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January 14, 2013

Quyen Tien
Division of Enforcement
Office of Compliance (HFS-608)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, Maryland 20740-3835

Re: Warning Letter No. 285519 (April 24, 2012)

Dear Mr. Tien:

We received a warning letter from Michael W. Roosevelt (the Roosevelt letter) dated April 24, 2012, regarding the marketing of our dietary supplements that contain the dietary ingredient 1,3-DMAA, and responded to that letter on May 15, 2012. Subsequent to that response, we have also had an opportunity to meet with FDA officials in order to obtain a more complete understanding of the issues raised in the Roosevelt letter. As promised in our May 15 response, we provided additional information that had become available after that initial response in our first supplemental submission to you dated September 28, 2012. In this second supplemental submission we are providing additional information relevant to the Roosevelt letter that has become available after our first supplemental submission of last September.

I. The Clinical Study by Professor Richard J. Bloomer et al. on the Safety of Caffeine and 1,3-Dimethylamylamine (1,3-DMAA)

Professor Richard J. Bloomer of the University of Memphis and his colleagues have conducted a 12-week placebo controlled clinical safety study on caffeine and 1,3-DMAA in 50 healthy young men. A copy of the report of this study, as it has been accepted for publication following peer review, is attached in Appendix A.

This paper reports an examination of the safety of either placebo 1,3-DMAA (50 mg/day), caffeine (250 mg/day), and 1,3-DMAA/caffeine combined, in healthy young men over a period of 12 weeks. Safety variables examined included blood pressure, 12-lead ECG, urinalysis, complete blood count, metabolic panel, lipid panel, and oxidative stress, inflammatory, and cardiac biomarkers (i.e., used to look for any signs of cardiac damage). The results of the study showed that 1,3-DMAA either by itself or in combination with caffeine did not lead to any statistically significant changes in any of these safety variables.

II. Rodricks et al. Letter to the Editor of the Annals of Emergency Medicine

In May 2012, Gee et al. published a report in the Annals of Emergency Medicine on cerebral hemorrhage in three individuals in New Zealand following recreational use of 1,3-DMAA. Attached in Appendix B is a Letter to the Editor by toxicologist Joseph V. Rodricks, Ph.D., and his colleagues, as it has been accepted for publication in the same journal.

The Rodricks Letter concludes that the Gee paper's published blood levels of 1,3-DMAA from these individuals, when considered with recently available pharmacokinetic data, show that these individuals consumed quantities of 1,3-DMAA far greater than those found in dietary supplements. The blood levels of 1,3-DMAA found in these individuals were 19-37 times higher than levels found in individuals consuming a 25 mg dose of DMAA (i.e., the dose found in typical dietary supplements, including Jack3d and OxyElite Pro). These individuals were also consuming recreational drugs or alcohol in combination with these extremely high amounts of 1,3-DMAA.

III. Rodricks et al. Letter to the Editor of the Archives of Internal Medicine

In May, 2012, Cohen published a Letter to the Editor of the Archives of Internal Medicine that contained substantial erroneous information about the safety of 1,3-DMAA. Attached as Appendix C is a Letter to the Editor by toxicologist Joseph V. Rodricks, Ph.D., and his colleague, as it has been accepted for publication in the same journal.

The Rodricks Letter first pointed out that Cohen was incorrect in stating that 1,3-DMAA is an "amphetamine derivative", because 1,3-DMAA is not synthesized from amphetamine nor does it possess the hallmark chemical moiety characteristic of all amphetamines, i.e., the benzyl ring. Cohen's referencing of a Health Canada review which concluded there is no evidence for 1,3-DMAA's natural occurrence failed to state that the Health Canada review did not consider the two published papers (i.e., Li and Fleming) which do show DMAA as a constituent (along with the original Ping study). Cohen relied upon case reports of extremely high levels of

recreational use such as those found in the Gee paper to support his assertion that 1,3-DMAA is dangerous, as opposed to published controlled clinical studies which utilized labeled amounts found in dietary supplements.

IV. Conclusion

The information contained in this second supplemental response to the April 24, 2012 Roosevelt letter provides further confirmation of the safety and legality of 1,3-DMAA as used in our products. We will provide final reports on the animal subchronic toxicity testing as soon as they become available.

V. Confidentiality

The information in this submission constitutes trade secrets and confidential information that is exempt from public disclosure under 5 U.S.C. § 1905 and Section 301(j) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 331(j).

Sincerely yours,

Kenneth F. Miles

Dr. Kenneth F. Miles
Chief Compliance Officer

Enclosures

Appendix A

Safety profile of caffeine and 1,3-dimethylamylamine supplementation in healthy men

Richard J. Bloomer, T.M. Farney, I.C. Harvey and R.J. Alleman

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Safety profile of caffeine and 1,3-dimethylamylamine supplementation in healthy men

Richard J. Bloomer, T.M. Farney, I.C. Harvey and R.J. Alleman

Abstract

Caffeine and 1,3-dimethylamylamine (DMAA) are widely used alone and in combination with dietary supplements. No investigation has determined the safety profile of chronic intake of caffeine or DMAA, alone or in combination, within the same study design. A total of 50 young and healthy men completed 12 weeks of daily supplementation with either a placebo ($n = 11$), caffeine at 250 mg day^{-1} ($n = 14$), DMAA at 50 mg day^{-1} ($n = 13$), or caffeine at 250 mg day^{-1} + DMAA at 50 mg day^{-1} ($n = 12$). Before and after 6 and 12 weeks of supplementation, the following variables were measured: body mass/composition, resting respiratory rate, blood pressure, 12-lead electrocardiogram, urinalysis, complete blood count, metabolic panel, lipid panel, and oxidative stress, inflammatory, and cardiac biomarkers. No interaction effects were noted for any variable ($p > 0.05$), with little change occurring across time for subjects in any of the four conditions. With the exception of urinary pH ($p = 0.05$; Pre (6.5 ± 0.1) higher than week 6 (6.1 ± 0.1)) and blood CO_2 ($p = 0.02$; week 12 (25.9 ± 0.3 mmol L^{-1}) higher than week 6 (24.8 ± 0.3 mmol L^{-1})), no time effect was noted for any other variable ($p > 0.05$). These data indicate that 12 weeks of daily supplementation with caffeine and DMAA, alone or in combination, does not result in a statistically significant change in any of the measured outcome variables.

Keywords

Dietary supplements; caffeine; DMAA; safety

Introduction

Both caffeine and 1,3-dimethylamylamine (DMAA) are widely used by individuals either as stand alone ingredients or within finished dietary supplements. Like caffeine, DMAA is a central nervous system stimulant and can induce transient sympathomimetic effects. DMAA can be commercially synthesized and has been detected in small quantities in cultivars of *Pelargonium graveolens*.[1,2] While the safety of daily caffeine use at moderate dosages is generally well accepted,[3] the safety of DMAA has been called into question recently. This is at least partly based on the case reports documenting adverse outcomes following ingestion of extremely high oral dosages of DMAA.[4,5] For example, in reports presented by Gee and colleagues, the amount of DMAA ingested by individuals was likely ~15–30 times the amount provided in most dietary supplements currently sold on the market. This hypothesis is based partly on the cited dosages indicated within the articles and partly on patients' plasma DMAA concentrations as reported by the authors,[5] when compared with plasma DMAA concentrations obtained from subjects following a 25-mg oral dosage of DMAA (unpublished findings). Moreover, as indicated in the articles of Gee and coworkers,[4,5] other chemicals may have been taken along with the DMAA (e.g. alcohol, caffeine, phenethylamine, and cannabis). Hence, to conclude on the safety profile of DMAA based solely on case reports would be problematic. This is particularly true when accepting testimony from individuals in a highly uncontrolled environment (i.e. local pub),

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Table 1. Characteristics of men assigned to placebo, caffeine, DMAA, or caffeine + DMAA for 12 weeks.[a]

Variable	Placebo ($n = 11$)	Caffeine ($n = 14$)	DMAA ($n = 13$)	Caffeine + DMAA ($n = 12$)
Age (years)	23.1 ± 1.5	23.0 ± 1.1	23.1 ± 1.8	23.6 ± 1.8
Height (cm)	178.7 ± 1.9	177.7 ± 1.7	177.2 ± 2.0	173.9 ± 1.7
Body weight (kg)	81.8 ± 6.9	81.6 ± 4.2	79.0 ± 2.4	82.8 ± 3.2
Body mass index (kg m^{-2})	25.5 ± 1.9	25.8 ± 1.2	25.2 ± 0.7	27.3 ± 0.8
Waist circumference (cm)	87.3 ± 4.1	87.5 ± 2.7	86.3 ± 2.5	90.9 ± 3.4
Hip circumference (cm)	106.9 ± 3.0	102.5 ± 3.2	99.8 ± 2.0	106.0 ± 1.9
Waist: hip	0.81 ± 0.02	0.86 ± 0.02	0.87 ± 0.03	0.86 ± 0.02
Weekly aerobic training (h)	2.3 ± 0.7	2.3 ± 0.5	1.7 ± 0.5	2.8 ± 0.7
Aerobic training history (years)[b]	2.5 ± 0.8	3.3 ± 0.7	4.6 ± 1.6	7.7 ± 1.8
Weekly anaerobic training (h)	2.9 ± 0.6	3.2 ± 0.5	4.4 ± 0.7	3.6 ± 0.8
Anaerobic training history (years)	3.1 ± 0.8	3.4 ± 0.7	3.2 ± 0.5	5.0 ± 1.4

DMAA: 1,3-dimethylamylamine.
[a]Values are mean ± SEM. No other differences of statistical significance noted ($p > 0.05$).
[b]$p = 0.05$; caffeine + DMAA > placebo.

potentially under the influence of alcohol and other drugs.

The reports of Gee and colleagues represent adverse outcomes following a single ingestion of very high dosage of DMAA,[4,5] which may have been due to the pressor effects of DMAA. In our early work using DMAA,[6] we noted an acute rise in systolic blood pressure following oral ingestion, which was dose dependent (higher with a 75-mg dosage when compared to a 50-mg dosage). Hence, it is logical to assume that a DMAA dosage of 10 times the amount provided in our early work (and likely the amount ingested by some patients in the Gee et al. reports[4,5]) would lead to adverse outcomes.

Within the weight loss and sport performance market, many individuals use caffeine and DMAA chronically at a much lower and recommended dosage (i.e. 150–250 mg caffeine and 25–50 mg DMAA). At such dosages and *in conjunction with other ingredients* contained within finished dietary supplements, we have noted no significant adverse outcomes in terms of elevations in resting heart rate, blood pressure, or blood borne markers of health (e.g. complete blood count, metabolic panel, lipid panel and liver function) in young, otherwise healthy subjects following eight[7] and ten weeks[8] of intake. In the present study, we extended our prior work by including (1) caffeine and DMAA alone and in combination (rather than as components of finished dietary supplements containing additional ingredients), (2) dosages of caffeine and DMAA that are routinely used by consumers of these ingredients, (3) an extended time frame of supplementation—12 weeks, and (4) additional measures of clinical safety—body mass and body composition, resting respiratory rate, 12-lead electrocardiography (ECG), urinalysis with microscopic examination, and oxidative stress, inflammatory, and cardiac biomarkers.

Methods

Subjects

Men were recruited to participate in this study via informal word of mouth conversations, formal presentations discussing study participation, online postings, and recruitment flyers posted on and off campus. All subject recruitment was performed by the investigators (TMF, ICH, and RJA). A total of 66 healthy men provided written informed consent to participate in this study. However, 16 men failed to complete all aspects of the study (e.g. missed one of the assessment days and decided to cease their participation due to time constraints). Therefore, only 50 men are included in the data analysis. Subject baseline characteristics are presented in Table 1. Women were not enrolled in this study in an attempt to maintain a more homogenous sample. Subjects were not current smokers and were considered to be in good overall health. They did not have a history of cardiovascular, neurological, or metabolic disorders (e.g. hypertension, seizures, and diabetes). Subjects were regular consumers of stimulants (e.g. caffeine) such as beverages or nutritional supplements, who did not report a history of adverse reactions to caffeine or other stimulants. Health history, medication and dietary supplement usage, and physical activity questionnaires were completed by all subjects and reviewed in detail by an investigator to determine eligibility. Prior to participation,

each subject was informed of all procedures, potential risks, and benefits associated with the study through both verbal and written form. The study procedures were approved by the University Institutional Review Board for Human Subjects Research (approval document number 2012). Subjects who completed the study protocol were compensated $200 for their time and effort.

Testing and supplementation

Following the initial lab visit in which subjects completed all paperwork, subjects returned to the lab on three occasions (before supplementation, after 6 weeks of supplementation, and after 12 weeks of supplementation) to complete the following assessments. On each occasion subjects reported to the lab following an 8-h overnight fast. Upon arrival, the following was performed:

1. Subjects turned in diet logs (described below).
2. Subjects voided. They were given a standard urine collection cup and provided with instructions for filling. Urine was processed immediately and analyzed within 24 h for a complete urinalysis with microscopic examination (using reagent strips and light microscopy).
3. Subjects were prepped for a resting 12-lead ECG and rested quietly for 10 min. An ECG was then analyzed using automated procedures (Mac 1200; GE Medical System).
4. Respiratory rate (in 60s) was counted by simple observation.
5. Blood pressure was measured using a stethoscope and cuff, while subjects were in a seated position.
6. A blood sample was taken and processed as described below.
7. Body mass and body composition were determined via dual energy x-ray absorptiometry (DEXA) using a 4-min fan array (Hologic QDR 4500W; Bedford, Massachusetts, USA).

Following the above assessments, subjects were randomly assigned to one of four conditions, in double-blind manner: placebo (cellulose), caffeine (250 mg), DMAA (50 mg), or caffeine (250 mg) + DMAA (50 mg). All conditions were produced under standard good manufacturing practices by a dietary supplement contract manufacturer. Quality assurance procedures confirmed the purity and potency of each condition. The study sponsor retained the blinding code until study completion.

For all conditions, subjects were instructed to consume one capsule per day during week 1, in order to acclimate to the condition. Then, beginning with week 2, subjects were instructed to consume two capsules every day of the week for the remainder of the 12-week intervention (one capsule upon rising in the morning and one capsule 4–6 h later). The final capsules were to be consumed on the day prior to the final test day; no capsules were consumed before assessments were performed on the mornings of test days. Capsule counts upon bottle return allowed for the calculation of compliance to intake.

Blood collection and analysis

Venous blood samples (~20 mL) were taken from subjects via needle and Vacutainer®. Blood samples were collected before starting supplementation (Pre) and after 6 and 12 weeks of supplementation. Following collection, samples were processed accordingly and fresh samples were analyzed for complete blood count (Coulter LH750, Beckman Coulter, Inc.), comprehensive metabolic panel (Roche/Hitachi Modular), and lipid panel (Roche/Hitachi Modular). In addition, fresh samples were analyzed for C-reactive protein (using a high-sensitivity, particle-enhanced turbidimetric immunoassay; Roche Integra 800) and cardiac troponin I (using an electrochemiluminescence immunoassay). Remaining blood was stored at −70°C and later analyzed for plasma malondialdehyde (using reagents purchased from Northwest Life Science Specialties, Vancouver, Washington, USA), advanced oxidation protein products (using reagents purchased from Cell Biolabs, San Diego, California, USA), and Trolox Equivalent Antioxidant Capacity (using reagents purchased from Sigma Chemical, St Louis, Missouri, USA).

Dietary records and activity

All subjects were instructed to maintain their normal diet throughout the study period, with the following exceptions: subjects were instructed not to consume caffeinated beverages such as "energy drinks", coffee, tea, or soda during the study period. They were also advised not to use dietary supplements containing caffeine or other stimulants (other than their assigned condition). Subjects were asked to record food and beverage intake during 72 h prior to each test day (pre, 6 weeks, and 12 weeks). Dietary records were reviewed with each subject for accuracy and then analyzed using Food Processor SQL, version

9.9 (ESHA Research, Salem, Oregon, USA). Subjects were asked to refrain from strenuous physical activity for 48 h prior to each test day, but they were to otherwise maintain their usual exercise training during the entire course of the study.

Statistical analysis

Data were analyzed using a 4 (condition) by 3 (time) analysis of variance. Tukey's post hoc testing was used as needed. The data are presented as mean ± SEM. All analyses were performed using JMP statistical software. Statistical significance was set at $p \leq 0.05$.

Results

Of the 50 subjects who completed the study, none reported a significant adverse event. Compliance to capsule intake was not different ($p = 0.36$) between placebo (88.5 ± 3.7%), caffeine (93.8 ± 2.4%), DMAA (91.7 ± 5.0%), or caffeine + DMAA (97.3 ± 1.1%). When considering all variables, no interaction effects were noted ($p > 0.05$). With the exception of urinary pH ($p = 0.05$; Pre higher than week 6) and blood CO_2 ($p = 0.02$; week 12 higher than week 6), no time effects were noted. Some condition effects were noted, as denoted under each table. Body mass ($p > 0.05$) and body composition ($p > 0.05$) assessed via DEXA were not impacted by any condition. Cardiorespiratory data are provided in Table 2. Urinalysis data are provided in Table 3. Oxidative stress, inflammatory, and cardiac biomarker data are provided in Table 4. Complete blood count, metabolic panel, and lipid panel data are provided in Tables 5 to 7, respectively. Dietary data are provided in Table 8.

Discussion

Findings from the present study indicate that 12 weeks of supplementation with caffeine and DMAA, whether alone or in combination, does not result in statistically significant changes in any measured variables. These data are specific to a sample of healthy, young men consuming moderate, and recommended daily dosages of caffeine (250 mg) or DMAA (50 mg). These findings confirm our initial results obtained from subjects ingesting finished dietary supplements containing these two ingredients.[7,8] However, our findings are in conflict with those of Gee and colleagues,[4,5] who reported adverse outcomes in four patients, who ingested dosages of DMAA that far exceeded the dosage provided in the current design. As with other widely consumed stimulants (e.g. caffeine), ingestion of multiple times the recommended dosage is highly unadvisable and could result in severe consequences.

Subject characteristics were very similar between conditions, with the exception of the number of years of aerobic exercise training—which was significantly higher for subjects in the caffeine + DMAA condition when compared with those in the placebo condition (Table 1). Although we do not have maximal oxygen uptake (VO_{2max}) data to confirm this, it is possible that these subjects (as a group) may have been more conditioned from a cardiorespiratory perspective than subjects in the other conditions. Likewise, it should be noted that subjects in this study were relatively young and healthy—and were regular users of stimulants prior to enrolling in the study. It is possible that the inclusion of older and sedentary adults (men or women), who are unhealthy and who do not regularly use stimulants, may yield different findings. The same may be true for younger individuals (preteens and teens), who appear to be regular users of "energy drinks" and other products containing stimulants. For these populations, the use of stimulants would be strongly ill advised.

In addition to subject characteristics, dietary intake was very similar between conditions, with intake as expected for younger and healthy men (Table 8). Therefore, we do not believe that our outcome measures between groups or across time were influenced by dietary intake.

With regard to the cardiorespiratory data presented in Table 2, a few variables deserve attention. First, subjects' heart rate increased in a nonstatistically significant manner (approximately 5 b/min) from pre to week 12 in the DMAA condition. Second and by default, the increase in heart rate produced a similar percentage increase in rate pressure product, as heart rate is used in the calculation of rate pressure product (systolic blood pressure × heart rate). Interestingly, no change was observed in the heart rate for subjects in the caffeine or caffeine + DMAA conditions. Third, respiratory rate for subjects in the caffeine + DMAA condition increased over time, which appeared somewhat additive when considering the small increase observed for both caffeine and DMAA alone. It is possible that a larger sample size, providing more statistical power, may have yielded statistically significant findings in the above measures. Future studies may include a larger sample of subjects ingesting DMAA alone or in combination with

Table 2. Cardiorespiratory data of men assigned to placebo, caffeine, DMAA, or caffeine + DMAA for 12 weeks.[a]

Variable	Placebo ($n = 11$)	Caffeine ($n = 14$)	DMAA ($n = 13$)	Caffeine + DMAA ($n = 12$)
Respiration (breaths min^{-1})				
Pre	13.7 ± 1.2	13.3 ± 1.1	13.1 ± 1.2	14.1 ± 1.3
Week 6	14.1 ± 0.9	13.4 ± 0.9	13.8 ± 1.2	15.4 ± 1.3
Week 12	13.4 ± 1.1	13.9 ± 1.0	14.3 ± 1.4	17.0 ± 1.1
Heart rate (b/min)[b]				
Pre	61.6 ± 3.1	63.9 ± 1.9	60.8 ± 2.5	68.0 ± 4.0
Week 6	57.7 ± 2.5	64.1 ± 3.1	64.7 ± 1.8	69.4 ± 4.2
Week 12	60.2 ± 3.5	63.9 ± 2.0	65.8 ± 3.2	66.2 ± 3.0
SBP (mmHg)				
Pre	120.2 ± 3.4	117.6 ± 3.5	120.6 ± 3.1	122.6.0 ± 2.7
Week 6	125.5 ± 2.9	122.1 ± 3.3	120.6 ± 2.9	124.0 ± 3.4
Week 12	126.5 ± 2.4	118.3 ± 3.3	122.2 ± 2.8	120.0 ± 3.0
DBP (mmHg)				
Pre	66.0 ± 2.2	65.6 ± 1.8	71.3 ± 3.8	71.0 ± 2.6
Week 6	72.2 ± 2.3	67.7 ± 3.6	71.2 ± 3.5	66.3 ± 3.3
Week 12	70.2 ± 3.7	66.7 ± 3.2	71.5 ± 4.0	66.0 ± 2.7
Rate pressure product				
Pre	7421.5 ± 432.3	7518.7 ± 301.4	7374.6 ± 416.5	8319.4 ± 494.1
Week 6	7223.1 ± 319.2	7855.3 ± 473.0	7835.5 ± 343.3	8615.3 ± 580.6
Week 12	7652.0 ± 529.2	7547.4 ± 312.1	8099.4 ± 522.4	7968.3 ± 478.1
PR interval (ms)[b]				
Pre	162.4 ± 5.4	172.0 ± 8.6	148.2 ± 6.4	151.5 ± 6.4
Week 6	158.4 ± 5.1	164.9 ± 10.4	146.6 ± 4.8	150.7 ± 6.7
Week 12	168.0 ± 7.3	172.0 ± 9.8	145.5 ± 5.1	148.3 ± 6.6
P wave duration (ms)[b]				
Pre	100.7 ± 3.6	106.6 ± 3.1	102.9 ± 3.1	101.0 ± 2.7
Week 6	102.0 ± 4.5	107.7 ± 4.1	103.2 ± 2.0	99.6 ± 2.2
Week 12	98.5 ± 3.4	103.3 ± 3.1	103.7 ± 2.5	98.8 ± 1.4
QRS duration (ms)				
Pre	96.4 ± 2.9	96.9 ± 1.8	97.1 ± 5.0	93.8 ± 2.3
Week 6	94.4 ± 3.4	97.0 ± 2.0	95.5 ± 3.4	95.3 ± 3.4
Week 12	97.1 ± 3.2	96.9 ± 1.9	95.8 ± 3.5	93.7 ± 2.9
QT interval (ms)[b]				
Pre	403.3 ± 8.8	400.1 ± 9.4	418.5 ± 8.3	387.3 ± 5.6
Week 6	397.1 ± 9.2	402.9 ± 7.2	404.8 ± 8.6	387.3 ± 5.3
Week 12	401.1 ± 9.7	406.0 ± 4.8	409.1 ± 11.0	391.3 ± 5.7
PP interval (ms)				
Pre	997.7 ± 52.8	899.3 ± 52.2	1005.4 ± 43.3	913.3 ± 51.5
Week 6	1023.3 ± 55.3	962.5 ± 47.6	935.4 ± 27.9	883.2 ± 49.8
Week 12	1031.4 ± 64.0	912.5 ± 47.7	937.3 ± 48.7	926.7 ± 42.9
RR interval (ms)				
Pre	982.0 ± 52.2	937.9 ± 30.3	999.5 ± 47.5	903.8 ± 49.9
Week 6	1022.4 ± 55.5	958.1 ± 52.2	929.5 ± 28.4	876.4 ± 46.3
Week 12	1024.5 ± 62.9	947.4 ± 35.6	928.3 ± 49.2	915.8 ± 41.3

SBP: systolic blood pressure; DBP: diastolic blood pressure; DMAA: 1,3-dimethylamylamine.
[a]Values are mean ± SEM. No other differences of statistical significance noted ($p > 0.05$).
[b]Condition effect for heart rate ($p = 0.04$), caffeine + DMAA > placebo; PR interval ($p = 0.0002$), caffeine + DMAA < caffeine, DMAA < caffeine and placebo; P wave duration ($p = 0.04$), caffeine + DMAA < caffeine; QT interval ($p = 0.007$), caffeine + DMAA < DMAA.

caffeine (and possibly other widely utilized stimulants) in an effort to extend and/or replicate our findings and to determine what, if any, clinical meaning these increases might have.

With regard to the oxidative stress, inflammatory, and cardiac biomarker data, a few variables deserve attention (Table 4). First, advanced oxidation protein products demonstrated a rather random increase

Table 3. Urinalysis data of men assigned to placebo, caffeine, DMAA, or caffeine + DMAA for 12 weeks.

Variable	Placebo ($n = 11$)	Caffeine ($n = 14$)	DMAA ($n = 13$)	Caffeine + DMAA ($n = 12$)
Specific gravity				
Pre	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0
Week 6	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0
Week 12	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0
pH[a]				
Pre	6.2 ± 0.2	6.5 ± 0.2	6.5 ± 0.2	6.5 ± 0.3
Week 6	6.1 ± 0.2	6.1 ± 0.1	6.3 ± 0.1	6.0 ± 0.1
Week 12	6.0 ± 0.2	6.3 ± 0.2	6.3 ± 0.2	6.5 ± 0.2

DMAA: 1,3-dimethylamylamine.
[a]Values are mean ± SEM. No other differences of statistical significance noted ($p > 0.05$). Urine color, appearance, white blood cell esterase, protein, glucose, ketones, occult blood, bilirubin, urobilinogen semi-Qn, and nitrite did not change significantly over time for any condition.
[a]Time effect ($p = 0.05$), week 6 < Pre.

Table 4. Oxidative stress, inflammatory, and cardiac biomarker data of men assigned to placebo, caffeine, DMAA, or caffeine + DMAA for 12 weeks.[a]

Variable	Placebo ($n = 11$)	Caffeine ($n = 14$)	DMAA ($n = 13$)	Caffeine + DMAA ($n = 12$)
Malondialdehyde (μmol L^{-1})				
Pre	0.8 ± 0.1	0.9 ± 0.1	0.8 ± 0.1	0.8 ± 0.1
Week 6	0.7 ± 0.1	0.9 ± 0.1	0.8 ± 0.1	0.8 ± 0.1
Week 12	0.6 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.7 ± 0.1
AOPP (μmol L^{-1})[b]				
Pre	46.3 ± 6.2	56.6 ± 7.7	57.7 ± 5.5	54.9 ± 7.9
Week 6	51.0 ± 6.4	65.1 ± 8.3	82.3 ± 11.6	61.4 ± 9.0
Week 12	43.8 ± 6.5	79.1 ± 10.7	65.7 ± 9.0	53.7 ± 7.3
TEAC (mmol L^{-1})[b]				
Pre	1.3 ± 0.0	1.3 ± 0.0	1.2 ± 0.0	1.2 ± 0.1
Week 6	1.4 ± 0.0	1.3 ± 0.0	1.3 ± 0.0	1.3 ± 0.1
Week 12	1.3 ± 0.0	1.4 ± 0.0	1.3 ± 0.0	1.3 ± 0.0
C-reactive protein (mg L^{-1})				
Pre	0.7 ± 0.2	0.8 ± 0.4	1.0 ± 0.1	1.2 ± 0.3
Week 6	0.7 ± 0.2	1.0 ± 0.5	0.6 ± 0.1	0.9 ± 0.2
Week 12	0.7 ± 0.2	1.1 ± 0.4	0.7 ± 0.2	0.9 ± 0.3
Troponin (ng mL^{-1})				
Pre	<0.31	<0.31	<0.31	<0.31
Week 6	<0.31	<0.31	<0.31	<0.31
Week 12	<0.31	<0.31	<0.31	<0.31

AOPP: advanced oxidation protein products; TEAC: trolox equivalent antioxidant capacity; DMAA: 1,3-dimethylamylamine.
[a]Values are mean ± SEM. No other differences of statistical significance noted ($p > 0.05$).
[b]Condition effect for AOPP ($p = 0.005$), caffeine and DMAA > placebo; TEAC ($p = 0.008$), DMAA and caffeine + DMAA < caffeine.

(in a nonstatistically significant manner) for subjects in both the caffeine and DMAA conditions, but did not do so in subjects in the caffeine + DMAA condition. Second, although not of statistical significance, C-reactive protein increased slightly in subjects in the caffeine condition but decreased in a similar manner in subjects in the DMAA and caffeine + DMAA conditions. Third, troponin I was below the limit of detection in all subjects, in all conditions, at all times of measurement—indicating that none of the conditions impacted cardiac muscle damage as determined by this marker.

The remaining measures related to complete blood count, metabolic panel, and lipid panel were unremarkable, with values remaining very stable across time for subjects in all conditions. These findings

Table 5. Complete blood count data of men assigned to placebo, caffeine, DMAA, or caffeine + DMAA for 12 weeks.[a]

Variable	Placebo ($n = 11$)	Caffeine ($n = 14$)	DMAA ($n = 13$)	Caffeine + DMAA ($n = 12$)
WBC (10^3 μL^{-1})[b]				
Pre	4.9 ± 0.4	5.0 ± 0.3	6.1 ± 0.3	5.7 ± 0.5
Week 6	5.1 ± 0.4	5.0 ± 0.3	5.9 ± 0.5	5.5 ± 0.4
Week 12	4.9 ± 0.4	5.0 ± 0.3	6.2 ± 0.4	5.0 ± 0.5
RBC (10^6 μL^{-1})				
Pre	5.1 ± 0.2	5.2 ± 0.1	5.1 ± 0.1	5.1 ± 0.1
Week 6	5.0 ± 0.1	5.1 ± 0.1	5.1 ± 0.1	5.1 ± 0.1
Week 12	5.0 ± 0.1	5.1 ± 0.1	5.0 ± 0.1	5.1 ± 0.1
Hemoglobin (g dL^{-1})				
Pre	14.5 ± 0.4	14.9 ± 0.2	14.7 ± 0.2	15.0 ± 0.3
Week 6	14.5 ± 0.4	14.7 ± 0.2	14.8 ± 0.2	14.9 ± 0.2
Week 12	14.2 ± 0.3	14.9 ± 0.2	14.5 ± 0.2	17.8 ± 0.3
Hematocrit (%)				
Pre	43.4 ± 1.0	44.8 ± 0.5	44.0 ± 0.5	44.3 ± 0.8
Week 6	43.3 ± 0.9	43.9 ± 0.5	44.4 ± 0.5	44.1 ± 0.7
Week 12	42.7 ± 0.8	44.4 ± 0.6	43.8 ± 0.4	43.9 ± 1.0
MCV (fL)				
Pre	86.1 ± 1.3	86.8 ± 1.1	87.2 ± 1.0	86.3 ± 1.0
Week 6	86.3 ± 1.4	86.4 ± 1.1	86.8 ± 1.0	86.5 ± 0.8
Week 12	86.4 ± 1.2	87.0 ± 1.2	87.2 ± 1.0	86.7 ± 0.8
MCH (pg)				
Pre	28.7 ± 0.6	28.8 ± 0.4	29.2 ± 0.4	29.2 ± 0.4
Week 6	28.8 ± 0.6	28.9 ± 0.4	29.0 ± 0.4	29.2 ± 0.4
Week 12	28.9 ± 0.6	29.1 ± 0.4	29.0 ± 0.4	29.2 ± 0.4
MCHC (g dL^{-1})				
Pre	33.4 ± 0.3	33.2 ± 0.2	33.5 ± 0.2	33.8 ± 0.2
Week 6	33.4 ± 0.3	33.5 ± 0.3	33.4 ± 0.3	33.8 ± 0.3
Week 12	33.4 ± 0.4	33.4 ± 0.3	33.0 ± 0.3	33.7 ± 0.3
RDW (%)				
Pre	13.2 ± 0.2	13.2 ± 0.1	13.4 ± 0.2	13.0 ± 0.1
Week 6	13.2 ± 0.1	13.2 ± 0.1	13.2 ± 0.1	13.3 ± 0.2
Week 12	13.2 ± 0.2	13.3 ± 0.1	13.2 ± 0.1	13.2 ± 0.1
Platelets (10^3 μL^{-1})				
Pre	224.3 ± 15.2	220.2 ± 11.0	245.7 ± 11.5	240.9 ± 7.5
Week 6	231.0 ± 17.2	222.9 ± 10.5	245.2 ± 16.2	244.5 ± 15.5
Week 12	229.2 ± 18.0	223.6 ± 12.2	248.2 ± 17.2	239.7 ± 8.8
Neutrophils (%)				
Pre	49.8 ± 2.7	51.6 ± 2.5	52.8 ± 2.5	51.8 ± 3.3
Week 6	51.0 ± 2.8	51.5 ± 2.3	49.9 ± 2.5	50.5 ± 3.1
Week 12	46.9 ± 3.0	51.7 ± 2.1	53.2 ± 2.2	48.3 ± 2.7
Lymphocytes (%)				
Pre	36.2 ± 2.1	35.9 ± 2.3	34.1 ± 2.3	35.6 ± 3.1
Week 6	35.3 ± 2.0	35.6 ± 2.1	34.6 ± 2.0	37.6 ± 2.8
Week 12	38.8 ± 2.4	34.9 ± 2.0	32.4 ± 2.0	38.6 ± 2.9
Monocytes (%)[b]				
Pre	10.2 ± 0.8	8.9 ± 0.5	9.2 ± 0.3	8.4 ± 0.6
Week 6	9.2 ± 1.0	8.7 ± 0.4	10.0 ± 0.6	8.4 ± 0.5
Week 12	9.9 ± 0.8	9.2 ± 0.4	9.0 ± 0.4	8.3 ± 0.4
Eosinophils (%)				
Pre	3.4 ± 0.7	3.1 ± 0.5	3.3 ± 0.6	3.8 ± 0.6
Week 6	4.0 ± 1.2	3.4 ± 0.5	4.6 ± 0.8	3.1 ± 0.5
Week 12	3.9 ± 0.7	3.5 ± 0.5	4.8 ± 0.9	4.3 ± 0.4
Basophils (%)				
Pre	0.5 ± 0.2	0.5 ± 0.1	0.5 ± 0.1	0.4 ± 0.1
Week 6	0.5 ± 0.2	0.6 ± 0.2	0.8 ± 0.2	0.5 ± 0.2

(continued)

Table 5. (continued)

Variable	Placebo ($n = 11$)	Caffeine ($n = 14$)	DMAA ($n = 13$)	Caffeine + DMAA ($n = 12$)
Week 12	0.5 ± 0.2	0.7 ± 0.2	0.7 ± 0.1	0.6 ± 0.1

DMAA: 1,3-dimethylamylamine; **RBC: red blood cell; WBC: white blood cell;** MCV: mean cell volume, MCH: mean cell hemoglobin, MCHC: mean cell hemoglobin concentration; RDW: red blood cell distribution width.
[a]Values are mean ± SEM. No other differences of statistical significance noted ($p > 0.05$).
[b]Condition effect for WBC ($p = 0.002$), DMAA > placebo and caffeine; monocytes ($p = 0.03$), caffeine + DMAA < placebo.

Table 6. Comprehensive metabolic panel data of men assigned to placebo, caffeine, DMAA, or caffeine + DMAA for 12 weeks.[a]

Variable	Placebo ($n = 11$)	Caffeine ($n = 14$)	DMAA ($n = 13$)	Caffeine + DMAA ($n = 12$)
Glucose (mg dL^{-1})				
Pre	88.5 ± 2.6	88.3 ± 1.7	87.9 ± 1.8	88.8 ± 2.0
Week 6	87.5 ± 2.1	89.2 ± 2.1	88.3 ± 1.8	91.8 ± 2.5
Week 12	90.3 ± 2.2	88.9 ± 2.1	87.2 ± 1.3	91.3 ± 1.5
BUN (mg dL^{-1})				
Pre	13.7 ± 1.0	15.9 ± 1.0	14.8 ± 1.2	15.8 ± 1.2
Week 6	14.0 ± 0.8	14.9 ± 0.8	13.3 ± 0.8	14.6 ± 0.8
Week 12	14.2 ± 0.8	16.3 ± 1.3	14.8 ± 0.7	14.9 ± 0.9
Creatinine (mg dL^{-1})[b]				
Pre	0.9 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0
Week 6	0.9 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0
Week 12	0.9 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0
BUN: creatinine				
Pre	14.8 ± 1.5	15.8 ± 0.8	14.9 ± 1.3	15.5 ± 1.0
Week 6	15.3 ± 0.7	14.7 ± 0.7	13.1 ± 0.7	14.2 ± 1.0
Week 12	15.3 ± 1.1	15.6 ± 0.9	15.0 ± 0.9	14.3 ± 0.8
Sodium (mmol L^{-1})				
Pre	139.8 ± 0.8	140.8 ± 0.5	140.1 ± 0.6	140.1 ± 0.6
Week 6	140.2 ± 0.4	141.4 ± 0.6	140.0 ± 0.6	140.6 ± 0.5
Week 12	140.1 ± 0.4	140.2 ± 0.7	139.3 ± 0.6	139.9 ± 0.7
Potassium (mmol L^{-1})[b]				
Pre	4.3 ± 0.1	4.7 ± 0.1	4.5 ± 0.1	4.5 ± 0.1
Week 6	4.4 ± 0.1	4.7 ± 0.1	4.4 ± 0.1	4.5 ± 0.1
Week 12	4.3 ± 0.1	4.7 ± 0.2	4.5 ± 0.1	4.6 ± 0.1
Chloride (mmol L^{-1})[b]				
Pre	101.1 ± 0.8	102.3 ± 0.6	101.5 ± 0.4	101.8 ± 0.6
Week 6	102.9 ± 0.8	103.0 ± 0.4	101.1 ± 0.5	101.7 ± 0.9
Week 12	102.9 ± 0.5	102.4 ± 0.4	101.2 ± 0.4	102.3 ± 0.7
CO_2 (mmol L^{-1})[c]				
Pre	24.6 ± 0.6	25.6 ± 0.6	25.4 ± 0.5	25.3 ± 0.5
Week 6	24.2 ± 0.5	25.2 ± 0.5	25.3 ± 0.6	24.5 ± 0.6
Week 12	26.4 ± 0.5	25.8 ± 0.4	26.3 ± 0.7	25.3 ± 0.7
Calcium (mg dL^{-1})				
Pre	9.5 ± 0.1	9.7 ± 0.1	9.5 ± 0.1	9.6 ± 0.1
Week 6	9.5 ± 0.1	9.7 ± 0.1	9.6 ± 0.1	9.5 ± 0.1
Week 12	9.4 ± 0.1	9.5 ± 0.1	9.5 ± 0.1	9.6 ± 0.1
Protein (g dL^{-1})				
Pre	6.8 ± 0.1	6.9 ± 0.1	6.8 ± 0.1	6.9 ± 0.1
Week 6	6.7 ± 0.1	6.8 ± 0.1	6.9 ± 0.1	6.8 ± 0.2
Week 12	6.6 ± 0.1	6.9 ± 0.1	6.8 ± 0.1	6.8 ± 0.1

(continued)

Table 6. (continued)

Variable	Placebo ($n = 11$)	Caffeine ($n = 14$)	DMAA ($n = 13$)	Caffeine + DMAA ($n = 12$)
Albumin (g dL^{-1})				
Pre	4.4 ± 0.1	4.5 ± 0.1	4.3 ± 0.0	4.4 ± 0.1
Week 6	4.4 ± 0.1	4.4 ± 0.1	4.4 ± 0.1	4.4 ± 0.0
Week 12	4.3 ± 0.1	4.4 ± 0.0	4.3 ± 0.0	4.4 ± 0.1
Globulin (g dL^{-1})				
Pre	2.4 ± 0.1	2.4 ± 0.1	2.5 ± 0.1	2.5 ± 0.1
Week 6	2.4 ± 0.1	2.4 ± 0.1	2.5 ± 0.1	2.4 ± 0.1
Week 12	2.3 ± 0.1	2.4 ± 0.1	2.4 ± 0.1	2.4 ± 0.1
A:G				
Pre	1.9 ± 0.1	1.9 ± 0.1	1.7 ± 0.1	1.9 ± 0.1
Week 6	1.9 ± 0.1	1.9 ± 0.1	1.8 ± 0.0	1.9 ± 0.1
Week 12	2.0 ± 0.1	1.9 ± 0.1	1.8 ± 0.1	1.9 ± 0.1
Bilirubin (mg dL^{-1})				
Pre	0.6 ± 0.1	0.5 ± 0.1	0.6 ± 0.1	0.6 ± 0.1
Week 6	0.6 ± 0.1	0.7 ± 0.1	0.7 ± 0.1	0.7 ± 0.1
Week 12	0.6 ± 0.1	0.6 ± 0.1	0.7 ± 0.1	0.7 ± 0.1
Alkaline phosphate (IU L^{-1})				
Pre	74.1 ± 9.2	77.1 ± 4.0	74.5 ± 4.8	76.1 ± 7.0
Week 6	76.8 ± 9.2	78.6 ± 4.9	78.3 ± 4.6	78.0 ± 6.4
Week 12	70.6 ± 8.9	77.4 ± 4.3	73.2 ± 3.9	75.5 ± 7.1
AST (SGOT) (IU L^{-1})				
Pre	25.1 ± 2.5	22.9 ± 2.3	22.8 ± 1.7	28.4 ± 2.8
Week 6	23.3 ± 2.7	25.9 ± 3.5	21.7 ± 1.6	25.8 ± 2.0
Week 12	22.7 ± 2.2	27.5 ± 4.5	24.7 ± 3.3	24.9 ± 2.5
ALT (SGPT) (IU L^{-1})				
Pre	23.8 ± 4.0	25.2 ± 4.3	22.2 ± 2.1	29.8 ± 5.0
Week 6	23.8 ± 5.3	24.8 ± 3.5	25.0 ± 4.0	23.5 ± 1.8
Week 12	23.5 ± 4.7	24.6 ± 3.5	26.0 ± 3.3	27.3 ± 4.0
GGT (IU L^{-1})				
Pre	16.0 ± 2.0	19.9 ± 3.0	20.4 ± 2.2	20.2 ± 2.7
Week 6	16.8 ± 3.2	19.2 ± 2.7	20.8 ± 2.1	17.5 ± 1.6
Week 12	15.8 ± 2.1	19.3 ± 2.7	20.9 ± 2.2	19.5 ± 3.0

DMAA: 1,3-dimethylamylamine; BUN: blood urea nitrogen; AST: aspartate transaminase; SGOT: serum glutamic oxaloacetic transaminase; ALT: alanine transaminase; SGPT: serum glutamic pyruvate transaminase; GGT: γ-glutamyl transpeptidase; A: adenine; G: guanine.

[a]Values are mean ± SEM. No other differences of statistical significance noted ($p > 0.05$).

[b]Condition effect for creatinine ($p = 0.02$), caffeine + DMAA > placebo; potassium ($p = 0.003$), caffeine > placebo; chloride ($p = 0.02$), DMAA < placebo and caffeine.

[c]Time effect ($p = 0.02$), week 12 > week 6.

agree with our prior work involving subjects' ingestion of finished dietary supplements containing caffeine and DMAA.[7,8]

When considering the typical user of dietary supplements containing caffeine and DMAA, it is important to note that most individuals will not use these products daily. Specifically, many individuals use the ingredients/supplement exclusively on exercise training days, which might consist of 3–5 days per week. Moreover, the dosage of caffeine and DMAA contained within one serving of many dietary supplements sold on the market is less than the amount ingested by subjects in the present study. Therefore, unless individuals are abusing the dietary supplements (which is certainly possible), the cumulative 12-week dosage provided in the present study should have allowed for a robust assessment of the health effects of caffeine and DMAA.

We conclude that 12 weeks of supplementation with caffeine and DMAA, whether alone or in combination, does not result in a statistically significant change in any of the measured outcome variables. Data are specific to a sample of healthy, young men consuming daily dosage of caffeine (250 mg) and

Table 7. Lipid panel data of men assigned to placebo, caffeine, DMAA, or caffeine + DMAA for 12 weeks.[a]

Variable	Placebo ($n = 11$)	Caffeine ($n = 14$)	DMAA ($n = 13$)	Caffeine + DMAA ($n = 12$)
Cholesterol (mg dL^{-1})[b]				
Pre	140.4 ± 9.3	148.5 ± 9.1	148.3 ± 7.6	170.8 ± 10.8
Week 6	133.4 ± 8.9	147.0 ± 9.1	150.1 ± 6.3	166.5 ± 10.7
Week 12	134.4 ± 7.1	148.9 ± 6.7	154.0 ± 7.6	167.7 ± 10.2
Triglycerides (mg dL^{-1})				
Pre	85.1 ± 13.1	92.9 ± 12.2	82.5 ± 13.8	89.3 ± 11.4
Week 6	74.0 ± 12.8	83.1 ± 11.9	84.6 ± 14.4	90.5 ± 9.6
Week 12	83.6 ± 29.0	88.7 ± 14.0	80.1 ± 14.7	86.3 ± 8.3
HDL-C (mg dL^{-1})[b]				
Pre	43.7 ± 2.8	47.3 ± 2.5	51.2 ± 2.7	44.3 ± 2.5
Week 6	43.2 ± 2.8	47.9 ± 3.3	50.6 ± 3.6	41.8 ± 3.8
Week 12	43.2 ± 3.0	46.9 ± 2.9	50.8 ± 3.0	48.2 ± 2.3
VLDL-C (mg dL^{-1})				
Pre	17.0 ± 2.6	18.5 ± 2.4	16.4 ± 2.8	17.8 ± 2.3
Week 6	14.6 ± 2.6	16.6 ± 2.4	16.8 ± 2.9	18.2 ± 1.9
Week 12	16.8 ± 5.8	17.6 ± 2.8	16.0 ± 3.0	17.2 ± 1.6
LDL-C (mg dL^{-1})[b]				
Pre	79.6 ± 7.3	82.7 ± 8.1	80.8 ± 7.9	108.8 ± 10.8
Week 6	75.5 ± 6.8	82.5 ± 7.7	82.6 ± 6.0	106.5 ± 11.9
Week 12	74.4 ± 4.8	84.5 ± 5.8	87.2 ± 7.5	102.3 ± 10.1
Total/HDL-C[b]				
Pre	3.3 ± 0.3	3.3 ± 0.3	3.0 ± 0.2	4.0 ± 0.4
Week 6	3.2 ± 0.3	3.2 ± 0.3	3.2 ± 0.3	4.7 ± 1.0
Week 12	3.4 ± 0.4	3.3 ± 0.3	3.2 ± 0.3	3.5 ± 0.2

DMAA: 1,3-dimethylamylamine; HDL-C: high-density cholesterol; LDL-C: low-density cholesterol.
[a]Values are mean ± SEM. No other differences of statistical significance noted ($p > 0.05$).
[b]Condition effect cholesterol ($p = 0.0004$), caffeine + DMAA > placebo and caffeine; HDL-C ($p = 0.02$), DMAA > placebo; LDL-C ($p = 0.0002$), caffeine + DMAA > placebo, caffeine, and DMAA; total/HDL-C ($p = 0.01$), caffeine + DMAA > caffeine and DMAA.

Table 8. Dietary intake of men assigned to placebo, caffeine, DMAA, or caffeine + DMAA for 12 weeks.[a]

Variable	Placebo ($n = 11$)	Caffeine ($n = 14$)	DMAA ($n = 13$)	Caffeine + DMAA ($n = 12$)
Kilocalories				
Pre	2416.4 ± 183.8	2358.9 ± 140.4	2413.5 ± 165.7	2254.5 ± 140.0
Week 6	2205.2 ± 179.2	2402.0 ± 181.1	2438.3 ± 147.3	2011.4 ± 183.3
Week 12	2188.4 ± 160.3	2371.6 ± 188.4	2470.2 ± 150.8	2015.5 ± 142.9
Protein (g)[b]				
Pre	117.0 ± 14.4	109.9 ± 7.9	145.1 ± 20.4	114.2 ± 9.4
Week 6	105.4 ± 12.9	109.8 ± 8.7	110.2 ± 10.7	93.4 ± 8.6
Week 12	108.9 ± 12.8	116.1 ± 9.8	135.5 ± 15.8	95.0 ± 8.5
Carbohydrate (g)				
Pre	304.7 ± 25.7	274.3 ± 19.5	255.8 ± 19.5	264.5 ± 19.3
Week 6	259.3 ± 24.8	280.6 ± 33.3	295.2 ± 21.8	248.6 ± 28.6
Week 12	256.3 ± 23.4	301.6 ± 41.6	266.5 ± 21.4	255.0 ± 25.6
Fat (g)[b]				
Pre	82.4 ± 7.4	87.2 ± 8.3	91.2 ± 8.0	79.6 ± 9.8
Week 6	85.5 ± 8.8	91.9 ± 10.9	89.9 ± 7.1	71.5 ± 9.2
Week 12	82.4 ± 9.0	76.5 ± 5.2	96.4 ± 7.6	69.3 ± 6.6
Saturated fat (g)				
Pre	26.7 ± 2.7	30.1 ± 3.6	28.3 ± 2.2	25.4 ± 3.4
Week 6	25.1 ± 2.7	30.3 ± 4.6	28.6 ± 2.9	23.2 ± 3.6
Week 12	27.5 ± 3.7	24.1 ± 1.8	33.3 ± 2.6	26.0 ± 5.5

(continued)

Table 8. (continued)

Variable	Placebo ($n = 11$)	Caffeine ($n = 14$)	DMAA ($n = 13$)	Caffeine + DMAA ($n = 12$)
Vitamin C (mg)[c]				
Pre	120.8 ± 22.6	75.4 ± 17.2	65.4 ± 9.7	96.0 ± 21.5
Week 6	73.6 ± 15.6	81.9 ± 18.4	62.1 ± 10.7	97.6 ± 34.1
Week 12	63.0 ± 15.4	137.5 ± 32.9	89.6 ± 19.0	49.9 ± 14.5
Vitamin E (mg)				
Pre	9.8 ± 3.1	4.3 ± 1.2	9.3 ± 2.7	6.1 ± 1.6
Week 6	4.6 ± 1.0	5.2 ± 1.1	4.6 ± 0.7	3.1 ± 1.1
Week 12	3.5 ± 1.3	10.1 ± 5.6	3.9 ± 0.5	7.8 ± 3.2
Vitamin A (RE)				
Pre	287.4 ± 66.7	383.6 ± 95.0	342.5 ± 89.5	326.7 ± 52.4
Week 6	313.1 ± 81.1	421.6 ± 97.3	380.3 ± 92.5	314.4 ± 109.2
Week 12	357.6 ± 99.4	433.4 ± 96.7	351.8 ± 71.0	275.5 ± 71.5
Selenium (μg)				
Pre	76.2 ± 25.1	52.0 ± 9.0	79.1 ± 17.6	64.6 ± 10.1
Week 6	73.4 ± 14.9	67.8 ± 10.3	94.9 ± 19.6	45.7 ± 10.8
Week 12	66.6 ± 10.7	89.6 ± 10.2	99.2 ± 23.3	104.7 ± 36.7

DMAA: 1,3-dimethylamylamine; RE: Retinol equivants.
[a]Values are mean ± SEM. No other differences of statistical significance noted ($p > 0.05$).
[b]Condition effect for protein ($p = 0.03$) and fat ($p = 0.05$); DMAA > caffeine + DMAA.
[c]Interaction effect for vitamin C ($p = 0.05$).

DMAA (50 mg) that are considered moderate and recommended. With the above understanding, it is possible that DMAA alone and in combination with caffeine may impact certain cardiorespiratory variables. Additional study may consider the use of a larger sample of subjects, perhaps of both genders and of various age groups, to more fully elucidate the safety profile of these ingredients when used alone and in combination for extended periods of time.

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Authors' contributions

RJB was responsible for the study design, biochemical work, statistical analyses, and manuscript preparation. TMF, ICH, and RJA were responsible for subject recruitment, data collection, data entry, and assistance with manuscript preparation. All authors read and approved the final manuscript.

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Appendix B

Pharmacokinetic Data Distinguish Abusive vs. Dietary Supplement Uses of 1,3-Dimethylamylamine

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1,3-Dimethylamylamine (DMAA) is a central nervous system stimulant that can be synthesized and has been detected in small quantities in *Pelargonium graveolens*[1,2]. Case studies of recreational DMAA use reported previously in the *Annals* indicate acute vascular toxicity[3]. DMAA-containing dietary supplement products, by virtue of their formulations and label instructions, may result in an order of magnitude lower DMAA consumption than from use of DMAA "party pills", which may contain 300 mg DMAA/pill. Authors of numerous clinical studies of DMAA in healthy adults[4] (ingesting 30-60 mg DMAA/day) report transient increases in blood pressure, but no toxic effects. Case studies may suggest that the implicit risk of adverse effects from DMAA consumption be defined by high-exposure hazards associated with recreational-abusive usage, rather than the dose-response over the continuum of uses. For many dietary supplements, the available dose-response information is data poor. However, for DMAA, preliminary results of human pharmacokinetic trials, which we discuss presently, make possible quantitative comparisons between internal body burden and clinical effects of low-dose dietary supplement use and high-dose recreational abuse.

One of the present authors (BKS) measured plasma DMAA time-course concentrations, heart rate, blood pressure, and body temperature in eight adult males following ingestion of 25mg DMAA[5], an amount approximating labeled serving size for some dietary supplements. All volunteers provided written informed consent; the trial was approved by the University of Memphis Institutional Review Board (Protocol #2102). Figure 1 shows the plasma profile for the group (data for 1 subject was excluded due to sample analysis problems). A mean maximum plasma DMAA concentration, 67 µg/L, was observed five hours after administration. There was no meaningful effect on body temperature, heart rate, or blood pressure.

These data are informative for comparison to plasma DMAA levels and cardiovascular effects in emergency room patient cases reported by Gee et al.[3]: three cases presenting with vomiting, neurological deficits, and cranial hemorrhage after consuming DMAA with alcoholic beverages. An adult female and two males presented with a blood DMAA levels of 1,090, 760, and 2,310 ug/L (100 minutes and 17 and 2 hours post-ingestion, respectively) , compared to approximately 56, 35, 62 ug/L for the [redacted] trial at the same time points. Thus, blood DMAA levels from three cases of recreational ingestion (obviously under-reported by case subjects to be between 13-150 mg DMAA[3]) were between 19- and 37-times higher than levels resulting from single-serving levels of DMAA in a dietary supplement product.

Our comparisons of DMAA blood levels from recreational and clinical administration emphasize the importance of assessing DMAA safety in the context of dose-response relationships, not hazard identification drawn from extreme exposures. Recreational substance exposures may be under-reported for reasons, including mental impairment at time of use. Clinical studies, such as that of [redacted], are significant for interpreting the data quality (e.g., estimated

exposures) and appropriate use of adverse event reports of substances found in dietary supplements.

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[redacted]

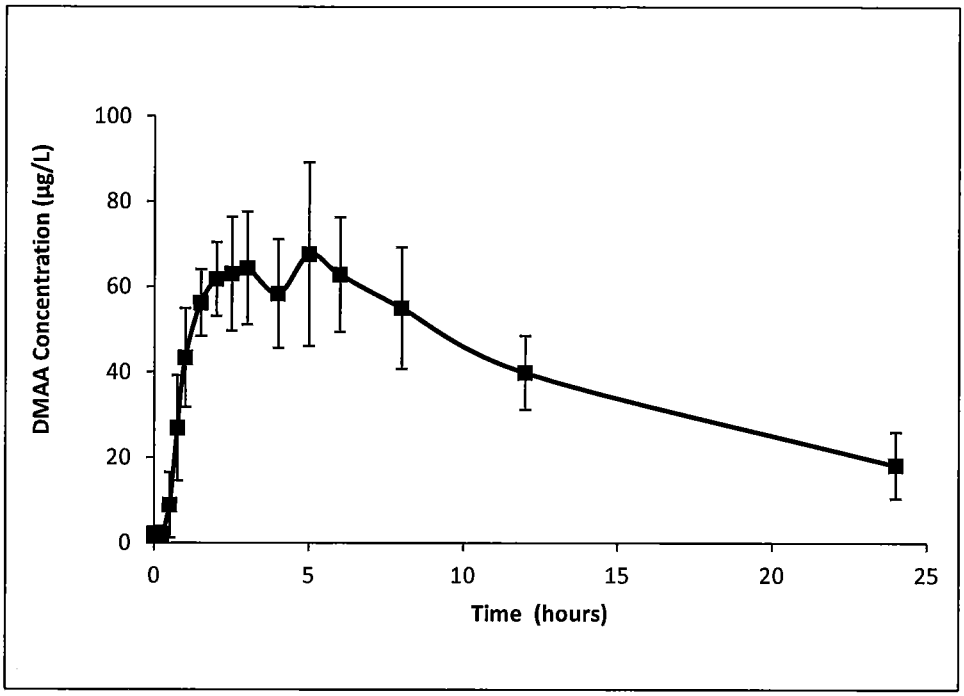

Figure 1. Mean (±SD) Plasma DMAA profile for seven volunteers ingesting 25 mg DMAA (Schilling 2012)

Appendix C

DMAA as a Dietary Ingredient: Response to Cohen Research Letter

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1,3-dimethylamylamine (DMAA) is an aliphatic amine added to some dietary supplement (DS) products. We are responding to Cohen's research letter[1], in which he discussed natural occurrence of DMAA, as well as labeling it a potent "amphetamine derivative" linked in case reports and the news media to adverse cardiovascular toxicity. We would like to offer the following points in the interest of moving forward the discussion of DMAA health effects within the context of sound toxicological and risk assessment principles.

We begin by correcting Cohen's assertion that DMAA is an amphetamine derivative. DMAA is not synthesized from amphetamine or amphetamine-like compounds, nor does it possess a terminal benzyl constituent found in amphetamine and catechols that is needed to induce specific neurotransmitter release cascades, in addition to providing adrenergic neuronal stimulation.

Cohen cited a Health Canada review which concluded that there is no credible evidence of DMAA as a plant constituent. However, other studies not considered by Health Canada have reported confirmation of the presence of DMAA in the geranium plant (68-496 ng/g, Fleming et al.[2]) and oil (14 ppb-13 ppm Li et al.[3]).

Cohen discussed DMAA hazards by referencing case studies, but did not consider the dose-response for DMAA or multiple published clinical studies of effects from DMAA intake levels recommended by a DS manufacturer. He cited cases of DMAA abuse presenting with cardiovascular pathology involving unknown or higher than DS label-recommended levels of DMAA consumption. Cohen mentioned one of six published clinical trials of volunteers consuming DMAA-containing products for up to 10 weeks [4], but did not note that increases in observed blood pressure were about 15% above resting baseline and transient. None of the adverse effects reported in the case studies occurred during this or any of the other five clinical

studies involving a subjects consuming DMAA. The clinical studies also reported clinical chemistry, hematology, urinalysis, and metabolic panels indicating no effect on liver and renal function after extended use at recommended intake levels. Any discussion on the safety of DMAA in particular and DS in general is informative only if appropriate data weighting is used when comparing controlled experimental exposure studies to case reports of questionable estimates of DS intake. Cohen's call for immediate recall of all DMAA-containing products is not based on data analysis using sound principles of risk assessment.

References

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