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Ephedra

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Abstract. In February 2004, the U.S. Food and Drug Administration (FDA) prohibited the sale of dietary supplements containing ephedrine alkaloids (ephedra), stating that such supplements present an unreasonable risk of illness or injury. The Dietary Supplement Health and Education Act (DSHEA) of 1994 (21 USC §301, 1994) governs dietary supplement regulation in the U.S. DSHEA places the burden of proof for safety on the government rather than on the manufacturer and thus differs significantly from regulations that govern the marketing of drugs. Part of the evidence the FDA used in reaching its decision was a systematic review of the efficacy and safety of ephedra conducted by the Southern California Evidence-Based Practice Center. In addition to a meta-analysis of controlled trial data, the review contained an evaluation of observational case report data, a study design that has limited inferential abilities regarding cause and effect.

How did the FDA decide what data were relevant to its decision? How did the FDA argument for the ban differ from a decision based solely on statistical hypothesis testing? This paper will address these questions by describing the systematic review approach, the evidence presented, the interpretation of that evidence by those on both sides of the argument and the process by which the decision was made.

Key words and phrases: Dietary supplements, meta-analysis, research synthesis.

1. INTRODUCTION

Imagine opening the *Los Angeles Times* on June 23, 2002. You, a baseball statistics aficiando, turn immediately to the sports section. You are saddened to see the headline "Kile's Death Stuns Baseball" (Newhan, 2002). The article reports that 33-year-old Darryl Kile, a St. Louis Cardinals pitcher, was found dead in his hotel room. He "had no health problems and was not on medication" (Newhan, 2002). The newspaper refuses to speculate on the cause of death. However, given the recent focus on severe adverse events such as heart attacks and deaths attributed to ephedra use, especially by high-profile athletes in the hope of enhancing their performance, you infer that the herbal dietary supplement may have been involved.

The next day you turn again to the sports section and another article titled "Exam Points to Kile's Heart" states that "preliminary autopsy findings reveal '80-to-90% narrowing' of two coronary arteries probably led to death" (Pugmire, 2002). You are reminded of one of the many fallacies discussed in Darrell Huff's influential volume, namely that of the eighth chapter: *Post Hoc Rides Again* (Huff, 1954). As Huff states, correlation is not causation and the Kile case could be said to have "cause and effect altogether confusingly distorted, reversed, and intermingled" (Huff, 1954).

Almost two years later, on February 6, 2004, the U.S. Food and Drug Administration (FDA) issued a final rule "prohibiting the sale of dietary supplements containing ephedrine alkaloids (ephedra) because such supplements present an unreasonable risk of illness or injury" (FDA, 2004a). How was this decision reached? This paper will describe the evidence presented, the interpretation of that evidence by those on both sides of

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the argument and the process by which the decision was made.

1.1 Background

Ephedra is an herb whose active alkaloid is ephedrine. Herbal ephedra has been used as part of Chinese traditional medicine for over 5,000 years. Dietary supplements containing ephedra have primarily been used in the United States since the 1980's to promote weight loss or to enhance athletic performance. Approximately three billion servings were consumed in the U.S. in 1999 according to a survey conducted by ephedra product manufacturers (Shekelle, Morton, Maglione et al., 2003).

A growing number of consumer complaints were made to the FDA and legal cases were filed against ephedra manufacturers in the 1990s (Shekelle, Morton, Maglione et al., 2003). Several adverse events possibly associated with ephedra use, including deaths of high-profile athletes, were reported and focused attention on the safety and efficacy of ephedra. As a result, the non-profit consumer group Public Citizen filed a petition with the FDA in 2001 asking for a ban on the production and sale of ephedra to protect public health.

1.2 The Dietary Supplement Health and Education Act (DSHEA)

Products containing ephedra are classified by the FDA as dietary supplements and are regulated by the Dietary Supplement Health and Education Act (DSHEA) of 1994 (21 USC §301, 1994). This Act differs considerably from the regulations that govern the marketing of drugs. Dietary supplement manufacturers are not required to conduct clinical studies to establish the safety of their products. Manufacturers are forbidden from making disease treatment claims but they are also not required to demonstrate the efficacy of their products.

DSHEA places the burden of proof for safety on the government. Specifically, the Act requires that the FDA monitor safety and "grants the FDA the authority to take action against a dietary supplement under certain circumstances, including when the product presents a significant risk, an unreasonable risk, or an imminent hazard, does not comply with good manufacturing practices, or makes an unsubstantiated structure-function claim" (21 USC §301, 1994).

1.3 Evidence Report on Ephedra

In June 2001, the National Institutes of Health Office of Dietary Supplements nominated the ephedra topic to the Agency for Healthcare Research and Quality (AHRQ) Evidence-Based Practice Center program. The Southern California Evidence-Based Practice Center (SCEPC) based at the RAND Corporation was awarded the contract to conduct a comprehensive literature review and synthesis of the evidence on the efficacy and safety of ephedra.

In June 2002, HHS Secretary Tommy Thompson announced RAND was conducting a review and said "by increasing our breadth of knowledge about these supplements, we can give consumers the information they need to make informed decisions about these products" (HHS, 2002). Senator Richard Durbin (Democrat, Illinois) introduced legislation in August 2002 "that would protect consumers from dangerous dietary supplements such as ephedra and other stimulants by requiring manufacturers to submit proof that their product is safe prior to bringing it to market" (Durbin, 2003). Acting Commissioner Lester Crawford stated this "scientific review will help guide the Department (FDA) and the Agency (HHS) in developing future FDA regulatory actions on ephedrine alkaloids" (Crawford, 2002).

The interest in this project continued to be high as indicated by a January 2003 article in *The Washington Post*:

> An independent safety review of the plant derivate by the Rand Corp. is slated for March release. If the report, ordered by the Bush administration, finds ephedra hazardous, the Department of Health and Human Services could initiate action to have it taken off the market. If that happens, said Larry Sasich, a pharmacist and spokesman for the Public Citizen Health and Research Group, ephedra would be the first supplement to run afoul of the Dietary and Supplements Health and Education Act of 1994 (DSHEA). "I have a feeling [ephedra] will eventually come off the market—but it could be quite a mess first," said Sasich (Redfearn, 2003).

2. EVIDENCE REPORT METHODS AND RESULTS

In conducting the *Ephedra: Clinical Efficacy and Side Effects Project*, the SCEPC addressed whether ephedra use:

- Produces weight loss?
- Improves athletic performance?

- Increases the risk of adverse events, including heart disease or other serious and life-threatening events?

The first two questions constitute the project's efficacy analysis, and the last question constitutes the safety analysis.

The systematic review and meta-analysis methodology is discussed in detail elsewhere (Shekelle, Hardy et al., 2003). A technical expert panel advised that the review should focus on studies of ephedra or ephedrine, and should not include studies on other alkaloids such as pseudoephedrine. Further, the panel provided guidance on issues such as inclusion/exclusion criteria for studies, specifying for example, that weight loss studies should have a follow-up period of at least six months. Due to paucity of such studies, this criterion was later relaxed to two months.

The SCEPC conducted a comprehensive literature search including unpublished and non-English literature, the latter being especially important given the role of ephedra in traditional Chinese medicine. Two reviewers independently reviewed titles and unmasked articles to identify controlled trials of ephedra or ephedrine in humans assessing weight loss or athletic performance. The reviewers assessed the trial quality and abstracted trial characteristics and outcome data. The SCEPC also identified case reports of adverse events associated with ephedra and, as discussed below, further included other data sources for the safety analysis.

The SCEPC identified 550 relevant articles, 530 of which were located. None of the 20 unobtainable articles appeared to report on controlled trials. Review of the 530 articles yielded 44 controlled trials on weight loss, eight controlled trials on athletic performance, and 65 case reports or case series (Shekelle, Hardy et al., 2003).

2.1 Efficacy Analysis

The SCEPC considered the 44 controlled trials for a meta-analysis of the efficacy of ephedra on weight loss. Eighteen trials were excluded since they had a duration less than two months; a further six trials were excluded for disparate reasons, including insufficient data. Based on the remaining 20 trials, the random effects pooled estimates (DerSimonian and Laird, 1986) of weight loss ranged from 0.6 kg per month in the ephedrine group above weight loss in the placebo group to 1.0 kg for the ephedrine and caffeine and ephedra with herbs containing caffeine groups (Table 1) (Shekelle, Hardy et al., 2003). The SCEPC concluded that there was sufficient evidence that ephedra or ephedrine, with and without caffeine, does produce weight loss on the order of about two pounds per month as compared to placebo in the short term. The weight loss observed is comparable to that observed for common weight loss medications.

TABLE 1
Weight loss per month above placebo estimated from the clinical trial data

Treatment group	Weight loss per month above placebo (95% confidence interval)
Ephedrine	0.6 kg (0.2, 1.0)
Ephedrine and caffeine	1.0 kg (0.7, 1.3)
Ephedra	0.8 kg (0.4, 1.2)
Ephedra with herbs containing caffeine	1.0 kg (0.6, 1.3)

The SCEPC found no studies that assessed the effect of ephedra on athletic performance. Only trials that assessed ephedrine or ephedrine plus caffeine were available. The eight trials were too heterogeneous in terms of the type of exercise involved and the outcomes measured to meta-analyze. All trials studied young males directly after a single dose of ephedrine or ephedrine and caffeine. Improved performance was reported only for ephedrine and caffeine. No studies evaluating long-term use were available.

2.2 Safety Analysis—Controlled Trial Data

To assess safety, the SCEPC first focused on the 44 weight loss trials and the eight athletic performance trials. Using "exact methods" (Cytel Software Corporation, 2000), the SCEPC found a 2.2- to 3.6-fold increase in the odds of adverse events such as heart palpitations and hypertension associated with ephedra use (Shekelle, Hardy et al., 2003).

No deaths, heart attacks or strokes were reported in the 52 trials that had been identified. However, one cannot conclude from this evidence that the risk of death is zero. Only 1706 patients were in the intervention (ephedra) groups of these trials. Had at least one death been observed, one would have concluded that the risk of death was greater than zero. The SCEPC asked the following question: how large must the risk of a serious adverse event be such that the probability of observing at least one death among 1706 individuals is at least 80%? The answer is that one cannot exclude an event rate of less than 1.0 per thousand. The death rate associated with ephedra might well be smaller. Thus, even though no deaths were observed among the 52 trials,

the relatively small aggregated sample size across all trials limits the strength of the conclusions. This limitation suggests the need for additional analyses based on observational data.

2.3 Safety Analysis—Observational Data

Given the limitations of the trial data, the SCEPC included case report data in the safety analysis, examining 65 case reports or series found in the published literature (Shekelle, Morton, Maglione et al., 2003). The SCEPC also examined the 1,469 reports submitted to FDA MedWatch (Shekelle, Morton, Maglione et al., 2003; FDA, 2004b), and 18,502 reports submitted to Metabolife, a manufacturer of an ephedra dietary supplement (Shekelle, Morton, Maglione et al., 2003). Metabolife turned over these data to the FDA at the request of the U.S. Department of Justice. For all reports, the SCEPC first categorized the event as serious (death, stroke, myocardial infarction (MI), seizure, and certain psychiatric symptoms) versus those considered moderately serious.

The SCEPC assessed whether each serious adverse event could be categorized as "sentinel" or idiopathic, meaning the cause is not known. For idiopathic cases, given the known pharmacology of ephedra, a potential role for ephedra in causing the event must be considered (Shekelle, Morton, Maglione et al., 2003). Briefly, the assessment consisted of determining if sufficient documentation existed such that one could be sure the adverse event occurred, that the individual took ephedra 24 hours or less prior to the event (the timing for psychiatric outcomes was different, as prolonged or chronic use of ephedra is hypothesized to contribute to those outcomes) and that all other causes for the event had been ruled out. For example, if the event were a death, the report would have to contain an autopsy and toxicology screen. Cases for which sufficient documentation existed and other potential causes might exist or were not effectively excluded were classified as "possible sentinel events."

The following is an example of a MedWatch death classified as sentinel (Case #14390):

> A 22-year-old female ... collapsed and died ... Ephedrine was found in the blood. The autopsy report stated that the coronary arteries were free of atherosclerosis. There was no myocarditis. The brain was normal ...There was no other cause of death. The death certificated listed "cardiac arrhythmia due to ephedrine-containing diet medication" (Shekelle, Morton, Maglione et al., 2003).

TABLE 2
Adverse events associated with ephedra and ephedrine

Adverse event	Number of events identified	Number of events classified as sentinel	Number of events classified as possibly sentinel
Death	84	5	12
Myocardial infarction or other cardiac event	56	5	10
Cerebrovascular event (stroke) or other neurologic event	56	11	13
Seizure	40	4	7
Psychiatric symptoms	91	8	8

The following is a MedWatch death classified as a possibly sentinel event due to a preexisting condition (Case #12485):

> A 38-year-old male collapsed and died after jogging. Prior to jogging, he had had a cup of coffee and Ripped Fuel supplements. At autopsy, he was found to have triple vessel coronary artery disease and cardiomegaly (Shekelle, Morton, Maglione et al., 2003).

The SCEPC classified five deaths and 28 other serious adverse events as sentinel (Table 2) (Shekelle, Hardy et al., 2003). About half occurred in persons aged 30 and younger. Unfortunately, the vast majority of case reports did not provide sufficient information. In addition, the SCEPC may not have had access to all reported events and obviously could not evaluate unreported cases. Some authorities consider adverse events to be grossly under-reported in spontaneous voluntary reporting systems like MedWatch. Thus, one might hypothesize that the number of sentinel events observed is an underestimate of the number that have occurred.

3. DISCUSSION

Conclusions about efficacy and safety need to be tempered by the limitations of the data and its analysis (Shekelle, Morton, Maglione et al., 2003). The efficacy meta-analysis is subject to the common limitations of meta-analysis: in particular, many trials had methodological problems such as high attrition. Though no evidence of publication bias was observed, there is no

way to be certain that such bias does not exist. Analogously, though heterogeneity was not observed among the trials, heterogeneity might have been difficult to discern had it existed. The SCEPC concluded that ephedra promotes modest short-term weight loss, and no conclusions about the effect beyond four months may be drawn. Furthermore, the trial results are applicable only to those persons studied and, as is usual for clinical trials, the study populations tended to be healthy. Whether similar efficacy would be seen for a more representative population is unknown.

The safety analysis is prone to more limitations, including missing and incomplete data as previously discussed. Without an estimate of the number of individuals taking ephedra, the risk/benefit tradeoff comparing ephedra to other substances cannot be evaluated. Finally, the case report study design is insufficient to warrant conclusions regarding causality, and SCEPC advised that a case-control study should probably be undertaken (Shekelle, Morton, Maglione et al., 2003).

Even given these limitations, a biologically plausible argument can be made as to why ephedra might result in serious adverse events. Ephedra acts on receptors in the brain and the cardiovascular system. Chemically related compounds such as amphetamines have been proven to cause the same adverse events. The sentinel events identified are a signal that ephedra may act similarly. A recent case-control study (Morgenstern et al., 2003) reported an increased risk (adjusted odds ratio of 3.95; 95% CI: $0.7 - 18.0$; $p = 0.07$) of hemorrhagic stroke associated with ephedra use.

4. REACTION

On February 28, 2003, HHS released the evidence report, and an article (Shekelle, Hardy et al., 2003) and editorial (Fontanarosa, Rennie and DeAngelis, 2003) appeared in the *Journal of the American Medical Association* (*JAMA*). The FDA proposed a new warning label on ephedra products and warned manufacturers against making claims that ephedra enhances athletic performance.

"We want to caution all Americans—particularly athletes and those who engage in strenuous activities—about using dietary supplements that contain ephedra," said Secretary of Health and Human Services Tommy G. Thompson. "There continue to be serious questions about the risks surrounding this particular dietary supplement" (FDA, 2003a). Thompson was widely quoted as saying "I would not take this; I would not give it to my family. And I don't know why anyone would take these products" (CNN.com, 2003). The agency invited public comment (FDA, 2003a).

The *JAMA* editorial (Fontanarosa, Rennie and DeAngelis, 2003) concluded that doubt exists about claims that ephedra promotes weight loss or enhanced athletic performance. Furthermore, the "findings strongly suggest increased risk of serious adverse effects associated with these products." (Fontanarosa, Rennie and DeAngelis, 2003) The authors added that "the most important lessons from the new information on ephedra are demonstration of the inadequate nature of the current system of regulation of dietary supplements and recognition that much more rigorous oversight of these biologically active agents is necessary to protect the health and safety of the public" (Fontanarosa, Rennie and DeAngelis, 2003).

The response from the Ephedra Education Council (EEC), a public relations firm representing the ephedra industry, focused on the clinical trial efficacy and safety analyses:

> More than 60 percent of Americans are overweight, and are at a higher risk of serious medical complications, including heart disease and diabetes. The RAND review of ephedra science confirms what weight loss experts have previously stated—that well-designed clinical trials consistently show that supplements help healthy, overweight people lose more weight than diet and exercise alone. . .
>
> Finally, we understand that the RAND review confirms what the EEC and scientific experts have said all along, that no serious events have occurred in any clinical setting, and that the risk of experiencing any adverse reaction to ephedra, if any, is small (Ephedra Education Council, 2003).

5. AFTERMATH

On February 6, 2004, after public and Congressional hearings, the FDA published a final rule prohibiting the sale of dietary supplements containing ephedrine alkaloids. The FDA concluded that the "risks are unreasonable in light of any benefits that may result from the use of these products" (FDA, 2004c). The FDA stated that the DSHEA burden of proof for unreasonable risk was met as the risks of ephedra outweighed the benefits. The agency did not address, nor did it need to under the standards of DSHEA, whether or not ephedra presents

an imminent hazard. The FDA was also not required to show evidence of harm to specific individuals.

The FDA stated that the pharmacological evidence bolsters the biologically plausible argument that ephedra affects individuals as similar products do. These related products have been determined by the FDA to be unsafe. In terms of published trial data, the FDA cited the design drawbacks of those studies, namely limited sample size, which impact the ability to infer about safety. Regarding adverse event data, the FDA stated that its conclusion did not depend on those reports. However, these reports "support the clinical and scientific evidence of the risks of these products" (FDA, 2004c).

In summary, the FDA weighed the risks against the benefits of ephedra use and concluded that the risks were not outweighed by the benefits. The short-term weight loss associated with ephedra was insufficient to produce meaningful health gains to the user. These dietary supplements "provide only temporary benefits that are trivial in comparison to the risk" (FDA, 2004c).

The FDA reasoning met the standards imposed by DSHEA, but it may be argued that these standards do not adhere to those required for scientific certainty if by the latter we mean meeting the traditional "p-value less than 0.05" level of statistical testing. An Institute of Medicine and National Research Council committee addressed this issue (Committee on the Framework for Evaluating the Safety of Dietary Supplements, 2004). The committee found that because of the limited data often available to evaluate risk for supplements, the "appropriate scientific standard to be used to overturn this basic assumption of safety is to demonstrate significant or unreasonable risk, not *prove* that an ingredient is unsafe" (Committee on the Framework for Evaluating the Safety of Dietary Supplements, 2004). This reasoning follows from the fact that supplements, unlike drugs, have been "*assumed* to be safe, but have not been required to be *proven* safe" (Committee on the Framework for Evaluating the Safety of Dietary Supplements, 2004).

On February 18, 2003, you open the newspaper to the sports section again, and are saddened to read of the death of Steve Bechler, a 23-year-old pitching prospect for the Baltimore Orioles (Kubatko, 2003). He is said to have died of complications related to heatstroke. A bottle of the diet supplement Xenadrine RFA-1, which contains ephedra, was found in his locker. The article states that among other factors that could have contributed to the heatstroke diagnosis are that Bechler was overweight and had high blood pressure.

About a month later, *USA Today* reports that Dr. Joshua Perper, the Broward County, Florida chief medical examiner, stated that "It is my professional opinion that the toxicity of ephedra played a significant role in the death of Mr. Bechler, although it's impossible to define mathematically the contribution of each one of the risk factors" (Bodley, 2003). Cytodyne Technologies, which makes Xenadrine, told the Associated Press that Perper rushed to judgment. "The fact that the medical examiner found traces of ephedra in Mr. Bechler's system does not mean that Mr. Bechler died from ephedra. He died from heatstroke," said Shane Freedman, legal officer for the manufacturer (Bodley, 2003).

First published in 1954, *How to Lie with Statistics* (Huff, 1954) does not discuss meta-analysis, not surprisingly as the term was first used by Glass (1976). Of course, as Olkin (1996) pointed out, the process of combining research results is not new, having been part of statistical methodology since the early 1900s. Indeed, the SCEPC ephedra analysis is not primarily a meta-analysis but rather a research synthesis comparing, contrasting and calibrating conclusions from different study designs. Synthesizing information from both randomized trials and observational studies is challenging. It is also necessary, especially in complex arenas such as that of public policy. The recent example of understanding discrepant conclusions about hormone replacement therapy (Col and Pauker, 2003) has demonstrated how difficult this task is. Given these challenges, have cause and effect altogether been separated on the ephedra issue? What would Darrell Huff say?

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