

# ACMD

## Advisory Council on the Misuse of Drugs

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Home Secretary  
Rt Hon. Theresa May, MP  
2 Marsham Street  
London  
SW1P 4DF

22<sup>nd</sup> October 2012

Dear Home Secretary,

**Re: ACMD advice on O-desmethyltramadol**

I am writing to provide you with the Advisory Council on the Misuse of Drugs' (ACMD) consideration of the compound O-desmethyltramadol.

O-desmethyltramadol (2-((dimethylamino)methyl)-1-(3-hydroxyphenyl)cyclohexanol) is the major metabolite of tramadol ((±)-*trans*-2-((dimethylamino)methyl)-1-(3-methoxyphenyl)cyclohexanol) and is a significantly more potent opiate than its parent drug.

The compound came to light as a material of concern during the ACMD's review of tramadol. The ACMD has sufficient concerns about the harmful properties of O-desmethyltramadol to submit advice separately and in advance of that on tramadol (scheduled for December 2012) so that early Ministerial consideration of the metabolite can be made.

O-desmethyltramadol is being offered for sale as a 'legal high' and has been identified as an undeclared ingredient of a 'legal high' product called 'Krypton'. 'Krypton' is sold as an herbal material, claimed to consist of Kratom leaves (*Mitragyna speciosa*) from a Southeast Asian tree which, when chewed, produce narcotic and opiate-like effects. The packaging of 'Krypton' is very similar to that of 'Spice' (an herbal material containing synthetic cannabinoids), that is, brightly printed foil sachets containing a few grams of ground herbal material of unknown origin and authenticity. As with 'Spice', the apparently natural herbal product has been found to be 'spiked', in this case

with synthetic *O*-desmethyltramadol, to produce additional psychoactive effects<sup>1</sup>.

Toxicology reports from Germany have identified traces of *O*-desmethyltramadol in the urine of 'Krypton' users without evidence of use of tramadol or *N*-desmethyltramadol, another major tramadol metabolite. This indicates that the users had been exposed directly to *O*-desmethyltramadol<sup>2,3</sup>. In late December 2010, authorities in Sweden reported a series of 9 fatalities associated with use of 'Krypton', apparently resulting from opiate-type respiratory depression, which could also result from Kratom ingestion. The presence of *O*-desmethyltramadol in urine samples in the absence of tramadol or other tramadol metabolites again indicated that the users had been exposed directly to *O*-desmethyltramadol. The authors suggested that the addition of the potent opiate synthetic *O*-desmethyltramadol to the naturally occurring opiate 7-hydroxymitragynine in herbal Kratom produced a lethal mixture<sup>4</sup>.

Pharmacological studies indicate that *O*-desmethyltramadol is significantly more potent in activating  $\mu$ -opiate receptors than its parent drug, and that it may account for most of tramadol's opiate-mediated activity. It is not in use as a pharmaceutical. As *O*-desmethyltramadol is a major, and pharmacologically active, metabolite of tramadol, the ACMD considers that the harms associated with the use of *O*-desmethyltramadol are similar to those of tramadol, for example confusion, dizziness, respiratory depression and seizures.

The harms associated with the use of *O*-desmethyltramadol are commensurate with other substances controlled as Class B under the Misuse of Drugs Act 1971. The ACMD therefore recommends that *O*-desmethyltramadol is controlled under the Misuse of Drugs Act 1971 as a Class B substance and, as it has no legitimate medical use, scheduled as a Schedule I substance under the Misuse of Drugs Regulations 2001.

Yours sincerely



**Professor Les Iversen**

Cc: Parliamentary Under Secretary of State for Health

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<sup>1</sup> EMCDDA, "Understanding the Spice Phenomenon", 2009

<sup>2</sup> Arndt *et al* (2011) Kratom alkaloids and *O*-desmethyltramadol in urine of a "Krypton" herbal mixture consumer. *Forensic Sci Int*. 2011 May 20;208(1-3):47-52.

<sup>3</sup> Phillip *et al* (2010) "Monitoring of kratom or Krypton intake in urine using GC-MS in clinical and forensic toxicology" *Anal Bioanal Chem*. 2011 Apr;400(1):127-35

<sup>4</sup> Kronstrand *et al* (2011) Unintentional fatal intoxications with mitragynine and *O*-desmethyltramadol from the herbal blend Krypton. *J Anal Toxicol*. 2011 May;35(4):242-7