Document Number:	TL15	Version Number:	3.0
Written by: Reviewed by:	*WADA* Science *WADA* Laboratory Expert Group	Approved by:	*WADA* Executive Committee
Date:	21 December 2020	Effective Date:	1 January 2021

HYDROMORPHONE

1.0 Introduction

WADA wishes to draw the attention of the Laboratories to the possible detection of the *Prohibited Substance* **Hydromorphone** in urine *Samples* resulting from the administration of the permitted drug **Hydrocodone** or from the administration of high doses of either the prohibited Threshold Substance **Morphine** or the permitted drug **Codeine**.

2.0 Detection of Hydromorphone as a Result of the Administration of Hydrocodone

It is indeed reported in the literature [1] that hydrocodone is metabolized by O-demethylation to hydromorphone and by N-demethylation to norhydrocodone (Figure 1).

[Comment: In single-dose administration studies [1,2] of hydrocodone, it was found that the levels of norhydrocodone in urine were always higher than or equal to (≥) the parent compound, whereas the levels of hydromorphone were lower (<). Additionally, norhydrocodone was detected in urine for a longer time than hydromorphone.

In a different study involving a population of 25,200 subjects treated with multiple doses of a hydrocodone/acetaminophen formulation, Barakat et al. [3] showed that the metabolic hydromorphone/hydrocodone ratio varied between 0.074 and 0.35.]

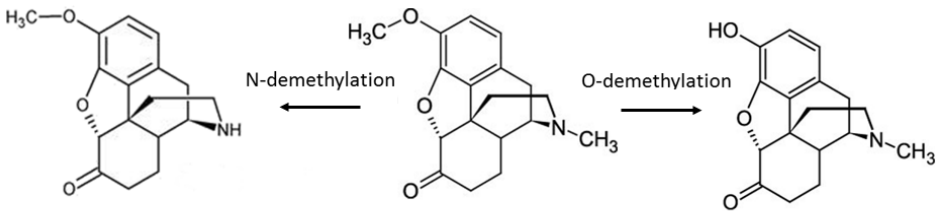

Figure 1: Metabolic pathway of hydrocodone (adapted from Valtier and Bebarta [1])

2.1 Analysis and Reporting Requirements

Before reporting a result as an *Adverse Analytical Finding* (*AAF*) for hydromorphone, Laboratories shall evaluate whether the finding is the result of the permitted administration of hydrocodone.

When detecting hydromorphone in a urine *Sample*, Laboratories shall:

- Check the Sample *Doping Control* Form (DCF) for a declaration of use of hydrocodone;

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- Whenever a Laboratory detects hydromorphone in an Initial *Testing* Procedure (ITP) of a urine *Sample*, an additional test for the presence of hydrocodone and norhydrocodone shall be included in the Confirmation Procedure (CP);
- Report the result as a Negative Finding if the concentration of total* hydromorphone is lower than or equal to (≤) the concentration of total hydrocodone or total norhydrocodone;
- Report the result as an *AAF* for hydromorphone if the concentration of total hydromorphone is higher than (>) the concentrations of both total hydrocodone and total norhydrocodone.

[In every case, total concentration refers to the sum of the concentrations of the respective free compound and its glucuroconjugated form(s).]*

3.0 Detection of Hydromorphone as a Result of the Administration of Morphine

Additionally, it was reported in the literature [4,5] that hydromorphone might be found as a minor *Metabolite* of the prohibited Threshold Substance morphine, more specifically in urines of patients treated with high doses of morphine (Figure 2).

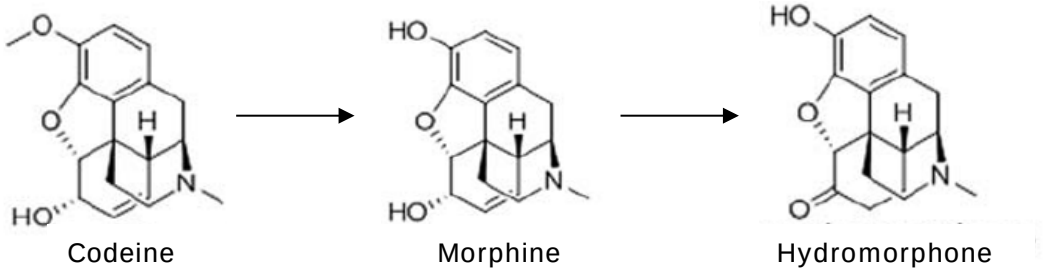

Figure 2. Metabolic pathway of codeine (Adapted from Barakat *et al*. [3])

Therefore, it is important to evaluate hydromorphone findings in the presence of total morphine at concentrations below (<) the *Decision Limit* (*DL*) for morphine of 1.3 µg/mL (or the adjusted *DL* if the SG is greater than (>) 1.018) [6].

[Comment: Studies [5,7] involving patients undergoing treatment with daily high-doses of morphine have shown that the ratio of total hydromorphone (free + glucuronide forms) to total morphine (free + glucuronide forms) ranged between 0.002 to 0.022 [7] or had a mean ± SD value of 0.024 ± 0.017 [5], with urinary morphine concentrations in the range of 103-537 µg/mL or 21 ± 7.0 µg/mL, respectively. In both studies, the concentrations of morphine were higher than (>) the DL [6].]

3.1 Reporting Requirements

If hydromorphone is detected in a urine *Sample* in the presence of morphine, Laboratories shall evaluate whether the finding is consistent with the formation of hydromorphone through the metabolism of morphine:

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[Comment: These conditions do not apply to the reporting of hydromorphone findings in the absence of morphine. In such cases, the finding should be reported as an AAF for hydromorphone if the concentration is higher than the Minimum Reporting Level (MRL) for hydromorphone [8].]

- Report the result as a Negative Finding for hydromorphone if:

  - The ratio of total* hydromorphone to total morphine is less than or equal to (≤) 0.05, even if the concentration of hydromorphone is greater than (>) the *MRL*; and/or

  - The concentration of total hydromorphone is lower than (<) the *MRL*, even if the ratio of total hydromorphone to total morphine is greater than (>) 0.05.

- Report the result as an *AAF* for hydromorphone only if the estimated concentration of total hydromorphone is greater than (>) the *MRL* **and** the ratio of total hydromorphone to total morphine is greater than (>) 0.05.

[In every case, total concentration refers to the sum of the concentrations of the respective free compound and its glucuroconjugated form(s).]*

4.0 References

[1] Valtier S., and Bebarta V.S. Excretion Profile of Hydrocodone, Hydromorphone and Norhydrocodone in Urine Following Single Dose Administration of Hydrocodone to Healthy Volunteers. *J Anal Toxicol* **36**: 507-514, 2012.

[2] Cone E.J., *et al*. Prescription Opoids. II. Metabolism and Excretion Patterns of Hydrocodone in Urine Following Controlled Single-Dose Administration. *J Anal Toxicol* **37**: 486-494, 2013.

[3] Barakat N.H., *et al*. Relationship between the Concentration of Hydrocodone and its Conversion to Hydromorphone in Chronic Pain Patients Using Urinary Excretion Data. *J Anal Toxicol* **36**: 257-264, 2012.

[4] Cone E.J., *et al*. Evidence of Morphine Metabolism to Hydromorphone in Pain Patients Chronically Treated with Morphine. *J Anal Toxicol* **30**:1-5, 2006.

[5] Wasan A.D., *et al*. Interpreting Urine Drug Tests: Prevalence of Morphine Metabolism to Hydromorphone in Chronic Pain Patients Treated with Morphine. *Pain Medicine* **9**: 918-923, 2008.

[6] *WADA Technical Document* TD DL: *Decision Limits* for the Confirmatory Quantification of Exogenous Threshold Substances by Chromatography-based Analytical Methods.

[7] Cone E.J., *et al.* Evidence that Morphine is Metabolized to Hydromorphone but not to Oxymorphone, *J Anal Toxicol* **32**: 319-323, 2008.

[8] *WADA Technical Document* TD MRPL: Minimum Required Performance Levels for Detection and Identification of Non-Threshold Substances by Chromatographic-Mass Spectrometric Analytical Methods.

[Current versions of WADA Technical Documents may be found at https://www.wada-ama.org/en/what-we-do/science-medical/laboratories]