REPORT OF THE DEPARTMENT OF DEFENSE
1,3 DIMETHYLAMYLAMINE (DMAA) SAFETY REVIEW PANEL

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1. Introduction

Since May 2011, four Soldiers who died following physical exercise were found to have traces of dimethylamylamine in their blood analyses. One Soldier died in the Pacific region and was found to have severe coronary disease on autopsy, but the other three were in the Southwestern United States and died of complications from rhabdomyolysis and severe metabolic acidosis. Two of these three Soldiers were reported to have had sickle trait. In a precautionary move in December 2011, the Army and Air Force Exchange System pulled all DMAA containing products off of its Exchange and concession shelves pending the results of a safety review. In December 2011, the Under Secretary of Defense for Personnel and Readiness, with the concurrence of the Assistant Secretary of Defense for Health Affairs, directed the removal of all products containing DMAA from Military Exchanges and concession stores on DoD installations pending further review of the product safety (Annex D: ALFOODACT 034-2011 and ALFOODACT 044-2011).

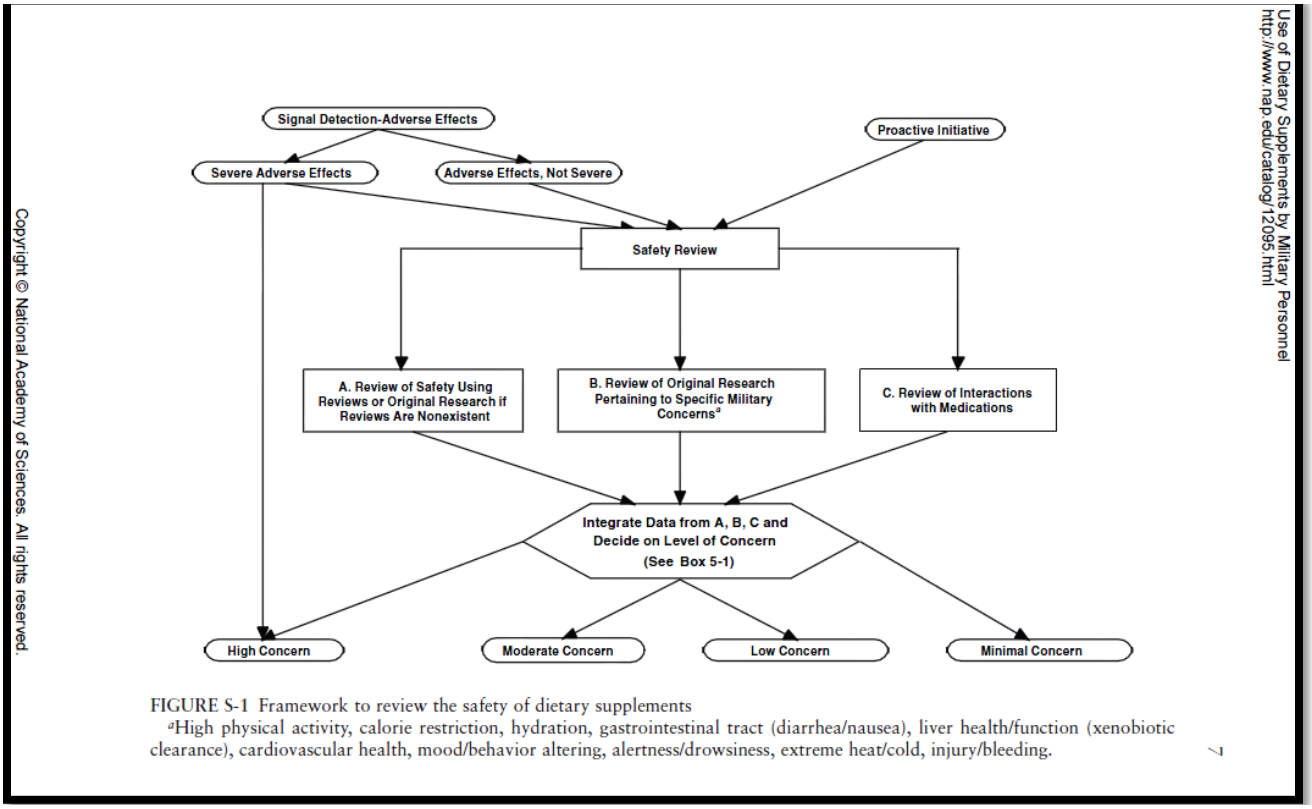
DMAA or methylhexanamine (MHA) has been an active ingredient in several performance enhancing dietary supplements (see Table 1). These products are commonly used to promote weight loss, bodybuilding and performance enhancement (OTSG, 2012). Because DMAA-containing products have been considered dietary supplements and not drugs, they are not subject to rigorous pharmaceutical trials that have oversight by the FDA. As a consequence, there is limited information available regarding their safety (FDA, 2012).

Table 1. List of DMAA-Containing Supplements Withdrawn from Military Exchanges as of 7 December 2011

Supplement Proprietary Name	Manufacturer
Jack3d (tropical fruit and lemon lime)	USPlabs
OxyELITE Pro	USPlabs
Lipo 6 Black	Nutrex Research Inc
Lipo 6 Black Ultra	Nutrex Research Inc
Hemo Rage Black	Nutrex Research Inc
PWR Ultra Concentrated Pre Workout Revolution	iSatori Technologies LLC
Neurocore Powder	MuscleTech
HydroxyStim	MuscleTech
Lean EFX	Fahrenheit Nutrition
Napalm	Muscle Warfare
K Otic	All American EFX
Nitric Blast	Sports Nutrition International
SSIN Juice Concentrate	BioRhythm-ADS
Code Red	MuscleMeds Performance Technologies
MethylHex4,2	SEI Pharmaceuticals
Arson Fat Burner Capsule	Muscle Asylum Project
Spirodex	Gaspari Nutrition

Source: ALFOODACT 036-2011 as cited in Cohen, 2012

The Assistant Secretary of Defense for Health Affairs asked the Army Surgeon General to lead a review of the available scientific evidence and adverse event data to better understand any potential relationship between DMAA and these adverse events. A panel was assembled that included representatives from all three Services, Health Affairs and the Army Public Health Command to evaluate the safety of the DMAA-containing products.



Framework to review the safety of dietary supplements *(Reprinted with permission from Institute of Medicine Report: Use of Dietary Supplements by Military Personnel,2008 by the National Academy of Sciences, Courtesy of the National Academies Press, Washington, D.C.)*

This Safety Review sought to follow the recommended structure described in the 2008 Institute of Medicine Report on "Use of Dietary Supplements by Military Personnel. Figure S-1, from their report, details the integration of available reviews, original research and medication interactions to determine the level of concern. (Greenwood and Oria, Editors, 2008)

This report summarizes the Department of Defense DMAA Safety Review Panel analysis and recommendations for senior DoD medical leaders.

Just prior to the release of this report, on 12 April 2013 the Food and Drug Administration declared DMAA-containing products to be illegal and potential health

risks. On 17 April 2013, USPLabs announced that it would reformulate its supplements without DMAA.

I am deeply grateful to senior Department of Defense leaders who received the multiple reports of the Safety Review Panel and who provided shaping guidance. I thank all of the contributors of the Safety Review Panel for their research, analysis and recommendations throughout the tenure of the review.
J.L.

2. **Executive Summary**

The Review Panel designed a phased process that included a collation of adverse event reports associated with DMAA use, a review of Food and Drug Administration adverse event reports, a literature review, structured interviews with ten Service members with adverse events for whom identifying information was available, a review of death cases with the Armed Forces Medical Examiners Section (AFMES), and a case-control study involving a survey distributed to nearly 5000 Army Soldiers across multiple installations. The DoD studies of DMAA took place in 3 phases:

- Phase I – Literature Review and Medical Care Provider Survey of Adverse Events.
- Phase II – Patient Interview of Adverse Events and Review of FDA Reported Adverse Events.
- Phase III – Armed Forces Medical Examiner Service Review and Case Control Study of the association between adverse health effects and the consumption of DMAA-containing products.

While the initial goal for review recommendations to assess the safety of DMAA-containing products was February 2012, the case-control study in Phase III was not completed until the end of December 2012.

DoD reviewers received information from industry representatives from USPLabs, manufacturers and distributors of the popular DMAA-containing products Jack3d™ and OxyELITE Pro™. On three occasions industry scientific experts met with Review Panel representatives to present results of their safety and toxicology reviews and scientific studies.

The Safety Review Panel met several times to review evidence and to discuss results of the components of the study. Regular reports were provided to Health Affairs oversight councils, the Force Health Protection Integrating Council and the Senior Military Medical Action Council.

In Phase I of the DoD studies, forty adverse medical event reports were collected from DoD medical providers. These reports included four deaths, three of which occurred during exercise and one from a presumed myocardial infarction in a 41-year-old with extensive coronary disease found at autopsy. There were two cases of liver failure that had no other apparent linked medication or product exposure. The remaining adverse medical events grouped into a muscle cluster (heat injury and rhabdomyolysis), heart cluster (cardiac palpitations and dysrhythmia), neurologic cluster (syncope and seizure), and liver and kidney failure. The spectrum of DoD adverse event reports aligned closely to non-DoD submitted FDA reports, which also included three deaths from 2010 until March 2012. The expert panel reviewed the likelihood of DMAA being causally linked with the events using a Naranjo Scale methodology. (see Annex F) Two cases of liver failure achieved a moderate likelihood of association according to this method.

Seven of the Service members described in the adverse event reports and three others identified during the case control study completed structured interviews with Army Public Health Command scientists. All were male, most were in their upper twenties. All used the products to increase energy and to enhance performance. Seven of the ten had Body Mass Indices of greater than 27, with three being more than 30. Seven of the ten Service members used tobacco products. Seven of the ten Service members interviewed reported taking additional dietary supplements or energy boosters with the DMAA-containing products. All described a spectrum of symptoms that they associated with the use of the products including palpitations, dizziness and tingling.

The literature review identified four patients with cerebral hemorrhage from New Zealand associated with very high recreational dosages of DMAA. (Gee, 2011, 2012) Young reported a nonfatal right midbrain thalamic stroke in a 26-year old Active Duty male using Jack3d™ who was serving in Afghanistan. (Young, 2012) Salinger described a 24-year old male who developed hypertension and acute heart failure of the Takotsubo type one hour after ingestion of Jack3d™. (Salinger et al, 2011) He required intensive care and endotracheal intubation and ventilation for a short interval. His echocardiogram showed transient apical akinesis with an ejection fraction of less than 20%. A transient pupillary mydriasis occurred in a 20-year old female marine who rubbed her eye after mixing Jack3d™. (McDermott, 2012) Armstrong reported an episode of transient atrial fibrillation with rapid ventricular response in an otherwise well 32-year old Special Operations Sailor. (Armstrong, 2012)

A series of eight studies from a research team at the University of Memphis demonstrated some dose-related acute blood pressure elevation and slightly decreased heart rates with DMAA use, but no significant blood chemistry, metabolic or oxidative changes with use of the products for up to four months. (Bloomer, Farney, McCarty and Whitehead, 2011 and 2012) Six of the studies received industry funding. The studies recruited only young, healthy volunteers. There are currently no published studies supporting the safety or efficacy of DMAA-containing products in more diverse subject populations, to include those who may use tobacco products, may be overweight or obese and who use these products under more extreme environmental conditions. No enhancement of performance was noted in a group of men and women administered DMAA or DMAA and caffeine prior to ten-kilometer test runs. The McCarthy et al study (2012a) included active individuals of whom 15 were normal weight, 13 were overweight, and four were obese, as defined by BMI.

During the course of the DoD review, the Food and Drug Administration (FDA), in an independent action in April and August 2012, sent warning letters to the manufacturers and distributors of DMAA-containing products citing them for failure to comply with the 1994 Dietary Supplements Health and Education Act that requires New Dietary Ingredient notifications for novel supplements introduced after 1994. The FDA stated that “there is no information demonstrating that dimethylamylamine was lawfully marketed as a dietary ingredient in the United States before October 15, 1994, nor is there information demonstrating that this ingredient has been present in the food supply as an article used for food in a form in which the food has not been chemically altered.

In the absence of such information, dimethylamylamine is subject to the notification requirement in 21 U.S.C. 350b(a)(2) and 21 CFR 190.6. Because the required notification has not been submitted, [DMAA-containing] products are adulterated under 21 U.S.C. 342(f)(1)(B) and 350b(a)." The FDA declared that "we know of no evidence that would establish that [the] products are not adulterated… To the best of FDA's knowledge, there is no history of use or other evidence of safety establishing that dimethylamylamine will reasonably be expected to be safe as a dietary ingredient. In fact, dimethylamylamine narrows the blood vessels and arteries, which increases cardiovascular resistance and frequently leads to elevated blood pressure. This rise in blood pressure may increase the work of the heart such that it could precipitate a cardiovascular event, which could range from shortness of breath to tightening of the chest and/or a possible myocardial infarction (heart attack). Therefore, in the absence of a history of use or other evidence of safety establishing that dimethylamylamine is reasonably expected to be safe under the conditions recommended or suggested in the labeling of Oxy Elite Pro and Jack3d™, [the] products are deemed to be adulterated under 21 U.S.C. 342(f)." (FDA letter to USPLabs, 24 Apr 2012)

Industry analysts cite two studies that claim to demonstrate small amounts of extractable DMAA from geranium stems and leaves from geranium plants grown in several provinces in China, but industry admits that the DMAA used in the supplements is synthetic in origin, coming from multiple sources. (Ping et al, 1996; Li and Chen, 2012) Health Canada found discrepancies in the paper, including an incorrect English translation in Ping et al. (1996). Their review of the DMAA literature led Health Canada to conclude that "there is no credible scientific evidence that DMMA is captured as an isolate of a plant…"

In Phase III of the DoD studies, the Armed Forces Medical Examiner System (AFMES) reviewed autopsy data and associated body fluid samples to check for DMAA in Service members who suffered sudden exercise-related death and deaths from heat stroke, acute myocardial infarction, stroke, or hepatic failure. It was the opinion of the AFMES that DMAA did not play a significant role in the deaths of these four Service members. This review did not identify any additional cases beyond the known deaths that were positive for DMAA.

Also in Phase III, the case control study was completed in December 2012. There were a total of 1789 responses for a 45.4% response rate among available non-deployed Soldiers. Respondents included 712 Soldiers who were considered as "cases" with diagnoses of cardiac dysrhythmia, heat injury, seizure, rhabdomyolysis, cerebral hemorrhage, acute kidney failure or acute and/or subacute necrosis of the liver documented during calendar year 2011 in the Armed Forces Health Surveillance Center database. These Soldiers were compared to 1077 randomly selected controls.

Analysis showed that Soldiers with these diagnoses were no more likely to have used DMAA-containing supplements than controls, with an adjusted Odds Ratio of 0.85. The 95% confidence interval includes 1.0 (OR=0.85; 95% CI, 0.59-1.23). An Odds Ratio of 1.0 means that the likelihood of the exposure (DMAA use) among the cases (adverse

medical events) is equal to the likelihood of the DMAA use among those without adverse medical events, supporting a conclusion of no observed association.

While subgroup analysis by diagnosis type likewise failed to show that Soldiers with these specific events were more likely to have used DMAA, the case control study showed that cases with multiple adverse events were twice as likely to have used DMAA than cases with only one adverse event [Odds Ratio 2.28 (95% confidence interval 1.01- 4.95), p=0.04]. The study also found that among cases, low frequency DMAA users (1-80 days) were 1.7 times more likely to have multiple outcomes, and high frequency DMAA users with more than 80 days of use were 3.5 times more likely to have multiple adverse events compared to non DMAA users. The trend analysis was significant at the p=0.02 level.

There also appears to be a possible increased likelihood of frequent DMAA use for more than 80 days in Soldiers who experienced heat injury and rhabdomyolysis with adjusted Odds Ratios greater than 1.0, but the numbers are too small and do not reach statistical significance. The survey identified a statistically significant association of adverse medical event diagnoses in 2011 with previously experienced adverse medical events, with an Odds Ratio of 18 (95% confidence interval 9.6 -33.11). The study also identified a higher likelihood of prescribed antidepressant and stimulant drug use among those with adverse medical events. The finding in the control group that DMAA-supplement use within the previous year was 15.4% suggested to reviewers a high prevalence of use of these products in the active-duty military population.

The Safety Review Panel concluded that the available evidence supports an elevated health risk associated with the use of DMAA-containing products. Given the high numbers of Service members who reportedly use these products, as high as 15% in the case control study, use of these supplements appears to convey low risk of serious harm for most healthy Service-members at the doses recommended by the manufacturer. However, there does appear to be a significant association of DMAA use, particularly high frequency DMAA use, and multiple adverse events. Further, the deaths, hepatic failure, myocardial infarction, heat stroke and rhabdomyolysis, seizure and stroke temporally associated with Service members' use of these products suggest that some individuals may be predisposed to severe health consequences after using DMAA.

All of the death cases summarized above occurred following physical exertion. Three of the four deaths occurred in the Southwestern region of the United States where high temperatures are common at most times of the year, although temperatures were between 70 and 80 degrees at the time of these events. There is no evidence of misuse or overuse of these products by the Service members with adverse medical events. Although direct causality cannot be concluded, the seriousness of the observed adverse medical events and deaths where Service members had used DMAA-containing products led Safety Review Panel members to assess DMAA-associated health risk as low to moderate.

The existing evidence does not conclusively establish that DMAA-containing substances are causally-associated with adverse medical events. However, a consistent theme among the studies is that DMAA use potentially affects cardiovascular function, just as other sympathomimetic stimulants. Without further rigorous study designs developed to evaluate the safety of DMAA, especially in patients with concomitant use of other substances, co-morbid conditions and high frequency use, the magnitude of the association of DMAA with adverse medical events is uncertain. Widespread use of DMAA-containing products by tens of thousands of Service members – often in combination with other substances – increases the likelihood of observing serious adverse events, even if the overall risk of a DMAA-related event is low, resulting in consequential impact to some Service members and other beneficiaries. DMAA should be further studied to evaluate its safety. Data from the case control study suggest that the frequency and amount of DMAA use and risk of specific AMEs, particularly heat injuries and rhabdomyolysis, need to be examined in greater detail.

The 2008 Institute of Medicine Report on *Use of Dietary Supplements by Military Personnel* commented on the challenges of insufficient data to assess dietary supplements: **"**Acquisition of sufficient scientific data from literature searches to support an informed decision about the safety and efficacy of a dietary supplement within the military will be a challenge. The committee emphasizes that absence of evidence of risk, a frequent reality, does not necessarily indicate that there is no risk, but might reflect inadequacy of the study design to identify risk." The IOM Committee noted that "dietary supplements commonly contain multiple ingredients, which are often reformulated with different ratios, amounts, and even constituents. Finding data on the safety of the multi-ingredient products in the market is a yet greater challenge than finding data for single-ingredient products." (Greenwood and Oria, 2008)

The Safety Review Panel recommended to the Force Health Protection Integrating Council and the Senior Military Medical Action Council to continue the prohibition of sales of DMAA-containing products in Exchanges and concessions. The Panel judged that the evidence supports sufficient risk, even if very low, of another death or catastrophic illness of a Service member who has used DMAA-containing products, without any offsetting benefit of these products. Using the suggested Institute of Medicine framework quoted in the Introduction, the Safety Panel retains "moderate concern". The Panel is also concerned about a tacit message of endorsement of these products if sales would be allowed to resume. As the IOM stated in the 2008 report: "While the military has not specifically endorsed the use of dietary supplements other than multivitamins (usually prenatal multivitamins), the fact that there are specific dietary supplement stores on many installations, dietary supplement sections in other stores (e.g., Exchanges and commissaries), as well as products being offered for sale in health promotion and fitness centers on base, may induce belief that the military leadership has evaluated and approved of their use."

The FDA-related actions provide additional context and justification for continued hold on DMAA-product sales in Exchanges and concessions, in order that the DoD avoid

violation of the prohibition of 21 U.S.C. § 331(c) against receiving in interstate commerce adulterated products.

3. **Dimethylamylamine – description of compound**
   Dr. Patricia Deuster
   COL John Lammie

DMAA Overview

The scientific name of DMAA is 1,3-dimethylamylamine or methylhexanamine, but the compound is also known as methylhexaneamine and pentylamine. It is a simple sympathomimetic aliphatic amine vasoconstrictor originally developed and patented by Eli Lily in 1944. (Schonle and Rohrmann, 1944) Its development was prompted by a simple synthetic process that was significantly less expensive than that of ephedrine at the time. According to the trademark, its first commercial use as a nasal inhalation drug to treat nasal congestion by the name of Forthane in 1948. (Eli Lilly, 1971)

Physiology studies of the compound in the 1940s and 1950s demonstrated its sympathomimetic physiological effects that mimic the action of epinephrine with both peripheral sympathetic neuron and central nervous system effects. These include increases in blood pressure due to the constriction of peripheral blood vessels, increased heart rate due to cardiac stimulation and increased blood sugar levels. (Chen, 1948; Beyer, 1946). In efficacy studies, local application of DMAA produced little or no effect upon the pulse rate or blood pressure in adult humans, although potential side effects included headache, nervousness, mental stimulation and tremors. The Council of Pharmacy and Chemistry of the American Medical Association therefore recommended discontinuation of the drug if such side effects occurred. The Council also noted DMAA's systemic toxicity to be more than ephedrine, but less than amphetamine, although the applicability of this data to humans is uncertain since it was based upon LD50 data from intraperitoneal injection of DMAA into mice. Its pressor action was subject to tachyphylaxis, a characteristic feature of indirectly acting sympathomimetic amines. (JAMA, 1950) DMAA was shown to be a much less potent vasopressor than epinephrine in dogs, but it had a longer duration of action (Marsh, 1948; Swanson and Chen, 1948).

The exact mechanism of action of DMAA has not been elucidated, but its structural cousin, tuamine (2-amino heptane), competitively inhibits norepinephrine reuptake in bovine chromaffin cells as well as the norepinephrine transporter. (Delicado et al, 1990) The latter potentiates the effect of norepinephrine on target receptors. (Schlessinger et al 2011) Ephedrine, pseudoephedrine, norepinephrine and norpseudoephedrine have a different mechanism of action, stimulating release of norepinephrine with agonistic action on the adrenoreceptors. DMAA is thus likely to be an indirect sympathomimetic, exerting its effects on the release or reuptake of norepinephrine. No studies have been published that examine DMAA or tuamine as direct sympathomimetics with direct action on the adrenoreceptors). DMAA was removed from the market in 1983 at the request of Eli Lily. (Federal Register, 1983)

It was re-introduced under the trade name “Geranamine” in 2006, with the claim that it was a constituent of geranium flower oil, and it began to appear in many dietary supplements. (Proviant Technologies, 2005) Some of these DMAA-containing products became very popular in mainstream nutrition stores to promote weight loss, bodybuilding and performance enhancement.

The intended route of administration for these supplements is oral ingestion, and the specific amount of DMAA is identified as a proprietary blend in research sponsored by one of the manufacturers. (Farney et al, 2011, McCarthy et al, 2011a, 2011b) Most supplements with DMAA contain multiple other ingredients. For example, one of the most popular, Jack3d™, contains DMAA, beta alanine, arginine alpha-ketoglutarate, caffeine, creatine monohydrate powder and Schizandrol A. Whereas the toxicological profiles of creatine, arginine, beta-alanine, Schizandrol A, and caffeine have been reported, little is known about DMAA. (Alvares et al, 2011; Artioli et al, 2010; Moffat et al, 2004; Sinclair, 1998)

Recent industry-sponsored toxicology studies estimate the maximum tolerated dose in rabbits and rats to be between 125 and 300 mg/kg body weight. Manufacturer recommended servings for DMAA-containing supplements in the United States are far lower. Both private and industry-sponsored studies by the University of Memphis researchers employed 50 mg and 75 mg of DMAA and/or 250 mg of caffeine in research subjects. (Bloomer et al, 2011a) (Bloomer et al, 2013) Even at the recommended doses, some users of these products have experienced changes in blood pressure, headaches, lightheadedness, and rapid heartbeat. Recent users of DMAA-containing products have reported experiencing headaches, lightheadedness, rapid or irregular heartbeat, panic attacks, urinary difficulties, seizures and heat stroke (OTSG, 2012). As of April 2012, forty-two adverse event reports on DMAA products had been received by the U.S. Food and Drug Administration (FDA, 2012).

To date, there is minimal scientific evidence regarding the association of DMAA consumption and adverse medical outcomes (FDA, 2012; Cohen, 2012).The risk of serious effects may be increased with the use of multiple stimulants (e.g. caffeine) and during extreme exertion in hot environments. Other sympathomimetics such as ephedrine are known to cause adverse events such as myocardial infarction, ventricular tachycardia, cardiac arrest, pulmonary arrest, transient ischemic attack, brain hemorrhage, seizure, psychiatric symptoms, and death, even in young, otherwise healthy individuals. (Shekelle et al, 2003) Sympathomimetics are generally available by prescription or at low dosages in over the counter preparations, and have package inserts that carry warnings about potential side effects.

In October 2008, the New Zealand Health ministry issued a request for the voluntary suspension of the sale of pure DMAA powder by retailers following adverse reactions in four patients who exhibited hypertension, agitation, headache, vomiting, bradycardia, and/or stroke after DMAA ingestion. (New Zealand Health Ministry, personal communication, 2011), (Gee et al, 2010) The powder is used recreationally at high

doses, ten or more times higher than recommended by DMAA-containing supplement makers.

Health Canada in August of 2011 classified DMAA as a drug, subject to its Food and Drug Regulations. Health Canada has further clarified that DMAA is not an acceptable non-medicinal ingredient in drugs or natural health products or as a food additive due to its pharmacological activity. All products containing DMAA must obtain drug approval by Health Canada. (Hussein et al, 2011) Ireland, Sweden, Denmark, and Finland have banned the substance, and authorities in France and Italy are considering similar action. DMAA is not authorized for use in food supplements in the European Union. The World Anti-Doping Agency formally specified DMAA as a prohibited stimulant in 2010. In the adjudication of their cases it became clear that athletes were testing positive from using dietary supplements that contained DMAA. The Therapeutic Goods Administration (TGA) of Australia added DMAA to its Appendix C meaning that sales, supply and use of DMAA would be prohibited due to safety concerns about the abuse of DMAA.

There has been recent debate whether DMAA is a natural component found in geranium plants as labeled by the manufacturers and suppliers of DMAA-containing products. Industry response hinges on the legitimacy of DMAA as a natural substance found in *Pelargonium graveolens* geranium oil. Reportedly, this species is widely cultivated for perfumes. The source for DMAA-containing varieties has been identified as China. Since the original paper in 1996 (Ping et al, 1996), a series of papers has analyzed Chinese-supplied geranium oil, leaf, and stem material with conflicting results. Recently, Fleming et al, in a careful industry-funded analysis, analyzed geranium extracts from three regions of China and demonstrated 1,3-DMAA and 1,4-DMAA in some of the samples with similar diastereomer distribution as synthetic controls. (Fleming et al, 2012) There are methodological concerns with chain-of-custody control of samples for analyses that have reportedly identified DMAA, and some researchers have questioned the finding of the same stereoisomer formations in natural samples as synthetic materials. Several studies have concluded the DMAA found in supplements could not have come from the geranium plant and therefore the substance does not qualify as “natural”. (Peterson, 2012; Dallas, 2012) (ElSohly et al, 2011; Lisi et al, 2011) No report documents use of DMAA and geranium products as naturally occurring performance enhancers prior to 2000.

On 24 April 2012, the Food and Drug Administration (FDA) sent warning letters to distributors and manufacturers of DMAA-containing products predicated on the failure of these groups to comply with New Dietary Ingredient provisions of the 1994 Dietary Supplement Health and Education Act. The warning letters stated the FDA’s determination that DMAA-containing products are adulterated, not lawfully introduced into interstate commerce, and subject to FDA enforcement action, such as seizure or injunction.

4. Phase I a: Literature Review

a. Physiologic studies and reports

A series of studies has been conducted at the University of Memphis by the Department of Health and Sports Sciences under the direction of the Department Chair, Dr. Richard Bloomer. Most have been supported by grants from one manufacturer of the products, USPLabs. These studies generally include a small number of young, healthy subjects taking DMAA-containing products in randomized placebo-controlled or crossover designs to measure physiologic and metabolic responses.

Safety Panel reviewers recommended that these studies should be interpreted with caution. The young, healthy volunteers in these studies may not be typical of users in our Service members and their families. It is unclear how the samples of participants were chosen, and there may be overlap of participants across the studies, introducing the possibility of bias that individuals known to not react poorly to DMAA were selected into the studies and were included in more than one study. It should be noted that these studies were designed to examine physiologic and metabolic effects of DMAA and not adverse health outcomes. As a consequence of the intent to assess physiologic outcomes, the sample sizes are too small to detect relatively rare health outcomes.

One study looked at heart rate and blood pressure responses in ten healthy young men (N=5; mean age=26 years) and women (N=5; mean age=23 years) who ingested caffeine alone in 250 mg doses, DMAA alone in 50 or 75 mg doses, or 250 mg caffeine with either 50 mg or 75 mg of DMAA in a cross-over design (Bloomer et al, 2011a). One dosing variation was given each day for five days. The study showed that systolic blood pressure readings were significantly increased under DMAA or DMAA with caffeine dosing at the 75 mg dose when compared to caffeine alone. Rate pressure product was also significantly increased for the caffeine plus DMAA 75 mg dose compared to caffeine alone. The effect appeared to be independent of concomitantly measured epinephrine and norepinephrine levels.

A second study by Bloomer et al (Bloomer et al, 2011b) randomized twelve young (mean age=21.9 yr) healthy men (N=6) and women (N=6) to ingest placebo, caffeine alone (4 mg/kg), DMAA alone (1mg/kg), or DMAA plus caffeine prior to a 10 km run on four different days. All six men and six women completed all four runs. There was no statistically significant difference in run performance times with DMAA with or without caffeine when compared to placebo or caffeine alone. Systolic blood pressure was significantly elevated for the groups taking caffeine and DMAA alone when compared to placebo. Surprisingly, systolic blood pressure measurements were similar to placebo for the DMAA plus caffeine group. Participants reported that the combination of caffeine and DMAA resulted in a sense of euphoria that the authors claimed may have impaired performance. Although not significantly different, the DMAA plus caffeine group reported the highest feeling of exertion and lowest mood.

A third study randomized 25 young men to either placebo (mean age=22 yr) or DMAA plus caffeine-containing Jack3d™ supplement (mean=23 yr) and evaluated consumption of one to three servings before exercise over ten weeks (Whitehead et al, 2012). While treatment assignment was blinded, the authors reported that stimulant effects of the supplement revealed treatment assignment. After ten weeks, no significant differences in any tested outcomes were noted between the DMAA and placebo groups. However, over the course of the study there was a nonsignificant increase in systolic blood pressure (6 mmHg) and decrease in diastolic blood pressure (4 mmHg) in the DMAA group. Even though the effect on systolic blood pressure was not statistically significant, the authors urged consumers with elevated blood pressure to avoid DMAA-containing supplements. Other noted changes include a statistically significant increase in creatinine levels (0.1 mg/dl) in the DMAA group and significant decreases in heart rate and alkaline phosphatase in both groups over the study period.

A fourth open label study compared two groups who ingested two servings of either OxyELITE Pro™ (N=7 men; mean age=24.9 yr) or Jack3d™ (N=4 men and 2 women; mean age=22.5 yr) once per day for two weeks (Farney et al, 2011). Common lab and vital sign values were measured at days 1 and 15. The OxyELITE Pro™ group reported significantly lower appetite and had a lower hear rate from day one to 15. The Jack3d™ group had a slight, nonsignificant rise in fasting glucose from 86.4 to 94.6 mg/dl. No other measures were significantly different across the two-week study period. Heart rate and blood pressure were also measured at 30, 60, 90, and 120 minutes post ingestion to measure acute effects of the supplements. Both supplements showed an acute increase in systolic blood pressure, diastolic blood pressure and rate pressure product over time. Four subjects on OxyELITE Pro™ dropped out of the study due to side effects including headaches, nausea, jitteriness, and sleeplessness. The authors recruited additional subjects to replace them. The authors warn that these supplements should be avoided by those with a resting blood pressure greater than or equal to 120/80 mmHg.

In another 8 week study comparing OxyELITE Pro™ to placebo, 16 young healthy subjects were randomly assigned to each group (mean age=23) and were instructed to ingest one to two capsules of treatment per day depending on tolerance of side effects. (McCarthy et al, 2012a) Blinding to treatment assignment appears likely to have been lost due to the stimulant effects of the supplement. No significant differences in outcome measures were noted for the supplement compared to placebo group except for an increase in glucose and alkaline phosphatase levels and decrease in potassium and malondialdehyde levels. Within-group comparisons over time showed that the DMAA-supplement group lost a significant amount of weight (1.9 kg), fat mass (1.2 kg), and waist circumference (2.6 cm) over two months in comparison to placebo. The supplement group also had significant increases in heart rate (7.1 bpm) and total serum cholesterol (8.4 mg/dl) that were not seen in the placebo group. Nonsignificant increases in systolic and diastolic blood pressure were noted after eight weeks in the supplement group.

Positive impacts on lipolysis noted in the previous study were also noted in a small crossover study with twelve healthy subjects (6 men mean age=24.8 and 6 women mean age=22.8) ingesting either placebo or OxyELITE Pro™ on two separate days. (McCarthy et al, 2012b) Significant increases were noted for glycerol, free fatty acids, and kilocalorie expenditure measured after two hours in the supplement compared to placebo exposure periods. However, heart rate, systolic blood pressure, and rate pressure product were also significantly increased during supplement exposure periods. The authors cautioned that it would be wise for individuals with blood pressure ≥120 mmHg to avoid use of the supplement.

Most recently, Dr Bloomer presented the results of a study of 50 young healthy men randomized into four groups, ingesting placebo (N=11; mean age=23.1), 250 mg caffeine (N=14; mean age=23.0), 50 mg DMAA (N=13; mean age=23.1), or 250 mg caffeine and 50 mg DMAA (N=12; mean age=23.6) on a daily basis for 12 weeks (Bloomer et al, in press). Sixteen subjects dropped out of the study from an initial 66. No significant changes over time were noted in the supplement groups for body mass or body composition, vital signs, common lab work, and metabolic and oxidative stress measurements. However, compared to placebo, there was a significant increase in heart rate, creatinine, and cholesterol in the DMAA plus caffeine group. There was also a significant decrease in the PR interval and P wave duration in the DMAA plus caffeine group compared to caffeine alone. Interestingly, despite randomization, the DMAA and DMAA plus caffeine group may have had better cardiovascular fitness at baseline since the DMAA groups had increased length of aerobic training history and weekly anaerobic training hours compared to the placebo group at baseline. A future paper will explore side effects or symptoms which were not described in this report. (Bloomer, personal communication)

Most of these papers were cited in reports submitted by Environ (Rodricks et al, May 2012) and Cantox (Cantox Health Sciences International; February 9, 2012) to support the position of USPLabs that these products are safe when used as directed. However these reviews do not assess the quality of the studies summarized in their reports. The Environ report reviews reported adverse events similar to those identified by the Safety Review Panel and compares them to observations from the Memphis studies. The Environ report highlights the consistent acute systolic blood pressure elevation in seven of nine cited studies. The Cantox report focuses more on the physiology literature dating into the 1940s, demonstrating the vasoconstrictor and sympathomimetic qualities of DMAA, generally much less potent and chemically different than amphetamine and epinephrine. It also draws data from the Memphis studies to demonstrate metabolic effects and safety profile. The report notes that in one of the studies comparing OxyELITE Pro™ and Jack3d™, some subjects reported jitteriness, sweating, shakiness, poor sleep quality and racing heart beat. (McCarthy et al, 2012a) The report cites a second OxyELITE Pro™ 2 week study with four men and two women. Four of the subjects dropped out because of jitteriness, nausea, inability to focus or sleeplessness. They were replaced with four other test subjects. In this study, the Jack3d™ participants did not drop out, but also reported improved focus and energy, feeling anxious, chills, tingling and fatigue. (Farney et al, 2012)

The Cantox report also reviews the various reports about the presence of DMAA in geranium oil.

b. Adverse case reports

Gee reported on four cases of stroke associated with recreational use of DMAA in New Zealand at doses up to ten times higher than recommended doses in US market ergogenic supplements. He described 21 year old and 41 year old males who each sustained basal ganglia hemorrhages. The 41 year old had a reported peak blood pressure reading of 240/120. He also reported a 23 year old female who developed hypertension (185/100) and a right frontal subarachnoid hemorrhage following the ingestion of two "party pills", likely containing up to 600 mg of DMAA. A 36 year old male sustained a right intraparenchymal hemorrhage. DMAA levels ranged from 0.76 mg/l to 2.31 mg/l, up to 100 times higher than levels observed in the Soldiers who died in the Southwestern United States. Some of the subjects in Gee's reports had concomitant use of large quantities of alcohol and caffeine. (Gee, 2011, 2012)

Young reported a nonfatal right midbrain thalamic stroke in 26 year old Active Duty male using Jack3d™ who was serving in Afghanistan. (Young, 2012) The Service member had been using DMAA-containing product for about three weeks and had stopped smoking a week before the event. He was diagnosed with a Dejerine-Roussy Syndrome type of lacunar thalamic stroke with hemidysesthesia and weakness and blurred vision and impaired accommodation in his left eye. Salinger described a 24 year old male who developed hypertension and acute heart failure of the Takotsubo type one hour after ingestion of Jack3d™. (Salinger et al, 2011) He required intensive care and endotracheal intubation and ventilation for a short interval to treat associated pulmonary edema. His echocardiogram showed transient apical akinesis with an ejection fraction of less than 20%. He presented with blood pressure of 180/100 and tachycardic with a heart rate of 130. His hospitalization was prolonged due to delirium, but following his discharge, a follow-up echocardiogram was normal. He reportedly worked for a distributor of Jack3d™, and he frequently used more product than recommended in order to achieve a more pronounced effect.

McDermott reported a transient papillary mydriasis in a 20 year old female Marine who rubbed her eye after mixing Jack3d™. The dilatation did not respond to pilocarpine challenge, and she recovered without sequelae. (McDermott, 2012) Armstrong reported an episode of transient atrial fibrillation with rapid ventricular response in an otherwise well 32 year old Special Operations Sailor, a case that is included among our forty adverse medical event reports. He had used the product for one week and then had stopped for one week. He had just resumed the use of the product when he developed the rapid irregular response. He required treatment with intravenous calcium channel blocker and beta blocker. Echocardiogram and lab studies were normal except for slightly elevated creatine kinase He made an uneventful recovery and was waivered to return to full Special Operations duty. (Armstrong, 2012)

While not specific to DMAA, Eckart, Gentlesk and Shry evaluated a population of 905 Service members who developed syncope or palpitations while deployed to Iraq and Afghanistan between January 2005 and October 2007. They found that 9.2% reported use of ergogenic or stimulant dietary supplements. Their mean age was 29.5 years. They identified atrial fibrillation or flutter in 29, premature vascular contractions in 27, premature atrial contractions in 9, and supraventricular tachycardia in 18. They noticed that Service members over 30 tended to have more significant systolic blood pressure elevations. Tachycardia was more common in those under 30 years of age: 35% of them experienced tachycardia, compared with 11.4% of those over 30. (Eckart, 2010)

5. Phase I b: DoD-Reported Adverse Events
COL Ted Cieslak

This section provides detail regarding Phase I of a 3-phased study of adverse clinical events temporally associated with DMAA-containing nutritional supplement use. Phase I requested and collated anecdotal reports of adverse events associated with use by Service members of DMAA-containing nutritional supplements.

In response to an initial data call, 50 potential cases of adverse medical events associated with DMAA-containing supplement use were reported to our investigative team. An exhaustive reconciliation process excluded duplicated and inappropriate reports, ultimately resulting in 40 cases with discreet, bona fide exposures associated with adverse events. The fortieth case was added following the death of a fourth Soldier with positive DMAA assay in the blood. (See Annex E)

We made initial contact with the reporting physician in each of the 39 early cases; in 31 of these, the physician was able to provide additional information, beyond that offered in the original report. A provider survey, constructed by experts at Army Public Health Command and sent to all reporting physicians, was returned in 27 of the cases. In two cases, the provider furnished some information, but declined to complete a full survey. In eight cases initially (ultimately in ten), patient contact information was available to enable a second survey instrument to be administered orally to the patient by a Public Health Command scientist.

Ten of the reported cases were provided by CDR Richard Sams of the U.S. Naval Hospital at Jacksonville FL and emanated from an epidemiologic study of supplement use that he and his colleagues conducted. While CDR Sams provided extraordinary input into our investigative efforts, the anonymous nature of his study precluded a determination of patient identities.

Of the 39 initial cases, three involved fatality: two heat injuries with rhabdomyolysis and hepatic injury and one Soldier with myocardial infarction. Of the remaining 36 cases, five additional patients sustained heat injury and/or rhabdomyolysis. Four each developed seizures or syncope, and four had tachycardia or palpitations. Four additional cases had hypertensive crises and/or cerebrovascular events, Three Service members developed paresthesias. Two Service members developed hepatic failure with no other apparent contributing factor, and two additional Service members developed renal failure.

The Naranjo algorithm (Naranjo et al, 1981 and at ANNEX F) was applied to 17 cases wherein adequate information was available. Both cases of hepatic failure had biopsy-proven cholestatic injury consistent with a drug-induced process. Neither was receiving any prescribed medication at the time they developed hepatic disease. In both cases, the attending gastroenterologist felt that the liver injury and pathologic findings could be explained only by exposure to a ‘drug’. In these instances, the only identified exposure was to DMAA. Each of these patients scored “6” on the Naranjo Scale (5-8 denoting a

‘probable’ association between drug and adverse event [0 = doubtful; 1-4 = possible; 9+ = definite]). In addition, there was one case of renal failure: a biopsy-proven Acute Tubular Necrosis (ATN) with no other known causes. The attending nephrologists believed that the kidney injury and pathologic findings could be explained only by exposure to a ‘drug’ which was Jack3d™ and was given a Naranjo Scale of 4.

Although no other case scored greater than a “4”, this lack of an association can be explained by the criteria for Naranjo Scales: if any alternative potential cause exists, it is accepted as the explanation. All three fatality cases occurred after exercise, and two were attributed to heat injury. It is well established that metabolic heat production increases when caffeine is combined with other stimulants. However, a heat stroke attribution would exclude any other possible explanation, regardless of the possible contribution of stimulants in supplements. Virtually all remaining cases had a score in the 2-4 range.

The Naranjo Scale has serious limitations with adverse events associated with dietary supplement research. A score of 9 or more would require three of the following conditions: 1) a dose-response demonstration, 2) a challenge/re-challenge to show that the same response can be elicited upon re-challenge; 3) a placebo effect, and 4) a previous patient experience. None of these are either possible or plausible in the case of death, liver failure or kidney damage. The Naranjo scoring of all DMAA cases is likely low because of an ethical inability to conduct repeated challenges, a lack of information on "toxic" versus "safe" doses of DMAA, a lack of known dose-response paradigm, lack of an antagonist, and lack of biopsy correlation except in the two hepatic cases.

The U.S. Preventive Services Task Force (August 1989) provides a method for stratifying both the "quality of evidence” as well as the ”recommendation for (or against) a clinical service”, based upon a risk/benefit analysis. Current anecdotal adverse event report evidence linking DMAA exposure to adverse clinical events is Level III (“expert opinion” and descriptive studies) in nature, justifying a Level D clinical recommendation (risk outweighs potential benefit).

6. Phase II a: In-depth Interviews of Service Members with Adverse Events Dr Theresa Jackson

This report provides a summary of results from patient interviews conducted by the U.S. Army Public Health Command (USAPHC) among Service Members who have experienced Adverse Medical Events (AMEs) potentially associated with 1,3 dimethylamylamine (DMAA) use.

In December 2011, the Department of Defense placed a temporary ban on dietary supplements/pre-workout products containing DMAA after two deaths and other AMEs among Service Members were potentially associated with their use. USAPHC was tasked to conduct a public health investigation of the potential association of DMAA use with AMEs.

From December 2011 to January 2012, Office of the Surgeon General Consultants surveyed providers who had previously reported cases of patients experiencing AMEs they believe may have been associated with dietary supplement use and provided the survey results to USAPHC (n=24). Of those, eight (33.3%) providers offered adequate information to contact the patient directly. In January-February 2012, USAPHC conducted structured interviews with seven of these eight Service Members. Three additional Service Members self-referred to be interviewed when they learned of the investigation. All interviews (*N*=10) consisted of 50 questions and lasted 30 minutes. A detailed summary of interview results is provided at ANNEX G.

The interview sample was largely Caucasian (n=6), enlisted (n=9), and male (n=9). Service Members from the Air Force (n=3), Marines (n=2), and Army (n=5) participated. The age of interviewees ranged from 20 to 39 years (mean: 29.5). Eight interviewees reported experiencing their AME between March and December 2011, and two interviewees reported experiencing their AME between July and September 2012. Four reported their AME occurred while deployed. The majority of interviewees (n=9) were overweight according to Body Mass Index (BMI) standards (BMI $\geq$ 25), including three whose BMI would classify them as obese (BMI $\geq$ 30). When asked about their most recent military physical fitness test (PFT) performance, of those who remembered their score (n=7), all performed well (Army/Marine PFT score > 280 out of 300, Air Force PFT score > 95 out of 100).

All interviewees reported using DMAA-containing dietary supplements within the 3 months prior to their AME. The majority (n=6) reported consuming DMAA within 24 hours of their AME, and one reported consuming DMAA within 48 hours of his event. Two interviewees reported stopping use of DMAA prior to their AME, one because he began using another non-DMAA containing supplement, and one because he was experiencing negative symptoms as a result of consuming the product.

Interviewees' self-reported length of DMAA use ranged from 3 days to 12 months, and nearly all (n=9) reported taking DMAA an average of at least 4 times per week. The most commonly cited reasons for consuming pre-workout products or energy boosters

included: to provide extra energy (n=9) to improve physical performance (n=9), and to enhance muscle building (n=8).

The AMEs for which interviewees received care included liver injury (n=2), rhabdomyolysis (n=2), cardiac symptoms (n=2), seizure (n=2), lactic acidosis (n=1), and urinary complications (n=1). When asked about specific symptoms they experienced prior to or at the time of their AME, interviewees most frequently indicated dizziness (n=9), rapid heart rate (n=9), tingling or numbness (n=7), and shortness of breath (n=6). The two interviewees seen for liver complications both noted experiencing a variety of symptoms for weeks prior to presentation to a medical provider.

The majority of interviewees (n=8) reported missed or limited duty as a result of their AME. The number of days to fully recover ranged from 1 to 150 (mean: 46 days). All but two interviewees reported their health has returned to its prior status, and those reporting liver injury reported the longest recovery times.

Self-reported levels of alcohol consumption were very low among all interviewees; however, the majority (n=7) were tobacco users at the time of their AME. Three interviewees reported taking prescription medications at the time of their AME, two of whom were taking Trazodone. The majority of interviewees (n=8) reported obtaining 5.5 or less hours of sleep per night on average at the time of their AME. Seven of the ten reported taking additional dietary supplements or energy boosters in addition to the DMAA-containing products, the most common of which was 5-hour Energy, a practice contrary to DMAA product labels which caution against the use of the products with other stimulants, including caffeine.

All interviewees perceived that consumption of DMAA-containing products was related to their AMEs and reported serious side effects that caused them significant discomfort. One interviewee noted he thought the products were addictive. All interviewees had stopped using these products since their AME. One interviewee commented on DMAA supplements, “with these supplements, it is not clearly outlined what is considered a safe use of the product.”

No clear patterns emerged regarding environmental conditions, specific activity conducted, or perceived level of physical activity immediately prior to the AMEs. Conclusions are limited because of the small sample size, variation across responses, and potential confounders. A causal relationship cannot be determined between DMAA use and AMEs based on these interviews.

7. Phase II b: Review of FDA Adverse Events
COL Ted Cieslak

As part of the scientific review of adverse events associated with 1,3-Dimethlyamylamine (DMAA), FDA reports in its MedWatch system from January 2004-early March 2012 were reviewed. Over 4000 pages and nearly 40,000 reports of events linked to foods, cosmetics, and nutritional supplements were reviewed.

Early MedWatch reports included serious adverse events associated with Ephedra-containing products, with at least ten deaths. A product known as Hydroxycut was involved in most of these events. The FDA banned Ephedra from nutritionals on 12 April 2004, but court challenges and illicit sources allowed for continuing access to Ephedra-containing products.

Despite the removal of ephedra from Hydroxycut, reports of adverse events continued. Roughly 800 serious adverse events (11 deaths, 350 cases of hepatic insufficiency or failure, and numerous cases of MI, CVA, renal failure, and rhabdomyolysis) were temporally associated with Hydroxycut use from 2009-2012, when caffeine was the only stimulant listed.

Several cases of myocardial infarction and death have been associated with other high-dose-caffeine-containing products, particularly NO Xplode™ and 5-hour Energy™ since 2009.

The first reported adverse events related to DMAA-containing products appeared in FEB 2010 with a case of seizure and shock associated with Jack3d™ and in JUL 2010 with several cases of renal failure and chest pain associated with OxyELITE Pro™. Four cases (including 1 death) were reported in 2011, and five cases (including 2 deaths, 1 CVA, and 1 case of anaphylaxis) have been reported in 2012 through early March. The 11 cases (including 3 deaths) reported by DoD in April 2012 had not yet reached the FDA database at the time of this review.

8. Phase III a: Armed Forces Medical Examiners Review
CAPT Edward Reedy, COL Timothy Lyons, LCDR Peter Seguin

The Mortality Surveillance Division (MSD) of the Armed Forces Medical Examiners maintains the military mortality registry, a searchable database of all active duty (regular and activated reserve) fatalities. In January 2012 at the request of the lead for the DoD Safety Panel, all fatalities involving exercise in which DMAA could have contributed to death, including those with a manner of death determined to be accidental, natural, or undetermined where identified. Between 7 December 2009 and 27 January 2012, there were 48 federal jurisdiction cases with samples amenable for retesting, and their identifiers were forwarded to the Forensic Toxicology Division (DFT).

After reviewing the circumstances of each case with COL Lyons, Chief, Directorate of Forensic Toxicology (DFT), additional cases in which DMAA was unlikely to have contributed to death were excluded, and the final number of samples re-tested for DMAA was 37. Of those cases tested, only two tested positive for DMAA. One was the previously reported Soldier, Case 1 below, who died at a Southwestern base, and the second was a Service member was killed while running after being struck by a car. In March 12, DoD requested the testing of cases in which the cause of death was heat stroke, acute myocardial infarction, stroke, or hepatic failure. A list of 37 potential cases with deaths between 17 January 2010 and 7 February 2012, were pulled by and forwarded to Forensic Toxicology Division, from which 34 cases were retested, and all were negative for DMAA.

The DFT pulled the blood and urine specimens for the 71 cases that were re-tested. These specimens were extracted per laboratory standard operating procedure and run by liquid chromatography-tandem mass spectrophotometry (LC-MS-MS) with a level of quantitation of 10 ng/ml. The results were then forwarded to the OTSG and the DMAA Safety Review Panel.

DEATH SUMMARIES:

Case 1 (01 June 2011): 22 year old male collapsed while running with his unit. Environmental temperature was about 70 degrees. He was new to the Southwestern base and had never performed PT with his unit previously. Taken to the Army hospital, he was in cardiac arrest, hyperthermic (105^{o}F), in disseminated intravascular coagulation (DIC) with rhabdomyolysis and metabolic acidosis. He was pronounced dead 3 hours after presentation. An autopsy was performed by the AFME on 02 June 2011. Autopsy findings included acute cerebral hypoxic/neuronal injury and microscopic evidence of DIC. Postmortem hemoglobin chromatography was normal (HgB A/A). Postmortem toxicological testing was negative for ethanol and positive for caffeine (2.9 mg/L) and DMAA (0.22 mg/L) in the blood. The cause of death was certified as HYPERTHERMIA and the manner of death was certified as ACCIDENT.

Case 2 (04 NOV 2011 – 13 December 2011): 31 year old female was running the APFT when she collapsed. Environmental temperature was about 70 degrees. She

was in cardiac arrest and taken to the Army hospital and noted to have rhabdomyolysis, lactic acidosis and hyperthermic (106^{o}F). She was resuscitated, and then transferred to a civilian university medical center for a higher level of care. While awaiting a liver transplant, the decedent expired with multi-organ system failure and sepsis approximately 6 weeks later. An autopsy was performed by local civilian authorities on 14 December 2011. Autopsy findings included obesity and necrosis of the liver and kidneys. Although reported to have sickle cell trait (HgB A/S), postmortem hemoglobin chromatography was normal (HgB A/A). Toxicological testing on admission (antemortem) was positive for caffeine (1.9 mg/L) and DMAA (0.04 mg/L) in the serum. The cause of death was certified as HYPERTHERMIA and the manner of death was certified as ACCIDENT.

Case 3 (10 February 2012): 41 year old male collapsed at the end of an 8 mile run with his unit. Bystander cardiopulmonary resuscitation was provided until EMS arrived to transport the Soldier to a local hospital where he was pronounced dead. An autopsy was performed by the AFME on 13 February 2012. Autopsy findings include obesity, coronary artery disease (critical stenosis of three vessels), aortic and iliac atherosclerosis and cardiomegaly. Postmortem hemoglobin chromatography was normal (HgB A/A). Postmortem toxicological testing was positive for doxylamine (0.08 mg/L) and DMAA (0.2 mg/L) in the blood. The cause of death was certified as ARTERIOSCLEROTIC CARDIOVASCULAR DISEASE and the manner of death was certified as NATURAL.

Case 4 (28 July 2012): 22 year old male collapsed after completing the APFT run but remained conscious for a period of time before becoming unresponsive. Environmental temperature was about 80 degrees. After transport to the Army hospital, heat stroke was suspected (102.2^{o}F) due to rhabdomyolysis and renal failure; he was admitted to the ICU where he expired less than 24 hours later. An autopsy was performed locally as A12-8 under the authority of the AFME as ME12-0449 on 30 JUL 2012. Autopsy findings include gross and microscopic changes consistent with multi-organ system failure. Postmortem hemoglobin chromatography was consistent with sickle cell trait (HgB A/S). Postmortem toxicological testing was positive for DMAA (0.026 mg/L) in the blood. The cause of death was certified as CARDIAC ARRHYTHMIA LEADING TO CARDIAC ARREST AND MULTI-ORGAN SYSTEM FAILURE and the manner of death was certified as NATURAL.

Conclusions and Opinion:

All of the cases summarized above occurred following physical exertion. Three of the four deaths above occurred in the Southwestern region of the United States where high temperatures are common at most times of the year. The fourth death occurred in the Pacific region. The cause of death in two of these four cases was certified as hyperthermia, and there was a strong clinical suspicion of heat injury in a third at a Southwestern base (DA/0501). Two deaths (Case 1 and Case 2) are clearly due to complications of hyperthermia and have well-documented elevated admission core temperatures. Case 3 had severe coronary artery disease, and Case 4 had both

elevated core temperature and sickle cell trait. Sickle cell trait is well known to be a significant cause of morbidity during a state of physical exertion and dehydration. Efforts should be directed at appropriate acclimatization of individuals to the heat at the Southwestern base prior to strenuous unit physical exercise. Adequate hydration should also be encouraged for all individuals, especially those who are sickle trait positive.

Although DMAA was detected in the blood of all four cases, the blood concentrations ranged from 0.026 – 0.22 mg/L. A recent study by Gee *et al.* (2012, Ann Emerg Med, in press) compared DMAA levels in three living patients with cerebral hemorrhage after ingesting DMAA-containing compounds, and the DMAA blood levels ranged from 0.76 mg/L to 2.31 mg/L. These levels are four to 100 times higher than those measured in the four cases above.

The lack of significantly elevated blood levels of DMAA in these cases suggests that it is unlikely that DMAA played a significant role in these four deaths.

9. Phase III b: Epidemiology of Non-Fatal Adverse Events: A Case-Control Study

Dr Bruce Jones, Ms Esther Dada

On 13 January 2012, the Assistant Secretary of Defense for Health Affairs (ASD/HA) requested that the Army Surgeon General lead a three-phased scientific effort to "better understand any potential relationship between DMAA and adverse [health] events." This scientific effort was intended to help determine appropriate future steps with regard to DoD policy and guidance surrounding the sales and use of DMAA within the U.S. Military. The Army Surgeon General asked U.S. Army Public Health Command (USAPHC) to design a study to assess the possible association between adverse health effects and consumption of DMAA-containing products.

As part of the Phase III safety review, the USAPHC designed a population-based, case-control study that built upon the work and lessons learned from scientific literature review and military medical provider surveys of suspected DMAA-related adverse events in Phase I and subsequent structured patient interviews in Phase II. This chapter summarizes results of the Phase III case-control study to provide information regarding the association between self-reported DMAA consumption and adverse medical outcomes among Soldiers in 2011.

1. Summary of Key Findings.

a. No statistically significant association was observed between self-reported DMAA use one or more times during the year examined and selected adverse medical events (AMEs) after controlling for relevant factors. Separate analyses of specific adverse medical outcomes, including cardiac dysrhythmia, heat injury, seizure, and rhabdomyolysis, similarly showed no statistically significant association with self-reported DMAA use.

b. However, the study did find that among those Service members who had experienced an adverse medical outcome (cases), those with multiple adverse outcomes in 2011 were more than twice as likely to have reported using DMAA in the same year. The study also found that among cases who used the products for more than 80 days, the likelihood of having multiple adverse events was 3.5-fold higher than among those who had not used DMAA products.

c. Data from this study suggest larger, more in-depth studies are needed to examine the effects of frequency and amount of DMAA use on risk of adverse medical outcomes.

d. This study found a number of factors other than DMAA that were strongly associated with selected AMEs.

(1) Prior history of any one of the AMEs was associated with an almost 18-fold increased risk of experiencing a current AME. The strongest predictor of adverse

medical outcomes was prior history of AME, suggesting the importance of prevention strategies to reduce the reoccurrence of adverse outcomes.

(2) Prescription antidepressant use was also strongly associated with experiencing an AME, with users at an almost 3-fold higher risk of having an AME than non-users.

(3) Combat deployment in 2011 appeared to be protective, possibly due to a healthy soldier effect.

2. Methods.

a. This epidemiological case-control study examined the relationship between the use of DMAA-containing supplements and other potential risk factors, and risk of experiencing certain adverse medical outcomes (including cardiac dysrhythmia, seizure, heat injury, rhabdomyolysis, cerebral hemorrhage, acute and subacute necrosis of liver, and acute kidney failure) among U.S. Army Soldiers. The study was determined to be public health practice by the USAPHC Public Health Review Board (PHRB) and conducted in accordance with the PHRB-approved protocol.

b. Data Sources. The primary sources of data included abstraction of medical and pharmacy records from the Defense Medical Surveillance System (DMSS) and Pharmacy Data Transaction Service. DMAA use and information on other potential risk factors were reported on a structured questionnaire.

c. Rationale for Study Design.

(1) As a basis for planning, a USAPHC team identified key AMEs based on reported cases and expert opinion for the purpose of determining the background rates of the most serious health events potentially associated with DMAA. The AMEs identified were cardiac dysrhythmias, heat injuries, seizures, rhadomyolysis, acute kidney failure, cerebral hemorrhage and acute/subacute liver failure. The rates of occurrence for the most common adverse events, cardiac dysrhythmias and heat injuries, were between 4 and 5 events per 1,000 Soldiers per year; for liver failure, cerebral hemorrhage, and kidney failure the rates were less than 0.5 per 1,000 Soldiers per year.

(2) In a teleconference on 24 January 2012, scientists from the USAPHC and the U.S. Army Research Institute of Environmental Medicine (USARIEM) decided that in order to achieve adequate statistical power, the sample size for a public health field investigation should be large enough to detect outcome rates in DMAA users 1.5 times higher than non-users. It was also assumed that at least 10 to 20% of Soldiers use DMAA-containing supplements and that background rates of adverse health events are 5 per 1,000 per year. Based on these assumptions, the group determined that a minimum of 3,000 participants would be needed for a case-control study design, and that a cohort or cross-sectional study design would require 30,000 to 50,000

participants. It was unanimously agreed that a case-control design was the most efficient approach. Approximating survey response rates at 40-60%, the group estimated 6,000 to 7,000 Soldiers would need to be contacted in order to achieve the required sample size of 3,000.

d. Study Population. The study population was comprised of active duty Army Soldiers who received treatment at a military medical facility or outsourced healthcare provider between 1 January 2011 and 31 December 2011, and who were stationed at one of twenty-one identified Army installations for study at the time of sample selection.

e. Case Selection. Potential cases were identified as Army patients with: (1) a hospital diagnosis of relevant *International Classification of Diseases, Ninth Revision, Clinical Modification* codes for cardiac dysrhythmia (427.XX), heat injury (992.0-992.7), seizure (780.39), rhabdomyolysis (728.88), cerebral hemorrhage (430.XX, 431.XX, 432.XX), acute/subacute necrosis of liver (570.XX), and/or acute kidney failure (584.XX), during calendar year (CY) 2011 or (2) a minimum of two primary ambulatory diagnoses of one of the selected adverse medical outcomes during CY 2011.

f. Control Selection. Potential controls had no reported medical diagnosis of any of the selected adverse medical outcomes during CY 2011.

g. Sample. The Armed Forces Health Surveillance Center drew the case-control sample of 6,881 Soldiers from the DMSS in May 2012. All potential cases were included in the sample. Controls were randomly selected to proportionately match cases by Army installation.

h. Data Collection.

(1) USAPHC, in consultation with USARIEM and other collaborators, designed the Soldier Health and Supplement Use Questionnaire to assess exposures to supplements and products containing DMAA. The multi-disciplinary team of epidemiologists; clinical researchers; and health promotion, nutrition, and exercise physiology experts addressed other factors potentially associated with AMEs in the questionnaire, including level of physical activity and fitness; substance use (i.e., caffeine, tobacco, and alcohol); prescription/over-the-counter medication use; and sleep. The questionnaire was pilot-tested with two small focus groups of Active Duty Army Soldiers.

(2) USAPHC employed a multimodal data collection process consisting of three stages that took place during June to December 2012:

- Stage I: *Electronic questionnaire delivery*. Soldiers identified to participate in the study were emailed a secured link to the USAPHC web-based questionnaire for completion.
- Stage II: *Mailing of paper questionnaires*. For Soldiers not responding to the

electronic questionnaire, paper questionnaires were mailed to their physical home of record. Soldiers had the option of completing the survey electronically or hard copy with return mail.

- Stage III: *Hand delivery of paper questionnaires*. Installation preventive medicine personnel made available paper questionnaires to Soldiers who had not previously responded. During this phase, Soldiers continued to have the option of completing the survey electronically.

i. Statistical Analysis.

(1) Conditional logistic regression was used to compute odds ratios and 95 percent confidence intervals. Bivariate relationships were explored between selected adverse medical outcomes and each of the various covariate measures that were tested for inclusion in the analysis models as predictors. Significant predictors of self-reported DMAA use were also retained in the final models. DMAA use was assessed both as a dichotomous variable (i.e., Yes/No in 2011) and as a multilevel categorical variable (i.e., <40, 40-79, and 80+ self-reported days of DMAA consumption in 2011). Sixteen additional potential covariates were identified for the bivariate analysis, including sex, age, race/ethnicity, education, rank, body mass index, prior history of AME, resistance training activity, aerobic physical activity, caffeine exposure, alcohol exposure, tobacco exposure, smokeless tobacco exposure, combat deployment, antidepressant drug prescription, and central nervous system stimulant drug prescription.

(2) Multivariate logistic regression was performed to examine associations between risk of AMEs and DMAA use in addition to other potential factors. Multivariate analyses were also conducted separately on the most prevalent specific AMEs (cardiac dysrhythmias, heat injury, seizure, and rhabdomyolysis) to determine the association of each of these outcomes and self-reported DMAA use. All statistical analyses were performed using SAS 9.1.3 (Cary, NC, USA).

(3) A subanalysis of cases was performed to assess the relationship between number of adverse medical outcomes (1 and 2 or more outcomes) in CY 2011 and DMAA use in the same year.

(4) Statistical significance was set at $p < 0.05$.

3. Results. Of the 3,944 Soldiers eligible to participate in the study, 1,789 Soldiers (45.4%) completed the questionnaire. The response rates for cases (46%) and controls (45%) were similar.

- Table 2 shows selected characteristics of cases and controls among respondents.

- Cases had nearly 2 times the odds of being 50 years of age and older, compared to controls (OR: 1.77, 95% CI: 1.10, 2.86).

- Cases were less likely to be Hispanic or Latino compared to controls (OR: 0.70, 95% CI: 0.50, 0.96).

- Additionally, cases had more than 17 times the odds of having a prior history of an AME compared to controls (OR: 17.35, 95% CI: 10.41, 28.93).

Table 2: Selected Characteristics of Cases and Controls among Respondents

Characteristic		Total n (%)	Case n (%)	Control n (%)	Unadjusted OR (95% CI)	p value
Total Respondents		1,789 (100.0)	712 (39.8)	1,077 (60.2)	-	-
Sex	Male	1,487 (83.1)	594 (83.4)	893 (82.9)	1.04 (0.81, 1.34)	0.78
	Female	302 (16.9)	118 (16.6)	184 (17.1)	1.0 (referent)	
Age	Less than 20	20 (1.1)	10 (1.4)	10 (0.9)	1.60 (0.66, 3.89)	**0.04**
	20 to 29	675 (37.7)	260 (36.5)	415 (38.5)	1.0 (referent)	
	30 to 39	626 (35.0)	233 (32.7)	393 (36.5)	0.95 (0.76, 1.18)	
	40 to 49	392 (21.9)	169 (23.7)	223 (20.7)	1.21 (0.94, 1.56)	
	50+	76 (4.2)	40 (5.6)	36 (3.3)	1.77 (1.10, 2.86)	
Race/ Ethnicity	White	1,119 (62.5)	462 (64.9)	657 (61.0)	1.0 (referent)	0.15
	Black	346 (19.3)	136 (19.1)	210 (19.5)	0.92 (0.72, 1.18)	
	Hispanic or Latino/a	192 (10.7)	63 (8.9)	129 (12.0)	0.70 (0.50, 0.96)	
	Other	92 (5.1)	34 (4.8)	58 (5.4)	0.83 (0.54, 1.29)	
	Unknown	40 (2.2)	17 (2.4)	23 (2.1)	-	
Education Level	High School Graduate or less	338 (18.9)	139 (19.5)	199 (18.5)	1.0 (referent)	0.83
	Some College	637 (35.6)	247 (34.7)	390 (36.2)	0.91 (0.69, 1.19)	
	Associate Degree	184 (10.3)	73 (10.3)	111 (10.3)	0.94 (0.65, 1.36)	
	Bachelor Degree	389 (21.7)	162 (22.8)	227 (21.1)	1.02 (0.76, 1.37)	
	Graduate Degree	241 (13.5)	91 (12.8)	150 (13.9)	0.87 (0.62, 1.22)	
Rank	E1-E4	520 (29.1)	210 (29.5)	310 (28.8)	0.92 (0.65, 1.30)	0.87
	E5-E6	521 (29.1)	204 (28.7)	317 (29.4)	0.87 (0.62, 1.23)	
	E7-E9	272 (15.2)	108 (15.2)	164 (15.2)	0.89 (0.61, 1.31)	
	W1-W5	66 (3.7)	22 (3.1)	44 (4.1)	0.68 (0.38, 1.22)	
	O1-O3	231 (12.9)	92 (12.9)	139 (12.9)	0.90 (0.60, 1.33)	
	O4-O9	179 (10.0)	76 (10.7)	103 (9.6)	1.0 (referent)	

Table 2: Selected Characteristics of Cases and Controls among Respondents (continued)

Characteristic		Total n (%)	Case n (%)	Control n (%)	Unadjusted OR (95% CI)	p value
Total Respondents		1,789 (100.0)	712 (39.8)	1,077 (60.2)	-	-
Body Mass Index (BMI)	Below 24.9	428 (23.9)	168 (23.6)	260 (24.1)	1.0 (referent)	0.29
	25.0 – 29.9	835 (46.7)	329 (46.2)	506 (47.0)	1.01 (0.79, 1.28)	
	30.0 and Above	352 (19.7)	155 (21.8)	197 (18.3)	1.22 (0.92, 1.62)	
	Unknown	174 (9.7)	60 (8.4)	114 (10.6)	-	
Prior History of Adverse Medical Event (AME)	Yes	172 (9.6)	155 (21.8)	17 (1.6)	17.35 (10.41, 28.93)	**<0.01**
	No	1,617 (90.4)	557 (78.2)	1,060 (98.4)	1.0 (referent)	

OR, odds ratio; CI, confidence interval. Prior history of adverse medical event (AME) experienced prior to the study period, calendar year 2011.
Bold values indicate statistical significance with a p-value from chi-square test less than 0.05.

- Table 3 shows selected exposure characteristics of cases and controls among respondents.

- Cases were statistically significantly different from controls at almost all levels of reported aerobic physical activity, where cases were less likely to engage in high (OR: 0.59, 95% CI: 0.44, 0.78) and very high (OR: 0.62, 95% CI: 0.46, 0.82) levels of aerobic physical activity than controls.

- Cases were statistically significantly less likely to consume very high levels of caffeine (OR: 0.73, 95% CI: 0.56, 0.95).

- Like caffeine, very high levels of alcohol consumption was less likely among cases as compared to controls (OR: 0.74, 95% CI: 0.56, 0.99).

- Deployment exposure was statistically significantly different between cases and controls: cases had lower odds of being deployed to a combat zone in 2011 (OR: 0.49, 95% CI: 0.39, 0.61) compared to controls.

- Cases appeared to have lower odds of being a current or former smoker, although this effect was only statistically significant for former smokers (OR: 0.62, 95% CI: 0.39, 0.99).

- Differences seen between cases and controls regarding prescription drug use were statistically significant, with cases having nearly 3 times the odds of using antidepressant prescription drugs (OR: 2.75, 95% CI: 2.12, 3.57), and nearly 2.5 times the odds of using CNS stimulant prescription drugs (OR: 2.43, 95% CI: 1.17, 5.04).

Table 3: Exposure Characteristics of Cases and Controls among Respondents

Characteristic		Total n (%)	Case n (%)	Control n (%)	Unadjusted OR (95% CI)	p value
Total Respondents		1,789 (100.0)	712 (39.8)	1,077 (60.2)	-	-
Physical Activity Exposure Characteristics						
Resistance Training Activity Exposure (1000 mins/week)	Very High	570 (31.9)	202 (28.4)	368 (34.2)	0.78 (0.60, 1.02)	0.06
	High	285 (15.9)	126 (17.7)	159 (14.8)	1.13 (0.83, 1.54)	
	Moderate	231 (12.9)	94 (13.2)	137 (12.7)	0.98 (0.70, 1.36)	
	Low	390 (21.8)	161 (22.6)	229 (21.3)	1.0 (referent)	
	Unknown	313 (17.5)	129 (18.1)	184 (17.1)	-	
Aerobic Physical Activity Exposure (MET-1000 mins/week)	Very High	427 (23.9)	153 (21.5)	274 (25.4)	0.62 (0.46, 0.82)	**<0.01**
	High	455 (25.4)	158 (22.2)	297 (27.6)	0.59 (0.44, 0.78)	
	Moderate	357 (20.0)	146 (20.5)	211 (19.6)	0.76 (0.57, 1.03)	
	Low	366 (20.5)	174 (24.4)	192 (17.8)	1.0 (referent)	
	Unknown	184 (10.3)	81 (11.4)	103 (9.6)	-	
Caffeine and Alcohol Exposure Characteristics						
Caffeine Exposure (100 mg/day)	Very High	448 (25.0)	163 (22.9)	285 (26.5)	0.73 (0.56, 0.95)	0.12
	High	449 (25.1)	173 (24.3)	276 (25.6)	0.80 (0.61, 1.04)	
	Moderate	445 (24.9)	179 (25.1)	266 (24.7)	0.85 (0.66, 1.11)	
	Low	447 (25.0)	197 (27.7)	250 (23.2)	1.0 (referent)	
Alcohol Exposure in 2011	Very High	366 (20.5)	137 (19.2)	229 (21.3)	0.74 (0.56, 0.99)	0.14
	High	396 (22.1)	155 (21.8)	241 (22.4)	0.80 (0.61, 1.05)	
	Moderate	551 (30.8)	213 (29.9)	338 (31.4)	0.78 (0.61, 1.01)	
	Low	444 (24.8)	198 (27.8)	246 (22.8)	1.0 (referent)	
	Unknown	32 (1.8)	9 (1.3)	23 (2.1)	-	
Tobacco Exposure Characteristics						
Tobacco Exposure in 2011	Current Smoker	455 (25.4)	177 (24.9)	278 (25.8)	0.89 (0.71, 1.11)	0.09
	Former Smoker	91 (5.1)	28 (3.9)	63 (5.9)	0.62 (0.39, 0.99)	
	Never Smoked	1,105 (61.8)	461 (64.8)	644 (59.8)	1.0 (referent)	
	Unknown	138 (7.7)	46 (6.5)	92 (8.5)	-	

Table 3: Exposure Characteristics of Cases and Controls among Respondents (continued)

Characteristic		Total n (%)	Case n (%)	Control n (%)	Unadjusted OR (95% CI)	p value
Total Respondents		1,789 (100.0)	712 (39.8)	1,077 (60.2)	-	-
Tobacco Exposure Characteristics						
Smokeless Tobacco Exposure in 2011	Current User	265 (14.8)	106 (14.9)	159 (14.8)	0.98 (0.75, 1.28)	0.85
	Former User	62 (3.5)	23 (3.2)	39 (3.6)	0.86 (0.51, 1.46)	
	Never Used	1,308 (73.1)	531 (74.6)	777 (72.1)	1.0 (referent)	
	Unknown	154 (8.6)	52 (7.3)	102 (9.5)	-	
Combat Deployment Exposure Characteristics						
Any Combat Deployment Exposure in 2011	Yes	544 (30.4)	154 (21.6)	390 (36.2)	0.49 (0.39, 0.61)	**<0.01**
	No	1,230 (68.8)	551 (77.4)	679 (63.1)	1.0 (referent)	
	Unknown	15 (0.8)	7 (1.0)	8 (0.7)	-	
Prescription Drug Exposure Characteristics						
Anti-depressant Prescription Drug Exposure in 2011	Yes	282 (15.8)	171 (24.0)	111 (10.3)	2.75 (2.12, 3.57)	**<0.01**
	No	1,507 (84.2)	541 (76.0)	966 (89.7)	1.0 (referent)	
CNS Stimulant Prescription Drug Exposure in 2011	Yes	31 (1.7)	19 (2.7)	12 (1.1)	2.43 (1.17, 5.04)	**0.02**
	No	1,758 (98.3)	693 (97.3)	1,065 (98.9)	1.0 (referent)	

OR, odds ratio; CI, confidence interval; DMAA, 1,3-dimethylamylamine; MET, metabolic equivalent; CNS, central nervous system.

Resistance training activity exposure (1000 min/week): very high (≥ 0.1575); high (0.0675-0.1574); moderate (0.0225-0.0674); and low (< 0.0225). Aerobic physical activity exposure: (MET-1000 min/week): very high (≥2.310); high (1.530-2.309); moderate (0.810-1.529); and low (< 0.810). Caffeine exposure (100 mg/day): very high (≥3.09); high (1.45-3.08); moderate (0.44-1.44); and low (< 0.44). Alcohol exposure represents an index score based on self-reported frequency of alcohol use in 2011, amount of alcohol use per occurrence in 2011, and frequency of consumption of 6 or more alcoholic beverages on one occasion in 2011: very high (>5), high (3 to 4), moderate (1 to 2), or low (0).

Bold values indicate statistical significance with a p-value from chi-squared test less than 0.05.

- Tables 4 and 5 show the association between DMAA use (as dichotomous and in multiple exposure levels) and adverse medical outcomes, both unadjusted and controlling for sex, age, BMI, prior history of AME, number of months deployed in 2011, alcohol exposure in 2011, resistance training activity, antidepressant use in 2011, and caffeine exposure, which was retained only in the models with DMAA multiple exposure levels.

- Soldiers reporting DMAA use in 2011 had almost 40% lower odds of having an adverse medical outcome (crude OR: 0.63, 95% CI: 0.47, 0.84), though this effect diminished and lost statistical significance when adjusting for covariates (adjusted OR: 0.85, 95% CI: 0.59, 1.23) (Table 4B).

- Cases were less likely than controls to consume DMAA at different levels of exposure: 40-79 days of use (crude OR: 0.61, 95% CI: 0.38, 0.99) and 80+ days of use (crude OR: 0.63, 95% CI: 0.40, 1.00), though the effect lost statistical significance when adjusting for covariates, (adjusted OR: 0.73, 95% CI: 0.41, 1.30) and (adjusted OR: 1.02, 95% CI: 0.58, 1.81), respectively (Table 5B).

- Having a prior AME history greatly increased the odds of having a current AME, almost an 18-fold higher risk (adjusted OR: 17.86, 95% CI: 9.60, 33.22) (Table 4A).

- Deploying more months in 2011 was associated with lower odds of an adverse medical outcome (adjusted OR: 0.88, 95% CI: 0.84, 0.92) (Table 4A).

- Being prescribed antidepressants was associated with almost 3 times the odds of an adverse medical outcome (adjusted OR: 2.75, 95% CI: 1.96, 3.87) (Table 4A).

Table 4A: Final Multivariate Logistic Regression Model to Assess the Association between Self-Reported DMAA Exposure and Adverse Medical Outcomes

Characteristic	OR	95% CI	p value	
DMAA Exposure in 2011 (adjusted)	0.85	(0.59, 1.23)	0.39	
Sex (Male:Female)	0.73	(0.51, 1.03)	0.07	
Age	0.98	(0.97, 1.00)	0.05	
Body Mass Index (BMI) grouping	1.02	(0.85, 1.22)	0.87	
Prior history of adverse medical event (AME)	17.86	(9.60, 33.22)	**<0.01**	**<0.01**
Number of months deployed to a Combat Zone (OEF/OIF/OND) in 2011	0.88	(0.84, 0.92)	**<0.01**	
Alcohol Exposure in 2011	0.96	(0.91, 1.01)	0.08	
Resistance Training Activity Exposure	0.95	(0.38, 2.38)	0.92	
Antidepressant Prescription Drug Exposure in 2011	2.75	(1.96, 3.87)	**<0.01**	

DMAA, 1,3-dimethylamylamine; OR, odds ratio; CI, confidence interval; OEF, Operation Enduring Freedom; OIF, Operation Iraqi Freedom; OND, Operation New Dawn.
Sex, Body Mass Index, Alcohol Exposure in 2011, and Resistance Training Activity Exposure were retained in the model as these factors were significant predictors in the DMAA exposure model.
Bold values indicate statistical significance with a p-value less than 0.05.

Table 4B: Association between Self-Reported DMAA Exposure and Adverse Medical Outcomes

Characteristic		Total n (%)	Case n (%)	Control n (%)	Unadjusted		Adjusted	
					OR (95% CI)	p value	OR (95% CI)	p value
Total Respondents		1,789 (100.0)	712 (39.8)	1,077 (60.2)	-	-	-	-
DMAA Use in 2011								
DMAA Use	Yes	239 (13.4)	73 (10.3)	166 (15.4)	0.63 (0.47, 0.84)	**<0.01**	0.85 (0.59, 1.23)	0.39
	No	1,545 (86.4)	638 (89.6)	907 (84.2)	1.0 (referent)	-	1.0 (referent)	-
	Unknown	5 (0.3)	1 (0.1)	4 (0.4)	-	-	-	-

DMAA, 1,3-dimethylamylamine; OR, odds ratio; CI, confidence interval.
Model adjusts for Sex, Age, Body Mass Index, Prior history of adverse medical event (AME), Number of months deployed to a Combat Zone (OEF/OIF/OND) in 2011, Alcohol Exposure in 2011, Resistance Training Activity Exposure, and Antidepressant Prescription Drug Exposure in 2011.
Bold values indicate statistical significance with a p-value less than 0.05.

Table 5A: Final Multivariate Logistic Regression Model to Assess the Association between Self-Reported DMAA Exposure Levels and Adverse Medical Outcomes

Characteristic	OR	95% CI	p value	
DMAA Exposure Levels in 2011 (adjusted)	0.96	(0.82, 1.14)	0.66	**<0.01**
Sex (Male:Female)	0.72	(0.51, 1.02)	0.06	
Age	0.98	(0.97, 1.00)	0.05	
Body Mass Index (BMI) grouping	1.03	(0.85, 1.24)	0.77	
Prior history of adverse medical events (AME) as documented from medical encounter records	17.88	(9.60, 33.28)	**<0.01**	
Number of months deployed to a Combat Zone (OEF/OIF/OND) in 2011	0.88	(0.84, 0.92)	**<0.01**	
Caffeine Exposure	0.99	(0.96, 1.02)	0.37	
Alcohol Exposure in 2011	0.95	(0.91, 1.00)	0.07	
Resistance Training Activity Exposure	0.99	(0.39, 2.51)	0.98	
Antidepressant Prescription Drug Exposure in 2011	2.89	(2.05, 4.09)	**<0.01**	

DMAA, 1,3-dimethylamylamine; OR, odds ratio; CI, confidence interval; OEF, Operation Enduring Freedom; OIF, Operation Iraqi Freedom; OND, Operation New Dawn.
Sex, Body Mass Index, Caffeine Exposure, Alcohol Exposure in 2011, and Resistance Training Activity Exposure were retained in the model as these factors were significant predictors in the DMAA exposure model.
Bold values indicate statistical significance with a p-value less than 0.05.

Table 5B: Association between Self-Reported DMAA Exposure Levels and Adverse Medical Outcomes

Characteristic		Total n (%)	Case n (%)	Control n (%)	Unadjusted		Adjusted	
					OR (95% CI)	p value	OR (95% CI)	p value
Total Respondents		1,789 (100.0)	712 (39.8)	1,077 (60.2)	-	-	-	-
DMAA Use in 2011								
DMAA Use (# of days)	0	1,545 (86.4)	638 (89.6)	907 (84.2)	1.0 (referent)	-	1.0 (referent)	-
	< 40	53 (3.0)	18 (2.5)	35 (3.3)	0.73 (0.41, 1.30)	0.29	1.09 (0.55, 2.16)	0.80
	40-79	83 (4.6)	25 (3.5)	58 (5.4)	0.61 (0.38, 0.99)	**<0.05**	0.73 (0.41 1.30)	0.28
	80+	91 (5.1)	28 (3.9)	63 (5.8)	0.63 (0.40, 1.00)	**<0.05**	1.02 (0.58, 1.81)	0.93
	Missing	17 (1.0)	3 (0.4)	14 (1.3)	-	-	-	-

DMAA, 1,3-dimethylamylamine; OR, odds ratio; CI, confidence interval.

Model adjusts for Sex, Age, Body Mass Index, Prior history of adverse medical event (AME), Number of months deployed to a Combat Zone (OEF/OIF/OND) in 2011, Caffeine Exposure, Alcohol Exposure in 2011, Resistance Training Activity Exposure, and Antidepressant Prescription Drug Exposure in 2011.
Bold values indicate statistical significance with a p-value less than 0.05.

- Table 6 shows the associations between DMAA use and specific adverse medical outcomes (cardiac dysrhythmia, heat injury, seizure, and rhabdomyolysis), both unadjusted and controlling for selected variables as noted above.

- Unadjusted, DMAA use showed a statistically significant decrease in the odds of cardiac dysrhythmia (crude OR: 0.51, 95% CI: 0.33, 0.78), although this effect lost magnitude and significance when adjusting for the control variables (adjusted OR: 0.70, 95% CI: 0.40, 1.23). Cardiac dysrhythmia was the only AME under study that demonstrated any statistically significant relationship with DMAA use.

Table 6: Association between Self-Reported DMAA Exposure and Specific AMEs: Cardiac Dysrhythmia, Heat Injury, Seizure, Rhabdomyolysis, and Heat Injury and/or Rhabdomyolysis

DMAA Use In 2011	Total n (%)	Case n (%)	Control n (%)	Unadjusted		Adjusted	
				OR (95% CI)	p value	OR (95% CI)	p value
Cardiac Dysrhythmia							
Yes	193 (13.8)	27 (8.5)	166 (15.4)	0.51 (0.33, 0.78)	**<0.01**	0.70 (0.40, 1.23)	0.21
No	1,198 (85.8)	291 (91.2)	907 (84.2)	1.0 (referent)	-	1.0 (referent)	-
Unknown	5 (0.4)	1 (0.3)	4 (0.4)				
Heat Injury							
Yes	187 (15.3)	21 (14.4)	166 (15.4)	0.92 (0.56, 1.50)	0.73	0.95 (0.51, 1.79)	0.88
No	1,032 (84.4)	125 (85.6)	907 (84.2)	1.0 (referent)	-	1.0 (referent)	-
Unknown	4 (0.3)	0 (0.0)	4 (0.4)				
Seizure							
Yes	177 (14.8)	11 (9.1)	166 (15.4)	0.55 (0.29, 1.04)	0.06	0.69 (0.30, 1.61)	0.40
No	1,017 (84.9)	110 (90.9)	907 (84.2)	1.0 (referent)	-	1.0 (referent)	-
Unknown	4 (0.3)	0 (0.0)	4 (0.4)				
Rhabdomyolysis							
Yes	179 (15.4)	13 (14.8)	166 (15.4)	0.95 (0.52, 1.75)	0.86	1.01 (0.49, 2.06)	0.99
No	982 (84.3)	75 (85.2)	907 (84.2)	1.0 (referent)	-	1.0 (referent)	-
Unknown	4 (0.3)	0 (0.0)	4 (0.4)				
Heat Injury and Rhabdomyolysis							
Yes	195 (15.1)	29 (13.4)	166 (15.4)	0.85 (0.55, 1.30)	0.44	0.92 (0.54, 1.55)	0.75
No	1,094 (84.6)	187 (86.6)	907 (84.2)	1.0 (referent)	-	1.0 (referent)	-
Unknown	4 (0.3)	0 (0.0)	4 (0.4)				

OR, odds ratio; CI, confidence interval.

Model adjusts for Sex, Age, Body Mass Index, Prior history of adverse medical event, Number of months deployed to a Combat Zone (OEF/OIF/OND) in 2011, Caffeine Exposure, Alcohol Exposure in 2011, Resistance Training Activity Exposure, Antidepressant Prescription Drug Exposure in 2011, Education (cardiac dysrhythmia, heat injury, and seizure only), and Smokeless Tobacco (seizure only).

Bold values indicate statistical significance with a p-value less than 0.05.

- Table 7 shows the associations between DMAA use levels and specific adverse medical outcomes (cardiac dysrhythmia, heat injury, seizure, and rhabdomyolysis), both unadjusted and controlling for selected variables as noted above.

- Unadjusted, DMAA use for 80 or more days was statistically significantly associated with lower odds of cardiac dysrhythmia (crude OR: 0.50, 95% CI: 0.25, 0.98), although this effect lost magnitude and significance when adjusting for covariates (adjusted OR: 0.68, 95% CI: 0.26, 1.73).

- It is important to note that the only values that show an adjusted OR of greater than 1 are for heat injury with frequent DMAA use for more than 80 days (adjusted OR: 1.66, 95% CI: 0.66, 4.19) and rhabdomyolysis for both less than 40 day (adjusted OR: 1.83, 95% CI: 0.59, 5.65) and more than 80 day groups (adjusted OR: 1.30, 95% CI: 0.48, 3.55). Interestingly the 40-80 day group adjusted OR is less than 1. The numbers are too small and do not reach statistical significance, but the results suggest that a sufficiently powered investigation of this specific association is needed.

Table 7: Association between Self-Reported DMAA Exposure Levels and Specific AMEs: Cardiac Dysrhythmia, Heat Injury, Seizure, Rhabdomyolysis, and Heat Injury and/or Rhabdomyolysis

DMAA Use (# of days)	Total n (%)	Case n (%)	Control n (%)	Unadjusted		Adjusted	
				OR (95% CI)	p value	OR (95% CI)	p value
Cardiac Dysrhythmia							
No DMAA	1,198 (85.8)	291 (91.2)	907 (84.2)	1.0 (referent)	-	1.0 (referent)	-
<40	41 (2.9)	6 (1.9)	35 (3.3)	0.53 (0.22, 1.28)	0.16	0.62 (0.19, 2.04)	0.43
40 to 80	68 (4.9)	10 (3.1)	58 (5.4)	0.54 (0.27, 1.07)	0.08	0.68 (0.27, 1.69)	0.41
80+	73 (5.2)	10 (3.1)	63 (5.9)	0.50 (0.25, 0.98)	**0.04**	0.68 (0.26, 1.73)	0.41
Unknown	16 (1.2)	2 (0.6)	14 (1.3)	-		-	
Heat Injury							
No DMAA	1,032 (84.4)	125 (85.6)	907 (84.2)	1.0 (referent)	-	1.0 (referent)	-
<40	38 (3.1)	3 (2.1)	35 (3.3)	0.62 (0.19, 2.05)	0.44	0.96 (0.27, 3.44)	0.95
40 to 80	67 (5.5)	9 (6.2)	58 (5.4)	1.13 (0.54, 2.33)	0.75	0.90 (0.35, 2.34)	0.82
80+	72 (5.9)	9 (6.2)	63 (5.9)	1.04 (0.50, 2.14)	0.92	1.66 (-0.66, 4.19)	0.29
Unknown	14 (1.1)	0 (0.0)	14 (1.3)	-		-	
Seizure							
No DMAA	1,017 (84.9)	110 (90.9)	907 (84.2)	1.0 (referent)		1.0 (referent)	-
<40	38 (3.2)	3 (2.5)	35 (3.3)	0.71 (0.21, 2.34)	0.57	0.82 (0.17, 4.06)	0.81
40 to 80	62 (5.2)	4 (3.3)	58 (5.4)	0.57 (0.20, 1.60)	0.28	0.54 (0.14, 2.10)	0.38
80+	66 (5.5)	3 (2.5)	63 (5.9)	0.39 (0.12, 1.27)	0.12	0.73 (0.17, 3.06)	0.67
Unknown	15 (1.3)	1 (0.8)	14 (1.3)	-		-	
Rhabdomyolysis							
No DMAA	982 (84.3)	75 (85.2)	907 (84.2)	1.0 (referent)	-	1.0 (referent)	-
<40	39 (3.4)	4 (4.6)	35 (3.3)	1.38 (0.48, 3.99)	0.55	1.83 (0.59, 5.65)	0.30
40 to 80	61 (5.2)	3 (3.4)	58 (5.4)	0.63 (0.19, 2.04)	0.44	0.48 (0.11, 2.07)	0.32
80+	69 (5.9)	6 (6.8)	63 (5.9)	1.15 (0.48, 2.75)	0.75	1.30 (0.48, 3.55)	0.61
Unknown	14 (1.2)	0 (0.0)	14 (1.3)	-		-	

Table 7: Association between Self-Reported DMAA Exposure Levels and Specific AMEs: Cardiac Dysrhythmia, Heat Injury, Seizure, Rhabdomyolysis, and Heat Injury and/or Rhabdomyolysis (continued)

DMAA Use (# of days)	Total n (%)	Case n (%)	Control n (%)	Unadjusted		Adjusted	
				OR (95% CI)	p value	OR (95% CI)	p value
Heat Injury and Rhabdomyolysis							
No DMAA	1,094 (84.6)	187 (86.6)	907 (84.2)	1.0 (referent)	-	1.0 (referent)	-
<40	41 (3.2)	6 (2.8)	35 (3.3)	0.83 (0.35, 2.01)	0.68	1.16 (0.45, 3.00)	0.76
40 to 80	68 (5.3)	10 (4.6)	58 (5.4)	0.84 (0.42, 1.67)	0.61	0.66 (0.28, 1.55)	0.34
80+	76 (5.9)	13 (6.0)	63 (5.9)	1.00 (0.54, 1.86)	1.00	1.39 (0.65, 2.98)	0.40
Unknown	14 (1.1)	0 (0.0)	14 (1.3)	-		-	

DMAA, 1,3-dimethylamylamine; OR, odds ratio; CI, confidence interval.
Model adjusts for Sex, Age, Body Mass Index, Prior history of adverse medical event, Number of months deployed to a Combat Zone (OEF/OIF/OND) in 2011, Caffeine Exposure, Alcohol Exposure in 2011, Resistance Training Activity Exposure, Antidepressant Prescription Drug Exposure in 2011, Education (cardiac dysrhythmia, heat injury, and seizure only), Tobacco Exposure in 2011 (cardiac dysrhythmia only), Smokeless Tobacco (seizure only), and CNS Stimulant Prescription Drug Exposure in 2011 (seizure only).
Bold values indicate statistical significance with a p-value less than 0.05.

Table 8: Odds Ratios of Self-Reported DMAA Exposure (Use) among Service Members with One and with Multiple (2+) Adverse Medical Outcomes

DMAA Use in 2011	Number of Adverse Medical Outcomes[a]		Unadjusted[b]	
	2+ outcomes	1 outcome	OR (95% CI)	p value
Yes	9	64	2.28 (1.01, 4.95)	**0.04**
No	37	601	1.0 (referent)	-

DMAA, 1,3-dimethylamylamine; OR, odds ratio; CI, confidence interval.
Bold value indicates statistical significance with a p-value less than 0.05.
[a]Multiple adverse medical outcomes (2+ outcomes) were diagnoses of 2 or more different types of adverse medical outcomes (i.e. cardiac dysrhythmia, seizure, heat injury, rhabdomyolysis, cerebral hemorrhage, acute and subacute necrosis of liver, and/or acute kidney failure) during the study period, calendar year, 2011.
[b]Due to the small number of cases with multiple adverse medical outcomes, only unadjusted results were calculated.

- Table 8 shows that cases with 2 or more adverse medical outcomes had more than 2 times the odds of using DMAA compared to cases with 1 outcome (OR: 2.28, 95% CI: 1.01, 0.04).

- In other words, Service Members with two or more adverse medical outcomes were more than twice as likely to have reported using DMAA compared to Service Members with one reported outcome.

Table 9: Odds Ratios of Self-Reported DMAA Exposure (Use) among Cases with 2 or More Adverse Medical Outcomes versus Cases with One Adverse Medical Outcome by Frequency of Use (0 day, 1-80 days, >80 days).

DMAA Use (# of days)	Number of Adverse Medical Outcomes[a]		Unadjusted[b]	
	2+ outcomes	1 outcome	OR (95% CI)	p value
No DMAA	37	601	1.0 (referent)	-
1-80 days	4	39	1.67 (0.57, 4.91)	**0.35**
80+ days	5	23	3.53 (1.27, 9.82)	**0.01**

***p-value for trend < 0.02**

DMAA, 1,3-dimethylamylamine; OR, odds ratio; CI, confidence interval.
Bold value indicates statistical significance with a p-value less than 0.05.
[a]Multiple adverse medical outcomes (2+ outcomes) were diagnoses of 2 or more different types of adverse medical outcomes (i.e. cardiac dysrhythmia, seizure, heat injury, rhabdomyolysis, cerebral hemorrhage, acute and subacute necrosis of liver, and/or acute kidney failure) during the study period, calendar year, 2011.
[b]Due to the small number of cases with multiple adverse medical outcomes, only unadjusted results were calculated.

- Among cases, low frequency DMAA users were 1.7 times more likely to have multiple outcomes (OR: 1.67, 95% CI: 0.57, 4.91), and high frequency DMAA users were 3.5 times more likely to have multiple outcomes, compared to non DMAA users (OR: 3.53, 95% CI: 1.27, 9.82).

- There was a significant trend with increasing likelihood of more frequent DMAA use for cases with multiple adverse medical outcomes (2 or more outcomes) (0 days, 1-80 days, 80+ days of DMAA use with respective ORs of 1 (referent), 1.7, and 3.5) ($p<0.02$).

4. Conclusions.

a. No statistically significant association was observed between self-reported DMAA use one or more times during the year examined and selected adverse medical outcomes after controlling for relevant factors. Separate analysis of specific adverse medical outcomes, cardiac dysrhythmia, heat injury, seizure, and rhabdomyolysis, similarly showed no statistically significant association with self-reported DMAA use.

b. However, the study did find that among those Service members who had experienced an adverse medical outcome (cases), those with multiple adverse outcomes in 2011 were more than twice as likely to report having used DMAA in the same year. The study also found that among cases, low frequency DMAA users were 1.7 times more likely to have multiple outcomes, and high frequency DMAA users with more than 80 days of use were 3.5 times more likely to have multiple adverse outcomes compared to non DMAA users. The trend analysis was statistically significant at the 0.02 level.

c. This study found a number of factors other than DMAA that were significantly associated with selected adverse medical outcomes. Prior history of one of the selected AMEs was associated with an almost 18-fold increased risk of having a current AME. Antidepressant prescription use was associated with an almost 3-fold increased risk of experiencing an AME. Combat deployment in 2011 appeared to be protective, possibly due to a healthy soldier effect. The strongest predictor of adverse medical outcomes was prior history of AME suggesting the importance of prevention strategies to reduce the reoccurrence of adverse outcomes.

d. This is the first population-based, epidemiologic study to investigate the association of DMAA and clinician identified AMEs. Although this study did not find that simply using DMAA one or more times in 2011 increased the likelihood of Service members experiencing an AME, the study did show that Service members with multiple AMEs were more than twice as likely to have used DMAA and that this effect seemed particularly likely with high frequency DMAA use. Data from this study suggest larger, more in-depth studies are needed to examine specific outcomes, such as heat injuries and rhabdomyolysis. Future epidemiologic studies should also look more closely at the health effects of exposure to DMAA in terms of frequency and amount.

10. Evaluation of Evidence

Dr Tamra Meyer
COL Trinka Coster

Review and Critique of Existing Evidence Linking Dimethylamylamine to Adverse Medical Events

Purpose: The Pharmacovigilance Center (PVC) reviewed the existing evidence linking dietary supplements containing dimethylamylamine (DMAA) to adverse medical events (AMEs) such as hepatic, renal or cardiac injury. In this document, we provide a summary review of the three disparate sets of evidence considered (1. adverse medical event [AME] reports and case studies from the Food and Drug Administration [FDA] and US Army Public Health Command [USAPHC], 2. published clinical studies, and 3. USAPHC case control study). Since there is no statistical method that can integrate these three evidentiary sources into a quantitative summary measure of safety, a qualitative review was conducted

Evidence:

a. An FDA notice of 42 cases of AMEs in patients who had used DMAA (FDA, 2012 and Section 7)
b. USAPHC Medical Care Provider Survey assessing 27 of 39 AME cases (Section 5)
c. USAPHC interviews with 7 of 24 patients reported by physicians as having AMEs possibly associated with nutritional supplements, and 3 additional self-reporting patients (Section 6)
d. Six published studies and one unpublished physiologic/metabolic study of DMAA effects (Bloomer et al, 2011a; Bloomer et al, 2011b; Bloomer et al, unpublished, Farney et al, 2011; McCarthy et al, 2012a; McCarthy et al, 2012b; Whitehead et al, 2012)
e. USAPHC Soldier Health and Supplement Use case-control study of nutritional supplement use and AMEs (DoD DMAA Study)

Review of the Evidence:

a. AME reports and case studies:
b. FDA reported 42 cases of adverse event reports submitted by physicians for events suspected to be related to use of DMAA-containing supplements. (FDA, 2012; DoD DMAA Study) Events included cardiac disorders, nervous system disorders, psychiatric disorders and death.
    i. The Safety Review Panel systematically consolidated information from providers for 27 of 39 reported AME cases within the Military Health System (MHS). Structured interviews were completed by USAPHC with seven of these patients and three additional patients identified through the case control study. Reported events included rhabdomyolysis or heat injury (n=7), seizures (n=4), syncope (n=4), tachycardia/palpitation (n=4), cerebrovascular events (n=4), myocardial infarctions (n=2), hepatic failure (n=2), renal failure (n=2), and paresthesias (n=3). From patient surveys, USAPHC noted that cases were commonly overweight or obese (n=9), used tobacco (n=7), and used other supplements or medications in addition to the DMAA-containing products (n=8).

ii. Because of the lack of controls when using case reports, the common presence of known cardiovascular risk factors in the cases, and the concomitant use of multiple substances, it was not possible to verify a causal relationship between DMAA and most of the suggested AMEs from these studies. One serious AME, hepatic failure, did describe a compelling case where there were no prior risk factors and no concomitant medications. Cardiovascular AMEs and heat related injuries resulting from DMAA are another biologically plausible category of events, since DMAA is a stimulant known to narrow the blood vessels and arteries, which can elevate blood pressure and as a sympathomimetic can increase heat production. These reports highlight the wide concomitant use of other supplements, medications, and tobacco as well as the common presence of cardiovascular risk factors among the cases

c. Published Physiologic/Metabolic Studies:
   i. Additional evidence supporting the potential for cardiovascular injury connected with DMAA use comes from the physiologic/metabolic studies of DMAA that were designed to evaluate DMAA effects (Bloomer et al, 2011a; Bloomer, unpublished manuscript; Farney et al, 2012; Whitehead et al, 2012) and efficacy (Bloomer et al, 2011b; McCarthy et al, 2012a; McCarthy et al, 2012b) in weight loss and exercise performance; these studies were not designed as safety studies. One unpublished and six published intervention studies were reviewed in which DMAA-containing supplements were given to volunteers. Two of the interventions were cross-over designs (Bloomer, 2011a; McCarthy, 2012b) that included measures of cardiovascular endpoints before and after dosing with DMAA, while others were randomized, placebo-controlled trials of DMAA that also included within-group measures of endpoints after dosing (Bloomer, 2011a; Farney, 2012; McCarthy 2012a; Whitehead, 2012). Overall, the studies showed inconsistent elevation of blood pressure and heart rate.
   ii. There were significant limitations across all of the studies. All studies had small sample sizes which limited their ability to detect adverse medical events. Despite small sample sizes, they did detect a number of significant physiologic responses.
   iii. The studies evaluated short durations of exposures (range: one dose on a single day to 10 weeks of use)
   iv. The use of healthy volunteers in the studies limits the ability to generalize the results of the studies. The interviews of Service members conducted by Public Health Command noted that cases were likely to be overweight or obese and to have concomitant use of other substances and preexisting health conditions (Sections 5 and 6)
   v. There could be a perceived conflict of interest since researchers received support from the makers of DMAA-containing supplements for some of the studies.
   vi. Three studies examined either DMAA alone or combination of DMAA and caffeine (Bloomer, 2011a; Bloomer 2011b; Bloomer, unpublished). The purpose of the other studies was to examine the effects of specific products. (Farney 2012; McCarthy, 2012a; McCarthy, 2012b;

Whitehead, 2012)

vii. Some statistically significant cardiovascular responses were found in participants. There was a minimal effect on heart rate and some mild to moderate elevation of blood pressure. The results can be interpreted as evidence of cardiovascular response after short-term use. Cardiovascular risk in those with long-term use, those using multiple supplements either individually or combined into a proprietary blend with cardiovascular activity, or in those with pre-existing conditions could not be determined from these studies.

d. Case-control study: The third line of evidence reviewed was a case-control study conducted by the USAPHC (Section 9). The study was designed to evaluate nutritional supplement use in cases identified through inpatient and outpatient medical encounters and a large sample of non-cases (individuals without diagnostic codes for the AMEs evaluated during 2011: cardiac dysrhythmia, heat injury, seizure, rhabdomyolysis, cerebral hemorrhage, acute kidney failure and acute and/or subacute necrosis of liver) from the Defense Medical Surveillance System. Cases included those with ICD-9 codes in any position during a hospitalization or two or more outpatient diagnostic codes in the primary position during the study period. Participants were invited to complete a self-administered internet questionnaire and non-responders were encouraged to participate through direct contact methods.

Over 3,900 people were invited to participate and about 1,800 responded (45%). Of the 1,789 responders (712 cases and 1,077 controls), 15% of the controls reported use of DMAA during 2011 while 10% of the cases reported use. While not statistically significant after adjustment, the study showed lower odds of exposure to DMAA in those who experienced one of the medical events evaluated than in those who did not have events. However, when analysis was limited to participants with an AME in 2011 (cases), those with 2 or more AMEs were twice as likely to have had exposure to DMAA-containing products than those with 1 AME. The study had several limitations.

i. Fifty-five percent of study subjects contacted did not participate in the study. The response rate was relatively low, but normal for electronic surveys. This can lead to reporter bias if those who responded had different distributions of exposure to DMAA or confounders than the overall target population.

ii. The case definition used a combination of ICD9-codes from inpatient and outpatient administrative medical records that may have misclassified some non-cases as cases and vice-versa resulting in a bias of the estimate, favoring the null. .

iii. Because a case-control study design was chosen to examine the association between DMAA and rare outcomes, establishment of temporality between exposures and events is beyond the capability of this design. This study relied on questionnaire data to assess past exposures, thus introducing the possibility of recall bias if cases remembered exposures more accurately than controls.

iv. While there was adjustment for sex, age, education, BMI, prior history of AME (pre-2011), months of combat deployment in 2011, caffeine

consumption, alcohol consumption, resistance training activity level, and anti-depressant prescription in 2011, this study may not have fully accounted for all other potential confounders.

11. Operation Supplement Safety
Dr Patricia Deuster

Background and Purpose

Operation Supplement Safety (OPSS) was officially launched in late November 2011 at the request of Dr. Woodson. The purposes of OPSS are to increase awareness within the DoD community about dietary supplements and provide tools to be "smart" supplement users. The target audiences are Service members, family members, Healthcare providers, leaders, retirees, and DoD civilians

Most consumers are generally uneducated about dietary supplements. Some categories of supplements, as determined the by Food and Drug Administration, are of concern. The reasons for concern are that dietary supplements are not regulated by the U.S. government the way drugs are and some products may contain ingredients not listed on their Supplement Facts panels—including drugs. Also we want our audiences to understand that the U.S. government does not review dietary supplements for safety before they enter the market and that manufacturers, not the FDA, are legally responsible for ensuring safety.

Two strong messages from OPSS are that 1) dietary supplements with independent, third party certification/verification are safest because they have been tested for purity and/or quality and 2) dietary supplements should not be a substitute for a healthy diet.

OPSS has produced a variety of resources that are available on the website http://hprc-online.org/dietary-supplements/opss. The resources include Information sheets (OPSS Campaign Overview, Red Flags—What You Need to Know, Reporting Adverse Events, Dietary Supplements Containing DMAA, Dietary Supplement Education for Warfighters, Dietary Supplements & Drug Testing, How to read supplement product labels), Videos (College athlete Jareem Gunter talks about adverse effects of supplements, Information about weight-loss supplements), Apps and Widgets (Warrior SUP OPSS App for Warfighters, Natural Medicines Comprehensive Database App for Providers, MyDS from Office of Dietary Supplements, NSF for Sport), multiple promotional materials to include Posters (Supplement Drug Interactions for Military Treatment Facilities and Pharmacies, Energy Drink/Energy Shot), tray mats, table tents, stickers, and pens. These resources can either be downloaded or ordered from the Army Public Health Information Products e-Catalog through the OPSS website.

Our FAQS are another feature of OPSS; the question and answer format provides information on a variety of issues ranging from general topics such as

- Is there some way I can let the FDA know that a supplement I've been taking is causing me problems?
- Is there a place where I can get a rating of the safety and effectiveness of a supplement?
- Is there an all-encompassing list of dietary supplements that are banned or illegal for use by military personnel?
- Why doesn't the FDA stop unsafe supplements from reaching the market?
- What role should leadership play regarding dietary supplement use?

- What's the definition of a dietary supplement?
- How do I know if I've had an adverse event?
- Are there specific requirements for labeling of dietary supplement products?
- What does the term "proprietary blend" on supplements mean?

to specific responses about particular dietary supplement ingredients (e.g. caffeine), performance and dietary supplements (e.g. energy drinks, deer velvet), dietary supplements and weight loss, and other frequently asked questions about dietary supplements.

Implementation

OPSS was officially launched in October 2012. On 9 November 2012 the Navy and Marine Corps Public Health Center announced OPSS and posted a link to OPSS website from their website. Additionally, the Navy has promoted OPSS on several ships and at several bases. The Marine Corps sent out a message to all Marines promoting on 9 October 2012 announcing and promoting OPSS, and the Secretary of the Air Force has announced it support of the campaign. Military Times, Stars and Stripes, the Colorado Springs Military Newspaper Group and other media have described the campaign and enhanced awareness. Both the Air Force and the Marine Corps have offered information booths at base commissaries and public service announcements at base movie theaters and on the Armed Forces Network and Pentagon Channel. The Coast Guard is also active in OPSS. Since the website launched in October, the OPSS site has had over 20,000 page views. In terms of products ordered through the e-catalogue, over 64,000 items have been shipped. We have a Facebook presence and links to OPSS are found on many military websites.

Other partners have included Defense Media Agency and the Visual Information Directorate at BUMED who have been developing videos and Public Service Announcements for OPSS. Overall, OPSS is a joint, grassroots campaign to address to promote education of Service members and families about supplement use and safety.

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ANNEX A. DMAA Timeline

29 July 1950 – JAMA article introduced methylhexamine (same product as 1,3-dimethylamylamine) or Forthane, a drug patented by Eli Lilly. It stated "The systemic toxicity of methylhexamine in animals is greater than that of ephedrine and less than that of amphetamine, its pressor action is more prolonged than that of epinephrine".

2006 – DMAA re-introduced under trademark name 'Geranamine', registered by Proviant Technologies.

7 Nov 09 - New Zealand government restricted sales of DMAA and advised it be scheduled as a restricted substance.

2009 - World Anti-Doping Agency (WADA) added Geranamine/DMAA to banned list

2009 - NCAA and many other professional athletic organizations banned DMAA

1 Jun 11 –22 yo Soldier collapsed during PT at Southwestern base with cardiac arrest and subsequently died from hyperthermia. Toxicology screen showed caffeine and DMAA – found in Soldier's quarters.

7 July 11 - Health Canada announced products containing DMAA must be authorized as drugs.

28 July 11 - CPT collapsed after PT run at Southwestern base and hospitalized for 4 days with exercise induced rhabdomyolysis, heat injury, temporary heart injury, and renal damage initially believed to be linked with DMAA, but not validated.

Aug 11 - American Herbal Products Association (AHPA) announced that members could not label 1,3-dimethylamylamine as any part of the geranium plant.

28 Oct 11 – The Exchange added Jack3d™ to new Sports Nutrition planogram #93702. GNC and other AAFES concessionaires were already carrying Jack3d™ and other products containing DMAA at AAFES concessions.

4 Nov 11 - SGT collapsed and nearly died at Southwestern base after APFT with cardiac arrest, multi-organ failure. Awaiting liver transplant, case linked to "Jack3d™"

9 Nov 11 –Chief Preventive Medicine at the Army hospital notified Southwestern base Exchange General Manager (GM) of Soldier in ICU who had taken Jack3d™. GM agreed to pull product off shelves at Southwestern base pending further guidance and asked GNC concession to remove product from their shelves.

9 Nov 11 – Dr Patty Deuster sends note to Army Surgeon General and COL Lammie recommending review of DMAA White Paper in support of ban of DMAA. COL Lammie responds supportively on 17 November, indicating that more complete response would be developed.

13 Nov 11 – SGT who collapsed on 4 Nov dies

15 Nov 11 – Chief Preventive Medicine at the Army hospital provided AAFES Chief of Staff with Dr Deuster's white paper describing DMAA and Jack3d™.

30 Nov 11 - Dr Deuster presents DMAA white paper and decision brief to Force Health Protection Integration Council to recommend ban of DMAA. DASD (FHP&R) requests additional information.

30 Nov 11 – MG Casella notified the Chairman of the AAFES Board of Directors, LTG Raymond Mason and the Senior Air Force Service Member, LTG Darrell Jones, of his action to remove DMAA products from Exchange activities. LTG Mason notified LTG Eric Schoomaker, Army Surgeon General, of AAFES' action to remove DMAA products.

30 Nov 11 – LTG Eric Schoomaker notified by LTG Mason of AAFES' action to remove DMAA products. Commander of unit and Southwestern base concurred with AAFES action to remove DMAA from Exchange activities.

1 Dec 11 - TSG directs OTSG HP&S and Public Health Command to coordinate Army response.

1 Dec 11 –MG Casella notified Mr. Robert Gordon, Deputy Assistant Secretary of Defense (Military Community and Family Policy) of his action to remove DMAA from Exchange activities.

1 Dec 11 – LTG Mason notified Chief of Staff of the Army of the action taken by MG Casella to protect Soldiers and their families.

2 Dec 11 – Mr. Fortunato, President/CEO of GNC, sent letter to Secretary of the Army, asking to meet with DoD officials and to share scientific data about DMAA. He courtesy copied Sen. Lindsay Graham, LTG Schoomaker, and MG Casella. In his letter, Mr. Fortunato claims request to remove DMAA products from all GNC AAFES concessions was based on anecdotal reports about DMAA safety and false positives for amphetamine use on drug testing.

2 Dec 11 – OTSG hosts with PHC a coordinating meeting with USUHS, HA, and other Service civilian partners to discuss scientific evidence and to detail response. Work group recommends RFI to RMCs and other Major Commands calling for adverse reports, and PHC begins to pull together educational materials.

3 Dec 11 – AAFES confirms that all dietary supplements containing DMAA have been pulled from all AAFES exchange stores and concessionaires world-wide.

3 Dec 11 - The Defense Logistics Agency issues a medical hold message, ALFOODACT 034-2011; subsequently, updated ALFOODACTs are issued by DLA: ALFOODACTS #034-2011, #036-2011, #041-2011 and #044-2011

14 Dec 11 – 32 yo Soldier at Southwestern base expires after month-long hospitalization

8 Dec 11 – Dr Guice, Mr Gordon, COL Lammie meet with SEN Graham staff and Mr Fortunato, President of GNC

9 Jan 12 – Force Health Protection Integrating Council Meeting

26 Jan 12 – Safety Review Panel Consensus Conference #1 The Tri-Service panel strongly recommended a ban of some kind but the vote split between an outright ban and continued medical hold: vote was tightly split between those recommending continued medical hold (7) and outright ban on the product (6), with 1 person recommending return to shelves.

3 Feb 12 – Meet with Dr Woodson and Mr Sipos to review results to date

10 Feb 12 - 41 year old male collapsed at the end of an 8 mile run with his unit in Pacific region; autopsy shows severe coronary artery disease and + DMAA in blood.

22 Feb 12 – Clinical Policy Steering Committee Meeting

29 Feb 12 – SMMAC Meeting – continue medical hold pending outcome of Safety Review

6 MAR 12 – Mr Sipos and COL Lammie and Safety Review Panel meet with Dr Rodricks and GNC/USPLab representatives for review of seven articles to demonstrate physiologic effects and safety

24 Apr 12 – FDA cites manufacturers and distributors of DMAA as being in violation of DSHEA (Dietary Supplement and Health Education Act) 1994 that requires firms to file New Dietary Ingredient application for synthetic dietary supplements. Charges that DMAA-supplements are adulterated products.

8 Jun 12 – COL Lammie and Safety Panel meet with Dr Richard Bloomer and Mr Bruce Deming and Dr Rodricks to discuss his scientific studies of DMAA and his future research

27July 12 – 3rd Soldier at Southwestern base dies following PT, 26 yo, + DMAA in serum

2 Aug 12 – COL Lammie and COL Stephens (M&RA) meet with SEN Graham's staff and attorneys from GNC and USPLabs.

Jul - Aug 12 – distribution of Case Control Survey questionnaires

27 Sep 12 – Second Consensus Conference of Safety Review Panel. Vote to continue medical hold pending completion of the case control survey and the resolution of the FDA judgment that DMAA-containing supplements are adulterated products.

10 Oct 12 – SMMAC – presentation of initial results, receive extension until 28 November to allow closure of survey submissions, continue medical hold. Look at educational programs for all care teams and at surveillance system.

28 Nov 12 – SMACC presentation of interim report

30 Nov 12 – FDA Teleconference to confirm willingness to meet with congressional staff with DoD

7 Dec 12 – Meeting of MG Stone, CAPT Biggerstaff, COL Stephens, COL Lammie with USP Labs/GNC counsels, Mr Kyle, Mr Deming, Mr Hutt. Discussion of progress report on safety review, and discussion about potential education campaign collaboration
24 Jan 13 – Third Consensus Conference of Safety Review Panel. Vote to continue medical hold pending completion of the case control survey and the resolution of the FDA judgment that DMAA-containing supplements are adulterated products.

29 Jan 13 – Call with Dr Bloomer from University of Memphis, Mr Kyle, Mr Deming from USPLabs to discuss latest research paper for 50 male healthy volunteers using DMAA for 120 days

6 Feb 13 – Meeting of Force Health Protection Integrating Council – presentation of summary findings of DMAA Safety Review Panel – FHPIC recommends return of products to exchange shelves

27 Feb 13 – SMMAC presentation of final results – recommends continued prohibition of sales of DMAA-containing products in Exchanges and concessions.

Annex B. DoD DMAA Safety Panel Members

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ANNEX C – Soldier Health and Dietary Supplement Use Questionnaire

PRIVACY ACT STATEMENT – HEALTH CARE RECORDS & U.S. ARMY PUBLIC HEALTH COMMAND SOLDIER HEALTH AND DIETARY SUPPLEMENT USE QUESTIONNAIRE

1. AUTHORITY FOR COLLECTION OF INFORMATION INCLUDING SOCIAL SECURITY NUMBER

Public Law 104-191, Section 1178; Executive Order 9397; Section 8103, Title 5, United States Code

2. PRINCIPLE PURPOSES FOR WHICH INFORMATION IS INTENDED TO BE USED

This form provides you the advice required by the Privacy Act of 1974. Over the last several years, the Army has observed an increase in the rates of several medical conditions such as liver and kidney injuries among Active Duty Soldiers. The information obtained from this project will be used to determine what might be contributing to these increases. More specifically, the questionnaire will be used to obtain information regarding your level of physical activity, dietary supplement use, other substance use, and sleep. We will link information collected in this questionnaire with data from your medical records such as information on illness, injuries, or medical conditions you may have experienced in the last year (from January-December 2011). We have created a unique identification number for you that will match data we obtain in this questionnaire to your medical records. We will never report any personal information like your name, social security number, or personal health information.

3. ROUTINE USES

The primary use of this information is to improve the health and fitness of U.S. Soldiers. The data obtained from the questionnaires will be included in a database that contains the same information for all Soldiers participating in this project. The only personnel having access to this information will be the public health officials who will analyze the information. You will not be personally identified in any report or any output of any type since the interest is in the health and fitness of the Army and not the health and fitness of any single individual.

The database that is established will be used to estimate the prevalence of a variety of conditions in the last year (January – December 2011) including liver disease, kidney disease, cardiac dysrhythmia, seizure, and heat injury. It will also be used to identify factors that increase or decrease Soldiers' level of risk for these conditions. Information from the database will be used to make recommendations to decision makers regarding programs and policies that might improve health and fitness and reduce the incidence of medical conditions and/or injuries in the Army and across the Department of Defense.

4. WHETHER DISCLOSURE IS MANDATORY OR VOLUNTARY AND EFFECT ON INDIVIDUAL OF NOT PROVIDING INFORMATION

Disclosure of the requested information is voluntary. If you do not disclose the information you will not be included in the database and you will not participate in the project designed to reduce injuries and improve the health and fitness of U.S. Army Soldiers.

U.S. ARMY PUBLIC HEALTH COMMAND SOLDIER HEALTH AND DIETARY SUPPLEMENT USE QUESTIONNAIRE

This questionnaire contains 46 questions and will take about 20 minutes for you to complete. Please answer all questions on this survey honestly and completely. There are no right or wrong answers and nothing you say will ever be linked to your name. The U.S. Army Public Health Command will keep all of your responses confidential and will only report information we learn in group form.

Some questions on this survey ask about your current health and behaviors and others ask about specific experiences you had LAST YEAR (in 2011).

Please read all instructions and questions very carefully before answering.

When filling in your responses, please darken all circles completely.

● not 

DEMOGRAPHICS

These first 8 questions ask some general information about you.

1. **What is your month and year of birth?** Month_____ Year _____

2. **What is your gender?**
   - O Male
   - O Female

3. **What is your race and/or ethnicity? (*Please select one or more responses*)**
   - O American Indian or Alaska Native
   - O Asian
   - O Black or African American
   - O Hispanic or Latino/a
   - O Native Hawaiian or Other Pacific Islander
   - O White

4. **How much do you weigh (in pounds)?** _____ pounds/lbs

5. **What is your height (in inches)?** _____ inches

6. **What is your marital status?**
   - O Single, never married
   - O Married
   - O Separated
   - O Widowed
   - O Divorced

7. **What is the highest level of education you have completed?**
   - O Some high school (but no GED or diploma)
   - O High school graduate (GED or diploma)
   - O Some college courses
   - O Associate degree (two-year college)
   - O Bachelor degree (four-year college)
   - O Graduate degree

U.S. ARMY EXPERIENCE

The next 6 questions ask about your experiences in the U.S. Army.

8. **What is your current rank?**
   - O E1-E4
   - O E5-E6
   - O E7-E9
   - O W1-W5
   - O O1-O3
   - O O4 or higher

9. **What is your current area of <u>assignment</u>?**
   - O Combat arms (Infantry, Armor, Field Artillery, Air Defense, Special Forces, Aviation)
   - O Combat support (Engineer, Chemical, Military Intelligence, Military Police, Signal, Civil Affairs)
   - O Combat service support (Ordnance, Quartermaster, Transportation, Adjutant, Medical, Finance, Chaplain, Judge advocate General, Inspector General)

10. **Are you Special Forces Qualified?**
   - O No
   - O Yes

11. **How many times have you been deployed to a <u>combat zone</u>, in your military career since September 11, 2001 (OEF/OIF/OND)? *Please do not include overseas contingency operations deployments such as missions in Japan, Haiti, Korea, and/or Germany*.**
   - O None (*Go to the Physical Activity and Physical Fitness Section*)
   - O Not sure
   - O 1 time
   - O 2 times
   - O 3 times
   - O 4 or more times

12. **What is your total combined time deployed to a <u>combat zone</u>, in years and months since September 11, 2001 (OEF/OIF/OND)?**
   - O Years _____ Months _____

13. **Were you deployed to a <u>combat zone</u> at all LAST YEAR (in 2011)? *Please do not include overseas contingency operations deployments such as missions in Japan, Haiti, Korea, and/or Germany***
   - O No
   - O Yes (*Please select ALL of the months when you were deployed to a combat zone in 2011.)*

O January	O April	O July	O October
O February	O May	O August	O November
O March	O June	O September	O December

PHYSICAL ACTIVITY AND PHYSICAL FITNESS

The next set of questions asks about your recent APFT performance, your level of physical activity, and your general weight and body composition goals.

14. **To the best of your recollection, what was the date and raw score of your LAST Army Physical Fitness Test (APFT)? *If you were on profile for one or more events, please mark the N/A bubble in the appropriate box*.**

Date of last APFT: _____(month) _____ (year)

Overall Score	**# of Pushups (repetitions)**	**# of Situps (repetitions)**	**2-Mile Run**	**OR**	**2.5 Mile Walk**
_____ out of 300	_____ number in 2 minutes	_____ number in 2 minutes	____ min ____ sec		____ min ___ sec
O N/A, I was on profile for one or more APFT events	O N/A, I was on profile for this event	O N/A, I was on profile for this event	O N/A, I was on profile for this event		O N/A, I was on profile for this event

15. **For EACH of the following categories of exercise intensity, please select your average <u>FREQUENCY</u> (*rarely/never, 1-2 times per week, 3-4 times per week, 5-6 times per week, 7+ times per week*) and <u>DURATION</u> of the activity (*<30 minutes, 30-60 minutes, 61-90 minutes, >90 minutes*) over the LAST 30 DAYS. *Please read all categories carefully before making your selection.***

	EXERCISE FREQUENCY					**EXERCISE DURATION**				
	How many times per week did you perform the exercise in the last 30 days?					**On days that you exercised, how many minutes did you spend performing the exercise?**				
Exercise Intensity	Rarely/ Never	1-2 times per week	3-4 times per week	5-6 times per week	7+ times per week	N/A (Select if you rarely/never perform this exercise)	<30 minutes	30-60 minutes	61-90 minutes	>90 minutes
***EXAMPLE*: "I perform vigorous physical activity (running: 3 times/week @ 45 minutes per session; interval training: 2 times/week @ 30 minutes per session)" = 5**	O	O	O	●	O	O	O	●	O	O

days of vigorous physical activity @ 30-60 minutes per session										
Vigorous Activity: Includes activities that take hard physical effort and make you breathe <u>much harder</u> than normal. *Examples: running, agility drills, calisthenics, interval training, sprints, road marches, and bicycling at high effort.*	O	O	O	O	O	O	O	O	O	O
Moderate Activity: Includes activities that take moderate physical effort and make you breathe <u>somewhat harder</u> than normal. *Examples: brisk walking, bicycling (flat, 5-9 mph), swimming (recreational), softball, shooting basketball, and tennis.*	O	O	O	O	O	O	O	O	O	O
Resistance Training: Includes activities that involve lifting using free weights, dumbbells, kettlebells, and/or Nautilus machines	O	O	O	O	O	O	O	O	O	O

16. **How would you rate your CURRENT physical activity level when compared to your activity level LAST YEAR (in 2011)?**
    - O I am much less physically active now than in 2011
    - O I am less physically active now than in 2011
    - O I am equally physically active now as I was in 2011
    - O I am more physically active now than in 2011
    - O I am much more physically active now than in 2011

17. **Do you currently consider yourself to be overweight, underweight, or about average?**
    - O Overweight
    - O Underweight
    - O About average

18. **What are you currently trying to do about your <u>weight</u>?**
    - O I am trying to lose weight
    - O I am trying to maintain my weight
    - O I am trying to gain weight

O I am not specifically trying to do anything about my weight

19. What are you currently trying to do about your <u>amount of muscle mass</u>?

O I am trying to lose muscle mass
O I am trying to maintain my amount of muscle mass
O I am trying to gain muscle mass
O I am not specifically trying to do anything about my amount of muscle mass

20. What are you currently trying to do about your <u>strength</u>?

O I am trying to lose strength
O I am trying to maintain my strength
O I am trying to gain strength
O I am not specifically trying to do anything about my strength

21. How do you believe each of the following currently compares to your average LAST YEAR (in 2011)? (***Please mark one column for each row.***)

	Much lower now than in 2011	Slightly lower now than in 2011	About the same now as in 2011	Slightly higher now than in 2011	Much higher now than in 2011
a. Weight	O	O	O	O	O
b. Amount of muscle mass	O	O	O	O	O
c. Body fat percent	O	O	O	O	O
d. Strength	O	O	O	O	O

22. Please select if you have used EACH of the following methods to meet your weight, body composition, or strength goals in the LAST 30 DAYS <u>and/or</u> LAST YEAR (in 2011). ***If you used in the last 30 days and/or in 2011, select the appropriate bubbles. If you did not use in the last 30 days or in 2011, select "Did not use".***

	Used in last 30 days	Used in 2011	Did not use
a. Eat fewer calories	O	O	O
b. Eat more calories	O	O	O
c. Eat less fat	O	O	O
d. Exercise more	O	O	O
e. Take supplements	O	O	O
f. Take diet pills to decrease your appetite	O	O	O
g. Fast for 24 hours or longer as part of your diet	O	O	O
h. Cause yourself to vomit after eating	O	O	O

CAFFEINE, SUPPLEMENT, AND OTHER SUBSTANCE USE

The next set of questions asks about your consumption of caffeine, supplements, and other substances like tobacco and alcohol. Some questions ask about your current use and others ask about your use LAST YEAR (in 2011).

23. Please estimate how many times you consumed EACH of the listed caffeinated products <u>IN THE LAST 30 DAYS.</u> Please indicate a number of times per day, week, or month. When applicable, select the number of ounces you consumed per cup/can.

*****Do not record things like water, beer, milk, juice, regular gum, and Gatorade, as these do not contain caffeine. <u>Reference for soda</u>: a can=12 fl oz, vending plastic bottle=20 fl oz, and a 2-liter bottle=68 fl oz. <u>Reference for hot beverages</u>: small=12 fl oz, medium=16 fl oz, large=20 fl oz***

	How many times did you consume the listed caffeinated product in the last 30 days?										**How many fluid ounces (fl oz) did you consume per serving?**				
		Number of times						*per*							
	Never	1	2	3	4	5	6+	Day	Week	Month	8 fl oz	12 fl oz	16 fl oz	20 fl oz	24+ fl oz
EXAMPLE: *I drink an 8 fl oz mug of coffee. 2 times a day*	O	O	●	O	O	O	O	●	O	O	●	O	O	O	O
COFFEE/TEA (caffeinated only)															
a. Coffee *(hot, cold, iced, blended, espresso)*	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O
b. Hot brewed Tea	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O
c. Iced Tea *(sweet, unsweet, canned, fresh brewed)*	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O
SOFT DRINKS (caffeinated only - regular & diet)															
d. Cola or Pepper type soda *(Coke, Pepsi, Dr. Pepper, etc.)*	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O
e. Mountain Dew/ Mellow Yellow	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O

ENERGY BEVERAGES (regular and diet)															
f. Energy Shot, 1-4 oz (*5-Hr Energy, Jolt Endurance, etc*)	O	O	O	O	O	O	O	O	O	O					
g. Energy Drink (*Examples: 8 oz: Red Bull; 16 oz: Monster, Rock Star, Rip-It; 24 oz: large Monster*)	O	O	O	O	O	O	O	O	O	O	O		O		O
CAFFEINATED GUM & MEDICATIONS/SUPPLEMENTS											**# of pills/sticks of gum per use (write in number)**				
h. Caffeinated Gum	O	O	O	O	O	O	O	O	O	O	1	2	3	4	5+
i. Caffeine Pills (*Vivarin/ NoDoz/Generic*)	O	O	O	O	O	O	O	O	O	O	1	2	3	4	5+
j. Dexatrim or other weight control aides	O	O	O	O	O	O	O	O	O	O	1	2	3	4	5+

24. **How does your level of caffeine consumption in the LAST 30 DAYS compare to your average level of caffeine consumption LAST YEAR (in 2011)?**
    - O I consumed more caffeine in the last 30 days than on average in 2011
    - O I consumed about the same amount of caffeine in last 30 days as on average in 2011
    - O I consumed less caffeine in the last 30 days than on average in 2011

25. **For EACH dietary supplement listed below, please estimate how often you used that product <u>LAST YEAR</u> (in 2011).**

    For each product USED in 2011, please select one bubble to answer each of the remaining questions on that row. If you use a Performance-enhancing/body building supplement not listed below, please write it in the "OTHER" category and complete the row.

	<u>In 2011</u>, in how many months did you use this product?	**During the months you used this product in 2011, how often did you take it?**	**Did you use this product as directed (on the label)?**	**Has this product caused you any side-effects?**	**Have you used, or do you plan to use this product in 2012?**

	NEVER	1-3 months	4-6 months	7 or more months	less than 1 day/wk	1-3 days/wk	4 or more days/wk	Yes	No, use more	No, use less	Yes	No	Yes	No
EXAMPLE: *I used Product X for 2 months in 2011, 2 times a week as directed. I did not experience side effects and I plan to use Product X in 2012.*	O	●	O	O	O	●	O	●	O	O	O	●	●	O
LIST OF SUPPLEMENTS														
a. **NOXplode 2.0**, BSN	O	O	O	O	O	O	O	O	O	O	O	O	O	O
b. **HydroxyStim**, MuscleTech	O	O	O	O	O	O	O	O	O	O	O	O	O	O
c. **CellMass**, BSN	O	O	O	O	O	O	O	O	O	O	O	O	O	O
d. **LIPO6 Black**, Nutrex	O	O	O	O	O	O	O	O	O	O	O	O	O	O
e. **NeuroCore**, Muscle Tech	O	O	O	O	O	O	O	O	O	O	O	O	O	O
f. **Muscle Milk**, CytoSport	O	O	O	O	O	O	O	O	O	O	O	O	O	O
g. **Red Line Ultra Hardcore,** VPX	O	O	O	O	O	O	O	O	O	O	O	O	O	O
h. **Animal Pak**, Universal	O	O	O	O	O	O	O	O	O	O	O	O	O	O
i. **OxyELITE Pro™**, USPlabs	O	O	O	O	O	O	O	O	O	O	O	O	O	O
j. **Syntha-6**, BSN	O	O	O	O	O	O	O	O	O	O	O	O	O	O
k. **Jack 3D**, USPlabs	O	O	O	O	O	O	O	O	O	O	O	O	O	O
l. **HEMO-RAGE Black Ultra Concentrate**, Nutrex	O	O	O	O	O	O	O	O	O	O	O	O	O	O
m. **Shred Matrix**, MusclePharm	O	O	O	O	O	O	O	O	O	O	O	O	O	O
n. Generic Protein Powder (whey isolate or soy)	O	O	O	O	O	O	O	O	O	O	O	O	O	O
o. Generic Nitric oxide boosting / arginine product	O	O	O	O	O	O	O	O	O	O	O	O	O	O
p. Generic Creatine	O	O	O	O	O	O	O	O	O	O	O	O	O	O
q. Generic 1,3 Dimethyl-amylamine (DMAA) capsules or powder	O	O	O	O	O	O	O	O	O	O	O	O	O	O
r. Carbohydrate / electrolyte sports drink, bar or gel (such as Gatorade; Power Bar; Gu)	O	O	O	O	O	O	O	O	O	O	O	O	O	O
OTHER PERFORMANCE-ENHANCING / BODY BUILDING SUPPLEMENTS														
Write in any supplements you used in 2011 that are not listed above.														
1.	O	O	O	O	O	O	O	O	O	O	O	O	O	O
2.	O	O	O	O	O	O	O	O	O	O	O	O	O	O
3.	O	O	O	O	O	O	O	O	O	O	O	O	O	O
4.	O	O	O	O	O	O	O	O	O	O	O	O	O	O

26. Which statement best describes your use of <u>tobacco products</u> (cigarettes, pipes, and cigars) LAST YEAR (in 2011)? Do not include your use of smokeless tobacco products.

O In 2011, I did not smoke tobacco products (*skip to 27*)
O I smoked tobacco products but quit (*continue to 26a*)
O I smoked tobacco products 3 or less times per week (*continue to 26a*)
O I smoked tobacco products 4-6 times per week (*continue to 26a*)
O I smoked tobacco products at least one time per day (*continue to 26a*)

26a. When you smoked LAST YEAR (in 2011), how many cigarettes did you smoke per day?

O Less than 1 cigarette per day
O 1 cigarette per day
O 2 to 5 cigarettes per day
O 6 to 10 cigarettes per day
O 11 to 20 cigarettes per day
O More than 20 cigarettes per day

27. Which statement best describes your use of <u>smokeless tobacco products</u> (chew, dipping, and pinching) LAST YEAR (in 2011)?

O In 2011, I did not use smokeless tobacco products (*skip to 28*)
O I used smokeless tobacco products but quit (*continue to 27a*)
O I used smokeless tobacco products 3 or less times per week (*continue to 27a*)
O I used smokeless tobacco products 4-6 times per week (*continue to 27a*)
O I used smokeless tobacco products at least one time per day (*continue to 27a*)

27a. When you used smokeless tobacco products LAST YEAR (in 2011), approximately how much were you chewing, dipping, or pinching per day?

O Less than ¼ can or pouch per day
O About ¼ can or pouch per day
O About ½ can or pouch per day
O About ¾ can or pouch per day
O 1 can or pouch per day
O More than 1 can or pouch per day

28. **Which statement best describes your use of any other type of <u>nicotine-delivery product</u> (electronic/e-cigarette or pipe, dissolvable tobacco, lotions or gel, tobacco mint) LAST YEAR (in 2011)?**
    - O In 2011, I did not use nicotine-delivery products
    - O I used nicotine-delivery products but quit
    - O I used nicotine-delivery products 3 or less times per week
    - O I used nicotine-delivery products 4 – 6 times per week
    - O I used nicotine-delivery products at least one time per day

29. **Which statement best describes your use of any <u>Nicotine Replacement Therapy</u> (NRT) Product (gum, patch, spray, lozenge) LAST YEAR (in 2011)?**
    - O In 2011, I did not use Nicotine Replacement Therapy products
    - O I used Nicotine Replacement Therapy products but quit
    - O I used Nicotine Replacement Therapy 3 or less times per week
    - O I used Nicotine Replacement Therapy 4 – 6 times per week
    - O I used Nicotine Replacement Therapy at least one time per day

30. **LAST YEAR (in 2011), how often did you have a drink containing alcohol?**

    - O Never
    - O Monthly or less
    - O Two to four times a month
    - O Two to three times per week
    - O Four or more times per week

31. **LAST YEAR (in 2011), how many standard drinks containing alcohol did you have on a typical day when you were drinking? *A standard drink is defined as 12 ounces of beer, 8 ounces of malt liquor, 5 ounces of wine, or 1.5 ounces (a "shot") of 80-proof distilled spirits or liquor (gin, rum, vodka, or whiskey)***O I do not consume alcoholic beverages
    - O 1 or 2 drinks per day
    - O 3 or 4 drinks per day
    - O 5 or 6 drinks per day
    - O 7 to 9 drinks per day
    - O 10 or more drinks per day

32. **LAST YEAR (in 2011), how often did you have six or more drinks on one occasion?**
    - O Never
    - O Less than monthly
    - O Monthly
    - O Two to three times per week
    - O Four or more times per week

SYMPTOMS, MEDICAL DIAGNOSES, AND MEDICATION USE

***The next set of questions asks about some of your medical symptoms, medical diagnoses, and medication use LAST YEAR (in 2011)*.**

33. **LAST YEAR (in 2011), did a medic or other medical provider determine that you were suffering from <u>heat exhaustion or heat stroke symptoms</u>?**

O No (go to question 34)
O Yes (continue ⇩)

If YES, what activity were you engaged in when the episode occurred (*please check all that apply*)?
O During or immediately following APFT
O During or immediately following vigorous cardiovascular exercise such as running, long road march, cycling, or rowing (not APFT)
O During or immediately following moderate to high weight lifting training
O While at rest or during low intensity or minimal exertion activity (such as sitting, waking up, walking)
O In hot environmental conditions
O Within 24 hours of taking a performance-enhancing supplement
O Drinking alcohol just prior or during episode

In 2011, did you experience any episodes of:	**If <u>YES</u>, what activity were you engaged in when the episode occurred (*please select all that apply*)?**
34. <u>unexplained (sudden) loss of consciousness</u> (black out)? O No (go to question 35) O Yes (continue to the right ⇨)	O During or immediately following APFT O During or immediately following vigorous cardiovascular exercise such as running, long road march, cycling, or rowing (not APFT) O During or immediately following moderate to high weight lifting training O While at rest or during minimal exertion activity (such as sleeping, sitting, waking up, walking) O In hot environmental conditions O Within 24 hours of taking a performance-enhancing supplement O Drinking alcohol just prior or during episode
35. <u>seizure-like activity</u> (uncontrollable rhythmic jerks of the arm(s), leg(s), hand(s), or head)? O No (go to question 36) O Yes (continue to the right ⇨)	O During or immediately following APFT O During or immediately following vigorous cardiovascular exercise such as running, long road march, cycling, or rowing (not APFT) O During or immediately following moderate to high weight lifting training O While at rest or during minimal exertion activity (such as sleeping, sitting, waking up, walking) O In hot environmental conditions O Within 24 hours of taking a performance-enhancing supplement O Drinking alcohol just prior or during episode
36. <u>severe muscle aches, stiffness and weakness in combination with very red or cola colored urine</u>? O No (go to question 37) O Yes (continue to the	O During or immediately following APFT O During or immediately following vigorous cardiovascular exercise such as running, long road march, cycling, or rowing (not APFT) O During or immediately following moderate to high weight lifting training O While at rest or during minimal exertion activity (such as sleeping, sitting, waking up, walking) O In hot environmental conditions O Within 24 hours of taking a performance-enhancing supplement

right ⇨)	O Drinking alcohol just prior or during episode
37. <u>unusual episodes of heart palpitations, irregular heartbeats, racing heart, and/or pounding chest</u>? O No (go to question 38) O Yes (continue to the right ⇨)	O During or immediately following APFT O During or immediately following vigorous cardiovascular exercise such as running, long road march, cycling, or rowing (not APFT) O During or immediately following moderate to high weight lifting training O While at rest or during minimal exertion activity (such as sleeping, sitting, waking up, walking) O In hot environmental conditions O Within 24 hours of taking a performance-enhancing supplement O Drinking alcohol just prior or during episode
38. <u>sudden chest pain associated with shortness of breath</u>? O No (go to question 39) O Yes (continue to the right ⇨)	O During or immediately following APFT O During or immediately following vigorous cardiovascular exercise such as running, long road march, cycling, or rowing (not APFT) O During or immediately following moderate to high weight lifting training O While at rest or during minimal exertion activity (such as sleeping, sitting, waking up, walking) O In hot environmental conditions O Within 24 hours of taking a performance-enhancing supplement O Drinking alcohol just prior or during episode
39. <u>unexplained lightheadedness followed by fainting</u>? O No (go to question 40) O Yes (continue to the right ⇨)	O During or immediately following APFT O During or immediately following vigorous cardiovascular exercise such as running, long road march, cycling, or rowing (not APFT) O During or immediately following moderate to high weight lifting training O While at rest or during minimal exertion activity (such as sleeping, sitting, waking up, walking) O In hot environmental conditions O Within 24 hours of taking a performance-enhancing supplement O Drinking alcohol just prior or during episode

40. LAST YEAR (in 2011), how many times did you experience severe dehydration characterized by brown urine and/or the need for medical intervention involving an IV drip?

O 0 times
O 1-2 times
O 3-5 times
O 6-10 times
O > 10 times

41. When you experienced symptoms listed in questions 33-40, were you taking any of the following prescription medications? (*please select all that apply*)

O N/A, I did not experience any of the symptoms above in 2011
O Ritalin
O Concerta
O Adderall

- O Provigel
- O Pseudoephedrine (prescription strength)
- O Dexadrine
- O Class of medications called Monoamine Oxidase Inhibitors (MAOIs such as *Hydrazines, Pirazidol, Minaprine, Selegiline*)
- O Anti-depressants (such as *Prozac, Effexor, Paxil, Zoloft, Celexa, Cimbalta, Trazodone*)
- O Other prescription medication (*Please specify*: _____)
- O I experienced a symptom above but was not taking any prescription medications at the time

42. When you experienced symptoms listed in questions 35-42, were you taking any of the following Over-The-Counter (OTC) medications or supplements? (*please select all that apply*)

O N/A, I did not experience any of the symptoms above in 2011
O Pseudoephedrine (such as *Actifed, Contac, Claritin-D, Zyrtec-D, Mucinex-D, and Sudafed*)
O Phenylephrine (such as *Benadryl Allergy, Tylenol Sinus, Theraflu, Robitussin CF, and DayQuil*)
O Propylhexedrine (such as *Bezedrex*)
O Ephedrine
O Cold medications that required you to present your Driver's License prior to purchase
O Other OTC medication (*Please specify*: _____)
O I experienced a symptom above but was not taking any OTC medications at the time

43. Has a medical provider <u>ever</u> told you that you have ANY of the following: (*please select all that apply*)

O Brain infections (such as *meningitis or encephalitis*)
O Head injury/head trauma
O High blood pressure
O Aneurysm
O Liver disease
O Liver failure/hepatic failure
O Kidney failure/renal failure
O Hypothyroidism
O Atrial fibrillation
O Heat exhaustion
O Heat stroke
O Seizures
O Abnormally rapid/irregular heart beat (such as *supraventricular tachycardia, Wolf-Parkinson-White syndrome*)
O Diabetes
O Hepatitis A, B, or C (*liver infection*)
O None of the above

SLEEP

The next three questions ask about your sleep patterns.

44. Regarding your sleep and sleeping habits, do you often… (*please select all that apply*):

- O Have difficulty falling asleep, staying asleep during the night, or waking up too early?
- O Have problems with unrestful sleep?
- O Have problems with daytime sleepiness such as dozing off or have difficulty staying awake during routine activities?
- O Get less than 5 hours of sleep on 3 or more consecutive nights?
- O None of the above

45. Within the last 30 days, what is the average number of hours of sleep that you get… (to the nearest hour)

	<2 hrs	2-3 hrs	4-5 hrs	6-7 hrs	≥ 8 hrs
a. On weeknights/work nights?	O	O	O	O	O
b. On weekends/non-work nights?	O	O	O	O	O

46. In general, how does this compare to the average amount of sleep you were getting LAST YEAR (in 2011)?

- O I get a lot less sleep now than I averaged in 2011
- O I get a little less sleep now than I averaged in 2011
- O I get about the same amount of sleep now than I averaged in 2011
- O I get a little more sleep now than I averaged in 2011
- O I get a lot more sleep now than I averaged in 2011

END

Thank you for completing this questionnaire!

Annex D: ALFOODACT 034-2011 Army Air Force Exchange Services

Subject: ALFOODACT 034-2011 Army Air Force Exchange Services (AAFES) Is Pulling Products Containing Dimethoxymethamphetamine (DMAA)
Date Issued: December 03, 2011

1. REFERENCES:
a. DLAR 4155.26/AR 40-660/NAVSUPINST 10110.8c/AFI 48-116/MCO 10110.38c, DOD Hazardous Food & Nonprescription Drug Recall System.
b. Allied Communications Publication 121, US SUPP-1 (f).

2. BACKGROUND:
As a apart of an ongoing investigation, AAFES is pulling items off of their shelves that contain the ingredient Dimethoxymethamphetamine (DMAA). AAFES has indicated that these are GNC products, DMAA is not an approved dietary supplement. DMAA functions as an amphetamine and may be associated with some recent deaths in soldiers. As a precaution, all stores need to physically check the ingredients on the GNC products and all dietary supplements, weight gain and muscle building products. If there are any products containing DMAA they need to be pulled, placed on medical hold and report inventory on hand.
As new information is received this ALFOODACT message will be updated.

3. PRODUCTION DATES/IDENTIFYING CODES:
A list of products carried by AAFES (to include GNC) includes:
USPlabs Jack 3D (Tropical Fruit and Lemon Lime)
USPlabs Oxy Elite Pro
Nutrex Lipo 6 Black Caps (his and hers)
Nutrex Lipo 6 Black Ultra Concentrated (his and hers)
Nutrex Hemo Rage Black Powder, Punch, Berry
Isatori PWR
Muscletech Neurocore
Muscletech Hydroxystim
Fahrenheit Nutrition Lean EFX
Muscle Warfare Napalm
All American Efx K-Otic
SNI Nitric Blast
BIORhythm SSIN Juice
Muscle Meds Code Red
SEI MethhlHex 4, 2
Grenade (universal) Grenade
M.A.P. (iovate) Arson
Gaspari Nutrition Spirodex

4. MANUFACTURER/DISTRIBUTOR:
AAFES/GNC Products

5. DISTRIBUTION: All

6. REASON FOR ACTION: Due to containing the ingredient Dimethoxymethamphetamine (DMAA)

7. INSTRUCTIONS AND ADDITIONAL INFORMATION FOR MESSAGE RECIPIENTS:

a. Immediately inventory stocks to identify the above items and secure in a "Medical Hold" status to provide assurance of no further issue/sale/use.
POSITIVE FINDINGS should be reported to Accountable Officers/Vendor Representatives of that facility. Accountable Officer/Agency representatives/Buyers/Contracting Officers should seek/refund/credit/replacement through the normal distribution channel with which the product was received (i.e. Distribution Centers, Prime Vendors, or Manufacturers).
b. Ships at sea are authorized to destroy or dispose of recalled products at their discretion. Documentation for the number of pounds and cases, and any additional pertinent information must be signed by the Accountable Officer and is required for the purpose of recouping to the government the cost of the product involved. In order to get credit please use a SF 364 and forward to your supporting FISC and copy furnished to NAVSUP 51.
Your supporting FISC should forward to the account manager at DLA Troop Support. The form should include the number of the recall authorizing the survey action. Home-ported ships/galleys will utilize DD form 1149 to transfer w/ reimbursement to the PV. The PV will submit credit invoice to the account manager at DLA Troop Support.
c. DLA Troop Support Subsistence Prime Vendors must report POSITIVE and NEGATIVE RESPONSES directly to the their DLA Troop Support Contracting Officer with a courtesy copy to the Consumer Safety Officer (dscpconssafofc@dla.mil)..
d. DeCA, AAFES, MWR, VA, MCCS, or other non-DLA Troop Support agencies SHOULD NOT respond to the DLA Troop Support Consumer Safety Officer. These agencies should report POSITIVE and NEGATIVE responses in accordance with their agency recall policies.
e. When corresponding with DLA Troop Support concerning this message please include this message's subject in your subject line.

8. The Point of Contact for this ALFOODACT message is CW3 Tony Hemphill, Consumer Safety Officer at DLA-FTW. VOICE, DSN: 444-2922, Commercial (215) 737-2922, or by FAX, DSN: 444-7526, or Commercial, (215) 737-7526, email dscpconssafofc@dla.mil .

9. Individuals or groups that would like to receive recall messages electronically can forward their email address to dscpconssafofc@dla.mil , with "add to list" in the subject line. To be removed from the list place "remove from list" in the subject line.

10. Previous recalls and frequently asked questions are available at the following web site:

http://www.troopsupport.dla.mil/subs/fso/alfood/alfood.asp . The navigation tool to the left allows you to also view DLA Troop Support Alerts and Archived Vendor Recalls.

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7
Subject: UPDATE to ALFOODACT 034-2011 and ALFOODACT 036-2011, and 041-2011 Dimethylamylamine (DMAA) Is Placed On Medical Hold Due To Possible Serious Adverse Health Effects
Date Issued: December 30, 2011

1. REFERENCES:
a. DLAR 4155.26/AR 40-660/NAVSUPINST 10110.8c/AFI 48-116/MCO 10110.38c, DODHazardous Food & Nonprescription Drug Recall System.
b. Allied Communications Publication 121, US SUPP-1 (f).

2. BACKGROUND/UPDATE:
UPDATE:
It has been determined that "Grenade (Universal) Grenade and M.A.P. (Iovate) Arson does not contain Dimethylamylamine (DMAA) and should be removed from medical hold and returned to the shelves for purchase. All other products that contain DMAA shall remain on medical hold status pending disposition instructions.
(December 22, 2011)
It has been determined that "All American EFX K-Otic" does not contain Dimethylamylamine (DMAA) and should be removed from medical hold and returned to the shelves for purchase. All other products that contain DMAA shall remain on medical hold status pending disposition instructions.

BACKGROUND: (December 7, 2011)
ALFOODACT 036-2011 Updates/Corrects ALFOODACTS 034-2011, for all references mentioning the ingredient Dimethoxymethamphetamine (DMAA) "THIS IS THIS INCORRECT INGREDIENT". The correct ingredient in question is Dimethylamylamine (DMAA). A vasoconstrictor and central nervous system stimulant, (DMAA) has been associated with potentially serious adverse health effects. All products containing DMAA should be secured and placed in medical hold status pending disposition instructions. There is an ongoing review by the Department of Defense regarding potentially serious adverse health effects associated with DMAA. As a precaution, all activities are required to physically check the ingredients on all dietary supplements, weight gain, and muscle building products. All products containing DMAA are to be pulled, and placed on medical hold. On hand inventories of products containing DMAA must be reported to accountable officers.

3. PRODUCTION DATES/IDENTIFYING CODES:
Listed below are known products that contain Dimethylamylamine (DMAA), this list is "NOT ALL INCLUSIVE":
USPlabs Jack 3D (Tropical Fruit and Lemon Lime)
USPlabs Oxy Elite Pro
Nutrex Lipo 6 Black Caps (his and hers)
Nutrex Lipo 6 Black Ultra Concentrated (his and hers)
Nutrex Hemo Rage Black Powder, Punch, Berry
Isatori PWR

Muscletech Neurocore
Muscletech Hydroxystim
Fahrenheit Nutrition Lean EFX
Muscle Warfare Napalm
SNI Nitric Blast
BIORhythm SSIN Juice
Muscle Meds Code Red
SEI MethhlHex 4, 2
Gaspari Nutrition Spirodex

4. MANUFACTURER/DISTRIBUTOR: Various Manufacturers

5. DISTRIBUTION: All

6. REASON FOR ACTION: Due to possible association with serious adverse health effects.

7. INSTRUCTIONS AND ADDITIONAL INFORMATION FOR MESSAGE RECIPIENTS:
a. Immediately inventory stocks to identify the above items and secure in a "Medical Hold" status to provide assurance of no further issue/sale/use.
POSITIVE FINDINGS should be reported to Accountable Officers/Vendor Representatives of that facility. Accountable Officer/Agency representatives/Buyers/Contracting Officers should seek/refund/credit/replacement through the normal distribution channel with which the product was received (i.e. Distribution Centers, Prime Vendors, or Manufacturers).
b. Ships at sea are authorized to destroy or dispose of recalled products at their discretion. Documentation for the number of pounds and cases, and any additional pertinent information must be signed by the Accountable Officer and is required for the purpose of recouping to the government the cost of the product involved. In order to get credit please use a SF 364 and forward to your supporting NAVSUP Fleet Logistics Center (NAVSUP FLC) and copy furnished to NAVSUP 51. Your supporting NAVSUP FLC should forward to the account manager at DLA Troop Support. The form should include the number of the recall authorizing the survey action. Home-ported ships/galleys will utilize DD form 1149 to transfer w/ reimbursement to the PV. The PV will submit credit invoice to the account manager at DLA Troop Support.
c. DLA Troop Support Subsistence Prime Vendors must report POSITIVE and NEGATIVE RESPONSES directly to the their DLA Troop Support Contracting Officer with a courtesy copy to the Consumer Safety Officer (dscpconssafofc@dla.mil)..
d. DeCA, AAFES, MWR, VA, MCCS, or other non-DLA Troop Support agencies SHOULD NOT respond to the DLA Troop Support Consumer Safety Officer. These agencies should report POSITIVE and NEGATIVE responses in accordance with their agency recall policies.
e. When corresponding with DLA Troop Support concerning this message please include this message's subject in your subject line.

8. The Point of Contact for this ALFOODACT message is CW3 Tony Hemphill, Consumer Safety Officer at DLA-FTW. VOICE, DSN: 444-2922, Commercial (215) 737-2922, or by FAX, DSN: 444-7526, or Commercial, (215) 737-7526, email dscpconssafofc@dla.mil.

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10. Previous recalls and frequently asked questions are available at the following web site: http://www.troopsupport.dla.mil/subs/fso/alfood/alfood.asp . The navigation tool to the left allows you to also view DLA Troop Support Alerts and Archived Vendor Recalls**.**

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ANNEX E: Table of DoD-reported Adverse Medical Events

Case	Death Case	Pathology	Info from Survey?	ID Info?	Naranjo
				Interviewed By APHC	(5-8 = Probable)
1		Syncope	Y		UTA (0)
2		Syncope	Y		UTA (0)
3	Death Case 1	Hyperthermia	Death	Y	2
4	Death Case 2	Liver Failure	Death	Y	2
5		Rhabdo	Y		2
6		Renal Failure	Note		4
7		Liver Failure	Y	Y	6
8	Death Case 3	Cardiac	Death	Y	UTA
9		Seizure	Y	Y	3
10		Flank Pain-Glomeruloneph	Y	Y	3
11		Hyperthermia	Y		UTA
12		Hypertension	Y		UTA (0)
13		ICH	Y		2
14		Mania			UTA
15		Palpitations	Y		2
16		Ruptured AVM			UTA
17		Seizure	Y		UTA
18		Liver Failure	Y	Y	6
19		Dyspnea	Y	Y	2
20		Stroke	Y		UTA
21		Tachycardia	Y		1
22		Urinary Retention	Y		UTA
23		Rhabdo	Y	Y	2
24		Urinary Retention	Y		UTA
25		Syncope			2
26		Syncope	Y		2
27		Tachycardia			2
28		Hyperthyroidism	Note		UTA
29		Seizure			UTA
30		IBD			UTA

Count	Death Case	Pathology	Info from Survey?	ID Info?	Naranjo
					(5-8 = Probable)
32		Seizure	Y		UTA
33		Renal failure	Y		3
34		Paresthesias	Y		UTA
35		Paresthesias	Y		UTA
36		Paresthesias	Y		UTA
37		A-Fib			UTA
38		Rhabdo			
39		AMI			
40	Death Case 4	Heat stroke, death	Note	Y	UTA

ANNEX F: The Naranjo adverse drug reaction (ADR) probability scale.

Table 2: The Naranjo adverse drug reaction probability scale; To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score	Yes	No	Do not know	Score
1. Are there previous *conclusive* reports on this reaction?	+1	0	0	
2. Did the adverse event occur after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0	
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could have on their own caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the blood detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
			Total	

The Naranjo adverse drug reaction (ADR) probability scale. The Naranjo criteria classify the probability that an adverse event is related to drug therapy based on a list of weighted questions, which examine factors such as the temporal association of drug administration and event occurrence, alternative causes for the event, drug levels, dose – response relationships and previous patient experience with the medication. The ADR is assigned to a probability category from the total score as follows: *definite* if the overall score is 9 or greater, *probable* for a score of 5-8, *possible* for 1-4 and *doubtful* if the score is 0. The Naranjo criteria do not take into account drug-drug interactions. Drugs are evaluated individually for causality, and points deducted if another factor may have resulted in the adverse event, thereby weakening the causal association.

ANNEX G: In-depth Interviews of Service Members with Adverse Events Summary Table

Question		Case									
		9	**12**	**13**	**21**	**22**	**26**	**37**	**A**	**B**	**C**
1	Age	37	31	28	23	35	26	26	20	30	39
3	Gender (Male)	+	+	+	+	+	0	+	+	+	+
4	Current Rank										
	E1-E3								+		
	E4-E6		+	+	+		+	+		+	
	E7-E9	+									+
	O1-O3					+					
5	Service										
	Air Force					+		+	+		
	Army		+		+		+			+	+
	Marines	+		+							
6	Race										
	White	+	+	+	+		+		+		
	Pacific Islander					+					
	Other							+		+	+
7	Weight	179	210	225	150	185	175	184	215	253	194
8	Height (inches)	68	73	72	71	66	68	71.5	70	77	68
	BMI	27.2	27.7	30.5	20.9	29.9	26.6	25.3	30.8	30.0	29.5
9	Adverse Event Date	7/31/ 2011	11/1/ 2011	3/31/ 2011	10/18/ 2011	12/15/ 2011	6/1/ 2011	7/25/ 2011	12/11/ 2011	9/10/ 2012	7/24/ 2012
	Initial Diagnosis										
	Seizure		+								+
	r/o urethritis			+							
	DILI				+						
	Lactic acidosis					+					
	Pneumonia					+					

Question		Case									
		9	12	13	21	22	26	37	A	B	C
	Hypokalemic myopathy						+				
	Rhabdomyolysis							+			
	Cardiac symptoms								+	+	
	Final Diagnosis										
	Seizure		+								
	Glomerulonephritis			+							
	Drug-induced liver injury				+						
	Hypokalemic myopathy						+				
	Rhabdomyolysis							+			
	Cardiac symptoms								+	+	+
10-12	Supplement Use										
	DMAA Containing Supplement Taken	Jack 3D	Jack 3D	Jack 3D	Jack 3D	Jack 3D	Jack 3D	Jack 3D	Jack 3D	Cellular C4 Extreme	Oxyelite Pro
	Time taken before AME	Hours	Day	Hours		31-60 min			1+	31-60 min	Day
	Frequency of use (times/week)	4-6	4 - 6	daily	4 - 6	1-3	4-6	daily	4-6	4-6	daily
	Amount taken on days used (scoops)	Rx serving	1/2 - 1 1/2	3	1-3	1	1-2	1-2	2	2	4 pills
	Length of use	6 weeks	3 weeks	3 days	8 months	3 weeks	2.5 months	2 weeks	6 months	4 months	12 months
	Other supplement used							+	+	+	+
13	Activity level prior to AME										
	Minimal		+		+		+		+		+
	Mild	+						+			
	Moderate			+						+	

Question		Case									
		9	12	13	21	22	26	37	A	B	C
	High					+					
14	Specific Activity performing during AME										
	Running for training									+	
	Running for PT test					+				+	
	Calisthenics									+	
	Marching with a load										
	Obstacle course										
	Sports		+								
	Standing in formation										
	Mission-related (deployed)			+							
	Lifting weights										
	Other	+					+	+	+		+
	Unknown										
15	Environmental Condition										
	Indoors		+				+	+	+		
	Outdoors in warm weather					+					+
	Other	+		+	+					+	
16	Reason for taking Supplement										
	Promote health	+		+				+	+		
	Lose weight			+		+					+
	Provide extra energy	+	+	+	+	+	+	+	+		+
	Enhance muscle building	+	+	+		+	+	+	+	+	
	Increase focus at work				+			+			
	Improve physical performance		+	+	+	+	+	+	+	+	+
	Stay Awake							+			

Question		Case									
		9	12	13	21	22	26	37	A	B	C
	Other	+	+								
17	AME Symptoms										
	Dizziness	+	+		+	+	+	+	+	+	+
	Abdominal pain	+		+				+			
	Dehydration					+		+		+	+
	Nausea	+	+		+		+			+	
	Tingling or numbness		+	+		+	+	+	+	+	
	Vomiting	+			+		+			+	
	Fatigue	+			+	+		+		+	
	Rapid heart rate	+	+	+		+	+	+	+	+	+
	Physical collapse	+				+		+		+	+
	Headache		+					+		+	
	Difficulty w/ urination			+				+			
	Seizures		+								+
	Shortness of breath	+			+	+		+	+	+	
	Chest pain	+				+			+	+	+
	Confusion		+		+			+		+	+
	Memory loss		+					+			
	Anxiety	+	+							+	
	Feeling of impending doom		+			+		+			+
	Hyper/manic behavior	+	+					+	+	+	
	Chills with sweating							+		+	
	Intense itching	+						+			
	Whites of eyes turned yellow	+						+			
	Other	+			+	+		+			+

Question		Case									
		9	12	13	21	22	26	37	A	B	C
18	Taking other energy booster during AME		+	+	+			+			+
19	Taking over the counter meds during AME	+	+							+	
20	Taking prescription meds during AME		+				+	+			
	Medications										
	Effexor		+								
	Clonidine		+								
	Trazodone						+	+			
	Prasin						+				
	Ambien						+				
	Ibuprophen						+			+	
	Oxycodon						+				
21	Treatment for AME received at:										
	Battalion Aid Station				+		+				
	Troop Clinic										+
	Emergency Room		+			+		+	+	+	
	Civilian Urgent Care Clinic										
	Hospital (not ER)										
	Other	+		+							
22	If treated in hospital, how many overnight days?										
	1-2 days					+					
	3-4 days				+				+		
	5-6 days						+	+			
	7 days										
	more than 7 days	+									

Question		Case									
		9	12	13	21	22	26	37	A	B	C
	Treated in hospital, not overnight		+							+	+
	not treated in a hospital			+							
23	Health returned to level it was prior to AME?	+	+	+	+		+	+	+	+	
24	Days taken to fully recover	120	1	6	79	3	21	150	60	2	18
25	Days of missed and/or limited duty	150	7	0	63	7	0	19	60	1	18
26	Prior medical problems										
	Heat injury										
	muscle break							+			
	kidney/renal failure					+					
	liver/hepatic failure					+					
	Fainting/syncope							+			
	seizures										+
	Rapid or irregular heart beat				+	+					+
	heart disease, angina pectoris, heart attack										
	aneurysms										
	sickle cell trait										
	high blood pressure		+				+				
	diabetes										
	substance abuse disorder										
	PTSD		+				+			+	
	generalized anxiety		+								
	depression		+								

Question		Case									
		9	12	13	21	22	26	37	A	B	C
	Other		+		+						+
	No history of medical conditions	+		+					+		
27	Other illness or disease at time of AME					+		+	+		
28	Hours of sleep/night	5	1.5	3.5	1.5	6.5	4	6.5	5.5	5.5	4
29	Smoker	+	+	+						+	+
30	Average # of cigarettes	2.5/ month	10/ day	3.5/ week						3/ day	10/ day
31	Smokeless tobacco products	+	+	+	+		+				
32	Amount of smokeless tobacco product used										
	Less than 1/4 can				+						
	About 1/4 can										
	About 1/2 can		+								
	About 3/4 can	+									
	1 can			+			+				
	more than 1 can										
33	Nicotine replacement products										
34	Type of nicotine replacement product										
	nicotine patches										
	nicotine gun										
	nicotine lozenges										
	other										
35	Nicotine replacement produce dose										
36	Alcohol consumption (days)		1/ week			2/ month	1/ month	3/ year	6/ month	1/ week	

Question		Case									
		9	12	13	21	22	26	37	A	B	C
37	Number of alcoholic drinks/day		1			1.5	1	3	5.5	2	
38	Drank alcohol within 24 hours of AME										
39	Days of exercise/week prior to AME (not running)										
	Never										
	1-2 days per week										
	3-4 days per week					+	+	+	+		+
	5+ days per week	+	+	+	+					+	
40	Days of running/week prior to AME										
	Never	+			+						
	1-2 days per week			+			+				
	3-4 days per week		+			+		+	+	+	+
	5+ days per week										
41	Days of sports participation/week prior to AME										
	Never	+		+	+	+	+				+
	1-2 days per week		+					+		+	
	3-4 days per week										
	5+ days per week								+		
42	Sports participated in				none	none	none			basket ball, football	none
43	Date of last mandatory PFT	Apr-11	Jan-11	Nov-11	Jul-11	Dec-12		Mar-11	Nov-11	Oct-13	May-13
44	Score of last mandatory PFT	280	287	281	291			99.6	95.7	300	
45	Service specific PFT										
	Air Force					+		+	+		

Question		Case									
		9	12	13	21	22	26	37	A	B	C
	1.5 mile run time							9:55	10:53		
	# of sit up					52		58	58		
	# of push-ups					57		67	76		
	Waist (in)					35		28.5	32		
	Army		+		+		+			+	+
	2 mile run time		14:00		12:45					16:30	31 mins (walker)
	# of sit up		80		73					89	50
	# of push-ups		90		82					85	40
	Marines	+									
	3 mile run time	<22:00									
	# of crunches	100									
	# of pull-ups	20									
	Navy										
	Time Run or Swim										
	Event time										
	# of curl-ups										
46	Recent fitness test performance compared to before AME										
	Better			+							
	Worse									+	
	About the same					+					
	No test since AME	+	+		+			+	+		+
47	Take booster and/or supplements prior to PFT	+	+							+	+
48	Belief: Impact of boosters/supplements on PFT performance. Performance is:										

Question		Case									
		9	12	13	21	22	26	37	A	B	C
	A lot worse										
	A little worse								+		
	About the same							+			+
	A little better		+			+					
	A lot better	+								+	
	N/A			+	+		+				
49	Experienced other AME		+					+	+		
50	Seek medical treatment for additional AME										
	Yes							+			
	No								+		
	No additional AME		+	+			+			+	+