6/17/20

The following information is being provided pursuant to the requirements of Executive Order 2011-01K and Senate Bill 2 of the 129th General Assembly, which require state agencies, including the State of Ohio Board of Pharmacy, to draft rules in collaboration with stakeholders, assess and justify an adverse impact on the business community (as defined by S.B. 2), and provide an opportunity for the affected public to provide input on the following rules.

Amend:

- 4729:9-1-01 – Adds isotonitazene as a schedule I controlled substance. **NOTE:** This amendment is intended to make permanent emergency rule 4729:9-1-01.2 of the Administrative Code.

Comments on the proposed rules will be accepted until close of business on June 30, 2020. Please send all comments to the following email address: RuleComments@pharmacy.ohio.gov

In addition, please copy your comments to: CSIPublicComments@governor.ohio.gov

Business Impact Analysis

Agency, Board, or Commission Name: State of Ohio Board of Pharmacy

Rule Contact Name and Contact Information: Cameron McNamee
Cameron.mcnamee@pharmacy.ohio.gov

Regulation/Package Title (a general description of the rules' substantive content):

Isotonitazene

Rule Number(s): 4729:9-1-01

Date of Submission for CSI Review: 6/17/20

Public Comment Period End Date: 6/30/20

Rule Type/Number of Rules:

New/___ rules

No Change/____ rules (FYR? ___)

Amended/__1_ rules (FYR? _Y_)

Rescinded/____ rules (FYR? ___)

The Common Sense Initiative is established in R.C. 107.61 to eliminate excessive and duplicative rules and regulations that stand in the way of job creation. Under the Common Sense Initiative, agencies must balance the critical objectives of regulations that have an adverse impact on business with the costs of compliance by the regulated parties. Agencies should promote transparency, responsiveness, predictability, and flexibility while developing regulations that are fair and easy to follow. Agencies should prioritize compliance over punishment, and to that end, should utilize plain language in the development of regulations.

Reason for Submission

1. **R.C. 106.03 and 106.031 require agencies, when reviewing a rule, to determine whether the rule has an adverse impact on businesses as defined by R.C. 107.52. If the agency determines that it does, it must complete a business impact analysis and submit the rule for CSI review.**

   Which adverse impact(s) to businesses has the agency determined the rule(s) create?

   The rule(s):

   a. ☐ **Requires a license, permit, or any other prior authorization to engage in or operate a line of business.**

   b. ☒ **Imposes a criminal penalty, a civil penalty, or another sanction, or creates a cause of action for failure to comply with its terms.**

Violation of these rules would result in a criminal penalty in accordance with Chapter 2925 of the Ohio Revised Code.

   c. ☐ **Requires specific expenditures or the report of information as a condition of compliance.**

   d. ☐ **Is likely to directly reduce the revenue or increase the expenses of the lines of business to which it will apply or applies.**

Regulatory Intent

2. **Please briefly describe the draft regulation in plain language.**
   Please include the key provisions of the regulation as well as any proposed amendments.

Amend:

- 4729:9-1-01 – Adds isotonitazene as a schedule I controlled substance. **NOTE:** This amendment is intended to make permanent emergency rule 4729:9-1-01.2 of the Administrative Code.

3. **Please list the Ohio statute(s) that authorize the agency, board or commission to adopt the rule(s) and the statute(s) that amplify that authority.**

   The proposed rule is authorized by sections 4729.26 and 3719.28 of the Ohio Revised Code. The following sections of the Ohio Revised Code are also considered authorizing statutes for this rule package: 3719.44.

4. **Does the regulation implement a federal requirement? Is the proposed regulation being adopted or amended to enable the state to obtain or maintain approval to administer and enforce a federal law or to participate in a federal program?**
   If yes, please briefly explain the source and substance of the federal requirement.

These rules do not implement a federal requirement.

5. **If the regulation includes provisions not specifically required by the federal government, please explain the rationale for exceeding the federal requirement.**

By scheduling isotonitazene as a schedule I controlled substance, an opioid drug not approved by the FDA, the Board hopes to reduce access to the supply of this potentially lethal drug and assist law enforcement is prosecuting individuals trafficking in these drugs. Further justification for schedule can be found in the 8-factor analysis produced by the Board that is included as an appendix to this document.

6. **What is the public purpose for this regulation (i.e., why does the Agency feel that there needs to be any regulation in this area at all)?**

Section 4729.26 and 3719.28 of the Ohio Revised Code authorizes the state board of pharmacy to adopt rules governing dangerous drugs, including controlled substances.

In the United States, isotonitazene is considered one of the most persistent and prevalent new opioids. Data from the Ohio Bureau of Criminal Investigation finds that isotonitazene has been identified in the state at least 14 times since the start of 2020.

By scheduling isotonitazene as a schedule I controlled substance, an opioid drug not approved by the FDA, the Board hopes to reduce access to the supply of this potentially lethal drug and assist law enforcement is prosecuting individuals trafficking in these drugs. Further justification for schedule can be found in the 8-factor analysis produced by the Board that is included as Appendix I of this document.

7. **How will the Agency measure the success of this regulation in terms of outputs and/or outcomes?**

As isotonitazene is considered one of the most persistent and prevalent new opioids in the US, the Board will work with law enforcement and forensic laboratories to ensure that they are made aware of the changes.

8. **Are any of the proposed rules contained in this rule package being submitted pursuant to R.C. 101.352, 101.353, 106.032, 121.93, or 121.931?**
   If yes, please specify the rule number(s), the specific R.C. section requiring this submission, and a detailed explanation.

No.

Development of the Regulation

9. Please list the stakeholders included by the Agency in the development or initial review of the draft regulation.
If applicable, please include the date and medium by which the stakeholders were initially contacted.

The rule in this package was reviewed by representatives of the Ohio Bureau of Criminal Investigation.

10. What input was provided by the stakeholders, and how did that input affect the draft regulation being proposed by the Agency?

- Stakeholders asked that the permanent rule (please note this provision is effective as part of emergency rule 4729:9-1-01.2 of the Administrative Code) classify the drug as an opiate rather than a opium derivative as listed in the emergency rule. This change was incorporated into the proposed rule amendment.

11. What scientific data was used to develop the rule or the measurable outcomes of the rule? How does this data support the regulation being proposed?

After a thorough review of all available data, the Board found that that isotonitazene:

1. Has a high potential for abuse;
2. Has no accepted medical use in treatment in this state;
3. Lacks accepted safety for use in treatment under medical supervision; and
4. Poses a risk to the public health of the citizens in this state.

The supporting data is included in the Board's scheduling resolution that is included with this document.

12. What alternative regulations (or specific provisions within the regulation) did the Agency consider, and why did it determine that these alternatives were not appropriate? If none, why didn't the Agency consider regulatory alternatives?

As the regulation is essential to protecting the public's safety by ensuring uniform rules for controlled substances, the State of Ohio Board of Pharmacy did not consider any regulatory alternatives.

13. Did the Agency specifically consider a performance-based regulation? Please explain.
Performance-based regulations define the required outcome, but don't dictate the process the regulated stakeholders must use to achieve compliance.

The Board did not consider a performance-based regulation for the rule in this package. It is the Board's responsibility to ensure that regulations are consistent throughout the state. It was the determination of the Board that the rule did not lend itself to performance-based regulations.

14. What measures did the Agency take to ensure that this regulation does not duplicate an existing Ohio regulation?

The Board of Pharmacy's Director of Policy and Communications reviewed the proposed rule to ensure that the regulation does not duplicate another State of Ohio Board of Pharmacy regulation.

15. Please describe the Agency's plan for implementation of the regulation, including any measures to ensure that the regulation is applied consistently and predictably for the regulated community.

The rule will be posted on the Board of Pharmacy's web site, information concerning the rule will be included in materials e-mailed to licensees, law enforcement, and laboratories. Board of Pharmacy staff are also available via phone or email to answer questions regarding implementation of the rule.

Board of Pharmacy staff receive regular updates on rules via a monthly internal newsletter, biannual staff meetings featuring a regulatory update, mandatory all-day law reviews for new employees, email updates and quarterly webinars from the Director of Policy and Communications and feedback from the Board's legal department for every citation submitted.

Adverse Impact to Business

16. Provide a summary of the estimated cost of compliance with the rule. Specifically, please do the following:

a. Identify the scope of the impacted business community; and

Persons possessing isotonitazene. NOTE: Research and other approved labs are lawfully able to possess schedule I controlled substances with valid licensure from the DEA and the Board of Pharmacy.

b. Identify the nature of all adverse impact (e.g., fees, fines, employer time for compliance,); and

Violation of these rules would result in a criminal penalty in accordance with Chapter 2925 of the Ohio Revised Code.

c. Quantify the expected adverse impact from the regulation.
The adverse impact can be quantified in terms of dollars, hours to comply, or other factors; and may be estimated for the entire regulated population or for a "representative business." Please include the source for your information/estimated impact.

Amend:

This should not have any adverse impact on business, as it is intended to target a drug that has not been approved by the FDA and has no current medical use.

17. Why did the Agency determine that the regulatory intent justifies the adverse impact to the regulated business community?

After a thorough review of all available data, the Board found that that isotonitazene:

1. Has a high potential for abuse;
2. Has no accepted medical use in treatment in this state;
3. Lacks accepted safety for use in treatment under medical supervision; and
4. Poses a risk to the public health of the citizens in this state.

The supporting data is included in the Board's scheduling resolution that is included with this document.

Regulatory Flexibility

18. Does the regulation provide any exemptions or alternative means of compliance for small businesses? Please explain.

This rule does not provide any exemptions or alternative means of compliance for small businesses. The law does not differentiate on the size of the business and therefore the regulation is uniform across Ohio.

19. How will the agency apply Ohio Revised Code section 119.14 (waiver of fines and penalties for paperwork violations and first-time offenders) into implementation of the regulation?

The State of Ohio Board of Pharmacy does not fine licensees or impose penalties for first-time paperwork violations. However, any failure of a standard of care in the practice of pharmacy is not considered a paperwork error but a quality assurance issue by the licensee that is necessary for the protection of the public.

20. What resources are available to assist small businesses with compliance of the regulation?

Board of Pharmacy staff is available by telephone and e-mail to answer questions. Board staff members also provide presentations to groups and associations who seek updates on current regulations and host regional meetings to discuss changes to Ohio laws and rules.

Proposed Rule

4729:9-1-01 – Schedule I Controlled Substances

…

(B) Narcotics-opiates

Any of the following opiates, including their isomers, esters, ethers, salts, and salts of isomers, esters, and ethers, unless specifically excepted under federal drug abuse control laws, whenever the existence of these isomers, esters, ethers, and salts is possible within the specific chemical designation (for purposes of 3-methylthiofentanyl only, the term isomer includes the optical and geometric isomers):

…

(68) N,N-Diethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1H-benzimidazole-1-ethanamine (isotonitazene).

Appendix I

PROPOSAL TO PERMANENTLY SCHEDULE ISOTONITAZENE

Section 1: Summary

The State of Ohio Board of Pharmacy (Board), pursuant to section 3719.44 of the Ohio Revised Code, proposes the placement of isotonitazene into Schedule I as an opiate.

Section 2: Background

Pursuant to section 3719.44 the Board may add or transfer a compound, mixture, preparation, or substance to schedule I when it appears that there is a high potential for abuse, that it has no accepted medical use in treatment in this state, or that it lacks accepted safety for use in treatment under medical supervision.

In making a determination to add an unscheduled compound, the Board is required to consider the following eight criteria:

(1) The actual or relative potential for abuse;
(2) The scientific evidence of the pharmacological effect of the substance;
(3) The state of current scientific knowledge regarding the substance;
(4) The history and current pattern of abuse;
(5) The scope, duration, and significance of abuse;
(6) The risk to the public health;
(7) The potential of the substance to produce psychic or physiological dependence liability; and
(8) Whether the substance is an immediate precursor.

Section 3: Evaluating Isotonitazene Under the Eight Criteria

(1) The actual or relative potential for abuse.

Isotonitazene is a synthetic opioid bearing structural resemblance to etonitazene, a synthetic opioid that is classified as a Schedule I controlled substance in Ohio and nationally. Isotonitazene and similar analogues (e.g. etonitazene, metonitazene, and clonitazene), known as benzimidazole opioids, were first synthesized and reported in the literature in the 1950s.[i] Most recently, isotonitazene was reported to be highly potent and efficacious for activation of μ-opioid receptors.[ii]

A review of U.S. isotonitazene-related deaths found that the drug is being used by individuals who are also currently abusing opioids and other controlled substances. Of the 18 deaths [Illinois (n=9), Indiana (n=7), Minnesota (n=1), and Wisconsin (n=1)] reported in the U.S., at least six of the decedents included individuals with a documented history of opioid-use disorder.[iii] In addition, isotonitazene was identified along with one or more other psychoactive substances (controlled drugs and new psychoactive substances) in all the deaths, which suggests that polydrug use was common in these individuals.[iv]

Pharmacological data suggest that the group of synthetic opioids that includes isotonitazene (along with etonitazene, metonitazene, and clonitazene) has potency similar to or greater than fentanyl based on their structural modifications. Etonitazene is reported to be the most potent of the group followed by isotonitazene and metonitazene.[v] The toxicity of isotonitazene has not been

extensively studied but recent association with drug user death leads professionals to believe this new synthetic opioid retains the potential to cause widespread harm and is of public health concern.[vi]

(2) The scientific evidence of the pharmacological effect of the substance.

Isotonitazene is a synthetic opioid bearing structural resemblance to etonitazene, a synthetic opioid that is classified as a Schedule I controlled substance in Ohio and nationally. Isotonitazene and similar analogues (e.g. etonitazene, metonitazene, and clonitazene), known as benzimidazole opioids, were first synthesized and reported in the literature in the 1950s.[vii]

Studies indicate that isotonitazene activates the μ-opioid receptors. A live cell-based reporter assay to assess the in vitro biological activity at the μ-opioid receptor (MOR) revealed that isotonitazene has a high potency (EC50 of 11.1 nM) and efficacy (Emax 180% of that of hydromorphone), thus confirming that this substance is a strong opioid.[viii]

Similar to other opioid analgesics, the most serious acute health risk from using isotonitazene is likely to be respiratory depression, which in overdose could lead to apnea, respiratory arrest, and death. This risk may be greater due to the fact that isotonitazene is the first of the benzimidazole opioids to be identified on the drug market in recent years, and users have no experience with this family of opioids, including a lack of information on what doses to use and what effects the substance can have. The timely administration of the antidote naloxone has been shown to be effective in reversing respiratory depression caused by potent opioid analgesics.[ix]

(3) The state of current scientific knowledge regarding the substance.

Although isotonitazene has not been formally studied in humans, a study published in 2019 has demonstrated that it is a highly potent, full mu-opioid receptor (MOP) agonist in vitro (Blanckaert et al., 2020), while an animal study published in 1960 has demonstrated that it has potent morphine-like centrally-mediated analgesic effects (Hunger et al., 1960b). Due to its lipophilicity, isotonitazene is expected to be rapidly absorbed and readily cross the blood-brain-barrier. Taken together, this information strongly suggests that isotonitazene will act as an opioid analgesic in humans. The major pharmacological effects of opioid analgesics are due to their activation of opioid receptors, and, in particular, the mu-opioid receptor. Besides their analgesic properties, a notable feature associated with opioid analgesics is that they cause dose-dependent respiratory depression (slowing down of breathing), in which overdose can be life-threatening. Other additional pharmacological effects include miosis, sedation, bradycardia, hypothermia, constipation, physical dependence, and changes in mood such as euphoria (Herz, 1993; Kieffer, 1999; Pasternak and Pan, 2013; Pattinson, 2008; Romberg et al., 2003).[x]

Based on the available pharmacological information, and similar to other opioid analgesics, the most serious acute risk from the use of isotonitazene in humans is likely to be from respiratory depression, which can lead to apnea, respiratory arrest, and death (Pattinson, 2008; Romberg et al., 2003; White and Irvine, 1999). Compounding this risk is that isotonitazene is the first of the 2-benzylbenzimidazole opioids to be identified on the drug market in recent years, and users have no experience with this group of opioids (such as how to dose the substance and the effects it causes) which may increase the risk of accidental overdose and cause life-threatening poisoning. This risk will be especially high if users are unaware that they are using isotonitazene, which may be the case when it is sold at street-level on the illicit opioid market. While clinical experience in treating poisonings caused by isotonitazene have not been reported, based on the pharmacological profile of the substance, naloxone is expected to work as an antidote and reverse respiratory depression (Boyer, 2012; Kim and Nelson, 2015).[xi]

(4) The history and current pattern of abuse.

As isotonitazene has only recently emerged on the drug market, it is important to note that its presence on the market and as the cause of serious adverse events (such as from acute poisonings presenting to hospital emergency rooms and medico-legal death investigations) may be undetected since the substance is not routinely screened for in some laboratories. An additional issue is that concentrations of isotonitazene in biological samples are typically low to sub-nanogram per milliliter which highlights a need for increased analytical sensitivity when testing for the substance. It is also important to note that, in some settings, the ongoing COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (ECDC, 2020; EMCDDA, 2020b; WHO, 2020) may have reduced the capacity of early warning systems, including forensic science and toxicology laboratories, to detect and report events involving isotonitazene.[xii]

Isotonitazene was first reported in August 2019 based on the results from seized drug and toxicology casework in Europe (Belgium) and Canada (Alberta); the Canadian toxicology case was collected in March 2019.[xiii] Although the size of the market is unknown, isotonitazene is sold online as a legal replacement to controlled opioids.[xiv] In March 2020, isotonitazene was found in 1,900 fake pharmaceutical pills in Nova Scotia and Newfoundland. The drug has been pressed into tablets to resemble Dilaudid, or hydromorphone. Dilaudid is a much-desired, highly euphoric synthetic opioid similar to oxycodone, aka Oxycontin.[xv]

Isotonitazene has been identified in at least 18 deaths in the United States. The deaths occurred between August 2019 and January 2020 and were from the Midwestern United States [Illinois (n=9), Indiana (n=7), Minnesota (n=1), and Wisconsin (n=1)]. Based on information from the death investigations and forensic toxicology results, at least some of the individuals were high-risk drug users and included people who had a history of injecting opioids such as heroin. Isotonitazene was identified along with one or more other psychoactive substances (controlled drugs and new psychoactive substances) in all the deaths, which suggests that polydrug use was common in these individuals. In particular, many of the cases involved the use of other CNS depressants along with isotonitazene (such as other opioids and/or benzodiazepines).[xvi]

(5) The scope, duration, and significance of abuse.

Isotonitazene was first reported in August 2019 based on the results from seized drug and toxicology casework in Europe (Belgium) and Canada (Alberta); the Canadian toxicology case was collected in March 2019.[xvii] Although the size of the market is unknown, isotonitazene is sold online as a legal replacement to controlled opioids.[xviii] In March 2020, isotonitazene was found in 1,900 fake pharmaceutical pills in Nova Scotia and Newfoundland. The drug has been pressed into tablets to resemble Dilaudid, or hydromorphone. Dilaudid is a much-desired, highly euphoric synthetic opioid similar to oxycodone, aka Oxycontin.[xix]

In the United States, isotonitazene is considered one of the most persistent and prevalent new opioids.[xx] Data from the Ohio Bureau of Criminal Investigation finds that isotonitazene has been identified in the state at least 11 times since the start of 2020.[xxi]

Isotonitazene has been identified in at least 18 deaths in the United States. The deaths occurred between August 2019 and January 2020 and were from the Midwestern United States [Illinois (n=9), Indiana (n=7), Minnesota (n=1), and Wisconsin (n=1)]. Based on information from the death investigations and forensic toxicology results, at least some of the individuals were high-risk drug users and included people who had a history of injecting opioids such as heroin. Isotonitazene was identified along with one or more other psychoactive substances (controlled drugs and new psychoactive substances) in all the deaths, which suggests that polydrug use was common in these

individuals. In particular, many of the cases involved the use of other CNS depressants along with isotonitazene (such as other opioids and/or benzodiazepines).[xxii]

(6) The risk to the public health.

Isotonitazene is not approved for medical use by the United States Food and Drug Administration. Additionally, researchers have issued warnings about the drug's potency and efficacy, stating:

> *The high potency and efficacy of isotonitazene, combined with the fact that this compound was being sold undiluted, represents an imminent danger to anyone aiming to use this powder.*[xxiii]

Pharmacological data suggest that the group of synthetic opioids that includes isotonitazene (along with etonitazene, metonitazene, and clonitazene) has potency similar to or greater than fentanyl based on their structural modifications. Etonitazene is reported to be the most potent of the group followed by isotonitazene and metonitazene. The toxicity of isotonitazene has not been extensively studied but recent association with drug user death leads professionals to believe this new synthetic opioid retains the potential to cause widespread harm and is of public health concern.[xxiv]

Similar to other opioid analgesics, the most serious acute health risk from using isotonitazene is likely to be respiratory depression, which in overdose could lead to apnea, respiratory arrest, and death. This risk may be greater due to the fact that isotonitazene is the first of the benzimidazole opioids to be identified on the drug market in recent years, and users have no experience with this family of opioids, including a lack of information on what doses to use and what effects the substance can have. The timely administration of the antidote naloxone has been shown to be effective in reversing respiratory depression caused by potent opioid analgesics. [xxv] [xxvi]

Isotonitazene has been identified in at least 18 deaths in the United States. The deaths occurred between August 2019 and January 2020 and were from the Midwestern United States [Illinois (n=9), Indiana (n=7), Minnesota (n=1), and Wisconsin (n=1)].[xxvii]

(7) The potential of the substance to produce psychic or physiological dependence liability.

According to the EMCDDA, the abuse liability and dependence producing potential of isotonitazene have not been studied. However, etonitazene and metonitazene, both closely related homologues to isotonitazene, as well other members of this group, have been studied to varying degrees. Similar to other opioid analgesics, these studies suggest that members of the 2-benzylbenzimidazole group of opioids, including isotonitazene, are likely to have an abuse liability and dependence-producing potential in humans. [xxviii] This includes studies that demonstrate etonitazene suppressed opioid abstinence syndrome in both humans and animals.[xxix] [xxx] [xxxi]

(8) Whether the substance is an immediate precursor.

Isotonitazene is not considered an immediate precursor.

Section 5: Finding of the Board

Section 3719.45 of the Ohio Revised Code authorizes the State of Ohio Board of Pharmacy to add a previously unscheduled compound, mixture, preparation, or substance to schedule I by emergency rule if the Board determines the compound has no accepted medical use in treatment in this state and poses an imminent hazard to the public health, safety, or welfare.

After a review of all available data, the State of Ohio Board of Pharmacy finds that isotonitazene:

1. Have a high potential for abuse;
2. Have no accepted medical use in treatment in this state;
3. Lack accepted safety for use in treatment under medical supervision; and
4. Pose a risk to the public health of the citizens in this state.

Based on these findings, the Board hereby concludes that isotonitazene warrants control in Schedule I and authorizes the filing of amended rule 4729:9-1-01 of the Administrative Code as found in Section 6 of this document.

Section 6: Proposed Rule

4729:9-1-01 – Schedule I Controlled Substances

…

(B) Narcotics-opiates

Any of the following opiates, including their isomers, esters, ethers, salts, and salts of isomers, esters, and ethers, unless specifically excepted under federal drug abuse control laws, whenever the existence of these isomers, esters, ethers, and salts is possible within the specific chemical designation (for purposes of 3-methylthiofentanyl only, the term isomer includes the optical and geometric isomers):

…

(68) N,N-Diethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1H-benzimidazole-1-ethanamine (isotonitazene).

Endnotes

[i] "Potent Synthetic Opioid - Isotonitazene - Recently Identified in the Midwestern United States." The Center for Forensic Science Reseach & Education. November 2019. https://www.npsdiscovery.org/wp-content/uploads/2019/11/Public-Alert_Isotonitazene_NPS-Discovery_111919-1.pdf

[ii] Blanckaert, P. Cannaert, A., Van Uytfanghe, K., Hulpia, F., Deconinck, E., Van Calenbergh, S. and Stove C. (2019), 'Report on a novel emerging class of highly potent benzimidazole NPS opioids: Chemical and in vitro functional characterization of isotonitazene', Drug Testing and Analysis. https://doi.org/10.1002/dta.2738

[iii] Krotulski, A., Papsun, D.M., Kacinko, S.L. and Logan, B.K., (2020), 'Isotonitazene quantitation and metabolite discovery in authentic forensic casework', Journal of Analytical Toxicology. https://doi.org/10.1093/jat/bkaa016

[iv] Krotulski, A., Papsun, D.M., Kacinko, S.L. and Logan, B.K., (2020), 'Isotonitazene quantitation and metabolite discovery in authentic forensic casework', Journal of Analytical Toxicology. https://doi.org/10.1093/jat/bkaa016

[v] "Potent Synthetic Opioid - Isotonitazene - Recently Identified in the Midwestern United States." The Center for Forensic Science Reseach & Education. November 2019. https://www.npsdiscovery.org/wp-content/uploads/2019/11/Public-Alert_Isotonitazene_NPS-Discovery_111919-1.pdf

[vi] "Potent Synthetic Opioid - Isotonitazene - Recently Identified in the Midwestern United States." The Center for Forensic Science Reseach & Education. November 2019. https://www.npsdiscovery.org/wp-content/uploads/2019/11/Public-Alert_Isotonitazene_NPS-Discovery_111919-1.pdf

[vii] "Potent Synthetic Opioid - Isotonitazene - Recently Identified in the Midwestern United States." The Center for Forensic Science Reseach & Education. November 2019. https://www.npsdiscovery.org/wp-content/uploads/2019/11/Public-Alert_Isotonitazene_NPS-Discovery_111919-1.pdf

[viii] Report on a novel emerging class of highly potent benzimidazole NPS opioids: Chemical and in vitro functional characterization of isotonitazene. https://pesquisa.bvsalud.org/portal/resource/pt/mdl-31743619

[ix] EMCDDA initial report on the new psychoactive substance N,N-diethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1H-benzimidazole-1-ethanamine (isotonitazene). April 2020. https://www.emcdda.europa.eu/publications/initial-reports/isotonitazene_en

[x] EMCDDA technical report on the new psychoactive substance N,N- diethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1H- benzimidazole-1-ethanamine (isotonitazene). https://www.emcdda.europa.eu/system/files/publications/13108/EMCDDA%20technical%20report%20on%20isotonitazene.pdf

[xi] EMCDDA technical report on the new psychoactive substance N,N- diethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1H- benzimidazole-1-ethanamine (isotonitazene). https://www.emcdda.europa.eu/system/files/publications/13108/EMCDDA%20technical%20report%20on%20isotonitazene.pdf

[xii] EMCDDA technical report on the new psychoactive substance N,N- diethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1H- benzimidazole-1-ethanamine (isotonitazene). https://www.emcdda.europa.eu/system/files/publications/13108/EMCDDA%20technical%20report%20on%20isotonitazene.pdf

[xiii] "Potent Synthetic Opioid - Isotonitazene - Recently Identified in the Midwestern United States." The Center for Forensic Science Reseach & Education. November 2019. https://www.npsdiscovery.org/wp-content/uploads/2019/11/Public-Alert_Isotonitazene_NPS-Discovery_111919-1.pdf

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[xv] Dangerous new street drug found in two Maritime provinces: police. CTV News. March 6, 2020. https://atlantic.ctvnews.ca/dangerous-new-street-drug-found-in-two-maritime-provinces-police-1.4839958

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