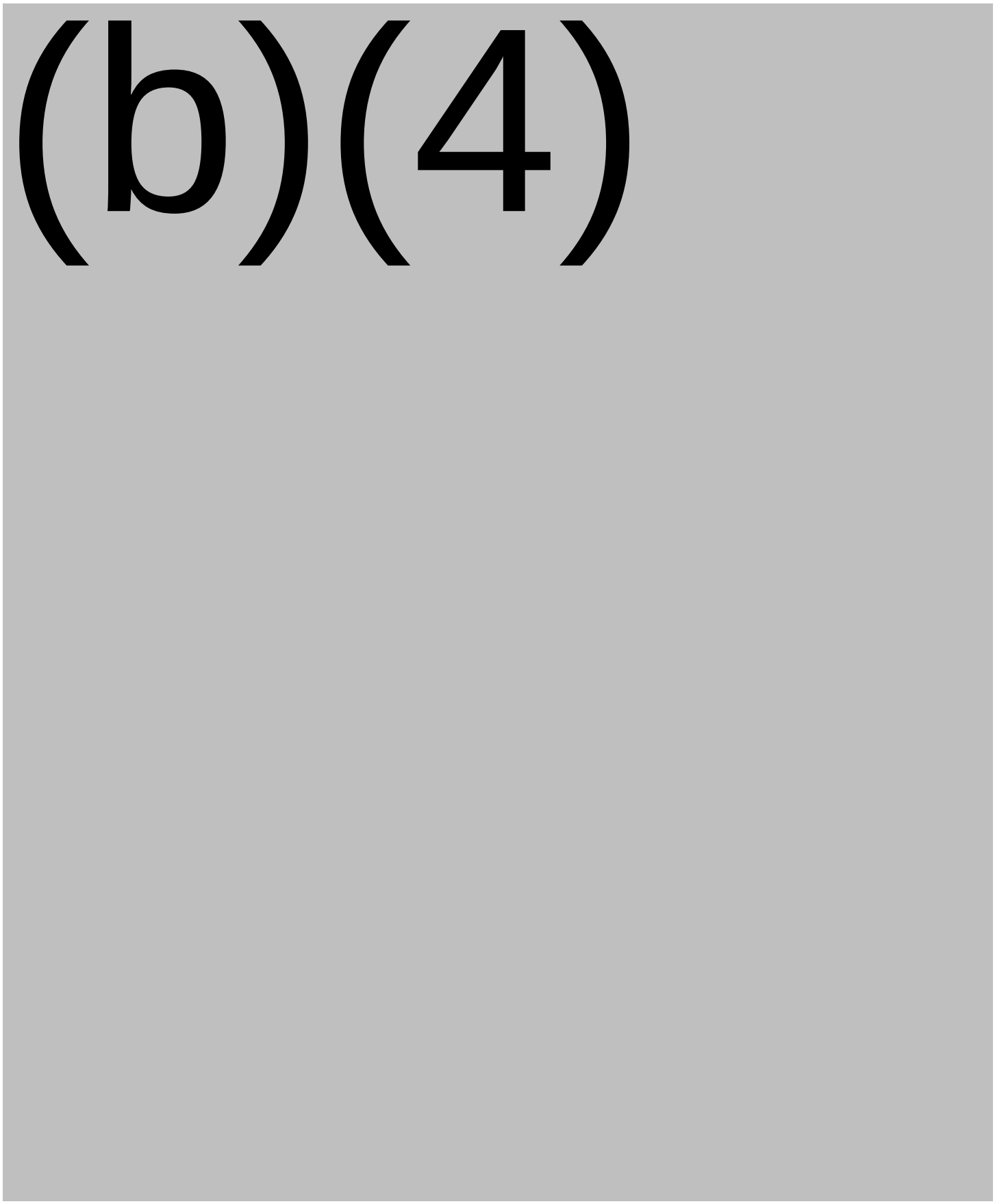
Figure 2.3.A: A schematic of the manufacturing process.



2.4. NDI specifications

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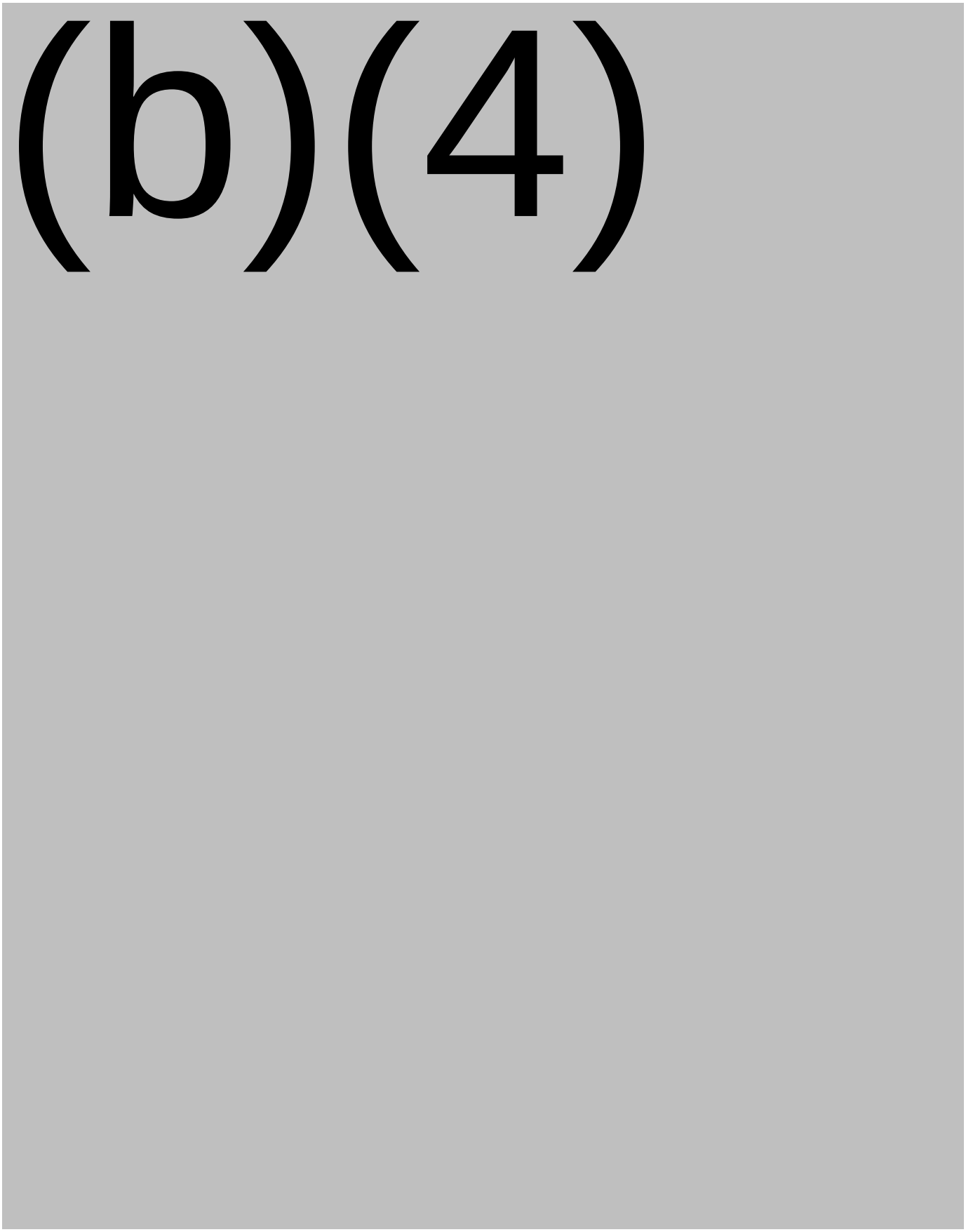
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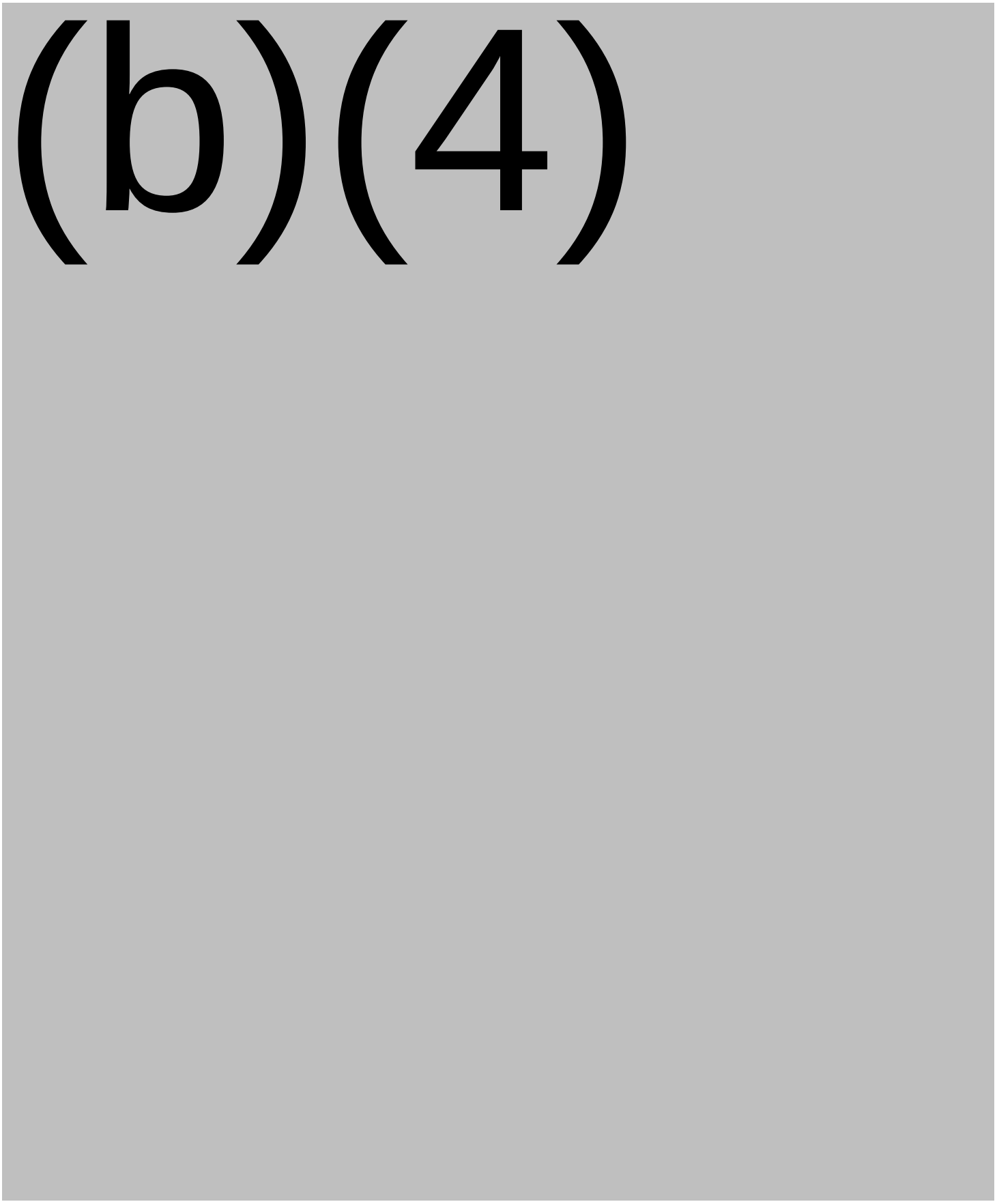
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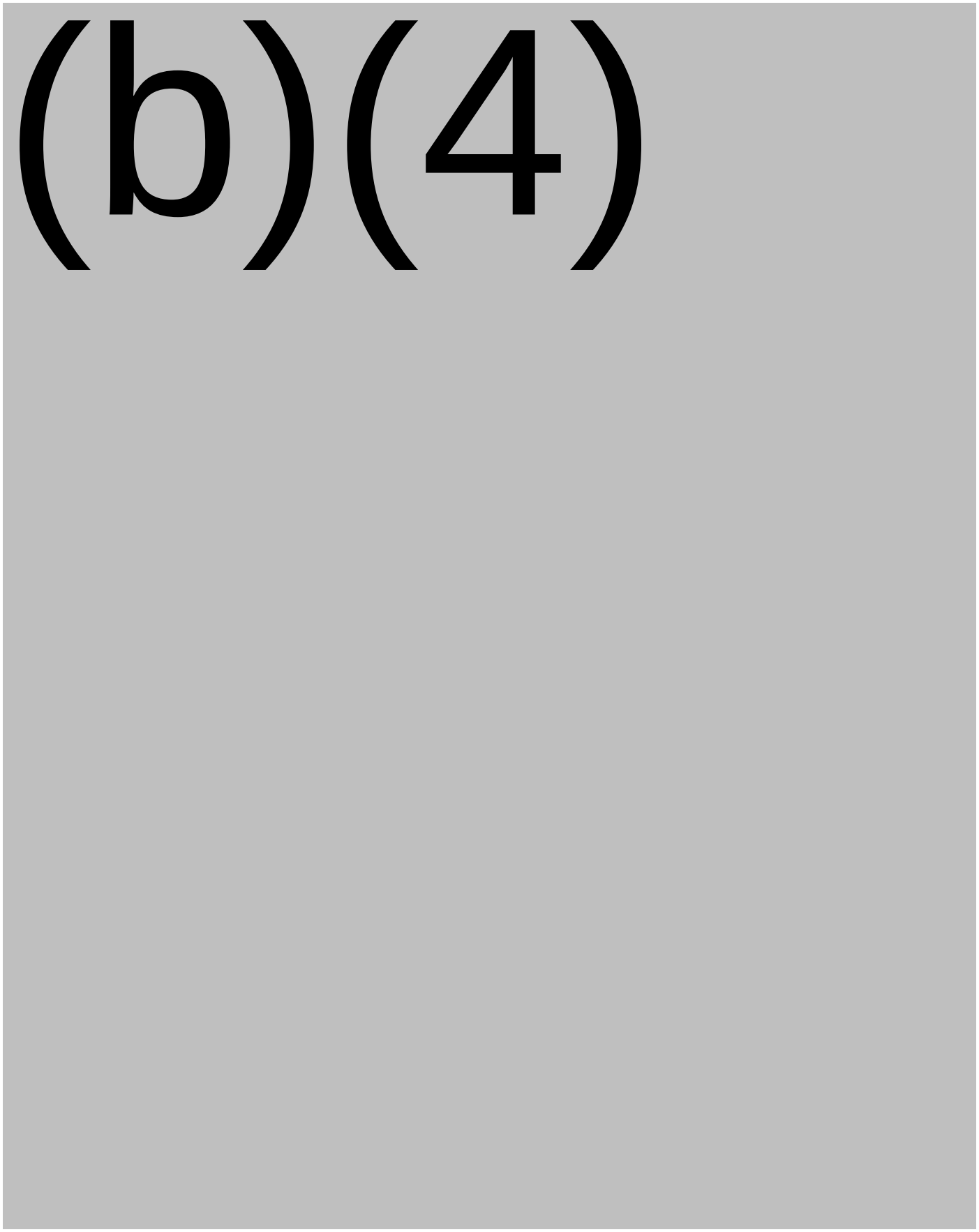
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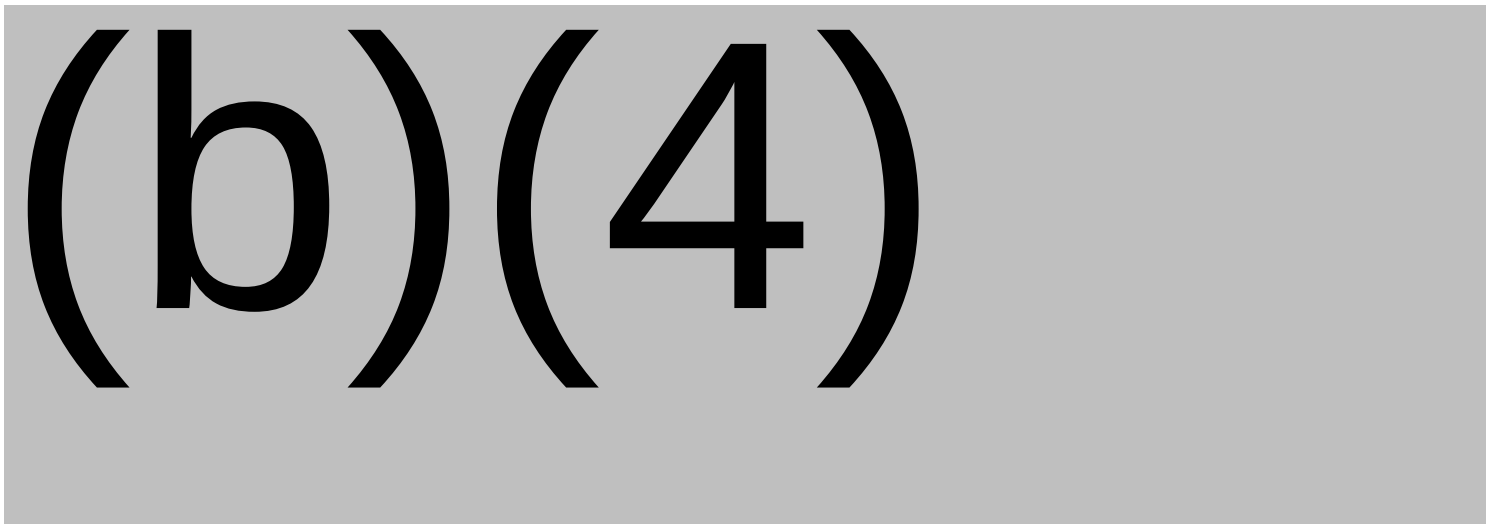
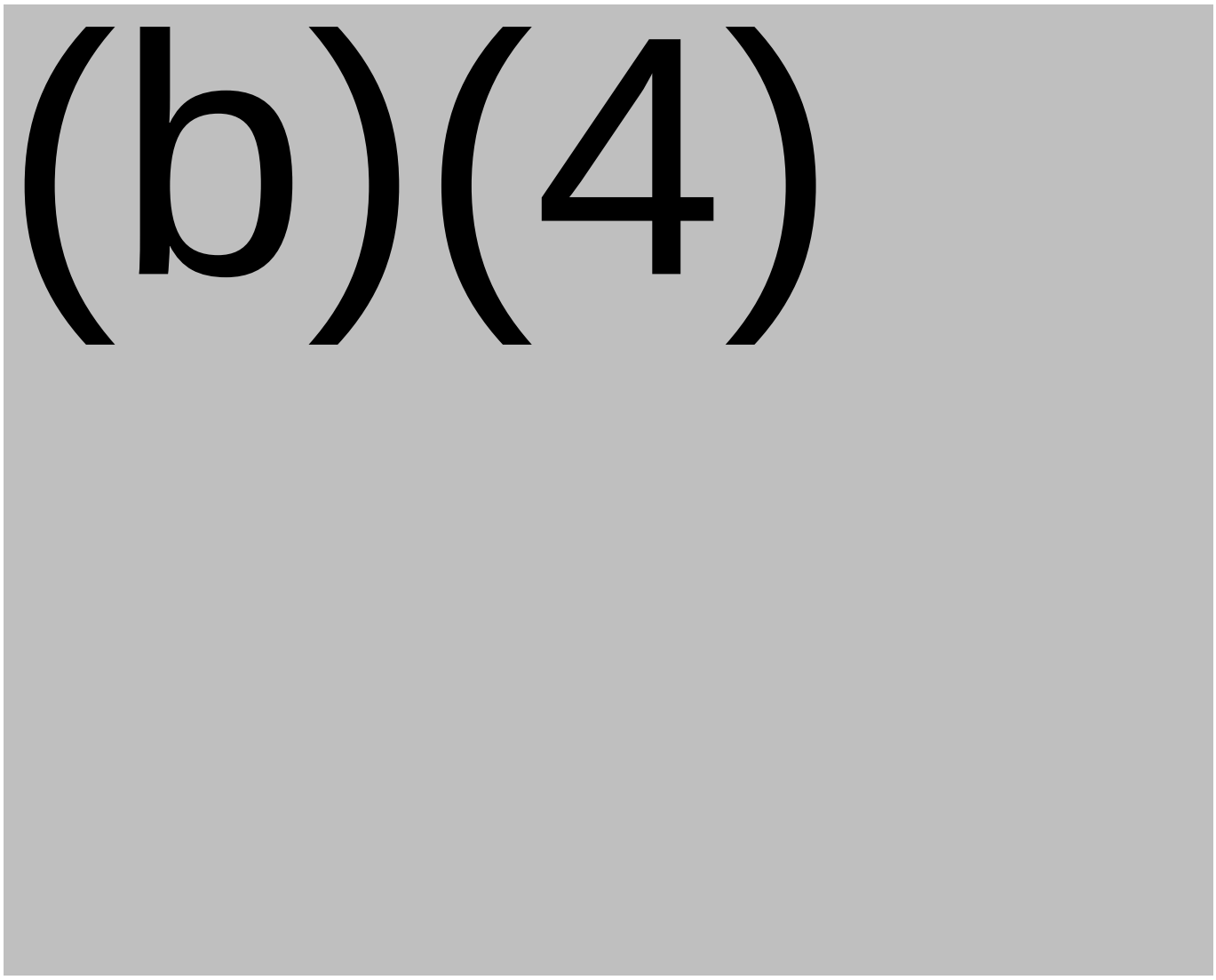


2.5. Methods of analysis



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2.5.4. Method and Specification for Strength of the NDI

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2.6. Analysis of potentially toxic processes

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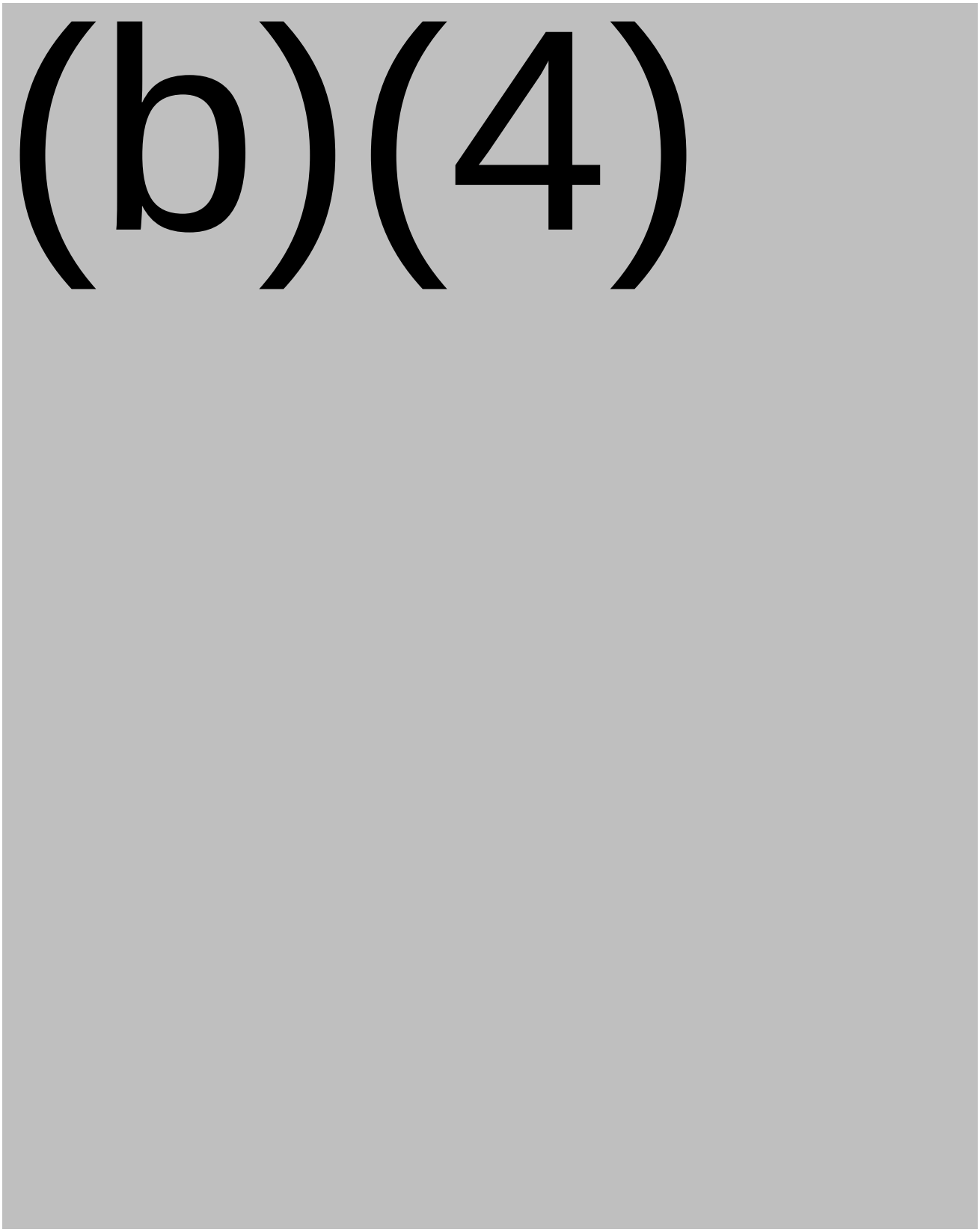

2.8. Shelf-life and conditions of storage

NA

3. Dietary Supplement Manufacture (Recommended)

(b)(4)

3.1. Raw materials

NA

3.2. Formulation ingredients other than the NDI

NA

3.3. Manufacturing process

NA

3.4. Product specifications

NA

3.5. Methods of analysis

NA

3.6. Analysis of potentially toxic processes

NA

3.7. Disintegration and dissolution profile

NA

3.8. Shelf-life and conditions of storage

NA

4. History Of Use Or Other Evidence Of Safety (Required)

4.1. History of use

4.1.1. Regulatory History of *Mitragyna speciosa*

Mitragyna speciosa or any products derived from the plant are not approved for any medical use in the United States. The United States Drug Enforcement Agency (DEA) filed a notice to place mitragynine and 7-hydroxymitragynine into the Controlled Substances Act (CSA) Schedule I but withdrew the notice [6, 7]. An eight-factor analysis (8-FA) was performed for kratom after which a formal scheduling recission was issued on 18 August, 2018 [8]. The scheduling was rescinded due to the fact that mitragynine does not satisfy the first of the three statutory requisites for schedule I and there is debate over whether kratom by itself is associated with fatal overdoses [9]. In 2021, the World Health Organization (WHO) Expert Committee on Drug Dependence (ECDD) concluded that there is "insufficient evidence to recommend a critical review of kratom" [10].

Despite the scientific data supporting kratom to remain accessible, there are also case reports of adverse events due to kratom use and/or intoxication which will be discussed further below (Section 6.4).

4.1.2. Description of the relationship between the historically consumed material and the NDI or dietary supplement containing the NDI

Mitragyna speciosa (kratom) has a history of traditional, safe use in Southeast Asia. Leaves are commonly brewed into teas or chewed. As chewed kratom is not directly applicable to this NDI, only results of studies using extracts of *Mitragyna speciosa* leaf material where the (b)(4)

The similarity of a brewed kratom juice to the NDI is that (b)(4)

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4.1.2.1. Pharmacology of *Mitragyna speciosa* leaf extract alkaloids

(b)(4)

Mitragynine is a partial, μ-opioid receptor agonist [11]. In preclinical models, it shows limited abuse liability [12] and does not induce respiratory depression [13]. It also has activity at serotonin, dopamine, and adrenergic receptors [14-18]. In one preclinical *in vivo* study, mitragynine was also found to exert some of its analgesia through serotonergic receptor signaling systems [19].

Speciociliatine, a diastereomer of mitragynine, has activity at opioid receptors while paynantheine, another diastereomer of mitragynine, and speciogynine have activity at serotonin receptors [15, 16, 19, 20]. The activity of kratom alkaloids at CNS receptors is summarized in Table 4.1.2.A with only activity in the low μM range being reported. Additionally, it was found that mitragynine was able to displace selective radioligands for the dopamine D2 receptor at 54% though further affinity studies have not been performed [21].

(b)(4)

(b)(4)

The primary liver enzyme responsible for the metabolism of kratom alkaloids is cytochrome P450 (CYP) 3A4 with contributions from CYP2C9, CYP2C19, and CYP2D6[22-24]. CYP3A and CYP2D6 are the major enzymes responsible for metabolism of about 50% of clinically used drugs so caution must be taken when kratom is consumed with pharmaceutical drugs [25]. This will be described in detail further with human clinical studies and adverse event case reports (Sections 4.2.1 and 4.1.4, respectively). To ensure safety of the NDI, the label shall include warnings for individuals to seek guidance from a healthcare professional prior to use if they are taking any other supplements or medications that are eliminated through similar metabolic pathways or have similar CNS receptor activity.

Preclinical pharmacokinetic studies have been performed in rats for isolated and purified mitragynine, speciociliatine, speciogynine, and paynantheine [19, 26, 27]. In rats, speciogynine and paynantheine are cleared from the systemic circulation more rapidly than either mitragynine or speciociliatine, this is hypothesized to be due to the configuration at the 3 carbon and has been found in humans as well after kratom tea consumption indicating rats are a good model for pharmacokinetic behavior of the major kratom alkaloids (see Section 4.2.1.). The results are summarized in Table 4.1.2.B.

Table 4.1.2.B. Preclinical pharmacokinetics of individual kratom alkaloids dosed intravenously in rats

Parameter	Alkaloid			
	Mitragynine[26]	**Speciociliatine[27]**	**Speciogynine[19]**	**Paynantheine[19]**
Dose	5 mg/kg	2.5 mg/kg	1.25 mg/kg	2.5 mg/kg

AUC (ng*h/mL)	4248.9 ± 563.9	4324.5 ± 670.8	618.9 ± 3.4	588.0 ± 22.3
CL (L/h/kg)	1.3 ± 0.1	0.7 ± 0.2	3.2 ± 0.0	5.3 ± 0.2
V_z (L/kg)	8.0 ± 1.5	6.2 ± 2.3	30.1 ± 8.4	71.9 ± 6.5
AUC = area under the plasma concentration time curve (exposure); CL = clearance; V_z = volume of distribution				

Additional studies looked at the comparative pharmacokinetics of kratom juice preparation versus kratom extract and the results are summarized in Table 4.1.2.C [26, 28]. In one study, only mitragynine levels were quantified prior to dosing and in the plasma. In another study, eleven alkaloids were analyzed and quantified only mitragynine and speciociliatine were quantifiable in the plasma and could be analyzed for pharmacokinetic parameters. It was found that a higher dose of kratom juice preparation resulted in greater maximum concentrations and exposure of mitragynine even when corrected for dose (~3-4-fold increase in maximum concentration and ~2-2.5-fold increase for exposure). The human equivalent dose (HED) of 20 mg/kg mitragynine is 225 mg in a 70 kg individual [29] which would be considered a high dose. At this dose level, competition for metabolizing enzymes may be taking place leading to an increase in the overall exposure of mitragynine. At lower doses (HED in a 70 kg individual = 65 mg for the kratom juice preparation and 108 mg for the commercial extract, respectively) there was no difference in the maximum concentration between an aqueous juice preparation and extract formulation but there was a moderate 1.6-fold increase in the exposure of mitragynine when delivered as an extract formulation. It is important to note that the formulations used in these preclinical studies contain all the same compounds as the NDI, but due to differences in the formulations, there are moderate

differences in the pharmacokinetics.

Table 4.1.2.C. Preclinical pharmacokinetics of kratom alkaloids delivered in a kratom juice preparation versus a commercially available extract formulation

	Kratom Juice Preparation [26]	**Kratom Juice Extract [26]**	**Kratom Juice Preparation [28]**	**Commercial Extract [28]**	**Kratom Juice Preparation [28]**	**Commercial Extract [28]**
Parameter	MTG	MTG	MTG	MTG	SPC	SPC
Dose	20 mg/kg	20 mg/kg	5.73 mg/kg	9.60 mg/kg	2.03 mg/kg	2.24 mg/kg
T_{max} (h)	3.4 ± 0.1	1.0 ± 51.1	1.3 ± 0.3	3.1 ± 1.7	1.8 ± 0.7	3.2 ± 1.6
C_{max} (ng/mL)	931.3 ± 23.6	657.2 ± 51.1	63.8 ± 6.2	111.9 ± 15.6	21.1 ± 3.3	23.8 ± 1.4
AUC (h*ng/mL)	4262.9 ± 273.2	5298.3 ± 397.2	479.6 ± 36.4	1306.8 ± 126.1	107.4 ± 25.4	222.7 ± 22.2
C_{max} /Dose (ng/mL/mg/kg)	46.6 ± 1.2	32.9 ± 2.6	11.1 ± 1.1	11.7 ± 1.6	10.4 ± 1.6	10.8 ± 0.6
AUC/Dose (h*ng/mL/mg/kg)	213.1 ± 13.7	264.9 ± 19.9	83.7 ± 6.4	136.1 ± 13.1	52.9 ± 12.5	101.2 ± 10.1

LKT = lyophilized kratom tea; T_{max} = time to reach maximum plasma concentration; C_{max} = maximum plasma concentration; AUC = exposure (area under the plasma concentration time curve)

Further preclinical work has been performed in beagle dogs where a single oral dose of 5 mg/kg (HED = 194 mg mitragynine in a 70 kg individual [29]) was well-tolerated with mild-sedation and anxiolytic effects observed[30].

4.1.3. Describe identity information verifying the relationship between the

historically consumed material and the NDI or dietary supplement containing the NDI

(b)(4)

4.1.4. Historical conditions of use and cumulative exposure estimate for the historically consumed material

A summary of traditional use safety data in kratom users from Southeast Asia can be found in Table 4.1.4.A. The relevance of this data to the proposed NDI is as follows:

(b)(4)

(b)(4)

In a Malaysian study, the mitragynine content per kratom juice serving was calculated as approximately 50 mg. Of the participants, 40% reported using 1-3 glasses of juice per day while 60% reported using > 3 glasses of juice per day [31]. An equivalent dose of the proposed NDI (b)(4)

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Several other studies that examined effects of regular and long-term use of kratom found similar mitragynine dosage ranging from about 75 mg to 150 mg per day. The clinical chemistry and hematological parameters of regular kratom users (76.3-114.8 mg mitragynine/day) were compared to control (no history of kratom use). Inclusion criteria in this study also required that the regular kratom users had been using kratom ≥ 2 years and had no other illicit substance use. It was found that there were no hematological or clinical chemistry parameters that fell outside the acceptable range except for the level of LDL cholesterol which was elevated in both the kratom user and healthy control groups [32]. A follow up study was conducted that looked specifically at kratom use and its effect on lipid profiles, finding that kratom users have lower LDL cholesterol and lower total cholesterol. The amount of mitragynine ingested by kratom users in this study was not quantified. In this study, liver function tests were also undertaken and all results were within the normal range for both groups

(control and kratom users)[33]. Another study looking at long-term kratom users (> 20 years regular use) found little change in hematological, kidney, liver, thyroid, inflammatory, and/or gastrointestinal analytes. However, there were changes in lipids and a moderate elevation of homocysteine levels. A limitation of this study is the small sample size (N=13) and the fact that all but one participant was a tobacco smoker so results cannot be connected to only kratom use[34]. Concerning cardiotoxicity or cardiovascular issues associated with kratom use, several studies have been performed. In one study, where participants took an average of > 400 mg mitragynine per day (equivalent to 727 mg of the proposed NDI; 8-fold the proposed serving size) there was no significant change in electrocardiograms between kratom users and the control group[35]. Reviews looking at the cardiotoxicity of kratom are inconclusive as most often polysubstance use is present in most case reports[36]. Additional study looking at kratom use and its effect on the endocrine system showed that tea consumption with a dose of 76.23–94.15 mg per day did not alter the levels of testosterone or any other gonadotrophin[37]. A cross-sectional study looking at quality of life (QoL) indicators in regular kratom users found that regular and prolonged kratom use did not significantly affect quality of life (at a level of 75-100 mg mitragynine per day)[38]. A study looking at the effect of long-term moderate to high kratom use on cognition found that performance versus the control was comparable in all neuropsychological domains[39]. Limitations of the above-mentioned studies are that they are undertaken

Table 4.1.4.A Summary of Safety of Traditional Use of *Mitragyna speciosa* Aqueous Extract

Reference	Description	Dose	Length	# of Subjects and Study Type	Results	Determination of safety
[31]	Motives for using Kratom (*Mitragyna speciosa* Korth.) among regular users in Malaysia	40% < 150 mg mitragynine daily; 60% >150 mg mitragynine daily	40% 1-6 years; 60% ≥ 7 years	N=116 Self-report survey	Average amount of mitragynine found in one serving of kratom juice was 48.35 mg mitragynine.	Regular consumption of kratom did not lead to serious health problems or social functioning problems.
[32]	Evaluating the Hematological and Clinical-Chemistry Parameters of Kratom (*Mitragyna speciosa*) Users in Malaysia	Average daily consumption 76.3-114.8 mg mitragynine	41% 5 years; 59% > 5 years	N=77; 58 regular kratom users, 19 healthy controls Cross-sectional study	No significant differences in the hematological or clinical-chemistry paramers of kratom users versus the health control except for HDL cholesterol which was higher in the kratom use group. Long-term, high dose (>5 years, 76.3-114.8 mg mitragynine) did not alter the hematological and biochemical parameters.	Daily, chronic consumption of 114.8 mg mitragynine is not harmful or toxic in humans.
[33]	Lipid profile of regular kratom (*Mitragyna speciosa)* users in the	Average daily consumption 4.49 glasses of kratom juice.	44% 1-5 years; 56% >5 years	N =200; 100 kratom users, 100 healthy controls Cross-sectional study	Lower serum cholesterol and LDL in kraotm users but within the normal reference range. Liver parameters all within normal range.	Kratom consumption does not impair liver funtion or alter lipid levels outside the normal range.

	community setting					
[34]	Long-Term Effects of Kratom (*Mitragyna speciosa)* Use	≥ 87.54 mg of mitragynine daily	≥ 20 years	N=13 Cross-sectional pilot study	No significant alterations in liver, thyroid, inflammatory and gastrointestinal analytes. >3 glasses per day exhibited higher lipid values (except HDL cholesterol) and a moderate elevation of homocysteine.	Prolonged kratom use not associated with significant alterations in hematological and biochemical profiles. However indications of increased cardiovascular risk were seen; 12 of 13 participants also smokers so further investigation needed.
[35]	Is kratom (*Mitragyna speciosa* Korth.) use associated with ECG abnormalities? Electrocardiogram comparisons between regular kratom users and controls	Estimated daily intake of 434.28 mg mitragynine	50% 1-6 years; 50% >6 years	N=200; 100 kratom users, 100 control subjects	Prevelance of ECG abnormalities did not differ between kratom users (28%) and controls (32%). Higher incidence of sinus tachycardia (OR = 8.61) among kratom users. Borderline QTc intervals higher in kratom users but not difference between kratom and control for prolonged QTc interals.	No link between regular kraotm use and electrocardiographic abnormalities with an average use of 434.28 mg mitragynine per day.
[37]	Assessment of Gonadotrophins and Testosterone Hormone Levels in Regular *Mitragyna*	76.23-94.15 mg mitragynine daily (3.5 glasses kratom juice)	37% 1-5 years; 63% >5 years	N=19 Cross-sectional study	No suppresion of testosterone of follicle stimulating hormone (FSH) in blood. Any hematological and biochemical profile changes remained within the reference range.	Long-term kratom use does not impair testosterone, FSH, or leutinizing hormone (LH) at doses of 76.23-94.15 mg mitragynine daily.

	speciosa (Korth.) Users					
[38]	Effect of regular kratom (*Mitragyna speciosa* Korth.) use on quality of life of people who use kratom	NA	All kratom users >12 months	N=200; 100 kratom users, 100 healthy controls Cross-sectional study	No difference in social relationship-related QoL between kratom users and control. Changes in physical health-related QoL assocaited with longer term kratom use and higher kratom dependence scores. Psychological and enrironmental-related QoL changes correlated to increases in kratom dependence scale scores.	Long-term kratom use may increase the risk for changes in physical health related QoL indicators. Kratom dependence can influence psychological and environment-related QoL indicators. Kratom use, even long-term, does not effect social relationship-related QoL indicators.
[39]	Long-Term Cognitive Effects of Kratom (*Mitragyna speciosa* Korth.) Use	72.5-74.9 mg mitragynine daily	Mean duration of use: 88.1 months	N=95; 70 kratom users and 25 control particiapants Cambridge Neuropsychological Test Automated Battery used	The performance of kratom users versus control were comparable on all neuropsychological domains.	Even high intake (>3 glasses) of kratom juice did not impair motor, memory, attention, or executive function.

in primarily Malaysian subjects, so genetic differences are not accounted for. Additionally, subjects are male as it is not common for women to use kratom in Southeast Asia so no sex differences can be documented in traditional use data.

The results from investigation of long-term kratom use in the traditional setting indicate that moderate kratom use (<150 mg of mitragynine per day) does not appear to cause any long-term negative health effects. When kratom use in the

traditional setting goes above 3 glasses per day (>150 mg mitragynine) there was a greater incidence of changes in health parameters in all studies.

4.1.5. Adverse events associated with historically consumed material

While *Mitragyna speciosa* (kratom) has been used for centuries in its native Southeast Asia, the prevalence of use in the United States has begun to increase significantly since the 2010s. Using national survey data from 2019, the estimated prevalence of kratom use was 0.7% of the population (2.3 million)[40] while another survey from 2018-2019 put use prevalence at 0.8% of the population (2.6 million)[41]. Other reports of prevalence are much higher with an estimated 10-16 million kratom users in the United States[42].

Consumption of kratom in the US varies from traditional use. In Southeast Asia, the fresh leaves are picked from the tree and chewed, brewed, or dried. In the US, dried kratom leaf is imported for direct sale or post-processing into extracts or other edible products. Risks associated with use of dried kratom leaf include microbial contamination and heavy metal contamination which could lead to adverse health effects. A properly prepared extract, like the proposed NDI (b)(4) [redacted]. Table 4.1.5.A summarizes the case reports found in the literature.

Table 4.1.5.A. Case reports of kratom associated adverse events (2011-2024)

Reference	Subject	Dose; Concomitant Medications	Clinical Findings	Affected Organs	Comments
[43]	64-year-old male	Not specified but regular use; Jimsonweed, cannabinoids, tricyclic antidepressants, oxycodone	Seizure activity	Brain	Polysubstance use; jimsonweed known to produce seizures and coma
[44]	25-year-old male	2 weeks 14-21 g/day (280-420 mg mitragynine)	Jaundice and pruritus, drug-induced cholestatic injury	Liver	Well above recommended daily intake for this NDI
[45]	44-year-old male	Tincture for 1 year; concomitant opioid use	Severe primary hypothyroidism	Thyroid	Resolved within 15 months; dose unknown
[46]	58-year-old male	1 tablespoon daily; quetiapine and sertraline	Liver abnormalities	Liver	Unknown dose
[47]	26-year-old male	Ingestion of kratom 24 h prior; codeine	Cardiorespiratory arrest; death	Heart	Unknown dose
[48]	57-year-old female	10g daily for 1 yr	Bile-duct dilation; cholestatic liver injury	Liver	200 mg mitragynine/daily; no update provided
[49]	40s-year-old female	8 x 400mg capsules; full bottle of liquid kratom extract	Pinpoint pupils; altered mental status; hypoxia; respiratory depression	Lungs	Naloxone treatment improved symptoms; unknown dose
[50]	47-year-old male	3 weeks; THC and benzodiazepines	Cholestatic liver injury; jaundice	Liver	Unknown dose; symptoms resolved after cessation of kratom
[51]	44-year-old male	Unknown dose; Hydromorphone; olanazapine	Death	-	Hydromorphone blood levels 74 ng/mL; mitragynine blood levels 560 ng/mL; Olanazapine blood levels 240 ng/mL; No kratom dose information
[52]	35-year-old male	Kratom 2 yr; marijuana; paliperidone injection; lurasidone	Delusions	Brain	History of AUD, mood disorders; had stopped taking his antipsychotics; symptoms

					did not resolve despite 7 weeks of antipsychotic treatment
[53]	40s-year-old female	2-3 teaspoons (6 g) daily; buspirone; quetiapine	Tremors, clonus, diaphoresis, and confusion 2 days after Paxlovid administration	Brain	Symptoms resolved with lorazepam treatment; patient resumed daily treatment regimen
[54]	37-year-old male	12-14 g/day for two weeks; amitriptyline	Xerostomia, dry eyes, constipation	Liver	Symptoms resolved upon cessation of kratom
[55]	56-year-old male	No dose information 1 yr; preexisting liver conditions	Acute liver injury; jaundice	Liver	Plasma exchange allowed patient to be discharged
[56]	31-year-old male	Kratom tea for 2 weeks to aid in opiate withdrawal.	Drug-induced hepatitis secondary to kratom consumption.	Liver	Unknown dose. Hepatitis treated with N-acetylcysteine
[57]	38-year-old male patient	5 doses of Tylenol along with kratom.	Acute cholestatic liver injury	Liver	Unknown dose. Kratom was stopped, the patient improved clinically and biochemically
[58]	19-year-old male	Several pills of kratom per day for a few months; marijuana, lisdexamfetamine dimesylate, alprazolam; alcohol	Recurrent seizures	Brain	29 months after the initial seizure associated with structural brain lesions on magnetic resonance imaging.
[59]	32-year-old male	60 tablets over 1 week (as per recommended dose on the bottle) chronic low back pain he required occasional acetaminophen use.	Cholestatic pattern of liver injury	Liver	Upon discharge, liver enzymes had not normalized.
[60]	40-year-old female	Took kratom once a week for the preceding month prior to the initial presentation. Also,	Mixed cholestatic and hepatocellular liver injury	Liver	Unknown dose. Discharged on prednisone and ursodiol. Twenty-one

		she revealed the use of nettle leaf supplements for the past 4 - 5 years, as well as oral contraceptives.			weeks after the initial presentation, she was off all medication for more than 3 weeks
[61]	52-year-old male	Patient was on acetaminophen taking kratom for at least a couple of months.	Evidence of acute cholestatic hepatitis highly suspicious of DILI	Liver	Unknown dose. 2-week follow-up no signs and symptoms of clinical deterioration
[62]	27-year-old male	combination of mitragynine and quetiapine.	Hyperthermia and seizure-like activity.	-	Unknown dose.
[63]	47-year-old male	21 days no dosage information	Mixed hepatocellular/ cholestatic pattern DILI caused by kratom abnormal liver tests	Liver	Unknown dose. Nine months after his liver tests returned to normal, he took kratom again, and after a latency of 2 days he developed signs of DILI
[64]	37-year-old female	Consumption of kratom for 2 weeks before onset of symptoms.	Nausea, decreased appetite, fatigue, and two days of jaundice	Liver	Unknown dose. Patient's symptoms and jaundice improved quickly.
[65]	15-year-old female	45 x 500 mg were ingested as a suicide attempt	Dry mouth, dizziness, restlessness, palpitations, nausea, and vomiting	Heart	Hours after ingestion, the symptoms were resolved.
[66]	29-year-old male	Used kratom for back pain, stimulant and euphoric effects. Used up to 30 g three times a day for 3 months	Patient reported cravings and withdrawal symptoms whenever he stopped using kratom, including insomnia, anorexia, diarrhea, restlessness, worsening mood, worsening	Brain	Clonidine and hydroxyzine were given for management of withdrawal symptoms related to kratom use.

			anxiety, and thoughts of self-harm		
[67]	45-year-old male	Patient took an "entire bottle" of kratom a week prior to an emergency room visit. Previously used 6-8 kratom pills a day on an occasional basis	Psychosis, hallucinations, insomnia	Brain	Treated with haloperidol and diphenhydramine, discharged from hospital within two days
[68]	37-year-old female	3 capsules daily for 1 yr; amphetamines	Abdominal pain, nausea, vomiting, watery diarrhea, pancolitis, elevated liver enzymes, cholestasis, colitis, jaundice, acute kidney injury	Multiple Organ Failure	Treated with ursodiol, corticosteroids. Subtotal colectomy with end ileostomy performed in the 4th week of hospitalization. Discharged after 10 weeks of hospitalization. Despite aggressive supportive care, her cholestatic liver injury persisted. Seventeen weeks after presentation, she underwent successful orthotopic liver transplantation for subacute liver failure secondary to DILI. Her diarrhea resolved but renal function did not, and she was placed on dialysis with end stage renal disease
[69]	39-year-old female	Used kratom for a few months	Catatonic state, unable to move or speak, nausea	Brain	Unknown dose. Symptoms resolved spontaneously after 1 hour

[70]	28-year-old male	Dose unknown, used for 1 week.	Acute renal failure, myoclonic jerking, severe metabolic acidosis and hyperkalemia, rhabdomyolysis, and elevated liver enzymes	Kidney	Intubated, underwent hemodialysis. Renal function never returned to baseline and a permanent hemodialysis catheter was placed.
[71]	45-year-old female	Overdosed with kratom and presented with lethargy, confusion, transient hearing loss, and right lower extremity swelling and pain associated with weakness who was found to have elevated creatinine phosphokinase.	Rhabdomyolysis, compartment syndrome, multiorgan dysfunction including acute kidney injury, liver dysfunction, and cardiomyopathy.	Multiple Organ Failure	Patient underwent emergent fasciotomy and required hemodialysis. Renal and liver function subsequently improved
[72]	23-year-old male	Vaped and smoked marijuana daily. Within the previous month, he ingested kratom at a high dose of 30 g per day for 14 days. His last dose was 7 days before symptom onset.	Jaundice, diffuse itching, pale stools, dark urine, vague abdominal discomfort, mild weight loss, excessive fatigue, easy bruising, elevated total bilirubin and alkaline phosphatase, and canalicular cholestasis, mixed portal inflammation, and perivenular necrosis in liver. Diagnosed with hepatitis	Liver	Treated with ursodiol, cholestyramine and hydroxyzine and rifampin and recovered in 8 weeks.

[73]	62-year-old male	Patient had a history of taking large daily doses (unspecified) of kratom and chronic alcoholism	Hyponatremia, altered mental status and restlessness	Brain	Received 3% sodium chloride at 30 mL/h, supplemented. with magnesium sulfate, folic acid, and thiamine on Day 1 of hospitalization, replaced by desmopressin and 5% dextrose in water (D5W) on Day 2 and D5W only on day 3. Was discharged over the next week with stable serum sodium and osmolality.
[74]	23-year-old male	Took kratom recreationally for 2 weeks as a treatment for his post-COVID insomnia. Kratom tea was ingested in a concoction containing Coca-Cola and diphenhydramine cough syrup. Subject also consumed 27 standard alcoholic beverages/week	Fatigue and nausea which was soon followed by pruritus, dark urine and jaundice. Liver enzymes were elevated upon hospital admission	Liver	Unknown kratom dose and high weekly alcohol consumption. Administered IV fluids for a week and discharged. Stable 3 months after discharge.
[75]	61-year-old male	Patient took kratom daily for 4 months and also was on rosuvastatin	The subject exhibited hyperkalemia which abated 1 month after discontinuing kratom	Blood	Unknown kratom dose
[76]	36-year-old male	Subject was a cigarette smoker with a history of polysubstance abuse	Diagnosis of adult respiratory distress syndrome	Lung	Unknown kratom dose Subject was a cigarette smoker

In the reported cases, 73.5% of the patients are male with 44.1% of the symptoms presenting as liver injury. The second highest organ system involved in kratom-related intoxications is the brain at 23.5%. Of the case-reports, only 20.6% reported kratom as the only compound being taken, most often polysubstance use or other over-the-counter medications were being used. The above case reports detail the negative consequences associated with kratom use, but do not analyze the kratom product used for alkaloid content and/or contaminants, analyze the patient blood for total alkaloid content, and/or there was concomitant medication use. Due to this, letters to the editor have been sent requesting that kratom case reports be more thorough when publishing case reports[77]. It is also very difficult to prove direct causation between kratom consumption and the ill-effects reported, but this data does provide a basis to included necessary labeling and cautions on the label of the NDI that recommend an individual consult a healthcare professional if they are taking any medications or have any preexisting conditions prior to use of the NDI.

Kratom contains pharmacologically active alkaloids that may interact with other medications, leading to adverse reactions or altered therapeutic effects as described in case-reports. Individuals taking prescription medications, particularly those with central nervous system depressant or stimulant effects, should consult a healthcare professional before using kratom supplements to avoid potential drug interactions[78]-[79]. Mitragynine (b)(4)

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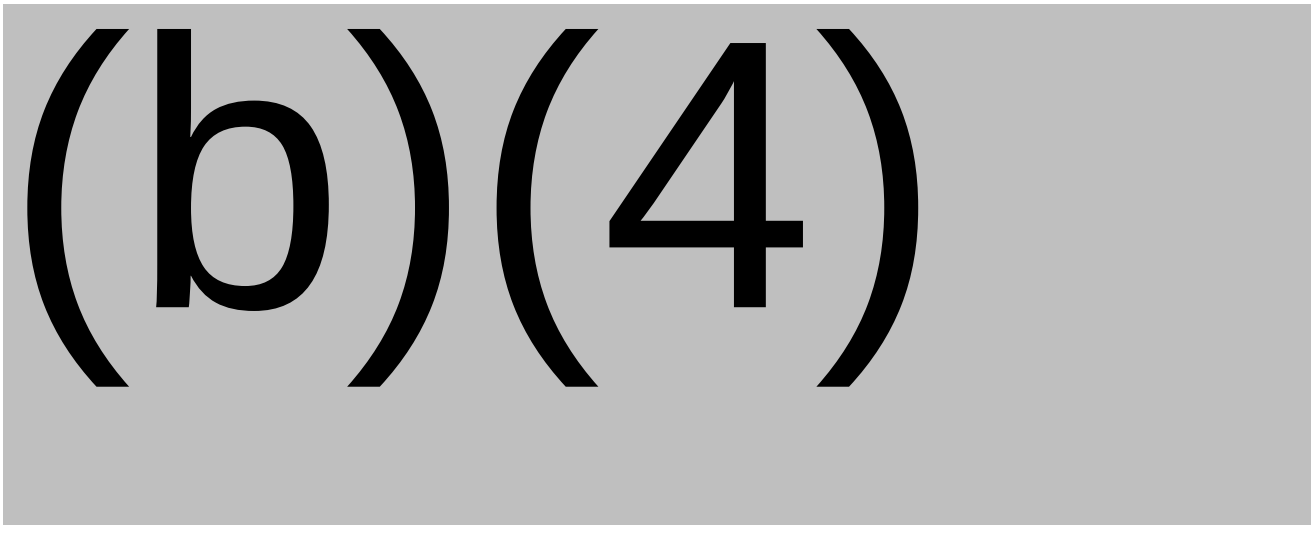
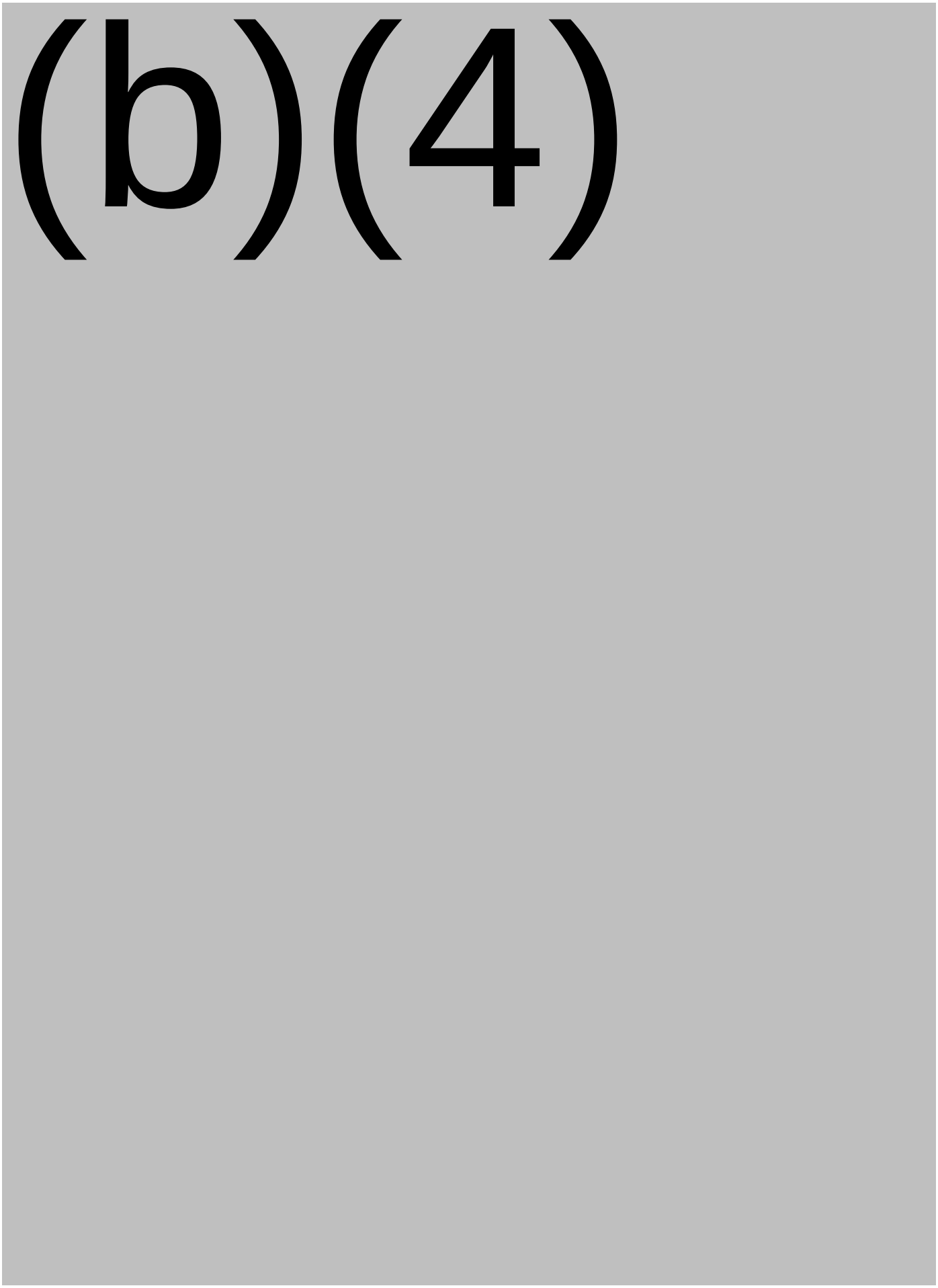
4.2. Other evidence of safety

4.2.1. Human Clinical Studies of *Mitragyna speciosa* aqueous extract

Two clinical studies have been conducted in the United States on healthy participants (Table 4.2.1.A). One study looked to characterize the pharmacokinetics of kratom alkaloids following a single oral dose (2 g of a 20 mg/g mitragynine leaf powder) brewed into a tea. In all participants that completed the study, the tea was well-tolerated and no severe adverse events occurred. In two participants (both female) that elected to withdraw from the study, nausea was encountered after dosing[81]. This study found differences in the pharmacokinetic parameters of alkaloids that have a 3*S* configuration versus a 3*R* configuration. The alkaloids with a 3*R* configuration (speciociliatine, mitraciliatine, isopaynantheine) have extended residence time, decreased clearance, and increased exposure/dose ratios as compared to the 3*S* configuration (mitragynine, paynantheine, speciogynine). These results indicate that a metabolic "soft spot" on the 3*S* alkaloids must become more difficult to access with the configuration change from *S* to *R.* These results were also seen in the preclinical pharmacokinetic study of kratom alkaloids in rats (Table 4.1.2.B.), indicating that rats are an adequate model for the pharmacokinetics of kratom alkaloids.



(b)(4)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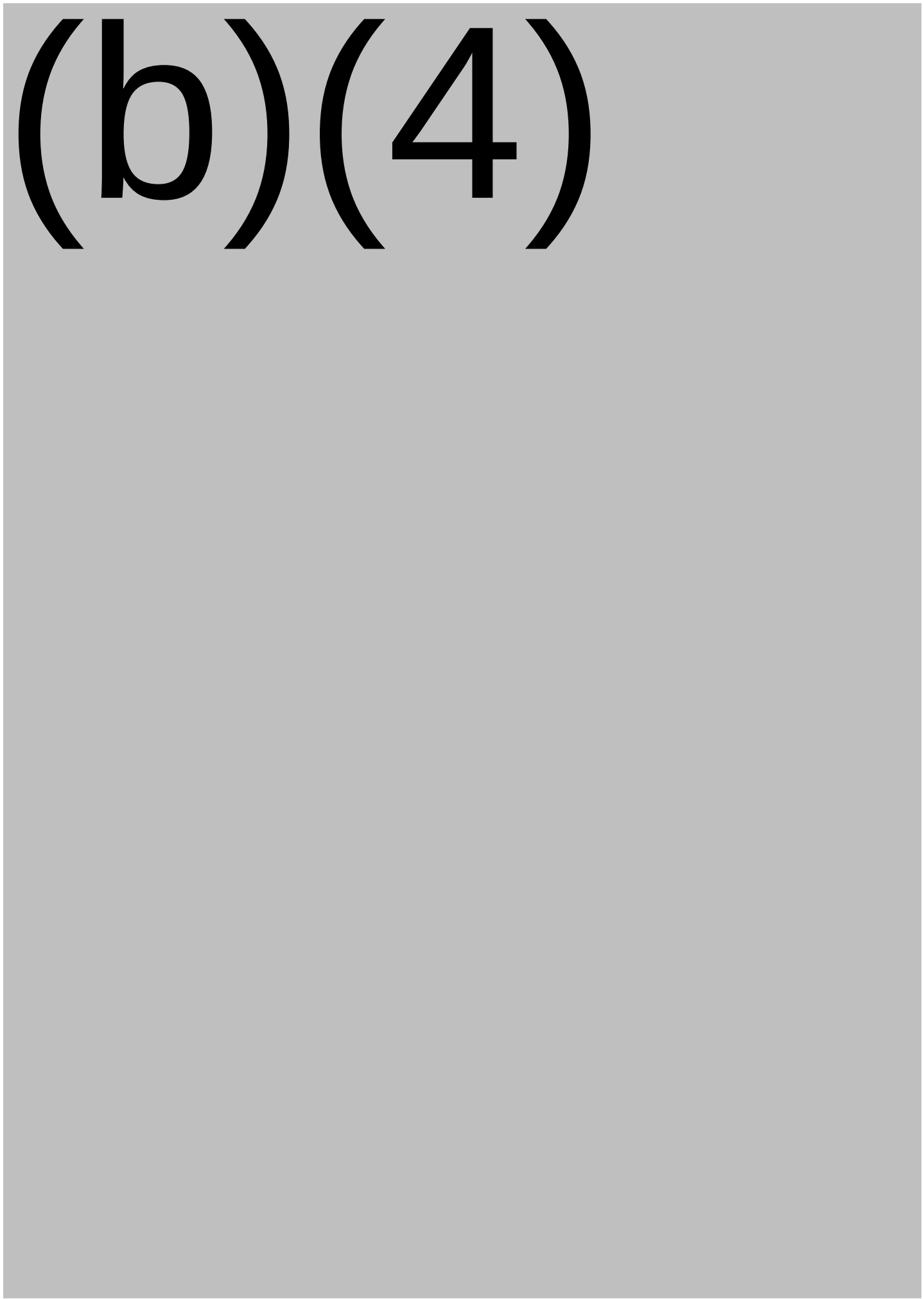
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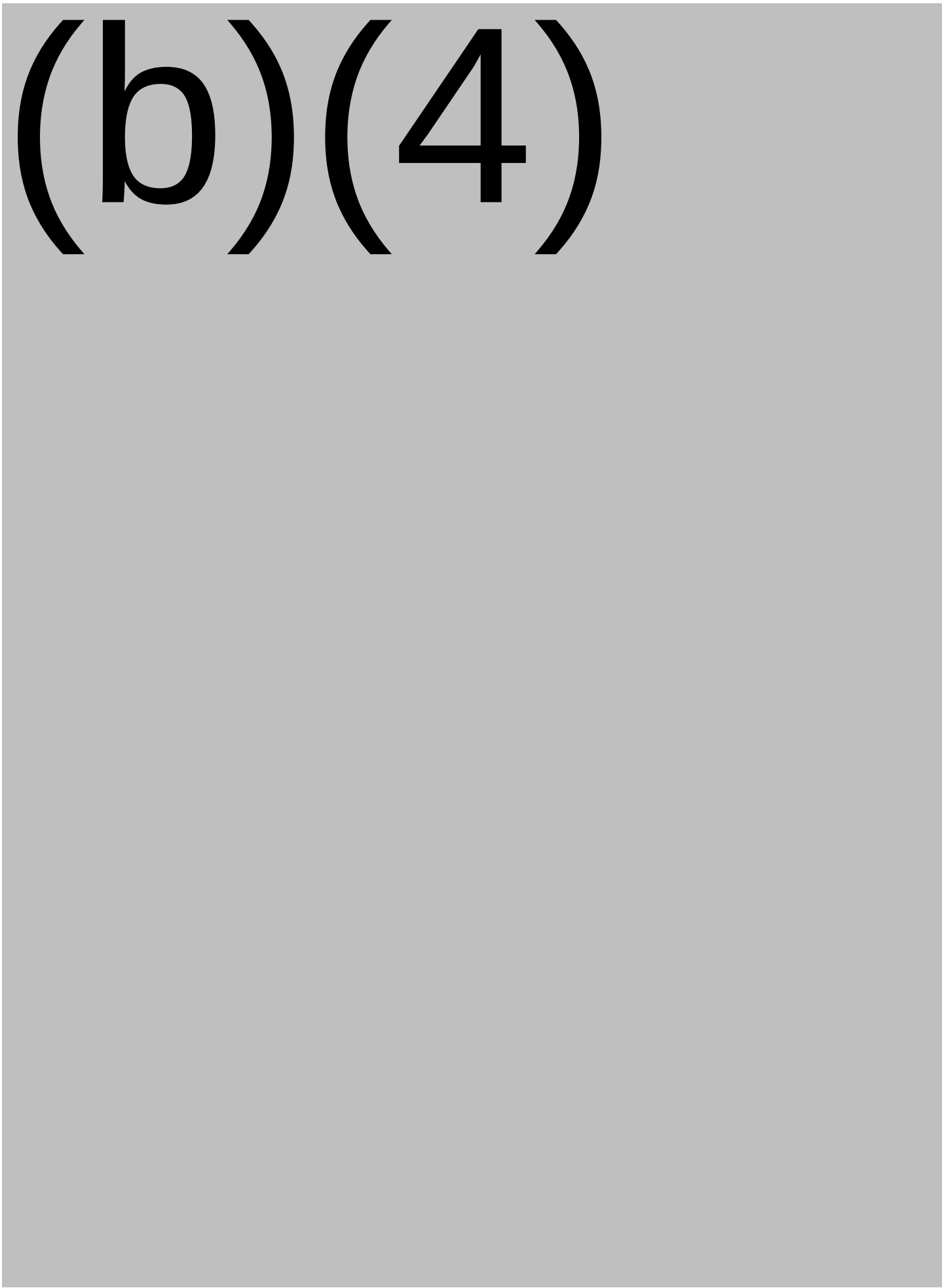
(b)(4)

(b)(4)

5. Basis For Concluding That the New Dietary Ingredient Will Reasonably Be Expected To Be Safe For Use in the Dietary Supplement (Required)

5.1. Determination of the No-Observed-Adverse-Effect-Level (NOAEL) or Lowest-Observed Adverse Effect Level (LOAEL)

The NOAEL was determined to be 150 mg/kg/bw/day of mitragynine in rats based on the study performed in 2023 by Hassan, et. al [92]. This is equivalent to 24.2 mg/kg bw/day of mitragynine in humans when using the well-established and widely accepted conversion factor of 6.2 to estimate the difference in body surface area between rats and humans[29].

5.2. Determination of safety factor

The safety factor being used for this application is 10 which is the default safety factor to be used in dose calculations[93]. No evidence exists that would support a lower or higher safety factor for the proposed NDI.

5.3. Determination of the Acceptable Daily Intake (ADI)

(b)(4)

5.5. Determination of margin of safety

(b)(4) .

5.6. Safety narrative and conclusion

The safety assessment provided herein of the NDI, *Mitragyna speciosa* leaf extract standardized to 75% mitragynine, is based in part on: (b)(4) .

6. Comments

6.1. Abuse Potential of *Mitragyna speciosa* extract

Chronic use of kratom has been associated with the development of tolerance, dependence, and withdrawal symptoms upon discontinuation. Withdrawal symptoms may include irritability, anxiety, insomnia, muscle aches, and cravings, resembling those observed with traditional opioids [94]. The report assessed the severity of pain and sleep problems during kratom cessation among regular kratom users. (b)(4)

A recent report from top scientists in the kratom field summarized the current thinking on kratom withdrawal and found that most kratom users who report dependence or withdrawal find it mild, tolerable, and self-manageable although risk of more severe symptoms increases with higher dose amounts and dose frequencies [95]. Yet, to fully educate and inform consumers, labeling for the proposed NDI (b)(4) .

(b)(4)

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U.S. FOOD & DRUG ADMINISTRATION

September 19, 2024

Todd Underwood
President
TNT Manufacturing dba Mitwellness
2857 SW US-40 Hwy
Blue Springs, Missouri 64015

Dear Todd Underwood:

Questions have arisen during FDA's review of your new dietary ingredient (NDI) notification concerning your new ingredient, "*Mitragyna speciosa* leaf extract standardized to 75% mitragynine", that you intend to market as a bulk dietary ingredient, about matters that, if unresolved, are likely to cause FDA to object to the marketing of your ingredient. Please provide an amendment addressing the following issues, including the appropriate documentation.

190.6 Concern:

Your notification does not include a copy of the following notification supporting documents, as required by 21 CFR 190.6(b)(4):

- **Reference 11.** Harun N, Kamaruzaman NA, Mohamed Sofian Z, Hassan Z: Mini review: Potential therapeutic values of mitragynine as an opioid substitution therapy. Neurosci Lett 2022, 773:136500.

- **Reference 16.** Obeng S, León F, Patel A, Restrepo L, Gamez-Jimenez L, Zuarth Gonzalez J, Pallares V, Mottinelli M, Lopera-Londoño C, McCurdy C et al: Serotonin 5-HT1A Receptor Activity of Kratom Alkaloids Mitragynine, Paynantheine, and Speciogynine. The FASEB Journal 2021, 35(S1).
    - **Only the abstract was provided for this reference. Please provide the full text reference.**

- **Reference 18.** Reeve ME, Obeng S, Oyola FL, Behnke M, Restrepo LF, Patel A, Ho NP, Williamson MR, Gamez Jimenez LR, McCurdy CR: The Adrenergic a2 Receptor-Mediated Discriminative-Stimulus Effects of Mitragynine, the Primary Alkaloid in Kratom (Mitragyna Speciosa) in Rats. The FASEB Journal 2020, 34(S1):1-1.
    - **Only the abstract was provided for this reference. Please provide the full text reference.**

- **Reference 77.** Smith KE, Dunn KE, Epstein DH, Feldman JD, Garcia-Romeu A, Grundmann O, Henningfield JE, McCurdy CR, Rogers JM, Schriefer D et al: Need for clarity and context in case reports on kratom use, assessment, and intervention. Subst Abus 2022, 43(1):1221-1224.

Please provide complete copies of these notification supporting documents with complete English translations. This information is requested to confirm that the notification meets the 21 CFR 190.6 requirements.

Because FDA is obligated to complete its review and send a response to your notification within 75 days of the filing date of September 16, 2024, I urge you to review these concerns and then upload an amendment to your notification within three business days. If you do not understand how to document the concerns discussed, FDA is prepared to make the scientists who are reviewing your notification available to you and/or your scientific staff during a telephone conference to help you understand our concerns and discuss responses that might address our concerns.

Note that any amendment will have to comply with all requirements of 21 CFR 190.6 including the requirement that it consist of a signed original document. FDA could consider the amendment a substantive amendment, which would result in resetting the original filing date for your notification (see 21 CFR 190.6(d)).

If you have any questions about this request or how to document your response, email us at NDITEAM@fda.hhs.gov.

Best regards,

Markeesa Scales, MPH
Identity and Status Branch
Division of Research and Evaluation
Office of Dietary Supplement Programs
Center for Food Safety and Applied Nutrition

20 September 2024

Markeesa Scales, MPH
Identity and Status Branch
Division of Research and Evaluation
Office of Dietary Supplement Programs
Center for Food Safety and Applied Nutrition

Re: NDI 1361 RFMI

Dear Markeesa,

TNT Manufacturing d/b/a MitWellness has received the request for more information regarding missing citations in NDI 1361. Below is the detailed response for each item.

- **Reference 11 has been added to the additional attachments section of the NDI.** (Ref 11. Harun N, Kamaruzaman NA, Mohamed Sofian Z, Hassan Z: Mini review: Potential therapeutic values of mitragynine as an opioid substitution therapy. Neurosci Lett 2022, 773:136500.)

- **Reference 77 has been added to the additional attachments section of the NDI.** (Ref 77. Smith KE, Dunn KE, Epstein DH, Feldman JD, Garcia-Romeu A, Grundmann O, Henningfield JE, McCurdy CR, Rogers JM, Schriefer D et al: Need for clarity and context in case reports on kratom use, assessment, and intervention. Subst Abus 2022, 43(1):1221-1224.)

- **References 16 and 18 only consist of a published abstract in the FASEB journal.** These are the abstracts of presentations given at a conference. There is no full-text reference and only information from the abstract was used as support in the NDI.

We hope that this satisfies section 21 CFR 190.6. We consider this letter to contain confidential commercial information and request it that it be redacted in its entirety from the public record of the NDIN that will be placed on dockets. Please reach out for further information if needed.

Sincerely,

Todd Underwood
President
TNT Manufacturing d/b/a Mitwellness
2857 SW US-40 Hwy
Blue Springs, Missouri 64015