ROUTING SLIP
GENERATED BY: HF-40
DATE: MAY 30,2003

FDA CONTROL NUMBER: 03 2588 **TRACER #:** **OS #:**

DATE. OF CORRESPONDENCE: 05/27/03 **DATE INTO FDA:** 05/30/03

TO: MARK MCCLELLAN, FDA - COMMISSIONER

FROM: A. WES SIEGNER, JR., HYMAN, PHELPS & MCNAMARA, P.C.

SYNOPSIS: WRITES ON BEHALF OF EPHEDRA EDUCATION COUNCIL (EEC) TO ESPOND TO EXCHANGE OF EMAILS BETWEEN DR. MCCLELLAN AND DR. PAUL SHEKELLE ON APRIL 4 AND APRIL 7. 2003; URGES FDA TO ISSUE FINAL RULE PROVIDING WARNING LABEL FOR EPHEDRA PRODUCTS; REF: TRAC 03-617.

LEAD'OFFICE: HFS-I **HOME OFFICE:** HF-40

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HFG-I
HF-40

SIGNATURE REQUIRED: COMMISSIONER

REFERRALS FROM HF-40

ASSIGNED TO	ACTION	DUE DATE
HFS-1	PREPARE RESPONSE FOR SIGNATURE	06113/03
REMARKS: PLEASE PREPARE RESPONSE: FOR DR. MCCLELLAN'S SIGNATUR DRAFT TO VWOLFHARD, HF-40, FOR SIGNATURE.		FORWARD
HFC-1	NECESSARY ACTION	
REMARKS: PLEASE COORDINATE WITH HF-40.		
HFG-I	NECESSARY ACTION	
REMARKS: PLEASE COORDINATE WITH HF-40		

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May 27, 2003

Mark B. McClellan, M.D., Ph.D.
Commissioner of Food and Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket 95N-0304
Dietary Supplements Containing Ephedrine Alkaloids

Dear Commissioner McClellan:

I am writing on behalf of the Ephedra Education Council (EEC) to respond to an exchange of e-mails between you and Dr. Paul Shekelle on April 4 and April 7, 2003. Attachment A. The EEC has serious concerns about this exchange, and is particularly concerned because Dr. Shekelle's response to your e-mail represents a dramatic departure from the objective, peer-reviewed findings of the RAND Report, "Ephedra and Ephedrine for Weight Loss and Athletic Performance Enhancement: Clinical Efficacy and Side Effects." Dr. Shekelle's response also makes a statement concerning the relationship between ephedra consumption and hemorrhagic stroke that is seriously in error but that has

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the potential for significantly influencing the ongoing Food and Drug Administration (FDA) rulemaking.

Because of the serious concerns that Dr. Shekelle's recent e-mail and other written statements raise, the EEC has submitted these supplemental comments and is requesting that, if FDA intends to rely on Dr. Shekelle's e-mail or any of this other post-RAND Report writings as a basis for making regulatory decisions, FDA arrange a meeting to permit a full discussion of the scientific issues that are raised in these comments. A meeting would be the best mechanism for resolving any remaining doubt that FDA might have concerning the questions raised given that FDA has indicated its intent to make a decision in the very near future regarding the regulation of ephedra products.

I. SUMMARY OF CONCERNS

The EEC has reviewed the April 4, 2003 e-mail from FDA Commissioner Dr. Mark McClellan to the author and director of the RAND Report on ephedra, Dr. Shekelle, and Dr. Shekelle's April 7 reply, and has the following serious concerns:

- Dr. Shekelle's brief and informal e-mail response concludes that there is "much more likely than not" a causal connection between ephedra and serious adverse events, and that the likelihood of causality "certainly exceeds by a substantial margin a '50% confidence' threshold." This statement is not consistent with the peer-reviewed RAND Report, which was careful to repeatedly emphasize that even the classification of an event as a "sentinel event" "does not imply a proven cause and effect relationship," and that a case control study would be necessary to even "assess the possible association."

- Dr. Shekelle's e-mail lists four bases for his new assessment that ephedra use is "much more likely than not" a cause of death and other serious adverse events. The first three bases are brief characterizations of information that was available to and reviewed by RAND, and that was part of the peer-review process. These first three bases were never represented in the RAND Report as supporting a conclusion that ephedra is "much more likely than not" causally connected to serious adverse events, the position that Dr. Shekelle now advocates in his e-mail. The fourth basis cited in Dr. Shekelle's e-mail is a new study published in the journal Neurology[1] that was not considered by

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[1] Morgenstern LB, Viscoli CM, Kernan WN, et al. Use of *Ephedra*-containing products and risk for hemorrhagic stroke. Neurology 2003; 60: 132-135.

RAND, and therefore is apparently the most important if not the only real basis for Dr. Shekelle's personal assessment of causality.

- Dr. Shekelle's analysis of the Neurology paper is simply wrong. According to Dr. Stephen Kimmel[2], Attachment B, there are several reasons why Dr. Shekelle's analysis of the Neurology paper is incorrect – specifically, neither the data nor the authors' conclusions from the Neurology paper supports Dr. Shekelle's conclusion that "this report alone would indicate that there was a relationship between ephedra consumption and the risk of hemorrhagic stroke with 90% confidence."

- Because Dr. Shekelle was an author of the RAND Report and his e-mail refers throughout to "we" rather than "I," his e-mail creates a serious concern that FDA and others will interpret Dr. Shekelle's e-mail as an extension or interpretation of the RAND Report, which was peer-reviewed by over 30 reviewers, when in fact the e-mail is at best very brief and poorly-drafted, and includes an erroneous interpretation of a published paper that has little relevance to ephedra safety other than to confirm what we already know – even though not a single serious adverse event has occurred in any clinical trial to date, further study ought to be conducted to determine whether there is any possible connection between ephedra consumption and increased risk of serious adverse events.

- Finally, Dr. Shekelle and his colleagues have recently published an article titled "Preponderance of the Evidence," the cover article for the Spring 2003 RAND Review, that implicitly calls for FDA to ban ephedra and includes emotional pictures of the grieving relatives of Steve Bechler and Sean Riggins, with misleading captions that make it clear that the authors have determined to use emotion and the press to make their case, regardless of the facts to the contrary. We are submitting new information from an expert cardiac pathologist from The Johns Hopkins University, Dr. Grover Hutchins, on the tragic death of Sean Riggins that shows that this widely publicized case, in the expert opinion of Dr. Hutchins, most likely had nothing to do with ephedra. Regardless, neither the use of emotive pictures and misleading captions in this article, nor the conclusions of the article, can be reconciled with the stated goal of "objectivity" or the conclusions of the RAND Report.

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2 Letter from Stephen E. Kimmel to A. Wes Siegner, Hyman, Phelps & McNamara (May 2, 2003).

II. THE OBJECTIVE FINDINGS OF THE RAND REPORT SUPPPORT CONTINUED MARKETING OF EPHEDRA, WHILE THE SUBJECTIVE CASE REPORTS RAISE "POTENTIAL" SAFETY ISSUES THAT DESERVE FURTHER STUDY

The RAND Report carefully and appropriately separates the conclusions that are based on the analysis of objective, "hypothesis-testing" clinical data, from the conclusions that are based on the analysis of subjective, "hypothesis-generating" information contained in case reports. The former conclusions are a valid basis for regulatory decisionmaking, while the latter are not.

The conclusions of the RAND Report that are based on objective clinical data are as follows:

- short-term use of ephedra leads to short-term weight loss, RAND Report pages vi, xii, 73-77, and 201-02 (this conclusion, and the likelihood of long-term benefits, is bolstered by a more recent 1-year study that RAND did not consider – see Comments of Dr. Greenway[3], previously submitted by the EEC on April 7, 2003, Attachment C – "In conclusion . . . ephedra/caffeine appear to be at least as efficacious for weight loss as the presently available prescription drugs approved for that purpose.");

- the use of ephedra is associated with an increased risk of mild to moderate side effects, RAND Report pages vii, xvi-xvii, 79 and 202; and

- "[n]o serious adverse events (e.g., death, myocardial infarction, stroke, etc.) were reported in the 52 clinical trials that reported sample sizes." RAND Report page 79.

According to the experts in weight loss such as Dr. Greenway who are best situated because of their training to assess the relative risks and benefits of ephedra products, the appropriate conclusion from the "objective" data is that properly formulated ephedra supplements have significant health benefits that far outweigh the relatively minor risks. See Comments of Dr. Greenway.

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3 Frank Greenway, Response to RAND Report on ephedra for weight loss 3 (Mar. 21, 2003).

In contrast to the objective findings based on clinical data, RAND stressed the subjective nature of analyzing case reports and that causality cannot be "assumed or proven" based on such reports.

In its assessment of case reports of adverse events, RAND was careful to stress the subjective nature of such reviews, the significant disagreement between reviewers of the same reports, and the inability to use such reports as "proof" of causality. RAND stated that the "peer review comments demonstrate that case report reviews involve considerably more subjective interpretation than do reviews of randomized trials. **Because our goal in this evidence report is to report the evidence as objectively as possible, we ceased to assign assessments of causality to the case reports.**" RAND Report page 30 (emphasis added). Instead, RAND defined certain events as "sentinel" events, but cautioned that "[c]lassification as a sentinel event does not imply a proven cause and effect relationship." Id. page xvii.

RAND itself had difficulty following its own criteria for the designation of reports of adverse events associated with ephedra as "sentinel events," a problem that provides strong support for RAND's cautions about drawing any conclusions from analyses of such case reports. RAND identified two deaths that occurred in conjunction with ephedra consumption as "sentinel events." RAND Report pages 81-82. However, these events were apparently not reviewed by an expert cardiac pathologist. Dr. Grover Hutchins, a Professor of Pathology at The Johns Hopkins University, is such an expert. He has already submitted comments to FDA revealing that in one of the two deaths described as a "sentinel event," RAND failed to include information that the heart from the decedent was studied by the Armed Forces Institute of Pathology and showed "active myocarditis," a condition "well known to cause sudden death" that is not consistent with ephedra or ephedrine consumption. Comments of Dr. Grover Hutchins[4], Attachment D.

In the second sentinel case, RAND omitted information contained in the report consistent with asthma as the cause of death. Comments of Dr. Grover Hutchins page 1. Therefore, both cases are inconsistent with RAND's own definition for sentinel events, which requires that "[a]lternative explanations where investigated and excluded with

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[4] Grover M. Hutchins, Comment on FDA Docket No. 95N-0304 "Dietary Supplements Containing Ephedrine Alkaloids: Reopening of Comment Period" 1 (Apr. 7, 2003).

reasonable certainty." RAND Report page 30. In Dr. Grover Hutchins' opinion, "[t]hese two cases do not appear to warrant any interpretation beyond the fact that the individuals had been exposed to ephedrine alkaloids, but died from conditions known to cause sudden death." Comments of Dr. Grover Hutchins page 1.

Consistent with the RAND Report's repeated cautions that "a causal relationship between ephedra or ephedrine use and these [reports of adverse] events cannot be assumed or proven," RAND Report page xvi, the Report concludes that "[s]cientific studies (not additional case reports) are necessary **in order to assess the possible association** between consumption of ephedra-containing dietary supplements and these serious adverse events." RAND Report page 203 (emphasis added).

In summary, RAND found that the subjective analysis of the evidence from the case reports created a question, or generated a hypothesis, that a causal connection between ephedra and serious events might exist. RAND was appropriately very careful not to estimate the "probability," or "level of certainty" as asked by Commissioner McClellan, of a causal relationship, because objective data on which such an estimate could be based do not exist. In fact, to quote RAND's summary of its review of the only objective data that relate to the potential association of ephedra with serious adverse events, "[n]o serious adverse events (e.g., death, myocardial infarction, stroke, etc.) were reported in the 52 clinical trials that reported sample sizes." RAND Report page 79. RAND concluded that more scientific studies, not additional case reports, would be needed to confirm the findings of these already-existing studies. RAND Report page 203.

III. DR. SHEKELLE'S E-MAIL AND OTHER POST-RAND WRITINGS ARE NOT CONSISTENT WITH THE RAND REPORT, MISINTERPRET THE NEUROLOGY ARTICLE, AND ABANDON THE GOAL OF OBJECTIVITY IN THEIR USE OF EMOTIONAL PHOTOGRAPHS AND MISLEADING CAPTIONS

The RAND Report is a peer-reviewed and published report. The peer-review process included over 30 reviewers. Dr. Shekelle's e-mail is of course not peer reviewed or published, and is on its face hurriedly and poorly written, as is often typical with e-mail correspondence. For this reason alone, the e-mail does not warrant serious consideration.

More important, Dr. Shekelle has shown through his e-mail and other written statements subsequent to the publication of the RAND Report that he and his colleagues who wrote the Report have abandoned the stated goal of the RAND Report – that goal was

"to report the evidence as objectively as possible," and adherence to that goal led these same scientist to the decision, after peer review, to "cease[] to assign assessments of causality to the case reports." RAND Report page 30.

FDA should be careful to separate the objective findings of RAND from the speculative, erroneous and personal views that Dr. Shekelle has offered to FDA and the public through his April 7 e-mail and other written statements released after the RAND Report. Dr. Shekelle's personal speculation and erroneous assessment of the Neurology paper is not supported by or consistent with the objective scientific data and therefore is not a valid basis for issuing a regulation.

Dr. Shekelle's first departure from the RAND Report's stated goal of objectivity occurred on the same day that the Report was published, February 28, 2003. In a News Release issued by RAND, Dr. Shekelle was quoted as stating that, "[w]ith regard to catastrophic events, [the RAND Report] findings are a strong signal that there is a link between use of ephedra or ephedrine and the occurrence of death, heart attack, stroke, seizures and serious psychiatric symptoms," and that "[i]t is more likely than not that there is a relationship, although the available evidence falls short of the conventional level of scientific proof."[5] Attachment E.

Approximately one month later, Dr. Shekelle through his April 7, 2003 e-mail elevated his assessment of the causal link between ephedra, death and other serious events from "more likely than not" to "much more likely than not." Attachment A. The only apparent reason for this elevation was Dr. Shekelle's review and comment on the Neurology paper, which in his assessment "indicates that there is a relationship between ephedra consumption and the risk of hemorrhagic stroke with 90% confidence." This statement is alarming both for its inaccuracy and its inconsistency with the peer-reviewed findings of the authors.

Dr. Kimmel, a Professor at the University of Pennsylvania, is an expert in cardiology, epidemiology and the statistical interpretation of epidemiological studies like the study addressed in the Neurology paper. Attachment F (Dr. Kimmel's curriculum vitae). According to Dr. Kimmel, Dr. Shekelle's assessment of the data in the Neurology

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5 Press Release, RAND Corp., RAND study raises safety concerns about Ephedra and Ephedrine (Feb. 28, 2003).

paper is incorrect. In Dr. Kimmel's view, "it is reasonable to interpret the paper in Neurology as a 'hypothesis-strengthening' study. However, the level of certainty that Ephedra could cause hemorrhagic stroke should rely on all considerations of the data, and certainly can not be quantified by the use of a p-value or confidence interval" as Dr. Shekelle has done in his e-mail. Letter from Dr. Kimmel to W. Siegner page 2.

The statements of the authors in the peer-reviewed Neurology paper that Dr. Shekelle seeks to interpret in his e-mail also fail to support Dr. Shekelle's finding that a relationship between ephedra and hemorrhagic stroke exists with "90% confidence." The peer-reviewed conclusion as stated in the abstract for this article is that "Ephedra is not associated with increased risk for hemorrhagic stroke, except possibly at higher doses." Morgenstern et al., 132. Consistent with Dr. Kimmel's assessment that these data do not lend themselves to quantifying the relationship between ephedra and stroke as Dr. Shekelle has done, the paper's authors make no attempt to so quantify the relationship between ephedra use and hemorrhagic stroke.

In sum, Dr. Shekelle's e-mail should be ignored for three reasons – (1) the e-mail is simply wrong on the science, (2) the attempt to quantify the level of confidence of any relationship between ephedra and serious events is admittedly speculative, and (3) the e-mail is inconsistent with the objective and even the subjective findings of the RAND Report.

RAND's recent publication of Dr. Shekelle's article "Preponderance of the Evidence" raises serious questions of personal bias against ephedra as well as the law that regulates dietary supplements.[6] Attachment G. In this case Dr. Shekelle and his colleagues have used the emotional impact of pictures of understandably grieving relatives to help make a case for the danger of ephedra without making appropriate inquiry as to the facts. Further, Dr. Shekelle and his colleagues incorrectly interpret the Dietary Supplement Health and Education Act (DSHEA) and vastly oversimplify this law, asserting that under

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6 Paul G. Shekelle et al., Preponderance of Evidence: Judging What To Do About Ephedra (2003).

DSHEA "manufacturers of dietary supplements need not show evidence of the efficacy or safety of the products prior to marketing them."[7]

The article's main message is that, while Dr. Shekelle and his colleagues could not prove that ephedra causes death and other serious adverse events, there is no question in these individuals minds that ephedra has and does cause such events, despite the RAND Report's emphasis on objectivity and the inability to draw conclusions of causality from the case reports. According to Dr. Shekelle, "we compiled enough evidence to reach fairly confident conclusions. Our efforts could serve as an example of how policymakers and researchers can help to keep the public safe despite the absence of incontrovertible scientific proof of danger." Shekelle et al., supra note 6, at 1.

To drive home the authors' real message behind the this statement, that ephedra should in their view be banned, the text quoted above is followed by emotion-laden pictures of Pat Bechler, the mother the recently deceased Baltimore Orioles pitcher, crying at a press conference, and of Kevin Riggins, described in the RAND article as "the father of Sean Riggins, a 16-year-old high school football player who died last fall after taking ephedra." The caption for this last picture also points out that Mr. Riggins is pictured speaking at the Illinois State Capitol building, and that "[o]n March 20, the Illinois state senate voted unanimously to ban the sale of ephedra products." Id. at 2.

The view of Dr. Shekelle and his colleagues is clear – ephedra is responsible for the deaths of Steve Bechler and Sean Riggins, regardless of the facts, and ephedra should be banned because of their subjective belief in a causal link, regardless of the objective findings of the RAND Report. But the facts, had Dr. Shekelle cared to evaluate them, point in a different direction. Dr. Shekelle does not mention any independent evaluation of the facts relating to the Riggins or Bechler cases, and it is clear that he did not conduct any such review. Had he contacted the EEC or other sources of information on ephedra, he would have learned significant facts that might have caused him to rethink his article, which plays to the emotional side of the ephedra debate rather than to objective science.

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[7] For a more thorough treatment of how DSHEA regulates dietary supplements and supplies the needed authority for FDA to assure the safety and benefits of these products, see Stephen H. McNamara & A. Wes Siegner, FDA has Substantial and Sufficient Authority to Regulate Dietary Supplements. 57 Food & Drug L.J. 15 (2002).

First, he would have learned that the only cardiac pathologist to review the Riggins case has determined, based on a review of the available information, including tissue slides, that "to a reasonable degree of medical certainty" Sean Riggins died as a result of a "severe inflammatory and necrotizing process in his heart that was ongoing over several days prior to his death," not from consuming ephedra.[8] Attachment H. The EEC wholeheartedly agrees with FDA's opinion that the product that Sean Riggins apparently consumed, Yellow Jackets, is not appropriate as a dietary supplement and that no ephedra products should be sold to minors. Nonetheless, Dr. Shekelle's attempt to use this death as support for his new position that ephedra should be banned is in direct conflict with the stated goals of the entire RAND review of ephedra.

Dr. Shekelle's use of the picture of an understandably grief-stricken Mrs. Bechler crying over the sudden and tragic death of her son is even more inappropriate. Although the coroner in the Bechler case was swayed to believe ephedra was implicated in Mr. Bechler's death, more knowledgeable experts have disagreed, and in this case the reasons for their disagreement were readily available on the internet.[9] Dr. Richard Krieder and his colleagues from Baylor University's Center for Exercise, Nutrition, & Preventive Health Research have publicly disagreed with the local coroner and provided detailed reasons for their conclusion that "[t]he supposed link that ephedra supplementation caused or contributed to heat stroke does not make sense from a physiological standpoint." Attachment I.

While the recent writings of Dr. Shekelle and his colleagues are hard to explain, there is no doubt that Dr. Shekelle and his colleagues are no longer engaged in objective scientific discourse. They have mischaracterized and misused case reports for emotional impact, they have assigned various levels of probability to the relationship between ephedra and serious adverse events in conflict with the stated goals of the RAND Report, and they have erroneously interpreted published data.

Their recent writings are based in part on admittedly subjective case reports and in part on incorrect analysis, and do not provide a scientific basis for rulemaking for ephedra

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8 Letter from Grover M. Hutchins to A. Wes Siegner, Hyman, Phelps & McNamara 2 (Jan. 11, 2003).

9 See http://www3.baylor.edu/HHPR/ESNL/EphedraStatement.htm.

dietary supplements. In contrast, the objective findings of the RAND Report do provide scientific support for the regulation and further scientific review of ephedra, including FDA's recent letters to companies marketing ephedra for performance enhancement, national warning labels, and further clinical study to assess the "possibility" of an association between ephedra and serious adverse events.

IV. CONCLUSION

Researchers and experts in weight loss agree that the findings of the RAND Report are consistent with what they have already determined through clinical research – that properly formulated ephedra products are safe when responsibly marketed and consumed and are one of the few very important options for those millions of Americans who need to lose weight. Banning ephedra based on what amounts to rumor and innuendo would be a serious public health mistake, even if these rumors are furthered by RAND scientists.

The recent e-mail and other written communications of Dr. Shekelle and his colleagues should be disregarded because they are a dramatic departure from RAND's stated goal of objectivity in the ephedra review. The conclusions of the e-mail should also be rejected because they present an incorrect scientific analysis of the Neurology paper.

The EEC is grateful for the opportunity to participate in this rulemaking and urges FDA to issue a final rule providing a national warning label for ephedra products and addressing the other action items identified by RAND in the very near future.

Sincerely,

A. Wes Siegner, Jr.

AWSjr/rh

From: Mayl, Sharon L
Sent: Tuesday, April 08, 2003 3:25 PM
To: Butler, Jennie C
Subject: FW: questions on Rand EPC report on ephedra

Please submit for the record.

-----Original Message-----
From: Hubbard, William K
Sent: Monday, April 07, 2003 4:54 PM
To: Mayl, Sharon L
Subject: FW: questions on Rand EPC report on ephedra

-----Original Message-----
From: Shekelle, Paul [mailto:shekelle@rand.org]
Sent: Monday, April 07, 2003 11:15 AM
To: 'McClellan, Mark, M.D.'; 'shekelle@rand.org'; Brook, Robert; Thomson, James; 'michael_rich@rand.org'
Cc: Troy, Daniel; Hubbard, William K; Crawford, Lester, D.V.M.; Wiley, Ladd (OS)
Subject: RE: questions on Rand EPC report on ephedra

Thank you Dr. McClellan for these questions. With regard to your first question, as you note in our Evidence Report we judged the available scientific evidence does not support a causal relationship between ephedra consumption and serious adverse events at the conventional 95% confidence interval threshold used in scientific studies of treatment efficacy. However, we judge that it is much more likely than not that such a relationship exists, i.e. we are much more than 50% confident that it exists. We base this conclusion on the following four lines of evidence:

1) the known pharmacologic actions of ephedrine. Namely, it is known that ephedrine effects receptors in the cardiovascular system and the brain.
2) the convincing evidence that compounds chemically related to ephedrine, namely amphetamines and phenylpropanolamine, are causally associated with the very same serious adverse events (death, myocardial infarction, stroke, psychosis).
3) the sentinel events that we documented in our Evidence Report, that describe numerous serious adverse events for which no apparent medical cause could be found for the event and for which it is known that ephedra consumption occurred prior to the event happening.
4) the recent publication of a case control study assessing the relationship between ephedra consumption and the risk of hemorrhagic stroke (Neurology, 2003;60:132-135). this article, which appeared too late to be incorporated into our Evidence Report, reported an adjusted odds ratio of 3.59 for the risk of hemorrhagic stroke and ephedra consumption. we calculated, and confirmed with the senior author of this paper Dr. Kernan, that the p value on this result was 0.07. while this does not reach the conventional "p less than 0.05" value accepted as conclusive evidence that a relationship exists, this report alone would indicate that there is a relationship between ephedra consumption and the risk of hemorrhagic stroke with 90% confidence.

factoring all these lines of evidence together, we conclude that, while the evidence does not meet the "95% confidence" threshold commonly used, it certainly exceeds by a substantial margin a "50% confidence" threshold, making it in our view much more likely than not that there is a causal relationship between ephedra consumption and serious adverse events.

with regard to your second question. while it is biologically plausible, we did not find sufficient evidence to reach firm conclusions regarding an increase in the risk of adverse events related to strenuous exercise or the consumption of other stimulants. this should not be construed as meaning that the risk is not increased in such circumstances, it means simply the evidence is insufficient to support or refute such a contention. with regard to dose, we would characterize the evidence as stronger for higher dosage levels. we found strong but not conclusive evidence that the risk of the less serious side effects such as nausea. vomiting, tremulousness, etc., are greatly increased with increasing doses. due to limitations of the available data, we could not attempt a dose analysis for the risk of serious adverse events, but a similar increase in risk of serious adverse events with higher doses would be expected.

please do not hesitate to contact me if there are any additional questions.

-----Original Message-----
From: McClellan, Mark, M.D. [mailto:MMcClellan@oc.fda.gov]
Sent: Friday, April 04, 2003 5:36 PM
To: 'shekelle@rand.org'
Cc: Troy, Daniel; Hubbard, William K; Crawford, Lester, D.V.M.; Wiley, Ladd (OS)
Subject: questions on Rand EPC report on ephedra

Dr Paul Shekelle
Rand Corp.

Dear Paul:

Thanks again for your recent comprehensive EPC report on what is known about the effectiveness and safety of ephedra. I have two further questions on which I would appreciate your views:

1) The Rand report concluded that the evidence on a causal relationship between ephedra use and serious adverse events (e.g., heart attack, stroke, death) was not sufficient to meet the standard of "95% certainty" that is often used to "prove" a relationship in scientific studies of treatment effects. Do you think the available evidence supports a causal relationship at a somewhat less certain level of scientific proof (e.g., 51%, 60%, etc.), and why?
2) Do you think the evidence of a causal relationship between ephedra use and adverse outcomes is more certain for the special circumstances suggested in FDA's proposed warning label, i.e., when ephedra is used with strenuous exercise, stimulants including caffeine, and certain preexisting health conditions? Do you think the evidence is stronger for higher dosage levels?

Thank you very much for your attention to these questions.

Best regards,

Mark McClellan

UNIVERSITY OF
PENNSYLVANIA
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Center for Clinical Epidemiology
and Biostatistics

University of Pennsylvania School of Medicine
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May 2, 2003

A. Wes Siegner, Jr., Esquire
Hyman, Phelps & McNamara, P.C.
700 Thirteenth Street N.W.
Suite 1200
Washington, DC 20005

Dear Mr. Siegner:

You have asked me to comment on Dr. Shekelle's statements related to some of the statistics in the paper *"Use of Ephedra-Containing Products and Risk for Hemorrhagic Stroke"* published in the journal *Neurology*. Specifically, Dr. Shekelle states, in an email to Dr. McClellan:

> "We calculated and confirmed with the senior author of the paper, Dr. Kernan, that the p-value on this result was 0.07. While this does not reach the conventional "$p<0.05$" value accepted as conclusive evidence that a relationship exists, this report alone would indicate that there was a relationship between Ephedra consumption and the risk of hemorrhagic stroke with 90% confidence."

I believe that there are two important issues in interpreting this study: statistical and epidemiological.

In terms of statistical, there are three important points. (1) Dr. Shekelle mentions that he calculated a p-value of 0.07. Because this study was a matched case-control study, I am not sure how he was able to calculate an accurate p-value without having the actual data. He states that he confirmed this with Dr. Kernan, but it is unclear whether the appropriate test of significance was done. In addition, because of the small numbers in the study, exact analyses would need to be performed. (2) Even if the calculation of the p-value is correct, the play of chance must be considered in any study in which the overall finding is negative (the overall odds ratio in this study was 1.00) and in which the "positive" finding is only seen in a subgroup. Although it is certainly possible that only higher doses of Ephedra are associated with an increased risk for hemorrhagic stroke, it is also possible that the odds ratio of 3.59 arose by chance. Similarly, the odds ratio of 0.13 for the $\leq$32 milligrams/day users should not be interpreted as a reduction in risk from Ephedra at lower doses. That is, the very low odds ratio for this group is likely just a chance finding. (3) Dr. Shekelle states that the p-value "would indicate that there is a

relationship between Ephedra consumption and the risk of hemorrhagic stroke with 90% confidence." I assume that this is based on the fact that he got a p-value of 0.07. However, the term "confidence" in the term "confidence interval" in no way states anything about the level of confidence that you can have in a specific point estimate, such as an odds ratio. As stated in Rothman and Greenland (Rothman and Greenland, Modern Epidemiology, page 189): "For example, if the confidence level of a valid confidence interval is 90%, the frequency with which the interval will contain a true parameter will be at least 90%; consequently, under the assumed model for random variability...and with no bias, we should expect the confidence interval to include the true parameter value in at least 90% of replications of the process of obtaining the data." That is, if a study were done many times, over and over again, 90% of the 90% confidence intervals would contain the true value. Thus, although commonly used in "laymen's terms" as reflecting the level of confidence that one has in the data, the confidence interval has really nothing to do with the confidence level that one should have in the results. Rothman and Greenland go on to state "it is preferable to view the confidence limits only as a rough guide, a minimum estimate, of the inherent uncertainty in an epidemiologic result...." Thus, the p-value of 0.07 does not mean that a reader can be at least 90% confident that an association exists based on the results of the study. The important point here is that the p-value should not be viewed as a measure of confidence in the data because of both other statistical issues (discussed above) and epidemiological issues (discussed below).

The second issue relates to epidemiological issues. Rothman and Greenland also state that the confidence interval is valid only *"If* the underlying statistical model is correct and there is no bias...." Because the hemorrhagic stroke project was not designed specifically to examine Ephedra-based products, issues related to recall bias, selection bias, uncontrolled confounding, and missing data could create invalid results.

Therefore, both statistical considerations, including the play of chance, and epidemiological considerations must go into the interpretation of the results of the paper in *Neurology*. I do not believe that the results of this study provide "90% confidence" that a relationship exists between ephedra consumption and the risk of hemorrhagic stroke. Because of the other pieces of evidence cited by Dr. Shekelle in his recent email, I believe that it is reasonable to interpret the paper in *Neurology* as a "hypothesis-strengthening" study. However, the level of certainty that Ephedra could cause hemorrhagic stroke should rely on all considerations of the data, and certainly can not be quantified by the use of a p-value or confidence interval.

Please contact me if you have any further questions.

Sincerely,

Stephen E. Kimmel, MD, MS

SEK/sab

COMMENTS ON PROPOSED RULE FOR DIETARY SUPPLEMENTS CONTAINING EPHEDRINE ALKALOIDS; FOOD AND DRUG ADMINISTRATION; HHS
[Docket No. 95N-0304]

Date: March 21, 2003

Response to Rand Report on ephedra for weight loss

I have enclosed a peer-reviewed article that I wrote and which was published in Obesity Reviews at the end of 2001 (1). It reviews the evidence for the efficacy of caffeine and ephedrine/ephedra for weight loss. Although my views about the efficacy of ephedra for weight loss remain essentially unchanged, there is now additional evidence to support my views. Since the Rand report stated under "Future Research" on page xvii "To improve health outcomes and reduce the risk of morbidities associated with being overweight, sufficient weight loss (5-10 percent of body weight) and long-term maintenance are necessary. Therefore, the benefit of ephedrine or herbal ephedra-containing dietary supplements for health outcomes is unknown.", I wanted to put their statement into the context of the approved obesity drugs.

The criterion for approving prescription obesity drugs is a one-year placebo controlled weight loss trial resulting in a 5% or greater weight loss than placebo. All of the presently approved prescription weight loss medications give weight loss for 6 months and weight loss is maintained by continued treatment during the rest of the one-year treatment. Sibutramine gave a weight loss that was 4.9% and 6.2% greater than placebo at 6 months with the 10 mg/day and 15 mg/day doses respectively, the two doses approved for prescription use (2). This corresponded with weight losses in the 10 mg/day and 15 mg/day doses of sibutramine of 6.1% and 7.4% respectively. Orlistat gave weight loss that was 2.9% (US trial) and 4.1% (European trial) greater than placebo at the 120 mg three times a day dose that is approved for prescription use (3, 4). This corresponded with weight loss of 10.2% and 8.7% in the orlistat groups of the US and European trials respectively. Despite the fact that only one dose out of the three approved met the suggested criteria, these drugs were approved on the basis that their efficacy outweighed their risks.

The six-month Danish registration trial of ephedrine/caffeine 20 mg/200 mg given three times a day gave a 3.9% greater weight loss than placebo, and the six-month trial of ephedra/caffeine 30 mg/64 mg given three times a day gave a 4.5% greater weight loss than placebo (5, 6). These differences corresponded

to weight losses of 17.5% and 8% in the ephedrine/caffeine and ephedra/caffeine groups respectively.

A year-long weight maintenance study was reported at the International Obesity Congress in Sao Paolo, Brazil in 2002 (7). Subjects were approximately 100 kg at the beginning of the study. A 6%-7% weight loss was induced with diet and the subjects were randomized to ephedrine/caffeine 10 mg/100 mg twice a day or a placebo for 1-year. At the end of the year the ephedrine/caffeine group lost 4.9% more weight than placebo that corresponded to a 7.3% weight loss in the ephedrine/caffeine group.

Therefore, in controlled trials of 6-months to 1-year ephedrine/caffeine and ephedra/caffeine gave weight losses that ranged from 7.3% to 17.5% that were greater than the placebo group by 3.9% to 4.9%. These results are comparable with the results of the weight loss drugs approved for use by prescription. In addition, the weight loss created by ephedrine/caffeine is selectively fat in contrast to prescription obesity drugs that cause more loss of lean tissue (8, 9, 10). Allison has correlated loss of lean tissue with increases in mortality and loss of fat with decreased mortality (11).

Sibutramine and ephedrine/caffeine are both capable of raising blood pressure, but blood pressure returns to baseline after 8 weeks of treatment with ephedrine/caffeine while it remains elevated with sibutramine (5, 2). Sibutramine and ephedra/caffeine both decrease LDL cholesterol and increase HDL cholesterol (2, 12). Thus, one could make the argument that ephedrine/caffeine and ephedra/caffeine are more efficacious and have greater safety than sibutramine.

Ephedra is composed of four isomers of which ephedrine is the most potent. Therefore, as was concluded in the Rand Report, the efficacy of ephedrine and ephedra containing products are directly comparable. Although the risk to benefit of ephedrine/caffeine and ephedra/caffeine for the treatment of obesity appears to be favorable compared to the obesity drugs approved for prescription use, this cannot necessarily be said for the other ingredients often included in ephedra/caffeine containing weight loss products. Some of the ingredients like bee pollen appear to be inactive, but their presence represents a potential source for developing an allergy, if not a drug interaction. Other ingredients like catechins, forskolin, phenylephrine and tyrosine have the potential for synergistic effects on the adrenergic system. Although they may be safe, it is my opinion that these ingredients should not be inlcuded unless there are clinical data to support their safety in the particular formulations in which they are found.

In conclusion, ephedrine/caffeine and ephedra/caffeine appear to be at least as efficacious for weight loss as the presently available prescription drugs approved

for that purpose. The obesity drugs available by prescription were approved based on a risk benefit assessment. Therefore, to the extent that approved obesity prescription medications are effective for weight loss and the treatment of obesity, ephedrine or ephedra with caffeine are as well. Thus, the statement quoted from the Rand Report in the first paragraph should not be interpreted as a lack of efficacy for ephedra or ephedrine with caffeine to help consumers lose weight.

Frank Greenway, M.D.
Medical Director and Professor

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April 7, 2003

Comment on FDA Docket No. 95N-0304 "Dietary Supplements Containing Ephedrine Alkaloids: Reopening of the Comment Period"

As an anatomic pathologist with a longstanding professional focus on autopsy pathology I have been particularly interested in the issue of the likelihood of any possible role of ephedrine alkaloids in causing death. To this end I have reviewed Adverse Event Reports (AERs) developed by the U.S. Food and Drug Administration (FDA) where death had occurred, the relevant medical literature on this subject, and the recent RAND Report by Shekelle et al. entitled Ephedra and Ephedrine for Weight Loss and Athletic Performance Enhancement: Clinical Efficacy and Side Effects. Obviously, death could potentially represent the most severe complication of ephedrine alkaloid exposure. Thus, it would seem important to assess the likelihood of any causative or contributing role of ephedrine alkaloids to death. The alternative being simply an association of ephedrine alkaloid exposure with a condition which would provide an explanation for the death to a reasonable degree of medical certainty.

Review of the deaths listed as Sentinel Events in the Rand Report shows that two of the four are AERs from the FDA. The first, AER 13914, was of a 21-year-old male who died suddenly during an agility run. The RAND Report does not include the information that the heart from this individual's autopsy was studied as a consultation for the medical examiner by the Armed Forces Institute of Pathology (AFIP). Examination of the slides prepared by the AFIP showed an active myocarditis with necrosis of myocytes. Such myocarditis is a well known cause of sudden death. The second sentinel death (AER 14390) was a 22-year-old female who weighed 183 pounds and was known to have asthma. The RAND Report description omits the information, contained in the AER, that after her collapse bystanders rolled her over and found her to be gasping for air. Given the information provided, it seems more probable than not that her death was due to asthma, a well known cause of sudden death, than "cardiac arrhythmia due to ephedra containing compound", as opined by the medical examiner. These two cases do not appear to warrant any interpretation beyond the fact that the individuals had been exposed to ephedrine alkaloids, but died from conditions known to cause sudden death.

On August 8, 2000, I presented my review of 22 AERs where death had occurred at the Department of Health and Human Services's Public Meeting on the Safety of Dietary Supplements Containing Ephedrine Alkaloids (1). My interpretation of the available information on these cases was that there was no consistent clinical or pathologic features of the cases and that it was not likely that ephedrine alkaloids were causative or contributing factors in the deaths. Subsequent publications have described some of these same deaths and interpreted AER information as demonstrating a role for ephedra in causing death. These papers had omitted important information that provides alternate explanations for the death that did not require invoking a role for ephedrine alkaloids.

Comment on FDA Docket No. 95N-0304 "Dietary Supplements Containing Ephedrine Alkaloids: Reopening of the Comment Period"

A paper by Haller and Benowitz (2) included eight of the 22 cases I had reviewed. In a letter to the editor (3), I pointed out that information pointing to alternate explanations of the death of these individuals were present in seven of the eight cases. In response to my letter (4), they speculated that exposure to ephedrine alkaloids could precipitate death from the underlying condition in the individual. Given the incomplete information in many AERs and the marked variation in clinical and anatomic features and the uncertainty of ephedrine alkaloid exposure in temporal relationship to the death in many cases this contention is difficult or impossible to prove or refute. Samenuk et al. (5), included six cases identifiable by AER in their table of seven deaths. Review of these AERs again showed that the information provided in the paper did not include important data from the AERs that pointed to alternate explanations for the death, not requiring implication of ehedrine alkaloids in the death. My comments on the specific cases were published in a letter to the editor (6), to which the authors of the original paper declined to respond.

In summary, the available information on deaths associated with ephedrine alkaloid exposure does not support the suggestion that the deaths are caused or contributed to by these agents when used in the recommended manner. I do agree with the suggestion of Haller and Benowitz (4) that the issue requires investigation through a large scale case-control study. Such an investigation would be preferable to making decisions based on anecdotal reports, frequently lacking crucial data, which is all that is currently available.

Thank you for your consideration of these comments.

Sincerely yours,

Grover M. Hutchins, M.D.

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RAND STUDY RAISES SAFETY CONCERNS ABOUT EPHEDRA AND EPHEDRINE

An exhaustive review by RAND researchers of health studies involving products containing the herb ephedra or the drug ephedrine raises concern about the safety of the products, which are used by millions of American seeking to promote weight loss or enhance athletic performance.

The available evidence is sufficient to conclude that these products are related to a two- or three-fold increase in side effects such as nausea, vomiting, jitteriness, and palpitations, according to a new RAND Health study released today. Furthermore, the evidence suggests a link between these products and catastrophic events such as sudden death, heart attack or stroke.

"With regard to catastrophic events, these findings are a strong signal that there is a link between use of ephedra or ephedrine and the occurrence of death, heart attack, stroke, seizures, and serious psychiatric symptoms," said Paul Shekelle, the RAND and Veterans Affairs physician who headed the study. "It is more likely than not that there is a relationship, although the available evidence falls short of the conventional level of scientific proof."

The RAND study concludes that more analyses of existing data are unlikely to settle the issue and that new data are needed.

"One of the most expeditious ways to test whether there is a relationship is to conduct a 'case-control' study, where ephedra use by people who suffered death or other serious illness is compared to use by similar individuals who have not

suffered the problem," said Sally Morton, holder of the RAND Endowed Chair in Statistics and a co-author of the study.

Such a case control study was recently used to establish a link between the use of phenylpropanolamine, a drug related to ephedrine and also used for weight loss, and an increased risk of hemorrhagic stroke in women.

The RAND study was requested and funded by the U.S. Department of Health and Human Services in 2001 to examine issues related to the safety and effectiveness of products containing ephedra and synthetic ephedrine (a stimulant found in ephedra). Ephedra is an herbal supplement promoted for weight loss and athletic performance, while ephedrine is found in over-the-counter drugs used to treat stuffy nose and asthma.

The RAND study also found some evidence of benefits of ephedra and ephedrine for weight loss. Dietary supplements containing ephedra, the drug ephedrine, and ephedrine plus caffeine promoted modest short-term weight loss, averaging about two pounds per month more than among people taking a placebo. However, none of the studies reviewed followed participants for longer than six months, less than the 12 months accepted as necessary to establish a drug's value as a weight-loss aid.

Although many of the ephedra supplements and ephedrine products are taken for boosting athletic performance, researchers found no evidence that ephedra—and scant evidence that ephedrine—enhances physical performance. They found no evidence that any of the products improve long-term physical performance among athletes or the general public.

The report on ephedra and ephedrine was released today by federal officials.

The study was done by the RAND-based Southern California Evidence-Based Practice Center, which also includes researchers from the Greater Los Angeles Veterans Administration Healthcare System and Cedars-Sinai Medical Center.

RAND researchers based their findings on a detailed review of 52 clinical trials of ephedrine or herbal ephedra for weight loss or athletic performance in humans. They searched the medical literature and other sources for both published and unpublished medical trials of the substances.

Researchers also analyzed more than 1,500 "adverse event reports" related to herbal ephedra and 125 such reports related to synthetic ephedrine-containing products, which were collected by the U.S. Food and Drug Administration. Researchers discovered 70 additional adverse events in the medical literature and received a computer file of more than 18,000 adverse events from Metabolife, a maker of ephedra products.

RAND Health is the nation's largest independent health policy research organization, with a broad research portfolio that focuses on medical quality, health care costs and delivery of health care, among other topics.

The Southern California Evidence-Based Practice Center is one of 13 evidence-based practice programs nationally sponsored by the federal Agency for Healthcare Research and Quality. The center conducts systematic reviews and technology assessments of all aspects of health care.

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RAND is a nonprofit institution that helps improve policy and decisionmaking through research and analysis.

View this RAND study (from JAMA or FDA) or the research brief.

UNIVERSITY OF PENNSYLVANIA-SCHOOL OF MEDICINE
Curriculum Vitae

Date: March, 2003

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Education:

1980-1984	A.B.	Princeton University (Magna Cum Laude)
1984-1988	M.D.	New York University School of Medicine
1992-1995	M.S.C.E.	University of Pennsylvania (Master of Science in Clinical Epidemiology)

Postgraduate Training and Fellowship Appointments:

1988-89	Intern, Internal Medicine, Brigham and Women's Hospital, Boston, MA
1989-91	Resident, Internal Medicine, Brigham and Women's Hospital, Boston, MA
1991-94	Fellow, Cardiology, Hospital of the University of Pennsylvania, Philadelphia, PA
1992-94	Fellow, Pharmacoepidemiology, University of Pennsylvania School of Medicine, Philadelphia, PA

Military Service: None

Faculty Appointments:

1994-	Assistant Professor of Medicine, Cardiovascular Division, Department of Medicine, University of Pennsylvania School of Medicine
1994-	Assistant Professor of Medicine, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine
1995-	Assistant Professor of Epidemiology, Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine
2003-	Associate Professor of Medicine, Cardiovascular Division, Department of Medicine, University of Pennsylvania School of Medicine (effective 7/1/03)
2003-	Associate Professor of Medicine, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine (effective 7/1/03)

2003- Associate Professor of Epidemiology, Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine (effective 7/1/03)

Hospital and Administrative Appointments:

1994- Attending Physician, Hospital of the University of Pennsylvania
1994- Attending Physician, Philadelphia Veterans Affair Hospital
1994- Director, Cardiovascular Epidemiology, Cardiovascular Division, Department of Medicine, University of Pennsylvania School of Medicine
1994- Senior Scholar, Center for Clinical Epidemiology and Biostatistics

1997- Director, Epidemiology Track, Master of Science in Clinical Epidemiology Program, University of Pennsylvania School of Medicine
2002- Co-Director, Master of Science in Clinical Epidemiology Program

Specialty Certification:

1991 Board Certified in Internal Medicine (recertified in 2001)
1996 Board Certified in Cardiology (recertified in 2001)
2001 American College of Epidemiology

Licensure: Commonwealth of Pennsylvania

Awards, Honors, and Membership in Honorary Societies:

1984 Phi Beta Kappa
1984 Sigma Xi Research Society
1984 Sigma Xi Award for Outstanding Research in Chemistry
1988 Alpha Omega Alpha
1993 American College of Cardiology/Merck Adult Cardiology Fellowship Award
1996 Award for Best Poster, International Conference on Pharmacoepidemiology
2001 Excellence in Teaching in Epidemiology Award, Master of Science in Clinical Epidemiology Program
2001 Leonard Berwick Memorial Teaching Award, University of Pennsylvania School of Medicine

Membership in Professional and Scientific Societies:

National Societies:

Member, Sigma Xi Research Society
Member, International Society of Pharmacoepidemiology
Member, American Heart Association Council on Epidemiology and Prevention
Fellow, American College of Cardiology
Elected Consultant, Society for Cardiac Angiography and Interventions
Member, Society for Epidemiologic Research (SER)
Member, American Society for Clinical Pharmacology and Therapeutics (ASCPT)
Member, American College of Epidemiology
Fellow, American Heart Association and American Heart Association Council on Epidemiology and Prevention

National Scientific Committees:

1998 Chair, Session at American College of Cardiology Annual Meeting
1999 Chair, Session at American College of Cardiology Annual Meeting
2000- Member, Program Committee, National American Heart Association Council on Epidemiology
2001- Appointed Member: Quality of Care and Outcomes Research Network of Experts, American Health Association
2001- Advisory Group, "One of a Kind", American Heart Association Quality of Care and Outcomes Research Expert Panel
2001 National Peer Review Committee, American Heart Association Outcomes Research
2002- Member, Advocacy Committee, Epidemiology and Prevention Council of the American Heart Association
2002 Chair, Session, The Genomics Revolution: Bench to Bedside to Community and the 42nd Annual Conference on Cardiovascular Disease Epidemiology and Prevention
2002- National Institutes of Health, National Heart, Lung, and Blood Study Section, ad hoc member reviewing all K-grants
2002- Member, American College of Cardiology, National Cardiovascular Data Registry, Scientific and Clinical Support Task Force

International Scientific Committees:

1998 ISPE Educational Committee
2000-2001 ISPE Board of Directors

Local Scientific Committees:

2000 Member, Health Measurement Task Force, Pennsylvania Delaware American Heart Association.

Editorial Positions:

1994- Editorial Consultant, Journal of General Internal Medicine
1995- Editorial Consultant, Annals of Internal Medicine
1996- Editorial Consultant, The Journal of the American Medical Association
1997- Editorial Consultant, Journal of the American College of Cardiology
1997- Editorial Consultant, American Heart Journal
1997- Editorial Consultant, New England Journal of Medicine
2002- Editorial Consultant, American Journal of Cardiology
2002- Editorial Consultant, Circulation
2002- Editorial Consultant, American Journal of Cardiovascular Drugs
2002- Editorial Consultant, Archives of General Psychiatry

1999- Associate Editor, Pharmacoepidemiology and Drug Safety

Academic Committees at the University of Pennsylvania and Affiliated Hospitals:

1997- Member, Master of Science in Clinical Epidemiology Admission Committee
1997- Member, CCEB Graduate Teaching Curriculum Committee

1998-	Member, PhD in Epidemiology Admission Committee
1998-	Member, BGS Curriculum/Academic Standards Committee
1998-2002	Chair, CCEB Awards Committee
1999-	Chair, CCEB Institutional Review Board Committee
2002-	Chair, Master of Science in Clinical Epidemiology Curriculum Committee

Major Teaching and Clinical Responsibilities at the University of Pennsylvania and Affiliated Hospitals:

1. Medicine 100 for Medical Students, Fall Semester
2. Medicine 101A for Medical Students, Spring Semester
3. Preceptor for EP 154, Medical Student Epidemiology Course, Spring/Fall Semester
4. Attending Rounds at HUP and VA Medical Center (2 months/year)
5. EP644 Cardiopulmonary Epidemiology, Advanced Master of Science in Clinical Epidemiology Course: Course Director and Teacher, Summer Semester
6. Clinic Supervisor, VA Medical Center and HUP
7. Methods in Clinical Research. Seminar Series for Cardiology Fellows, Medical Residents, and Medical Students
8. Faculty Preceptor, Cardiology Journal Club

Lectures By Invitation: (past 5 years)

January 23, 1997	"Aspirin and 'Primary' Prevention of Cardiovascular Disease" - US Food and Drug Administration, Gathersburg, MD
May 14, 1998	"Drug Safety Case Reports: From Calcium Blockers to FenPhen" - American Society of Hypertension, 13th Annual Meeting, New York, NY
June 4, 1999	"Sexual Activity and Cardiac Risk – Epidemiology" – International Consensus Conference – Sexual Activity and Cardiac Risk, Princeton, NJ
June 29, 1999	Testimony on Ephedra Dietary Supplements before the Joint committee on Health Care at the Commonwealth of Massachusetts House of Representatives, Boston, MA
December 2, 1999	"Coronary Stents", Cardiology Grand Rounds, Hospital of the University of Pennsylvania, Philadelphia, PA
December 10, 1999	"The Health Risks of Obesity" - 1999 AHPA Ephedra International Symposium, Arlington, VA

March 12, 2000	"Clinical Epidemiology—What Qualifies As A Valid Study and What Isn't Ready For Prime Time?" ACC Medical Writers Symposium (in conjunction with the American College of Cardiology 49th Annual Scientific Session), Anaheim, CA
August 8, 2000	"Review of Available Data on Ephedra Alkaloids" Department of Health and Human Services Office of Women's Health, Washington, DC
September 29, 2000	"Coronary Stents: The Good, the Bad, or the Ugly?" Northwestern University School, Cardiology Grand Rounds, Chicago, IL
March 2, 2001	"Clinical Outcomes Research in Cardiology: A Broad Range of Research Opportunities" 41st Annual Conference on Cardiovascular Disease Epidemiology and Prevention, San Antonio, TX
March 18, 2001	"Common Sense and Statistics in Identifying the High-Risk Patient" American College of Cardiology 50th Annual Scientific Session (ACC 2001), Orlando, FL
November 12, 2001	"Volume-Outcome Relationship for PCI and CABG: Lessons from Registries" 2001 American Heart Association Scientific Sessions, Anaheim, CA
November 26, 2001	"Non-Steroidal Anti-Inflammatory Medications and Myocardial Infarction: Study Designs Issues." Epidemiology Advisory Panel, Pfizer, New York, NY
January 25, 2002	"The Epidemiology of Antidepressant Therapy" Duke University Depression and Cardiovascular Disease Meeting, Baltimore, MD
March 23, 2002	"Assisting Trained Clinicians to Become Researchers" 60th Association of Teachers of Preventive Medicine Annual Meeting, Washington, DC

June 6, 2002	"NSAIDs and COX-2 Inhibitors: Good for You, or Dangerous?" Hospital of the University of Pennsylvania, Cardiology Grand Rounds, Philadelphia, PA
June 8, 2002	"Volume and Outcomes in Primary Angioplasty for Acute MI" Ohio-American College of Cardiology Annual Meeting, Huron, OH
October 17, 2002	"NSAIDs, Aspirin and COX-2 Inhibitors: Risky Business or Unexpected Benefits?" University of Pennsylvania, Center for Clinical Epidemiology and Biostatistics Seminar, Philadelphia, PA
November 17, 2002	"Selection of Pharmacological Approaches for Patients with Cardiovascular Disease and Depression." 2002 American Heart Association Scientific Sessions, Chicago, IL

Organizing Roles in Scientific Meetings:

2000- Member, Program Committee, National American Heart Association Council on Epidemiology

Bibliography:

Research Publications, peer reviewed:

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Books:
None

Alternative Media:
None

Patents:
None

Preponderance of Evidence

Judging What to Do About Ephedra

By Paul G. Shekelle, Margaret Maglione, and Sally C. Morton

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Since the 1980s, the herb ephedra has been purported to increase weight loss and to enhance athletic performance. In recent years, though, a string of athletes and other individuals who apparently had ingested the herb have collapsed and, in some cases, died. In the wake of the death of Baltimore Orioles pitcher Steve Bechler this spring, the voices of government officials and the public at large have grown increasingly louder in demanding proof of the safety and efficacy of the herb.

Unfortunately, scientific proof has become exceedingly difficult to attain. As a result of the 1994 Dietary Supplement Health and Education Act (DSHEA), substances that are classified as "dietary supplements" (including herbs such as ephedra) are not considered to be "drugs" and thus are not subject to the same rigorous regulatory standards as drugs are. According to the legislation, manufacturers of dietary supplements need not show evidence of the efficacy or safety of the products prior to marketing them. Therefore, the usual regulatory pressure to produce clinical studies assessing efficacy and risk does not exist. Consequently, we could find only limited scientific data about ephedra.

However, we did find sufficient evidence of danger associated with ephedra, along with insufficient evidence of its efficacy for athletic performance, to compel the U.S. Department of Health and Human Services and the U.S. Food and Drug Administration (FDA) to take preliminary regulatory measures against the herb. On Feb. 28, 2003, the FDA proposed a strong new warning label on ephedra products, warned manufacturers against making unsubstantiated claims that the products could enhance athletic performance, and invited public comment on the risks associated with ephedra to support new restrictions on the products.

The FDA is now seeking public comment to determine whether dietary supplements containing ephedra present a "significant or unreasonable risk of illness or injury." This is the standard that must be met under DSHEA before the FDA can take further regulatory action. This standard also reveals an indirect effect of the DSHEA law. By presuming that dietary supplements are safe and absolving manufacturers from proving that the supplements are safe, the law places the burden of proof on the FDA instead. The agency must somehow prove that a supplement is risky, even in the absence of clinical studies conducted by manufacturers.

Our study could not prove with scientific certainty that ephedra is unsafe. However, we compiled enough evidence to reach fairly confident conclusions. Our efforts could serve as an example of how policymakers and researchers can help to keep the public safe despite the absence of incontrovertible scientific proof of danger.

AP/WIDE WORLD PHOTOS/TERU IWASAKI

Food and Drug Administration Commissioner Mark McClellan, foreground, with Health and Human Services Secretary Tommy Thompson, tells reporters on Feb. 28 that bottles of the popular dietary supplement ephedra should bear warning labels that the pills can cause heart attacks, strokes, or even death.

AP/WIDE WORLD PHOTOS/GREG WAHL-STEPHENS

Pat Bechler, mother of Baltimore Orioles pitcher Steve Bechler, addresses a packed auditorium during a March 8 memorial service in Medford, Ore., for the 23-year-old pitching prospect, who died of heatstroke on Feb. 17. A Florida medical examiner linked the death to ephedra. Steve's older brother Mike is at left.

AP WIDE WORLD PHOTOS/RANDY SQUIRES

Kevin Riggins—the father of Sean Riggins, a 16-year-old high school football player who died last fall after taking ephedra—speaks at the state capitol building in Springfield, Ill., on March 12. On March 20, the Illinois state senate voted unanimously to ban the sale of ephedra products.

Lengthy Deliberations

The active stimulant in ephedra is called ephedrine, which is found in over-the-counter drugs used to treat stuffy nose and asthma. The difference between the herb ephedra and the drug ephedrine is analogous to the difference between coffee beans and caffeine. Ephedra, known as "ma huang" among Chinese herbalists, is a shrub. Ephedrine is the active stimulant found in the shrub.

To determine if either substance could improve weight loss or enhance athletic performance, we searched the medical literature as well as other sources for published and unpublished clinical trials of the substances. We based our conclusions about efficacy on a detailed review of 52 trials of ephedra or ephedrine for weight loss or athletic performance.

Many of the 52 trials involved only small numbers of people, covered only short periods of time, or suffered from other limitations. For example, all of the trials for athletic performance involved just a couple of dozen young fit males, who were not representative of the general population. Even in aggregate, the 52 trials offered only weak evidence for assessing the relationship between rare adverse

events and the use of ephedra or ephedrine.

To determine with greater confidence if it is safe to take ephedra or ephedrine, we analyzed nearly 18,000 case reports of adverse events. Consumers had contacted the FDA to provide the agency with 1,820 "adverse event reports," the vast majority of which dealt with ephedra rather than ephedrine. The FDA shared these reports with us. We discovered 71 additional reports in the medical literature. The largest repository of reports came from a computer file of 15,951 cases reported to Metabolife, a San Diego-based maker of ephedra-containing dietary supplements.

Except in extraordinary circumstances, case reports cannot be considered to be conclusive evidence of a cause-and-effect relationship. However, case reports can be useful to establish the *potential* for a causal relationship.

Weight Loss

We found some evidence of the benefits of ephedra and ephedrine for weight loss. Dietary supplements containing ephedra alone, ephedrine alone, ephedra with herbs containing caffeine, or ephedrine plus caffeine promoted modest short-term weight loss of about two pounds per month more than among people taking a placebo. But none of the available studies followed participants for longer than six months. A study of 12 months is generally accepted as necessary to establish a drug's value as a weight-loss aid.

Of the 52 clinical trials, 44 assessed ephedra, ephedrine, or ephedrine plus other compounds used for weight loss. Of these 44 trials, we excluded 18 because the duration of treatment was less than eight weeks. We excluded six other trials for a variety of reasons.

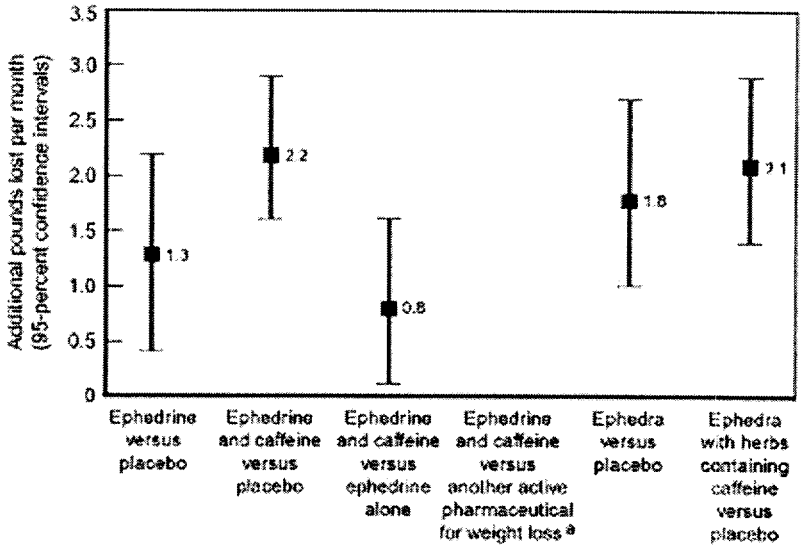
In the remaining 20 trials, we found comparisons made in six categories. We highlight the results below and in Figure 1.

- *Ephedrine versus placebo.* In five trials, the average weight loss for a person treated with ephedrine was 1.3 pounds per month more than the average weight loss for a person treated with a placebo.
- *Ephedrine and caffeine versus placebo.* In 12 trials, the average weight loss for a person treated with ephedrine and caffeine was 2.2 pounds per month more than the average weight loss for a person treated with a placebo.
- *Ephedrine and caffeine versus ephedrine alone.* In three trials, the average weight loss for a person treated with ephedrine and caffeine was 0.8 pounds per month more than the average weight loss for a person treated with ephedrine alone.
- *Ephedrine and caffeine versus another active pharmaceutical for weight loss.* In two trials, we found no statistically significant difference in weight loss. One trial compared the combination of ephedrine and caffeine to dexfenfluramine. The other trial compared the same combination to diethylpropion.
- *Ephedra versus placebo.* In a single trial, the average weight loss for a person treated with ephedra was 1.8 pounds per month more than the average weight loss for a person treated with a placebo.
- *Ephedra with herbs containing caffeine versus placebo.* In four trials, the average weight loss for a person treated with this ephedra mixture was 2.1 pounds per month more than the average weight loss for a person treated with a placebo.

In Figure 1, we show the average increase in weight loss in each case as a black square and give its value. We also include a vertical line that illustrates the 95 percent confidence interval around the average value. For example, the average additional weight loss for a person treated with ephedrine alone was 1.3 pounds per month.

We are 95 percent confident that the true additional average weight loss would fall somewhere between 0.4 and 2.2 pounds per month.

Figure 1—Taking Ephedrine or Ephedra Can Increase Weight Loss in the Short Term



SOURCE: "Efficacy and Safety of Ephedra and Ephedrine for Weight Loss and Athletic Performance: A Meta-Analysis," 2003.

[a] Only two trials were available assessing this comparison; neither showed a statistically significant difference.

Athletic Performance

We found no trials of ephedra on athletic performance—and thus no evidence that ephedra could enhance athletic performance. We found only minimal evidence that ephedrine could enhance athletic performance. Even here, there appeared to be no athletic benefit from ephedrine beyond an immediate boost.

There were eight trials of ephedrine on athletic performance. All but one included caffeine. Each trial involved different types of exercise and different outcome measures, so we analyzed each trial individually.

Six of the eight trials assessed the exercise capacity of small groups of healthy males. Each trial included 24 or fewer subjects. The trials concluded that neither caffeine nor ephedrine alone had significant effects on various parameters of exercise performance, such as oxygen consumption, time to exhaustion, or carbon dioxide production. However, the combination of ephedrine and caffeine consistently demonstrated a 20-30 percent increase in short-term performance.

One trial of strength training showed an improvement in muscle endurance—but only on the first of three repetitions. The remaining trial reported no statistically significant improvement in a battery of tests of physical function, including oxygen uptake, measures of endurance and power, reaction time, hand-eye coordination, speed, and self-perceived exertion.

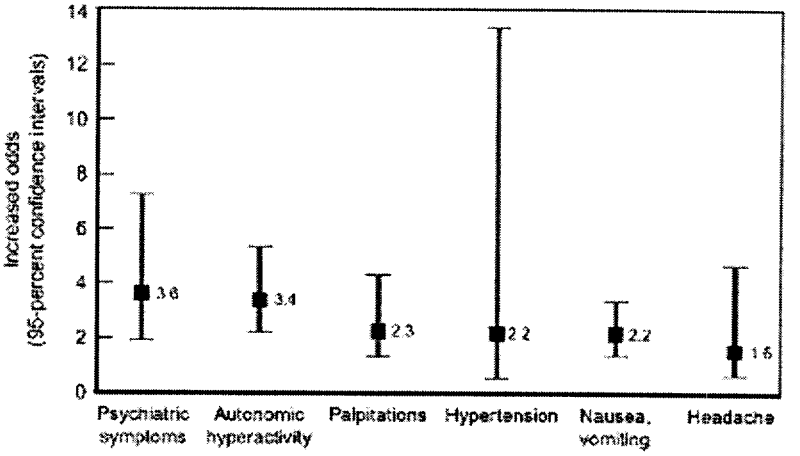
Safety

The clinical trials of ephedra and ephedrine reported numerous adverse side effects. We grouped the symptoms into clinically similar categories, as follows:

- psychiatric symptoms: those described in the trials as euphoria, neurotic behavior, agitation, neuropsychiatric symptoms, depressed mood, giddiness, irritability, or anxiety
- autonomic hyperactivity: those symptoms described as tremor, twitching, jitteriness, insomnia, difficulty sleeping, increased perspiration, or sweating
- palpitations: those symptoms described as palpitations, irregular heartbeat, loud heartbeat, heart pounding, or increased or stronger heartbeat
- hypertension: those symptoms described as hypertension, increased systolic blood pressure, or increased diastolic blood pressure
- upper gastrointestinal symptoms: those described as nausea, vomiting, abdominal pain, upset stomach, heartburn, or gastroesophageal reflux
- headache
- tachycardia: those symptoms described as tachycardia, or slightly elevated heart rate.

Figure 2 shows our estimates of the increased odds of suffering these adverse events when taking ephedra or ephedrine. Once again, we show each estimate as a black square and give its value. We also include a vertical line that illustrates the 95-percent confidence interval around the estimated value. For example, we estimate that the odds of a person suffering psychiatric symptoms were 3.6 times higher if the person took ephedra or ephedrine. We are 95 percent confident that the true value of the increased odds of suffering psychiatric symptoms would fall somewhere between 1.9 and 7.3.

Figure 2—Taking Ephedra or Ephedrine Increases the Odds of Suffering Adverse Events



SOURCE: *Ephedra and Ephedrine for Weight Loss and Athletic Performance Enhancement*, 2003.

Overall, people who received ephedra or ephedrine had between 2.2 and 3.6 times higher odds of suffering harmful side effects—including psychiatric symptoms, jitteriness, palpitations, nausea, and vomiting—than did people taking a placebo. There appeared to be a similar increase in the incidence of hypertension, but the increase was not statistically significant. There was also a trend toward a higher risk of adverse events with higher doses of ephedrine, but the data were sparse, and, once again, the differences were not statistically significant.

We could not estimate the increased odds of experiencing tachycardia because there were zero cases of tachycardia reported among people taking a placebo. In comparison, there were six cases of tachycardia among people taking ephedra or ephedrine.

It was impossible to estimate the degree to which caffeine contributed to the results, because there were too few trials of ephedrine alone or ephedra alone to isolate the role of caffeine. However, the one trial of ephedra without herbs containing caffeine reported a statistically significant twofold increase in gastrointestinal symptoms.

The additional evidence we gathered from the case reports raised even greater concerns about consumer safety. We screened the nearly 18,000 case reports and then reviewed in detail 284 reports of either death, heart attack, other cardiac symptoms, strokes, neurologic symptoms, seizures, or serious psychiatric symptoms.

We searched each of the 284 reports to assess whether ephedra or ephedrine was, indeed, a likely cause of the adverse event. We judged each case report by the following three criteria:

1. Documentation that an adverse event had occurred.

2. Either documentation that the subject had consumed ephedra or ephedrine within 24 hours prior to the adverse event *or* a toxicological examination revealing the presence of ephedrine or an associated product in the blood or urine. (For example, we did not require psychiatric symptoms to become manifest within 24 hours of using ephedra or ephedrine.)

3. Documentation that an adequate investigation had excluded other potential causes.

Cases meeting all three criteria were labeled "sentinel events." Cases meeting the first two criteria but having other possible causes were labeled "possible sentinel events." We solicited the judgment of expert

clinicians to assess whether causes other than ephedra or ephedrine had been adequately evaluated and excluded.

From the 284 reports of serious adverse events, we identified two deaths, three heart attacks, nine strokes, three seizures, and five psychiatric cases as sentinel events with prior ephedra consumption. We identified three deaths, two heart attacks, two strokes, one seizure, and three psychiatric cases as sentinel events with prior ephedrine consumption. About half of the sentinel events occurred in people aged 30 years or younger. We identified 43 additional cases as possible sentinel events with prior ephedra consumption and 8 additional cases as possible sentinel events with prior ephedrine consumption.

In aggregate, the case reports suggest a link between products containing either ephedra or ephedrine and catastrophic events, such as sudden death, heart attack, stroke, seizures, and serious psychiatric symptoms.

The Verdicts

Regarding weight loss, we found enough evidence to conclude that the short-term use of either ephedrine alone, ephedrine and caffeine combined, ephedra alone, or ephedra with herbs containing caffeine all promote weight loss in selected patient populations. However, all but three of the trials lasted for less than six months. Ideally, the trials should assess not only the results of a full year of treatment but also what happens after the treatment is discontinued.

Caffeine clearly adds additional efficacy to ephedrine in promoting weight loss. The effects of ephedrine and caffeine together are roughly equal to the effects of ephedra with or without herbs containing caffeine. Each results in about two pounds per month of weight loss over four months.

To put these pounds in context, though, competing FDA-approved weight loss drugs have been shown to be about equally as effective. The drugs sibutramine (Meridia) and orlistat (Xenical) have both resulted in average weight loss of 6-10 pounds over 6-12 months, and the drug phentermine (often used in combination with fenfluramine as "phen-fen") has resulted in average weight loss of 16 pounds over 9 months.

Regarding athletic performance, the few trials of ephedrine that we identified did not study the drug as used by the general population—that is, repeated use. Therefore, the effect of ephedra or ephedrine to enhance athletic performance over the long term is completely unknown.

Regarding safety, we conclude from the clinical trials that ephedrine and ephedra are associated with two to three times the odds of experiencing psychiatric symptoms, autonomic symptoms, upper gastrointestinal symptoms, and palpitations. It is not possible to separate out the effect that caffeine may contribute to these events.

We conclude from the case reports of ephedra and ephedrine that serious adverse events have occurred in young adults without other apparent causes. There *may* be a causal relationship between taking the substances and suffering rare serious adverse events. Catastrophic effects of ephedra, including death, cannot be ruled out at a rate of less than one person per thousand.

AP/WIDE WORLD PHOTOS/ED BAILEY

Bottles of Ripped Fuel Metabolic Enhancer, which contains ephedra, are shown in New York on June 18, 2002. A

Our study has several limitations. As we note above, many

bottle of Ripped Fuel was found in the locker of Minnesota Vikings tackle Korey Stringer after he collapsed and died during a training camp practice on Aug. 1, 2001.

of the clinical trials themselves had design limitations, and all of the weight loss trials were of short duration. In addition, the results of the weight loss trials may *understate* the dangers for the general population. These trials frequently involved medical screening to exclude people with preexisting conditions, such as heart disease, that could have predisposed the people to increased risks. It is unknown whether administering ephedra or ephedrine without such screening would increase the risks.

Despite these limitations, we found sufficient evidence to conclude that dietary supplements containing ephedra or ephedrine are associated with a modest increase in weight loss in the short term—but also an increase in a variety of serious health risks. We hope that our efforts in compiling medical evidence, even when it cannot be gleaned from clinical trials alone, can help others in the field find ways to reach similarly useful conclusions.

Related Reading

"Efficacy and Safety of Ephedra and Ephedrine for Weight Loss and Athletic Performance: A Meta-Analysis," *Journal of the American Medical Association*, Vol. 289, No. 12, March 26, 2003, pp. 1537-1545, Paul G. Shekelle, Mary L. Hardy, Sally C. Morton, Margaret Maglione, Walter A. Mojica, Marika J. Suttorp, Shannon L. Rhodes, Lara Jungvig, James Gagné.

Ephedra and Ephedrine for Weight Loss and Athletic Performance Enhancement: Clinical Efficacy and Side Effects, Paul Shekelle, Sally Morton, Margaret Maglione, et al., Evidence Report/Technology Assessment No. 76, Rockville, MD: Agency for Healthcare Research and Quality, February 2003, http://www.fda.gov/OHRMS/DOCKETS/98fr/95n-0304-bkg0003-ref-07-01-index.htm.

Contents

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January 11, 2003

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Re: Sean Riggins; DOB: 03/24/86; DOD: 09/03/02; CC-307-02

Dear Mr. Siegner:

As you requested I have reviewed the autopsy report and pathology slides from the above case. In brief, Mr. Riggins was a 16 year old high school student. On Saturday, August 31, 2002, he had been at a lake with friends. He subsequently developed abdominal discomfort, pain, and nausea. He did not play as scheduled in a high school football game on Monday, September 2, 2002, because of his illness. The next day he saw a physician because of a headache and vomiting and was felt to have bronchitis. He was treated with Reglan and a cough medication and given prescriptions for Compazine and doxycycline. He was found unresponsive at home later that day and could not be resuscitated. Laboratory studies showed elevated levels of cardiac enzymes

A complete autopsy was performed. Accompanying the body were two bottles of Concerta, one bottle of prochlorperazine, and one bottle of doxycycline. The number of pills remaining in the bottles was determined to be consistent with the prescriptions. The body was 65.5 inches in length and was estimated to weigh 190 pounds. The 410 gram heart showed coronary arteries that had no significant disease but appeared small. The myocardium was diffusely softened and mottled. A few epicardial petechiae were present. Each lung weighed 620 grams and had mild edema. The remaining organs and tissues examined showed nothing of significance. Microbiological studies were unrevealing. Blood toxicology showed only lidocaine. Urine toxicology showed Reglan, ephedrine and/or pseudoephedrine, and benzyl alcohol. Investigation revealed that Mr. Riggins had taken "Yellow Jackets", a dietary supplement containing ephedra, prior to wrestling meets. However, he had not been observed to take them in the several days prior to his death. Histologic slides of the heart were examined at the Centers for Disease Control (CDC) and found to be negative for bacteria, Neisseria meningitides, and Spotted Fever Group Rickettsia.

There are 11 histologic slides available for review that are labelled: CC-307-02. In addition, the slides are individually designated as 1 through 11. Slides 3, 4, 8, and 9 have the notation Rc and contain sections of the heart. There is a severe injury to the myocardium, especially in the left ventricle, which is characterized by necrosis of myocytes, usually with an identifiable contraction band change. The age of the necrosis ranges from very fresh to five or six days. There is a widespread acute inflammatory cell infiltrate with some areas of subacute inflammation. In general, the myocardial necrosis and the inflammatory cell response are associated with each other. However, there are areas of inflammation without necrosis and areas of contraction band change without inflammation. Since the cells in the latter areas show good preservation of myocyte nuclei it is more probable than not that these areas of contraction band necrosis arose during attempted resuscitation.

Re: Sean Riggins; DOB: 03/24/86; DOD: 09/03/02; CC-307-02

As noted, the inflammation and necrosis is most severe in the left ventricle, occurring in all areas of the sections from that chamber. The right ventricular myocardium is less severely involved and the right and left atria show no necrosis and only slight inflammation in the left atrial section. An inflammatory cell reaction of is present in the epicardial tissues and in the endocardium. The myocardial blood vessels show no abnormality.

The lung has mild edema, slight peribronchial mononuclear cell accumulations, and basement membrane thickening in larger bronchi. There is a healing granuloma in the lung which contains a few capsules suggestive of Cryptococci. There is mild fatty change in the liver, small hemorrhages in a lymph node, and red neurons in brain sections. The reminaing tissues show nothing of note.

Contraction band formation in myocytes is a non-specific change that is seen most commonly in autopsy cases as necrosis arising from reperfusion of unperfused myocardium. Thus, it is common following resuscitation of individuals where a cardiac arrest has occurred. It may be seen following certain cardiac surgical or interventional procedures. It may develop as a component of myocardial infarcts where the predominant form of necrosis is coagulation necrosis. These and other circumstances where contraction band necrosis is found support the concept that the common denominator of contraction band development is an alteration of the myocyte membrane that allows excessive influx of calcium into the sarcoplasm of the myocyte. This calcium causes the destruction of the mitochondria, alters the contractile elements, and kills the cell. Contraction bands are also found in cells that have been directly injured as by surgical incision or by organisms.

The character of the timing and spatial relationships of the necrotic and inflammatory processes in Mr. Riggins' heart, as described above, appears more consistent with an infectious process than an ischemic process. The inability to see infectious agents in the hematoxylin and eosin stains and the failure to find them in the studies performed by the CDC do not exclude this explanation. It is well recognized that Chlamidia and Mycoplasma may cause myocarditis. These organisms cannot be demonstrated in tissues by the standard methods that have been used in this case.

In summary it is my opinion to a reasonable degree of medical certainty that Mr. Riggins' died as result of a severe inflammatory and necrotizing process in his heart that was ongoing over several days prior to his death. The pattern of injury and inflammation seems more likely than not to have been caused by an infectious agent such as Chlamydia or Mycoplasma. The pathology seen, in the context of the clinical and investigative information, is not likely to have been due to a coronary artery vasospastic process such as has been postulated to occur with ephedrine. Further investigation of the heart tissue obtained at autopsy may clarify the issue.

Sincerely yours,

Grover M. Hucthins, M.D.

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CENPHR

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The Alleged Role of Ephedra in the Death of a Professional Baseball Player

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*Mike Greenwood, PhD, CSCS*D*
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February 21, 2003

As active researchers in the area of exercise physiology, sport nutrition, strength and conditioning, and sports medicine, we would like to make the following comment and observations regarding the current controversy about the supposed link of ephedra supplementation to the tragic death of Baltimore Orioles pitcher Steve Bechler due to multiple organ failure, as a result of heat stroke, on Feb.17, 2003.

- Heat stroke fatalities are preventable if proper screening, conditioning, acclimatization, and precautions are employed to ensure that athletes train safely in hot and humid environments.

- The local coroner and members of Orioles management have suggested that Mr. Bechler's death was related and/or caused by the possible consumption of a dietary supplement containing the herb ephedra.

- These reports have caused a flurry of reports in the media questioning the safety of ephedra supplementation and calls to ban the use of ephedra in Major League Baseball and/or sale of ephedra in over the counter dietary supplements.

- At this point, toxicology reports have yet to confirm that Mr. Bechler had taken an ephedra supplement prior to practice.

- Clinical studies published in peer-reviewed journals have indicated that ephedrine and herbal ephedra supplementation can significantly promote weight loss with no major side effects in overweight but otherwise healthy individuals. There is also evidence that taking ephedra and caffeine during training may help promote greater fat loss. Most studies show that ephedra or ephedrine has no ergogenic benefit in and of itself. Claims that ephedra is a "performance enhancing substance" is not supported by the scientific literature. However, there is data showing that caffeine has ergogenic value and that there may be some ergogenic value of ingesting supplements that have ephedra and caffeine.

- Many over-the-counter medications (e.g., cold medications) contain ephedrine alkaloids (e.g., pseudoephedrine, etc.) at higher concentrations than found in nutritional supplements containing ephedra.

- Closer examination of contributing factors related to Mr. Bechler's death reveals that even if Mr. Bechler did consume the supplement, it was probably the least of the contributing factors leading to his death—and it may not have been a factor at all.

- According to reports in the media, Mr. Bechler had the following risk factors for heat stroke:

    1. a prior history of heat illness episodes while in high school - which heightens the probability of reoccurring incidents;

    2. a family history of sudden death following exercise (his half-brother died of an aneurysm at the age of 20 after overheating from playing baseball);

    3. a history of hypertension and liver problems;

    4. he had not eaten solid food for a day or two, in an apparent attempt to lose weight;

    5. he was apparently not adequately acclimatized to training in the heat and humidity of South Florida;

    6. it appeared that he was wearing two or three layers of clothing during workouts, again, in an attempt to lose weight;

    7. he was overweight and did not have a high enough fitness level to make it through conditioning drills; and,

    8. he was allowed to exercise until he collapsed with a core temperature reportedly of 106° F before being removed from the field.

- It has been extensively documented that untrained, overweight, and unacclimatized people who perform excessive exercise in heat/humidity are at great risk of heat illness and heat stroke—particularly if they have become dehydrated and are trying to lose weight quickly.

- These pre-existing conditions raise serious questions as to the appropriate medical screening, conditioning, and supervision of Mr. Bechler participating in spring conditioning drills as follows:

    1. Were team athletic trainers and conditioning specialists aware of Mr. Bechler's prior history of heat illness or stroke? If they were aware, why weren't additional exercise precautions taken to ensure that he was adequately trained, acclimatized, hydrated, and fed prior to his participation in intense conditioning drills?

    2. Media reports indicate that Mr. Bechler had a prior history of reporting to camp overweight and out of shape. If this is the case, was Mr. Bechler given appropriate training and dietary counseling and/or placed on a pre-camp conditioning and nutrition program to make sure he reported in good condition? Excess body fat is a major liability when exercising in hot/humid climates because it increases the insulation properties of the body which in turn reduces the amount of body heat that can be released through perspiration. Fatal heat strokes occur 3.5 more times in obese populations than any other population.

    3. Why didn't pre-participation medical screening identify the risk factors to heat stroke described above? Complete pre-participation exercise stress tests and/or fitness/sprint tests would have indicated that Mr. Bechler was not in sufficient physical condition to perform intense training. Further, that he was not adequately acclimatized to exercise in the heat. According to media reports, Orioles coaches knew that his conditioning was "not good". If this is the case, then how was he

allowed to participate in intense conditioning training? Medical screening should have also revealed a history of hypertension and liver problems. These are all contraindications to performing excessive exercise particularly in hot/humid environments.

4. Where was the supervision to notice signs of heat illness in Mr. Bechler? Media reports indicate that he was dizzy, he was only able to perform 60% of the conditioning drills, and that he collapsed on the field. These are all signs and symptoms of heat intolerance and/or heat illness. It is the responsibility of athletic trainers and strength and conditioning specialists to make sure that athletes safely engage in physical activity. If athletes are showing signs of abnormal responses to exercise, it is the responsibility of coaches, team physicians, athletic trainers and/or strength and conditioning specialists to pull the athlete out of conditioning drills – not the athletes.

5. Did the athletic trainers, team physicians, and/or strength and conditioning specialists know that Mr. Bechler evidently was not eating solid food? Training camp is not an appropriate time for athletes to diet. Allowing athletes to train when they are dehydrated and/or not well fed is dangerous. Athletes who report to camp overweight should be given proper nutritional counseling about safe and effective ways to lose weight.

6. Team physicians , athletic trainers, and strength and conditioning coaches should know what supplements athletes are taking so they can counsel them about whether or not they are safe, legal, effective, and/or appropriate to take at a given time during training. In this case, a supplement bottle was purportedly found in Mr. Belcher's locker yet team officials were supposedly unaware of him taking supplements. This is troubling given that he had pre-existing medical conditions that were contraindicated for use of the purported supplement.

- The supposed link that ephedra supplementation caused or contributed to heat stroke does not make sense from a physiological standpoint for the following reasons:

1. Some of Mr. Bechler's teammates claimed that he usually took three supplement capsules (1.5 servings) in the morning. According to that product's label, that would have provided 30 mg of herbal ephedra. This is one third of the dose shown in long-term clinical trials to be safe.

2. There is no scientific or medical evidence to indicate that ephedra/caffeine supplementation significantly increases thermal stress (increases core temperature 2-3 degrees above normal) during exercise, that it promotes dehydration, or increases the incidence of heat illness.

3. The thermogenic effects of ephedra and caffeine are relatively small, typically increasing resting caloric expenditure by 5-10 kcals per hour. One oral dose of ephedra/caffeine usually lasts less than 3 hours. Therefore, the total caloric (i.e., heat) load would be 15 – 30 calories in a 2-3 hour period following ingestion of one serving of an ephedra containing supplement. While this may be sufficient to promote a gradual weight loss (if one took 2-3 servings per day for 2-6 months), it would have minimal, if any, affects of core body temperature.

4. In contrast, athletes commonly expend 600-1,200 kcals per hour during intense exercise or 1,800 – 3,600 calories during an intense 3 hour practice. The thermal load of exercise generally increases core body temperature by 2-3 degrees when properly regulated.

5. The primary way heat from exercise is dissipated is through evaporation of sweat. Exercise in humid environments decreases the ability of sweat to evaporate making it more difficult to regulate body temperature. When the humidity is very high (i.e., > 70%), sweat may not fully evaporate which increases susceptibility to heat disorders. Humidity is higher in morning and evening hours. This is the primary

rationale why intense exercise should be avoided during humid conditions and/or additional precautions should be employed to supervise athletes training or performing in hot/humid environments.

6. The media scare linking Mr. Bechler's heatstroke death with ephedra places emphasis on the unknown (pending toxicology results), and ignores known and obvious contributing factors already detailed here.

- Unfortunately, these media reports may mislead some to conclude that simply prohibiting athletes from taking ephedra supplements will eliminate the risk of heat fatalities.

- Instead, we should be stressing the importance of properly educating athletes, coaches and athletic trainers about the risks of training in hot and humid environments when participants are poorly conditioned, have not acclimatized to the heat and humidity, have engaged in dehydration practices, have medical histories that should have raised warning flags, and have not been sufficiently supervised.

- It seems that Major League Baseball and others want to blame ephedra for the death of Mr. Bechler, rather than admit that they may have been negligent in screening, conditioning, and supervising their athletes.

- The tragedy is that if Mr. Bechler had been properly screened and conditioned; if he had acclimatized properly to high heat and humidity conditions; if he had been adequately supervised; and if he had been properly educated about diet, weight loss, and the use of dietary supplements, he may be alive today.

In our view, this is another example of poor supervision and screening of athletes and not an issue of inappropriate use of a dietary supplement.

Tips to Prevent Heat Illness and Heatstroke in Athletes

- Conduct a comprehensive medical examination to examine past history and risk factors to heat illness.

- Make sure the athlete is adequately trained to participate in high intensity exercise prior to the start of conditioning.

- Acclimatize the athlete to training in hot/humid environments by beginning with brief and low intensity exercise sessions and progressing up to longer and more intense training sessions during the first few days of training.

- Make sure the athlete is eating a healthy and nutritious diet and is well-hydrated prior to the start of each practice.

- Monitor ambient environmental conditions (temperature, humidity, heat index, etc) and adjust workout intensity, duration, and frequency as necessary to reduce risk to athletes.

- Monitor pre- and post practice weight changes. Ingest 3 cups of water or sports drink for every pound lost during practice.

- Do not allow athletes who lost more than 3% of their body weight to practice again until their weight is up to acceptable ranges.

- Do not allow athletes to wear excessive clothing which can impede sweat evaporation and therefore reduce cooling.

- Provide frequent and planned water/sports drink breaks during practice. Ensure that the athlete drinks 1-2 cups of water or sports drink every 15-20 minutes during exercise in the heat/humidity.

- Watch for signs of heat illness including cramping, dry mouth, fatigue, dizziness, loss of concentration, palor, vomiting, cessation of sweating, dry and hot skin, and inability to maintain exercise workloads.

- Do not excessively train athletes in hot/humid environments. The higher the intensity of training, the greater amount of heat produced. This means that if it is very hot/humid, practices should be rescheduled and/or involve less intense training. Athletes should be pulled from conditioning drills if they are unable to perform them and not allowed to train until they collapse.

- Provide appropriate medical supervision at a supervisor to athlete ratio that will allow signs and symptoms of heat illness to be immediately recognized.

- Provide prompt medical care when signs are observed of abnormal responses to exercise in the heat.

- Have emergency procedures well defined so that prompt medical attention can be provided in the event heat illness is observed.

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* The comments provided above represent the scientific opinions of the authors and do not necessarily reflect those of Baylor University and/or professional organizations that the authors may belong.
