Analyses Fuel Controversy Over ‘Dendrobium Extract’-Aiming Sports Supplements

Ts and officials question the legality, source, and safety of what all the new DMAA

*Note: This article has been updated and expanded from a previous version that appeared in the December 2013 HerbalEGram.*

In July 2013 publication of a USA TODAY investigation of Matt Cahill and his infamous dietary supplement, three teams of researchers have reported the presence of undisclosed amphetamine-like compounds in some of the pre-workout supplement Craze, and other supplements alleged to contain extracts of dendrobium tatum spp., (Orchidaceae). In its online product description, Craze — one of Cahill’s best-selling formula-BodyBuilding.com’s 2012 New Supplement of the Year — touts an ability to provide users with “seemless energy,” “heightened focus,” and “unrelenting confidence.”

Dendrobex, however, differs from DMAA in that it is not a single chemical. From early 2011 through 2013, there was debate over the natural or synthetic origin of DMAA in supplements, its status as a new dietary ingredient (NDI), whereby requiring a US Food and Drug Administration (FDA) review for its safety prior to being introduced into the market, and whether or not the compound could be found in geranium plants — its alleged source — at any measurable level. According to the FDA, “[although] DMAA at one time was approved as a drug for nasal congestion, no medical use of DMAA is recognized today,” nor is there any reliable published scientific data showing that it occurs naturally in plants. As the American Botanical Council and others have reported previously, several authoritative studies published in peer-reviewed journals have discredited its alleged botanical origins.

“DMAA was, in some ways, symbolic of the challenges facing sports nutrition products. Not only was it chemically and biologically different from its predecessors, but it was also a potential replacement for DMAA in May 2012 (email, September 25, 2013)." As such, I expect the process — unclear natural origin, insufficient sourcing of the raw material to realistically meet market demand, lack of NDI’s and safety dossiers around the synthetic analogues, FDA scrutiny, media scandal, retailers and manufacturers quickly distancing themselves from the ingredient — to repeat itself, with dendrobium next in line.”

### Table 1. List of Craze® Ingredients

| Dendrobex® (dendrobium stem extract), consisting of: | Dendrobine, dendroxine, dendramine, beta-phenylethylamine, N,N-dimethyl-beta-phenylethylamine, and N,N-diethyl-beta-phenylethylamine |
| Other ingredients: | Creatine monohydrate, trimethylglycine (betaine anhydrous), L-citrulline, beta-phenylethylamine HCl, Citrimine® (Citrus reticulata fruit extract, concentrated for N-methyltyramine content), caffeine anhydrous |

*PEA Prominence: Recent Analyses Reveal “Meth-Like” Compound*

Amid the growing confusion surrounding...
“dendrobium”-containing supplements and prompted by reports of high-profile athletes failing drug tests after consuming such products, Drs. ElSohly and Gul tested samples of Craze and Detonate for three structurally similar chemicals with stimulant properties. N-ethyl-alpha-ethyl-phenethylamine (ETH, or N,α-DEPEA) and N,N-diethyl-phenethylamine (N-DEPEA), a labeled component of Craze and an ingredient that recently has caught the attention of regulatory bodies such as the FDA.

“What’s on our radar is people are claiming that dendrobium has certain phenylethylamines,” said Daniel Fabricant, PhD, director of the FDA’s Division of Dietary Supplement Programs (oral communication, September 26, 2013). “Phenylethylamines do not have a profound regulatory action, not dissimilar from some of the things we’ve recently taken action on.”

PEA, Dr. ElSohly explained in his December 2013 paper, is a natural monoamine alkaloid that belongs to a class of chemicals with many compounds of known psychoactive and stimulant effects. Although PEAs occur in trace amounts in some foods such as chocolate, minor structural changes have profound effects on the chemicals’ activity and toxicity. This is particularly evident in N,α-DEPEA, the chemical structure of which differs from methamphetamine by only two chemical groups.

Using liquid chromatography tandem mass spectrometry (LC-MS-MS) — a sensitive analytical method capable of distinguishing chemicals with similar structures — Dr. ElSohly found N,α-DEPEA in quantities ranging from 4.27 to 8.5 mg/g in four of the five tested lots of Craze and in both samples of Detonate (23.4 and 18.4 mg/capsule). The PEA derivative NDP was not detected in the tested supplements, but PEA was found in varying levels in all lots of Craze and Detonate.

“Preliminary data show that the presence of [N,α-DEPEA and PEA] could be easily detected at the 10 ppm level,” the authors stated in their paper. “Whether our not Dendrobium contains these compounds will be the subject of another investigation.”

Similarly, in October 2013, scientists from Harvard Medical School and NSF International, a nonprofit third-party testing organization, reported the presence of N,α-DEPEA in three samples of Craze purchased from various retailers. Using established reference standards and sensitive analytical methods, Cohen et al found N,α-DEPEA concentrations ranging from 21 to 35 mg per serving in the tested supplements.

Working in conjunction with Cohen et al, researchers from the Korean Forensic Service confirmed the chemical’s signature in two separate batches of Craze. As reported in Forensic Toxicology, Lee et al. found 0.40 and 0.44% N,α-DEPEA, respectively — the equivalent of roughly 23 mg per serving.

Although N,α-DEPEA was originally patented in 1988 by Knoll Pharmaceuticals for cognitive-enhancing effects and the ability to increase pain tolerance, N,α-DEPEA was never manufactured or marketed as a drug. Since then, according to the authors of the aforementioned analyses, no human studies have been conducted on the compound.

“There is no possibility that [N,α-DEPEA] has a stimulating effect similar to methamphetamine because their chemical structures are very similar,” stated Lee et al. “The manufacturer of the supplement has advertised that the effects of the product are caused by the labeled ingredients including creatinine [sic] and dendrobium extract. However, the stimulating effects or intoxications induced by the product are probably caused by the presence of an effective dose of undeclared [N,α-DEPEA].”

Dr. ElSohly mentioned other potential health issues in an article on ESPN.com. “The problem with this compound is that it hasn’t been studied,” he was quoted as saying. “At some levels, you could see blood pressure go up. At larger levels, you could be talking about serious side effects, maybe heart attacks.”

Due to the compound’s similarity to methamphetamine and unknown health effects in humans, both research teams called for immediate action from the FDA and other regulatory bodies, including consumer warnings and the removal of all N,α-DEPEA-containing supplements from the market.

In October 2013, in response to the negative publicity resulting from these analyses, Driven Sports issued a statement on its blog refuting the authors’ findings. The company wrote that analyses of Craze conducted on its behalf indicate the presence of N-beta-DEPEA, not N,α-DEPEA.10

“This is a related but very different substance from the one identified by NSF,” Driven Sports states on its website.

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Table 2. Chemical Synonyms for ETH

<table>
<thead>
<tr>
<th>Name</th>
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<tbody>
<tr>
<td>N-alpha-diethyl-phenethylamine (N,α-DEPEA)</td>
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<tr>
<td>N-ethyl-alpha-ethyl-phenethylamine</td>
</tr>
<tr>
<td>N-ethyl-1-phenyl-butan-2-amine</td>
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<tr>
<td>N-ethyl-1-phenyl-2-butanamine</td>
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"It is also very difficult to distinguish these two substances unless you know precisely what you are looking for and are using the proper test methodology....Because of its similar chemical composition, failure to take into account the presence of n-beta could cause a mistaken conclusion that any given sample contains n-alpha."¹⁰

Despite the structural similarity of the alpha and beta forms of DPEA, researchers can differentiate the compounds with appropriate analytical methods. "Using [gas chromatography-mass spectrometry] I can easily distinguish these from each other," said natural products analytical expert James Neal-Kababick, founder and director of Oregon-based Flora Research Laboratories. "They are positional isomers of the same molecule, but that could have a dramatic pharmacological difference."

In their recently published analyses, Cohen et al used ultra-high-performance liquid chromatography (UHPLC) and quadruple-time-of-flight (Q-TOF) mass spectrometry,¹ while Lee et al utilized gas chromatography and mass spectrometry.² "Having reviewed the data from these papers I believe that they were well done and fairly comprehensive," Neal-Kababick said.

In a statement published in USA TODAY, Cohen et al dismissed Driven Sports' argument, saying that the company was "just throwing out new chemical names to try to confuse.... We stand 100% behind our results."¹¹

Driven Sports' confirmation of N,β-DEPEA in Crazed, however, may also be troubling to some regulators. "[N,β-DEPEA] is a positional isomer of N,α-DEPEA] and may still be considered an analogue of amphetamine under the [Federal Analog Act of 1986]," Neal-Kababick noted. "What differs is [one] carbon ... that the side chain is attached to (that is, the alpha or beta carbon)."

Previous Analyses, Contradictory Findings

In June 2012, the US Anti-Doping Agency (USADA) added Crazed to its High Risk Dietary Supplement List, citing stimulant ingredients prohibited by the World Anti-Doping Agency (WADA).¹² According to USADA, the lot of Crazed they tested contained "amphetamine," "N-meth-
ylphenethyamine," "Beta-methylphenethyamine," and "ethylamphetamine." Additionally, the organization’s High Risk List includes Gaspari Nutrition’s Detonate supplement, which also claims to contain dendrobium extract. Detonate — which as of December 2013 is no longer for sale on Gaspari Nutrition’s website — was similarly cited for containing the WADA-prohibited stimulants "Beta-methylphenethyamine," "N-methylphenethyamine," "ethylamphetamine," and "amphetamine."

In April 2013, Craze made headlines after the Swedish National Laboratory of Forensic Science detected the presence of "N-ethyl-1-phenyl-butan-2-amine" — otherwise known as N,α-DEPEA — and "fenetylin," or phenylethylamine in English. Driven Sports responded, calling the findings erroneous and blaming the results on the laboratory’s testing of an inauthentic, or "copycat," version of Craze.

From April to July 2013, Driven Sports had more than 30 lots of Craze tested for N,α-DEPEA by Avomeen Analytical Services, a Michigan-based independent chemical testing laboratory. Using liquid chromatography-mass spectrometry (LC-MS) and a certified reference standard, Avomeen failed to detect the presence of N,α-DEPEA in all samples. Driven Sports has made the certificate of analysis available to the public on its blog.

Mass spectrometry, as performed in LC-MS and GC-MS analyses, works by separating a test compound into charged fragments (often by hitting the compound with a beam of energy) and analyzing the resulting patterns, which provides the test compound’s mass.

The differences between the analytical methods, Flora Research’s Neal-Kababick explained, are subtle but significant. "The issue with LC-MS over GCMS is that [with] LCMS ... the data [are] not always directly comparable to data from other systems with the same system with different collision voltages."

Also in July 2013, the sports supplement manufacturer Tiger Fitness commissioned Dr. Elsöhly’s Phytochemical Services Inc. to test two batches of Craze using a LC-MS-MS. The lab confirmed the presence of "N-ethyl-1-phenyl-2-butyramine" — another synonym for N,α-DEPEA — in both batches.

Regardless of the nuances of various analytical methods, Neal-Kababick emphasized that experience is vital to getting accurate and reproducible results. "A lab can have technology and all sorts of fancy accreditations and such but that does not make them experts in clandestine adulteration screening," he stated. "If labs are not experts in this area, they are likely to miss things and encounter challenges."

DMAA Déjà Vu: Questions of Legality

Roughly two years after Matthew Cahill introduced Craze into the marketplace, questions remain about its status as a legal dietary supplement. Do the components of Craze’s "dendrobium extract" occur naturally in dendrobium? Are the "botanical-sourced" ingredients in Craze natural or synthetic? Is dendrobium extract a new dietary ingredient, which would require that its marketer notify FDA with appropriate safety data 75 days prior to putting the ingredient on the market? Regardless of the answers to these questions, the analyses published in October 2013 that detected the presence of N,α-DEPEA in various lots of Craze may render these regulatory questions moot.

Analogs of Controlled Substances?

"N,alpha-diethylphenylethylamine is a chemical analogue, a cousin if you will, of methamphetamine," explained John Travis, PhD, a senior research scientist at NSF International and co-author of the October 2013 Drug Testing and Analysis paper (email, December 5, 2013). "It differs by an additional methyl group on the N-alkyl chain and an additional methyl group on the backbone alkyl chain. Because of this similarity, it would be regulated under the Federal Analog Act of 1986. A compound like this should never be found in any dietary supplement."

The Federal Analog Act of 1986 states that a "controlled substance analogue shall, to the extent intended for human consumption, be treated, for the purposes of any Federal law as a controlled substance in schedule I." Since both methamphetamine and amphetamine — as well as their salts, isomers, and salts of isomers — are considered schedule II stimulants (i.e., substances that have "a high potential for abuse, but some "accepted medical use ... with severe restrictions") — an analog of any of these chemicals would be considered a schedule I substance (defined as having "a lack of accepted safety for use under medical supervision") if it were found in a product intended for human use, such as a dietary supplement.

US Drug Enforcement Administration (DEA) spokesman Rusty Payne reiterated this point in an October 2013 USA TODAY article — one of many in the paper’s investigative series on questionable products being marketed as dietary supplements. "Anytime there’s a controlled substance or an analog of a controlled substance, that becomes a criminal issue," he said. "If designer drugs are now making their way into dietary supplements across the world, that’s obviously dangerous and very scary."

In the same article, FDA’s Dr. Fabricant agreed that the legal implications in this case are clear. "If [the DEA] determine[s] something is an analog, our law ties directly into that," he was quoted as saying. "If an analog of a controlled substance is in a product sold as a dietary supplement, it is not legally a dietary supplement."

New Dietary Ingredient?

Even if the DEA and/or FDA were to forgo action based on the Federal Analog Act, the status of dendrobium extract as a legal dietary ingredient remains murky. According to FDA’s background document for NDI’s, an NDI is defined as "a dietary ingredient that was not marketed in the United States in a dietary supplement before October 15, 1994."

Furthermore, a dietary supplement is considered adulterated under the law unless each dietary ingredient was
the food supply or the manufacturer provides of safety” when the supplement is used as dietary supplements with “structure/function” were additional, undefined “substantiation that truthful and not misleading.”

he question is, is it chemically altered from what merce before?” asked Dr. Fabricant in an interface.

To extract that compound in any ity, did you have to treat the material…or did use a specific solvent that would really under- chemical alteration?" dendraobium’s established use in Traditional medicine (TCM), only certain preparations tid would qualify as old dietary ingredients. Dendraobium is one of the fundamental botanicals md has been used for millennia," Neal-Kabat said (email, December 5, 2013). “It is also listed erican Herbal Products Association’s Herbs of 2nd edition [and] monographed in the PPRC nacopedia of the People’s Republic of China, 2010 dentrobium stem. Thus, dendraobium or simple the same would not be NDIs. That said, this ean that a highly purified fraction necessarily the same definition.”

cant noted that the FDA pays particular atten- suppleme claims. “If there are products this wonderful effect, like a drug, that’s where get very interested,” he said. And substantiation ms, he says, should be based on human data. “If loing it in a human study, how is it exactly that stantiating the claim?”

2013 blog entry, Driven Sports wrote that a safety studies examining the effects of acute use of Craze had been completed and published: “expected soon.” Roughly eight months after cevment, results of two randomized, double- es were published in the January 2014 issue of tional Journal of Medical Sciences. The first trial hanges in blood pressure, heart rate, and elec- (ECG) activity in subjects 30, 60, 90, and s after consuming Craze or a placebo. Subjects ned Craze had significant increases in systolic ure (SBP) compared to the placebo group, but differences in ECG readings were observed. Those acebo were found to have significantly reduced as well.

cond study — a six-week, placebo-controlled researchers measured physical performance and 1 levels of energy, fatigue, and concentrationnts following a standardized workout program. o the study authors, “six weeks of supplementa- rage in concert with a heavy resistance training is associated with significantly higher subjective energy levels and significantly improved concen- tances in physical performance, however, were ally significant.”

ors write that the six-week trial “is the first in vivo trial in humans of a pre-workout product containing Dendraobex™ or any product containing components of dendraobium,” but they acknowledge the problematic nature of interpreting study results for products with multiple active ingredients. Among other limitations, the subjects' adherence to the workout program and supplement usage could not be closely monitored or confirmed.

Importantly, the authors disclose that Driven Sports sponsored the study in addition to providing the samples of Craze used in the trials. According to the paper, the samples were analyzed by independent laboratories for amphetamines and “controlled substance adulterants” using GC-MS. Additionally, the authors note that one sample of Craze was “ex post facto analyzed for [the] presence of Nα,α-DEPEA” via [LC-MS] of reference standard PEA and its analogs … with no detection.

Natural, Plant-Sourced Constituents?

One particularly contentious issue associated with DMAA was whether or not the chemical existed naturally in any species in the genus Pelargonium (as claimed by some manufacturers of DMAA-containing products), or in any other plant. As noted, credible published analyses of sports supplements containing DMAA as well as verified material and oil from Pelargonium species have demonstrated DMAA is synthetic and is not found naturally in any plant. Similarly, some of the ingredients found in Craze, particularly Nα,α-DEPEA, are clearly synthetic, according to the experts consulted for this article. Nα,α-DEPEA “is not listed on the Craze label (although, as shown above, it has been found in Craze), nor has it ever been identified in any plant (including dendraobium),” Cohen et al. explained in their recent paper.

As president and CEO of the sports supplement company Gen8, Anthony Almada, wryly explained, “Let’s follow you to your [dendraobium] orchid factory where you grow them in a hot house then watch as you take the stems of the orchids…and put them through your extraction machinery and equipment and out the other end comes a high-purity… extract,” he said (oral communication, July 2, 2013). “They don’t do that.”

However, even if all of the components of Dendra- bex were found naturally in plants, the low yields of such compounds would prevent any manufacturer from using actual, dendraobium-derived sources.

“If you start doing the economic botany calculations, it [would] be an unfathomable undertaking to create [pure dendraobium-derived compounds] in the amounts that are being put into these products,” Almada said. “It [would] be prohibitively expensive.”

Despite the economic unfeasibility, Driven Sports maintains its claim of pure, plant-sourced dendraobium. “Our dendraobium extract is not synthetic or a ‘synthetic botani- cal’,” an unnamed company representative wrote in an email to HerbalGram (Driven Sports email to T. Smith, October 1, 2013). “It’s an all natural extract of dendraobium.”
Descendants of DMAA: The Trend Continues

On the surface, the controversy over "dendrobium extract"-containing supplements such as Craze is following a timeline strikingly similar to that of DMAA: (1) a discredited sports supplement figure introduces as a dietary ingredient a compound originally of pharmaceutical interest; (2) USADA adds questionable products to its Dietary Supplement High Risk List based on WADA restrictions; (3) ingredient in question receives international media attention; and (4) researchers attempt to determine the product's contents, origin, and/or human health effects.

Fortunately, serious adverse effects — such as the multiple deaths associated with DMAA — have not yet surfaced for supplements that allegedly contain dendrobium extract. A Freedom of Information Act request by USA TODAY uncovered one report from November 2012 of a 15-year-old boy found "unconscious and unresponsive" after ingesting Craze; but as with adverse event reports in general, the product in question has only a correlational — not causal — link to the incident.

One lawsuit filed against Driven Sports in 2012 was dismissed in February 2013 after the plaintiffs failed to provide evidence that Craze was unlawfully adulterated with amphetamine, but a new class-action lawsuit was filed in California four days after the publication of Cohen et al.'s paper, alleging that the company marketed and sold products containing an unlabeled chemical similar to the illicit street drug methamphetamine.

On October 15, 2013 — just one day after the reports in the Journal of Analytical Toxicology of N,α-DEPEA in various lots of Craze samples were published — Driven Sports revealed on its blog that the company had voluntarily halted production and sales of the popular supplement sometime in the past "several months."

The unfolding story of Craze — one fraught with public skepticism, dubious manufacturer claims, potential regulatory concerns, and nuanced analytical findings — reflects the complexity and challenges that exist in the sports supplement sector. How the Craze controversy will end remains to be seen.

"It would not surprise me to see dendrobium go the way of DMAA and to see another ingredient rise up to take dendrobium's place," said New Hope's Marc Brush. "Given the pattern, the botanicals sector seems a likely source of candidates for the next heir apparent."

Despite the past frustration, some, like Brush, see reason for cautious optimism. "DMAA set a precedent, after much handwringing by the responsible elements of the industry, over how to effectively self-police when faced with such a popular bad actor, and that precedent will effect more rapid purging in the years to come of any 'new DMAAs,'" Brush said. "Given the heightened attention from media and regulators, I don't believe the market opportunity remains as great for descendants of DMAA."

—Tyler Smith

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& REGULATORY


17. Mass spectrometry. Michigan State University website. Available at: www2.chemistry.msu.edu/faculty/reusch/VitrtTextml/
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