

Defense Health Board, August 2013

Dietary Supplements: Policy, Science and the DoD



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Disclaimer

This work was supported by the U.S. Army Medical Research and Materiel Command (USAMRMC) and the Department of Defense Center Alliance for Dietary Supplement Research. The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Army or the Department of Defense. Human subjects participated after giving their free and informed voluntary consent.

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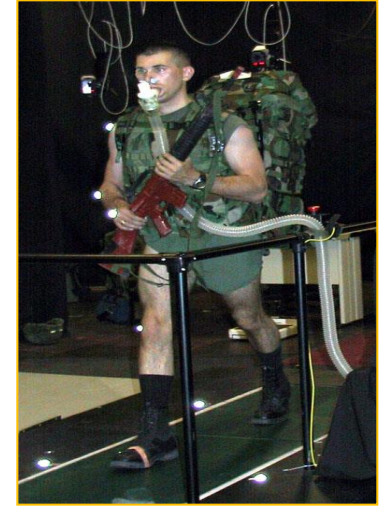
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200 USARIEM PERSONNEL

31% Military
48% Civilian
21% Contractor



Topics to be Addressed

- Regulation of Dietary Supplements in the United States.
- Safety and Efficacy of Dietary Supplements.
- Use of Dietary Supplements and Caffeine by Uniformed DoD Personnel, Including Use in Afghanistan.
- Relevant DoD Committees & Programs



Regulatory Status of Dietary Supplements in U.S.

- Drugs: Intensively regulated by U.S. Food & Drug Administration (FDA).
- Dietary supplements: Limited regulation by FDA.
 - Can only be withdrawn if FDA can prove clear and present danger
 - Unlike drugs, onus is on FDA to prove danger, not manufacturer to prove safety
 - Supplement must pose “a significant or unreasonable risk of illness or injury” before FDA can take action
- Congress recently added new requirements for certification of purity of dietary supplements to current law – DSHEA.



Dietary Supplement & Health Act of 1994 (DSHEA)

Deregulation of Supplements in the U.S.

- Dietary supplements are not subject to pre-market FDA approval unless they contain a “New Dietary Ingredient”.
- Demonstration of Safety & Efficacy by manufacturer is not required.
 - But claims are restricted
- Most naturally-occurring substances, except those already classified as drugs, can be labeled as a dietary supplement.
 - For example: ephedra, melatonin
- Clinical trials of supplements are not regulated by the FDA.
- Without “National Standards” that establish safety and efficacy, the DoD should have processes for monitoring supplement use and abuse since ~70% of Warfighters regularly take a DS or related product.



Drug vs. Dietary Supplement Approval Process

Requirements for FDA Approval of a Drug

Safety & Efficacy

- 1) Pre-clinical animal efficacy and safety data: Extensive animal toxicology testing, conducted with multiple species and doses
- 2) Phase I: Initial testing on human subjects to determine safety and possible side effects (20-80 subjects minimum)
- 3) Phase II: Test efficacy of drug in treatment of patients with specific disease or condition (several hundred subjects)



Drug vs. Dietary Supplement Approval Process

Requirements for FDA Approval of a Drug, cont'd

- 4) Phase III: Conclusive evidence of efficacy (several hundred to several thousand subjects)
 - Strict statistical criteria established by regulatory authorities
 - Data must meet formal chain-of-custody and audit requirements – significantly stricter than any peer-reviewed publication

\$ Estimated cost – \$800 million or more for complete process!

- 5) Formal post-marketing surveillance and regular inspections by FDA

**No similar requirements exist for dietary supplements.
'Natural' substances can be toxic and must be proven safe and effective.**

DS Efficacy – Lots Of Claims

Large, Well-Controlled Clinical Trials of Promising Dietary Supplements and a Meta-Analysis

1. Effect of *Hypericum perforatum* (St. John's Wort) in Major Depressive Disorder: A Randomized Controlled Study; Journal of the American Medical Association, 2002.

- **No beneficial effect**



N = 340

2. Effects of Long-Term Vitamin E Supplementation on Cardiovascular Events and Cancer: A Randomized Controlled Trial; The HOPE and HOPE-TOO Trial; Journal of the American Medical Association, 2005.

N = 3994

- **Significant adverse effects (13% greater incidence of heart failure in patients at high risk for cardiovascular disease)**

Large, Well Controlled Clinical Trials of Promising Dietary Supplements

3. Effect of Raw Garlic vs. Commercial Garlic Supplements on Plasma Lipid Concentrations in Adults with Moderate Hypercholesterolemia: A Randomized Clinical Trial; *Archives of Internal Medicine*, 2007.

N = 192



- **No beneficial effects**

4. Mortality in Randomized Trials of Antioxidant Supplements for Primary and Secondary Prevention: Systematic Review and Meta-analysis; *Journal of the American Medical Association*, 2007.

N = 232,606

- **Treatment with beta carotene, vitamin A and vitamin E may increase mortality**

5. Ginkgo for Memory Enhancement: A Randomized Controlled Study, *Journal of the American Medical Association*, 2002.

- **No beneficial effects**



N = 230

NEGATIVE RESULTS IN LARGE, APPROPRIATELY DESIGNED TRIALS OF SUPPLEMENTS ARE TYPICAL

Ginkgo: Unanticipated Adverse Effects of a Widely-Used Ancient Herbal Remedy

- 2013 Toxicology and Carcinogenesis Studies of *Ginkgo biloba* Extract in Rats and Mice; conducted by National Toxicology Program, NIH
- **Increased prevalence of thyroid and liver cancer; especially in males**

N = over 1000 animals





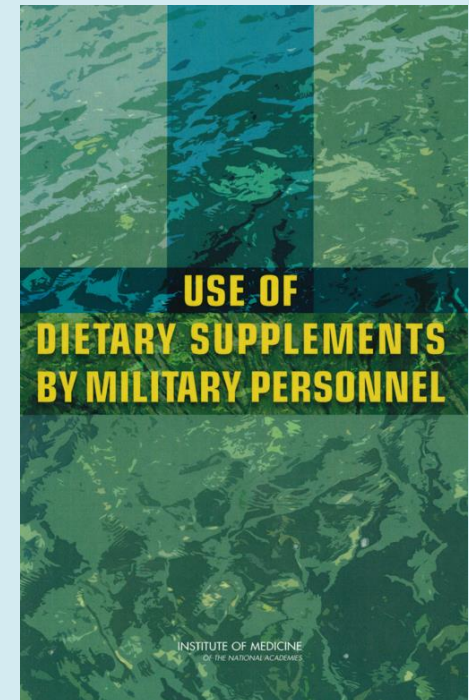
Dietary Supplements and the DoD

- Unique regulatory status of dietary supplements (DSHEA) provides no statutory pathway for establishing safety and efficacy for use in DoD personnel – or any other populations
- In 2008, the Institute of Medicine of the National Academy of Sciences, recommended the DoD establish processes to monitor, sponsor research, and develop policies on use of dietary supplements
 - The study was funded and conducted at the request of the DoD (MEDCOM/MRMC)

2008 Institute of Medicine Report

Use of Dietary Supplements by Military Personnel

The committee recommended that the DoD designate a committee/entity to be responsible for oversight and coordination of dietary supplement related activities, and provide guidance to military leadership about other activities related to management of dietary supplement use (e.g. research, outreach and education, adverse event reporting).





Department of Defense **INSTRUCTION**

DoD ***Nutrition Policy***

NUMBER 6130.05
February 18, 2011

b. The Dietary Supplements and Other Self-Care Products Subcommittee shall make policy recommendations to the Military Services and other DoD beneficiary groups regarding the use of dietary supplements, where indicated, in areas including, but not limited to:

- (1) Dietary supplement education.
- (2) Military-specific research.
- (3) Adverse event reporting and monitoring.
- (4) Human performance optimization.
- (5) Military Service special operations.
- (6) Identification of research gaps and requirements.
- (7) Identification of opportunities for resource sharing and cost containment among the Military Services.



Service Members and Supplements

- Unique occupational demands placed on service members may result in unique patterns of supplement use.
 - Chronic sleep loss, intense cognitive and physical demands and environmental stress
- Physical fitness and weight status are regularly assessed in all service members, and failure to meet standards can lead to adverse career actions.
- Many dietary supplements and related products are marketed as enhancing physical and/or mental performance and aiding weight loss.
- Military personnel are targeted in advertising and promotions.



Service Members and Supplements

- Service members believe dietary supplements can help meet their unique occupational requirements, and are more likely to use them than civilians
- Use of dietary supplements by service members is also of concern as adverse events may be exacerbated by the stressors service members experience:
 - sustained and extensive physical and mental demands
 - environmental stress
 - sleep loss, continuous operations
 - battlefield and other deployment risks
 - repeated deployment to combat theatres

Use of Dietary Supplements in the DoD



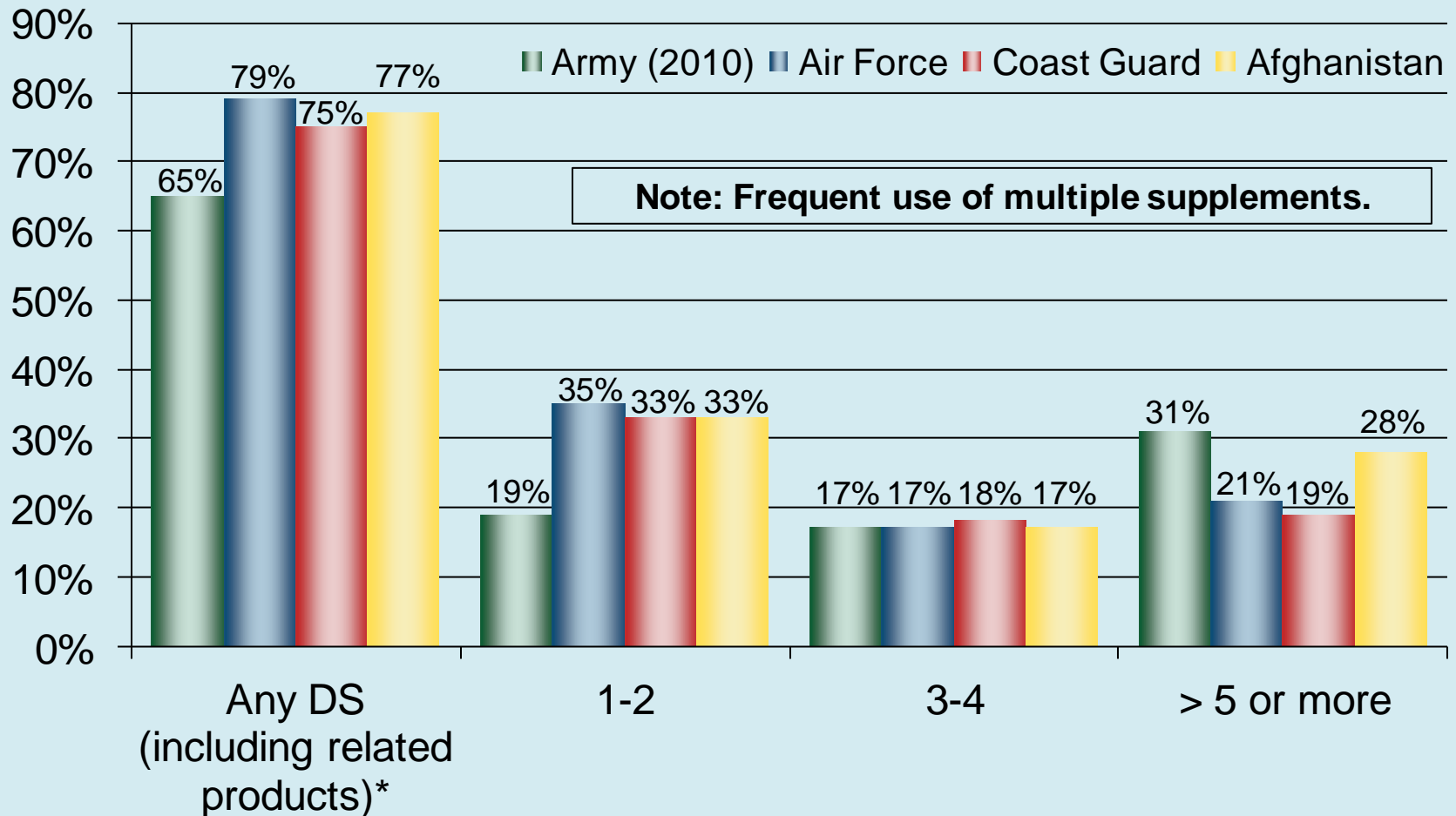


Dietary Supplements & Caffeine: US DoD & Coast Guard Surveys

- We conducted multiple detailed, anonymous surveys of uniformed personnel supplement use, and demographic and lifestyle factors associated with use.
- Over 4000 randomly selected uniformed personnel at Army, Air Force and Coast Guard bases located in the United States and abroad, including Afghanistan, in 2010-2011.
 - Navy and Marine study in planning.
- Use of sports beverages, bars and gels and meal replacement drinks was also assessed.
 - Although they are not classified as dietary supplements, they are often marketed for claimed performance-enhancing properties and weight loss.
- Total caffeine intake from all sources assessed.



Survey Results: Reported Intake of Dietary Supplements and Related Products at least once a week *

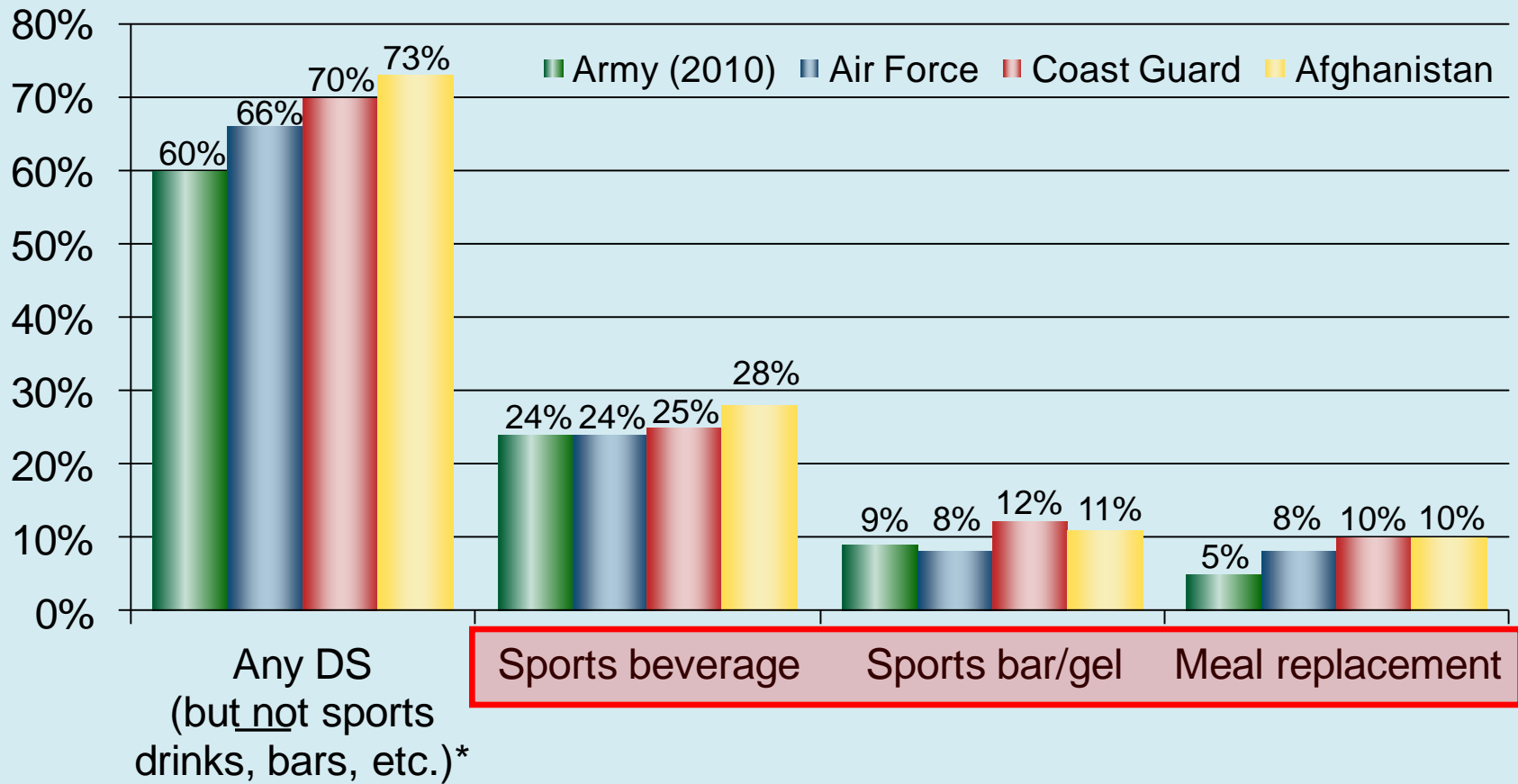


* Including sports drinks/bars/gels, meal replacements, and energy drinks/shots



Reported Intake of Dietary Supplements* and Related Products At Least Once per Week

Army, AF and CG vs. Afghanistan



*Not including sports drinks/bars/gels, meal replacements, or energy drinks/shots



MALES

Most Popular Dietary & Nutritional Supplements

Army-wide (2010) vs. Afghanistan (2010) Weekly Use

<i>Army-wide</i>		<i>Afghanistan</i>	
Supplement	% Consuming	Supplement	% Consuming
1. Energy drink	43	1. Multivitamin/mineral	48
2. Multivitamin/mineral	37	2. Protein & AA powder	46
3. Protein & AA powder	32	3. Energy drink	44
4. Body-building DS	26	4. Body-building DS	42
5. Sports drink	24	5. Sports drink	27
6. Individual vitamin or mineral (e.g. Vitamin C, Vitamin D, Vitamin E)	19	6. Individual vitamin or mineral (e.g. Vitamin C, Vitamin D, Vitamin E)	22
7. Other DS	17	7. Other DS	18
8. Caffeine	11	8. Caffeine	11
9. Sports bar/gel	9	9. Sports bar/gel	10
10. Herbal DS	8	10. Weight loss DS	9



FEMALES

Most Popular Dietary & Nutritional Supplements

Army-wide (2010) vs. Afghanistan (2010) Weekly Use

<i>Army-wide</i>		<i>Afghanistan</i>	
Supplement	% Consuming	Supplement	% Consuming
1. Multivitamin/mineral	43	1. Multivitamin/mineral	56
2. Individual vitamin or mineral (e.g. Vitamin C, Vitamin D, Vitamin E)	33	2. Individual vitamin or mineral (e.g. Vitamin C, Vitamin D, Vitamin E)	44
3. Energy drink	24	3. Sports drink	33
4. Body-building DS	18	4. Energy drink	29
5. Sports drink	18	5. Protein & AA powder	27
6. Other DS	15	6. Other DS	21
7. Herbal DS	10	7. Body-building DS	17
8. Weight loss DS	9	8. Weight loss DS	15
9. Caffeine	9	9. Sports bar/gel	14
10. Meal replacement	8	10. Caffeine	10



Why Do Service Members Take Supplements?

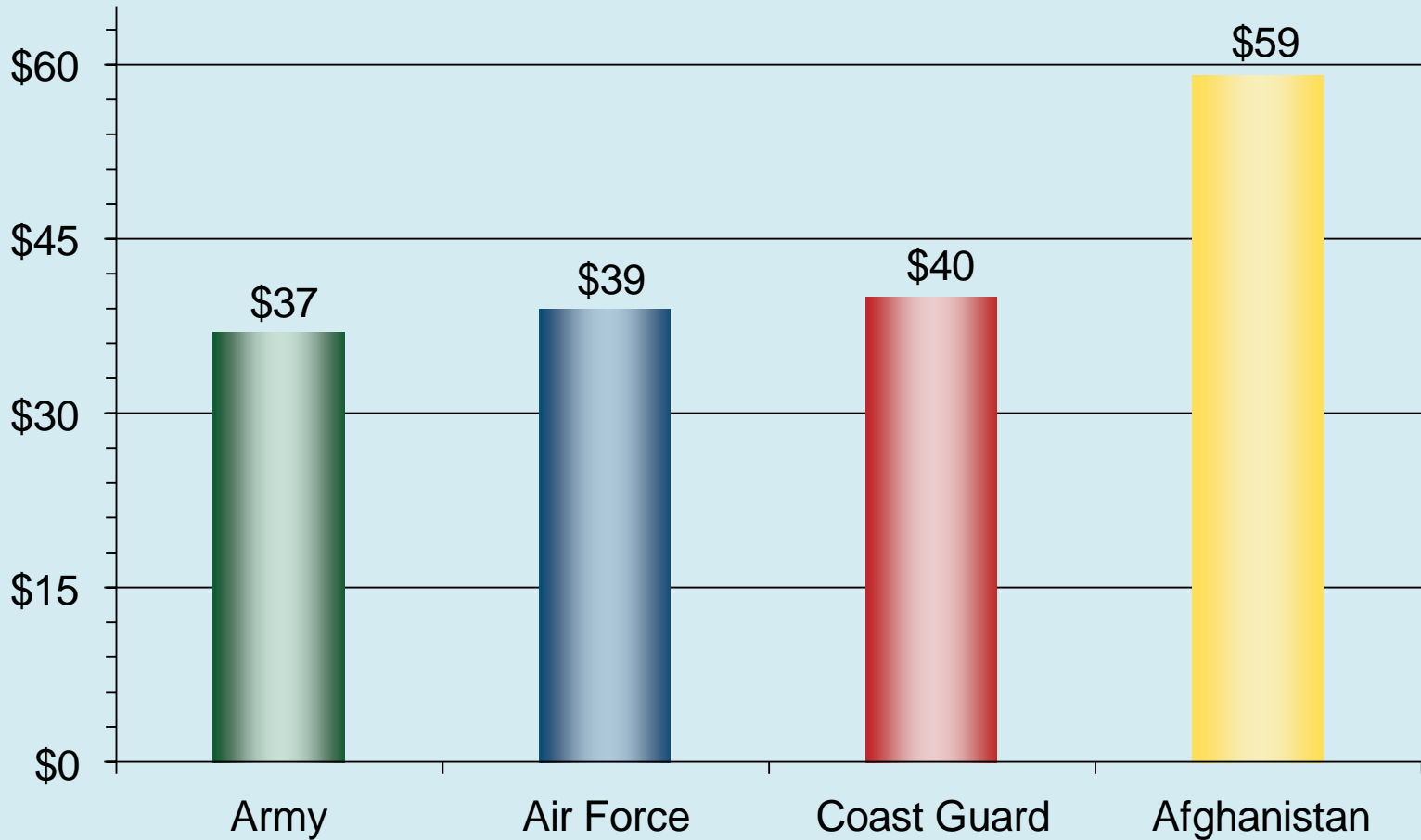
Reasons for use	% Army-wide (2010)*	% Afghanistan (2010)*
Promote general health	41	50
Greater muscle strength	20	30
Performance enhancer	21	27
Give more energy	20	25
Increased endurance	11	14
Weight loss	17	12
Not sure	7	4

**NOT INCLUDING ENERGY DRINKS (e.g. Monster), ENERGY SHOTS, OR SPORTS DRINKS, GELS, CHEWS, etc. (e.g. Gatorade)*



2010 Survey: Average Reported Monthly Expenditures on Dietary Supplements

Army vs. Air Force vs. Coast Guard vs. Afghanistan

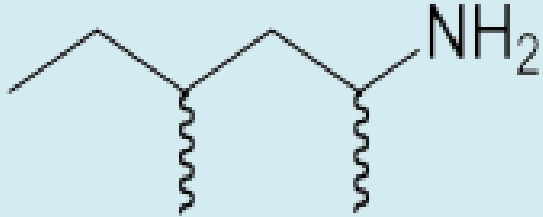


1,3-Dimethylamylamine (DMAA)

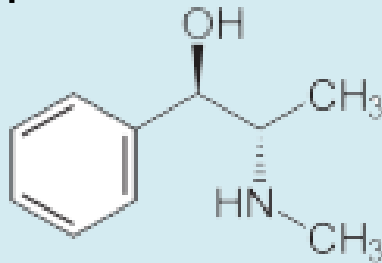
- Key example of how critical dietary supplement adverse events may be for DoD Force Health Protection.
- Introduced as a new dietary supplement for workout energy and weight loss a few years ago.
 - Rapidly became very popular with young males, especially service members.

1,3-Dimethylamylamine (DMAA)

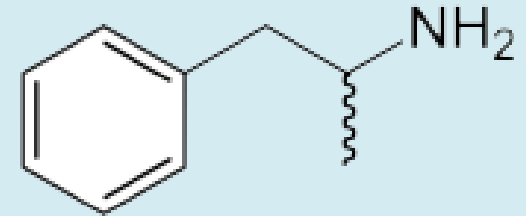
- DMAA is an amphetamine-like drug, first developed for use as a prescription drug.
 - Structure similar to ephedra and amphetamine



DMAA



Ephedrin



Amphetamine

- DS manufacturers claim DMAA is found in geranium species (*Pelargonium graveolens*) and, therefore, would be permitted in DS per DSHEA.
- Due to serious adverse events reported to FDA including death of several service members, the FDA warned manufacturers to remove DMAA from their products.

Is 1,3-Dimethylamylamine (DMAA) in *Pelargonium graveolens* (Geraniums)?





U.S. Armed Forces DMAA Dietary Supplement Usage Patterns 2010

Military Branch	% Using DMAA DS Daily^a	% Using DMAA DS \geq 1x/week^b	% Using DMAA DS \geq 1x/month^c
Air Force (wide) 2010/2011	4.8 % (76)	12.3 % (194)	13.4 % (211)
Coast Guard (wide) 2011	3.5% (37)	9.2% (98)	10.1% (108)
Army (Afghanistan & Kuwait) 2010	4.3 % (21)	8.6 % (42)	8.8 % (43)

^a Includes only respondents who indicated that they consumed the supplement daily.

^b Includes respondents who indicated that they consumed the supplement at least 1x/week or 2-6x/week or daily.

^c Includes respondents who indicated that they consumed the supplement at least 1x/month or 1x/week or 2-6x/week or daily.



The DoD and DMAA

- Adverse Events:
 - Deaths of three Soldiers associated with use of DMAA-containing supplements (2011-2012)
 - DoD Initiated temporary hold on sale of DMAA-containing supplements (January 2012)
- Division of Forensic Toxicology, Armed Forces Medical Examiner:
 - Due to false positives in the Army Drug Testing Program, studied DMAA supplement use and interference with amphetamine assay (Spring 2010)
- USARIEM:
 - Studied prevalence of DMAA use by military personnel (Fall 2010-Fall 2011)
 - Determined DMAA is not present in geraniums or pelargoniums (2012)
- Army Public Health Command:
 - Military personnel with multiple adverse events were twice as likely to have used a DMAA containing supplement (2012-2013)



FDA: DMAA Warning (Not Recalled)

- As of April 2013, 86 officially-reported adverse events from the use of DMAA
 - Psychiatric disorders
 - Heart problems
 - Nervous system disorders
 - Death
- FDA ruled DMAA was an illegal ingredient in DS (April 2012)
 - Insufficient reliable, scientific evidence to prove DMAA is a naturally occurring substance and is safe for use.
 - New Dietary Ingredient (NDI) not filed.
 - No evidence chemical compound is directly a component of the food chain.

Caffeine and Energy Drinks

- Only food/dietary supplement with proven ability to enhance cognitive and physical performance
- Demonstrated efficacy in operational scenarios
- No other supplements have demonstrated efficacy in operational scenarios
- Very controversial due to popularity of Energy drinks, which typically contain same amount of caffeine as coffee





DoD Dietary Supplement Activities

- Proactive
- Repeatedly withdrew DS from stores on DoD bases prior to FDA action (ephedra, DMAA)
- Policy – Based on independent scientific guidance from Institute of Medicine
 - DoD Instruction 6130.05
- Research – Center Alliance for Dietary Supplement Research
 - Robust, provided most of the data in this presentation
- Education – Human Performance Resource Center (HPRC), Uniformed Services University of the Health Sciences (USUHS)



Education



Operation Supplement Safety: A DoD-wide Educational Campaign

Dr. Patricia Deuster

**Uniformed Services University of the Health Sciences
(USUHS)**



OPSS Overview

- **Purpose**
 - Increase awareness within the DoD community about dietary supplements
- **Provide tools to be “smart” supplement users**
 - Service members
 - Leaders
 - DoD civilians
 - Family members
 - Healthcare providers
 - Retirees



HUMAN PERFORMANCE RESOURCE CENTER

A DoD initiative under the Force Health Protection and Readiness Program



- HOME
- PHYSICAL FITNESS
- ENVIRONMENT
- NUTRITION
- DIETARY SUPPLEMENTS
- FAMILY & RELATIONSHIPS
- MIND TACTICS
- TOTAL FORCE FITNESS

THE EDGE YOU NEED FOR TOTAL FITNESS

HPRC's human performance optimization (HPO) website is for U.S. Warfighters, their families, and those in the field of HPO who support them. The goal is Total Force Fitness: Warfighters optimized to carry out their mission as safely and effectively as possible.



OPERATION SUPPLEMENT SAFETY

A DoD and HPRC DIETARY SUPPLEMENT RESOURCE FOR WARFIGHTERS



FEATURED UPDATES

Natural Medicines Comprehensive Database App

Healthcare provider app to get answers and data on natural medicines at any time.

hprc-online.org/

More...

NATURAL MEDICINES COMPREHENSIVE DATABASE

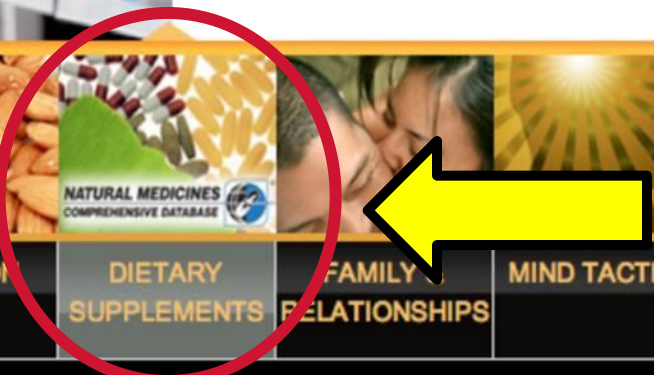
Information on supplements for Warfighters and healthcare professionals



PRESCRIBER'S LETTER



- PHYSICAL FITNESS
- ENVIRONMENT
- NUTRITION
- DIETARY SUPPLEMENTS
- FAMILY RELATIONSHIPS
- MIND TACTICS
- TOTAL FORCE FITNESS



Knee Hug - In Place



DoD Center Alliance for Dietary Supplement Research

Steering Committee Co-Chairs:

Dr. Patricia Deuster, USU/CHAMP

Dr. Andrew J. Young, USARIEM



Mission Statement

- Monitor use, safety and efficacy of DS relevant to DoD
- Transition information regarding Dietary Supplements to appropriate DoD elements including OSD, HA, Service SG's

Program Area Oversight

Steering Committee

Co-Chairs:

- USU/CHAMP
- USARIEM

Members:

- MRMC
- Health Affairs Rep
- US Air Force SG Rep
- US Navy SG Rep
- US Army SG Rep
- US Marine Corps Rep
- Coast Guard
- NIH-ODS
- USAPHC
- DoD Combat Feeding Directorate
- USAMMDA – procurement MRMC

Research Area Managers:

- USARIEM
- USU/CHAMP



Program Objectives/Deliverables

- Establish and operationalize standardized, evidence-based processes for formal integration into DoD regulations and clinical and business practices to:
 - 1) Monitor DS use by DoD personnel
 - 2) Identify DS that pose a threat to force health protection
 - 3) Document adverse health effects associated with DS
 - 4) Identify DS that provide health and performance benefits to DoD
 - 5) Test approaches for delivering beneficial DS products to DoD personnel, including in rations
 - 6) Provide DS policy and program recommendations to mitigate health threats

Conclusions

- Dietary supplements are largely unregulated in the US.
 - Demonstration of safety and efficacy is not required
- Service members use large numbers of dietary supplements, including in theatre.
- Service members have different patterns of supplement use than civilian peers.
- Energy drinks are very popular and controversial, but typically contain no more caffeine than coffee.
- DoD has been proactive within boundaries of law regarding DS policies, programs and education.
- **Continued research, surveillance and education is essential to protect the health of Service Members.**

THE END

This work was supported by the US Army Medical Research and Materiel Command (USAMRMC) and the Department of Defense Center Alliance for Dietary Supplement Research, a Defense Medical Research and Development Program.