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Addendum to ACMD's report on the use and harms of 2-benzyl benzimidazole ('nitazene') and piperidine benzimidazolone ('bromphine-like') opioids

On 18 July 2022 the Advisory Council on the Misuse of Drugs (ACMD) published its advice on 2-benzyl benzimidazole (nitazene) and piperidine benzimidazolone (bromphine-like) opioids.

On 19 December 2022, the ACMD published an addendum to this advice recommending control of a further 2-benzyl benzimidazole, *N*-desethyl isotonitazene, following detections in drug seizures and review of its potential harms.

The ACMD has recently been alerted to a further four 2-benzyl benzimidazole compounds which have now been detected in the UK:

- *N*-Pyrrolidino protonitazene
- Ethyleneoxynitazene
- *N*-Desethyl protonitazene
- *N*-Desethyl etonitazene

N-Pyrrolidino protonitazene, ethyleneoxynitazene, *N*-desethyl protonitazene and *N*-desethyl etonitazene are potent Mu-opioid receptor (MOR) agonists [Vandeputte et al., 2023; Krotulski et al., 2023; CSFRE 2023; Cayman Chemicals 2023]. The ACMD has concluded that their potential harms are commensurate with those of the other nitazene compounds listed in Recommendation 1 of our 2022 report.

Therefore, the ACMD recommends these compounds be added to Class A of the Misuse of Drugs Act 1971, consistent with the classification of other potent opioids. As these compounds also have no known legitimate medicinal uses, as confirmed by the Medicines and Healthcare products Regulatory Agency (MHRA), the ACMD recommends that they should be added to Schedule 1 of the Misuse of Drugs Regulations 2001 (as amended).

N-Pyrrolidino protonitazene, *N*-desethyl protonitazene and *N*-desethyl etonitazene would be caught by the generic definition proposed in Recommendation 3 of the July 2022 ACMD report. However, ethyleneoxynitazene appears to fall outside the proposed generic definition. The ACMD is therefore currently considering whether the proposed generic definition could be expanded to address ethyleneoxynitazene and other structurally related compounds that might appear in the future.

Revised Recommendation 1:

The following compounds should be added to Class A of the Misuse of Drugs Act 1971, consistent with the classification of other potent opioids.

As these materials have no medical use it is recommended that they should be placed in schedule 1 of the Misuse of Drugs Regulations 2001 (as amended).

- Metonitazene
- Protonitazene
- Isotonitazene
- Butonitazene
- Flunitazene
- Metodesnitazene (metazene)
- Etodesnitazene (etazene)
- *N*-Pyrrolidino etonitazene (etonitazepyne)
- *N*-Piperidinyl etonitazene (etonitazepipne)
- Brorphine
- *N*-Desethyl isotonitazene
- ***N*-Pyrrolidino protonitazene**
- **Ethyleneoxynitazene**
- ***N*-Desethyl protonitazene**
- ***N*-Desethyl etonitazene**

Lead: Home Office

Measure of outcome: The inclusion of the listed compounds in Class A of the Misuse of Drugs Act 1971 and Schedule 1 of the Misuse of Drugs Regulations 2001.

References

Cayman Chemicals (2023). Product Information N-desethyl etonitazene. [32512.pdf \(caymanchem.com\)](#)

Centre for Forensic Science Research and Education (CFSRE, 2023). N-Pyrrolidino Protonitazene. <https://www.cfsre.org/nps-discovery/monographs/n-pyrrolidino-protonitazene>

Krotulski, A.J., Papsun, D.M., Kacinko, S.L., et al. Isotonitazene quantitation and metabolite discovery in authentic forensic casework. *J. Anal. Toxicol.* 44(6), 521-530 (2020).

Krotulski, AJ; Walton, SE; Papsun, DM; DeBord, J; Fogarty, MF; Logan, BK. (2023) New Nitazene Analogue N-Pyrrolidino Protonitazene Impacting Drug Markets In North America and Europe, Center for Forensic Science Research and Education, United States.

Vandeputte, M., Van Uytfanghe, K., Layle, N., St Germaine, D., Iula, D., Baumann, M., Stove, C. (2023). When a prophecy comes true: ethylenoxynitazene as a 'prophetic' member of the emerging class of 2-bezylbenzimidazole 'nitazene' synthetic opioids. TIAFT (The International Association of Forensic Toxicologist) Annual Meeting August 2023 Presentation 017