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# Temporal trends in dietary supplement prescriptions of United States military service members suggest a decrease in pyridoxine and increase in vitamin D supplements from 2005 to 2013

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ABSTRACT

Dietary supplements (DSs) can be obtained over-the-counter but can also be prescribed by health-care providers for therapeutic reasons. Few studies have documented this later source despite the fact that 79% of physicians and 82% of nurses have recommended DSs to patients. This investigation assessed prevalence and temporal trends in oral DS prescriptions filled by all United States service members (SMs) from 2005 to 2013 (n = 1 427 080 ± 22 139, mean ± standard deviation (SD)/y). We hypothesize that there would be temporal variations in specific types of DSs. Data obtained from Department of Defense Pharmacy Data Transaction System were grouped by American Hospital Formulary System pharmacologic-therapeutic classifications and prevalence examined over time. About 11% of SMs filled one or more DS prescriptions of 235 180 ± 4926 (mean ± SD) prescriptions/y over the 9-year period. Curve-fitting techniques indicated significant linear declines over time for multivitamins ($P = .004$), iron preparations ($P < .001$), antacids ($P < .001$), and vitamin B and B complex vitamins ($P < .001$). There were significant quadratic trends indicating a rise in early years followed by a leveling off in later years for replacement preparations ($P < .001$) and vitamin C ($P < .001$). There were significant quadratic trends ($P < .001$) for vitamin E indicating a decline in early years and leveling off

*Abbreviations:* AI, Adequate Intake; AHFS, American Hospital Formulary System; AFHSB, Armed Forces Health Surveillance Branch; COX, Cyclooxygenase; DS, Dietary Supplement; GC3, Generic Class 3; GERD, Gastroesophageal Reflux Disease; IOM, Institute of Medicine; NDC, National Drug Code; NHANES, National Health and Nutrition Examination Surveys; PDTS, Pharmacy Data Transaction System; PEC, Pharmacoecomomic Center; RDA, Recommended Daily Allowance; SD, Standard Deviation; SM, Service Member; TLESR, Transient Lower Esophageal Sphincter Relaxation; US, United States; USPSTF, United States Preventive Services Task Force; PPI, proton pump inhibitor; H2RA, histamine 2 receptor antagonist.

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in later years, and vitamin D indicating little change in early years followed by a large rise subsequently (P < .001). This study identified temporal trends in specific DS categories that may be associated with changing perceptions of prescribers and/or patients of the appropriate roles of DSs in medicine and public health.



## 1. Introduction

Dietary supplements (DSs) are commercially available products that are consumed as an addition to the usual diet. DSs include vitamins, minerals, herbs (botanicals), amino acids, and a variety of other substances [1]. Recent surveys of health care providers found that 79% of physicians, 82% of nurses, and 97% of dietitians had recommended DSs to their patients [2,3]. It is estimated that about 50% of Americans and 60% to 70% of US military personnel use DSs.[4-6]. The Dietary Supplement Health and Education Act (DSHEA) of 1994 [7] established the regulatory framework for DSs in the US. Since DSHEA became law, US sales of DSs has increased from $4 billion in 1994 to $37 billion in 2014, [8,9] a >9-fold increase over 20 years.

Individuals can obtain DSs from over-the-counter sources like drug stores, grocery stores, and retailers that specialize in these substances. In addition to these sources, DSs can be obtained from prescriptions written by medical care providers. The types of DSs that are medically prescribed and their prevalence of use likely differ from those obtained over-the-counter. The primary reason individuals report for using over-the-counter DSs is to promote general health [10-12]. DSs prescribed by medical personnel are for particular therapeutic purposes, for example to correct vitamin, mineral, or nutritive (e.g., amino acid) deficiencies [13]. DSs can also be recommended by health care providers as alternatives to other types of medications. Pharmaceutical grade DSs do not appear to carry the same potential risk for contamination or adverse effects as do some over-the-counter products [14-16].

A number of investigations have quantified the prevalence of over-the-counter DS use among civilians [5,6,17,18] and military personnel [4,10,16]. However, investigations on medically prescribed DSs are more limited. A few studies have examined population-level prescribed DS use among civilians, but these studies are based on self-reports rather than information obtained from medical records [19-21]. Other studies have examined some limited prescription data within the US military medical system [22-24].

In the US military health care system, medical care is freely available to service members (SMs) and since there are no charges for prescription medications, SMs are likely to fill prescriptions within the system. Information on prescriptions dispensed to SMs is documented by the US Department of Defense Pharmacy Data Transaction System (PDTS), thereby providing an opportunity to examine prevalence and temporal trends in prescriptions filled by all US SMs. These temporal trends may reflect patterns present in the general medical community for which such comprehensive data are not available. We hypothesized that although the overall prevalence of prescriptions would remain relatively stable over time, there would be temporal variations in specific categories of DSs. We tested this by obtained DS data from the PDTS, grouping these data by American Hospital Formulary System (AHFS) pharmacologic-therapeutic classifications, and examining changes over time in DS prescriptions.

## 2. Methods and materials

This was a descriptive study designed to identify patterns of oral DSs filled by the entire population of US military SMs from 2005 through 2013. SMs included only active duty personnel in the Army, Navy, Marine Corps, Air Force, and Coast Guard. DSs were defined based on the Dietary Supplement Health and Education Act of 1994 as "…a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: (*a*) a vitamin; (*b*) a mineral; (*c*) a herb or other botanical; (*d*) an amino acid; (*e*) a dietary substance for use by man to supplement the diet by increasing total dietary intake; or (*f*) a concentrate, metabolite, constituent, extract or combination of any ingredient in clause a to e" [1]. The study was approved by the institutional review board of the US Army Research Institute of Environmental Medicine in accordance with Army Regulation 70-25 (Use of Volunteers as Subjects of Research).

### 2.1. *Identification of dietary supplements*

To identify DSs available for prescription to SMs, 2 databases were queried. One database was the Food and Drug Administration National Drug Code (NDC) database, obtained in November 2013 [25]. At the time, the NDC database contained 65 536 listed substances. The other database was the basic and extended core formularies of the US Defense Health Agency's Pharmacoeconomic Center (PEC) [26]. Using the search engine at the PEC website [26], the following search terms were used to identify substances classified by First Data Bank as Generic Class 3 (GC3) categories of drugs which could also be DSs: vitamins, minerals, protein and amino acids, herbs and botanical ingredients, fish oil, creatine, joint support, digestive, and dietary supplements. The GC3 system utilizes 3 characters (alpha, numeric, and alpha) to represent the organ system, pharmacological class, and specific therapeutic class. A total of 34 901 listed substances were identified and the corresponding NDC numbers, GC3 numbers, and generic names were provided by a pharmacist from the Defense Health Agency Pharmacy Operations Division. A nutritionist and a physiologist/epidemiologist knowledgeable in DSs each independently examined the two databases to identify DSs. After the independent evaluations, the 2 individuals met to resolve any discrepancies. Only substances

listed as orally consumed were considered and all substances listed as "unapproved homeopathics" were excluded. After eliminating overlapping substances in the two databases, the process resulted in the identification of 25 291 unique oral DS substances with distinctive NDCs and GC3s (A1B, B3K, C1B, C1D, C1F, C1H, C1P, C1W, C3B, C3C, C3M, C5B, C5F, C5G, C5H, C5U, C6A, C6B, C6C, C6D, C6E, C6F, C6G, C6H, C6I, C6L, C6M, C6N, C6P, C6Q, C6R, C6T, C6Z, C8E, D4B, D4N, D6S, E0A, E0G, M4B, M4O, P4D, U5B, U6 W, and Z1E) codes.

### 2.2. *Extraction of pharmacy records*

Once the DSs were identified, data were extracted from PDTS records. PDTS is a central data system for all prescription data from all Department of Defense pharmacy services and civilian pharmacies that fill prescriptions for SMs. It contains the name and NDCs of prescriptions dispensed to SMs. NDCs were used as the unit of identification to obtain DSs dispensed to SMs. The PDTS database was queried to obtain both the number of SMs filling one or more DS prescriptions and the number of prescriptions for each year from 2005 through 2013. Because of the large number of NDCs, the list was further reduced by grouping the NDC codes according to their generic names, as listed in the database (eg, aluminum hydroxide, cholecalciferol, arginine, calcium, psyllium). In 53 cases, there were no generic names listed but 48 of these records were some form of Vitamin E and so these were given this generic name. The other 5 substances were not prescribed in the period examined. Using generic names resulted in 1711 categories. Of the 1711 generic categories, 488 had at least one SM receiving a prescription in the survey period.

A pharmacist placed the generic substances into the AHFS Pharmacologic-Therapeutic classifications [13]. After this, several AHFS Pharmacologic-Therapeutic classifications were combined because they were subcategories of higher tier AHFS codes, had a small number of prescriptions in the particular therapeutic classes, and/or had very similar therapeutic classifications. One group of pharmacologic-therapeutic classifications that were combined were 28:20.00 (Anoxergenic Agents and Respiratory and Cerebral Simulants), 28:20.32 (Respiratory and Central Nervous System Stimulants), and 28:20.92 (Anoxergenic Agents and Stimulants, Miscellaneous). The other pharmacologic-therapeutic classifications that were combined were 92:00.00 (Miscellaneous Therapeutic Agents) and 92:92.00 (Other Miscellaneous Therapeutic Agents). This resulted in 14 AHFS classification groups.

### 2.3. *Statistical analyses*

Two measures were calculated for each year for each AHFS pharmacologic-therapeutic classification. The first calculation involved the number of SMs filling DS prescriptions and the second calculation involved the number of DS prescriptions dispensed. The first calculation was called the "SM prevalence" and was calculated as (∑ of SMs filling one or more prescription in a particular year and AHFS classification divided by ∑ of SMs for the year) × 1000 (SMs with one or more prescriptions/1000 SMs). The second calculation was called the "prescription prevalence" and was calculated as (∑ prescriptions in a particular year and AHFS classification divided by the ∑ SMs for the year) × 1000 (prescriptions/1000 SMs). The second number was greater than the first because SMs could fill more than one prescription in a therapeutic classification for a particular year. The Armed Forces Health Surveillance Branch (AFHSB) of the Defense Health Agency provided denominators (∑ SMs for each year) that allowed calculation of SM and prescription prevalence.

Data were graphed by year to examine trends in prescriptions by AHFS codes [13] during the survey period. Descriptive statistics were not necessary since the data included all SMs and the point values on the graphs represent the population values. To more adequately describe the trends, curve-fitting techniques were applied to the graphed data, primarily using linear and quadratic models [27]. The trend line for the technique that best fit the data (ie, highest $r^2$) was displayed on the graphs along with the equation. With 7 degrees of freedom (number of survey years minus two), an $r \geq 0.67$ was significant at the $P \leq .05$ level and $r \geq 0.80$ was significant at the $P \leq .01$. In the case where a simple linear regression fit the data, it was possible to estimate the change in prevalence over the survey period. This was not possible with polynomial fitting techniques because the change varied over time (ie, was not linear).

## 3. Results

Table 1 presents the total number of SMs in the years 2005 through 2013. The highest service member census was in 2010, the lowest in 2007, and the mean ± SD was 1 427 080 ± 22 139 SMs. During the 9-year surveillance period, 2 116 617 prescriptions for oral DSs were filled for SMs, a mean ± SD of 235 180 ± 4926 per year. A number of SMs filled multiple prescriptions: 1 448 752 SMs filled one or more prescriptions for oral DSs during the period a mean ± SD of 160 972 ± 5128 per year. The yearly mean ± SD for SMs was 1 427 080 ± 22 139 so that 11.3% (160 972/1 427 080) of SMs filled a prescription for an oral DS during the survey period.

Table 2 presents the yearly number of SMs filling oral DS prescriptions and the number of prescriptions filled, both classified by AHFS codes. There were very few prescriptions for the AHFS pharmacologic-therapeutic categories (1)

**Table 1 – Service members by years 2005 through 2013 [a]**

| Year | Total population (n) | Men (%) | Women (%) |
|---|---|---|---|
| 2005 | 1 415 217 | 85.5 | 14.5 |
| 2006 | 1 405 170 | 85.6 | 14.4 |
| 2007 | 1 399 799 | 85.9 | 14.2 |
| 2008 | 1 419 049 | 85.7 | 14.2 |
| 2009 | 1 444 132 | 85.7 | 14.3 |
| 2010 | 1 458 363 | 85.5 | 14.5 |
| 2011 | 1 456 505 | 85.4 | 14.6 |
| 2012 | 1 435 364 | 85.2 | 14.8 |
| 2013 | 1 410 123 | 85.2 | 14.8 |

[a] Service members represents the entire population of service members (Army, Navy, Air Force, Marine Corps, and Coast Guard) for the years specified. Data are obtained from the Armed Forces Health Surveillance Branch of the Defense Health Agency.

**Table 2 – Oral dietary supplements dispensed to active duty service members by year and categorized by AHFS pharmacologic-therapeutic classifications**

| AHFS Code | AHFS description | Generic categories (n) | Service members filling oral DS prescriptions (n) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2005–2013 |
| 20:04.04 | Iron preparations | 58 | 17 876 | 17 502 | 17 538 | 17 269 | 17 488 | 17 288 | 17 350 | 16 909 | 16 254 | 155 474 |
| 28:20.00, 28:20.32, 28:20.92 | Anoxergenics; respiratory, CNS stimulants | 3 | 3 | 5 | 3 | 1 | 3 | 3 | 2 | 5 | 4 | 32 |
| 40:12.00 | Replacement preparations | 48 | 21 402 | 22 345 | 26 026 | 29 101 | 28 706 | 31 642 | 32 278 | 29 254 | 25 373 | 246 127 |
| 40:20.00 | Caloric agents | 8 | 16 | 17 | 47 | 25 | 68 | 48 | 18 | 18 | 54 | 311 |
| 56:04.00 | Antacids and absorbents | 14 | 11 690 | 12 022 | 8923 | 7300 | 7740 | 6307 | 6382 | 5562 | 4963 | 70 889 |
| 56:12.00 | Cathartics and laxatives | 19 | 22 795 | 23 631 | 23 397 | 23 317 | 17 768 | 17 431 | 19 412 | 21 465 | 21 447 | 190 663 |
| 56:92.00 | GI Drugs, miscellaneous | 1 | 1 | 2 | 3 | 2 | 1 | 2 | 1 | 1 | 0 | 13 |
| 88:04.00 | Vitamin A | 4 | 37 | 26 | 11 | 25 | 20 | 14 | 9 | 12 | 23 | 177 |
| 88:08.00 | Vitamin B and B-complex | 48 | 20 818 | 20 540 | 18 876 | 16 846 | 15 666 | 14 329 | 13 780 | 13 715 | 12 379 | 146 949 |
| 88:12.00 | Vitamin C | 3 | 6739 | 8750 | 10 857 | 12 089 | 12 324 | 11 709 | 11 678 | 12 503 | 11 512 | 98 161 |
| 88:16.00 | Vitamin D | 5 | 469 | 718 | 1112 | 2097 | 4643 | 11 043 | 15 154 | 18 903 | 25 786 | 79 925 |
| 88:20.00 | Vitamin E | 4 | 1409 | 912 | 793 | 702 | 410 | 361 | 322 | 381 | 392 | 5682 |
| 88:28.00 | Multivitamin preparations | 222 | 51 253 | 49 453 | 49 988 | 50 997 | 51 691 | 51 039 | 50 229 | 49 123 | 48 423 | 452 196 |
| 92:00.00, 92:92.00 | Therapeutic agents; miscellaneous therapeutic agents | 51 | 218 | 160 | 196 | 232 | 411 | 230 | 216 | 250 | 243 | 2156 |

| AHFS Code | AHFS Description | Generic Categories (n) | Total Prescriptions for Oral DSs (n) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2005–2013 |
| 20;04.04 | Iron preparations | 58 | 24 833 | 24 187 | 24 212 | 22 928 | 23 478 | 23 638 | 23 483 | 23 370 | 22 547 | 212 676 |
| 28:20.00, 28:20.32, 28:20.92 | Anoxergenics; respiratory, CNS stimulants | 3 | 3 | 4 | 3 | 0 | 3 | 3 | 2 | 6 | 4 | 28 |
| 40:12.00 | Replacement preparations | 48 | 30 513 | 31 637 | 35 133 | 38 170 | 37 608 | 41 100 | 42 079 | 38 737 | 34 502 | 329 478 |
| 40:20.00 | Caloric agents | 8 | 16 | 18 | 52 | 27 | 68 | 49 | 19 | 20 | 58 | 327 |
| 56:04.00 | Antacids and absorbents | 14 | 14 871 | 15 044 | 11 479 | 9415 | 9979 | 7905 | 8240 | 7203 | 5984 | 90 120 |
| 56:12.00 | Cathartics and laxatives | 19 | 27 092 | 28 141 | 27 729 | 27 335 | 21 417 | 21 167 | 23 656 | 26 261 | 26 076 | 228 874 |
| 56:92.00 | GI Drugs, miscellaneous | 1 | 1 | 3 | 3 | 2 | 1 | 2 | 1 | 1 | 0 | 14 |
| 88:04.00 | Vitamin A | 4 | 44 | 31 | 15 | 30 | 23 | 17 | 12 | 16 | 33 | 221 |
| 88:08.00 | Vitamin B and B-complex | 48 | 50 195 | 53 372 | 49 333 | 41 489 | 36 062 | 33 092 | 31 046 | 30 177 | 24 678 | 349 444 |
| 88:12.00 | Vitamin C | 3 | 8110 | 10 098 | 12 503 | 13 644 | 14 334 | 13 358 | 13 811 | 14 855 | 13 751 | 114 464 |
| 88:16.00 | Vitamin D | 5 | 885 | 1167 | 1786 | 3256 | 7195 | 16 158 | 22 116 | 27 284 | 36 875 | 116 722 |
| 88:20.00 | Vitamin E | 4 | 2043 | 1380 | 1128 | 1084 | 576 | 478 | 455 | 616 | 594 | 8354 |
| 88:28.00 | Multivitamin preparations | 222 | 77 168 | 74 636 | 74 599 | 72 329 | 74 845 | 74 580 | 72 651 | 72 086 | 69 898 | 662 792 |
| 92:00.00, 92:92.00 | Therapeutic agents; miscellaneous therapeutic agents | 51 | 269 | 211 | 258 | 340 | 513 | 349 | 364 | 412 | 384 | 3100 |

anoxergenics, respiratory, and central nervous system stimulants, (2) caloric agents, (3) gastrointestinal drugs, (4) Vitamin A, and (5) therapeutic agents. These 5 categories accounted for <0.2% of all individuals filling prescriptions and were not considered further. Multivitamin preparations were the AHFS category accounting for the largest number of individuals filling prescriptions, followed by replacement preparations, cathartics and laxatives, iron preparations and B and B-complex vitamins. Multivitamin preparations were also the AHFS category accounting for the largest number of prescriptions filled while B and B-complex vitamins had the second highest number of prescriptions, followed by replacement preparations, cathartics and laxatives, and iron preparations.

### 3.1. *Overall prevalence and trends and multivitamin prevalence and trends*

Fig. 1A shows the trend in all oral DS prescriptions. There were only small yearly increases in the prevalence of SMs filling prescriptions (0.93 prescriptions/1000 SMs/y) and little systematic change in prescription prevalence. SM prevalence varied between 109.3 and 118.3 SMs/1000 SMs, while prescription prevalence varied between 163.4 and 170.8 prescriptions/1000 SMs. For multivitamin preparations (Fig. 1B), there was a very slight decline over time in the prevalence of SMs filling prescriptions and the prevalence of prescriptions filled. Linear regression (slope of the regression equation) indicated the decline in the SM prevalence for multivitamins was 0.23 SMs/1000 SMs/y, and the decline in prescription prevalence was 0.59 prescriptions/1000 SMs/y. SM prevalence varied from 34.2 to 36.2 SMs/1000 SMs, while prescription prevalence varied from 49.5 to 54.5 prescriptions/1000 SMs.

### 3.2. *Iron preparations*

For iron preparations (Fig. 2A), there was a very small decline in the prevalence of SMs receiving these, amounting to 0.19 SMs/1000 SMs/y. or 1.71 SMs/1000 over the 9-year period. This slight decline was also seen in the prevalence of prescriptions amounting to 0.13 SMs/,1000 SMs per year or 1.17 SMs/1000/y over the 9-year period. SM prevalence varied from 11.5 to 12.6 SMs/1000 SMs, while prescription prevalence varied from 16.0 to 17.6 prescriptions/1000 SMs.

### 3.3. *Replacement preparations*

For replacement preparations (Fig. 2B), there was an increase from 2005 to 2011 in both the prevalence of SMs filling prescriptions and the prevalence of prescriptions filled. This was followed by a small decline from 2011 to 2013. From 2005 to 2011, the prevalence of SMs filling prescriptions increased from 15.1 to 22.2 SMs/1000 SMs, and prescriptions from 21.5 to 28.9 prescriptions/1000 SMs.

In the present study, 97% of replacement preparations involved calcium salts (74%), zinc preparations (12%) and potassium preparations (11%). When the replacement preparations were partitioned into these three major mineral compounds (Fig. 3A), it could be seen that prescriptions for calcium salts were increasing while those for zinc preparations declined precipitously beginning in 2007, reaching a very low level by 2009.

### 3.4. *Antacids and absorbents*

The prevalence of SMs filling antacids/absorbent prescriptions (Fig. 2C) declined at a rate of 0.81 SMs/1000 SMs per year

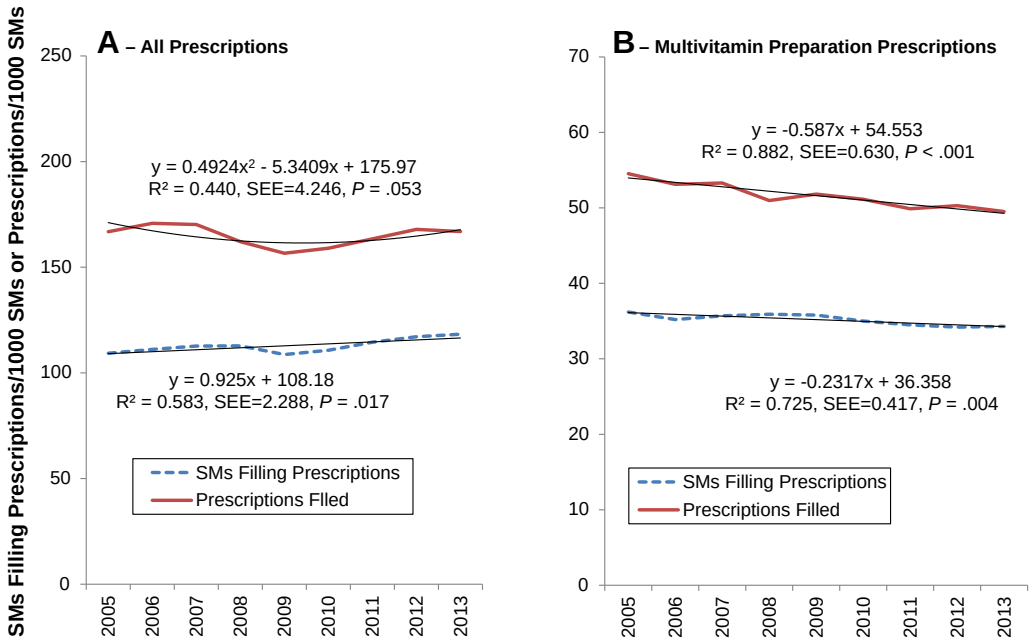


**Fig. 1 – Service member prevalence and prescription prevalence for all prescriptions (A) and multivitamin preparation (B) prescriptions. Data were graphed by year to examine trends in prescriptions by AHFS codes during the survey period. Curve-fitting techniques were applied to the graphed data, primarily using linear and quadratic models. For details see the statistical analyses section.**

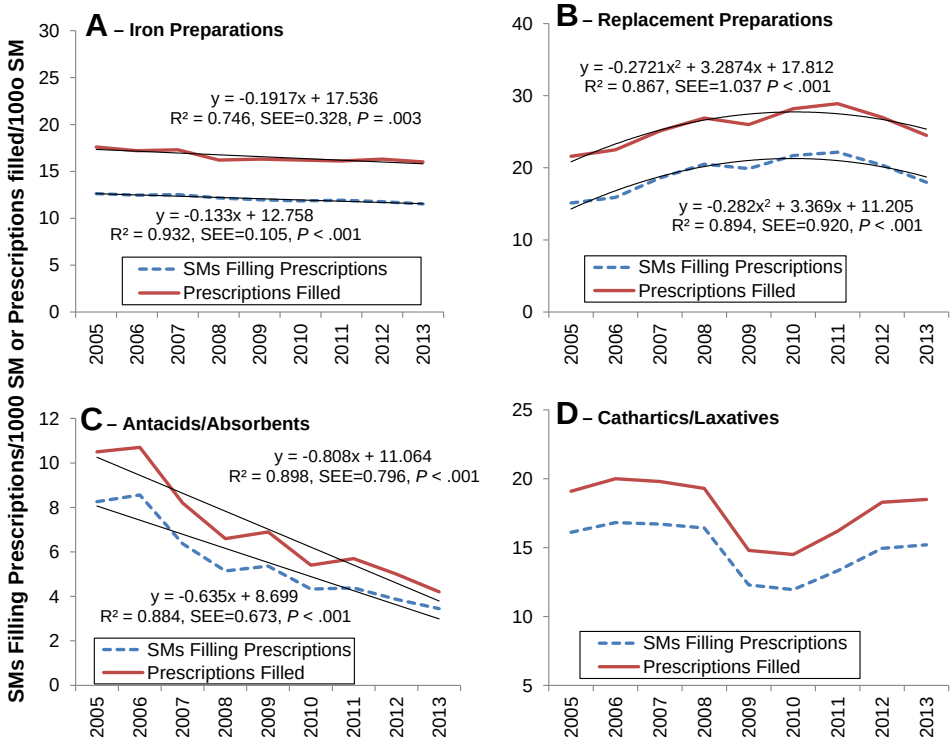


**Fig. 2 – Service member prevalence and prescription prevalence for iron preparations (A), replacement preparations (B), antacids/absorbents (C), and cathartics/laxatives (D). Data were graphed by year to examine trends in prescriptions by AHFS codes during the survey period. Curve-fitting techniques were applied to the graphed data, primarily using linear and quadratic models. For details see the statistical analyses section.**

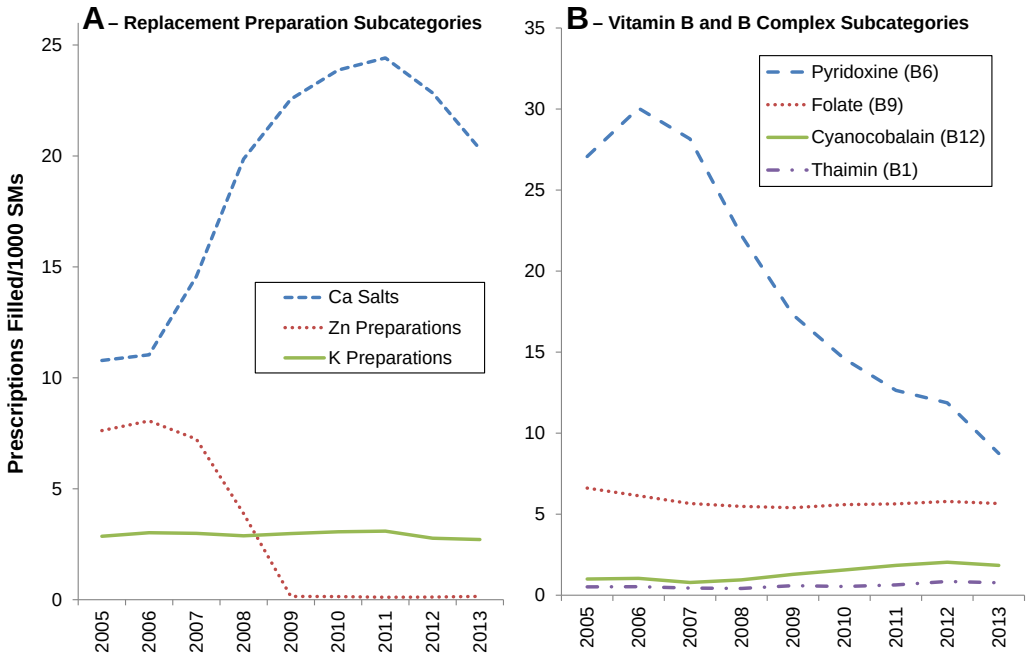


**Fig. 3 – Prescription prevalence for subcategories of replacement preparations (A), and B and B-complex vitamins (B). Data were graphed by year to examine trends in prescriptions by AHFS codes during the survey period. Curve-fitting techniques were applied to the graphed data, primarily using linear and quadratic models. For details see the statistical analyses section.**

or 7.29 SMs/1000 SMs over the 9-year period. The prevalence of prescriptions for antacids/absorbents declined at a rate of 0.64 prescriptions/1000 SMs per year or 5.76 prescriptions/1000 SMs over the 9-year period. SM prevalence declined from 8.3 SMs/1000 SMs in 2005 to 3.5 SMs/1000 SMs in 2013; prescription incidence declined from 10.5 prescriptions/1000 SMs in 2005 to 4.2 prescriptions/1000 SMs in 2013.

### 3.5. *Cathartics and laxatives*

Trends in cathartics and laxatives are shown in Fig. 2D and required complex curve-fitting techniques that did not assist in interpreting the trends over time. In general, there was a decline in both SM and prescription prevalence after 2008 which returned to near 2008 levels after 2012. Yearly SM prevalence varied between 12.0 and 16.8 SMs/1000 SMs while prescription prevalence varied between 14.5 and 19.8 prescriptions/1000 SMs.

### 3.6. *Vitamins*

Fig. 4 shows trends in prescriptions for four vitamins. The prevalence of SMs receiving B and B-complex vitamins (Fig. 4A) declined at a rate of 2.86 SMs/1000 SMs/y., or 26.01 SMs/1000 SMs over the 9-year period. The prevalence of prescriptions declined at a much slower rate, 0.82 prescriptions/SMs/y. or 7.38 prescriptions/1000 SMs over the 9-year period. These data demonstrated that a smaller number of SMs were receiving more B and B-complex vitamin prescriptions as the 9-year period progressed. Vitamin C prescriptions (Fig. 4B) almost doubled in both SM prevalence and prescription prevalence from 2005 to 2008–2009 but after 2009 there was little change in either measure. For Vitamin D (Fig. 4C), both SM and prescription prevalence increased dramatically during the 9-year survey period. For SM prevalence, the change was 55-fold (0.3 to 18.3 SMs/1000 SMs) and for prescription prevalence, the change was 42-fold (0.6 to 26.2 prescriptions/1000 SMs). Finally, Vitamin E SM and prescription prevalence declined over the survey period from 2005 to 2009 and then changed little in the following years (Fig. 4D).

Prescriptions filled by SMs for B and B-complex vitamins primarily consisted of pyridoxine (70%), folate (21%), Vitamin $B_{12}$ (5%), and thiamin (2%). When portioned into these individual substances (Fig. 3B), the decline in B and B-complex vitamin prescriptions was accounted for almost exclusively by pyridoxine (Vitamin $B_6$).

### 3.7. *Botanicals*

A number of botanical substances (i.e., derived from plants) were included in the generic classifications. These included 34 generic substances that did not contain any other substances (single botanicals), and 9 that were botanicals with other substances. Of the single botanicals, sennosides and psyllium (both classified as cathartics/laxatives) accounted for 64.4% and 32.5% of the SMs filling prescriptions, respectively. Other single botanicals (in order of the proportion of SMs filling single botanical prescriptions) included baicalin/catechin

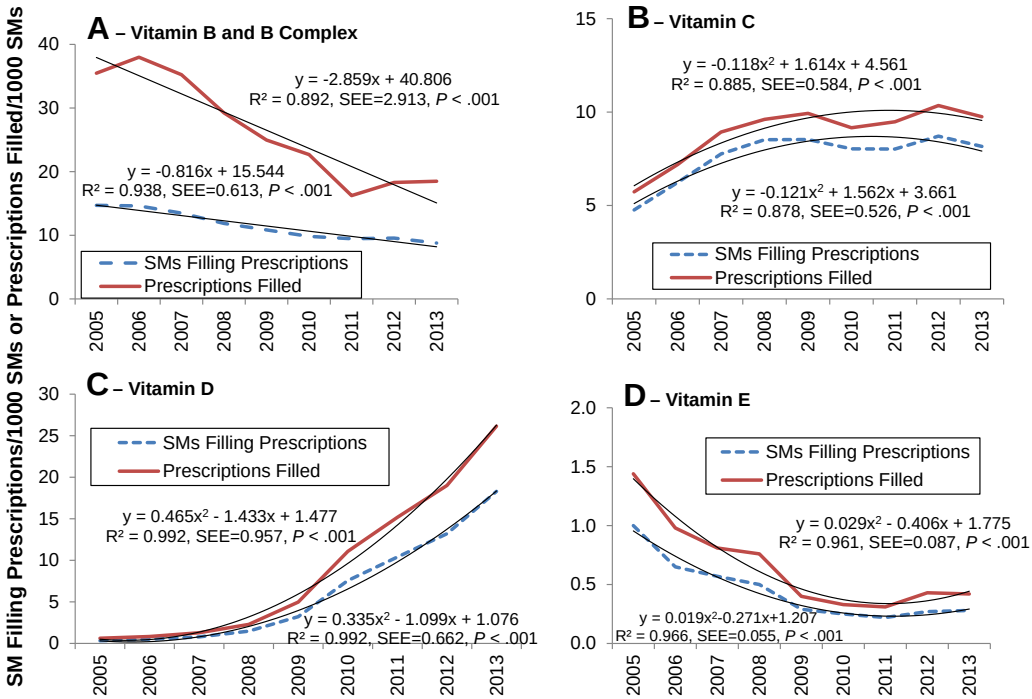


**Fig. 4 – Service member prevalence and prescription prevalence for vitamins including vitamin B and B-complex (A), vitamin C (B), vitamin D (C), and vitamin E (D). Data were graphed by year to examine trends in prescriptions by AHFS codes during the survey period. Curve-fitting techniques were applied to the graphed data, primarily using linear and quadratic models. For details see the statistical analyses section.**

(0.81%), ginseng (0.38%), *Ginkgo biloba* (0.36%), flaxseed (0.34%), garlic (0.24%), and green tea leaf extract (0.23%). Psyllium with sugars or amino acids accounted for 99.9% of the SMs filling prescriptions for botanicals that included other substances.

## 4. Discussion

This is the first investigation to describe the prevalence and temporal trends in all oral DS prescriptions filled by SMs and was based directly on pharmacy records classified using the AHFS. During the study's 9-year surveillance period about 11% of SMs filled at least one prescription for a DS each year, about 235 180 ± 4926 (mean ± SD) prescriptions per year. We hypothesized that the overall prevalence of prescriptions would remain relatively stable over time but there would be temporal variations in specific categories of DSs. There was a very small increase in the overall prevalence of SMs filling prescriptions for oral DSs from 2005 through 2013 so we had to reject the first part of the hypothesis. However, DSs were subcategorized into AHFS pharmacologic-therapeutic categories, significant trends for some classes of DSs were apparent so the second part of our hypothesis was accepted. There were increases over time in prescriptions for Vitamin D, Vitamin C, and replacement compounds; decreases over time in prescriptions for antacids, B and B-complex Vitamins, and Vitamin E; and although there was a significant decline in prescriptions for multivitamins and iron preparations, the absolute changes over time were relatively small. These temporal trends may be associated with the changing perceptions of prescribers of the therapeutic value of these substances in medicine and public health. In addition, some patients may have requested specific DSs from their providers and the nature of these requests may have changed over time based on patient perceptions of the health or other benefits of these supplements. Similar changes may have occurred among civilian healthcare providers and should be investigated.

The most dramatic trend observed was a large increase in Vitamin D prescriptions over the survey period. A similar temporal trend was noted over a shorter, less recent timeframe (2007–2011) in other data obtained from the PDTS [24]. In 1997, an Institute of Medicine (IOM) report set the adequate intake (AI) level of Vitamin D at 200 International Units (IU) or 5 μg/d for adults 19 to 70 years of age. This level was based on the amount of intake necessary to achieve a serum level of plasma 25-hydroxyvitamin D (25(OH)D) (the accepted clinical indicator of Vitamin D status, including contributions from both cutaneous and dietary sources) of about 30 nmol/L (12 ng/L). Subsequently, substantial additional research indicated that either the plasma 25 (OH) D levels or the dietary intake of Vitamin D of Americans was insufficient [28-30]. This was followed by considerable media attention both in the popular press [31-33] and in scientific/medical journals [34-36]. More accurate methods of measuring 25(OH)D also became available, although each method had limitations [37]. In 2009, an IOM working group concluded there was significant new and relevant research available to warrant a reevaluation of the dietary recommendations for Vitamin D and calcium [38]. In 2011, the IOM published a new monograph on Vitamin D [39] based on a comprehensive analysis of the new information. It suggested that 25(OH)D levels <30 nmol/L were associated with reduced calcium absorption and osteomalacia in young and middle aged adults but there was little evidence of benefits for levels >50 nmol/L. Based on achieving a plasma level of 50 nmol/L, the committee updated the recommended daily allowance (RDA) of Vitamin D for those 1 to 70 years of age to 600 IU/d (15 μg/d) tripling the allowance [39]. The increasing attention devoted to Vitamin D in the popular and medical literature, better availability and more accurate assay procedures, knowledge that large portions of individuals may be Vitamin D deficient, and the change in national policy may account for the increase in Vitamin D prescriptions during the survey period.

In contrast to Vitamin D, the data indicated that prescriptions for Vitamin E declined from 2005 to 2009 in agreement with another study using PDTS data [24]. The actual prescription prevalence was relatively low, with a high of about 1.4 prescriptions/1000 SMs in 2005 and declining and stabilizing at about 0.3 to 0.4 prescriptions/1000 SMs after 2009. During the survey period, several meta-analytic studies appeared suggesting that high-dosage Vitamin E supplementation may increase all-cause mortality [40-42], although the applicability of these meta-analyses to healthy individuals was questioned [43]. The recommendation for Vitamin E intake was 15 mg/day for adults 19 to 50 years of age [44] but data from the NHANES 2003–2006 indicated that Americans consumed about 7 mg/day [45]. Nonetheless, signs of overt Vitamin E deficiency were rare and usually associated with malnutrition, rare genetic conditions, and certain chronic diseases [46-50]. While observational epidemiological studies suggested that Vitamin E may reduce cardiovascular events, large randomized prospective cohort trials have generally not demonstrated favorable effects on cardiovascular disease [51-53]. Methodological problems with observational epidemiological studies have been comprehensively outlined [51,54]. The US Preventive Services Task Force (USPSTF) recommended against the use of Vitamin E for the primary prevention of cancer or cardiovascular disease [55,56]. Overall, the meta-analytic studies suggesting high-dose Vitamin E increases mortality, results of large randomized prospective cohort trials suggesting little effect on cardiovascular disease and cancer, and recommendations of the USPSTF may at least in part account for and justify the decline in Vitamin E prescriptions.

Another interesting trend was the linear decline in prescriptions for antacids and absorbents. The shape of the curve suggested that the decline in the survey period may be a continuation of declines from previous years, although without prior year data this cannot be determined with certainty. Based on the procedures used by NHANES [57] we included antacids in our study since they provide users with specific minerals. Antacids included substances such as calcium carbonate, magnesium carbonate, magnesium hydroxide, sodium bicarbonate, aluminum hydroxide and other substances mixed with these compounds (e.g., calcium carbonate with glycine). Antacids are typically prescribed for rapid relief of mild, infrequent gastroesophageal reflux disease (GERD) whereby antacids act as buffering agents to

neutralize gastric acids [58,59]. In the 1970's, a class of acid suppressive drugs, histamine 2 receptor antagonists (H2RAs), was developed. In the 1990's, proton pump inhibitors (PPIs) were developed that were extremely effective in blocking the final common pathway of gastric acid secretion, the hydrogen/potassium-APTase proton pump [60]. Other drugs in development or on the market for GERD include potassium-competitive acid blockers and drugs that reduce transient lower esophageal sphincter relaxation (TLESR reducers) [61]. A study of a nationally representative sample of emergency rooms found that while the prescriptions for PPIs more than doubled from 2001 to 2010, prescriptions for H2RAs and antacids decreased 16% and 25%, respectively [62]. The reduction in prescribed antacids seen in the present study was much greater over a similar period of time (9 years), but the present data includes all oral prescriptions rather than just those provided in emergency rooms. It is possible that the development and use of advanced drugs for treating GERD resulted in a decline in prescriptions for antacids during the survey period.

Replacement preparations are a very broad category of substances designed to treat a variety of specific nutritional deficiencies. Prescriptions for replacement preparations increased from 2005 to 2011 then declined very slightly. When partitioned into the mineral compounds accounting for most of these (calcium salts and zinc preparations), it could be seen that prescriptions for calcium salts were increasing while those for zinc preparations declined precipitously. Despite differences in methodology noted earlier (i.e., subject population and timeframe), Attipoe et al [23] noted similar trends in calcium and zinc prescriptions. In the present investigation, there were 22 generic calcium compounds classified as replacement preparations and 14 (64%) of these contained some form of Vitamin D. The reasons cited above for the increases in Vitamin D prescriptions may also, at least partly, account for the increase in calcium salt preparations over the survey period. Zinc preparations were primarily zinc acetate, zinc gluconate, or zinc sulfate in the form of tablets, capsules, or lozenges. Summaries of studies prior to 1998 suggested that zinc preparations may reduce the duration and symptoms of the common cold [63] but after this time studies were published indicating that this intervention may not be effective [64,65], and a structured review of randomized placebo controlled studies in 2007 suggested there was no therapeutic benefit from zinc lozenge consumption [66]. Problems with the taste of placebos [67] and the chemistry of formulations [68] emerged, adding to the uncertainty. The latest Cochrane review of 18 trials indicated that oral zinc administered within 24 hours of symptom onset may slightly shorten the duration of the common cold in healthy people. There was no association between oral zinc supplements and symptom severity, and the prevalence of adverse effects with zinc lozenges was high [69]. Other applications for oral zinc preparations for infectious, chronic, and age-related diseases have also been suggested [70,71]. Nonetheless, the uncertain effectiveness of zinc substances for treating the common cold may explain, at least in part, the decline in prescriptions for zinc preparations.

Prescriptions filled by SMs for B and B-complex vitamins declined during the survey period, accounted for almost exclusively by a decline in pyridoxine (Vitamin $B_6$). Reasons for this are not clear. Pyridoxine comprised a single generic category, "pyridoxine HCL". Pyridoxine is present in a wide variety of foods so actual deficiency is rare [72]. The RDA for adults is 1.3 mg/day[72] and, based on data from NHANES, average intake from food is 1.9 mg/day with 75% of Americans consuming at least 1.4 mg/day [45]. Clinical uses of pyridoxine include treatment for certain types of anemia, morning sickness, premenstrual syndromes, impaired renal function, and hyperhomocystemia [73-78]. Early observational epidemiological studies suggested that higher levels of pyridoxine or its bioactive metabolite (pyridoxal 5′-phosphate) reduced the risk of cardiovascular disease [79,80], possibly through an effect on homocysteine that has a dose–response relationship with cardiovascular disease [81]. However, subsequent randomized prospective placebo controlled trials showed that supplemental pyridoxine did not affect homocysteine levels or the incidence of cardiovascular events [82,83]. Pyridoxine has also been suggested for the treatment of peripheral neuropathies including carpal tunnel syndrome [84,85] but randomized double-blinded placebo controlled studies or a meta-analysis found no evidence of advantageous therapeutic effects [86-88]. Although it is difficult to make direct comparisons for reasons noted above (participant population and timeframe), as well as the fact that only the total number of prescriptions was examined, Krieger et al. [22] noted a decline in overall prescriptions Vitamin B and in pyridoxine prescriptions in military medical treatment facilities from 2007 to 2011.

Vitamin C prescription prevalence rose from 2005 to 2009, almost doubling in this period, and then leveled off over the remainder of the surveillance period. Morioka et al. [24] using PDTS data reported a small increase in Vitamin C prescriptions in the period 2007–2011 which is relatively consistent with the data reported here. Of the 3 generic categories for Vitamin C, over 99% of the prescriptions were for "ascorbic acid" with very few prescriptions for the other two generic categories (ascorbic acid with ascorbate sodium and ascorbic acid with Vitamin E). Since 1970, when Linus Pauling published a book claiming that Vitamin C prevents and ameliorates the common cold, this has been a controversial topic [89]. In 2004, a systematic review was published indicating that dosages of 200 mg/day or greater did not appear to reduce the incidence of colds in the general population; however, studies involving military personnel and participants living under conditions similar to those of military recruits (i.e., close living quarters and heavy physical exercise) generally indicated that Vitamin C reduced the incidence of common colds and pneumonia [90]. Subsequently, other systematic and narrative reviews published between 2005 and 2013 came to similar conclusions [91-95]. With regard to the treatment or prevention of cancer or cardiovascular disease, systematic and narrative reviews of randomized clinical trials have generally concluded that Vitamin C is not effective [56,96-98]. One problem with intervention studies is that Vitamin C is tightly regulated in humans by mechanisms involving absorption, tissue accumulation, and renal reabsorption and excretion. In studies where subjects' baseline Vitamin C levels were already saturated, supplementation may have no effect [99]. A recent randomized double-blinded placebo controlled trial of healthy men with

adequate-to-low plasma Vitamin C concentration (47% were below adequate, <28 μmol/L) found that 1gm/day of oral Vitamin C reduced the incidence and duration of colds compared to a placebo [100]. It is possible that favorable reviews regarding Vitamin C and the common cold in military personnel influenced the trend in Vitamin C prescriptions.

Sennosides and psyllium were the most commonly prescribed substances derived from botanical constituents. These two substances have well known and well established therapeutic uses as laxatives [101-103] and were classified as such in the AHFS codes. In addition, psyllium has been used for the treatment of hypercholesterolemia, diabetes, irritable bowel syndrome, ulcerative colitis, and other maladies [103-105]. The third most common botanical was baicalin/catechin (primarily Limbrel®), which is a flavonoid derivative and a cyclooxygenase inhibitor (COX 1 and COX 2) used in the treatment of osteoarthritis [106,107]. Other botanicals such as *Ginkgo biloba*, flaxseed, garlic, green tea leaf extract and ginseng may have some therapeutic applications, but have also been associated with adverse effects [108-110]. It is not clear why they had been prescribed by medical care providers.

The present study found that about 11% of SMs filled at least one prescription for a DS each year. We previously found that 60% to 70% of SMs self-reported using at least one DS [4]. Thus, it seems likely that most SMs obtain their DSs from over-the-counter sources.

The strength of this study is that the data on prescribed DSs are likely to be complete. Prescription medication is free for SMs and SMs are likely to use the military medical system for this reason. Further, the data includes the actual DS dispensed from the pharmacies and not just those prescribed. However, there is no guarantee that the SM will use the DS once obtained. Two individuals independently selected the DSs and there were few disagreements with these resolved by consensus. Future studies may attempt to combine medical records data with pharmacy data to see if prescriptions are appropriate to the problem.

In summary, the present study describes trends in prescribed oral DSs dispensed to military personnel from 2005 through 2013. We found that 11% of SMs filled one or more oral DS prescriptions in this period. There were increases over time in prescriptions for Vitamin D, Vitamin C, and replacement compounds; decreases over time in prescriptions for antacids, Vitamin B and B-complex, and Vitamin E; and little change for iron preparations and multivitamins. Accounting for these trends is likely complex, and an attempt was made here to explain the observed patterns in terms of changes in the roles of DSs in therapeutics and public health. Both provider and patient perceptions and knowledge are likely important in interpreting the trends. If a patient is seeing a provider, it is relatively easy to request a DS the patient may consider important for health but not associated with the specific problem of the visit. Knowledge and perceptions of the uses of DSs will continue to evolve and continuing surveillance of these DSs will identify if the trends observed here continue into the future or if new patterns emerge.

## Disclaimer

The views, opinions, and findings in this report are those of the authors and should not be construed as an official Department of Defense or Army position, policy, or decision, unless so designated by other official documentation. 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. The investigators have adhered to the policies for protection of human subjects as prescribed in DOD Instruction 3216.02 and the research was conducted in adherence with the provisions of 32 CFR Part 219.

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