Project Seven-0

June 24, 2025

New York | Washington, D.C. | London
+1 212.532.3651 | www.marwoodgroup.com

Table Of Contents And Project Overview

Table Of Contents

Project Overview

The industry advocacy organization, HART sought an independent analysis addressed to federal and state legislators on the impact of expanded access to 7-hydroxymitragynine (7-OH)

- The client seeks to utilize Marwood's value story to defend their efforts to combat restriction of 7-hydroxymitragynine sales (i.e., not scheduled, not restricted in place of sale and not restricted in volume of purchase)
- The output is a value story informed by an overview of the state & federal policy landscape and analysis of the scientific literature in the space

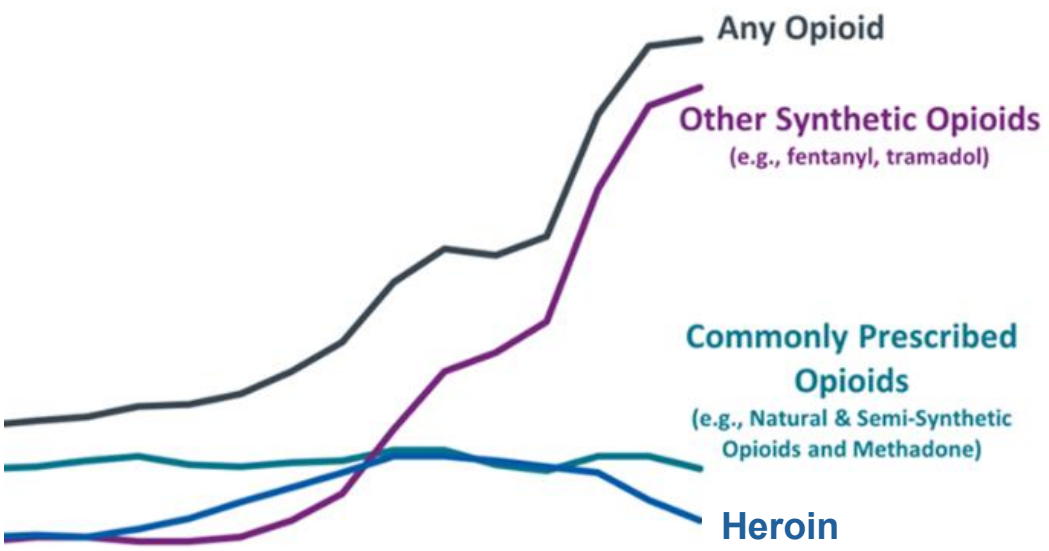
Disclaimer

Marwood does not endorse or recommend 7-hydroxymitragynine. The slide may contain general information relating to various medical conditions and their treatment. Such information is provided for informational purposes only and is not meant to be a substitute for advice provided by a doctor or other qualified health care professional. Patients should not use the information contained herein for diagnosing a health or fitness problem or disease. Patients should always consult with a doctor or other health care professional for medical advice or information about diagnosis and treatment.

1 | Value Story

In An Epidemic Characterized By Three Successive Waves Of Abuse-Related Deaths, The Alkaloid 7-Hydroxymitragynine (7-OH) Is Structurally Distinct From Opioids

Opioid-involved Deaths Have Increased Substantially In 3 Successive Waves Since The 1990s



7-OH Has A Low Adverse Event Incidence; Particularly Compared To Opioids

There is limited preclinical or clinical data connecting 7-OH with overdose deaths, in sharp contrast to opioids

- A scan of the FDA Adverse Event Reporting System since 2023 reveals no deaths associated with 7-OH alone (a mere 2 cases when including polydrug overdose deaths) despite upwards of 1 million consumers; >100-fold less per 100,00 lives than the >3 million overdose deaths associated with synthetic opioids in that time period[1]
- 7-OH has a low likelihood to molecularly signal respiratory depression – a cause of mortality among other opioids[2]
- 7-OH in poly-drug abuse, a contributor to overdose deaths, is relatively minimal in comparison to synthetic opioids like fentanyl and other natural and semi-synthetic opioids[3]

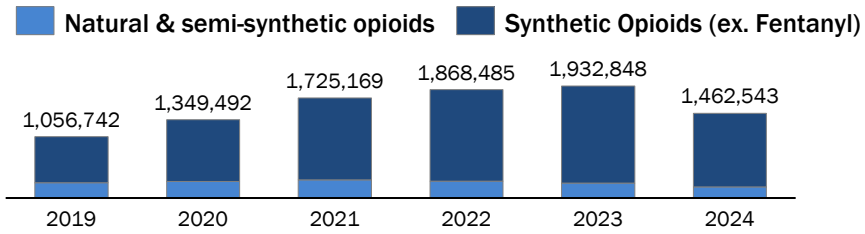
Sources: 1) FDA.gov **2)** Todd et al. (2020) Nature 10(19158)

3) Krotulski et al. Temple University. Presentation. https://www.cfsre.org/images/K52_AKrotulski_Polydrug_Use_Tox_Perspective_REDUCED.pdf

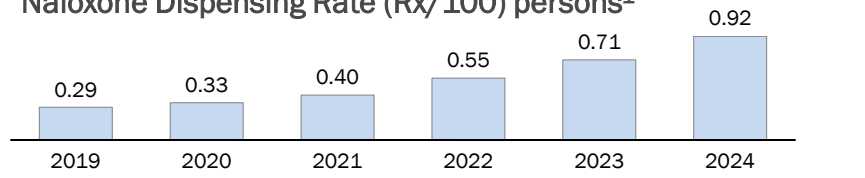
7-OH Consumption Has Increased Concurrent To A Decrease In Opioid Overdose Deaths; Trends In Naloxone Availability Alone Are Insufficient To Explain This Trend

National Opioid Overdose Deaths Have Declined Since 2023

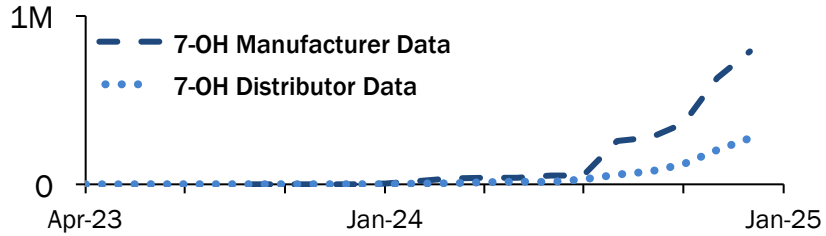
Opioid Overdose Deaths[1]



Naloxone Dispensing Rate (Rx/100) persons[1]



7-OH Consumers Per Month[2] (Estimated From Units)



7-OH Sales Have Increased Opioid-Related Deaths Have Declined

Overdose control and substitution may both be contributing to a decline in opioid-related deaths

- Naloxone dispensing alone has been insufficient to explain the sudden reversal in opioid deaths
- Illegally manufactured fentanyl has declined in quantity and quality, due to increased enforcement
- As the quality of fentanyl has declined under pressure, researchers note that users are seeking out alternatives[3]

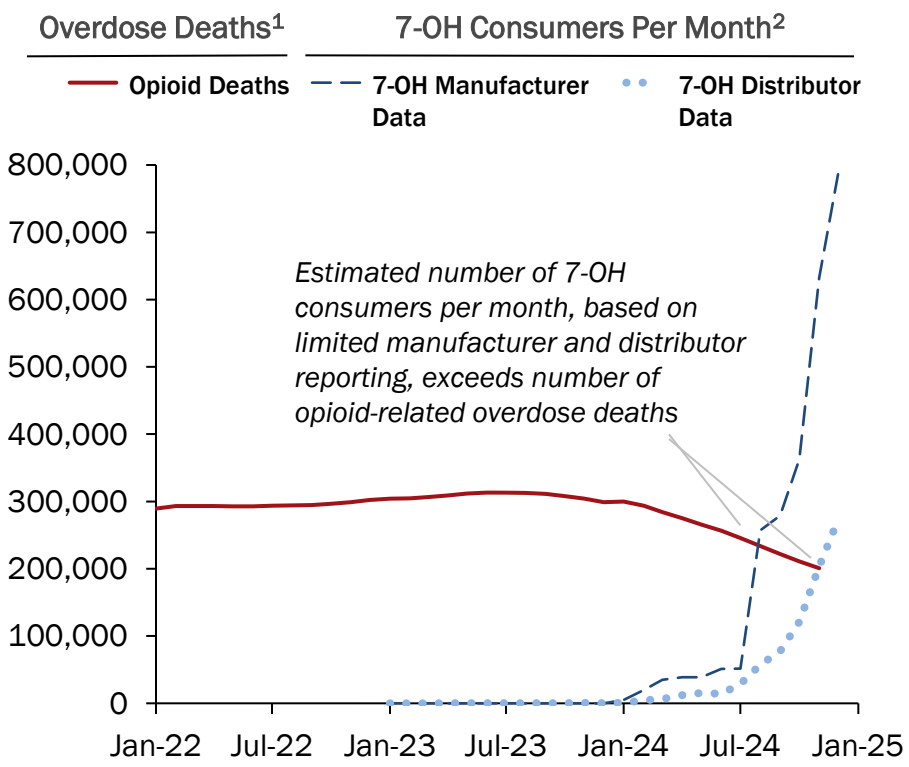
7-OH provides an alternative to fentanyl and other opioids, without the withdrawal symptoms seen with Kratom, in preclinical studies

- 7-OH produces comparable pain control to strong opioids such as morphine[4]
- 7-OH exhibits cross-tolerance with other mu-opioid receptor agonists; this would indicate opioid users could cross over to 7-OH[4]
- 7-OH is a partial opioid agonist that binds to mu-opioid and other receptors distinctly from opioids such as morphine and fentanyl[5]

Sources: 1) CDC.gov **2)** Estimate based on limited reporting of 7-OH manufacturer/distributor data **3)** npr.org/transcripts/1210938287 **4)** Matsumoto et al. (2005) Life Sciences 78 (1): 2-7. **5)** Todd et al. (2020) Nature 10(19158)

7-OH Consumption Has Increased Concurrent To A Decrease In Opioid Overdose Deaths; Testimonials Concur With Studies On 7-OH As A Substitute For Powerful Opioid Agonists

National Opioid Overdose Deaths[1] Have Declined; 7-OH Doses Have Increased, Since 2023



Testimonials – An Alternative To Street Drugs

7-OH is the only reason I didn't go to the streets. I could be dead from a fentanyl overdose. Banning this would be killing a lot of people. [4]

Since I found 7-OH I always have it to go to instead of the hard drugs... [it] has help me and so many others, having a viable option to turn to. [3]

7-OH makes my life manageable and my addiction tameable. It's just like taking suboxone once daily. [4]

7-OH saves [lives]! [It has] kept me drug free and a functioning member of society for years now...I had a crazy dope addiction... it worked for me. [4]

7-OH isn't kratom...I've been taking it for over two years, and it has kept me clean. [4]

So easy to taper off and withdrawal is child's play compared to fentanyl. [4]

Sources: **1)** CDC.gov **2)** Estimate based on limited reporting of 7-OH manufacturer/distributor data; **3)** Industry-provided testimonials; **4)** Marwood-identified testimonials from internet blog sites.

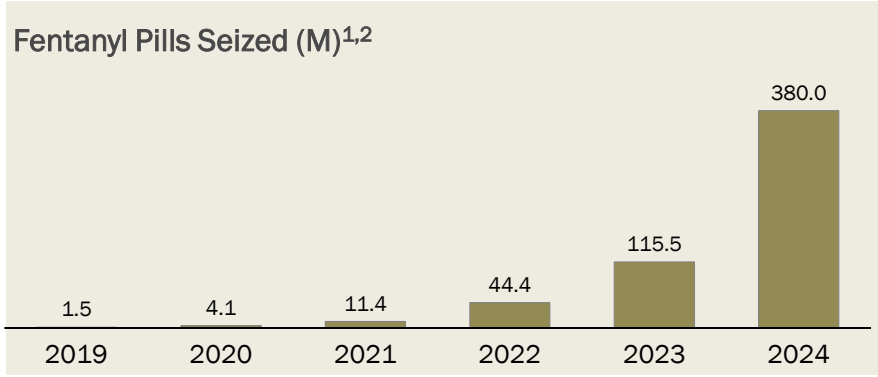
Marwood does not endorse or recommend 7-hydroxymitraginine. The slide may contain general information relating to various medical conditions and their treatment. Such information is provided for informational purposes only and is not meant to be a substitute for advice provided by a doctor or other qualified health care professional. Patients should not use the information contained herein for diagnosing a health or fitness problem or disease. Patients should always consult with a doctor or other health care professional for medical advice or information about diagnosis and treatment.

Strictly Manufactured, Dosed And Labeled 7-OH Is A Standardized Alternative To Illegally Manufactured Fentanyl Products

Laced Synthetic Opioids Are A Growing Threat To Public Health

Constrained supply has led to inconsistently formulated and often laced illegal fentanyl products

- >40% of illegally manufactured fentanyl products contain a potentially fatal dose[1]
- With expanding seizures, reduced fentanyl supply has led to an increasing number of illicit drug mixtures
  - The DEA has reported widespread threat of fentanyl mixed with non-opioid sedatives such as xylazine[1]



7-OH Manufacturers Provide A Standardized Alternative

The 7-OH industry seeks consistent and compliant manufacturing, labeling and sales, maintaining access to those most in need

- Holistic Alternative Recovery Trust (HART) member companies offer to comply with all laws and regulations applicable to the marketing, distribution and sale of 7-OH:
  - **Good Manufacturing Practices (GMP)** for dietary supplements to ensure products are free from contaminants and consistently meet quality standards
  - **Testing** to verify the consistency, purity, and potency of 7-OH products, with test results made publicly available.
  - **Strict labeling and safe packaging** of 7-OH products to include labeling of 7-OH content, recommended serving sizes, daily intake limit recommendations, appropriate warnings, and usage instructions as well as child safety packaging
  - **Health-related claims substantiated** by credible scientific evidence and complying with FTC truth-in advertising requirements

Sources: 1) DEA.gov **2)** NIDA.NIH.GOV

Marwood does not endorse or recommend 7-hydroxymitraginine. The slide may contain general information relating to various medical conditions and their treatment. Such information is provided for informational purposes only and is not meant to be a substitute for advice provided by a doctor or other qualified health care professional. Patients should not use the information contained herein for diagnosing a health or fitness problem or disease. Patients should always consult with a doctor or other health care professional for medical advice or information about diagnosis and treatment.

2 | Federal Regulatory And Legislative Analysis

Internal Background Materials

Federal Action On 7-OH And Its Derived Source, Kratom, Has Been Limited, Although Prior Actions Indicated Headwinds For Both Products

Federal action on 7-OH and its source, Kratom, has been muted to date, although prior actions have indicated headwinds on the semi-synthetic derivative and leaf

- In 2016, DEA published notice of its intent to place mitragynine and 7-hydroxymitragynine in Schedule I on an emergency basis, which would have criminalized possession of kratom and made distribution a felony
  - However, after receiving numerous comments from some members of Congress, advocacy groups, and others, DEA withdrew that notice
  - DEA has listed kratom as a Drug and Chemical of Concern but to date has not exercised its authority to schedule kratom or its active compounds under the CSA.
- FDA has approved no drug products containing kratom, mitragynine, or 7-hydroxymitragynine
  - FDA has also taken the position that kratom is an unapproved new dietary ingredient and therefore may not be marketed in the United States as either a nutritional supplement or a food additive
    - Under the Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended, the Food and Drug Administration (FDA) may regulate drugs and dietary supplements sold in the United States.
  - In February 2025 the FDA issued an import alert regarding kratom products
    - The alert included a “Red List” of companies importing kratom, where inspectors could detain product without physical examination
    - FDA has also seized kratom products manufactured in the United States, including an April 2023 seizure of kratom products worth approximately $3 million from an Oklahoma company
- In January 2024, the FDA issued a Grant Opportunity notice to study the human abuse potential of botanical kratom

The DEA Withdrew Its Notice To Schedule Kratom Derived Products In 2016 Due To Significant Stakeholder Pushback

Marwood believes the DEA proposed to temporarily reclassify kratom as a Schedule 1 drug, but withdrew its notice due to significant stakeholder pushback

- In August 2016, the Drug Enforcement Agency (DEA) proposed to temporarily reclassify kratom as a Schedule I drug
  - Schedule I is the most strict classification, and is typically reserved for drugs with a high propensity for abuse, and has no medical purpose (usually defines as FDA approval for a particular disease)
  - Some Schedule I drugs are not particularly addictive, such as cannabis
  - Cocaine is highly addictive, but is classified as Schedule II because it was historically used as a local anesthetic in dental surgery
- The DEA issued its proposal on the basis that it needed to determine if kratom products might pose "an imminent hazard to public safety"
  - Prior to this the product had been regulated as a herbal product by the FDA and therefore considered to be legal in most states
  - Emergency scheduling would have likely lasted 2 years, with the option for a one-year extension.
- Following the DEA's proposal there was public pushback and even calls on Congress to over rule the agency on its plans
- In October 2016, the DEA withdrew its notice and solicited additional public comment
- Opposition to scheduling was led by American Kratom Association and the Botanical Educational Alliance, and a petition with over 100,000 signatures was sent to the White House
  - Supporters claim that kratom is much less addictive than prescription opioids and submitted many testimonials from users who described the beneficial effects of kratom
  - A letter signed by 50 members of Congress, led by Mark Pocan (D-WI) and Matt Salmon (R-AZ) was sent to the head of the DEA requesting the agency delay any decision banning kratom
- There has been no further action by the DEA to schedule kratom, although it is listed as a "Drug and Chemical of Concern"

The DEA Was Planning To Employ The Eight Factor Test To Examine Kratom Products

Marwood believes that the DEA was planning to employ the "Eight Factor Test" to examine kratom products

- The "Eight Factor Test", examines data on a drug's potential for abuse, its pharmacology, and its potential risks
  - Factor 1: Actual or relative potential for abuse
  - Factor 2: Scientific evidence of pharmacological effect
  - Factor 3: Current state of scientific knowledge
  - Factor 4: History and Current Patterns of Abuse
  - Factor 5: The Scope, Significance and Duration of abuse
  - Factor 6: What, if any, Risk is there to the Public Health
  - Factor 7: The psychic or physiological dependence liability
  - Factor 8: Is the substance or any of its components scheduled
- Factors 1, 4 and 5 are required to be considered for a determination of temporary scheduling
- Among other factors the DEA cited an increase in seizures associated with recreational use of kratom
  - Seizures are a known side effect of opioids in some people
- The DEA also noted that users report dose-dependent psychoactive effects including euphoria, simultaneous stimulation and relaxation, analgesia, vivid dreams, and sedation.
  - In addition, the DEA noted that addiction or dependence and withdrawal have been documented with long-term, regular use of kratom
  - Another concern was the wide variability in dose of the active ingredients in kratom products, which could potentially lead to unexpected effects

The FDA Considers Kratom Products To Be An Unsafe Food Additive Within The Meaning Of Section 409, And Therefore Is Considered Adulterated Under Section 402(a)(2)(c)(i)

Marwood believes that the FDA has determined that kratom is not dietary supplement

- In 2018, Commissioner Gottlieb issued a statement concerning kratom
  - He discussed a new analysis that supported the idea that mitragynine is a mu opioid receptor agonist
- The FDA notes that the two main active ingredients of kratom, mitragynine and 7-hydroxymitragynine are not components of any legally marketed drug in the U.S.
  - Further, the FDA determined that kratom is a new dietary ingredient
  - Information is lacking as to whether there is sufficient data to establish that these ingredients do not pose a significant or unreasonable risk of illness or injury
  - The FDA therefore considers dietary supplements containing kratom products to be adulterated under the meaning of the Food Drug & Cosmetic Act
  - The FDA considers kratom products to be an unsafe food additive within the meaning of section 409, and therefore is considered adulterated under section 402(a)(2)(C)(i)
- The FDA considers kratom to be not lawfully marketed in the USA
- In February 2025 the FDA issued an import alert regarding kratom products
  - The alert included a “Red List” of companies importing kratom, where inspectors could detain product without physical examination
- In January 2024, the FDA issued a Grant Opportunity notice to study the human abuse potential of botanical kratom
  - The grant had a budget of $2 million

Congressional Proposals To Protect Access To Kratom Have Stalled

Congressional action to protect access to Kratom have stalled

- In October 2023, members introduced essentially identical bills in both the House and the Senate to "protect access to kratom"
  - Members introduced similar bills in the House and the Senate in the 117th Congress
  - These bills would neither ban kratom nor impose new regulations on kratom
    - Instead, the bills would direct the HHS Secretary to gather information about kratom and would limit the Secretary's authority to impose regulations on kratom
    - The bills would require the Secretary to hold at least one public hearing to discuss the safety of kratom products
    - That hearing would have to cover several specified topics, including any potential benefits of kratom usage and any adverse health impacts of a kratom ban
    - The bills would also require the Secretary to establish a task force to coordinate and report on federally funded kratom-related research
    - Before promulgating any new rule regulating kratom, the Secretary would have to follow procedures for formal rulemaking and to have public, in-person hearings
  - The bills would prohibit the Secretary from:
    - Imposing requirements on kratom that are more restrictive than those for foods, dietary supplements, or dietary ingredients under the FD&C act;
    - Requiring kratom to follow the notification requirements for new dietary ingredients
    - Using certain specified grounds to treat kratom as an adulterated dietary supplement
    - Enforcing any import alert for kratom products absent evidence that the particular product is adulterated
    - Each bill contains a nonpreemption provision, which would leave existing state laws—whether banning kratom or regulating it—in place

3 | State Regulatory And Legislative Overview

Internal Background Materials

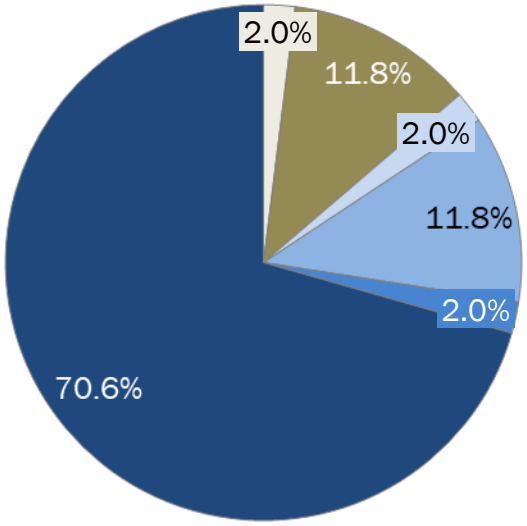
State Regulation Is Largely Of Kratom, Given The Recency Of 7-OH Products, Following Several Major Themes Around Age Restriction, Adulteration, Marketing And Labeling

State regulation of Kratom And 7-OH follows a number of themes

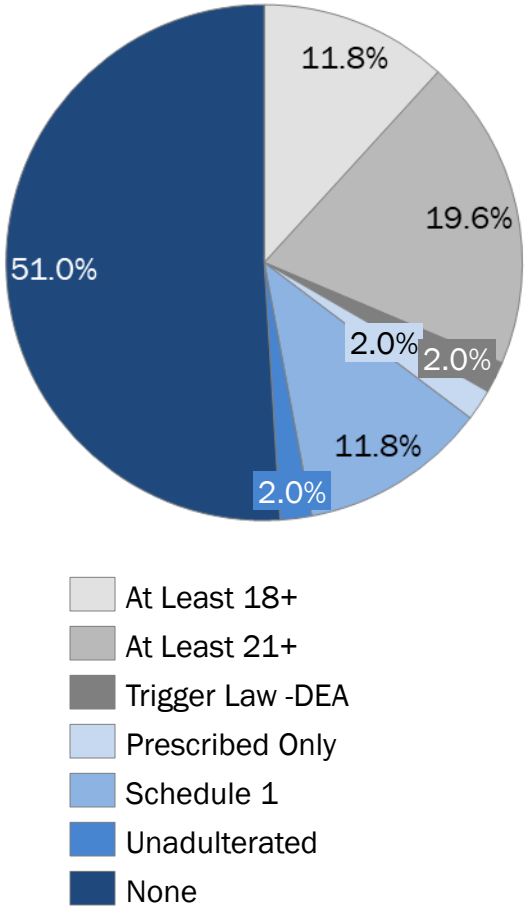
- Age restrictions to persons under 18 or 21 years of age
- Marketing to children
- Adulteration and contamination with non-kratom substances
- Strength, which is most relevant to 7-OH, in limiting concentration to a maximum of 1-2%
- Labeling with directions for safe use, warnings, manufacturer or distributor information, alkaloid (7-OH) content, ingredients and/or factual basis in representation
- Testing and sampling laws confirming the items on the label
- Registration and permitting of Kratom sellers
- Synthetic alkaloid laws which in some cases include extracts of the Kratom leaf itself (i.e., 7-OH)
- Local authority allowances, wherein localities can adopt stricter control of Kratom
- Private rights of actions permitting individuals harmed by violations of their Kratom laws to bring private civil action for damages
- Tax law providing for tax on Kratom

While Legislation Specific To 7-OH Is Only Found In A Quarter Of States, A Risk Of Current Regulation Or Pending 7-OH Legislation Is Found In Over Half Of States

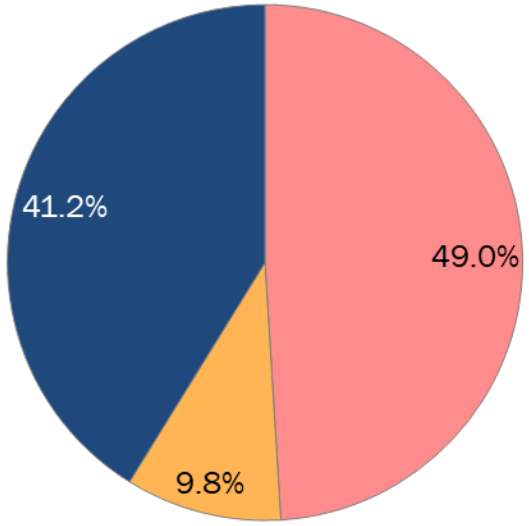
Significant State Restrictions on 7-OH



State Restrictions on Kratom



7-OH At Risk Of Current Regulation Or Pending Legislation



State Regulation And Pending Legislation (AL – IL)

State Regulation & Pending Legislation					
State	7-OH Regulation	Kratom	Proposed Legislation	Impact of Pending On 7-OH	At Risk of 7-OH Restriction*
Alabama	Schedule 1	Schedule 1	None		High
Alaska	None	None	None		Low
Arizona	<2% 7-OH	Unadulterated	None		High
Arkansas	Schedule 1	Schedule 1	Pending	From Schedule 1 to <2%	High
California	None	None	Pending	At Least 21+	Low
Colorado	None	At Least 21+	Pending	Limit 7-OH Concentration	Moderate
Connecticut	None	None	Pending	At Least 21+	Low
Delaware	None	None	None		Low
District of Columbia	Schedule 1	Schedule 1	None		High
Florida	None	At Least 21+	Pending	Specific requirements	Moderate
Georgia	Unadulterated	At Least 21+	Pending	Registration	High
Hawaii	None	None	Pending	At Least 18+	Low
Idaho	None	None	None		Low
Illinois	None	At Least 18+	Pending	Unadulterated; Schedule 3	Moderate

State Regulation And Pending Legislation (IN – NV)

State Regulation & Pending Legislation					
State	7-OH Regulation	Kratom	Proposed Legislation	Impact of Pending On 7-OH	At Risk of 7-OH Restriction*
Indiana	Schedule 1	Schedule 1	Pending	At Least 21+	High
Iowa	None	None	Pending	<2%	High
Kansas	None	None	Pending	unadulterated	High
Kentucky	<2% 7-OH	At Least 21+	Pending	<2%	High
Louisiana	None	Trigger Law -DEA	Pending		Low
Maine	None	None	None		Low
Maryland	<2% 7-OH	At Least 21+	Pending		High
Massachusetts	None	None	Pending	Unadulterated	High
Michigan	None	None	None		Low
Minnesota	None	At Least 18+	None		Low
Mississippi	None	None	Pending	Schedule 3	High
Missouri	None	None	Pending	unadulterated	High
Montana	None	None	Pending	At Least 18+	Low
Nebraska	None	None	Pending	Schedule 1	High
Nevada	None	At Least 18+	Pending	Registration	Low

State Regulation And Pending Legislation (NH - TX)

State Regulation & Pending Legislation					
State	7-OH Regulation	Kratom	Proposed Legislation	Impact of Pending On 7-OH	At Risk of 7-OH Restriction*
New Hampshire	None	None	None		Low
New Jersey	None	None	Pending	Unadultered	High
New Mexico	None	None	None		Low
New York	None	None	Pending	Schedule 1	High
North Carolina	None	None	Pending	Schedule VI	High
North Dakota	None	None	Pending	Schedule 1	High
Ohio	None	None	None		Low
Oklahoma	<1% 7-OH	At Least 18+	Pending		High
Oregon	None	At Least 21+	None		Low
Pennsylvania	None	None	Pending	At Least 21+	Low
Rhode Island	Schedule 1	Schedule 1	Pending	Schedule 1	High
South Carolina	None	None	Pending	Unadultered	Moderate
South Dakota	<2% 7-OH	At Least 21+	None		High
Tennessee	None	At Least 21+	None	Ban	Moderate
Texas	<2% 7-OH	At Least 18+	Pending	Penalty Group 1	High

State Regulation And Pending Legislation (TX - WY)

State Regulation & Pending Legislation					
State	7-OH Regulation	Kratom	Proposed Legislation	Impact of Pending On 7-OH	At Risk of 7-OH Restriction*
Texas	<2% 7-OH	At Least 18+	Pending	Penalty Group 1	High
Utah	<2% 7-OH	At Least 18+	Pending	Compounded	High
Vermont	Prescribed Only	Prescribed Only	Pending	Registry	High
Virginia	None	At Least 21+	None		Low
Washington	None	None	None		Low
West Virginia	None	At Least 21+	Pending		Low
Wisconsin	Schedule 1	Schedule 1	Pending		High
Wyoming	None	None	None		Low

4 | Scientific Viewpoint

Internal Background Materials

Pre-clinical Safety And Efficacy Data Indicates The Alkaloid 7-OH To Be A Highly Potent Opioid Agonist

Marwood believes that the prevailing preclinical scientific literature indicates 7-OH to be a highly potent opioid agonist; scientists have noted risk of high abuse potential based on in in vitro binding studies and in vivo animal models

- 7-OH is a potent opioid agonist, although framed as a partial opioid agonist in a subset of the literature
  - 7-OH is structurally different from the other opioid agonists with a higher affinity for μ-opioid receptors relative to the other opioid receptors (1)
    - Its effect has been found to be >10x more potent than morphine (2,3)
    - It is speculated that 7-hydroxymitragynine binds opioid receptor sites other than those morphine does (3)
      - Mitragynine and 7-hydroxymitragynine both bind to the human μ-opioid and ƙ-opioid receptors (hMOR, hKOR) with nanomolar affinity, and function as partial agonists at the μ-opioid receptor and weak antagonists at ƙ-opioid and δ-opioid receptors (5, 6,7)
  - 7-OH is less likely to produce respiratory depression than other opioids (5)
    - 7-OH also activates the G-protein-coupled intracellular signaling pathway while having little or no effect on the beta-arrestin pathway; ligands that preferentially activate the G-protein-coupled intracellular signaling pathway should have greater efficacy in producing analgesia and lesser efficacy in producing respiratory depression
- 7-OH, unlike mitragynine, exhibits signaling characteristics aligned with high abuse potential (5)
  - In contrast to mitragynine, repeated administration of 7-hydroxymitragynine produces antinociceptive tolerance as well as cross-tolerance to morphine's antinociceptive action and induces physical dependence in murine models (1)
  - 7-OH, but not mitragynine, exhibits abuse liability in rodent models of human drug-taking (4)
  - As is generally accepted, the potent and repeated stimulation of opioid receptor agonists leads to the development of physical dependence
    - Physical dependence following chronic treatment with 7-hydroxymitragynine was studied and withdrawal signs were observed after naloxone injection, demonstrating that repeated administration of 7-hydroxymitragynine induces physical dependence (1)

1.) Matsumoto et al. (2005) Life Sciences 78 (1). **2.)** Takayama et al. (2002) J Medicinal Chemistry 45(9). **3.)** Matsumoto et al. (2004) Life Sciences 74(17). **4.)** Hemby et al. (2019) Addiction Biology 24(5). **5.)** Todd et al. (2020) Nature 10(19158). **6.)** Kruegel et al. (2016) J Am. Chem Soc 138. **7.)** Varadi et al. (2016) Med Chem 59.