Social Pain Institute
Neuroscience of social pain and the endogenous opioid system

Denver, Colorado
socialpain.org

September 8, 2026

The Honorable Brian Christine
Assistant Secretary for Health
Department of Health and Human Services
200 Independence Avenue SW
Washington, DC 20201

Re: Docket No. HHS-OASH-2026-0232 — Temporary Placement of 7-Hydroxymitragynine Above a Specified Threshold in Schedule I; Request for Information (FR Doc. 2026-13608)

Filer: Social Pain Institute, a Colorado nonprofit

Financial interest in kratom or 7-OH products: None. SPI receives no funding from any manufacturer, distributor, retailer, or trade association in this industry, and holds no position adverse to it.

Summary

The Social Pain Institute translates neuroscience concerning social pain and the endogenous opioid system into clinical research and policy. We take no position on whether any scheduling action should occur, and address only the two questions OASH has posed. This comment was written by SPI's director, whose interest is disclosed at the end. A technical appendix carries the method and literature behind it.

Our comment makes five points:

1. **On Question 1**, the record does not identify a concentration or quantity of 7-OH that constitutes an imminent hazard, and this is not contested. Filers on both sides — ASAM, the APA, the AAP, FED UP!, Shatterproof, R Street, and the Consumer Choice Center — say so in their own words.
2. **On Question 2**, the threshold is disjunctive, and the operative prong is the 1.00 milligram-per-"article" limit, not the 0.050 percent concentration limit. "Article" is undefined, so no measurement expression here has a determinate meaning.
3. **The harm data cannot currently be attributed to the product class the threshold defines.** 7-OH in a toxicology result may come from a concentrated product, from kratom leaf, or from metabolism of mitragynine. The discriminator is not reported in DEA's 85-case series, and the pro-scheduling filer closest to that data is asking DEA to release it.
4. **The exposure characterization is incomplete in a nameable way.** FDA states that surveillance cannot supply a prevalence estimate for 7-OH use. Within the uncounted population is a cohort using 7-OH for anxiety, depression, and trauma-related distress — large enough to appear at scale in this docket's own record, and characterized by no organizational filer.
5. **The care pathway the record proposes is narrower than the population it is meant to catch.** The two filers who address displacement name two routes, opioid use disorder treatment and pain management. Both are gated on a diagnosis a measurable part of this cohort does not have.

I. Question 1 — whether the record identifies a hazard concentration

OASH asks: *whether any additional data exist that further support this or an alternative threshold level, and specifically, what concentration or quantity of 7-OH in a product constitutes an imminent hazard to public safety.*

SPI has no additional dose-response data, and we are not aware that anyone does. What we can offer is a reading of the record OASH already holds.

The record's own most credentialed participants say the threshold is not derivable

This is the unusual feature of this docket, and it holds across the policy divide. Each of these filers reaches the same conclusion from a different starting position:

Filer	Position on scheduling	What they say about the threshold
American Society of Addiction Medicine	Supports acting	"Current evidence is insufficient to validate 0.050%, 1mg, or any alternative human harm threshold at present."
American Psychiatric Association	Supports scheduling	"There are no controlled human dose-response studies that would allow identification of a precise human toxicity threshold for 7-OH."
American Academy of Pediatrics	Wants a *stricter* threshold	The proposed threshold "does not yet meet the evidentiary standards to be considered a no-effect or safe level."
FED UP! Coalition	Strongly pro-scheduling; filed the docket's largest harm series (85 cases, 55 fatal)	"There is no established human therapeutic range, toxic range, or lethal blood concentration that would allow a scientifically confident determination that a particular consumer dose — such as 1 milligram — is below the level associated with imminent hazard."
Shatterproof	Supports scheduling	Asks why "the notice does not explain how HHS arrived at 1 milligram as the appropriate quantity."
R Street Institute	Opposes this mechanism	"The evidence establishes hazard, but not the proposed dividing line."
Consumer Choice Center	Opposes	"0.050 percent and 1.00 milligram are not findings. They are selections."

A pattern is visible in that list and worth stating plainly: **the more clinical credibility a filer has, the more explicitly it declines to name a number** — regardless of whether it wants scheduling to proceed.

No filer derived a threshold from dose-response

Five filers name a figure: HART 5 mg per dosage unit, Outpost Brands 10 mg per declared serving, Reason Foundation 20 mg per serving, the Foundation for Drug Policy Solutions (FDPS) zero, and Kratom Truth Project a qualitative separation it expressly declines to convert into a cap. None derives its number from a human dose-response relationship, because no such relationship has been established, and four say so in terms. Outpost offers 10 mg "not as a scientifically derived safe level, which the present record cannot establish…" HART's own toxicological reviewer reports that he "could find no data regarding the PK (or pharmacodynamics) of 7-OH when ingested alone in humans," and that "there is no scientifically established serum/blood concentration of 7-OH at or above which respiratory depression is likely to occur."

Two filers hold blood-concentration data — FED UP! (mean 463.23 ng/mL across its series) and FDPS (a 0.15 mg/L forensic fatality) — and neither converts those concentrations into a product-content limit. That conversion is what Question 1 asks for, and no one in the record performs it.

SPI's answer to Question 1 is therefore: the present record does not identify such a concentration, and no filer claims otherwise on the merits. We note this without inferring anything about the correct regulatory response.

II. Question 2 — the measurement expression

OASH asks: *whether data exist supporting alternative measurement expressions for purposes of specifying the threshold.*

The threshold is disjunctive, and the second prong is the operative one

The proposed threshold captures a product containing 7-OH at more than 0.050 percent w/w, w/v, or v/v **or greater than 1.00 milligram**. Discussion has concentrated on the percentage. The milligram prong determines outcomes, because essentially every commercially available product contains far more than one milligram, at any concentration.

"Article" is nowhere defined, and filers who want scheduling to proceed say so as plainly as those who do not. FED UP!: "The term 'article' is not defined." Shatterproof: "The proposed rule does not clearly define 'article.'" Tablet, serving, bottle, retail package, and bulk container are all available readings, producing different legal results for the same physical product. R Street shows that a 100 g product at one-fifth the proposed concentration can still breach the milligram prong if the package is the "article"; FED UP!, arguing *for* scheduling, shows that thirty compliant 2-gram candies deliver 30 mg while no individual candy exceeds either limit. Appendix E gives both, with Kratom Truth Project's certificates of analysis.

A rule that a pro-scheduling filer reads as too permissive and an anti-scheduling filer reads as categorically prohibitive, on the same text, is not yet specifying anything.

What consumers report actually taking

The docket contains one attempt to anchor a threshold in real-world dosing: Reason Foundation's 20 mg figure, drawn from Hill et al.'s survey of **vendor label** recommendations. Labels are not consumption. The comment record itself contains a large body of self-reported dosing that no filer has extracted.

SPI screened the deduplicated comment corpus for first-person dosing statements, excluding any sentence that also refers to the proposed rule — a necessary exclusion, since roughly 4,900 mentions of the proposed "1 mg" figure otherwise contaminate the sample. From 2,635 comments, 3,065 dose figures:

	Self-reported dose
5th percentile	5 mg
25th percentile	15 mg
Median	**30 mg**
75th percentile	60 mg
90th percentile	90 mg
At or below 1 mg	2.9%

	Self-reported dose
At or below 5 mg	7.1%

The proposed 1.00 mg per-article limit sits at approximately the third percentile of self-reported consumer doses. The median is thirty times it.

This is the consumer-side counterpart to Kratom Truth Project's laboratory finding that "there is no retail package size in this category that falls below the limit," reached from independent data. A limit set below the 3rd percentile of reported use does not regulate a market; it ends one. That may or may not be the intended policy, but it should be identified as the policy under consideration, because it is not what a "threshold" ordinarily denotes.

These figures are self-reported and unverified, tolerance means a current dose is not a starting dose, and counts are of dose figures rather than of people. Method and full limitations are in Appendix B; the extraction is reproducible.

III. The exposure characterization is incomplete in a specific way

Both questions require knowing who is exposed and to what. FDA's own assessment states that "surveillance systems do not provide estimates for the prevalence of 7-OH use and are only beginning to track the specific involvement of 7-OH enhanced products in exposure cases and overdoses," and that "large national surveys such as the National Survey on Drug Use and Health include questions about use of kratom, but not 7-OH" (*7-Hydroxymitragynine (7-OH): An Assessment of the Scientific Data and Toxicological Concerns Around an Emerging Opioid Threat*, FDA, at 11, 13). The denominator is absent, and counts without an exposed population cannot be converted into rates.

SPI's contribution is to name a component of that missing denominator.

A psychiatric-indication cohort is present in the record at scale

7-HOPE Alliance's national survey of 1,521 adults who have used 7-OH reports reasons for use including chronic pain 74%, **anxiety 53%, depression 45%**, and support during opioid addiction 23%. SPI analyzed the full comment corpus for this docket, retrieved from the regulations.gov API on August 19, 2026; after collapsing near-duplicate campaign submissions, **19,344 distinct comments** remain. Counts are presence per comment, not occurrences:

Term	Comments	Share
Anxiety	2,262	11.7%
Depression	1,682	8.7%
Suicidality or self-harm	451	2.3%
PTSD / complex PTSD	280	1.5%
Any psychiatric or neurodevelopmental term, or a general mental-health reference	**3,997**	**20.7%**
Any of the above, with no pain or physical-condition term	**1,089**	**5.6%**

The full thirteen-term table, the deduplication procedure, and the limitations are in Appendix A. For reference, 60.5% of distinct comments mention pain in some form and 23.9% mention chronic pain specifically.

These counts are floors, and the instrument is the reason. A public federal docket, signed and permanently searchable, describing conduct that is becoming a federal offense, is close to the worst possible instrument for measuring a population defined by stigmatized history. Whatever this cohort's true size, a comment record will understate it.

Neither source can establish a rate: the 7-HOPE survey is a non-probability sample, and our own count is keyword prevalence in unstructured text. What the two independently establish is a floor — a cohort using 7-OH for affective and trauma-related indications exists, is not small, and is invisible to every measurement instrument in this record.

We reviewed the organizational attachments in this docket. Where anxiety, depression, or mental health appear at all, the mentions are incidental — items in lists of reported reasons for use, not a population whose exposure requires characterization. The American Psychiatric Association filed a substantive comment addressing both questions and did not raise it.

IV. The endpoint set the threshold is calibrated against is incomplete

OASH has stated it is not soliciting comment on permanent scheduling or on the general safety of kratom-derived products. SPI accepts that scope. The cohort described above is in scope for a specific reason: **the endpoints used to calibrate a threshold determine what it protects against, and the current set omits a class of effects a μ-opioid ligand is known to produce.**

Every threshold proposal in this record is calibrated against respiratory depression, sedation, overdose, and dependence. Those are the right endpoints for the harms they measure, and they are not the complete set of clinically significant effects of μ-opioid pharmacology. Yovell et al. (2016) randomized patients with severe suicidal ideation to ultra-low-dose sublingual buprenorphine or placebo and found rapid, significant reduction in suicidal ideation (*Am J Psychiatry*, doi:10.1176/appi.ajp.2015.15040535). Tucciarone et al. (2026), a randomized, double-blind, placebo-controlled trial at Stanford, found that low-dose sublingual buprenorphine sustained and enhanced that reduction after a single ketamine infusion, where placebo did not (*Am J Psychiatry*, doi:10.1176/appi.ajp.20250840). Appendix C sets out the wider literature.

The record itself supplies the link. Obeng et al. (2021) measured μ-opioid efficacy at the human receptor: **7-OH and buprenorphine are close to indistinguishable on that measure**, at 41.3% and 42.8% maximal stimulation respectively, against DAMGO at 103% and fentanyl at 110% (*J Pharmacol Exp Ther*, doi:10.1124/jpet.120.000189). That is efficacy in one assay system and we use it for nothing more; 7-OH's μ binding affinity is roughly 86-fold lower than buprenorphine's, so the two are not interchangeable at equal doses.

We are explicit about what this does and does not establish. It does not establish that 7-OH has antidepressant or antisuicidal effects. No controlled human study has tested that, and we would resist anyone citing this comment as though it had. What it establishes is narrower: a compound this record describes as pharmacologically buprenorphine-like is being consumed at scale by a population reporting affective indications, and **no threshold proposal here is calibrated against the class of effects that pharmacology predicts.**

That is the same finding ASAM, the APA, and FED UP! reach by another route. Appendix D sets out a related gap: whether the dose escalation this record documents reflects tolerance, drug-induced hyperalgesia, or both — a dose-response question nobody in this docket has asked.

V. The care pathway the record proposes is narrower than the population

Two filers anticipate that scheduling will displace consumers with unmet clinical needs. Pinney Associates writes that "these individuals' underlying need for care does not disappear when the products are scheduled," and recommends "supporting access to FDA-approved medications for opioid use disorder" together with preparing clinicians to manage withdrawal. The American Psychiatric Association recommends "[e]xpanding access to evidence-based treatment for opioid use disorder, including medications such as buprenorphine and methadone, and improving access to appropriate pain management services."

Between them the record offers two routes: opioid use disorder treatment and pain management. Both are sound for the populations they name. Neither reaches the cohort in Section III, for a structural reason.

Both routes are gated on a diagnosis. Medications for opioid use disorder require an opioid use disorder diagnosis; pain management requires a pain condition. In the only survey in this record, 23% described themselves as currently addicted, while 53% and 45% reported using 7-OH for anxiety and depression. In this docket's own corpus, 1,089 comments — 5.6% of distinct comments, and more than a quarter of those raising any psychiatric term — raise a psychiatric or neurodevelopmental term with no pain or physical-condition term at all. That is the group both routes miss by construction.

There is no alternative indication. A person using 7-OH for persistent emotional distress and seeking a clinically supervised alternative has no diagnostic route to a μ-opioid agent outside opioid use disorder treatment, pain management, or a research protocol. Buprenorphine has no FDA-approved indication for depression, suicidality, or trauma-spectrum conditions. Consumers in this cohort are therefore offered a choice between accepting a diagnostic label that may not fit and receiving no care at all. In the same survey, 17% reported they would consider suicide if access were eliminated.

SPI makes no recommendation that any 7-OH consumer switch to buprenorphine or to any other agent, and we would oppose that framing. Our point is confined to the record: *"route displaced consumers toward treatment" is not yet a plan for this cohort, and the filings proposing it have not noticed that the cohort exists.* The size of the population a scheduling action would displace without a care pathway is part of what an imminent-hazard determination has to weigh, and it is currently unmeasured.

VI. The harm data cannot be attributed, and the effect of restriction cannot yet be measured

First: the harm data cannot be attributed to the products the rule would schedule

Detecting 7-OH in a decedent does not establish that the decedent consumed a concentrated 7-OH product. Doctors for Drug Policy Reform state it directly: "Detection of 7-OH in toxicology testing does not necessarily indicate consumption of a concentrated 7-OH product because 7-OH is both a naturally occurring constituent of kratom and an in vivo metabolite of mitragynine."

A discriminator has been proposed, and it is not in the record's data. The analysis Dr. Boyer submitted through 7-HOPE describes it: "The ratio of mitragynine to 7OH in forensic examinations is critically important," because kratom use yields a high ratio, while "Use of 7OH commercial

products would lead to the reverse." Whether it performs as described is itself unvalidated, and it requires the examiner to quantify both alkaloids.

The government's own case series does not report it. DEA's 85 overdose cases through March 5, 2026 (55 fatal, 30 nonfatal, mean 463.23 ng/mL) are cited in support of this action. FED UP! — which strongly supports scheduling, and has engaged this data most closely — asks DEA to release the "concentrations of mitragynine and mitragynine pseudoindoxyl" for those cases. Those are the values needed to determine whether the 85 exposures came from concentrated products or from botanical kratom.

And the surveillance systems aggregate the two. Pinney Associates: "most national surveillance systems do not distinguish products with concentrated levels of 7-OH… from traditional botanical kratom." FDA reaches the same conclusion in its own assessment: the epidemiologic data "often lack sufficient detail to distinguish with confidence involvement of botanical kratom products from 7-OH enhanced" products (FDA assessment, at 13).

The convergence is again cross-partisan: a pro-scheduling coalition, a consultancy that supports the threshold framework, a physicians' group, and FDA itself all describe the same gap. **A rule that would schedule concentrated 7-OH products above a threshold is supported by harm data that cannot currently be attributed to concentrated 7-OH products rather than to botanical kratom.** That is not an argument that the harms are unreal, but that the record does not yet connect them to the product class the threshold defines.

Second: the effect of restriction cannot be measured yet either

Three claims need to be kept separate:

Claim	Status
Prohibiting 7-OH has increased overdose deaths	**Not supportable.** No data exists. We do not make it.
Prohibiting 7-OH has not increased overdose deaths	**Also not supportable**, for the reason below.
Whether prohibition changes total overdose mortality cannot currently be determined	**Supportable, and independently checkable.**

Every outcome measure cited in this docket is an event attributed to a named substance: poison center reports mentioning kratom, or kratom detection in fatal overdoses. If consumers displaced from a regulated product substitute an unregulated supply, the resulting deaths are recorded as fentanyl deaths — they leave the measured category by construction. R Street, which cites these studies, disarms them itself: they "do not establish causation, isolate concentrated 7-OH, measure illicit purchases, determine whether consumers switched to other substances…" Jurisdictional fatality data is also not finalized until roughly 12 to 18 months after a year begins (Appendix E), so finalized post-restriction data cannot yet exist for 2025–2026 actions. **The absence of evidence here is a surveillance-latency artifact, not a null result.**

VII. Scheduling forecloses the research that would answer Question 1

The record cannot identify a hazard concentration because no controlled human dose-response study of isolated 7-OH exists — ASAM says so explicitly. Schedule I placement makes conducting that study materially harder. ASAM is the only organizational filer to treat this seriously, warning: "Experience with cannabis research has demonstrated that such regulatory and product-access barriers can impede research needed to answer public health questions," and asking that any interim

action facilitate "timely access to research grade 7-OH, representative market products, and efficient protocol review and approval."

The sharpest statement of the problem comes from an individual commenter — HHS-OASH-2026-0232-0481: "Schedule I forecloses the controlled research that would establish the very hazard concentration this RFI seeks, rendering the question permanently unanswerable." We adopt R Street's calibration rather than the strongest version: scheduling adds friction, cost, and delay to precisely the research this proceeding has identified as missing.

One consequence is specific to Section III's cohort and is not reversible. That population is, today, locatable and studiable. Scheduling does not pause it; it disperses it, and makes its members unwilling to be studied, because participating becomes disclosing a federal crime. The exposure characterization missing from this record becomes harder to obtain at exactly the moment the action making it necessary takes effect.

VIII. Recommendations

SPI recommends that OASH, and the Attorney General in receiving this record:

1. **Define "article"** on the face of any rule adopting a per-unit quantity, or replace it with a defined unit — the finished retail product at point of sale, expressed per declared serving. Until this is done, neither prong has a determinate meaning, independent of what number is chosen.
2. **State on the record what the threshold is and is not.** If a number is adopted, characterize it as the policy judgment the APA describes rather than as a validated no-effect level. This is the AAP's request, and it costs the agency nothing while preserving the ability to revise.
3. **Specify what evidence would revise the line**, and pair any interim action with access to research-grade 7-OH and representative market products for controlled human study, as ASAM requests. A threshold that names its own revision criteria is self-correcting; one that does not is permanent by default.
4. **Treat the exposure characterization as incomplete, and say which part.** The population using 7-OH for affective and trauma-related indications is part of the denominator FDA says it cannot supply. Any research agenda attached to this action should include measuring it, with validated instruments rather than surveillance proxies. This cohort is characterizable now and materially harder to reach afterward.
5. **Report, or obtain, the data that would attribute the harm cases.** For the overdose cases cited in support of this action, the mitragynine and mitragynine pseudoindoxyl concentrations alongside the 7-OH concentrations, and the distribution separately for fatal and nonfatal cases. FED UP! asks for the same while supporting scheduling. Without those values the record cannot establish that its harm data concerns concentrated products rather than leaf.
6. **Do not treat substance-attributed surveillance as evidence on displacement.** Poison center reports and kratom-detected fatalities cannot detect substitution into an unregulated supply, and no post-restriction outcome data can yet exist for 2025–2026 actions. The honest characterization is that the competing hazard is unmeasured, not that it is absent.

SPI supports rigorous research, validated analytical testing, accurate labeling, and age restrictions. We do not support replacing an inadequate evidence base with a number, and the filers best positioned to defend the proposed numbers on the merits have declined to do so. A threshold the record cannot support should at minimum be labeled as what it is, so that the research able to correct it remains possible.

Disclosures

The Social Pain Institute has no financial interest in kratom or 7-OH products and receives no industry funding.

This comment was written by SPI's director, whose professional interest is in the endogenous opioid system as a therapeutic target rather than in any particular compound, and who is not and has not been a 7-OH consumer — concentrated 7-OH products were restricted in Colorado, where SPI is based, before the director became aware of them. This comment takes no position on the relative merits of any μ-opioid agent, and recommends none.

The comment-corpus figures in Section III were derived from the complete set of comments posted to this docket as of August 19, 2026, retrieved from the regulations.gov API on that date. The deduplication and screening code, the random seed, and the list of retained comment IDs are available on request.

Respectfully submitted,

Jesse Haigh
Executive Director
Social Pain Institute
Denver, Colorado

Technical Appendix

This appendix supports the Social Pain Institute's comment on Docket No. HHS-OASH-2026-0232 and is filed alongside it. It contains the method behind the figures reported in that comment, the literature behind its Section IV, and the filed passages it summarizes. Nothing here is necessary to follow the comment's argument; it is here so that every figure and every characterization can be checked.

A. Comment-corpus method and full results

Corpus

The complete set of comments posted to this docket as of August 19, 2026 was retrieved from the regulations.gov API on that date. The comment period was open at the time of retrieval, so comments posted after that date are not included. Of 26,545 posted comments, 111 carry an organization field. Of the remaining 26,117 with substantive text, near-duplicate campaign submissions were collapsed to one comment per cluster, using Jaccard similarity ≥ 0.75 on five-word shingles, leaving **19,344 distinct comments**.

Exact-match collapsing alone gives 20,810; the Jaccard rule catches 1,466 more. The representative kept is the latest-received comment in each cluster, ties broken by highest ID suffix, on the reasoning that later submissions of a template are the most-evolved form and personal text is appended more often than removed.

The two largest clusters contain 4,493 and 1,506 copies. Collapsing them matters, because neither template mentions any psychiatric condition and both would otherwise dilute every figure below.

Sensitivity. Rerunning with the earliest comment in each cluster as the representative moves the two headline figures by one comment each, from 3,997 to 3,996 and from 1,089 to 1,088.

Residual limitation. Locality-sensitive hashing is a recall heuristic, so a small number of true ≥ 0.75 pairs may be missed. Every pair that was collapsed has been exactly verified, so the error runs toward under-collapsing, which makes the reported percentages floors.

Counting rule

Presence per comment, not occurrences. A comment naming anxiety six times counts once. A comment may count toward several terms.

Term presence — 19,344 distinct comments

Term	Comments	Share
Anxiety	2,262	11.69%
Depression (excl. "respiratory depression")	1,682	8.70%
Mental health (general)	723	3.74%
Suicidality / self-harm	451	2.33%

Term	Comments	Share
PTSD / complex PTSD	280	1.45%
Panic	191	0.99%
ADHD / attention deficit	141	0.73%
Trauma (other)	127	0.66%
Autism / Asperger's / AuDHD / neurodivergent	60	0.31%
Bipolar	38	0.20%
Schizophrenia spectrum / psychosis	35	0.18%
OCD	33	0.17%
Personality disorder (excl. "addictive personality")	12	0.06%
Any psychiatric/neurodevelopmental term	**3,997**	**20.66%**
Any such term, no pain/physical term	**1,089**	**5.63%**

Physical-condition set

Used for the second headline figure: pain (generic) 60.46%, chronic pain 23.88%, back/spine 8.29%, arthritis 3.20%, autoimmune 2.58%, cancer 1.62%, fibromyalgia 1.26%, neuropathy 0.88%, migraine 0.83%, Ehlers-Danlos and hypermobility 0.41%, endometriosis 0.30%, CRPS 0.26%, POTS and dysautonomia 0.08%. The autoimmune pattern covers autoimmune (generic), lupus, rheumatoid, multiple sclerosis, Crohn's, ulcerative colitis, psoriatic disease, Sjögren's, ankylosing spondylitis, and Hashimoto's.

The wider the physical-condition net, the more conservative the psychiatric-term-with-no-pain-term figure becomes.

Limitations

These are keyword prevalences in unstructured text. They are direction-agnostic — comments opposing 7-OH also mention these terms — and they are not a prevalence estimate for any population. Comments are self-selected and signed, which is why the comment treats these figures as floors rather than as estimates. No claim of representativeness is made or intended.

Reproducibility

The deduplication and screening code, the random seed, and the list of retained comment IDs are available on request.

B. Dose extraction

Run over the deduplicated corpus. The extractor takes milligram figures from first-person dosing sentences and excludes any sentence that also references the proposed rule.

	Value
Comments with a usable dose statement	2,635
Dose figures extracted	3,065
Median	30 mg

	Value
Mean	53.6 mg
5th percentile	5 mg
25th percentile	15 mg
75th percentile	60 mg
90th percentile	90 mg
95th percentile	150 mg
At or below 1 mg	88 (2.9%)
At or below 5 mg	219 (7.1%)

The rule-exclusion filter is not optional. Without it, roughly 4,900 instances of people quoting the proposed "1 mg" figure enter the sample and drag the apparent median from 30 mg to 7.5 mg. Anyone reproducing this who omits the filter will get a different answer.

Limitations

These figures are self-reported and unverified. A stated "30 mg" is 30 mg as labeled or believed, and filings in this docket document considerable label inaccuracy, so the relationship to delivered 7-OH is uncertain. Because 7-OH induces tolerance, a current dose is not a starting dose, and this is a cross-sectional reading that cannot describe any individual's trajectory. Counts are of dose figures, not of people, and a comment stating several doses contributes several figures.

C. μ-opioid signaling and affect

The comment cites two randomized trials. The wider literature is set out here because it establishes that the endpoint omission described in Section IV is a general property of μ-opioid pharmacology rather than an artifact of two studies.

Buprenorphine and affective endpoints

- **Yovell et al. (2016)** randomized patients with severe suicidal ideation to ultra-low-dose sublingual buprenorphine (mean 0.44 mg/day) or placebo and found rapid, significant reduction in suicidal ideation. *Am J Psychiatry*, doi:10.1176/appi.ajp.2015.15040535.
- **Tucciarone et al. (2026)**, a randomized, double-blind, placebo-controlled trial at Stanford, found that low-dose sublingual buprenorphine (0.2–0.8 mg/day) following a single ketamine infusion produced significantly greater and more sustained reduction in suicidal ideation than placebo (mean SSI change −11.6 vs −6.3), with no significant separation on depression scores. *Am J Psychiatry*, doi:10.1176/appi.ajp.20250840.
- **Karp et al. (2014)** found low-dose buprenorphine improved treatment-resistant depression in midlife and older adults. doi:10.4088/JCP.13m08725.
- Review-level syntheses reach the same conclusion about the mechanism: **Cameron et al. (2021)**, doi:10.3389/adar.2021.10009; **Namchuk et al. (2022)**, doi:10.3389/adar.2022.10254.

The sublingual daily doses in these trials — 0.2 to 0.8 mg, with a mean of 0.44 mg in Yovell — are one to two orders of magnitude below sublingual maintenance dosing in opioid use disorder treatment. We give the sublingual figures alone rather than a combined range across studies, because buprenorphine's bioavailability differs substantially by route of administration and milligram doses are not interchangeable across formulations.

A double-blind, placebo-controlled crossover trial at UCLA — "Low-dose Buprenorphine as a Modulator of Social Motivation in Schizophrenia" (NCT05778591, A. Bershad, PI) — is currently recruiting, administering a single 0.15 mg buccal dose of buprenorphine against placebo with social approach and avoidance motivation as the primary outcome. No results are available, and we cite it only for what it shows about the state of the field: the effect of a partial μ-opioid agonist on social motivation is a live empirical question that investigators are currently spending research resources to answer.

Neurodevelopmental conditions

A smaller set of comments — 60 mentioning autism or neurodivergence, 141 mentioning ADHD — describes something the pain-and-overdose endpoint set does not contemplate at all. Several describe social function specifically: reduced social anxiety, leaving the house, returning to company.

μ-opioid signaling is central to social reward and attachment: μ-opioid receptor knockout mice show broken attachment behavior (**Moles et al., 2004**, doi:10.1126/science.1095943) and a comprehensive autistic-like phenotype (**Becker et al., 2014**, doi:10.1038/npp.2014.59). The current framing is not the discredited "opioid excess" hypothesis but its near-opposite — blunted opioid-mediated social reward (**Pellissier et al., 2018**, doi:10.1111/bph.13808) — and human PET imaging now reports regionally altered μ-opioid receptor availability in autistic adults, with no overall group difference in the region-of-interest analysis (**Noppari et al., 2025**, doi:10.1007/s00259-025-07620-5) — a small study, 16 adult males with high-functioning ASD against 24 matched controls, whose authors note the male-only sample may not generalize.

Two features of that literature matter more than the mechanism does.

First, **the direction is informative.** Opioid *antagonists* have been trialed in autism for decades; a systematic review found naltrexone reduces self-injurious behaviour and "may improve hyperactivity and restlessness," but that there was "not sufficient evidence that it had an impact on core features of autism" (**Roy et al., 2015**, doi:10.1111/jir.12122). A negative result on the blocking side is what a blunted-reward model predicts.

Second, **there is no approved treatment for the social domain.** The only medications approved in autism are for irritability — risperidone and aripiprazole, both indicated for "irritability associated with autistic disorder." Nothing is approved for the social and motivational features that the comments above describe. The direct evidence for a partial μ-opioid agonist in autism is a single case report (**Skoglund et al., 2022**, doi:10.1186/s13256-022-03384-w), which is a hypothesis generator and nothing more.

The consequence for this proceeding is not that 7-OH treats autism. It is that a population with no approved pharmacological option for the symptoms limiting their lives has found something over the counter and reports functional change in exactly the domain the mechanism predicts, entirely outside the endpoint set, the surveillance systems, and the care pathways described anywhere in this record.

Why a comment about psychiatric indications turns to pain

Social pain and physical pain share neural substrate. Social exclusion activates the dorsal anterior cingulate cortex in proportion to reported distress (**Eisenberger, Lieberman & Williams**, *Science* 2003, doi:10.1126/science.1089134); the relationship is now a substantial literature (**MacDonald & Leary**, *Psychol Bull* 2005, doi:10.1037/0033-2909.131.2.202; **Eisenberger**, *Nat Rev Neurosci* 2012, doi:10.1038/nrn3231). A large part of that shared substrate is the endogenous opioid system. Social rejection releases endogenous opioids in the human brain, measured directly by PET (**Hsu et al.**, *Mol Psychiatry* 2013, doi:10.1038/mp.2013.96). Blocking opioid receptors with naltrexone reduces

everyday feelings of social connection (**Inagaki et al.**, *SCAN* 2016, doi:10.1093/scan/nsw006). And the traffic runs both ways: acetaminophen, an ordinary analgesic, reduces hurt feelings and blunts neural responses to rejection (**DeWall et al.**, *Psychol Sci* 2010, doi:10.1177/0956797610374741).

We state the limit as well. The strong form of the claim — that social and physical pain are the same experience — is disputed, and later multivariate imaging work distinguishes them even where gross activation overlaps: Woo et al. found fMRI pattern classifiers for pain and for rejection each performed at chance on the other, with uncorrelated representations inside the dorsal anterior cingulate itself (*Nat Commun* 2014, doi:10.1038/ncomms6380). The defensible version is narrower and sufficient here: **these are distinct experiences running partly on shared machinery, and the endogenous opioid system is a substantial part of what they share.**

Two consequences follow. **First, a μ-opioid ligand does not act on "pain" and "mood" as separable targets.** Whatever 7-OH does to nociception and whatever it does to affect are not independent findings about two different systems. A threshold reasoning only about one of them is reasoning about part of the compound's action.

Second, pain is the legible indication and emotional pain is not. A person can say "my back hurts" and be understood as describing a medical problem with an accepted class of treatments. A person saying that being alive among other people hurts has no comparable vocabulary, no diagnostic code that leads anywhere useful, and no accepted pharmacological target. When a survey asks why someone uses a substance, the answer people can give is shaped by which answers are receivable.

Nothing in that observation implies that anyone's physical pain is not real. It is the opposite claim: social pain is not a metaphor, and the people reporting chronic pain in this record are reporting chronic pain. The point is about measurement. The 7-HOPE survey's categories — chronic pain 74%, anxiety 53%, depression 45% — are not disjoint populations, cannot be added, and cannot be assumed to separate cleanly, because the same person may belong to several and because the reason offered is the reason that is hearable. That is one more reason the exposed population cannot be characterized from the instruments currently available.

D. Hyperalgesia, κ-opioid activity, and an unasked dose-response question

The endpoint set is incomplete in a second direction, and this one concerns pain rather than mood.

Opioids can produce hyperalgesia as well as analgesia — an increase in pain sensitivity caused by the drug itself. This matters because a large share of 7-OH consumers use it for chronic pain over extended periods: 7-HOPE's survey reports chronic pain as the most common reason for use at 74%, with 97% of those respondents describing it as effective. That 97% establishes the scale of chronic-pain exposure and nothing more; self-reported effectiveness does not distinguish analgesia from antihyperalgesia.

Whether buprenorphine differs from conventional opioids on this axis is unsettled in humans.

Koppert et al. (2005), a randomized, double-blind, placebo-controlled crossover study in fifteen volunteers using an intradermal electrical sensitization model, found buprenorphine's antihyperalgesic effects *exceeded* its analgesic effects — a median antihyperalgesia-to-analgesia ratio of 2.6 intravenously and 1.9 sublingually, with antihyperalgesia outlasting analgesia (288 vs 171 minutes). Re-analyzed data from the same laboratory put the equivalent ratios for the pure μ-agonists fentanyl and alfentanil at 0.6 and 0.3, with intervals extending below zero; the authors note that "negative ratios indicate hyperalgesic effects, i.e. larger hyperalgesic areas following opioid application." *Pain* 2005, doi:10.1016/j.pain.2005.06.030.

Two subsequent studies did not reproduce the differential effect.

- **Ravn et al. (2013)**, a five-arm, double-blind, placebo-controlled crossover study in 28 volunteers using a thermal injury model, compared intravenous buprenorphine (0.3 and 0.6 mg) against intravenous morphine (10 and 20 mg) and "could not demonstrate any significant differences between morphine and buprenorphine in the profiles of antihyperalgesia and analgesia." *J Pain Res* 2013, doi:10.2147/JPR.S36827.
- **Tröster et al. (2012)**, from Koppert's own group and using a similar paradigm, reported antihyperalgesia and analgesia without publishing the ratio; Ravn et al., estimating from the published figures, put it at 0.75–0.80 for both buprenorphine and fentanyl — again no differential effect. *Clin J Pain* 2012, doi:10.1097/AJP.0b013e318241d948.

Both studies measured secondary hyperalgesia, as Koppert did. Ravn et al. identify three differences that may account for the discrepancy: the electrical model stimulates axons directly and is "probably more suitable for examination of central components," whereas the thermal injury model "reflects both peripheral and central components"; the stimulation patterns differed in duration; and Koppert et al. "used 25%–50% of the buprenorphine doses used in the present study," by bolus rather than steady-state infusion. The distinctive profile appeared at 0.15 mg and was not detected at two to four times that dose. Whether buprenorphine's antihyperalgesic effect is a low-dose phenomenon is not something these three studies can settle, and we do not assert that it is.

The relevant conclusion is the one that holds across all three: the human evidence on opioid antihyperalgesia is unresolved for buprenorphine — a compound in clinical use for decades and far better characterized than 7-OH.

7-OH's κ-opioid activity is established; its clinical consequence is not

The mechanism most often proposed for a buprenorphine-specific effect is κ-opioid antagonism. Koppert et al. describe it as "yet unclear" and offer it as a hypothesis: systemic opioid administration increases spinal dynorphin, an endogenous κ-receptor agonist "shown to promote hyperalgesic pain states **and antinociceptive tolerance**," so buprenorphine "might counteract these mechanisms by its κ-receptor antagonistic properties."

On the receptor pharmacology, 7-OH resembles buprenorphine here too, and this is not speculative. Kruegel et al. (2016) assayed the Mitragyna alkaloids at human opioid receptors and found 7-OH to be a **competitive antagonist at the human κ-opioid receptor**, with Schild analysis giving pA2 = 490 ± 131 nM, and a competitive antagonist at the human δ-opioid receptor. *J Am Chem Soc* 2016, doi:10.1021/jacs.6b00360. Obeng et al. (2021) is consistent: 7-OH binds the κ receptor at Ki 220 nM (95% CI 162–302) and the δ receptor at Ki 243 nM (168–355), 2.8- and 3.1-fold lower affinity than at μ, with no significant agonist activity at either. Buprenorphine's profile in the same table is comparable in shape: μ Ki 0.903 nM, δ 1.51 nM, κ 1.29 nM.

So 7-OH is, like buprenorphine, a partial μ-agonist with κ- and δ-antagonist activity at human receptors. **What does not follow is any conclusion about effects in people.** Three limits apply, and they are the reason this is a research recommendation rather than a claim:

1. Kruegel et al. found marked interspecies variation in this alkaloid class, though not in 7-OH itself. Mitragynine is a partial agonist at the human μ receptor but "act[s] as a competitive antagonist at mouse MOR," while "the activity of 7-OH was similar at the rodent receptors." The authors write that these observations "complicate the interpretation of prior reports of analgesic effects elicited by mitragynine in rodent models," and that "activity in rodent models may not be easily translatable to man." Much of the preclinical record cited in this docket is rodent, and much of it concerns mitragynine rather than 7-OH.
2. κ antagonism in the sub-micromolar range says nothing by itself about whether that activity is engaged at the concentrations human consumers achieve. That depends on human

pharmacokinetics for isolated 7-OH, which is the evidence ASAM and FDA both say does not exist.
3. Even where the κ-antagonist mechanism is present and engaged, its antihyperalgesic consequence is, per the three studies above, unresolved in humans.

The question this produces

Two facts in this record make it more than academic.

First, **this record documents tolerance and dose escalation.** R Street reports a patient who "developed tolerance within days and progressed to using a film every one to two hours," and another whose use "escalated to 360 mg per day." Apex Recovery reports "a half-life of approximately 2.5 hours in acute exposures, driving rapid-onset withdrawal." Our reading of self-reported consumer doses, in Appendix B, gives a median of 30 mg and a 90th percentile of 90 mg.

Second, **tolerance and drug-induced hyperalgesia are distinct mechanisms that present identically** — to the consumer, to a prescriber, and to a surveillance system. Both produce dose escalation.

That produces a question nobody in this docket has asked: **when 7-OH consumers escalate their dose, is that tolerance, drug-induced hyperalgesia, or both?**

We are careful about the direction of this point, because it does not run the way a reader might assume. If the κ-antagonist activity described above is not engaged at the concentrations consumers achieve, some part of the escalation documented above may be drug-induced hyperalgesia, and the compound would be worsening the condition most of its consumers report using it to treat. That is a reason for concern, not reassurance. If it is engaged, it may not be. **SPI does not know which, and neither does anyone else: the receptor pharmacology is characterized, the human pharmacokinetics are not, and the clinical question is unresolved even for buprenorphine.** We raise it because it is a dose-response question, the same class of question Question 1 asks, about the largest single group of people this action would affect.

E. Filed passages summarized in the comment

The five named figures, and what each filer says about the basis for it

- **HART** (5 mg per dosage unit) offers the only worked pharmacokinetic chain in the record, and shows it. The filing states that a dosage unit containing up to 5 mg "would be expected to produce plasma concentrations approximately fifteen times lower than those observed in published human kratom studies that reported no signal of serious toxicity or respiratory depression," and the independent toxicological review it attaches sets out the arithmetic: a rat volume of distribution of 2.7 L/kg, roughly 90% plasma protein binding, an estimated unbound concentration of 0.46 ng/mL for a 1 mg dose, compared against the 30.5 ng/mL 7-OH Cmax that Huestis et al. measured after a 59.2 mg mitragynine dose. The step a reader should examine is the comparison itself, which sets an estimated unbound 7-OH concentration against a measured total plasma concentration arising from mitragynine, using a rodent volume of distribution. That step is checkable, which is the relevant difference between this filing and the others. What it is not is a derivation from human dose-response, and its author says so: he "could find no data regarding the PK (or pharmacodynamics) of 7-OH when ingested alone in humans," and reports that "there is no scientifically established serum/blood concentration of 7-OH at or above which respiratory depression is likely to occur." His stated caveat is that "[i]deally, PK studies of 7-OH would be

performed," which "would eliminate some of the extrapolations being relied upon for my opinion."

- **Outpost Brands** (10 mg per declared serving) reasons from DEA's own Three-Factor Analysis and self-disclaims: it "offers 10 milligrams not as a scientifically derived safe level, which the present record cannot establish, but as the minimum figure consistent with the quantified evidence the agencies have themselves advanced."
- **Reason Foundation** (20 mg per serving) states its number is "not because this is a pharmacologically derived 'safe' dose, but because it reflects the actual average dose currently consumed."
- **Foundation for Drug Policy Solutions** (zero / limit of quantitation) derives from the absence of a safe-dose study rather than from a hazard calculation, and says so: "Because no safe dose of 7-OH has been established, there is no scientific basis for identifying a permitted quantity of this potent opioid above zero." Where administrability requires a number, it "recommends setting it at the analytical limit of quantitation."
- **Kratom Truth Project** identifies a genuine analytical separation between conventional and converted products, and expressly declines to convert it into a per-serving milligram cap. It reports measured per-serving content of roughly 14 to 21 mg, then declines to build a figure on it: "We do not offer an estimate of typical daily consumption, because the record contains none… the agency should characterize actual consumption before fixing any figure. Setting a cap without that characterization would reproduce, in the alternative framework, the same defect this comment identifies in the proposed threshold."

Laboratory data on the per-article prong

From Kratom Truth Project's own certificates of analysis: a botanical gummy at 0.0125% dry weight contains 0.731 mg in one 5.87 g unit. It clears the concentration test fourfold while consuming 73% of the entire per-article allowance; two units exceed it. A separate extract at 0.007% w/w clears concentration sevenfold but breaches 1.00 mg at roughly 14 grams of package.

Kratom Truth Project's conclusion from its own data is that "there is no retail package size in this category that falls below the limit."

Surveillance latency

As of a February 12, 2026 presentation by the Denver Department of Public Health & Environment and the Denver Office of the Medical Examiner, all 2025 Denver overdose fatality data remained "preliminary and subject to change," with final figures expected in spring 2026; the stated causes of delay included an 18-week toxicology turnaround and ongoing death investigations. A jurisdiction's fatality data for a given year is therefore not final until roughly 12 to 18 months after that year begins. This is the basis for the timing constraint stated in Section VI of the comment.

Why substance-attributed surveillance cannot detect substitution

Substance-attributed surveillance is expected to show a decline after a ban for at least three reasons unrelated to whether total harm fell: substitution moves events across categories; 7-OH is not on standard toxicology panels and is less likely to be assayed where it is illegal; and people report a controlled substance less readily to a poison center, an emergency department, or an investigator.