NOVEL PSYCHOACTIVE SUBSTANCES: ISOTONITAZENE

JUNE 2023

The Legislative Analysis and Public Policy Association (LAPPA) is monitoring the emergence of novel psychoactive substances (NPS) appearing on the illicit drug market in the United States. The term "novel" does not denote a brand new, never-before-seen substance, but rather a substance that is newly available in the drug market. This fact sheet, the fourth in a series highlighting these dangerous drugs, is an examination of isotonitazene (or "Iso"), a synthetic opioid recently classified as a Schedule I controlled substance under the federal Controlled Substances Act (CSA).

Scientists first synthesized isotonitazene in the mid-1950s as part of an effort to develop safer opioid analgesics.[1] This effort did not prove successful, and there is currently no accepted medical use for isotonitazene in the U.S. or in any other country. Isotonitazene is a mu-opioid receptor agonist and is 500 times more potent than morphine.[2] The chemical structure of isotonitazene resembles other synthetic opioids, such as etonitazene and clonitazene, which are both Schedule I controlled substances under the CSA. As with other opioids, naloxone is effective in reversing an isotonitazene-caused overdose.

Isotonitazene first emerged on the U.S. illicit drug market in April 2019 when U.S. Customs and Border Protection officials seized 1.6 grams of it in California. Since the first identification of isotonitazene in the U.S., the number of confirmed cases continues to increase. According to the National Forensic Laboratory Information System database, there were 738 reported seizures of isotonitazene between 2019 and 2022 in the U.S.[3] Experts believe that isotonitazene is mixed into other drugs to make the combined product more potent and profitable for the dealer. Law enforcement reports encountering isotonitazene both in powder form, which appears yellow, brown, or off-white in color, and also as counterfeit pills. Based on the most recent data available as of June 2021, there have been more than 250 reported fatalities in the U.S. involving isotonitazene.[4]

SCHEDULING ISOTONITAZINE

On August 20, 2020, the U.S. Drug Enforcement Administration (DEA) issued a temporary scheduling order to place isotonitazene in Schedule I of the CSA.[5] The DEA declared the temporary scheduling necessary to "avoid an imminent hazard to public safety."[6] The DEA cited isotonitazene's high risk of abuse, similarity to other Schedule I controlled substances, and lack of accepted medical use as justification for temporarily placing it in Schedule I.[7] The temporary scheduling order was set to expire on August 20, 2022 unless the DEA extended the order or made the scheduling permanent.

---

[1] "Isotonitazene," Drug Enforcement Administration, last modified December 2022, https://www.deadiversion.usdoj.gov/drug_chem_info/isotonitazene.pdf.
[2] Mu-opioid receptors are a type of receptor in the brain that is responsible for pain control, drug reward, and addictive behaviors. Mu-opioid receptor agonists, such as morphine and heroin, effectively bind to mu-opioid receptors and produce a physiological response in the body. Gavril W. Pasternak and Ying-Xian Pan, "Mu-opioids and Their Receptors: Evolution of a Concept," *Pharmacological Reviews* 64, no. 4 (October 2013): 1257-1317, https://doi.org/10.1124/pr.112.007138.
[3] U.S. Drug Enforcement Administration, Diversion Control Division. (2023, May 2). Isotonitazene reported nationally [NFLIS-Drug Data Query System analysis]. Retrieved from https://www.nflis.deadiversion.usdoj.gov/.
[4] Marthe M. Vandeputte, et al., "The Rise and Fall of Isotonitazene and Brophine: Two Recent Stars in the Synthetic Opioid Firmanment," *Journal of Analytical Toxicology* 46, no. 2 (March 2022): 117, https://doi.org/10.1093/jat/bkab082.
[5] Temporary Placement of Isotonitazene in Schedule I, 85 Fed. Reg. 51,342 (Aug. 20, 2020).
[6] *Id.*
[7] *Id.*

In November 2020, the Director-General of the World Health Organization recommended to the Secretary-General of the United Nations (Secretary-General) that isotonitazene be placed in Schedule I of the United Nations Single Convention on Narcotic Drugs (Single Convention)[8] due to the substance's similarity to other drugs already placed in Schedule I due to their potential for dependance and abuse.[9] On June 10, 2021, the Secretary-General advised the U.S. Secretary of State that the United Nations Commission on Narcotic Drugs (Commission) voted to place isotonitazene in Schedule I of the Single Convention.[10] If the Commission votes to add a substance to one of the schedules, the terms of the Single Convention obligate its member states to control the substance under their respective national drug control laws.[11] Under 21 U.S.C. 811(d)(1), if control of a substance is required "by United States obligations under international treaties, conventions, or protocols in effect on October 27, 1970, the Attorney General shall issue an order controlling such drug under the schedule he deems most appropriate to carry out such obligations, without regard to the findings required by 21 U.S.C. 811(a) or 812(b), and without regard to the procedures prescribed by 21 U.S.C. 811(a) and (b)."[12] Therefore, to fulfill U.S. obligations under the Single Convention, the DEA issued an order on November 4, 2021 to permanently place isotonitazene in Schedule I of the CSA effective December 6, 2021.[13]

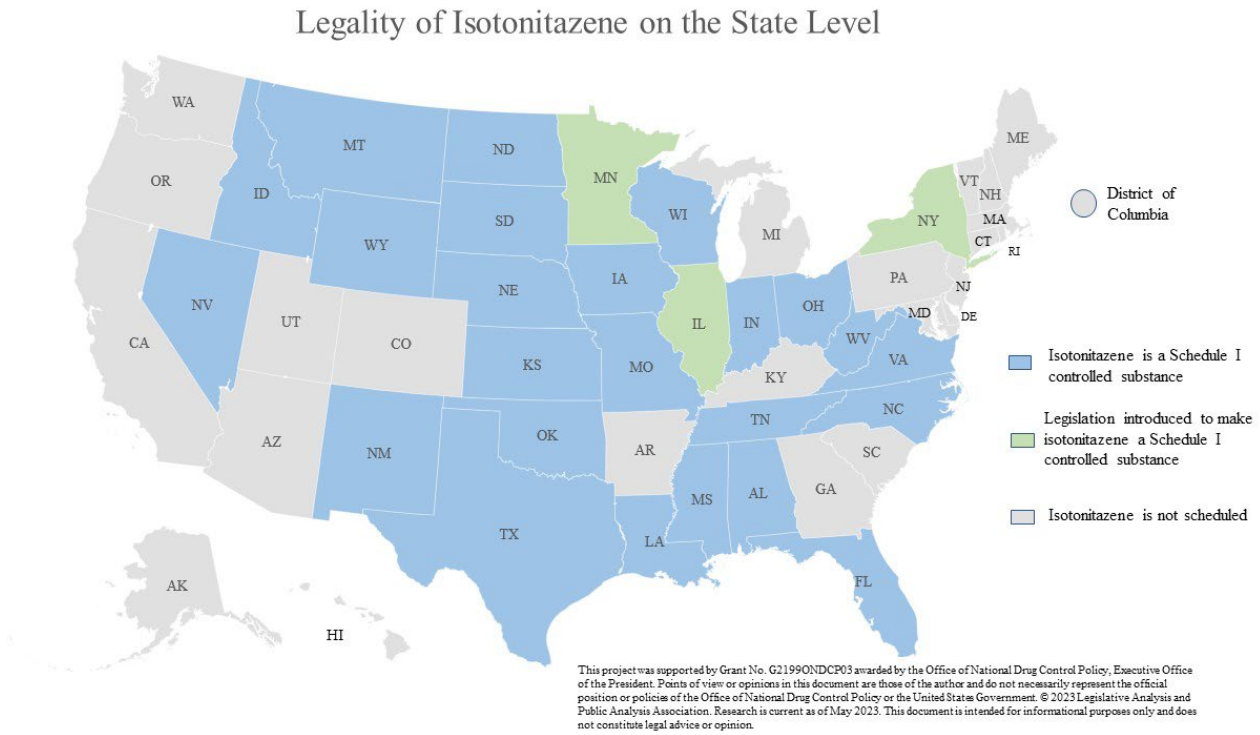
In addition to the scheduling of isotonitazene on the federal level, as of May 2023, 24 states now classify isotonitazene as a Schedule I controlled substance (Alabama, Florida, Idaho, Indiana, Iowa, Kansas, Louisiana, Mississippi, Missouri, Montana, Nebraska, Nevada, New Mexico, North Carolina, North Dakota, Ohio, Oklahoma, South Dakota, Tennessee, Texas, Virginia, West Virginia, Wisconsin, and Wyoming).[14] Moreover, thus far in 2023, three states (Illinois, Minnesota, and New York)[15] have introduced legislation to make isotonitazene a Schedule I controlled substance.

CONCLUSION

Although isotonitazene has been listed as a Schedule I controlled substance on the federal level and in a number of states, the prevalence of isotonitazene will likely continue to increase in the U.S. illicit drug market along with other novel synthetic opioids. To ensure public safety and reduce harm, public health and safety officials should advise their communities about isotonitazene (and other potent novel synthetic opioids) and the dangers associated with its use. LAPPA will continue to monitor its spread and any new regulatory responses at the state and federal levels.

---

[8] Single Convention on Narcotic Drugs, March 30, 1961, 18 U.S.T. 1407 (entered into force June 24, 1967).
[9] Placement of Isotonitazene in Schedule I, 86 Fed. Reg. 60,761 (Nov. 4, 2021).
[10] *Id.*
[11] *Id.*
[12] *Id.*
[13] *Id.*
[14] ALA. ADMIN. CODE r. § 420-7-2 App. (2022). Effective January 5, 2022; FLA. ADMIN. CODE ANN. r. 2ER22-1 (2023). Effective April 26, 2022; IDAHO CODE ANN. § 37-2705 (West 2022). Effective July 1, 2022; IND. CODE ANN. § 35-48-2-4 (West 2022). Effective July 1, 2021; IND. CODE ANN. § 35-48-2-4 (West 2022). Effective July 1, 2021; IND. CODE ANN. § 35-48-2-4 (West 2022). Effective July 1, 2021; IOWA CODE ANN. § 124.204 (West 2022). Effective May 10, 2021; KAN. STAT. ANN. § 65-4105 (West 2022). Effective June 9, 2022; LA. STAT. ANN. § 40:964 (West 2022). Effective August 1, 2022; MISS. CODE ANN. § 41-29-113 (West 2022). Effective July 1, 2021; MO. CODE REGS. ANN. tit. 19, § 30-1.002 (West 2023). Effective November 16, 2020; S.B. 67, 2023 Leg., Reg. Sess. (Mont. 2023) (signed into law April 19, 2023); NEB. REV. STAT. ANN. § 28-405 (West 2022). Effective August 18, 2021; NEV. ADMIN. CODE § 453.510 (West 2022). Effective June 13, 2022; N.M. CODE R. § 16.19.20.65 (West 2023). Effective September 14, 2021; N.C. GEN. STAT. ANN. § 90-89 (West 2022). Effective December 1, 2021; N.D. CENT. CODE ANN. § 19-03.1-05 (West 2021). Effective April 16, 2021; OHIO ADMIN. CODE 4729:9-1-01 (West 2022). Effective October 19, 2020; S.B. 452, 2023-2024 Leg., Reg. Sess. (Okla. 2023) (signed into law April 28, 2023); S.D. CODIFIED LAWS § 34-20B-12 (West 2023). Effective February 17, 2021; TENN. COMP. R. & REGS. 0940-06-01-.01 (West 2022). Effective December 23, 2021; TEX. HEALTH & SAFETY CODE ANN. § 481.032 (West 2021). Effective July 17, 2022.; VA. CODE ANN. § 54.1-3446 (West 2022). Effective June 8, 2023; W. VA. CODE ANN. § 60A-2-204 (West 2023). Effective July 1, 2021; WIS. ADMIN. CODE CSB § 2.72 (West 2022). Effective June 5, 2020; and 015.0015-1 WYO. CODE R. § 3 (West 2023). Effective August 28, 2020.
[15] S.B. 1987, 103rd Gen. Assemb., Reg. Sess. (Ill. 2023); H.F. 1665, 2023-2024 Leg., Reg. Sess. (Minn. 2023); and S. 4007 and A. 3007, 2023-2024 Leg., Reg. Sess. (N.Y. 2023).



This project was supported by Grant No. G2199ONDCP03 awarded by the Office of National Drug Control Policy, Executive Office of the President. Points of view or opinions in this document are those of the author and do not necessarily represent the official position or policies of the Office of National Drug Control Policy or the United States Government. Research is current as of May 2023. This document is intended for informational purposes only and does not constitute legal advice or opinion.

RESOURCES

"Emergence of New Synthetic Opioid Isotonitazene," United Nations Office on Drugs and Crime, last modified June 2020, https://www.unodc.org/LSS/Announcement/Details/2d09cc01-3272-45e1-a898-b98898b9215c.

"New, Dangerous Synthetic Opioid in D.C., Emerging in Tri-state Area," Drug Enforcement Administration, last modified June 1, 2022, https://www.dea.gov/stories/2022/2022-06/2022-06-01/new-dangerous-synthetic-opioid-dc-emerging-tri-state-area.

Shover, Chelsea L., et al., "Emerging Characteristics of Isotonitazene Involved Overdose Deaths: A Case-control Study," *Journal of Addiction Medicine* 15, no. 5 (Sept/Oct 2021): 429-431, https://doi.org/10.1097/ADM.0000000000000775.

Vandeputte, Marthe M., et al., "The Rise and Fall of Isotonitazene and Brophine: Two Recent Stars in the Synthetic Opioid Firmament," *Journal of Analytical Toxicology* 46, no. 2 (March 2022): 115-121, https://doi.org/10.1093/jat/bkab082.

ABOUT LEGISLATIVE ANALYSIS AND PUBLIC POLICY ASSOCIATION

The Legislative Analysis and Public Policy Association (LAPPA) is a 501(c)(3) nonprofit organization whose mission is to conduct legal and legislative research and analysis and draft legislation on effective law and policy in the areas of public safety and health, substance use disorders, and the criminal justice system.

LAPPA produces timely model laws and policies that can be used by national, state, and local public health, public safety, and substance use disorder practitioners who want the latest comprehensive information on law and policy as well as up-to-the-minute comparative analyses, publications, educational brochures, and other tools ranging from podcasts to fact sheets. Examples of topics on which LAPPA has assisted stakeholders include law enforcement/community engagement, naloxone laws, alternatives to incarceration for those with substance use disorders, medication for addiction treatment in correctional settings, and the involuntary commitment and guardianship of individuals with alcohol or substance use disorders.

For more information about LAPPA, please visit: https://legislativeanalysis.org/.