SUBSTANCES OF ABUSE UNDER THE 2021 WORLD ANTI-DOPING CODE

GUIDANCE NOTE FOR ANTI-DOPING ORGANIZATIONS

Pursuant to Article 4.2.3 of the 2021 World Anti-Doping Code (the Code), some substances on the International Standard of the List of Prohibited Substances and Prohibited Methods (Prohibited List) were identified as Substances of Abuse "*because they are frequently abused in society outside the context of sport*".

WADA's Prohibited List Expert Advisory Group (LiAEG) identified the following substances as Substances of Abuse in the Prohibited List.

- Cocaine (S.6a – Non-specified Stimulants);
- Methylenedioxymethamfetamine (MDMA / "ecstasy") (S.6b – Specified Stimulants);
- Diamorphine (Heroin) (S.7 – Narcotics); and
- Tetrahydrocannabinol (THC) (S.8 – Cannabinoids).

As per Code Article 10.2.4.1, where the Anti-Doping Rule Violation involves a Substance of Abuse and "*the Athlete can establish that any ingestion or Use occurred **Out-of-Competition** and was **unrelated to sport performance**, then the period of Ineligibility shall be three (3) months. In addition, the period of Ineligibility calculated may be reduced to one (1) month if the Athlete or other Person satisfactorily completes a Substance of Abuse treatment program approved by the Anti-Doping Organization with Results Management responsibility*".

It is important to note that the definition of **In-Competition** is as follows: "*The period commencing at 11:59 p.m. on the day before a Competition in which the Athlete is scheduled to participate through the end of such Competition and the Sample collection process related to such Competition. Provided, however, WADA may approve, for a particular sport, an alternative definition if an International Federation provides a compelling justification that a different definition is necessary for its sport; upon such approval by WADA, the alternative definition shall be followed by all Major Event Organizations for that particular sport.*"

For the application of this Code provision, the analytical concentrations reported by WADA-accredited Laboratories should in principle be interpreted as follows:

For Diamorphine (Heroin):

Introduction:
Heroin (diamorphine or diacetylmorphine) is a semi-synthetic opioid derived from morphine, that is chemically processed and more potent than morphine itself. The most common ways of using heroin are by injection, snorting (insufflation), and inhalation by smoking.

Heroin binds to opioid receptors on cells located in brain areas such as those involved in pain, pleasure and in controlling heart rate and breathing. Following administration, the user experiences an initial surge of euphoria, followed by a period of sedation. Heroin is highly addictive, both physically and psychologically. Diamorphine is a controlled drug that is used medically in a few countries for the treatment of severe pain associated with surgical procedures, myocardial infarction (heart attack), or in medication-assisted drug treatment programs.

Heroin use for doping dates back many years and is known to be a historical component of doping drug mixtures such as the "*pot belge*".

Results Management
The main target analyte for the detection of diamorphine (heroin) is 6-acetylmorphine (6-AM). This metabolite is the optimal marker to detect the use of diamorphine in competition due to its rapid elimination time.

- The presence of 6-AM above the MRL of 25 ng/mL is the result of the in-competition use of diamorphine.

For Cocaine:

Introduction:
Cocaine is considered the most potent stimulant of natural origin. Cocaine is mainly snorted, smoked, or injected. The most popular route of administration is snorting, which produces peak effects in 5-15 minutes, lasting for up to one hour. Cocaine hydrochloride solutions offer limited medical application as a local anesthetic, except in certain cases of ear, nasal or throat surgery used in few countries.

Cocaine administration produces euphoria, tachycardia, hypertension and appetite suppression, and has a strong reinforcing action, causing rapid psychological dependence and craving. The euphoric rush quickly wears off, producing a depressed mood, or feeling down, which leads to the use of more cocaine, sometimes just to feel normal.

Initial evidence of cocaine use in sport dates back to the early 20th century. Until today, amfetamine and cocaine are still at the top of positive doping control tests in the class of Stimulants (S6) in the Prohibited List.

Results Management
The following situations should be considered likely to correspond to an In-Competition use of cocaine:

- Presence of cocaine parent compound at an estimated urinary concentration above (>) 10 ng/mL; [regardless of the presence of benzoylecgonine (BZE)] or
- Presence of BZE (main metabolite of cocaine) at a urinary concentration above (>) 1000 ng/mL combined with the presence of cocaine parent compound between (≥) 1 ng/mL and (≤) 10 ng/mL.

Notes:
1. Cocaine in the absence of reported BZE (i.e. below MRL of 50 ng/mL) could indicate very recent use.
2. Concurrent intake of alcohol and cocaine neither alters the length of excretion nor the urinary concentrations of cocaine, while the concentration of BZE is significantly decreased during the first 24 h period.
3. Consumption of 'Coca tea', as observed in some restricted parts of the world, prior to a competition, could lead to an Adverse Analytical Finding for cocaine.

For Tetrahydrocannabinol (THC):

Introduction:
Cannabis is the most abused substance, other than alcohol, in the world. In recent years, cannabis legalization and/or cultural acceptance increased in some countries, but it still remains an illegal substance in the majority of the world. The List Expert Advisory Group recently conducted a review of the status of cannabis in the Prohibited List. The outcome of these discussions can be found in: *Hudzik TJ, et al.,. Cannabis and sport: A World Anti-Doping perspective. Addiction. 2023 Aug 13; 118:2040-2042. doi: 10.1111/add.16315. Epub ahead of print. PMID: 37574590.*

Results Management:
Presence of carboxy-THC at a concentration above (>) the Decision Limit (DL) (1) of 180 ng/mL should be considered likely to correspond to an In-Competition use of cannabis.

Note:
1. For carboxy-THC, a Decision Limit is already established (pre-2021 Code), so no Adverse Analytical Finding shall be reported for concentrations below the Decision Limit.

REFERENCES

Heroin

- Cone, E J et al. "Forensic drug testing for opiates: I. Detection of 6-acetylmorphine in urine as an indicator of recent heroin exposure; drug and assay considerations and detection times." *J. Anal. Toxicol*. vol. 15,1 (1991): 1-7. doi:10.1093/jat/15.1.1
- Cone, E J et al. "Forensic drug testing for opiates. VII. Urinary excretion profile of intranasal (snorted) heroin." *J. Anal. Toxicol.* vol. 20,6 (1996): 379-92. doi:10.1093/jat/20.6.379
- Sawynok, J. "The therapeutic use of heroin: a review of the pharmacological literature." *Canadian J Physiol Pharmacol* vol. 64,1 (1986): 1-6. doi:10.1139/y86-001.
- Smith, M L et al. "Urinary excretion profiles for total morphine, free morphine, and 6-acetylmorphine following smoked and intravenous heroin." *J Anal Toxicol*. 2001;25(7):504-514. doi:10.1093/jat/25.7.504

- UNODC "Terminology and Information on Drugs" (2016) 3rd Edition. Accessed 24 January 2024. https://www.unodc.org/documents/scientific/Terminology_and_Information_on_Drugs-E_3rd_edition.pdf.
- Wang L et al. "Comparison of the Detection Windows of Heroin Metabolites in Human Urine Using Online SPE and LC-MS/MS: Importance of Morphine-3-Glucuronide." *J Anal Toxicol* vol. 44,1 (2020): 22-28. doi:10.1093/jat/bkz040

Cocaine

- Ambre J. The urinary excretion of cocaine and metabolites in humans: a kinetic analysis of published data. *J Anal Toxicol.* 1985;9(6):241-245. doi:10.1093/jat/9.6.241
- Anti-doping testing figures, WADA website, accessed 31 October 2023 https://www.wada-ama.org/en/resources/anti-doping-stats/anti-doping-testing-figures-report
- Cami J, Farré M, González ML, Segura J, de la Torre R. Cocaine metabolism in humans after use of alcohol. Clinical and research implications. *Recent Dev Alcohol*. 1998;14:437-455. doi:10.1007/0-306-47148-5_22
- Carrera MR, Meijler MM, Janda KD, Cocaine pharmacology and current pharmacotherapies for its abuse, *Bioorg Med Chem*, Vol 12, Issue 19, 2004,Pages 5019-5030.
- Cone EJ, Hillsgrove M, Darwin WD. Simultaneous measurement of cocaine, cocaethylene, their metabolites, and "crack" pyrolysis products by gas chromatography-mass spectrometry. *Clin Chem*. 1994;40(7 Pt 1):1299-1305.
- Cone EJ, Sampson-Cone AH, Darwin WD, Huestis MA, Oyler JM. Urine testing for cocaine abuse: metabolic and excretion patterns following different routes of administration and methods for detection of false-negative results. *J Anal Toxicol*. 2003;27(7):386-401. doi:10.1093/jat/27.7.386
- elSohly MA, Stanford DF, elSohly HN. Coca tea and urinalysis for cocaine metabolites. *J Anal Toxicol*. 1986;10(6):256. doi:10.1093/jat/10.6.256
- Epstein DH, Silverman K, Henningfield JE, Preston KL. Low-dose oral cocaine in humans: acquisition of discrimination and time-course of effects. *Behav Pharmacol*. 1999;10(5):531-542. doi:10.1097/00008877-199909000-00011
- Farré M, de la Torre R, Llorente M, et al. Alcohol and cocaine interactions in humans. *J Pharmacol Exp Ther*. 1993;266(3):1364-1373.
- Harris DS, Everhart ET, Mendelson J, Jones RT. The pharmacology of cocaethylene in humans following cocaine and ethanol administration. *Drug Alcohol Depend*. 2003;72(2):169-182. doi:10.1016/s0376-8716(03)00200-x
- Huestis MA, Darwin WD, Shimomura E, et al. Cocaine and metabolites urinary excretion after controlled smoked administration. *J Anal Toxicol*. 2007;31(8):462-468. doi:10.1093/jat/31.8.462
- Jufer RA, Wstadik A, Walsh SL, Levine BS, Cone EJ. Elimination of cocaine and metabolites in plasma, saliva, and urine following repeated oral administration to human volunteers. *J Anal Toxicol*. 2000;24(7):467-477. doi:10.1093/jat/24.7.467
- Jufer R, Walsh SL, Cone EJ, Sampson-Cone A. Effect of repeated cocaine administration on detection times in oral fluid and urine. *J Anal Toxicol*. 2006;30(7):458-462. doi:10.1093/jat/30.7.458
- Kiszka, M., Buszewicz, G., Madro, R. Stability of cocaine in phosphate buffer and in urine. *Z Zagadnien´ Nauk S dowych, z.XLIV*, (2000) 7–23.

- Martindale: The Complete Drug Reference. 40th Edition (2020) Pharmaceutical Press.
- Mazor SS, Mycyk MB, Wills BK, Brace LD, Gussow L, Erickson T. Coca tea consumption causes positive urine cocaine assay. *Eur J Emerg Med*. 2006;13(6):340-341. doi:10.1097/01.mej.0000224424.36444.19
- McCance-Katz EF, Price LH, McDougle CJ, Kosten TR, Black JE, Jatlow PI. Concurrent cocaine-ethanol ingestion in humans: pharmacology, physiology, behavior, and the role of cocaethylene. *Psychopharmacology (Berl)*. 1993;111(1):39-46. doi:10.1007/BF02257405.
- Preston KL, Epstein DH, Cone EJ, Wtsadik AT, Huestis MA, Moolchan ET. Urinary elimination of cocaine metabolites in chronic cocaine users during cessation. *J Anal Toxicol*. 2002;26(7):393-400. doi:10.1093/jat/26.7.393.
- Puet BL, Claussen K, Hild C, Heltsley R, Schwope DM. Presence of Parent Cocaine in the Absence of Benzoylecgonine in Urine. *J Anal Toxicol*. 2018;42(8):512-517. doi:10.1093/jat/bky057
- Roque Bravo R, Faria AC, Brito-da-Costa AM, Carmo H, Mladěnka P, Dias da Silva D, Remião F, on behalf of The OEMONOM Researchers. Cocaine: An Updated Overview on Chemistry, Detection, Biokinetics, and Pharmacotoxicological Aspects including Abuse Pattern. *Toxins*. 2022; 14(4):278. https://doi.org/10.3390/toxins14040278
- Smith ML, Shimomura E, Paul BD, Cone EJ, Darwin WD, Huestis MA. Urinary excretion of ecgonine and five other cocaine metabolites following controlled oral, intravenous, intranasal, and smoked administration of cocaine. *J Anal Toxicol*. 2010;34(2):57-63. doi:10.1093/jat/34.2.57

Tetrahydrocannabinol

- Huestis MA, Sempio C, Newmeyer MN, et al. Free and Glucuronide Urine Cannabinoids after Controlled Smoked, Vaporized and Oral Cannabis Administration in Frequent and Occasional Cannabis Users. *J Anal Toxicol*. 2020;44(7):651-660. doi:10.1093/jat/bkaa046
- Huestis MA. Human cannabinoid pharmacokinetics. *Chem Biodivers*. 2007;4(8):1770-1804. doi:10.1002/cbdv.200790152