

PA House Health Committee Hearing

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### **Written Testimony**

Chairpersons Frankel and Rapp, distinguished Committee members, staff, and fellow panelists, thank you for allowing me the opportunity to share my experience and published data on these various substances that are currently available for sale in Pennsylvania: Delta-8 tetrahydrocannabinol (THC), cannabidiol (CBD), tianeptine, and kratom.

Beginning in early 2021, we began to recognize cases of delta-8 tetrahydrocannabinol (THC) toxicity, particularly among children who were admitted to the hospital. The first cases I cared for directly were a 3 and 5 year old brother and sister in February, 2021. They had eaten their father's delta-8 THC gummies that he purchased to help treat chronic back pain. They were sold at a shop that sold cannabidiol (CBD) and kratom products. He assumed that since they were sold legally and alongside CBD products, that they would have similar effects and be safe to take. He was unaware that they might be psychoactive or dangerous. His children found these gummies while he was sleeping and ate most of two small bags. Each ended up comatose with intermittent agitation and slow heart rates in the Pediatric ICU for two days before recovering. Upon speaking with the children's father, he indicated that before bringing them to the hospital, he performed an internet search which reassured him that it was "impossible to overdose" on

THC. He even emailed the company on the product label who encouraged him to watch the children at home and make sure they were hydrated. Since then during the course of the last 2 years, my group of toxicology physicians has cared for 12 additional children, ages 19 months to 14 years, who were admitted to the hospital due to toxicity resulting from ingesting products sold as delta-8 THC. Of those, nearly half required ICU admission, 3 had low blood pressures that required treatment interventions to prevent life threatening consequences, and one 2 year old child had to be placed on a ventilator to protect his airway and ability to breathe.

Pennsylvania poison centers documented 78 human exposure cases related to delta-8 THC in 2022 compared to 0 in 2020 and 33 in 2021. It is important to remember that poison center cases only represent cases that were actively reported and underestimate the true exposure prevalence. Of those poison center cases, more than 1/3 were reported in kids aged 10 or under and 97% of cases in kids under age 6 required management in a healthcare facility.

Delta-8 THC is a psychoactive cannabinoid that is present in very low concentrations in cannabis plants including hemp. At natural concentrations, it is felt to have minimal pharmacologic effect. However, delta-8-THC can be synthesized using a process called cyclization from cannabidiol (CBD). The Agriculture Improvement Act of 2018 (aka the "Farm Bill") defined hemp as including "all derivatives, extracts, cannabinoids, isomers, acids, salts and salts of isomers" of CBD. Delta-8 THC is both an isomer and a derivative of CBD, however it does require synthesis through chemical processing to create sufficient quantities for sale placing it in a legal gray area. (Tagen 2022) From a pharmacologic perspective, delta-8 THC (much like similarly derived delta-10 THC), acts on CBD receptors with similar though less potent clinical effects as delta-9 THC, the psychoactive compound in marijuana that is a Schedule I drug according to the Drug Enforcement Administration (DEA). Depending upon the dose or amount taken, the effects can be the same as delta-9 THC. (Tagen 2022) According to a survey of participants who used delta-8 THC, 68% reported euphoria, 81% reported difficulty concentrating, 80% reported difficulty with short-term memory, and 74% reported an altered sense of time. (Kruger 2022)

Nationwide, poison centers reported 2,362 exposures to delta-8 THC between January 1, 2021 and February 28, 2022. Of those cases, 41% involved children less than 18 years of age and 70% required healthcare facility evaluation with one reported death. (FDA 2022<sup>9</sup>). Cases such as these prompted the Centers for Disease Control and Prevention (CDC) to release a Health Alert Network advisory in September, 2021, warning of the risks associated with delta-8 THC and recommending that consumers be warned of the psychoactive properties of delta-8 THC as well as labeling packages with accurate THC content information. (CDC 2021) The Food and Drug Administration (FDA) has issued letters to multiple manufacturers outlining safety concerns, citing that delta-8-THC is not approved to treat any medical condition or as a food additive, and that packaging lacks adequate directions for use. (FDA 2022<sup>10</sup>)

According to discussions with DEA as well as local school principals and superintendents, THC vape products, including delta-8-THC, have become increasingly common and account for a significant number of seized vape cartridges. An evaluation of vape cartridges seized from high school students in western Pennsylvania over a 3 year period from 2019-2022 showed 17% contained cannabis products. (Debord 2023) Of those, all but one contained either delta-8, delta-9, or both delta-8 and delta-9 THC. More than half of the vape cartridges that contained primarily delta-8-THC also contained delta-9 THC. (Debord 2023) It was not known how the purchased product was labeled or the source of the product, e.g. local store vs. online purchase. It is unclear if products containing both delta-8 and delta-9 THC were labeled as only "delta-8 THC", but both are frequently found in the same products. Hospitals do not have the ability to differentiate delta-8 from delta-9 THC in toxicology testing. Exposure to either can result in positive THC drug testing. Another important finding was that 20.6% of the cannabis vape cartridges contained Vitamin E acetate which is strongly associated with "E-cigarette or Vaping Associated Lung Injury" (EVALI), a condition responsible for thousands of hospitalizations and dozens of deaths. (CDC 2020, Zou 2020)

In addition to concerns about delta-8 THC, FDA has also issued letters to manufacturers of CBD over concerns related to product labeling and therapeutic claims. (FDA 2022<sup>10</sup>) Multiple peer-reviewed reports have found that CBD products are frequently inaccurately labeled, make unsupported therapeutic claims, and either over or under-report the concentrations of CBD present with variability between lot numbers of the same product. (Miller 2022, Johnson 2022, Spindle 2022) In one report, 35% of CBD products contained THC at concentrations <0.3% with 11% of those products labeled “THC Free” and 51% making no mention of THC on the label. (Spindle 2022) While CBD does not impart psychoactive effects and products sold as CBD largely adhere to requirements to maintain THC concentrations <0.3%, consumers cannot rely on the labeling of the product to guide purchases or predict intended effect.

Recently there has been increasing popular media and regulatory attention paid towards tianeptine. Tianeptine is a pharmaceutical agent approved for the treatment of depression in some European countries that has antidepressant, stimulant, and opioid properties. (McEwen 2009) It has not been approved for use in the U.S. for treatment of any condition. The FDA has issued warnings regarding risks associated with tianeptine as well as concerns that products are “making dangerous and unproven claims that tianeptine can improve brain function and treat anxiety, depression, pain, opioid use disorder, and other conditions.” (FDA 2022<sup>11</sup>) These concerns are founded in published accounts of non-medical tianeptine use and toxicity. Reports of tianeptine exposure, toxicity, and withdrawal began to increase significantly in 2015-2016. (El Zahran 2018) Acute exposures reported to poison centers can result in agitation due to the antidepressant effects or opioid toxicity including sedation and respiratory depression requiring naloxone. (Rushton 2021) Most patients required hospitalization with almost 2/3 of admitted patients requiring intensive care unit treatment. (Rushton 2021) At least 2 deaths have been reported due to tianeptine toxicity. (Bakota 2018) Here in Pennsylvania, poison centers have received 9 reports of tianeptine toxicity which all required hospitalization. Just this past week, I cared for an individual who started taking tianeptine to self-treat severe depression associated with a family tragedy. Unfortunately, once he started taking tianeptine, he was unable to stop due to severe withdrawal symptoms including typical opioid withdrawal as well as severe

worsening of his depression. Managing this combined withdrawal syndrome requires coordinated care and careful monitoring. While some countries have approved tianeptine for the management of depression, that approval is contingent upon medical supervision and prescribing. Tianeptine has a complex pharmacologic profile that can result in toxicity, dependence, addiction, and withdrawal, particularly with unregulated, unsupervised use.

Another unregulated plant product commonly sold alongside CBD, delta-8 THC, and tianeptine is “kratom”. Kratom is a common name for a plant, *Mitragyna speciosa*, native to Southeast Asia which contains multiple psychoactive alkaloids, but the primary active ingredient is mitragynine. (Eastlack 2020) A secondary constituent and metabolite, 7-hydroxy(OH)-mitragynine, has been shown to have more potent opioid effects with associated risk of dependence and addictive behavior. (Hemby 2018) Mitragynine and 7-OH-mitragynine confer both mild stimulant and opioid properties with many users reporting stimulant effects at lower doses and opioid effects with higher doses. (Grundman 2017) Pharmacology studies indicate that the activity on the opioid receptor differs from typical opioids and does not initiate the signaling pathway that is associated with respiratory depression. (Varadi 2016) Kratom has been used homeopathically in Southeast Asia for many years and more recently in the U.S. to self-treat pain, opioid withdrawal symptoms, and anxiety as well as recreationally. Nationwide, an estimated 1.7 million people used kratom in 2021. (SAMHSA 2022) A review of more than 2,300 cases of kratom exposure reported to poison centers showed that between 10-20% of cases included agitation, elevated heart rate, sedation, and/or vomiting with 6% of cases reporting seizures, 3% with respiratory depression, and 0.6% with cardiac or respiratory arrest. (Eggleston 2019) While deaths have been associated with mitragynine and 7-OH-mitragynine, they are nearly all associated with other drugs that likely contributed to the deaths. (UN 2021) In Pennsylvania, 144 cases have been reported to PA poison centers since 2020. Of those, more than half (57%) required hospital treatment with 21% of those patients admitted to the intensive care unit.

At this time, mitragynine and 7-OH-mitragynine are not approved for therapeutic use in the U.S. (FDA 2022<sup>12</sup>) However, given its historical use and anecdotal reports of benefit combined with its pharmacologic profile, there is interest in evaluating clinical use of kratom products with enforced quality standards and established dosing regimens for the management of pain and opioid use disorder. (Grundman 2018, Eastlack 2020)

Despite the potential for therapeutic benefit, the unregulated marketplace allows for unsubstantiated claims of benefits, variable concentrations of the active ingredients, as well as adulteration with unanticipated toxins. In natural *Mitragyna speciosa* plants, mitragynine accounts for ~66% of the alkaloids present while 7-OH-mitragynine accounts for ~2%. (Lydecker 2016) Evaluation of “kratom” purchased online indicates that many of these products contain substantially larger, up to 500% of expected, concentrations of 7-OH-mitragynine which is the substance primarily associated with opioid activity and dependence. (Lydecker 2016) Additionally, internet vendors typically do not require age verification and frequently do not recognize local or state regulation of kratom products. (Williams 2020) Kratom products have also been found to be contaminated with heavy metals such as lead or nickel and Salmonella. (FDA 2019; Dixon 2019) While kratom products have been widely used for self-therapeutic purposes throughout the world, they are associated with dependence, addiction, withdrawal, and adverse effects which is complicated by the variability in concentrations of the psychoactive constituents present in different samples and contamination with non-pharmaceutical substances.

In conclusion, we all see the signs at gas stations, vape shops, and other outlets for products including delta-8 THC, CBD, kratom, and tianeptine. They are also sold on numerous sites online. Consumers throughout Pennsylvania can easily find and purchase these products. However, it is less clear that consumers truly understand the effects of the products they are purchasing including potential risks and the current state of peer-reviewed scientific evidence of effectiveness. Even if these data are understood, purchasers are unable to make truly informed

decisions about products as most labeling either does not reflect all the active ingredients present or provides misleading and inaccurate claims regarding concentrations of those substances and associated health effects. While new regulations should be approached cautiously with consideration of unintended consequences, data, and public opinion, accurate information regarding substances that people ingest is critical to supporting informed and autonomous decision-making. People have a right to know what they are putting in their bodies and storing in their homes while vendors have a responsibility to provide their customers with accurate information.

Thank you again for the opportunity to share my thoughts and opinions developed from personal experience and review of medical literature and regulatory data. I am happy to take any questions the committee members might have.

## Key Takeaways

- THC can be associated with significant toxicity, primarily in children
- Delta-8 THC, while derived and synthesized from CBD in hemp, is structurally and pharmacologically much more similar to delta-9 THC
- Adolescents have easy access to THC-containing products, particularly in the form of vape cartridges
- THC gummies are the primary source of severe toxicity in young children
- Tianeptine has complex pharmacologic properties with structure and activity similar to prescription tricyclic antidepressants as well as opioids
- Tianeptine toxicity can be severe and has been associated with deaths
- Tianeptine use can lead to dependence and withdrawal that can be difficult to treat
- Kratom refers to a plant with multiple psychoactive alkaloids, mainly mitragynine and 7-OH-mitragynine, which have both stimulant and opioid properties
- Kratom use, particularly 7-OH-mitragynine, is associated with acute toxicity as well as misuse, dependence, and withdrawal with fatalities typically associated with combined substance use
- Mitragynine has therapeutic potential, but has not been rigorously tested for clinical use
- Neither delta-8 THC, tianeptine, nor kratom have been approved by the FDA for treatment of any medical condition and they are not “generally recognized as safe and effective”
- Unregulated products including delta-8 THC, CBD, tianeptine, and kratom frequently do not accurately report and label the constituents and concentrations of the ingredients in their products
- Unregulated products frequently make claims regarding therapeutic effect that are not supported by peer-reviewed literature or the FDA



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