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REVIEW

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Multi-Criteria Decision Analysis Model for Assessing the Risk from Multi-Ingredient Dietary Supplements (MIDS)

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ABSTRACT

Military personnel use dietary supplements (DS) for performance enhancement, bodybuilding, weight loss, and to maintain health. Adverse events, including cardiovascular (CV) effects, have been reported in military personnel taking supplements. Previous research determined that ingestion of multi-ingredient dietary supplements (MIDS), can lead to signals of safety concerns. Therefore, to assess the safety of MIDS, the Department of Defense *via* a contractor explored the development of a model-based risk assessment tool. We present a strategy and preliminary novel multi-criteria decision analysis (MCDA)-based tool for assessing the risk of adverse CV effects from MIDS. The tool integrates toxicology and other relevant data available on MIDS; likelihood of exposure, and biologic plausibility that could contribute to specific aspects of risk.

Inputs for the model are values of four measures assigned based on the available evidence supplemented with the opinion of experts in toxicology, modeling, risk assessment etc. Measures were weighted based on the experts' assessment of measures' relative importance. Finally, all data for the four measures were integrated to provide a risk potential of 0 (low risk) to 100 (high risk) that defines the relative risk of a MIDS to cause adverse reactions.

We conclude that the best available evidence must be supplemented with the opinion of experts in medicine, toxicology and pharmacology. Model-based approaches are useful to inform risk assessment in the absence of data. This MCDA model provides a foundation for refinement and validation of accuracy of the model predictions as new evidence becomes available.

KEYWORDS

Cardiovascular; dietary supplements; multi-ingredient dietary supplements; risk; safety prediction; syncope

Abbreviations: AE: Adverse Effects; AERs: Adverse event reports; AUC: Area Under the Concentration Time Curve; CV: Cardiovascular symptoms; DoD: US Department of Defense; DS/DSs: Dietary Supplement(s); EP: Expert Committee; FDA: Food and Drug

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Administration; IOM: Institute of Medicine; MCDA: Multi-Criteria Decision Analysis; MIDS/MIDSs: Multi ingredient dietary supplement(s); NMW: Natural Medicines Watch; OSM: Online Supplemental Material; PKPD: Pharmacokinetics/Pharmacodynamics data; QSAR: Quantitative Structure-Activity Relationship; SAR: Structure activity relationships; USP: United States Pharmacopeia

Introduction

Use of dietary supplements (DS) by military personnel is well acknowledged and documented in a review conducted by the Institute of Medicine (IOM) (Institute of Medicine (IOM) 2008), which found that the youngest, least-educated soldiers use fewer DS than their more educated, older colleagues; and female military personnel use more DS than males consistent with patterns of use in the civilian US population (Bailey et al. 2011; Fennell 2004). Service members are more likely to be involved in demanding physical tasks requiring strength and endurance, and therefore may be more similar (appropriately compared) to elite athletes than to the general population. About 50% of military personnel use multiple DS to enhance their performance, for bodybuilding, and for weight loss (Coulter et al. 2011; Jacobson et al. 2012; Lieberman et al. 2010). Some DS used by military personnel contain multiple ingredients, include Arginine, caffeine, creatine, synephrine and yohimbine; and specific concerns regarding the safety of DS use by the military arise due to the unique challenges, needs, and responsibilities of this specific population. One retrospective review found that cardiovascular (CV) symptoms, including syncope, were more likely during exertion in military personnel taking DS (Eckart et al. 2010). Additionally, adverse events (U.S. Food and Drug Administration 2006) may have much greater impact to military personnel than the civilian population. For example, induction of diuresis may not be a "serious adverse event" for the general population but could severely affect the operational readiness of a service member. Thus, for the military, the distinction between "non-serious adverse events" (U.S. Food and Drug Administration 2006) and "serious adverse events" (FDA 2007) is based on the extent of impact on their performance or the survivability of service members, taking into consideration their tasks (both physical and mental), the environmental surroundings (e.g. high altitude or extreme temperatures), and risks (e.g. bleeding, dehydration, infection, or stress).

To appropriately advise military personnel about the use of MIDS, the United States Department of Defense (DoD) sought an evidence-based review to evaluate the safety of MIDS containing these DS ingredients. Notably, the IOM recognized the use of DS by military personnel (Institute of Medicine (IOM) 2008) and briefly reviewed caffeine and creatine DS use but provided no information on MIDS. Furthermore, our search of the literature did not find any information on the safety of MIDS. To begin to address the question of the safety of MIDS use by military personnel, we present a preliminary multi-criteria decision analysis (MCDA)-based tool that can be applied to toxicologically relevant adverse effects. In this work we focus on CV-related adverse effects.

Methods

This MCDA tool was developed by volunteer experts with qualified experience in diverse areas to ensure the appropriate review of available information according to the

Table 1. Hypothetical combination MIDS made up of arginine (A), caffeine (Ca), creatine (Cr), synephrine (S), and yohimbine (Y).

Acronym	Combination of ingredients
A Cr	Arginine + Creatine
A Cr S	Arginine + Creatine + Synephrine
A Cr S Y	Arginine + Creatine + Synephrine + Yohimbine
A Cr Y	Arginine + Creatine + Yohimbine
A S	Arginine + Synephrine
A S Y	Arginine + Synephrine + Yohimbine
A Y	Arginine + Yohimbine
Ca A	Caffeine + Arginine
Ca A Cr	Caffeine + Arginine + Creatine
Ca A Cr S	Caffeine + Arginine + Creatine + Synephrine
Ca A Cr S Y	Caffeine + Arginine + Creatine + Synephrine + Yohimbine
Ca A Cr Y	Caffeine + Arginine + Creatine + Yohimbine
Ca A S	Caffeine + Arginine + Synephrine
Ca A S Y	Caffeine + Arginine + Synephrine + Yohimbine
Ca A Y	Caffeine + Arginine + Yohimbine
Ca Cr	Caffeine + Creatine
Ca Cr S	Caffeine + Creatine + Synephrine
Ca Cr S Y	Caffeine + Creatine + Synephrine + Yohimbine
Ca Cr Y	Caffeine + Creatine + Yohimbine
Ca S	Caffeine + Synephrine
Ca S Y	Caffeine + Synephrine + Yohimbine
Ca Y	Caffeine + Yohimbine
Cr S	Creatine + Synephrine
Cr S Y	Creatine + Synephrine + Yohimbine
Cr Y	Creatine + Yohimbine
S Y	Synephrine + Yohimbine

Rules and Procedures of the United States Pharmacopeial Convention (USP) Council of Experts (USP 2015), including declaration of any conflict-of-interests. The expertise covered by the USP Dietary Supplement Safety Modeling Expert Panel (EP) included medicine, nutrition, public health, regulatory toxicology, pharmacology, and statistical modeling. To address the question of safety of MIDS, we developed a hypothetical situation where five ingredients—arginine (A); caffeine (Ca); creatine (Cr); synephrine (S); and yohimbine (Y)—are used to formulate a MIDS. By assuming equal chances for the incorporation of each of the five ingredients into a MIDS (each only once), we generated 26 possible combinations containing the five ingredients (Table 1), but we did not consider the different amounts of each ingredient (dosage/intake amounts) that may be incorporated into MIDSs. We then asked the question whether any of the 26 MIDS combinations *would present a risk of adverse CV effects in active healthy adults?*

The primary reasons for focusing on CV effects were that these symptoms, including syncope, are reportedly more likely to occur during exertion in military personnel taking DS, classified as "signal medical event" (Eckart et al. 2010).

We identified and collated four categories of data that could contribute to determining the safety of MIDSs. Data streams included the following: first, observational data (clinical studies, case reports, MedWatch, and Natural Medicines Watch); second, structure-based computational prediction data [quantitative structure-activity relationship (QSAR) and Pharmacokinetics/Pharmacodynamics data (PKPD) predictions]; third, exposure data from surveys of military personnel including expert judgment about exposure; and fourth, mechanistic modeling of multi-ingredient combinations derived by aggregating and distilling molecular pathway information across a range of peer-reviewed journals (CytoSolve) (V. A. Ayyadurai and Dewey 2011). Brief descriptions of

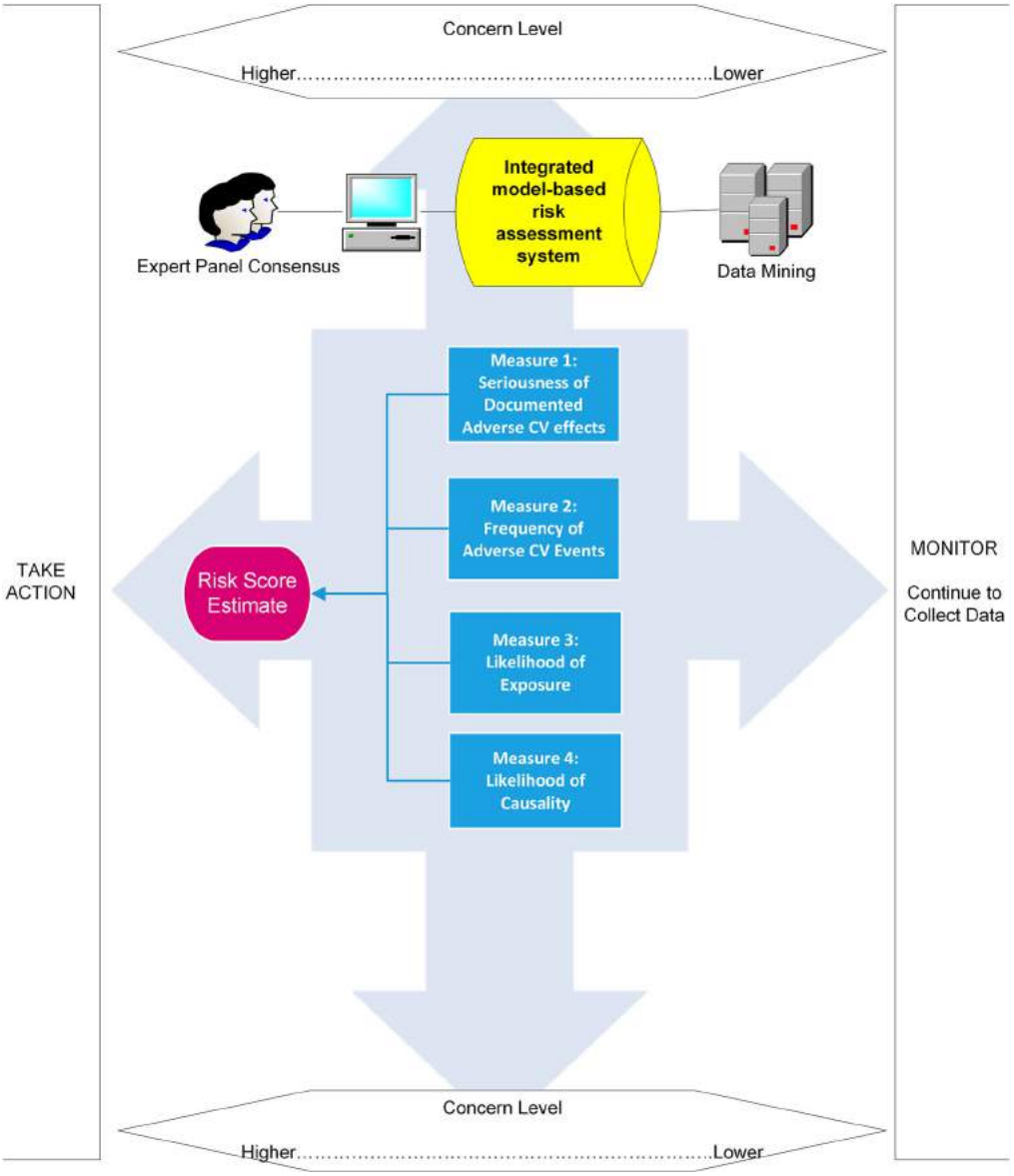

Figure 1. Schematic of the model-based risk assessment framework.

data collection and handling follow below. We then constructed four measures that align with exposure and consequences (see Figure 1), the product of which is a risk score that represents the relative risk for the MIDS.

Observational data

Systematic review of published literature

A systematic review was conducted to determine whether any of the 26 MIDSs combinations presented a risk of adverse CV effects in active adults. The review was based on the methods for conducting systematic reviews, as outlined in the IOM Standards for

Systematic Reviews (Institute of Medicine (IOM) 2011), with the exception of small modifications, as indicated below.

Electronic literature search

The search was conducted in PubMed, covering the period from 1946 through December 2013. The search strategy included names of 26 combinations of the five ingredients of interest, key words, and their Medical Subject Headings (MeSH) terms, augmented with appropriate synonyms for the ingredients of interest, e.g. the term "energy drink(s)" for MIDS containing caffeine. Details of the search strategy are available in Appendix A1, A1.1 & A2, online supplementary information (OSM).

Study selection process and eligibility criteria

Titles and abstracts identified through the literature searches were screened independently by two reviewers, to identify studies that evaluated a combination of two or more of the five ingredients. Discrepancies between the two screeners' decisions were resolved by consensus after discussions. A web-based citation-screening tool, Abstrakr™ (http://abstrackr.cebm.brown.edu/) was used to facilitate the abstract screening process. Full-text articles of relevant abstracts were reviewed by one investigator and a second investigator confirmed the article's inclusion based on eligibility criteria outline below (details on Literature search, Selection Process, and Eligibility Criteria are available in Appendix A2, OSM):

- Human intervention and observational studies including case reports that investigated a combination of two or more of the five ingredients of interest. Studies that included other ingredients of no interest were included except where a constituent was known to have cardiovascular related adverse effects such as Ephedra.
- Unpublished/other studies identified through reference mining of selected review articles.
- Criteria for exclusion were:
  - Studies of substances not included in the model that are generally known to be associated with adverse events or banned by regulatory agencies (e.g., ephedra, which was banned by the Food and Drug Administration (FDA) from the US market because of adverse CV effects) (FDA 2004).
  - Study populations with known genetic conditions that can interfere with metabolism of any of the five ingredients of interest (e.g., study population with a transporter defect, affecting one of the ingredients for example creatine transporter defect) (Longo et al. 2011).

Data extraction

One reviewer extracted data and the second verified the data. Extracted data included study characteristics, study participant characteristics, interventions and controls, a list of the outcomes/endpoints examined in the original studies, and the results of safety-related outcomes or adverse effects (AEs). The standardized data extraction form is

provided in Appendix A3–A5, OSM. The safety outcomes of interest were CV-related AEs e.g. increased blood pressure reported in clinical trials, case reports, or in adverse event reports (AERs) (see Appendix A6, OSM).

Risk of Bias (ROB) assessment for clinical trials

ROB (or methodological quality/quality assessment) was calculated for each clinical trial using the Cochrane ROB tool (Higgins and Green 2011), which consists of five domains: randomization, allocation concealment, blinding, incomplete data reporting, and selective outcome reporting (Appendix A7, OSM).

Quality assessment for case reports or case series

The quality of AERs in case reports or case series was assessed using a 5-point assessment scale with scores of 0 [low quality] or 1 [high quality] for each domain and the sum of domains ranging from 0 to 5, with 0 representing the highest ROB and 5 no ROB (details in Appendix A7.1, OSM).

FDA MedWatch and Natural Medicines Watch database AERs

AERs filed in the period from January 2008 to November 2013 were obtained from the FDA through Freedom of Information Act (FOIA) requests for DS products containing caffeine, including in combination with two or more of the five ingredients. To augment the search strategy, a list of popular product names containing multiple ingredients of interest, such as Jack3d, Yok3d, and others, were used as search terms (see Appendix B in the OSM for complete details). The DoD files AERs in the Natural Medicines Watch database (NMW) (NMCD 2012); therefore, reports from NMW are directly relevant in assessing the safety of DSs for military personnel. The DoD provided AERs in NMW database related to DS products containing the five ingredients of interest (Appendix C, OSM).

Data extraction from AERs (from MedWatch and NMW)

To identify reports on the various possible combinations of the five ingredients, data were transferred to an Excel 2010 file and filtered using the ingredient names as keywords. For example, the name of a single ingredient was used as a key word and then two ingredients, and then three, and so on. Only AERs related to CV reactions citing terminologies meeting system organ class terms listed: 1010 = Cardiovascular Disorders, General; 1020 = Myocardial, Endocardial, Pericardial and Valve Disorders; 1030 = Heart Rate and Rhythm Disorders; and 1040 = Vascular (Extracardiac) Disorders from the Council for International Organizations of Medical Sciences (CIOMS 1999) were extracted (for data extraction details, see Appendix B1, OSM).

Quality assessment for AERs

The same process as described in Appendix A7.1-OSM for case reports or case series was followed.

Prediction Data

QSAR/SAR modeling data

Structure-activity relationship (SAR) and QSAR models were applied to analyze the molecular structural similarities between the five ingredients and other related substances and generate chemical structure–based assessments of potential toxicity. Structure-based assessments analyze for the presence of structural alerts that may be used with expert interpretation to signal toxicity based on a knowledge base or training set of compounds with known toxicity (Derek Nexus 3.0.One and ToxTree 2.5) (Judson 2012). In addition, chemical structure searches of the databases were performed to identify publicly available toxicity data.[1] The research and validation testing of the computational models used here (Leadscope 1.6.0.Three and Symmetry 1.0.3.2-R3) were previously published by the US FDA (Valerio 2013). Endpoints modeled in the various computational platforms included CV AEs ("QT/QT prolongation" and "cardiac arrhythmia – Torsade de Pointes", both based on human clinical trials data) (see Appendix D, OSM).

Pharmacokinetics data

PKPD data related to the five ingredients of interest was extracted from articles retrieved during the systematic review of the literature. Data on study population, peak concentration (C_{max}), time to peak concentration (t_{max},), clearance (K), and area under the concentration time curve (AUC) were extracted from studies on MIDS. Where unavailable, clearance values were calculated as amount exposed/AUC, and where information related to AUC or amount exposed to was not available, concentration-time data points were extracted from figures in relevant articles by using DataThief III [ver 1.6, November 2010 (datathief.org)]. The AUC and clearance values were calculated from extracted concentration time series using the "AUC" complete function of the R package [Version 1.3-3] PK software (Jaki and Wolfsegger 2012). If an ingredient was present in plasma prior to the dose studied, the background concentration was subtracted from all data points prior to calculation of the AUC. A summary of the pharmacokinetics data extracted is provided in Appendix E, OSM.

Exposure data

Data on exposure were obtained from surveys of military personnel (Stephens 2013), supplemented with expert judgment as detailed in Appendix F, OSM. The IOM report summarized data on surveys of military personnel (Institute of Medicine (IOM) 2008), including information on the frequency of DS use, the number of different DS used, and variety of DS used. However, ingredients in the DS were not specified in most cases, and only the product type was provided, e.g. "weight loss product", or "protein

[1]SAR/QSAR modeling predictions were conducted based on the computational analysis by Dr. Luis Valerio, (at the time Dr. Valerio was with the FDA at CDER) CDER, FDA, under the framework of Research Collaboration Agreement between USP and FDA. Disclaimers: No proprietary information were released from the computational models or presented in this article. No review of data submitted to FDA were presented. The data in this article may contain computer-generated predictions and do not in themselves represent a complete analysis of risk or a final regulatory decision or policy regarding the safety of any DS. The analyses do not imply the official position of FDA.

powder". The energy drink survey provided estimates of use by of the military at various pay levels, as well as a list of the most popular energy drinks (Institute of Medicine (IOM) 2008). To determine the ingredients in the energy drinks described in the IOM report, we searched the Internet for product labels. Expert judgment regarding the use of these DS was provided in the form of comments from DoD and knowledge about ingredient availability or likelihood of use from the expert panel members.

Cytosolve mechanistic modeling of multi-combinations of ingredients

CytoSolve provides a platform for mechanistic modeling of complex molecular pathways (V. A. Ayyadurai and Dewey 2011; V. A. Ayyadurai 2010), integrating existing molecular pathway information derived from peer-reviewed journals and clinical data to produce mechanistic models (Al-Lazikani et al. 2012). CytoSolve data were available for two of the five ingredients, L-arginine and caffeine, and on their interaction with the nitric oxide (NO) pathway model, an important aspect of CV function in the human body (Kelly et al. 1996). CytoSolve identified molecular pathway maps, critical rate constants, and molecular species' interaction of L-arginine as well as caffeine interactions with NO pathways, as described for *in vitro* and *in vivo* experiments. Articles were searched by CytoSolve, as detailed in Appendix G & J, OSM. A recently published CytoSolve molecular pathway model of NO production (Koo et al. 2013) obviated the need to perform a significant number of CytoSolve mechanistic modeling steps (V. A. Ayyadurai and Dewey 2011) [described in Appendix G.1, OSM]. Data on the NO pathway obtained from the publication (Koo et al. 2013) were used to model the interaction between L-arginine and caffeine with NO Production [details in Appendix G, OSM].[2]

Multi-Criteria Decision Analysis (MCDA)

Decision analysis is a systematic, quantitative approach for enumerating key factors for decision making and assessing the relative value of one or more different decision options (Goel 1992). The MCDA framework provides a systematic way of handling the tradeoffs between different aspects of decision-making. Here, MCDA provided a framework for integrating evidence-based data on prevalence of population exposures, risk levels at different exposures, uncertainty, and experts' valuation to enable evaluation and risk ranking of the 26 possible ingredient combinations.

Integration and analysis of evidence using Multi-Criteria decision model

Four measures of exposure and/or consequences were identified as follows: measure 1—severity of CV effects; measure 2—frequency of CV events; measure 3—likelihood of exposure; and measure 4—biologic plausibility. Measures 1, 3 and four were assigned a

[2]The multi-combination modeling predictions were based on the use of CytoSolve by Dr. V.A. Shiva Ayyadurai under an agreed upon framework where such use of CytoSolve, Inc.'s technology and personnel resources were donated for this modeling effort. Disclaimers: No proprietary information were released from the computational models or presented in this article. The data in this article may contain computer-generated predictions and do not in themselves represent a complete analysis of risk or a final regulatory decision or policy regarding the safety of the interaction of L-arginine and caffeine.

Table 2. Measure 1: Severity of documented adverse CV effects.

High[4]	Medium[4]	Low[4]
One or more well-documented[1] clinical study, case report, or AER that demonstrate probable or certain[2] causality of the serious[3] CV risk for a MIDS (one of the 26 defined combinations).	One or more reports filed as serious events, but do not include complete information necessary to demonstrate the causality of serious reaction for a MIDS. Such incomplete reports may be speculative. Reports filed as serious events involving heterogeneous combination (that includes ingredients other than the 5 identified ingredients in a combination).	No documentation available for serious adverse CV reaction reported for combination.

[1]A well-documented report should meet at least four of the following criteria derived from the WHO-UMC Causality Categories (http://who-umc.org/Graphics/24734.pdf): 1) ingestion of DS shortly before AE; 2) no underlying disease/medical conditions that are known to be associated with the AE; 3) no other drugs/supplements/ingredients concurrently in use; 4) de-challenge; and 5) re-challenge. Each report receives a rating of 1 (high quality) when it meets a requirement and 0 when the requirement is not met or the data is not clear or unreported, for a maximum of five points.

[2]Causality is determined according to the WHO Causality Assessment System (http://who-umc.org/Graphics/24734.pdf) when information is available to determine the causality (product description, temporal correlation between exposure and event, dechallenge / rechallenge, prior medical history, and concurrent medication use). MedWatch reports typically do not include complete information to determine causality.

[3]A serious adverse reaction/event is one that (A) result in: i) death; ii) a life–threatening experience; iii) inpatient hospitalization; iv) a persistent or significant disability or incapacity; or v) a congenital anomaly or birth defect; or (B) require, based on reasonable medical judgment, a medical or surgical intervention to prevent an outcome described under subparagraph (A).

[4]The assignments assumed a value of "low" severity for combinations with no documented adverse CV effects and "medium" severity for combinations with documented adverse CV effects.

risk potential that was categorized as high, medium, or low with reference to CV AEs; whereas measure two was the total counts of AERs (from FDA MedWatch, Natural Medicines Watch, and clinical trial reports). AE counts from clinical trials only included those reported in the intervention group. Of note is that measure one considers only the severity of serious cardiovascular effects while measure two considers the total number of all adverse events regardless of seriousness. Each MIDS combination was assigned a value for each measure based on the best available evidence supplemented by expert opinion. The measures and their potential values and criteria for assigning values are defined in Tables 2–5.

Qualitative analysis for risk rating

A Rating and Evidence Summary sheet was developed for each of the 26 hypothetical MIDS combinations and each EP member provided a summary of the risk ratings for the four risk measures and the overall risk. Each summary sheet contained: 1) overall rating for a combination as the individual ratings separated by dashes (e.g. M-105-H-L means: medium severity, 105 reports, high exposure, and low likelihood of biologic plausibility); 2) evidence for the rating in the form of a list of the data relevant to that measure; 3) a conclusion and level of confidence in the conclusion. Ratings for measures 1, 3 and four were translated to scores such that "high" = 1, "medium" = 0.5, "unknown" = 0.25, and "low" = 0. Measure two was on a linear scale so that the combination with the largest number of reports i.e. caffeine + yohimbine with 104 AERs

Table 3 Measure 2: Frequency of adverse CV effects.[1,2]

The number of documented cases of serious as well as non-serious CV adverse effects; a number from 0 to the maximum number of reports of any ingredient combination being considered

[1]This measure was assigned a numerical value representing the total number of AERs from FDA MedWatch and Natural Medicines Watch and in clinical trial reports (see **Appendix H1,** OSM).

[2]The frequency does not take into account other ingredients ingested. Supposing we had three ingredients: A, B, and C. We had 20 cases of A + B, 20 of A + B + C, 0 of A + C, and 0 of B + C. The frequency would be 40 for A + B, 20 for A + B + C, and 0 for all other combinations of these ingredients. Combinations with a large number of documented reports merit additional review regardless of the seriousness of those events, the likelihood of exposure, or even the background risk factors of individuals described in the reports.

Table 4. Measure 3: Likelihood of exposure.[1]

High: Known use.	**Medium:** Suspected use.	**Low:** Unlikely for potential use
Strong evidence for common use of the MIDS exists. Information from IOM reports, comments from DoD, surveys, or expert opinion may be the basis for this parameter. If the individual ingredients are in different products, both products are likely to be used concurrently.	Plausible argument or incomplete evidence for the MIDS use exists.	There are no known compelling arguments for plausible use of these DS together.
Information on % population exposed, level of intake / duration / frequency of use is available and indicates high likelihood of exposure.	Information on population exposed, level of intake / duration / frequency of use is incomplete or suggests low overall exposure.	

[1]Preliminary values were assigned by assuming "medium" exposure if the combinations included yohimbine or synephrine, because of low prevalence of MIDSs with this combination and "high" exposure otherwise.

was assigned a score of one and combinations with no reports were given a score of 0, ended up with a fraction.

Expert opinions

Ranking and weighting of measures

By means of an online questionnaire, EP members ranked the four measures on a scale of 1 to 4, and the data were used to calculate mean ranks (survey questions and results in Appendix H1-1, OSM). EP members also provided a weight value ranging between 0% and 100% based on their perception of each measure's relative importance in determining safety of a MIDS.

EP members then reviewed the summary data sheets for the 26 possible combinations of caffeine, L-arginine, creatine, synephrine, and yohimbine (see Appendix H4, OSM). They evaluated the preliminary ratings that had been assigned by USP staff for each combination and voted to "Agree" or "Disagree," and where they disagreed, provided other values and justification for their proposed new value as well as any other comments. Seven of the 10 EP members and one observer (a DoD staff member who helped design the study) responded to the survey. Of the three EP members who were did not respond, one left the EP and two were unable to respond due to personal situations unrelated to the study.

Table 5. Measure 4: Predictions of biologic plausibility.

High: This combination could likely cause adverse CV effects.	**Medium**: This combination could possibly cause adverse CV effects.	**Low:** This combination would probably not cause adverse CV effects.	**Unknown:** There is not sufficient information to determine the potential risk posed by this combination.
Pharmacokinetics: Multi-ingredient pharmacokinetics data suggest interaction between ingredients (ingredient-ingredient interaction) that increases **either** internal exposure (peak plasma concentrations-C_{max} or AUC) or exposure to known toxic metabolites, or reduces time to maximum plasma concentration (t_{max}), or inhibits pertinent metabolic process.	Pharmacokinetics: Data are available that suggest potential accumulation of at least one ingredient in the combination in plasma or other body tissues after consumption of the DS. There is no multi-ingredient pharmacokinetics data for ingredient-ingredient interactions. Multi-ingredient pharmacokinetics data suggest interaction between ingredients (ingredient-ingredient interaction) that increases **either** internal exposure (peak plasma concentrations-C_{max} or AUC) or exposure to known toxic metabolites, or reduces time to maximum plasma concentration (t_{max}), or inhibits pertinent metabolic rates.	Pharmacokinetics: Data are available that suggest no accumulation of any ingredients in the combination in plasma or other body tissues after consumption of the DS. Multi-ingredient pharmacokinetics data suggest ingredient-ingredient interaction that decreases **either** internal exposure (peak concentrations and AUC) or exposure to known toxic metabolites. Bioavailability of individual components of a combination is either not affected or reduced.	Pharmacokinetics: No pharmacokinetics data on combinations of ingredients. Pharmacokinetics data that suggests one or more ingredients in the combination are present in plasma or other body tissues after consumption of the DS is not available.
CytoSolve's Mechanistic Multi-Combination Modeling predicts reduction in NO production rate by 40% or greater for this combination of ingredients at ingredient doses likely to be taken by the population of interest.	*CytoSolve's* Mechanistic Multi-Combination Modeling predicts reduction in NO production rate of 20 – 40% for this combination of ingredients at ingredient doses likely to be taken by the population of interest.	CytoSolve's Mechanistic Multi-Combination Modeling predicts reduction in NO production rate of 0 – 20% for this combination of ingredients, at ingredient doses likely to be taken by the population of interest.	*CytoSolve's* Mechanistic Multi-Combination Modeling predictions unavailable or predicts reduced NO production for one or more ingredients in the combination, but predictions for the combination as a whole are not available.
QSAR Models[1] consistently predict with high probability positive CV toxicity for multiple ingredients in the combination of ingredients at ingredient doses likely to be taken by the population of interest.	*QSAR* Models consistently predict with high probability positive CV toxicity for at least one ingredient in the combination.	*QSAR* Models predict negative CV toxicity for all ingredients in the combination.	*QSAR* Models do not exist for all ingredients or predictions from different models are not in the same direction for the same reaction (e.g., one model predicts positive toxicity and one predicts negative toxicity) for ingredient in the combination.

[1]QSAR models provide a measure of confidence in the prediction generated by the software (negative = 0.4 or less; equivocal = 0.4 to 0.6; positive = more than 0.6). Predictions based on *in silico* (QSAR) models do not provide high plausibility for an adverse reaction to occur by themselves. Consistency of high-positive predictions in multiple models indicates high-risk potential. Confidence in the plausibility of a reaction increases when the QSAR models independently predict the observations adverse reaction from clinical or AER data

Table 6. Measure ranks and weights-Expert Panel members' assignments and computed mean ranks and weights.

Summary of EP members mean ranks and weights for measures 1 to 4						
	Rank 1	Rank 2	Rank 3	Rank 4	Mean Rank	Mean Weight
Measure 1: Severity of Documented Adverse CV effects	5	1	0	1	1.6	32
Measure 2: Frequency of Adverse CV effects	1	2	4	0	2.4	25
Measure 3: Likelihood of exposure	1	2	3	1	2.6	28
Measure 4: Predictions of biologic plausibility	0	2	0	5	3.4	19

Mcda analysis

Logical Decisions® software was used to analyze and integrate the data from the four measures as agreed upon by the EP members; the assigned weights were also used. The outcome was a risk score for each MIDS combination that defines its potential risk relative to other MIDS analyzed.

Results and discussion

Ranks and weights for measures

Mean ranks and weights for measures as provided by EP members are presented in Table 6 (detailed information on ranking and weighting by EP members and data are available in Appendix H1, OSM).

The majority of EP members assigned a higher rank to severity of AEs and frequency, which they considered as the most relevant for which data were available but tended to assign a low rank to biologic plausibility. Severity of AEs and frequency of AEs offer actual data on the combinations in the human population. Biological plausibility data from animal studies, cell culture, etc., carry important uncertainties that would need interpretation to confer clinical meaning. Some experts indicated that exposure was not as important as other measures because all the five ingredients were of interest to the stakeholder (DoD), and thus could be assumed to present exposure levels high enough to be of concern.

The mean values of EP members' assigned weights were consistent with rankings (see Table 6) and were incorporated into the MCDA analysis.

Measure values for the 26 combinations

Table 7 lists the 26 possible combinations of the five ingredients of interest and a value for measures 1–4 for each combination. The measure values agreed upon by the EP members are summarized in Appendix H2, OSM. For each measure, a mean of the values agreed upon by the EP members formed the measure's final value. The following is a general summary of EP members input on each measure (detailed data for each combination are provided in Appendix H3.One and H3.2, OSM).

Multi-criteria analysis

Most experts agreed with the preliminary values for the 26 combinations for Measures 1–4. However, for Measure 3 some EP members recommended higher exposure ratings

Table 7. Measurements are L:low; M:medium; H:high; Unk:unknown [measure 1 (m1), measure 3 (m3); measure 4 m4)]; #=total number of AERs in (from MedWatch, case reports, clinical studies) measure 2 (m2).

Combination	Measure1 L/M/H			Measure2 #	Measure3 M/H		Measure4 U/L/M			Measure Values used in MCDA (average after expert input)			
	Number of EP members responding for m1, 2, 3 & 4									*Value of measure after expert input*			
	L	M	H	count	M	H	U	L	M	m1	m2	m3	m4
A Cr	0	5	1	30	0	6	5	2	0	med	30	high	unk
A Cr S	0	6	0	2	5	1	6	0	0	med	2	med	unkn
A Cr S Y	6	0	0	0	6	0	2	0	5	low	0	med	med
A Cr Y	0	6	0	1	5	1	1	0	5	med	1	med	med
A S	4	1	1	2	6	0	1	0	5	low	2	med	med
A S Y	6	0	0	0	5	1	2	0	5	low	0	med	med
A Y	0	5	1	4	6	0	1	0	5	med	4	med	med
Ca A	0	5	1	40	0	6	1	0	5	med	40	high	med
Ca A Cr	0	5	1	30	0	6	0	0	6	med	30	high	med
Ca A Cr S	0	5	1	2	5	1	0	0	6	med	2	med	med
Ca A Cr S Y	6	0	0	0	4	2	1	0	5	med	0	med	med
Ca A Cr Y	0	6	0	2	4	2	0	0	6	med	2	med	med
Ca A S	4	1	1	2	6	0	0	0	6	low	2	med	med
Ca A S Y	6	0	0	0	6	0	0	0	6	low	0	med	med
Ca A Y	0	6	0	4	6	0	0	0	6	med	4	med	med
Ca Cr	0	5	1	35	0	6	0	0	6	med	35	high	med
Ca Cr S	4	1	1	2	6	0	0	0	6	low	2	med	med
Ca Cr S Y	6	0	0	0	6	0	0	0	6	low	0	med	med
Ca Cr Y	0	6	0	6	6	0	0	0	6	med	6	med	med
Ca S	0	5	1	14	5	1	0	0	6	med	14	med	med
Ca S Y	0	5	1	2	5	1	0	0	6	med	2	med	med
Ca Y	0	5	1	104	6	0	2	0	5	med	104	med	med
Cr S	0	5	1	2	6	0	2	0	5	med	2	med	med
Cr S Y	6	0	0	0	6	0	2	0	5	med	0	med	med
Cr Y	0	5	1	5	6	0	2	0	5	med	5	med	med
S Y	0	5	1	2	6	0	2	0	5	med	2	med	med

for combinations containing caffeine + synephrine because the two ingredients are documented to affect CV system (Schmitt et al. 2012; Venhuis et al. 2014). One expert suggested that all combinations containing arginine + creatine or caffeine + synephrine (and the following combinations: A + Cr + S, A + Cr + Y, A + S + Y, Ca + A+Cr + S, Ca + A+Cr + S + Y, Ca + S) be assigned a "High" rating and not the preliminary "Medium". This was done to address the DoD's concern and because of the high prevalence of use of DSs that contain these combinations. For Measure 4, experts recommended assigning "unknown" instead of "medium" for combinations that were missing data or where data from various sources were inconsistent and this was implemented. Table 7 shows measures values after EP members' input (additional information is available in Appendix H3, OSM); the measures were analyzed using Logical Decisions®, which resulted in the output in Table 8 1A and Table 8 1A -continued.

The bar chart in Figure 2 list combination products that contained caffeine. The highest relative risk score was for a combination containing caffeine + yohimbine. Surprisingly, other combinations that include these two ingredients, together with other additional ingredients, showed lower risk scores. This appears to imply, albeit erroneously, that adding more ingredients to a combination of two ingredients presenting a high risk could decrease the overall risk. This outcome may be explained by the fact that our risk score takes probability and consequence into account such that if exposure

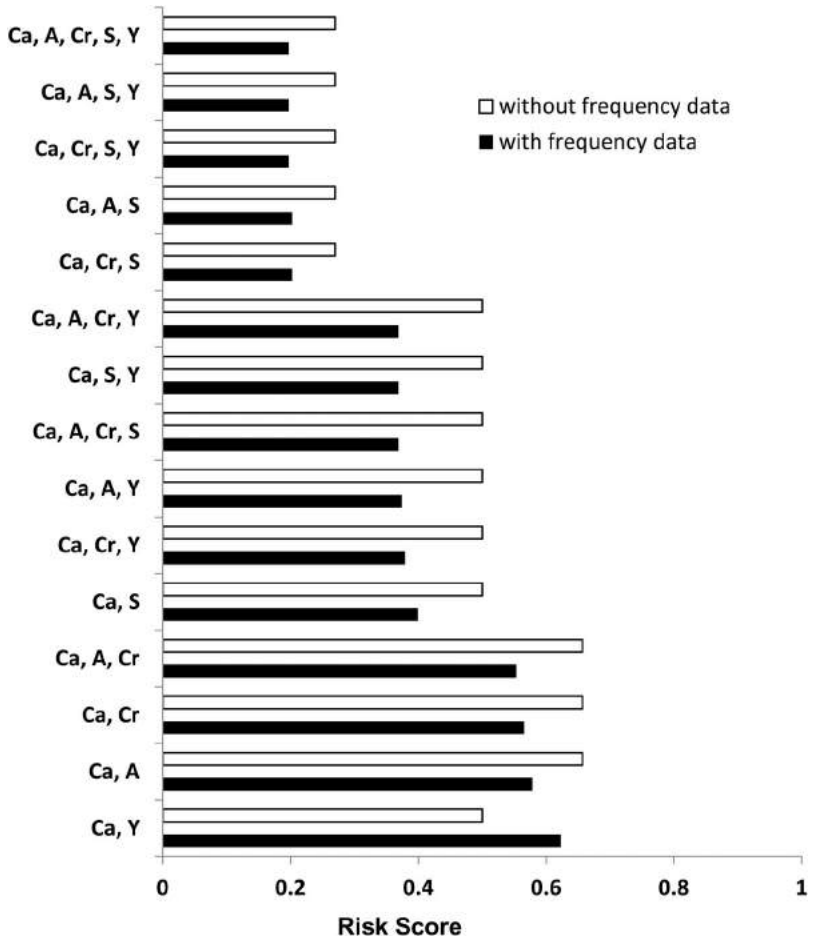

Figure 2. Risk Score for combinations with caffeine (Ca). Risk score generated with/without frequency (measure 2) data.

to the products containing fewer ingredients is more frequent (compared to products containing more ingredients) the probability of exposure to these is greater and could result in a comparatively higher risk score.

A similar trend was observed with other combinations containing two ingredients. In the case of a caffeine + yohimbine combination, one likely explanation for the highest risk score obtained is that the frequency of CV AERs was highest for this combination ($n = 104$) compared to all other combinations. On the other hand, the frequency of CV AERs was zero for the combination containing all 5 ingredients (Ca + A+Cr + S + Y) and the risk score was lowest. To test the effect of frequency of AERs on the relative risk score, the MCDA analysis was performed with the weight of measure 2 (frequency of AERs) set to zero (open bars in Figure 2). The resulting score was lower for the Ca + Y combination but surprisingly higher for other combinations relative to frequency data, although the same overall trend was visible. This observation underscores the influence of AERs in determining the safety of MIDS and suggests the need to further investigate the effect of AERs in this system and find means of improving AER data

acquisition. These findings also emphasize the need to validate the MCDA model for potential false negative results.

A recent study implies that approximately 0.7% of the adverse events related to DS that were encountered by military physicians are ever reported (Pascale et al. 2016), indicating that the available AER data may represent only a miniscule fraction of the true number of AERs that might be are associated with DS consumption. The results of the MCDA run the limitations of comparing estimated risk across combinations with varying amounts of missing data. In this assessment, the strength of evidence for combinations was evaluated as a whole, without taking into consideration the possible associations between the observed CV AEs and the many other ingredients that were present in the MIDSs. These results should be interpreted with caution and an understanding of the limitations of this novel assessment method.

It is important to note that a lower risk score does not attest to the inherent safety of a combination. The results of this analysis can only assist to identify combinations that present signals of concern and should not be interpreted as a commentary on the inherent safety of a MIDS under any or all conditions of use. The safety of a MIDS should be evaluated according to the conventional norms of toxicological and clinical studies.

Taken together, this preliminary MCDA tool integrated the available evidence with input from experts and calculated a semi-quantitative risk score by using predefined criteria for determining the levels of four risk measures for each combination of ingredients. Figure 1 illustrates the essential components of this tool. The outcome presented in the hypothetical run indicates the need for further developments of this model. Specifically, the model needs to be refined and validated to improve the accuracy of predictions. When finalized the model could provide a framework for facilitating decision-making regarding the potential of a MIDS to cause harm when uncertainty exists. It will be the purview of the user to develop risk threshold(s) for action(s).

Research gaps and recommendations for future studies

Apparent risk and MIDS

Risk involving combinations of many ingredients may be underestimated in this model due to the scarcity of AE data, even when the risk assessment tool has built-in corrections. It was noted that adding other compounds to a risky combination is unlikely to reduce the risk. The question is whether they increase risk, which is the product of a consequence and a probability. The addition of an ingredient may, make it more difficult to manufacture and reduce the probability that a combination is consumed, thus reducing the overall risk, without substantially changing the consequence. The use of a measure such as the Likelihood Ratio Test (Huang et al. 2011) may enable some correction of this issue by accounting for the relative numbers of reports containing ingredients and resulting in certain CV effects.

Incomplete and missing data

It is conceivable that we did not receive all the FDA MedWatch AERs for the 26 combinations. Only 11 reports were received in response to our FOI request to the FDA for

Table 8. Run 1 A. Logical decisions output by risk score using weights from mean of Expert Panel assessment.

Weight	1.000	0.335	0.271	0.229	0.166
	FINAL Risk Score Goal	1. Severity of CV Effects Measure	2. Frequency of CV Effects Measure	3. Likelihood of Exposure Measure	4. Biologic plausibility Measure
Ca, Y	0.623	0.500	0.954	0.500	0.500
Ca, A	0.578	0.500	0.367	1.000	0.500
Ca, Cr	0.566	0.500	0.321	1.000	0.500
Ca, A, Cr	0.553	0.500	0.275	1.000	0.500
Ca, S	0.399	0.500	0.128	0.500	0.500
Ca, Cr, Y	0.379	0.500	0.055	0.500	0.500
Ca, A, Y	0.374	0.500	0.037	0.500	0.500
Ca, A, Cr, S	0.369	0.500	0.018	0.500	0.500
Ca, S, Y	0.369	0.500	0.018	0.500	0.500
Ca, A, Cr, Y	0.369	0.500	0.018	0.500	0.500
Ca, Cr, S	0.202	0.000	0.018	0.500	0.500
Ca, A, S	0.202	0.000	0.018	0.500	0.500
Ca, Cr, S, Y	0.197	0.000	0.000	0.500	0.500
Ca, A, S, Y	0.197	0.000	0.000	0.500	0.500
Ca, A, Cr, S, Y	0.197	0.000	0.000	0.500	0.500
A, Cr	0.512	0.500	0.275	1.000	0.250
Cr, Y	0.377	0.500	0.046	0.500	0.500
A, Y	0.374	0.500	0.037	0.500	0.500
S, Y	0.369	0.500	0.018	0.500	0.500
Cr, S	0.369	0.500	0.018	0.500	0.500
A, Cr, Y	0.367	0.500	0.009	0.500	0.500
A, Cr, S	0.328	0.500	0.018	0.500	0.250
A, S	0.202	0.000	0.018	0.500	0.500
Cr, S, Y	0.197	0.000	0.000	0.500	0.500
A, Cr, S, Y	0.197	0.000	0.000	0.500	0.500
A, S, Y	0.197	0.000	0.000	0.500	0.500

AERs related to DS products containing caffeine and in combination with any combinations of the four ingredients of interest. Therefore, any AERs that are related to products lacking caffeine but containing L-arginine, synephrine, yohimbine, and/or creatine would be missing from our MedWatch report. Our analysis demonstrates the potential negative impact of using incomplete AER data; missing AERs likely significantly affected the risk score.

Need for refinement and validation of measures

Developing measures that appropriately reflect the likely level of risk based on the available evidence is an iterative process. One suggested future improvement might entail refining measure definitions to include, for example, assessments by experts with high knowledge of the measures (e.g. physicians or risk assessors to determine the values for measure 1).

Other data sources relevant to the safety of MIDS could be added, as our list may not have included all possible sources. For example, using data on a specific dose of the ingredients of interest and comparing the outcome of the prediction with known outcomes from a review of a data set, such as the ephedra adverse event data which have been analyzed several times including by the second author. In this case the outcome resulted in a regulatory decision to ban ephedra from use as an ingredient in dietary supplements. The ephedra data would provide a good practical test of this MCDA

model Another possibility would be to analyze data on products that have been recalled by FDA due to a cluster of adverse events. Analyses using this model would be expected to result in a score higher risk score.

Need for a risk threshold for action

In this analysis we set the hypothetical threshold score at 0.5 (this threshold is theoretical and soley for demonstration). Consequently, the five combinations with risk scores greater than 0.5 were identified as the most likely to be of concern. Setting a threshold for action would be the function of a decision maker using the model. Thresholds for action could take into consideration conditions of use, which would include the target population(s) characteristics so that, for example, a sensitive population (e.g. pregnant women) might necessitate a lower threshold than other adults in the general population. Automation of the data gathering, mining and integration may facilitate dissemination. For the model to be implemented in a cost-effective manner, it would be best to rely upon publicly available information and databases.

Conclusions

Considering the lack of controlled clinical studies reporting AEs, and the absence of well-documented AERs to establish causal relationship between the exposure to a MIDS and a toxicological adverse outcome, a tool to integrate the available evidence from multiple sources is needed. We initiated the development of a model for semi-quantitative risk assessment of MIDS and combinations of multiple single ingredient supplements by using MCDA. To our knowledge, this is the first risk-assessment model that considers and incorporates information from many areas of science relating to the safety of MIDS. The model we developed uses a MCDA framework to integrate the data, and thus, facilitates decision-making regarding a MIDS' potential to cause harm when uncertainty exists. For the initial model, we tentatively identified five hypothetical combinations out of 26 possible combinations from five ingredients, that should pose the highest risk for CV reactions (caffeine + creatine, caffeine + L-arginine, caffeine + creatine + L-arginine, caffeine + yohimbine, and L-arginine + creatine). The 26 possible combinations are hypothetical and were generated based a hypothetical situation whereby five ingredients—arginine (A); caffeine (Ca); creatine (Cr); synephrine (S); and yohimbine (Y)—are used to formulate a MIDS, assuming equal chances for the incorporation of each of the five ingredients (each only once), not considering amounts of each ingredient (dosage/intake amounts) that may be incorporated into MIDSs. The signal generated by the MCDA tool should be investigated with due consideration to the amount of each ingredient in the DS and the unique environmental occupational and behavioral factors surrounding the military. The analysis shows that the frequency of AERs is an important factor with regard to risk associated with MIDS. Given the limitations of AER data, the impact of their frequency on the final risk rating requires further investigation. Prior to deployment as a screening tool, this model must be further updated, refined, and validated and to fully develop its potential application to assess AEs for multiple system organ classes for assessing risk from human exposure to

MIDS. Importantly, a team of qualified experts must evaluate the relevance and scientific validity of the available evidence before their use in this tool. Information derived from using such a tool may only be applicable for identifying MIDSs that present signals of safety concern, not as a commentary on the inherent safety of a combination under all conditions of use. Specifically, because this model was developed with the military personnel in mind, the data incorporated may result in predictions more applicable to the military personnel than the civilian population because of their unique needs that drive their use of DSs. For example, the "frequency of use data" for DSs containing high caffeine content may be of greater concern for military personnel's readiness unlike the general populace who don't undergo high levels of physical activity during training as military personnel do. Safety of combinations should be established according to the conventional norms of clinical and toxicological studies.

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Declaration statement

The authors have no relevant interests to declare.

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Declarations

The USP Dietary Supplements Safety Modeling Expert Panel (MLH, VASA, MAF, SAJ, MM, DRM, REO and CY, DNS, HAO and GIG) designed and conducted the research and analyzed the data assisted by AP, MC and DD; VASA provided the in silico simulation results from the multi-combination mechanistic modeling of L-arginine and caffeine with the integrative model of nitric oxide; HAO and MC wrote the report; HO drafted the paper. All authors read, edited and approved the final manuscript." PAD contributed to project conception, design, and oversight.

The opinions or assertions contained herein are the private views of the authors and are not be construed as official or as reflecting the views of the Uniformed Services University of the Health Sciences or the Department of Defense.

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References

Al-Lazikani B, Banerji U, Workman P. 2012. Combinatorial drug therapy for cancer in the post-genomic era. Nat Biotechnol. 30(7):679–692. Jul. nbt.2284 [pii]. PubMed PMID: 22781697; eng. doi:10.1038/nbt.2284.

Ayyadurai VA, Dewey CF. 2011. CytoSolve: a scalable computational method for dynamic integration of multiple molecular pathway models. Cel Mol Bioeng. 4(1):28–45. Mar. PubMed

PMID: 21423324; PubMed Central PMCID: PMC3032229. Eng. doi:10.1007/s12195-010-0143-x.

Ayyadurai VA. 2010. Services-based systems architecture for modeling the whole cell: a distributed collaborative engineering systems approach. Future Visions on Biomedicine and Bioinformatics 1. Springer; pp. 115–168.

Bailey RL, Gahche JJ, Lentino CV, Dwyer JT, Engel JS, Thomas PR, Betz JM, Sempos CT, Picciano MF. 2011. Dietary supplement use in the United States, 2003-2006. J Nutr. 141(2): 261–266. Feb. [pii]. PubMed PMID: 21178089; PubMed Central PMCID: PMC3021445. eng. doi:10.3945/jn.110.133025.

CIOMS. Reporting of adverse drug reactions – Definitions of terms and criteria for their use. Council for International Organizations of Medical Sciences (CIOMS). 2014. Available from http://www.cioms.ch/publications/reporting_adverse_drug.pdf. Accessed April 11, 1999.

Coulter ID, Newberry S, Hilton L. Regulation of dietary supplements in the military. Arlington (VA): RAND Corporation; 2011. Available from: http://www.rand.org/content/dam/rand/pubs/conf_proceedings/2011/RAND_CF288.pdf.

Eckart RE, Gentlesk PJ, Shry EA. 2010. Differential manifestation of cardiovascular complaints as a function of utilization of ergogenic supplements. Pacing Clin Electrophysiol. 33(3):286–289. Mar. PACE2610 [pii]. PubMed PMID: 20015135; eng. doi:10.1111/j.1540-8159.2009.02610.x.

FDA. FDA acts to remove ephedra-containing dietary supplements from market. 2004. Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2004/ucm108379.htm.

FDA. Guidance for industry: questions and answers regarding adverse event reporting and recordkeeping for dietary supplements as required by the dietary supplement and nonprescription drug consumer protection Act. 2007. Available from: http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm171383.htm.

Fennell D. 2004. Determinants of supplement usage. Prev Med. 39(5):932–939. Nov. PubMed PMID: 15475026; eng. doi:10.1016/j.ypmed.2004.03.031.

Goel V. 1992. Decision analysis: applications and limitations. The Health Services Research Group. CMAJ. 147(4):413–417. Aug 15. PubMed PMID: 1498753; PubMed Central PMCID: PMC1336239. eng.

Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions. West Sussex, England.: Wiley-Blackwell; 2011.

Huang L, Zalkikar J, Tiwari RC. 2011. A likelihood ratio test based method for signal detection with application to FDA's drug safety data. J Am Stat Assoc. 106(496):1230–1241. doi:10.1198/jasa.2011.ap10243.

Institute of Medicine (IOM). Finding what works in health care: standards for systematic reviews. Washington (DC): National Academy of Sciences; 2011.

Institute of Medicine (IOM). Use of dietary supplements by military personnel. Washington (DC): National Academies Press; 2008. Available from: http://www.nap.edu/catalog/12095.html.

Jacobson IG, Horton JL, Smith B, Wells TS, Boyko EJ, Lieberman HR, Ryan MAK, Smith TC. 2012. Bodybuilding, energy, and weight-loss supplements are associated with deployment and physical activity in U.S. military personnel. Ann Epidemiol. 22(5):318–330. May. S1047-2797(12)00046-4 [pii]. PubMed PMID: 22445519; eng. doi:10.1016/j.annepidem.2012.02.017;.

Jaki T, Wolfsegger MJ. 2012. Non-compartmental estimation of pharmacokinetic parameters for flexible sampling designs. Statist Med. 31(11-12):1059–1073. May 20 PubMed PMID: 21969306; eng. doi:10.1002/sim.4386.

Judson P, 2012. The Application of Structure–Activity Relationships to the Prediction of the Mutagenic Activity of Chemicals. In: Parry J, Parry E, editors. Genetic Toxicology. Methods in Molecular Biology (Methods and Protocols), vol. 817. New York, NY: Springer.

Kelly RA, Balligand JL, Smith TW. 1996. Nitric oxide and cardiac function. Circ Res. 79(3): 363–380. Sep. PubMed PMID: 8781470; eng. doi:10.1161/01.RES.79.3.363.

Koo A, Nordsletten D, Umeton R, Yankama B, Ayyadurai S, García-Cardeña G, Dewey CF. 2013. In silico modeling of shear-stress-induced nitric oxide production in endothelial cells through systems biology. Biophys J. 104(10):2295–2306. doi:10.1016/j.bpj.2013.03.052.

Lieberman HR, Stavinoha TB, McGraw SM, White A, Hadden LS, Marriott BP. 2010. Use of dietary supplements among active-duty US Army soldiers. Am J Clin Nutr. 92(4):985–995. Oct. doi: ajcn.2010.29274 [pii]. PubMed PMID: 20668050; eng. doi:10.3945/ajcn.2010.29274.

Longo N, Ardon O, Vanzo R, et al. 2011. Disorders of creatine transport and metabolism. Am J Med Genet C Genet. 157C(1):72–78. Feb 15 PubMed PMID: 21308988; eng. doi:10.1002/ajmg.c.30292.

Natural Medicines Comprehensive Database. Available from: https://www.therapeuticresearch.com/nd/adverseevent.aspx?s=ND. 2012 [cited September 24, 2012].

Pascale B, Steele C, Attipoe S, O'Connor FG, Deuster PA. 2016. Dietary supplements: knowledge and adverse event reporting among American Medical Society for Sports Medicine physicians. Clinical Journal of Sport Medicine. 26(2):139–144. doi:10.1097/JSM.0000000000000213.

Schmitt GC, Arbo MD, Lorensi AL, Maciel ÉS, Krahn CL, Mariotti KC, Dallegrave E, Leal MB, Limberger RP. 2012. Toxicological effects of a mixture used in weight loss products: p-synephrine associated with ephedrine, salicin, and caffeine. Int J Toxicol. 31(2):184–191. doi:10.1177/1091581811435708.

Stephens MB. Energy drink survey. 2013. Available from: http://ods.od.nih.gov/pubs/energydrinks2013/Stephens.pdf. [cited.

U.S. Food and Drug Administration. Dietary Supplement and Nonprescription Drug Consumer Protection Act (Online). Rockville, MD; 2006.

USP. U. S. P. C. Rules and procedures of the 2015-2020 council of experts provisionally approved 2015-07-20. 2015. Available from: http://www.usp.org/sites/default/files/usp_pdf/EN/aboutUSP/governance/provisionally_approved_2015-2020_coe_rules.pdf. Rockville, Maryland.: USP; [cited 2016 March 15, 2016].

Valerio LG. Jr. 2013. Predictive computational toxicology to support drug safety assessment. Methods Mol Biol. 930:341–354. doi:10.1007/978-1-62703-059-5_15. PubMed PMID: 23086849; eng.

Venhuis B, Keizers P, van Riel A, de Kaste D. 2014. A cocktail of synthetic stimulants found in a dietary supplement associated with serious adverse events. Drug Test Analysis. 6(6):578–581. doi:10.1002/dta.1664.