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Enantiomeric biodistribution and toxicity of 3-chloromethcathinone (3-CMC) in Wistar rats after acute exposure – preliminary data

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Abstract

Background: There has been a surge in global attention to New Psychoactive Substances (NPS) [1]. Synthetic cathinones stand out as a widely consumed NPS class. Notably, 3-chloromethcathinone (3-CMC) accounted for over 34% of NPS seizures in 2021 [2], which underscores concerns regarding its consumption and health effects. Of note, 3-CMC is chiral and mostly sold as a racemate. As human metabolism and pharmacological effects can be enantioselective [3], determination of the impact of enantioselectivity in toxicokinetics/toxicodynamics is essential for the assessment of 3-CMC effects. **Objective:** This work aimed to evaluate *in vivo* the enantioselective biodistribution and toxicity of racemic 3-CMC, after an acute exposure to 3-CMC. **Methods:** Ten-week-old male Wistar rats were administered intraperitoneally with saline or 3-CMC (10 or 20 mg/kg; n=6). Twenty-four hours after, animals were deeply anesthetized and nine organs (brain, liver, kidneys, lungs, heart, spleen, gut, muscle, adipose tissue), blood and urine were collected. For evaluation of the enantiomeric biodistribution, a previous *in house* established indirect method by gas chromatography [3], was adapted and validated. Some biochemical analysis was performed using an analyser, whereas TBARS, ATP, glutathione and total protein were determined by spectrophotometry. Organs were also processed for histological analysis. **Results:** After 24 h, 3-CMC was not found in most organs. Both enantiomers were detected in urine with one dominant enantiomer, suggesting enantioselectivity in metabolism. The histopathological results showed possible central chromatolysis in the brain (20 mg/kg), liver inflammation, renal lesions, lungs' haemoptysis, and alveolar haemorrhage, in most 3-CMC-exposed animals. No differences were observed in the heart. **Conclusions:** Our findings show rapid 3-CMC renal elimination, with enantioselectivity in metabolism. Although biochemical evaluations are ongoing, the results are expected to give further insights on the 3-CMC toxicity and histological abnormalities found in the brain, kidneys, liver and lungs.

Keywords: new psychoactive substances; drugs of abuse; enantioselectivity; toxicokinetics; risk assessment

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