Short communication

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A methamphetamine analog (*N,α*-diethyl-phenylethylamine) identified in a mainstream dietary supplement

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Pharmaceuticals and banned substances have been detected in hundreds of purportedly natural supplements. Recently, several athletes have been disqualified from competition after testing positive for the methamphetamine analog *N,α*-diethyl-phenylethylamine (*N,α*-DEPEA). Athletes have claimed they unknowingly consumed the banned stimulant in workout supplements. Three samples from different lot numbers of Craze, a workout supplement, were analyzed to detect the presence and concentration of *N,α*-DEPEA. Two labs independently identified *N,α*-DEPEA in the supplement using ultra high performance liquid chromatography (UHPLC) coupled to an LTQ Orbitrap XL mass spectrometer and UHPLC-quadruple-time-of-flight mass (Q-TOF) spectrometer, respectively. The identity of *N,α*-DEPEA was confirmed using nuclear magnetic resonance and reference standards. Manufacturer recommended servings were estimated to provide 21 to 35 mg of *N,α*-DEPEA. *N,α*-DEPEA has never been studied in humans. *N,α*-DEPEA is a methamphetamine analog; however, its stimulant, addictive and other adverse effects in humans are entirely unknown. Regulatory agencies should act expeditiously to warn consumers and remove *N,α*-DEPEA from all dietary supplements. Copyright © 2013 John Wiley & Sons, Ltd.

Keywords: methamphetamine; dietary supplements; adulteration

Introduction

Pharmaceuticals and banned substances have been found in hundreds of dietary supplements.[1–4] After several athletes failed urine drug tests because of a new methamphetamine analogue,[5] we were concerned that a widely available workout supplement, Craze (Driven Sports, Inc.), might contain the banned stimulant. Craze is marketed as 'performance fuel' that provides 'the ultimate in pre-workout power'. [6] The supplement is labelled as containing a dendrobium orchid extract comprising several phenylethylamines including *N,N*-diethyl-phenylethylamine (*N,N*-DEPEA). [6] *N,N* -DEPEA is a structural isomer of the methamphetamine analog *N,α*-diethyl-phenylethylamine (*N,α*-DEPEA). We therefore tested the supplement to determine the presence of *N,α*-DEPEA.

Methods and results

Sample 1 was purchased from a US online supplement retailer (The Natural Health Shoppe; www.thenaturalhealthshoppe.com). An aqueous/methanolic extract of the supplement was analyzed by NSF International (Ann Arbor, MI, USA) using its standard approach of ultra high performance liquid chromatography (UHPLC) coupled to an LTQ Orbitrap XL mass spectrometer. Briefly, separations were performed on a Acquity UHPLC BEH C18 column (2.1 mm ID x 50 mm, 1.7 mm particle size) with a gradient of 0.1% formic acid in water and acetonitrile. Full-scan data was collected at 30 000 FWHM. Product ion spectra were collected in parallel using data dependent acquisition and unit mass resolution on the linear ion trap. A reference standard was not available at the time of analysis. The accurate mass measured was within 0.79 ppm of the theoretical mass of protonated *N,α*-DEPEA ($C_{12}H_{20}N$.) The fragmentation of the compound exhibited a loss of 45da, which strongly indicated the presence of *N,α*-DEPEA as opposed to *N,N*-DEPEA, which would be expected to have a loss of 73da (Figure 1). Sample 1 was sent to the US Food and Drug Administration (FDA).

Sample 2 was purchased in the USA from a GNC store, a mainstream retailer of supplements, and analyzed by NSF International using the same methodology as above which strongly indicated the presence of *N,α*-DEPEA. The identity of *N,α*-DEPEA in Sample 2 was confirmed by comparison of the retention time, accurate mass and product ion spectrum with a *N,α*-DEPEA reference standard (Enamine product no. EN300-106805) (Figure 1). Quantitative UHPLC analysis of Sample 2 showed a concentration of 4.0 mg/g of *N,α*-DEPEA, corresponding to 21 mg per manufacturer recommended serving.

Sample 3 was purchased from a European online supplement retailer (BodyStore.nl; www.bodystore.nl). A methanolic extract of the supplement was analyzed at the Netherland's National Institute for Public Health and the Environment (NIPHE) using its standard method of UHPLC-Synapt G2 Q-TOF-MS/MS analysis strongly indicating the presence of *N,α*-DEPEA. The identity of *N,α*-DEPEA was confirmed by the Korean Forensic Service using

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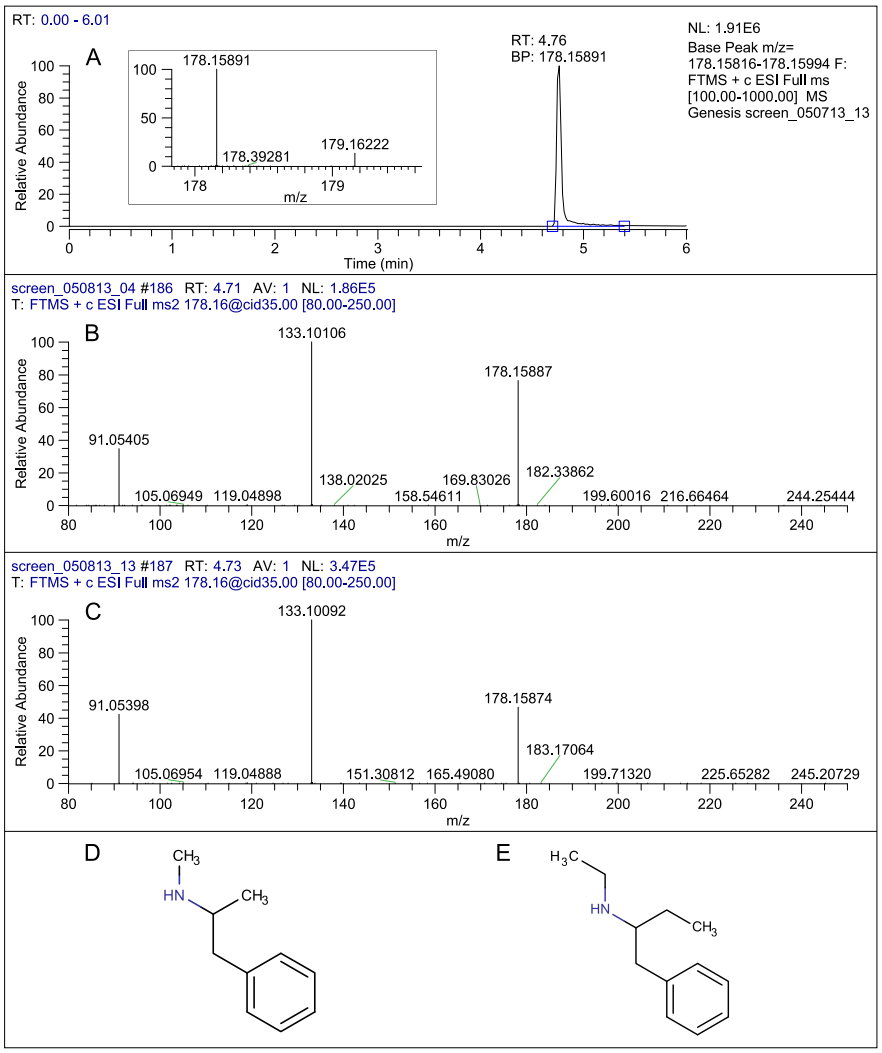

Figure 1. Total ion chromatogram and collision induced dissociation of Sample 2; structures of methamphetamine and *N,α*-DEPEA. (A) Chromatogram of Sample 2 with mass spectrum (inset). (B) Collision induced dissociation (CID) spectrum of authentic *N,α*-DEPEA. (C) CID spectrum of compound identified as *N,α*-DEPEA in Sample2. (D) Structure of methamphetamine. (E) Structure of *N,α*-diethyl-phenylethylamine (*N,α*-DEPEA).

a reference standard and nuclear magnetic resonance (NMR) after acid/base separation of the supplement. Quantitative NMR analysis performed at NIPHE showed a concentration of 6 mg/g of *N,α*-DEPEA, corresponding to 35 mg per manufacturer recommended serving.

Each sample had a different lot number.

Comment

We found a potentially dangerous designer drug, *N,α*-DEPEA, in three separate lots of a widely available dietary supplement. *N,α*-DEPEA is a structural analogue of methamphetamine; however, its stimulant, addictive, and other adverse effects in humans are entirely unknown.

N,α-DEPEA is described in the patent literature,[7] but, to our knowledge, it has never been studied in humans. *N,α*-DEPEA has been described in only four peer-reviewed publications.[8–11] In the early 1990s, *N,α*-DEPEA was identified as a potential designer drug and its cross-reactivity with several commercial urine amphetamine tests was studied (1 of 5 were positive).[9,10] More recently, a batch of pure *N,α*-DEPEA was seized in Korea and suspected of being distributed as an illicit designer drug.[8] Contemporaneous with our investigation, the Korean Forensic Service also confirmed the presence of *N,α*-DEPEA in two additional samples of Craze.[11]

The Craze supplement is labelled as containing several phenylethylamines claiming to be derived from dendrobium.[6] Phenylethylamines include a very broad category of chemicals that range from benign compounds found in chocolate to synthetically produced illicit drugs. The phenylethylamine that we identified, *N,α*-DEPEA, is not listed on the Craze label nor has it ever been identified in any plant (including dendrobium). The quantities per serving of $>$20 mg strongly suggest that *N,α*-DEPEA is not a minor contaminant resulting from the manufacturing process nor a previously undiscovered trace component of dendrobium. Of note, the supplement label listed *N,N*-DEPEA, a structural isomer of the actual ingredient. The listing of a structural isomer might mislead regulators trying to determine the actual ingredients in the supplement.

A limitation of our research is that we did not analyze all workout supplements labelled as containing dendrobium. Therefore, we cannot exclude the possibility that other supplements labelled as containing dendrobium may also contain *N,α*-DEPEA.

If our findings are confirmed by regulatory authorities, the FDA should take immediate action to warn consumers and remove all *N,α*-DEPEA-containing supplements from the marketplace.

Conflicts of interest

Drs Cohen & Venhuis have no conflicts of interest. Mr Travis is an employee of NSF International. Some of NSF International's clients are dietary supplement manufacturers.

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