Dietary Supplements: Policy, Science and the DoD

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The investigators adhered to the policies for protection of human subjects as prescribed in Army Regulation 70-25, and the research was conducted in adherence with the provisions of 32 CFR part 219. Citations of commercial organizations and trade names in this report do not constitute an official Department of the Army endorsement or approval of the products or services of these organizations.

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US Army Research Institute of Environmental Medicine (USARIEM)
Natick, MA

COMMANDER & STAFF

Research Support Division

Thermal & Mountain Medicine Division (TMMD)
Biophysics & Biomedical Modeling Division (BBMD)
Military Nutrition Division (MND)
Military Performance Division (MPD)

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  – Can only be withdrawn if FDA can prove clear and present danger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)
Drugs 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.
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

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.
   - Significant adverse effects (13% greater incidence of heart failure in patients at high risk for cardiovascular disease)
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.
   • No beneficial effects

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

   • No beneficial effects

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

\[ N = \text{over 1000 animals} \]
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)
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).
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
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


<table>
<thead>
<tr>
<th>Army-wide</th>
<th>% Consuming</th>
<th>Afghanistan</th>
<th>% Consuming</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Energy drink</strong></td>
<td>43</td>
<td>1. Multivitamin/mineral</td>
<td>48</td>
</tr>
<tr>
<td><strong>2. Multivitamin/mineral</strong></td>
<td>37</td>
<td>2. Protein &amp; AA powder</td>
<td>46</td>
</tr>
<tr>
<td><strong>3. Protein &amp; AA powder</strong></td>
<td>32</td>
<td>3. Energy drink</td>
<td>44</td>
</tr>
<tr>
<td><strong>5. Sports drink</strong></td>
<td>24</td>
<td>5. Sports drink</td>
<td>27</td>
</tr>
<tr>
<td>Individual vitamin or mineral (e.g. Vitamin C, Vitamin D, Vitamin E)</td>
<td>19</td>
<td>Individual vitamin or mineral (e.g. Vitamin C, Vitamin D, Vitamin E)</td>
<td>22</td>
</tr>
<tr>
<td><strong>7. Other DS</strong></td>
<td>17</td>
<td>7. Other DS</td>
<td>18</td>
</tr>
<tr>
<td><strong>8. Caffeine</strong></td>
<td>11</td>
<td>8. Caffeine</td>
<td>11</td>
</tr>
<tr>
<td><strong>10. Herbal DS</strong></td>
<td>8</td>
<td>10. Weight loss DS</td>
<td>9</td>
</tr>
</tbody>
</table>
## FEMALES

Most Popular Dietary & Nutritional Supplements


<table>
<thead>
<tr>
<th>Army-wide</th>
<th>Afghanistan</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Supplement</strong></td>
<td><strong>% Consuming</strong></td>
</tr>
<tr>
<td>----------------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>1. Multivitamin/mineral</td>
<td>43</td>
</tr>
<tr>
<td>Individual vitamin or</td>
<td></td>
</tr>
<tr>
<td>mineral (e.g. Vitamin C,</td>
<td>33</td>
</tr>
<tr>
<td>Vitamin D, Vitamin E)</td>
<td></td>
</tr>
<tr>
<td>5. Sports drink</td>
<td>18</td>
</tr>
<tr>
<td>6. Other DS</td>
<td>15</td>
</tr>
<tr>
<td>8. Weight loss DS</td>
<td>9</td>
</tr>
<tr>
<td>10. Meal replacement</td>
<td>8</td>
</tr>
</tbody>
</table>
Why Do Service Members Take Supplements?

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

*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

- Army: $37
- Air Force: $39
- Coast Guard: $40
- Afghanistan: $59
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

![Structures of DMAA, Ephedrin, and Amphetamine](image)

- DS manufacturers claim DMÅA 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)?
<table>
<thead>
<tr>
<th>Military Branch</th>
<th>% Using DMAA DS Daily&lt;sup&gt;a&lt;/sup&gt;</th>
<th>% Using DMAA DS ≥ 1x/week&lt;sup&gt;b&lt;/sup&gt;</th>
<th>% Using DMAA DS ≥ 1x/month&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air Force (wide) 2010/2011</td>
<td>4.8 % (76)</td>
<td>12.3 % (194)</td>
<td>13.4 % (211)</td>
</tr>
<tr>
<td>Coast Guard (wide) 2011</td>
<td>3.5% (37)</td>
<td>9.2% (98)</td>
<td>10.1% (108)</td>
</tr>
<tr>
<td>Army (Afghanistan &amp; Kuwait) 2010</td>
<td>4.3 % (21)</td>
<td>8.6% (42)</td>
<td>8.8% (43)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Includes only respondents who indicated that they consumed the supplement daily.

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

<sup>c</sup> 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
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.
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

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