Bloomer RJ, et al., J Altern Complement Integr Med 2018, 4: 057
DOI: 10.24966/ACIM-7562/100057

HSOA Journal of Alternative, Complementary & Integrative Medicine

Review

1,3-Dimethylamylamine (DMAA): A Brief History and Review of Anecdotal and Laboratory Findings

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Abstract

DMAA (1,3-dimethylamylamine) was once a popular ingredient for inclusion within dietary supplements, in particular those marketed to the bodybuilding community as "pre-workouts." Also known as methylhexanamine, and geranium extract, DMAA was not in supplements prior to the Dietary Supplement and Health Education Act of 1994 (DSHEA); hence, DMAA would be classified as a New Dietary Ingredient (NDI) by the Food and Drug Administration (FDA). In 2012, the FDA issued warning letters to manufacturers and distributors calling for cessation of DMAA sales and use within dietary supplement formulations, partly because required safety data supporting DMAA's use was lacking. Thus, supplements containing DMAA were considered "adulterated". Adverse event reports following DMAA ingestion prompted the FDA's actions. Though the use of DMAA has since decreased considerably, sales of dietary supplements containing DMAA or close derivatives continue. Currently, no scientific evidence exists to support DMAA's use as an ergogenic aid, notwithstanding widespread anecdotal reports of improved exercise performance and focus following DMAA ingestion. While reports have documented an association between DMAA ingestion and adverse events, it remains unclear as to the causal role of DMAA, in particular considering the fact that specific to the reported events, DMAA was often used in combination with other dietary ingredients, prescription medications or recreational drugs. This review discusses the history of DMAA, anecdotal and laboratory findings pertaining to its use, and its use today within the dietary supplement market.

Keywords: Dietary supplement; Ergogenic aid; Stimulant; Weight loss

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Citation: Bloomer RJ, Smith NJC, Moore DC, Yates CR (2018) 1,3-Dimethylamylamine (DMAA): A Brief History and Review of Anecdotal and Laboratory Findings. J Altern Complement Integr Med 4: 057.

Received: December 07, 2018; **Accepted:** December 20, 2018; **Published:** December 28, 2018

Introduction

While the ingredient referred to as DMAA was once a highly utilized ingredient in sport nutrition and weight loss dietary supplements, it has been the target of much controversy. Also known by the names 2-amino-4-methylhexane, 1,3-dimethylamylamine, 1,3-dimethylpentylamine, methylhexanamine, 4-methyl-2-hexylamine and "Geranamine™" (as well as others), this agent has been largely removed from the marketplace due primarily to concerns regarding its overall safety profile. In particular, a variety of case reports describing individuals experiencing adverse events following the use of DMAA alone or within dietary supplements have fueled these concerns.

In 2012, the United States Food and Drug Administration (FDA) issued warning letters to companies informing them that products containing DMAA should be removed from the market or reformulated without the inclusion of DMAA. Also in 2012, the United States Department of Defense removed all DMAA containing products from stores on military bases [1]. Although most companies complied with the recommendation for removal and cessation of use, some companies continued to sell DMAA containing products. Most appeared to be newly formulated products within the sport nutrition market, as highlighted in the report of the Human Performance Resource Center Operation Supplement Safety and noted here (https://www.opss.org/docs/dietary-supplements-containing-dmaa) [2].

While the overall question regarding the safety of DMAA appears to be of greatest importance to most individuals, the issue of whether or not the ingredient can be legally included within dietary supplements has also been a topic of discussion. Based on guidelines regulating what is considered a New Dietary Ingredient (NDI), the FDA claims that DMAA lacks safety data to support its inclusion in dietary supplements. This point alone, the lack of adequate safety data and not the assertion that DMAA is unsafe, may have been the rationale used by the FDA to call for the removal of DMAA from dietary supplements.

Regardless of the reason for the FDA's action, DMAA containing products still exist and it is logical to assume that such products are being regularly used. If this is the case, users should understand that this ingredient might promote an acute dose-dependent elevation in blood pressure. In addition, since some individuals may use DMAA to enhance sports performance, they should know that DMAA is a banned substance by most sporting agencies, including the World

Anti-Doping Agency. As such, users may test "positive" for a banned substance and face the consequences of doing so.

This paper provides a historical overview of DMAA, a summary of the anecdotal and laboratory findings pertaining to its use, as well as the authors' perspective concerning this ingredient.

Brief History of DMAA

The original trademark for DMAA, since expired, was granted to Eli Lilly and Company in 1971 (US trademark number: 72382454) for Forthane™. The first recorded use of this original trademark document was October 4, 1948, and Forthane™ was indicated as a "vasoconstrictor preparation used in the treatment of nasal decongestion and consisting of methylhexanamine." The use of DMAA within the sport supplement world began in approximately 2006, possibly in relation to the banning of ephedrine in April 2004. The name Geranamine™ was trademarked by Proviant Technologies, Inc., in 2005 (US trademark number: 78542697) and indicated as a "constituent of flower oil sold as an integral component of nutritional supplements." The ingredient was then promoted as an ergogenic aid and very quickly gained popularity within the dietary supplement market as both a "weight loss" and "pre-workout" product in particular within the bodybuilding market. In fact, between 2010 and 2012, it was estimated that approximately 200 different DMAA containing products were being manufactured.

In 2012 following the reporting of multiple adverse events, the FDA issued warning letters to companies thought to be responsible for a high percentage of the DMAA products sold in the United States [3]. Marketing and sales of DMAA containing products subsequently declined. However, to our knowledge and as noted here (https://www.opss.org/docs/dietary-supplements-containing-dmaa), several DMAA containing products continued to be sold. The companies responsible for the continued sales of DMAA appear to be relatively small in comparison to the market leaders. Regardless, due to the apparent demand for this ingredient, it is possible that sales volumes will be relatively significant.

Proposed Mechanism of Action and Related Concerns

DMAA appears to provide a sympathomimetic effect in human subjects. It mimics the effects on the sympathetic nervous system of neurotransmitters such as epinephrine, norepinephrine and dopamine. By doing so, it delivers a stimulatory effect, as well as a claimed feeling of euphoria - a response cited in several anecdotal reports. That said, few human studies have been conducted using DMAA or DMAA containing supplements. Therefore, scant data exist regarding its precise mechanism (s) of action. Like other sympathomimetics, acute use of DMAA appears to promote vasoconstriction, which can lead to a dose-dependent elevation in blood pressure - a finding that has been documented in controlled laboratory studies [4,5]. Individuals using DMAA or DMAA containing dietary supplements should be fully aware of the potential blood pressure elevating effects of this agent. This is particularly important for those who may be hypertensive, those who use other supplements or drugs known to elevate blood pressure, and/or those using DMAA in the context of strenuous resistance exercise, an activity known to have the potential to induce an acute hypertensive response [6].

DMAA Pharmacokinetics

A thorough understanding of a molecule's Pharmacokinetics (PK) is required for a full assessment of the relationship between drug exposure and response. To date, only a handful of studies have examined DMAA PK in humans. For example, Perrenoud and co-workers assessed DMAA urinary excretion in two human subjects following oral administration of a single 40 mg dose of DMAA [7]. DMAA was reported to be detectable in the two subjects' urine for 80 and 105 hours, respectively, after administration. In another study, DMAA (dose not reported) was administered orally to a single subject and urinary excretion was determined [8]. DMAA was detectable in the urine over the entire 24-hour collection period. The urine concentration time profile was similar to that obtained over the first 24-hours in the study conducted by Perrenoud et al., suggesting the oral DMAA dose, although not reported, was similar to that in the Perrenoud et al., study (i.e., approximately 40 mg). Based on these data, it appears that very little of the parent DMAA is recovered in the urine, suggesting that a significant fraction of DMAA is metabolized and/or excreted in the bile.

Our group conducted an oral PK study in order to determine the plasma concentration time profile in humans (n=7) following ingestion of a single 25 mg DMAA dose [5]. Oral Clearance (CL) values (CL/F; F represents oral bioavailability) were found to be relatively low (20±5.0 L/hr), whereas oral Volume of distribution (V/F) was relatively high (236±38.0 L). A 25 mg single oral dose resulted in a maximum plasma concentration (C_{max}) of 76.5 ng/mL, which occurred approximately 4 hours post-ingestion. C_{max} values were approximately 15-30 times lower than those reported in case studies linking DMAA intake with severe adverse events, suggesting that the reported adverse events were associated with a DMAA intake much higher than the 25 mg dose in our study [9,10]. Additionally, the potential impact of drug-drug interactions should be considered when interpreting DMAA adverse event reports. Because DMAA PK data suggest that a significant fraction of an orally administered DMAA dose is metabolized, concomitant administration of common ingredients that are also metabolized (e.g., caffeine), may lead to exaggerated DMAA concentrations by inhibiting DMAA clearance.

DMAA Physiological/Performance Effects

To determine the physiologic response to DMAA (25 mg), we measured resting heart rate, blood pressure and body temperature at multiple intervals over a 24-hours period [5]. Heart rate, blood pressure, and body temperature were minimally impacted by DMAA ingestion. For example, during the initial 8-hours post ingestion period, the mean heart rate remained between 61 and 65 beats per minute, the mean systolic blood pressure remained between 115 and 120 mmHg, the mean diastolic blood pressure remained between 78 and 82 mmHg, and the mean body temperature remained between 96.5 and 97.5ºF. In many cases, the respective values were lower during the post ingestion period as compared to pre-ingestion.

As stated above, most dietary supplements containing DMAA were manufactured or are presently being manufactured and marketed for purposes of weight/fat loss and/or improved physical performance. DMAA purportedly aids in weight/fat loss when combined with caffeine and other agents [11]. However, since this study involved the use of a multi-ingredient formulation, there is no way to know the contribution of DMAA to these outcomes. To our knowledge, DMAA alone has not been rigorously evaluated for its potential impact on weight/fat loss using an intervention design.

Arguably the most common use of DMAA is as an ergogenic aid; specifically, as an aid that will help to improve physical performance. This may be appealing to competitive athletes and non-athletes alike, such as individuals who perform resistance or cardiovascular exercise to improve physical strength, muscle mass, cardio respiratory endurance, or enhance aesthetics. In fact, this latter category of non-competitive athletes (e.g., resistance-trained men) likely makes up the largest consumers of "pre-workout" dietary supplements that might contain DMAA.

In the lone human study conducted to determine a physical performance benefit from using DMAA, no ergogenic effect was noted [12]. Subjects performed a 10 km outdoor run after receiving oral DMAA alone or in combination with caffeine. Performance, based on time to complete the run, was not different for subjects when receiving DMAA or caffeine alone, together, or when using a placebo. Heart rate, perceived exertion, and vigor was not different between conditions during the run. Specifically, heart rate was 181 bpm for placebo, 179 bpm for caffeine, 182 bpm for DMAA and 179 bpm for caffeine +DMAA. Blood pressure (systolic in particular) was similar between caffeine and DMAA during the post-exercise period, both of which demonstrated a greater blood pressure response as compared to caffeine +DMAA.

To our knowledge, all claims of an ergogenic effect of DMAA have been anecdotal and reported on various blogs and message boards, with individuals noting increased energy, enhanced mood, "laser-like" focus, and improved exercise performance. Scientific evidence to support such claims is lacking. To our knowledge, there have been no published studies to evaluate the ergogenic effects of DMAA other than that performed by Bloomer and colleagues [12]. Perhaps future studies may be conducted which provide evidence to support the anecdotal reports. However, it is unlikely that such studies will be performed unless a more rigorous assessment of its safety is first completed.

Aside from an impact on exercise performance, Powers and colleagues examined neurocognitive performance following acute consumption of a DMAA-containing dietary supplement [13]. The ImPACT test, a computerized neurocognitive assessment, was used to measure neurocognitive performance such as attention, verbal recognition memory and visual working memory. Results indicated that participants had significantly improved reaction time and increased scores on the cognitive-efficiency index following ingestion of the DMAA containing supplement. Although this may be promising, it should be noted that these findings cannot be directly attributed to DMAA alone, as the supplement also contained caffeine and other ingredients. It is possible that caffeine alone will have been responsible for the noted findings in this investigation. Moreover, this is only one study and included a sample size of only five men and seven women. Additional studies would be needed to fully characterize the effect of DMAA alone on cognitive performance in men and women.

Safety Concerns of DMAA

As stated, the FDA issued warning letters in 2012 requesting voluntary recall of all products containing DMAA. This appeared because the appropriate safety data had not been provided to support the marketing of DMAA as a NDI. Prior to the warning letters, safety concerns were raised from multiple sources, including those within and outside of the United States.

Notable case reports have associated DMAA consumption with cerebral hemorrhaging, Myocardial Infarction (MI), liver injury and death. In two publications, Gee et al., reviewed four separate cases in which individuals reported ingesting pure DMAA in conjunction with alcohol in recreational settings [9,10]. Individuals experienced adverse outcomes, including severe headaches, vomiting and involuntary twitching. Hospitalization revealed cerebral hemorrhaging in all cases. Following post-hospitalization analysis, Gee and colleagues attributed the cerebral hemorrhages to DMAA ingestion, noting that DMAA is structurally similar to amphetamines, which can cause cerebral hemorrhaging [14-16]. The amount of DMAA ingested by individuals described in these reports was estimated to be approximately 15 to 30 times the amount provided in a usual serving of most dietary supplements containing DMAA. This hypothesis was based on the cited dosages indicated within the papers by Gee and colleagues, in conjunction with individuals' plasma DMAA concentrations as reported by the authors, as compared to plasma DMAA concentrations obtained from subjects following a 25 mg oral dosage of DMAA within a controlled laboratory investigation [5,9,10]. In addition, as noted in the papers of Gee and colleagues [9,10], other chemicals may have been taken along with the DMAA (e.g., caffeine, phenethylamine, alcohol and cannabis). Hence, the likelihood exists that the adverse events noted by Gee et al., are linked to 1) ingestion of very high doses of DMAA and 2) confounding variables, which may have exacerbated the pressor effects of DMAA and/or promoted other untoward effects leading to the noted outcomes.

Cerebral Hemorrhage

In one of the cases presented by Gee and colleagues in which the authors report cerebral hemorrhage, a 23-year old woman reported ingestion of two tablets of "Pure X-S" party pills [10]. The pills contained DMAA at an estimated dose of approximately 150 mg based on labeled dose information (lab analysis confirmed dosage of 132 mg), a dose approximately 3-5 times that normally suggested by most pre-workout dietary supplements. In our prior work using a dosage of 50 mg and 75 mg of DMAA, we noted a dose-dependent increase in blood pressure. Specifically, we observed a mean increase in systolic blood pressure of 16 mmHg with the 75 mg DMAA dosage and approximately 24 mmHg when 250 mg of caffeine was added to the 75 mg DMAA dose [4]. Ingestion of double this amount of DMAA by a young woman is extremely unwise, in particular with the co-ingestion of caffeine and alcohol.

Another individual, a 36-year-old man, also suffered a cerebral hemorrhage [10]. He was drinking alcoholic beverages at a public bar and decided to purchase a legal party drug called "Cocaine Party Powder". The authors cite a listed composition of 50 mg of DMAA and state that the individual "took one quarter of the packet with a drink" [10]. An online review (https://www.pills4party.com/dex-party-powder.html) noted that such powder packets often contain multiple dosages, with one advertisement claiming, "…each bag contains a mind blowing 40 doses." If consuming one quarter of the packet and assuming that said packet contained multiple dosages, it is possible that this individual consumed a very high quantity of DMAA. When coupled with alcohol and nicotine, this indeed presents a potentially harmful combination.

A 41-year-old man was also highlighted in the Gee et al. report [10]. The man was supposedly, "offered a white powder dissolved in water as a pick-me-up in a bar" [10]. He collapsed 30 minutes later

with a severe headache and upon analysis, it was noted that he also suffered a cerebral hemorrhage. His blood DMAA levels were extremely high (2.31 µg/mL), which is a DMAA level associated with ingestion of at least 30 times the dose reported in our DMAA PK study, viz., 25 mg [5]. At such a high dosage of DMAA, it is not surprising that the individual experienced an adverse outcome.

Finally, Gee and coworkers reported on a patient who was claimed to ingest two "tablets" containing DMAA (later confirmed by analysis to contain 278 mg of DMAA per "capsule": total dosage=556 mg), along with 150 mg of caffeine and one can of beer [9]. The following day the patient reported to the ER and was found to suffer from a large hemorrhage in the region of the left basal ganglia.

Considering the above information presented by Gee and colleagues, one issue is clear and needs to be understood: individuals ingesting DMAA at extremely high dosages are subject to adverse outcomes likely involving elevated blood pressure and associated problems. Gee and colleagues [10] comment within their paper that, "The stated doses of DMAA in party pills sold in New Zealand range between 50 and 300mg per pill." The products are often combined with caffeine. Considering that our work demonstrated a clear dose-dependent increase in blood pressure following DMAA use [4], with a mean increase in systolic blood pressure of 16 mmHg with a 75 mg dosage of DMAA, it is not surprising that adverse events are noted when individuals consume doses that are several fold higher. Couple this with caffeine ingestion and the intake of alcohol and other drugs, and adverse events are likely. Individuals considering DMAA use, as well as healthcare providers, who may be providing care to such individuals, should understand the potential risks of using DMAA. Like all stimulants, caution needs to be used as related to the total dosage ingested.

Myocardial Infarction and Cardiac Arrest

Acute MI has also been associated with DMAA consumption. A case report by Smith et al., in 2012 highlighted a 22-year-old male who suffered an acute MI [17]. The authors reported that the man was otherwise healthy and presented none of the traditional risk factors for MI. Three weeks prior to hospitalization, the man reported daily ingestion of a DMAA containing supplement, as well as another product containing *Citrus aurantium*, caffeine and other ingredients. With a lack of traditional risk factors, the authors speculated that the joint stimulatory effects of DMAA and *Citrus aurantium* caused the MI. No information was presented regarding the dosage of supplements taken by the individual. As with many users of sports supplements, it is possible that this individual consumed more than the recommended serving size of each product. If so, the caffeine intake alone could have been a few hundred milligrams. In such a case, it is important to raise awareness as to the potential for adverse events when individuals consume multiple stimulants, possibly at high dosages and in the context of strenuous exercise. As noted by Forrester in a summary of DMAA related exposure cases, "…adverse clinical effects may be due to other ingredients in the DMAA containing products, such as caffeine" [18].

In a similar situation, Karnatovskaia et al., reported the case of a 21-year-old male who suffered cardiac arrest while exercising [19]. Again, the individual examined presented none of the typical risk factors for heart disease. However, the individual had consumed for the first time an unnamed pre-workout supplement that reportedly contained DMAA. With a lack of other risk factors present, Karnatovskaia and coworkers attributed the arrest to the consumption of DMAA. No data were presented as to how much of the dietary supplement was consumed by the individual, including the quantity of DMAA. Moreover, no information was presented as to which other ingredients were contained within the supplement. In almost all cases, pre-workout dietary supplements containing DMAA are formulated with multiple ingredients, including caffeine and additional stimulants. The caffeine content of these products is typically 8-10 times that of DMAA (e.g.,25 mg DMAA and 250 mg caffeine). This should be considered in the case analyses.

Liver Injury

A series of case reports composed by Foley et al., focused on the DMAA containing supplement OxyELITE Pro and the association between its ingestion and acute liver injury in United States military personnel [20]. All individuals were relatively young (aged 19-45 years), and none reported prior history of liver injury. All individuals reported ingesting the supplement at some point, either alone or in conjunction with other dietary supplements. The range of intake of the supplement spanned from one week to three years. All individuals experienced liver injury, with the most common symptoms reported being jaundice, fatigue, exercise intolerance, abdominal pain and vomiting.

A report composed by Roytman et al., described eight previously healthy overweight and obese individuals who developed hepatitis after prolonged consumption of OxyELITE Pro [21]. The cases were severe, with one individual dying and two requiring liver transplants. While six of the eight individuals highlighted in this paper had used the original OxyELITE Pro product containing DMAA, the authors focused more heavily on the potential cause of liver injury being an ingredient known as aegeline, contained within a reformulated version of the OxyELITE Pro, rather than DMAA. Clearly, it is unknown what ingredient (s) may have been associated with the cases noted above. As with all multi-component products, it is difficult to determine the direct contribution of DMAA to the outcomes, as multiple other ingredients are contained within the OxyELITE Pro.

Fatal Outcomes

In two cases of alleged DMAA ingestion, one male and one female soldier collapsed during physical testing from suspected cardiac arrest and ultimately died [22]. These soldiers were reportedly ingesting dietary supplements containing DMAA. The authors indicate that the male soldier was taking only one dietary supplement, according to persons in his immediate community. The authors assumed that the female soldier was taking two dietary supplements containing DMAA, because the supplements were found in her car. In the case of the female soldier, a blood creatine kinase level of 161,000 U/L with rhabdomyolysis was noted (normal creatine kinase values are typically 100-200 U/L). In both cases, soldiers' core temperature was ≥105º F, indicative of heat stroke. As stated by the Mayo Clinic, "This most serious form of heat injury, heatstroke can occur if your body temperature rises to 104º F or higher" [23]. A recent report published in the Journal of the American College of Cardiology highlights the dangers of heat stroke, with authors stressing the association of heat stroke with multi-organ dysfunction, sometimes culminating in cardiac arrest [24-26]. The author's state, "Moreover, in an athlete admitted after sudden collapse, the diagnosis of heat stroke will be missed if as often happens the core body temperature is not immediately

measured. In such cases, a primary cardiac disorder may be suspected when arrhythmias predominate the clinical presentation at the time of collapse" [24]. Considering the evidence presented by Eliason and colleagues, heat stroke and its complications may have been present. Related to this and to our knowledge, there exists no evidence that DMAA elevates body temperature and this has been noted in a controlled laboratory environment [5].

Another case of death associated with physical exercise was documented in 2012, when a 30-year-old woman died prior to completing the London Marathon in 2012 [27]. It was reported that the woman ingested a DMAA containing dietary supplement mixed in her water bottle. No additional information is available in the scientific literature pertaining to this case. Therefore, it is difficult to draw conclusions specific to the role that the supplement may have played in this situation.

Scientific and Controlled

Besides the observations presented above, there exists a small number of controlled laboratory studies focused on the study of DMAA, which are described below [4,5,11,28-31]. This includes work using DMAA alone, in conjunction with caffeine and within a finished dietary supplement.

DMAA as a Stand-Alone Ingredient

From the work focused on the acute ingestion of DMAA, it is apparent that DMAA has vasoconstrictor properties, leading to a pressor effect that results in elevated blood pressure. However, the impact of DMAA on blood pressure elevation is dose dependent, with either no change in mean blood pressure when ingested at a recommended dosage of 25 mg, a 7 mmHg mean increase when ingested at a dosage of 50 mg, or a 16 mmHg mean increase when ingested at a dosage of 75 mg [4,5]. We also noted a mean increase in SBP of 14 mmHg when a dosage of 50 mg of DMAA was ingested along with 250 mg caffeine, an effect that was additive when considering the findings for DMAA and caffeine alone. To put the above into context, consider the increase in blood pressure with caffeine. Caffeine is consumed by approximately 80% of the world's population each day and approximately 87% of the United States population [32], including 74% of children [33]. In the United States, adults consume on average, 4 mg per kg of body weight of caffeine per day, which equates to 280 mg for a 70 kg (154 lb) individual [34]. Nawrot and colleagues estimated a safe level of daily caffeine consumption to be 400 mg/day the amount contained in approximately three standard cups of coffee [35,36].

With acute ingestion, caffeine elevates both systolic and diastolic blood pressure, typically in a dose dependent manner, which persists for up to three hours following ingestion. For example, Karatzis and coworkers reported a 4 mmHg increase in both systolic and diastolic blood pressure when 80 mg of caffeine was ingested within coffee [37,38]. Robertson et al., provided a dosage of 250 mg caffeine to healthy men and women and noted an increase in systolic and diastolic blood pressure of 14 mmHg and 10 mmHg, respectively (one hour after caffeine ingestion) [39]. In a review and meta-analysis, it was determined that when analyzing data from five trials, the administration of 200-300 mg caffeine produced an average increase of 8.1 mmHg in systolic blood pressure and 5.7 mmHg in diastolic blood pressure [40]. Collectively, these data indicate that DMAA at dosages up to50 mg promotes a similar increase in mean blood pressure than does caffeine when ingested at a dosage of 250 mg or the amount contained within approximately two cups of coffee.

Aside from acute ingestion of DMAA as a stand-alone ingredient, one multi-week study was conducted to assess the safety of DMAA ingestion. We investigated the safety profile of DMAA and caffeine, alone or in combination, when ingested for a period of 12 weeks [28]. Fifty young and healthy men (mean age of 23 years) completed 12 weeks of daily supplementation with either a placebo, caffeine at 250 mg/day, DMAA at 50 mg/day, or caffeine at 250 mg/day + DMAA at 50 mg/day. Before and after 6 and 12 weeks of supplementation, the following variables were measured in the morning following an overnight fast: body mass/composition, respiratory rate, blood pressure, 12-lead ECG, complete urinalysis, complete blood count, metabolic panel, lipid panel, oxidative stress, inflammatory and cardiac biomarkers. Results indicated that little to no change occurred across time for subjects in any of the four conditions, with no interaction effects noted ($p>0.05$). An increase in heart rate (~5 bpm) was observed for subjects in the DMAA condition, as well as an increase in respiratory rate for subjects in the caffeine +DMAA condition (~3 breaths per minute). Apart from urinary pH (Pre [6.5±0.1] higher than week 6 [6.1±0.1]) and blood CO_2 (week 12 [25.9±0.3 mmol/L] higher than week 6 [24.8±0.3 mmol/L]), no time effect was noted for any variable ($p>0.05$).

Studies Involving DMAA within Finished Dietary Supplements

The following studies include DMAA within the dietary supplement known as Jack3D (containing a blend of DMAA, caffeine, arginine alpha-ketoglutarate, creatine monohydrate, beta alanine and schizandrol A). In one study, seven men (25±4yrs) ingested two servings per day of Jack3D for two weeks [29]. On days 1 and 15, resting heart rate and blood pressure were measured and fasting blood samples were analyzed for complete blood count, comprehensive metabolic panel and lipid panel. On days 1 and 15 following blood collection, subjects ingested two servings of the supplement and heart rate and blood pressure were recorded at 30-minutes intervals for two hours. It was noted that after two weeks of supplementation, resting heart rate and blood pressure were not increased above day 1 values ($p>0.05$). No significant changes were noted in any measured blood parameters, except for an increase in fasting blood glucose. In response to acute intake, no measured variable increased in a statistically significant manner. However, compared to pre-ingestion, an increase of 5-15% was observed in blood pressure, with a peak occurring at the 60 or 90-minute post-ingestion time. It was concluded that acute intake of Jack 3D (at a dosage of two servings) results in an increase in blood pressure. Chronic intake of two servings per day of Jack 3D over a 14-days period does not result in an elevation in resting heart rate or blood pressure. No significant changes were noted in any measured bloodborne variable following 14 days of ingestion, except for an increase in blood glucose of approximately 8 mg/dL. Regarding this increase in blood glucose, it should be noted that in one other study using Jack 3D for a period of 10 weeks and in one study using DMAA alone for a period of 12 weeks, no increase in blood glucose was observed [28,31]. In fact, a slight decrease was noted in both studies.

In a longer-term study of Jack 3D, 25 healthy men (mean age of 23 years) were randomly assigned to either a placebo (n=13) or to Jack 3D (n=12) for a period of 10 weeks [31]. Subjects were instructed

to consume 1-3 servings on each workout day. The mean number of workout days per week for subjects was four and the mean number of servings of the supplement consumed on workout days was 2.4±0.3 (approximately 50 mg DMAA and 300 mg caffeine). Before and after the intervention, resting blood pressure and heart rate were measured, and blood samples were collected for determination of complete blood count, metabolic panel and lipid panel. It was found that no significant differences were detected between conditions for blood pressure ($p>0.05$), although systolic blood pressure increased approximately 6 mmHg with Jack 3D, while diastolic blood pressure decreased approximately 4 mmHg. Heart rate was noted to decrease slightly from pre-to post-intervention. There were significant main effects for time for creatinine (increased from pre-to post-intervention; $p=0.043$) and alkaline phosphatase (decreased from pre-to post-intervention; $p=0.009$), with no condition differences noted ($p>0.05$). There was a significant interaction noted for low density lipoprotein cholesterol ($p=0.043$), with values decreasing for subjects assigned to Jack 3D by approximately 7 mg/dL. An approximate 5% reduction was also noted in total cholesterol for subjects assigned to Jack 3D. No other effects of significance were noted for blood parameters. It was concluded that Jack 3D does not result in a statistically significant increase in resting heart rate or blood pressure (although systolic blood pressure was increased approximately 6 mmHg with supplement use). The supplement did not negatively impact blood-borne markers of health but may improve the blood lipid profile, as evidenced by the noted reduction in total and LDL cholesterol.

Studies have also been conducted using the product OxyELITE Pro, containing a blend of DMAA, caffeine, *Bauhinia purpurea*, *Bacopa monniera*, *Cirsium oligophyllum* and Rauwolscine Extract. In one such study, 4 men and 2 women (22.5±1.8 yrs) ingested two servings (two capsules) per day of OxyELITE Pro for two weeks [29]. On days 1 and 15, resting heart rate and blood pressure were measured and fasting blood samples were analyzed for complete blood count, comprehensive metabolic panel and lipid panel. On days 1 and 15 following blood collection, subjects ingested two servings of the supplement and heart rate and blood pressure were recorded at 30-minutes intervals for two hours. No change was noted in the measured variables following 15 days of supplementation. In response to acute intake, heart rate and diastolic blood pressure were increased approximately 6 bpm and 6 mmHg, respectively. Systolic blood pressure was increased approximately 15 mmHg with acute treatment of two capsules of OxyELITE Pro.

Using an acute study design, twelve subjects (men 24.8±4.3 yrs; women 22.8±0.4 yrs) ingested OxyELITE Pro or a placebo, on two separate days in a double blind, crossover design [30]. Breath samples were collected immediately before ingestion and at 30, 60, 90 and 120 minutes post ingestion, for a measure of energy expenditure. Heart rate and blood pressure were recorded at all times. Acute ingestion of two capsules of the supplement increased energy expenditure, heart rate and blood pressure above pre-ingestion values; values were greater than observed for placebo. Specifically, heart rate was stable for men (~ 60 bpm at all measurement times) but increased 7 bpm for women. Systolic blood pressure increased approximately 20 mmHg for men and 12 mmHg for women, while diastolic blood pressure increased approximately 8-10 mmHg for both men and women. We concluded that, "These latter findings (increased SBP in particular) may warrant caution, in particular in those with pre-hypertension or hypertension. The use of a lower dosage may attenuate this response."

In another study to investigate OxyELITE Pro, exercise-trained subjects between the ages of 19 and 36 years were randomly assigned in double-blind manner to ingest either OxyELITE Pro (n=16; aged 22.8±0.7) or a placebo (n=16; 22.5±0.5) every day for eight weeks [11]. Subjects were provided the option to use either 1 or 2 capsules per day. This was done to duplicate the conditions in which individuals would use this dietary supplement in a non-laboratory setting. For both conditions, capsules were taken with water on an empty stomach in the early morning, and if taking a second dosage, this was to be taken during the early to mid afternoon. Body weight, body composition, complete blood count, comprehensive metabolic panel, resting heart rate and blood pressure were measured (pre-andpost-intervention). When comparing pre-and post-intervention values for the supplement, significant decreases were noted in body weight and body fat percentage, while an increase was noted for resting heart rate (approximately 6 bpm). Blood pressure was increased slightly with the supplement (approximately 3 mmHg) but not with placebo. Of the 16 subjects assigned to OxyELITE Pro, 11 ingested two capsules per day and five ingested only one capsule per day. These five subjects indicated that the ingestion of two capsules was associated with increased feelings of jitters and sleeplessness. None of the remaining 11 subjects assigned to the supplement noted any adverse effects of treatment.

Abuse Liability of DMAA

Because of the chemical composition of DMAA and its similarity to other compounds, it has been suggested that the user may become dependent to this agent [41,42]. Dolan and Gatch, using a rodent model, investigated the abuse liability profile of DMAA compared to cocaine and methamphetamine [43]. Results indicated that DMAA produced reward-like effects and may produce subjective effects like that of abused psycho stimulants. Because this study was conducted using mice, with dosing delivered via intraperitoneal injection at amounts that may not be representative of what most humans would ingest (0.3, 1, 3 and 10 mg/kg), it is unknown how exactly these findings apply to humans. Regardless, this outcome illustrates the potential to abuse and misuse DMAA, something that has been noted anecdotally by those claiming to use this ingredient. Clearly, more human studies would be needed to more fully understand the potential abuse liability of DMAA.

Impact of DMAA on Body Temperature

Some individuals have suggested that DMAA ingestion results in elevated body temperature and impaired thermoregulation. We are unaware of evidence that supports this assertion. Our work indicates that body temperature is maintained within one degree Fahrenheit during a 24-hours post ingestion period after men received a single dosage of 25 mg of DMAA [5]. In support of the above findings, other well-recognized stimulants such as caffeine and ephedrine have been noted to have minimal to no impact on body temperature, even during exercise heat stress [44,45].

For example, one study conducted by investigators at the Army Research Institute of Environmental Medicine used a sample of 10 men who exercised in the heat (104ºF) [44]. The authors noted that even when caffeine was provided at an extremely high dosage of 9 mg/kg body weight (585-855 mg caffeine for 65 to 95 kg individuals), heat production was only marginally higher for caffeine as compared to placebo and likely due to the increase in oxygen consumption.

The authors concluded, "The magnitude of the increase in heat production was small and heat losses appeared unaffected. As a result, elevations in mean body temperature were marginal, physiologically unimportant, and unlikely to predispose athletes or military personnel to an increased risk of heat illness" [44]. Roti et al., concluded that acute caffeine ingestion, in chronically consuming subjects (3 and 6 mg/kg per day), did not alter fluid-electrolyte, exercise endurance or thermoregulatory responses during 90 minutes of walking in the heat (100ºF) when compared with no caffeine [46]. In addition, Del Coso and colleagues reported that caffeine ingestion at 6 mg/kg body mass was not thermogenic and did not impair heat dissipation when men exercised in the heat (97ºF) for two hours [47].

Aside from caffeine alone, investigators from the Canadian Defense and Civil Institute of Environmental Medicine provided a dosage of 5 mg/kg caffeine + 1 mg/kg ephedrine to 10 men who exercised in a hot environment (104ºF) [45]. The authors noted no increase in internal body temperature during exercise, despite the high dosage of stimulant provided. Collectively, these studies indicate that well-known stimulants fail to increase internal body temperature, even when provided at very high dosages.

Considering the minimal effects of DMAA and caffeine on human body temperature, there is no scientific basic to claim that DMAA at a dosage of 25-50 mg would lead to a significant increase in body temperature [5,44]. Such a suggestion is mere speculation and fails to consider the available science.

Natural Versus Synthetic DMAA

Aside from the overall safety concerns raised, additional discussion has centered on DMAA in relation to its origin. That is, some authors have reported that DMAA is found naturally in plants, while others disagree with this assertion [8,48-52].In a review of this topic, Gauthier concluded that, "…differences in the samples sources, extraction procedures and methods of analysis may account for the conflicting results" [53].

In one study by Fleming and colleagues in which DMAA was detected in small quantities in cultivars of *Pelargonium graveolens*, the authors report, "The results reported here provide evidence that 1,3-DMAA naturally occurs in geranium plants" but go on to state that their work disagrees with other previous articles by well-respected chemists [48]. The authors follow by stating that, "…this may not be a case of right or wrong. In analytical chemistry, the critical review of data is important for explaining differences in reported results. These differences can also provide insight into why analysis of seemingly identical plant species can result in very different outcomes" [48].

In short, scientists continue to disagree on whether DMAA can be identified in plant species. Regardless, it is obvious that despite its claimed existence in plants or the plant oils, since the quantities of detection are very small, dietary supplements using dosages of 20-30 mg of DMAA per serving must include synthetic DMAA in these preparations. It would be difficult for a manufacturer to provide support to the contrary. As such, labeling the product as "natural" is misleading to the consumer, as many may believe that the entirety of the product is natural when in fact, it is not.

Assuming that DMAA is of natural origin, the question arises as to whether or not use of a synthetic version of the ingredient within dietary supplement preparations would be of concern. For some individuals, the answer is likely yes, as they believe that all dietary supplements should be natural and contain no synthetic components. Other might argue, no; they are fine with the use of synthetic ingredients as long as said ingredient does exist in nature. The rationale for the latter might be the simple fact that the use of synthetic ingredients within dietary supplements is common. A quick review of many off the shelf multi-vitamin/mineral supplements will confirm this. For example, synthetic vitamin E (dl-alpha-tocopherol) has been used for many years, although well-documented to be inferior to the natural form of this vitamin. The same is true for many other agents that are naturally occurring but are used in synthetic form within dietary supplements. Synthetic when it comes to dietary supplements does not necessarily equate to harm, which is often the implication. It simply means different and in some cases, inferior. In other cases, such as with vitamin C, "different" may not matter at all [54].

Should DMAA Dosing be Considered?

Physicians and pharmacists understand clearly that two vital components are necessary to obtain the desired outcome when it comes to the use of prescription pharmaceuticals: 1) the drug itself and 2) the dosage and dosing frequency. The same concept applies to multiple areas, including nutritional intake and physical exercise. The desired outcome is only achieved when the agent of change is delivered at the optimal dosage and frequency. Anything below the optimal dosage may lead to negligible changes, while anything above the optimal dosage may lead to adverse outcomes. This principle needs to be applied to dietary supplements and, in the case of our discussion, DMAA.

As mentioned above, in many of the case reports noting significant adverse outcomes from DMAA ingestion, quantities of use appeared to be far greater than what would be recommended by the manufacturer or tolerated by human consumption. Based on a review of product labels and anecdotal reports, most DMAA containing dietary supplements are thought to include approximately 25 mg of DMAA per serving. We know from our prior controlled studies using DMAA that blood pressure increases in a dose-dependent manner with treatment. That is, at 25 mg we observe essentially no change in blood pressure, with a 7 mmHg mean increase at a dosage of 50 mg and a 16 mmHg mean increase at a dosage of 75 mg [4]. If our calculations are accurate and certain individual cases as reported in the papers of Gee and colleagues were consuming 15+ times the recommended dosage, these individuals may have ingested 375 mg of DMAA (on the low end), in addition to other stimulants [9,10]. If this was the case, it is not surprising that adverse effects were noted. Such activity is extremely unwise and should be strongly discouraged.

The above would be akin to an individual ingesting 3,750 mg of caffeine in the morning rather than the usual 250 mg found in two cups of coffee; or perhaps drinking 15-20 glasses of wine with dinner rather than an acceptable, one or two glasses. Likewise, it would be similar to the cardiologist prescribing 375 mg of Atenolol to their patient rather than a more typical dosage of 25 mg of this beta-blocker. No rational person would consider doing such things, as they know the results could be devastating. Yet, this is the sort of practice that appeared commonplace with DMAA, in particular when used within "party pills". The outcome is dependent on more than the agent; it is also dependent on the dosage of agent being delivered and this should always be taken into account.

Grounds for DMAA Removal

Many individuals have questioned whether DMAA should have been targeted for removal from the market based on the available evidence. From a scientific point of view, there exist very few studies focused on the safety of DMAA. Those that have been conducted have failed to note any significant adverse effects with regular DMAA ingestion, other than an acute rise in blood pressure with use. That said, as in any area of science, replication of findings is important and additional, longer-term studies are needed to determine the safety profile of DMAA. To be clear, the volume of well-controlled, long-term safety studies involving DMAA are scant and based on this, some believe that DMAA should not be allowed for use in dietary supplements.

What we know at present is that multiple adverse event reports have been filed which cite the involvement of DMAA. These events may be linked to the well-described pressor actions of DMAA and the resulting dose-dependent rise in blood pressure with use. It only follows that the FDA would need to investigate these reports and take the appropriate action. While their decision of removing DMAA from the marketplace is not popular with many, they must have believed it was the correct and responsible action in this case. Unfortunately, many individuals are prone to reckless behavior and it may have been the FDA's belief that reckless behavior involving the ingestion of high quantities of DMAA needed to be stopped. Just as a protective parent steps in to regulate the activities of their children, the FDA may have believed that their actions helped to regulate the activity of would-be DMAA users. In such a case, protecting individuals who refuse to protect themselves seems appropriate. Whether this is right or wrong and/or whether this infringes on individuals' rights to make their own choices remains a topic of debate.

Beyond the above, the overarching question is whether DMAA qualified for inclusion within dietary supplements in the first place. This is based on the issue of NDI status. Unlike the Dietary Supplement Health and Education Act of 1994, which places the burden of proof on the FDA, the NDI guidelines require that the company provide the FDA with information pertaining to the overall safety of the ingredient of interest. If this was never done and if DMAA was considered A NDI, this presents a separate topic for discussion.

Conclusion and Suggestions for Moving Forward

To summarize, much controversy has surrounded the use of the ingredient known as DMAA. This is based largely on two factors: 1) the assertion that DMAA is a NDI and requires reporting to the FDA prior to being introduced to commerce, inclusive of information supporting the conclusion that the dietary supplement is reasonably expected to be safe and 2) the number and severity of adverse events involving men and women purported to use supplements containing DMAA. Related to the latter, there is no question that DMAA can elevate blood pressure with acute use and does so in a dose-dependent manner. This has the potential to lead to significant complications and should be understood fully by those planning to use this ingredient.

It is apparent that consumer education is needed, including instruction as to how to report adverse events. While this is specific to DMAA in our current discussion, it certainly should not end with this one ingredient. There are many dietary ingredients being sold and used today by consumers for which we know little about in terms of efficacy, dosing, and safety. Rather than constantly battling over so many issues, the medical community, FDA and dietary supplement community need to come together to develop a comprehensive plan of action that will serve to help the people who need it most the consumers. Without this, more confusion will arise and people across groups will continue to be frustrated.

Since some companies continue to manufacture products containing DMAA, strict adherence to current Good Manufacturing Practice should be adhered to by all contract manufacturers. Should practice containing DMAA, strict adherence to current Good Manufacturing Practice. While most companies selling dietary supplements do not manufacture the products on their own, they should make certain that they have an excellent working relationship with their contract manufacturer and can assure customers that they can trust label claims for product purity and potency. If a company continues to use DMAA in their formulas, it would be wise to limit the amount contained in the product, to avoid the elevated blood pressure that is well documented with DMAA use.

If DMAA continues to be sold, long-term safety studies should be initiated in order to expand on our understanding of DMAA. These studies should include men and women, as well as those of various ages and fitness levels. Since many overweight/obese individuals may opt to use products containing DMAA to lose body weight/fat, such individuals should be included in the subject pool. Using DMAA within the context of exercise stress should also be done, as most users will ingest the supplements prior to acute exercise. Moreover, since DMAA is typically used in conjunction with other ingredients (e.g., caffeine), the combination of ingredients should be considered in study designs.

If people continue to use this agent, it is imperative that they understand the potential harm of doing so, in particular when using DMAA in high quantities. Specifically, blood pressure will likely be elevated acutely with use and this may pose a problem for those who may already be hypertensive and/or are using DMAA in the context of strenuous, high force resistance exercise. Companies who continue to market and sell DMAA containing products should focus efforts on educating the consumers of the potential safety concerns of using DMAA. This should extend to the issue of DMAA being banned by most sporting agencies, raising the possibility of athletes testing positive on mandatory drug tests and subsequently being ineligible to compete.

As with all stimulants, the potential for elevated heart rate and blood pressure exists. Additional complications may arise based on an individual's sensitivity to the agent. For example, some subjects who have used DMAA and other stimulants note feeling jittery and anxious, while sometimes having difficulty falling asleep at night. These are undesirable outcomes for many individuals. Users need to understand that, not unlike medications, when using certain dietary supplements, some degree of risk is involved. This is the reality, and companies who market such products need to specify what these risks might be in order to better educate potential consumers.

Acknowledgment

Funding for this work was provided by The University of Memphis.

Author Disclosure Statement (Declaration of Interests)

RJB and CRY have in the past, received research funding from, or acted as a consultant to, dietary supplement companies, including those who may have sold DMAA containing products. No ongoing

work is being conducted using DMAA. Other authors have no conflicts to disclose. All authors read and approved of the manuscript.

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