The Current Regulatory 8-Factor Analysis (8FA) and Its Use on Substance Abuse Liability

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Symposium 6: The tight rope of substance abuse potential – the pre-clinical and clinical factors that make or break the scheduling of a substance, using Kratom (Mitragyna speciosa) as an example

Bellevue, WA, Sept. 10-13, 2023 Track: Clinical Drug Development & Investigations

Monday, September 11, 2023, 8:00 AM – 9:30 AM

Disclosure

Through PinneyAssociates I provide scientific and regulatory consulting to support drug development & new drug applications, abuse potential assessments and Controlled Substance Scheduling in the United States and globally

My work includes psychedelic medicines development, new dietary ingredient notifications, cannabinoid product development, and noncombustible tobacco harm reduction products such as electronic nicotine delivery systems

Specific to Kratom, through PinneyAssociates, I advise the American Kratom Association on science & regulation, and Johnson Foods on new dietary ingredient development

Goals

1. Overview Controlled Substances Act (CSA)abuse potential assessment & 8-Factor Analysis (8FA) guided drug scheduling
2. Summarize kratom abuse potential in the framework of the 8FA
3. Discuss how CSA scheduling can contribute to public health by finding the appropriate balance of control and access and when other regulatory and policy tools may more effectively support public health

Assessment of Abuse Potential of Drugs

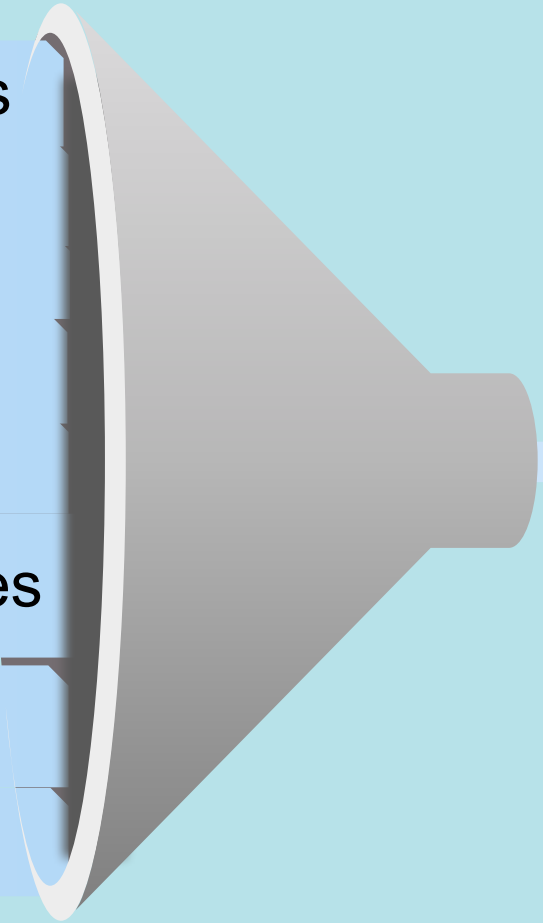
Guidance for Industry

- U.S. Department of Health and Human Services
- Food and Drug Administration
- Center for Drug Evaluation and Research (CDER)
- January 2017

This is the key resource for abuse potential assessment for potential FDA regulated products

Abuse Potential Assessment
A Relative & Comparative Process

- Chemical Structure: precursor & metabolites
- Brain absorption, binding sites & activity
- Pharmacokinetics & dynamics (behavioral)
- Animal studies of discrimination & reward
- Human Abuse Potential Studies (HAP)
- Abuse-related data & AEs - all clinical studies
- Epidemiology and history of related substances
- Literature and current relevant research



Abuse Potential Relative to Other Substances & Products

Three Agencies Contribute to CSA Drug Scheduling

FDA (with NIDA input)

recommends: If FDA recommends CSA control it also recommends to DEA the schedule via the Assistant Secretary of Health Secretary of Health (ASH)

NIH National Institute on Drug Abuse

FDA

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA ·

DEA *schedules:* within 90 days of FDA drug approval as per 2016 CSA Amendment (Regulatory Transparency for New Medical Therapies Act)

U.S. JUSTICE DEPARTMENT DRUG ENFORCEMENT ADMINISTRATION

8 Factors of the CSA Guide Drug Scheduling

1. Actual or relative potential for abuse
2. Scientific evidence of pharmacological effect
3. Current scientific knowledge regarding the drug
4. History and current pattern of abuse
5. Scope, duration, and significance of abuse
6. Public health risk
7. Psychic or physiological dependence liability
8. Whether the substance is an immediate precursor of an already controlled substance

5 Schedules or Classes – Often designated CI, CII, etc. (with or without a hyphen according to the CSA)

Schedule I: Not approved by FDA for therapeutic use; “high” abuse potential and with highly restrictive applications and licensing protocols through DEA – in practice “high” means sufficiently high to warrant scheduling, thus psilocybin, THC, heroin, and methamphetamine are all in CI because they are not approved for therapeutic use despite wide variation in actual abuse related risks

Schedules II-V: For FDA approved substances or drug products warranting CSA control – thus FDA approval of a CI product requires that product be appropriately rescheduled or removed from control prior to marketing

CII is most restrictive (e.g., amphetamine, cocaine & oxycodone)

CIII (e.g., buprenorphine, ketamine, nalorphine, Marinol & perampanel)

CIV (e.g., diazepam, fospropofol, sibutramine, tramadol & zolpidem)

CV is least restrictive (e.g., low dose oral codeine + acetaminophen) – in practice CV seems increasingly used for products that appear on the borderline of warranting control (e.g., lacosamide, pregabalin & the initial scheduling of Epidiolex (CBD))

Populating the Factors – F1 –

Using kratom as an example and building on new data presented by Drs. Grundmann and Smith

Factor 1: Actual or relative potential for abuse: This is the BIG factor in most 8FAs. It addresses what is known from mechanism of action to animal & human studies and epidemiology

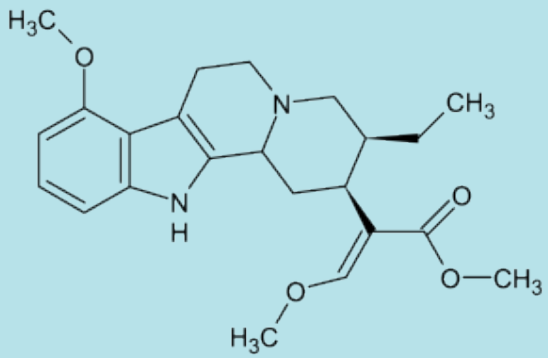
1. Abuse related target receptor binding profiles
2. Animal intravenous self-administration studies
3. Clinical evidence of euphoria
4. Relevant epidemiology of the substance and/or analogs?
5. Physical dependence/withdrawal are not indicative of abuse potential in their own right and many drug not abused show withdrawal, but withdrawal is an important labeling issue and may exacerbate SUD (see FDA 2017 Guidance)

NIDA Kratom Facts Website Summarizes some key 8FA evidence

"People typically use kratom by swallowing raw plant matter in capsule or powder form, mixing kratom powder into food or drinks, brewing the leaves as a tea, or taking liquid kratom extract. People who use kratom report both stimulant-like effects (increased energy, alertness and rapid heart rate) and effects that are similar to opioids and sedatives (relaxation, pain relief and confusion)."

JEH note: Note the forgoing is in contrast to most drugs with high abuse potential in which users often seek to heighten euphoriant effects by rapid routes of administration (e.g., injection, nasal insufflation, and smoking)

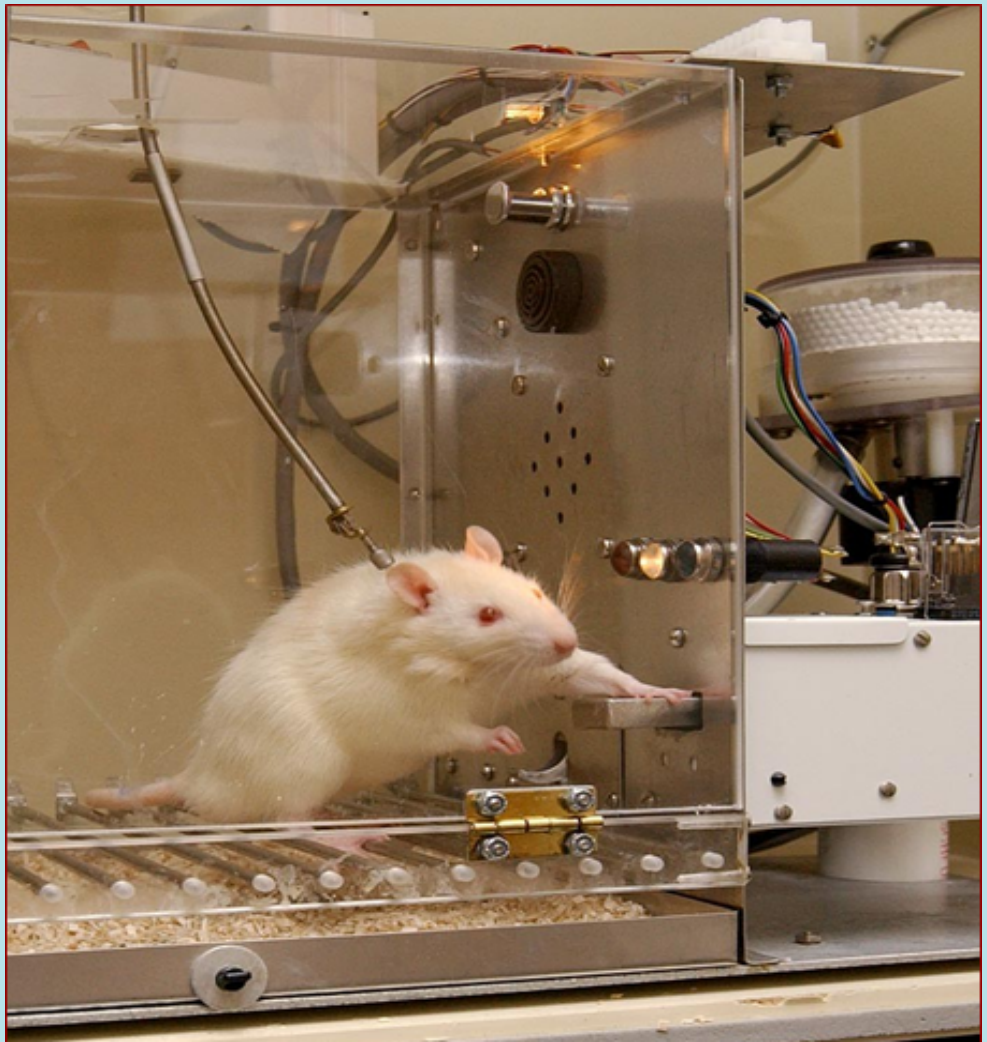
"Preliminary data from anonymous surveys of people who use kratom suggest a minority of people report experiencing kratom-related withdrawal symptoms and a smaller minority report experiencing substance use disorder symptoms related to kratom use."

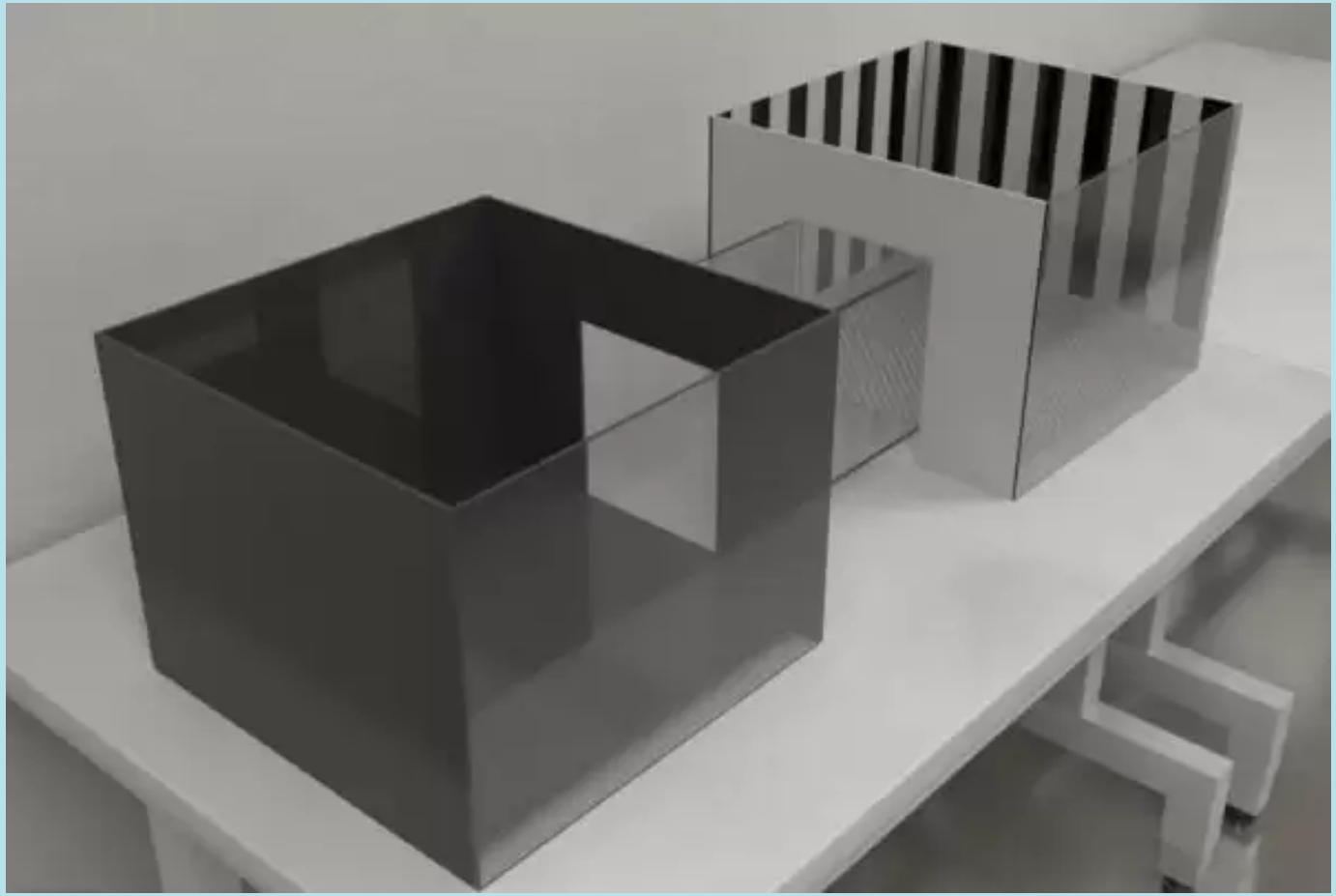


Mitragynine

- Low affinity, partial μ-opioid receptor agonist, Ki ~ 709 nM
  - Does not activate β-arrestin-2 pathway that is implicated in adverse effects of respiratory depression & constipation
  - Antagonist at κ-opioid receptor & also an agonist at α-adrenergic (α1A, α1B, α1D, α2A, α2B & α2C), 5-HT_{1A}, 5-HT_{2C} & 5-HT_7 serotonin, D2 dopamine & A_{2A} adenosine receptors
  - Mitragynine pharmacology different than prototypical opioids

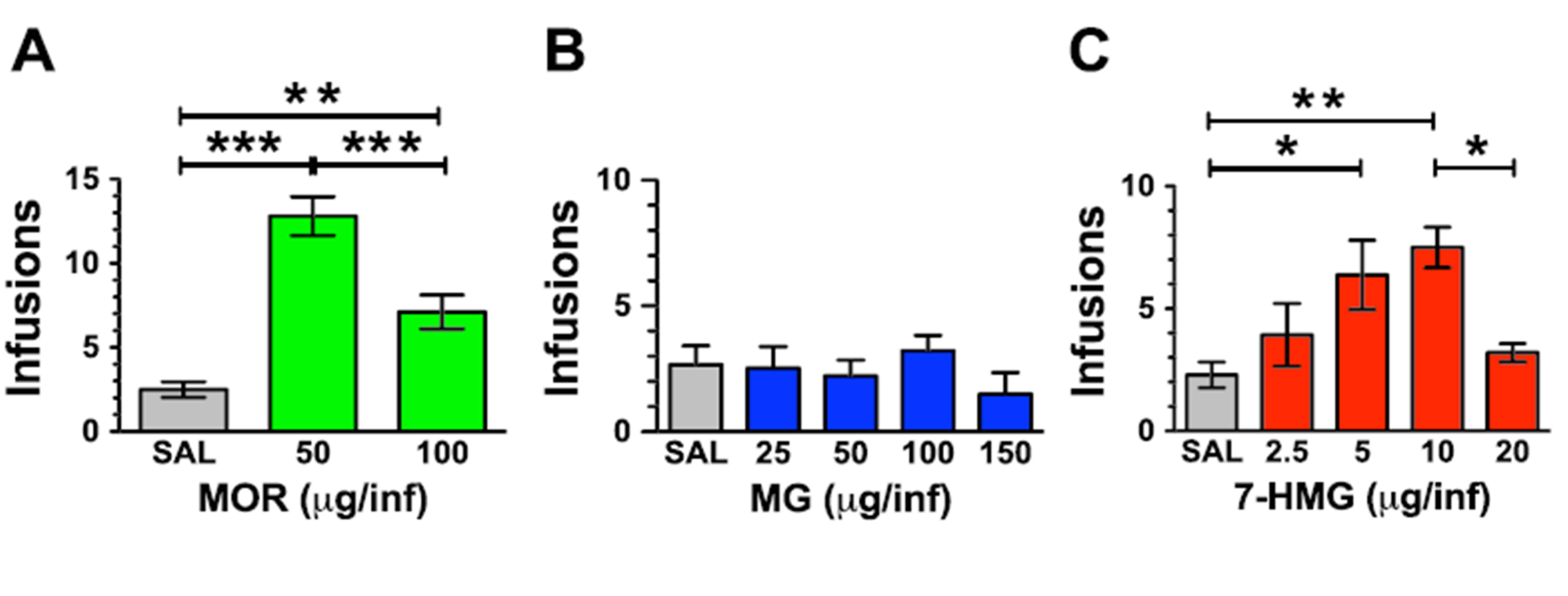
Animal Models: IV Drug Self-Administration, Discrimination, Conditioned Place Preference, Physical Dependence, Tolerance & Withdrawal





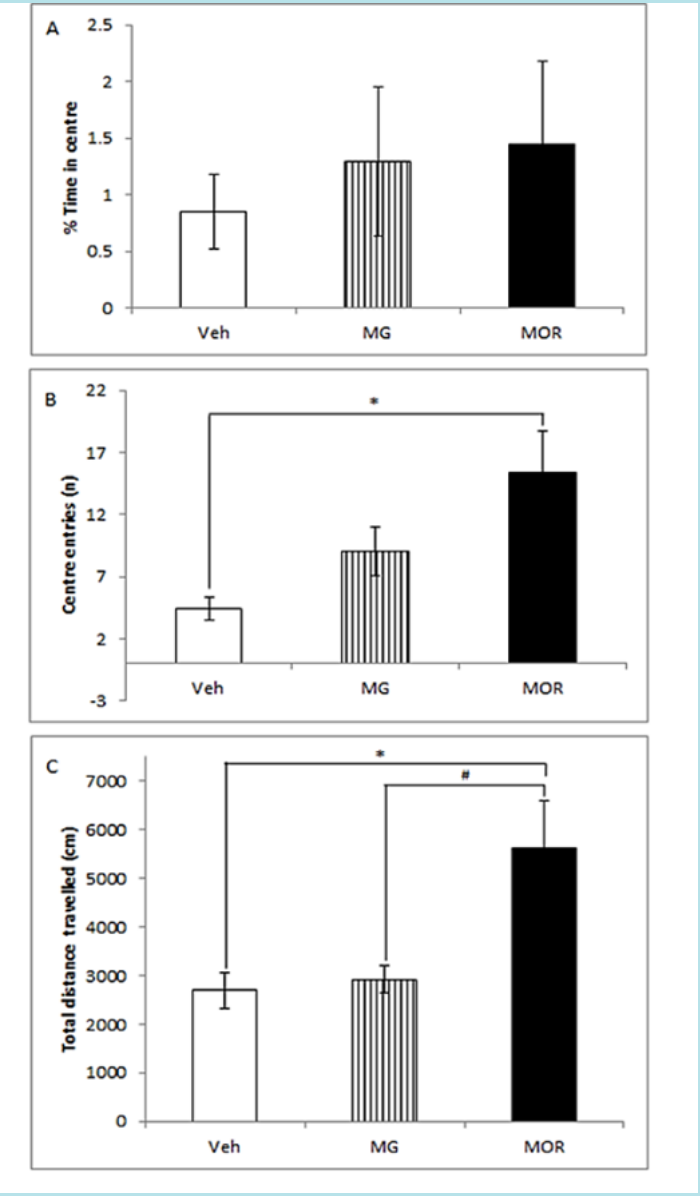
Animal Abuse Potential: MG and 7-OHMG Compared to Morphine in Rat IV Self-Administration Model (Hemby, McIntosh, Cutler & McCurdy, 2018)

- Rats did not develop MG self administration. Pretreatment with MG reduced morphine SA consistent with kratom user reports
- At extraordinarily high doses, 7-OHMG can serve as a reinforcer supporting regulation to not allow levels exceeding those typically found in natural kratom



Animal Physical Dependence/Withdrawal Potential for MG

Harun, Johari, Japarin, Baker, Mat, Zurina Hassan & Haniza Hassan, 2021 – Figure 1



Naloxone precipitated morphine like withdrawal in both morphine and MG treated rats, however, Global Withdrawal Scores were significantly higher in morphine treated rats than MG treated rats

Anxiogenic behaviors in Open Field and Elevated-Plus Maze tests were elevated for morphine but not MG suggesting that anxiety is not an MG withdrawal effect

Populating the Factors – F2 & 3

- Factors 2 &3 include evaluation of latest findings on chemistry, neuropharmacology, and pharmacokinetics & dynamics (PK&PD), and safety/toxicity
- Address the “physiochemical” aspects of the formulation and specific product that may contribute to abuse
- Help differentiate CNS active substances consistent with the intent of the CSA from substances that may be dangerous, but are used for reasons that do not appear primarily driven by euphoria & CNS rewarding effects

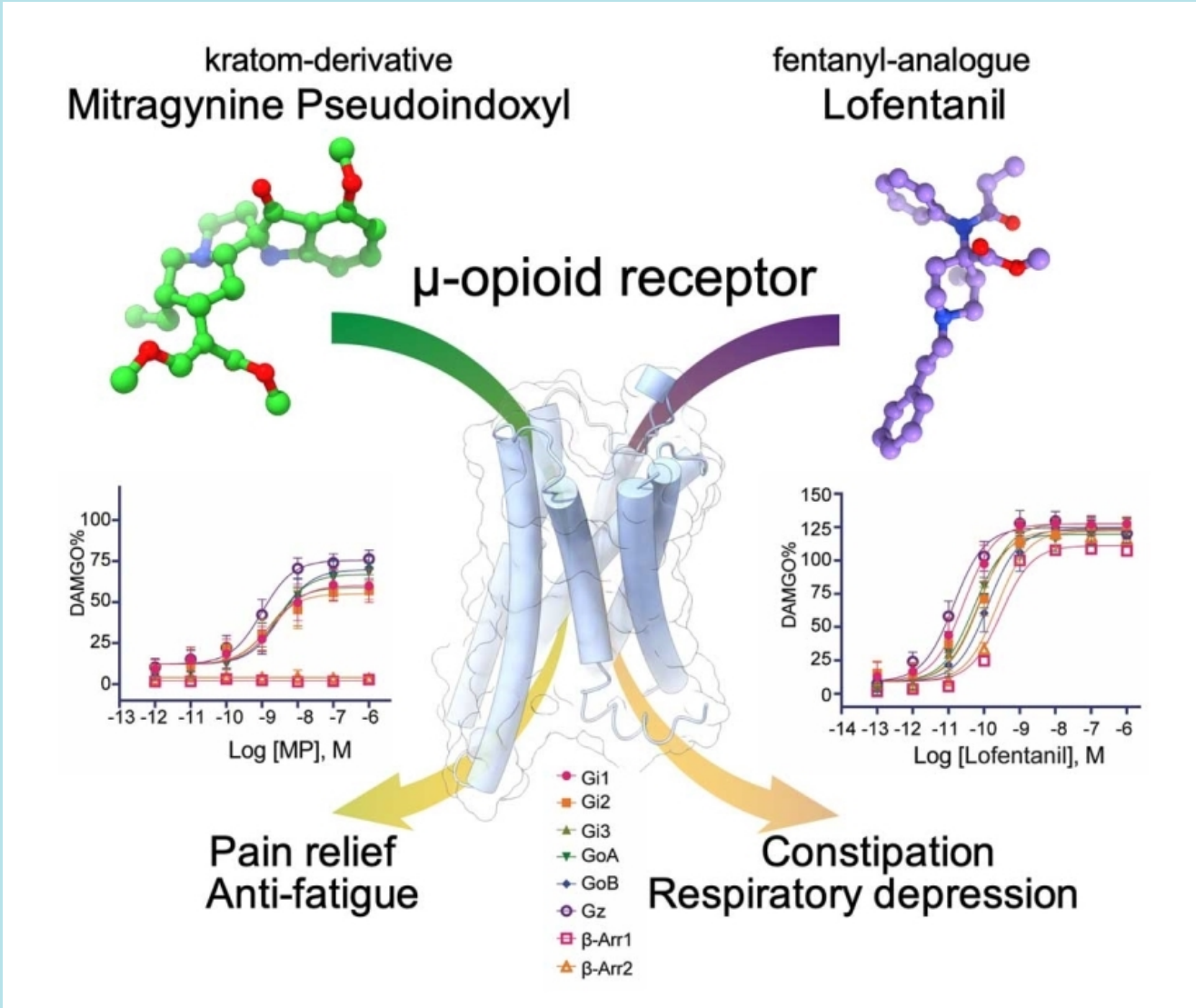
  e.g., placing anabolic steroids used extensively for “body building” and GHB due to its “use” in sexual assault were viewed by many scheduling experts as inappropriate uses of the CSA to control the problems associated with these substances

NIDA-funded study highlighted on NIDA Website: Implications for kratom abuse potential & Safety and New Medicines Development

Insights into distinct signaling profiles of diverse mu-opioid agonists

(Qu et al. Nature Chemical Biology Nov. 2022 Online)

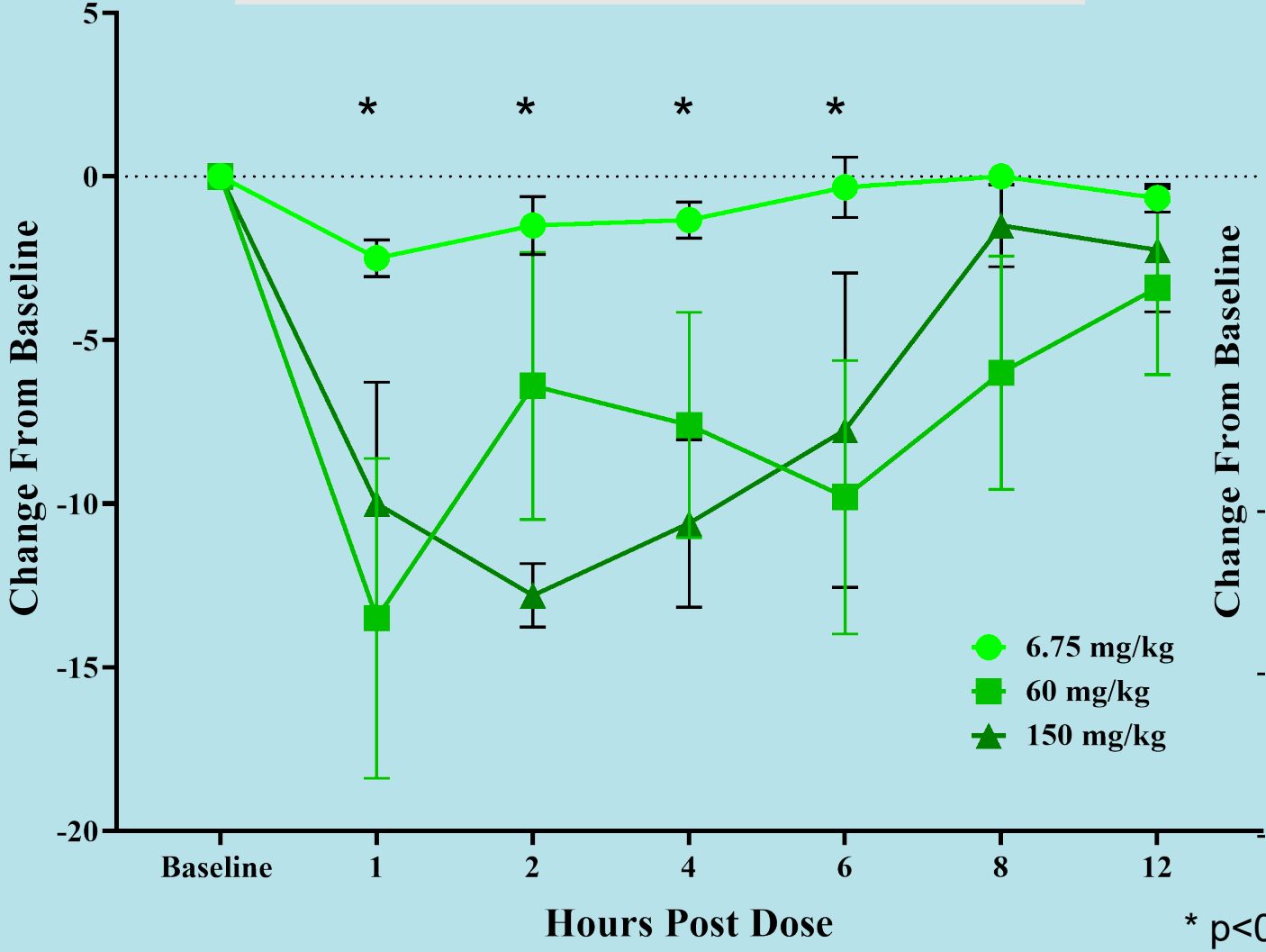
- Chemical structure-related signaling pathways of kratom alkaloid compared to full mu-opioid agonist (Lofentanil)
- MP & Lofentanil have distinct signaling profiles at G protein receptors, β-arrestin recruitment, and ligand binding interactions & dynamics help understand the striking differences in respiratory, safety and possibly abuse potential between MP & full mu-opioid agonists



Respiratory effects of oral mitragynine and oxycodone in a rodent model

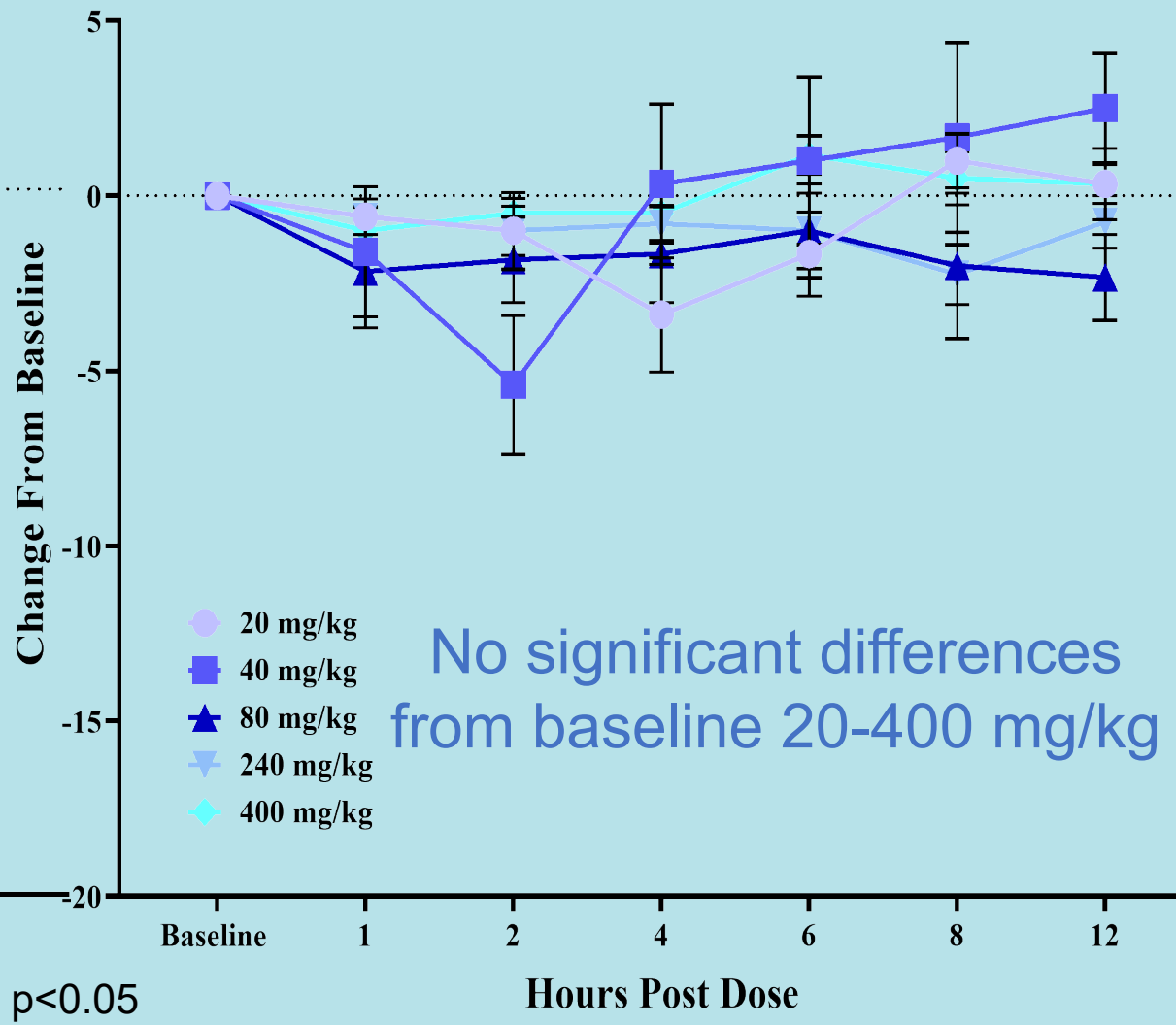
Henningfield, Rodricks, Magnuson & Huestis, Psychopharmacology, 2022

Oxycodone



* p<0.05

Mitragynine



No significant differences from baseline 20-400 mg/kg

10+ Studies Do Not Show Lethal or Meaningful Respiratory Depression for Mitragynine or Kratom “tea” – several studies compared to morphine

- 5 Species
  - Rat
  - Mouse
  - Dog
  - Monkey
  - Human

Populating the Factors – F4, 5 & 6

- *Factors 4 (Scope, duration, and significance of abuse), 5 (Scope, duration, and significance of abuse) & 6 (Public health risk), are the Public Health factors - Does the substance pose a known or imminent risk or threat to the public health?*

- F4 – 6 are key to determining whether scheduling is needed, e.g., caffeine meets pharmacological criteria but factors 4-6 do indicate a threat to public health that warrants CSA scheduling

- F4 – 6 are also the basis for DEA temporary (aka, “emergency”) scheduling orders for a substances not approved by FDA

- **BENEFITS** – are not mentioned in the 8F listing. However, risk is generally evaluated in the context of benefits. Thus, this is where the benefits can also be evaluated. A strong benefit profile is a reminder to avoid overly restricting access by a level of scheduling that may not be warranted. These might include both therapeutic benefits and safety benefits relative to products in the same therapeutic category

Surveillance by Multiple Systems Address Potential Threat to Public Health

- DEA National Forensic Laboratory Information System (NFLIS) and Annual Nation Drug Threat Report
- Drug Abuse Warning Network (DAWN) – “old” 1974-2011 & “new” 2021/2022
- FDA Adverse Events Reporting System (FAERS)
- NIDA Monitoring the Future Survey (MTFS)
- NIDA National Drug Early Warning System (NDEWS)
- SAMHSA National Survey on Drug Use and Health (NSDUH)
- SAMHSA Treatment Episode Data Set (TEDS)
- Published internet surveys (Grundmann, 2017; Coe et al. 2019; Garcia-Romeu et al. 2020) Also see Grundmann et al & Smith et al. summarized in this symposium)

None of these systems suggests kratom is a National Drug Threat and DEA has never listed kratom as such – Nonetheless some people do report “addiction” and/or withdrawal

Do manufactured extract products carry higher risk than ground kratom leaf products?

- Opinions vary widely based on assumption that serious AE & OD rates are higher in the US than Southeast Asia (SEA) where kratom “tea” is more popular than more concentrated extracts - HOWEVER
- *No US surveillance system supports assumption*
- *SEA countries (e.g., Malaysia & Indonesia) lack comparable surveillance system to US*
- *Serious AE and OD rates are very low for all products*
- *Main risks appear due to contamination & adulteration – not product form*
- *No established lethal oral dose for any kratom constituent*

Abuse Potential & Mitragynine Overdoses & Deaths


From DEA Fentanyl Website

- US reported 106,699 overdose deaths in 2021, with 75.7% opioid overdoses
  It is not clear if any of these reports were primarily attributed to kratom
- In most cases where mitragynine is listed as a cause of death, other drugs were present in concentrations that could result in death including new psychoactive substances (NPS); thus, the potential contribution of kratom to U.S. drug overdose deaths is not clear
- BENEFITS: The evidence is strong and widely acknowledged (see NIDA) that many people use kratom to manage OUD and withdrawal and reduce opioid use and other drug use

Populating the Factors – F7

Factor 7 - Psychic or physical dependence liability: Data in F7 are often summarized in F1 but in practice F7 often provides an in-depth evaluation of clinical trial adverse event data potentially suggestive of dependence and withdrawal

Surveys summarized in F4,5&6 can be cited as pertains to withdrawal and “dependence” or SUD

Clinical studies, if available, are most important

Two recent studies help understand kratom dependence and withdrawal risk

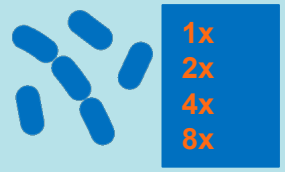
- Johnson Foods Clinical Safety Trial approved by Health Canada
- Vicknasingham et al. 2020 pain tolerance & withdrawal study

Johnson Foods recently completed the largest, most comprehensive kratom clinical trial to date

N = 198
Participants

Randomized
& Placebo
Controlled

3 Kratom
Formulations
Discussing Kratom
Leaf today



4 Dose
Cohorts

30 In-Person
Visits
Over 47 Days

Study Design

Days 0-7
Single Dose
7-Day Monitoring

Days 10-24
15 Consecutive Daily
Doses

Days 25-47
Follow-up Monitoring

Clinical Safety Data & Pharmacokinetics

Respiratory

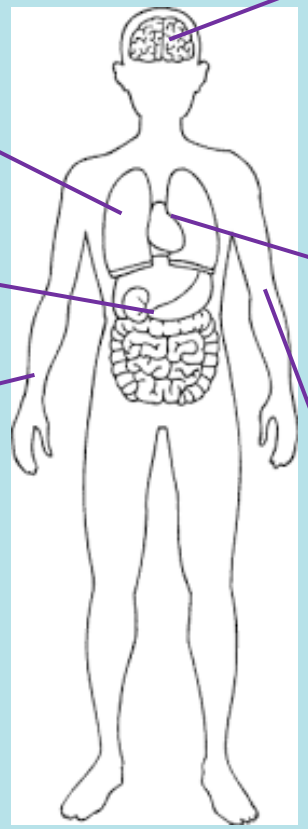
- Blood Oxygen Saturation
- Respiratory Rate

Liver & Kidney

- AST & ALT Liver Enzymes
- Creatinine, BUN & Bilirubin

Hematology

- Basophils
- Eosinophils
- Hematocrit
- Hemoglobin
- Lymphocytes
- MCH
- MCHC
- MCV & MPV
- Monocytes
- Neutrophils
- Platelets
- RBD
- RDW
- WBC



Neurological Effects

- Cognitive Function
- Drug Effect Questionnaire
- COWS & SOWS

Vitals & Cardiac Health

- Heart Rate &Blood Pressure
- 12-Lead ECG
- Body Temperature

Comprehensive Chemistry

- Glucose
- Calcium
- Na, K, CO_2, Cl
- Total Protein, Albumin
- Bilirubin

COWS & SOWS

- Clinical Opiate Withdrawal Scale (COWS): 11-item clinician administered scale assessing opioid withdrawal symptoms
- Subjective Opiate Withdrawal Scale (SOWS): participant self-administered scale to assess 16 symptoms of opioid withdrawal
- Measured at baseline, & 12, 24, 48 & 72 h after 15 days oral kratom
- Multiple doses including up to 53.2 mg mitragynine
- **MAIN FINDING:** COWS & SOWS scores did not increase up to 72 h after the last of 15 daily doses & no participant reported withdrawal symptoms

Clinical Withdrawal Assessment with SOWS & COWS in Pain Study of Chronic daily kratom users

(Vicknasingham et al. 2020)

Summary from Henningfield, Chawarski, Garcia-Romeu et al. 2023 commentary on kratom physical dependence & withdrawal

"… an assessment of a standardized dose of a kratom liquid on pain tolerance in the cold pressor test in "chronic "male participants with a mean of 6.1 years kratom use and self-administered kratom "multiple times per day " for 7 days before testing (Vicknasingam et al., 2020). After testing, withdrawal was assessed using the COWS and self-reports of potential discomfort.

Pain tolerance was significantly increased for two hours following kratom administration as compared to placebo.

No signs or symptoms of withdrawal were evident by COWS or self-reports."

Populating the Factors – F8

Factor 8: Whether the substance is an immediate precursor of an already controlled substance

Not a study-based factor but rather may be considered a factual or administrative determination based on prior scheduling actions and chemical structures and synthesis of the substances

It also implies that prodrugs such as lisdexfetamine which many experts considered to be of lower abuse potential than amphetamine but was placed in Schedule II largely because it was a precursor for CII d-amphetamine and with similar overall pharmacology as d-amphetamine

Abuse Potential & Scheduling Relevant Main Conclusions

- Kratom is not characterized as an “opioid” by nature, chemistry or pharmacology
- Animal pharmacology generally consistent with human reports suggesting low abuse potential and less severe withdrawal compared to typical opioids
- Factors 4-6 do not support the characterization of kratom as a public health threat & DEA has not come to this conclusion, in contrast, informal therapeutic use including OUD and withdrawal is well supported self-reports & field studies
- MG does not appear to have opioid-like respiratory effects in animal studies but respiratory effects with other substances or disease conditions cannot be ruled out. Users should not assume “no risk”
- The problems associated with kratom contamination, adulteration, erratic labeling and claims can be addressed by FDA regulation with performance standards
- Those problems cannot be addressed by FDA regulation if the products are banned and it is foreseeable that they would worsen because the licit market would be quickly replaced by illicit marketers

Assistant Secretary of Health Dr. Brett Giroir Kratom Scheduling Recission letter to DEA, August 16, 2018

- “Pursuant to the Controlled Substances Act... I am rescinding our prior recommendation… that mitragynine and 7-hydroxmitragynine be permanently controlled in Schedule I of the CSA. HHS is instead recommending…[kratom]...not be controlled… until scientific research can sufficiently support such an action…. This decision is based on many factors, in part on new data, and in part on lack of evidence, combined with an unknown and potentially substantial risk to public health if these chemicals were scheduled at this time. Further research [should be] undertaken…”
- “[Scheduling would lead to]… kratom users switching to highly lethal opioids… risking thousands of deaths…”
- “…inhibition of patients discussing kratom use with their primary care physicians leading to more harm, and enhancement of stigma…”
- “I am also concerned about the stifling impact of scheduling kratom on our ability to conduct research…”

Conclusions

- Earlier findings of low abuse potential, lack of public health threat, and evidence suggesting public health benefits support access to kratom – not placement in Schedule I – which generally requires evidence of "high" abuse potential and "known or imminent public health threat"
- New science supports earlier conclusions by DEA, NIDA & DHHS, and the WHO Expert Committee on Drug Dependence & helps understand neuropharmacological differences between kratom, its alkaloids, and classic drugs of abuse, as well as potential therapeutic use
- Although many states are beginning to regulate or considerer kratom regulation, FDA regulation at the national level is needed to for consistent product performance and labeling standards