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POSSIBLE METABOLIZATION OF PROGUANIL INTO CHLORAZANIL

1.0 Introduction

WADA wishes to draw the attention of the Laboratories to the possible detection of the *Prohibited Substance* **Chlorazanyl** in urine *Samples*, which may result from the administration of the permitted anti-malaria drug **Proguanil**.

A structural similarity between chlorazanyl and proguanil is given but no direct metabolic relation has been reported in the scientific literature. Moreover, chlorazanyl has not been confirmed as a drug impurity of proguanil. However, proguanil is metabolized in humans to N-(4-chlorophenyl)-biguanide, which represents a chemical precursor in the synthesis of chlorazanyl. In the presence of formic acid, formaldehyde, or formic acid esters, **N-(4-chlorophenyl)-biguanide** converts to chlorazanyl ^[1].

2.0 Reporting Requirements

Before reporting a result as an *Adverse Analytical Finding (AAF)* for chlorazanyl, Laboratories shall evaluate the presence of proguanil or its *Metabolite(s)* **Cycloguanil** and N-(4-chlorophenyl)-biguanide in the *Sample* in order to exclude proguanil as the primary source of chlorazanyl.

Particular attention should be given to the Doping Control Form (DCF) for any relevant declaration of proguanil.

3.0 References

[1] Thevis, M., *et al.* Formation of the diuretic chlorazanyl from the antimalarial drug proguanil — Implications for sports drug testing. *J Pharm Biomed Anal.* **115**: 208-213, 2015.