



The Detection of Phenethylamine and other Aromatic Amine Stimulants in UK Supplement Products



White Paper

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LGC Sport and Specialised Analytical Services

Introduction

Phenethylamine (PEA; Figure 1a) is a naturally occurring amine which acts as a central nervous system stimulant. The chemical shares structural similarities with a range of other compounds, including substituted phenethylamines which contain additional structural groups (e.g. amphetamine; Figure 1b and other substituted phenethylamines shown as Figure 1c-i). This class of compound is very diverse, consisting of both synthetic and naturally occurring chemicals, with numerous biological modes of action. It is also reported that fermented foods contain elevated amounts of certain substituted phenethylamines, which may be due to microbial action^{1,2}.

PEA and substituted phenethylamines are found in some pre-workout and / or weight management supplements, where their presence may be associated with the use of botanical ingredients (e.g. *Eria jarensis*), the addition of synthetic phenethylamines, fortification with natural phenethylamines or a combination of sources. In some instances, the use of particular botanical ingredients or phenethylamines in supplements has been disputed: In 2016, the FDA issued warning letters to supplement manufacturers regarding the use of *A. rigidula*, as it deemed products containing this particular botanical to be adulterated. Similarly, warning letters were issued by the FDA in 2017 regarding the inclusion of the stimulant β -MPEA^{3,4}. Where fortified, levels present in supplements may exceed assessed efficacy / toxicity levels or the safety levels within humans may be unknown.

Pre-workout and weight management supplements that contain PEA and substituted phenethylamines may indicate their presence by inclusion of chemical names or associated natural ingredients within product labelling information. Table 1 contains examples reported within supplements, chemical synonyms, and attributed botanical source.

Substituted phenethylamines are prohibited by the World Anti-Doping Agency (WADA) for use by athletes in competitive sport (Prohibited List 2024, S6B, Specified Stimulants, Phenethylamine and its derivatives⁵), and

the US Food and Drug Administration (FDA) continually assesses botanical ingredients and other additives to products. Therefore, their inclusion within supplement products not only poses a risk to elite athletes subject to doping control, they also pose a risk to health.

This paper summarises the findings of a study undertaken at LGC to investigate the prevalence of substituted phenethylamines, the link between supplement label versus actual phenethylamine content and the concentrations within these supplements.

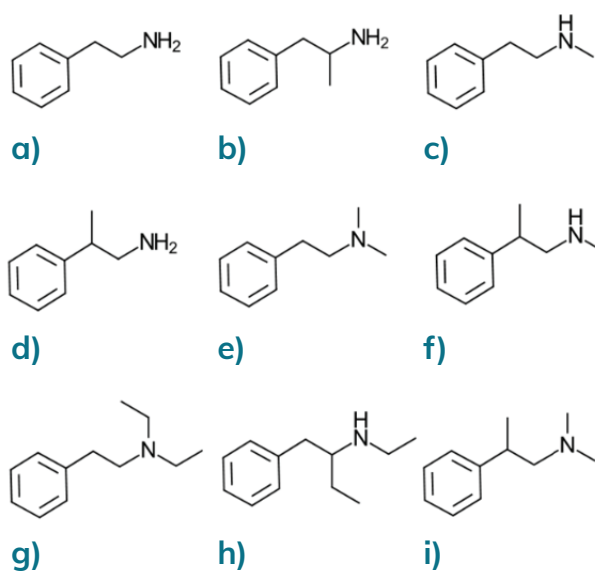


Figure 1: Structures of a) PEA, b) amphetamine, c) N-MPEA, d) β -MPEA, e) N,N-DMPEA, f) N, β -DMPEA, g) N,N-DEPEA, h) N, β -DEPEA and i) N,N-DMPPA



Table 1: WADA named compounds. The WADA prohibited list has leeway for PEA derivatives and similar structures / effects. (WADA terms are in bold).

Compound	Chemical Synonyms ^a	Attributed Botanical Sources ^a
Phenethylamine (PEA)	Phenylethylamine 2-Phenethylamine 2-Phenylethylamine 2-Phenylethanamine Benzeneethanamine beta-Phenethylamine beta-Phenylethylamine 1-Amino-2-phenylethane (2-Aminoethyl)benzene beta-Aminoethylbenzene 1-Phenyl-2-aminoethane 2-Amino-1-phenylethane	<i>Eria jarensis</i> <i>Senegalia berlandieri</i> (<i>Acacia berlandieri</i>) <i>Senegalia catechu</i>
N-Methylphenethylamine (N-MPEA)	N-Methyl-2-phenylethanamine N-Methyl-benzeneethanamine N-Methyl-2-phenylethylamine N-Methyl-N-(2-phenylethyl)amine 1-Phenyl-2-methylaminoethane N-Methyl-beta-phenylethylamine	<i>Eria jarensis</i> <i>Senegalia berlandieri</i> (<i>Acacia berlandieri</i>)
β-Methylphenethylamine (β-MPEA)	BMPEA beta-Methylphenylethylamine beta-Phenylpropylamine 2-Phenylpropylamine 2-Phenylpropan-1-amine 1-Amino-2-phenylpropane 1-Phenyl-1-methyl-2-aminoethane alpha-Benzylethylamine	<i>Acacia rigidula</i> (<i>Vachellia rigidula</i> ; <i>Blackbrush</i>) <i>Eria jarensis</i> <i>Senegalia catechu</i>
N,N-Dimethylphenethylamine (N,N-DMPEA)	N,N-Dimethylphenylethylamine N,N-Dimethyl-N-phenethylamine N,N-Dimethyl-2-phenylethanamine N,N-Dimethyl-2-phenylethylamine N,N-Dimethyl-beta-phenethylamine N-Phenyldimethylamine 2-Dimethylamino-1-phenylethane 2-Phenylethyl-N,N-dimethylamine	<i>Eria jarensis</i> <i>Dendrobium</i> <i>Senegalia berlandieri</i> (<i>Acacia berlandieri</i>)
N,β-Dimethylphenethylamine (N,β-DMPEA)	Methyl(2-phenylpropyl)amine Phenpromethamine N-Methyl-2-phenylpropan-1-amine N,beta-Dimethylbenzeneethanamine	<i>Eria jarensis</i> <i>Dendrobium</i> <i>Senegalia berlandieri</i> (<i>Acacia berlandieri</i>)
N,β-Diethylphenethylamine (N,β-DEPEA)	N,alpha-Diethylphenylethylamine N,alpha-Diethylbenzeneethanamine	
N,N-dimethylphenylpropanamine (N,N-DMPPA)	N,N-dimethyl-2-phenylpropan-1-amine	

^a synonyms and botanical sources listed are not exhaustive and other synonyms / attributed sources may exist.

Experimental

Supplement Samples

Supplement samples were purchased from five online retailers supplying the UK market. Products were found via a search of the suppliers' respective websites. Specific focus (in respect of selection criteria) was placed on pre-workout and weight management products. Supplements declaring phenethylamine (including derivatives and structural analogues) and/or botanical ingredients (attributed as a source of such compounds) were also purchased. Upon receipt, containers were checked to confirm the integrity of product seals and a sub-portion transferred to a suitable container for further analysis.

Analysis

Briefly, portions of calibrator samples (containing reference standards of substituted

phenethylamines at known concentrations) and supplement samples were extracted and analysed using Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS). The instrument and method were optimised before use to allow for the separation of the analytes of interest and collection of sufficient data to ensure the correct identification of substituted phenethylamines (where present). Identities were further confirmed by analysis of the samples using Liquid Chromatography – High Resolution Accurate Mass (HRAM) Mass Spectrometry. Where substituted phenethylamines were identified, the concentrations present were calculated by comparison to the calibrator samples. An example LC-MS/MS chromatogram is shown in Figure 2.

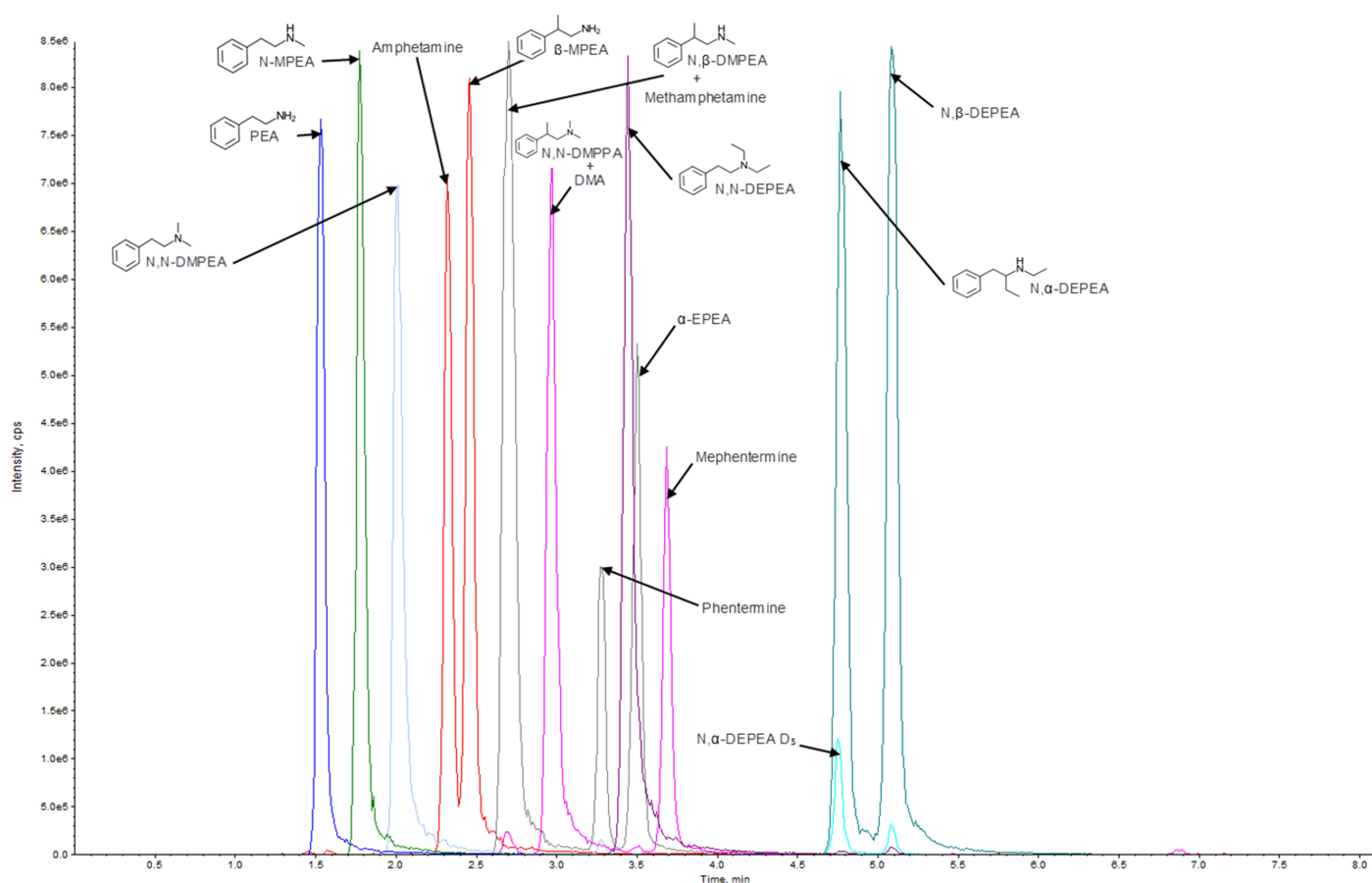
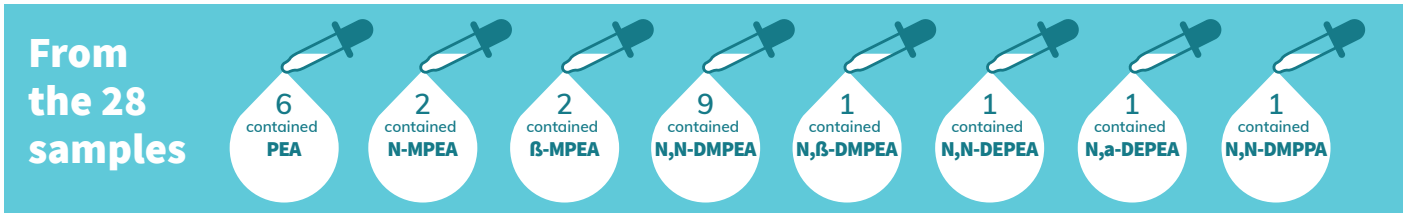


Figure 2: Representative LC-MS/MS chromatogram of substituted phenethylamines in a calibrator sample (different colours represent different MRM transitions)

Results

Table 2 summarises the results of the analysis of the 28 supplement samples, focussing specifically on substituted phenethylamines (in some cases other WADA prohibited substances were found and have been reported elsewhere⁶).



The FDA has cautioned against the use of the stimulant β-MPEA in supplement products. However, this study demonstrates that this substance together with other substituted phenethylamines are available to the UK market.

Table 2: Results of the Analysis of Samples

Supplement Number	Declared Contents ^{b,c}	Identified Contents ^{d,e}	Estimated Concentration (mg/g)	Estimated Daily Intake Based on Suggested Serving (mg/day)
S1	β-phenylethylamine HCl; N,N-dimethylphenethylamine HCl; Citrus aurantium extract [Bitter orange]; Thermopsis lanceolata	PEA N,N-DMPEA	26 15	416-832 240-480
S2	Phenylethylamine; 2-aminoisoheptane; Huperzia serrata (Moss) [Huperzine A]; Nelumbo necifera [Higenamine]	PEA	40	540
S3	β-phenylethylamine; N-methyl-β-phenylethylamine; N-phenethylidimethylamine; Methylhexanamine HCl; Erythroxylum coca extract (leaves); Senegalia berlandieri extract (leaves); Naringen (fruit); Caralluma extract (cactus); Evodiae rutaecarpa extract (fruit) [Tetradium rutilcarpum]	PEA N-MPEA N,β-DMPEA N,N-DEPEA	0.7 33 29 20	0.8-2.4 38-113 33-99 23-68
S4	2-aminoisoheptane HCl; Phenylethylamine; N-methyl-β-phenylethylamine; N,N-dimethylphenylethylamine; Senegalia berlandieri extract (leaves); Yohimbe extract (bark); Green tea extract (leaves); Ephedra extract (leaves) [Ephedra sinica]; Naringen (Fruit)	PEA N,N-DMPEA N-MPEA N,N-DMPPA	67 38 33 17 ^f	89-173 73-98 64-85 33-44 ^f
S5	Cutch tree extract (seed) [Senegalia catechu]; Walnut extract (bark); Christmas bush (leaf); Cacao extract (bean) [Theobroma cacao]; Tangerine extract (fruit)	PEA β-MPEA	41 53	258-517 333-668
S6	Eria jarensis extract; Juglans regia extract (root) [Walnut]; Centroglossa macroceras extract; Theacrine [Camellia sinensis]; Sceletium tortuosum; Astragalus membranaceus extract (root) [Astragalus propinquus]; Panax notoginseng extract (root); Vaso6 [from green tea]; Pomegranate powder extract	N,N-DMPEA	16	167
S7	2-aminoisoheptane; Dandelion root extract; Eria jarensis; Erythrolalum scandens extract	N,N-DMPEA	88	124
S8	DMHA; Cymbidium goeringii; Eria jarensis	N,N-DMPEA	41	23-93
S9	Eria jarensis; Juglans regia extract [Walnut]; Sophora japonica (flower bud) [Rutin]; Rhodiola rosea extract [Rosavin, salidroside]; Coffea arabica (bean) [Green coffee, chlorogenic acid]	β-MPEA	54	222-333
S10	Eria jarensis	N,N-DMPEA	10	100
S11	Ashawagandha [Withania somnifera]; Eria jarensis	N,N-DMPEA	30	290
S12	St. John's Wort extract; Eria jarensis; Juglans regia extract [Walnut]; Rauwolfia serpentina [Rauwolscline (α-yohimbine)]; Olive leaf extract [Oleuropein]; Gynostemma pentaphyllum leaf extract [Damulin A & B]; Aframomum melegueta [6-paradol]; Haematococcus pluvialis extract [Astaxanthin]; Ginger root extract [Zingiber officinale]	N,N-DMPEA	30	123

Table 2: Results of the Analysis of Samples

Supplement Number	Declared Contents ^{b,c}	Identified Contents ^{d,e}	Estimated Concentration (mg/g)	Estimated Daily Intake Based on Suggested Serving (mg/day)
S13	Methylhexanamine HCl; <i>Rauwolfia serpentina</i> [<i>Rauwolscine</i> (α -yohimbine)]	-	-	-
S14	DMHA; <i>Astragalus</i> root extract [<i>Astragalus propinquus</i>]; <i>Panax ginseng</i> extract [<i>Panax notoginseng</i>]	-	-	-
S15	AMP Citrate; <i>Mucuna pruriens</i> [Velvet bean]	-	-	-
S16	<i>Juniperus communis</i> (berry) [Juniper]; <i>Ginkgo biloba</i>	-	-	-
S17	Methylhexanamine HCl; <i>Camellia sinensis</i> (leaf) [Green tea]	-	-	-
S18	<i>Bauhinia purpurea</i> (leaf & pod) [<i>Phanera purpurea</i>]; Hawthorn extract (fruit); <i>Kigelia africana</i> extract (fruit); Bitter orange extract (fruit) [<i>Citrus aurantium</i>]	-	-	-
S19	Theacrine [<i>Camellia sinensis</i>]; Vaso6 [from green tea]; <i>Theobroma cacao</i> extract (seed)	-	-	-
S20	<i>Juglans regia</i> extract [Walnut]; <i>Kigelia africana</i> extract	N,N-DMPEA	8	123
S21	<i>Theobroma cacao</i> extract; <i>Camellia sinensis</i> extract; <i>Juniperus communis</i> (berry) [Juniper]; Naringin [<i>Citrus grandis</i> (fruit)]	-	-	-
S22	<i>Bauhinia purpurea</i> (leaf & pod) [<i>Phanera purpurea</i>]; Cacao extract (fruit); <i>Cymbidium goeringii</i> extract (whole plant); <i>Kigelia africana</i> extract (fruit)	PEA N, α -DEPEA	205 33	171 28
S23	1,3-dimethylamylamine; <i>Schisandra chinensis</i> extract (berry)	-	-	-
S24	2-amino-6-methylheptane; Theacrine [<i>Camellia sinensis</i>]	-	-	-
S25	1,3-dimethylamylamine HCl; Yohimbine extract; Green tea extract (leaves); Sandalwood extract	-	-	-
S26	2-aminoisooheptane; Arecoline hydrobromide [<i>Areca catechu</i>]; <i>Aconitum kusnezoffi</i> ; <i>Citrus aurantium</i> [Bitter orange]	-	-	-
S27	1,3-dimethylamylamine; Bitter orange (fruit) [<i>Citrus aurantium</i>]; <i>Panax ginseng</i> (stem & leaves); <i>Cassia nomame</i> (plant); <i>Taraxacum</i> (leaves); Green tea extract (leaves); Bearberry (leaves); <i>Phyllanthus emblica</i> (fruit)	-	-	-
S28	Octodrine; <i>Panax ginseng</i> [<i>Panax notoginseng</i>]	-	-	-

^b Contents in bold correspond to chemical names of phenethylamine and substituted phenethylamine compounds (PEAs).

^c Contents underlined correspond to purported botanical sources of PEAs.

^d Identified contents refer specifically to PEAs.

^e Identified compounds that were below the level of quantification (BLQ) are not included.



The supplement samples tested by LGC could be broadly broken into the following categories based upon their labelling:

- 1) Supplements with substituted phenethylamines as ingredients – 4 samples (S1-S4; Table 2)
 - a. The chemical nomenclature in use by the supplement manufacturers was found to be largely accurate. In all cases, the substituted phenethylamines listed on the supplement container were detected. In 1 of these samples, an ingredient was listed as N,N-DMPEA however N,N-DEPEA and N, β -DMPEA were identified as present.
- 2) Supplements with botanical ingredients that have been quoted as (yet unproven, tentatively identified or refuted) sources of substituted phenethylamines – 10 samples (S3-S12; Table 2)
 - a. Of the 2 samples that listed *Senegalia berlandieri* as a botanical source, PEA and N-MPEA were identified (PEA and N-MPEA have been reportedly identified in *Senegalia berlandieri*⁷). In 1 of these samples, N, β -DMPEA and N,N-DEPEA were also identified. In the other, N,N-DMPEA was detected.
 - b. Of the remaining 8 samples declaring botanical ingredients, one detailed *Senegalia catechu* and in this sample PEA and β -MPEA were identified (*Senegalia catechu* is an attributed botanical source of these substituted phenylamines). The remaining 7 samples declared *Eria jarensis* and 6 were found to contain N,N-DMPEA (N,N-DMPEA has been reportedly identified in *Eria jarensis*⁸). The remaining sample was found to contain β -MPEA (also linked to *Eria jarensis*).
 - c. One supplement was found to contain N,N-DMPPA. This substituted phenethylamine is not a commonly detected compound, having only been reported once previously within a supplement sample⁹. There is no overlap between the ingredients listed in the literature-reported supplement ('caffeine and adrenergic amines such as acacia rigidula') and the supplement tested as part of this study (S4; Table 2). N,N-DMPPA is a designer stimulant, with no evidence of a naturally occurring source, and was detected within urine samples of 4 athletes in 2013 and 2014.
- 3) Supplements where there is no indication of the presence of substituted phenethylamines (either as a specific chemical additive or botanical ingredient) – 17 samples (S13-S28; Table 2)
 - a. Of the 16 supplements where there was no indication from the manufacturer of substituted phenethylamine content (either as a specific ingredient or a botanical extract), one were found to contain N,N-DMPEA and the other was found to contain both PEA and N, β -DEPEA.

The assertion by some manufacturers that the presence of substituted phenethylamines in their products is due to the inclusion of botanical ingredients is contentious. As the declared presence of the same botanical ingredient in different products is associated with different compounds, it is reasonable to assume that in some instances that synthetic additives have been introduced to some supplements during their manufacture. This is more likely the case for the 14% of products where no declaration of substituted phenethylamine content was made either directly (chemical) or implied through the inclusion of botanical ingredients.





Substituted Phenethylamine Concentrations

The concentrations of substituted phenethylamines detected in the samples varied between supplements. The amount a consumer would ingest following the manufacturer's instructions ranged from:

0.8 to 832 mg per day for PEA	37 to 112 mg per day for N-MPEA	221 to 667 mg per day for β-MPEA	23 to 480 mg per day for N,N-DMPEA
33 to 99 mg per day for Nβ-DEPEA	22 to 68 mg per day for N,N-DEPEA	27 mg per day for Nβ-DEPEA	33 to 44 mg per day for N,N-DMPPA

Conclusions

Phenethylamine is a naturally occurring compound found in food stuffs such as chocolate. However, the levels present in normal foodstuffs is generally relatively low (< 0.003 mg / g¹⁰) in comparison to some of the levels detected within the supplements tested.

It is unclear what corresponds to a safe dose of the substituted phenethylamines found in the supplements tested, it is difficult to confirm what (if any) the long-term health impact would be on individuals consuming the supplements tested in this study. Although there is no proven causation, there are reports of haemorrhagic stroke coincident with the use of supplements containing substituted phenethylamines^{11,12}.

An additional consideration is that these supplements do not contain substituted phenethylamines in isolation from other compounds and they are likely to contain other stimulants such as caffeine and methylhexaneamine-type compounds (1,3-DMAA). It is unclear what the cumulative effect of these stimulants would be, however supplement adulterants such as β -MPEA have a demonstrable biological effect¹³.

In Summary

The analysis of a range of weight management (fat burning) and pre-workout supplement samples purchased from UK suppliers brings to light the ready availability of substituted phenethylamines such as N-MPEA, β -MPEA, N,N-DMPEA, N, β -DMPEA, N,N-DEPEA, N,N-DMPPA and N, β -DEPEA to individuals, in addition to PEA. Many of these compounds have limited or no clinical approval and the health implications of their regular intake (along with other stimulant ingredients) are not known. The content labelling of these supplement samples is sometimes inadequate, with no indication on the container as to the presence of substituted phenethylamines.

The assessment of stimulant content by the consumer in many cases has to be made via interpretation of botanical ingredients listed e.g. Guarana as a source of caffeine. The results of this study indicate that this approach cannot provide any certainty of stimulant content or intake making it near impossible for the end user to make an informed decision.

A Doping Risk

Based on the outcome of this study, there is a definite risk for athletes who are subject to routine doping control. Although it cannot be stated categorically that PEA and N,N-DMPEA (both known to be naturally occurring) would result in a doping violation, the levels at which these compounds are present within supplement products raises significant concerns and serves to increase risk. However, the presence of other derivatives of phenethylamine (particularly at the concentrations determined) indicate a significant risk to the athlete both from a doping perspective and a potential health perspective.

For athletes subject to doping control, this study demonstrates the importance of ensuring that the supplements they use have been subject to a rigorous testing programme such as Informed Sport or Informed Choice. LGC retains its position as the market leader in this area due to a commitment to the continuous development of intelligence-led testing, combined with ongoing research and development activity.

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