Evidence Report/Technology Assessment
Number 76

Ephedra and Ephedrine for Weight Loss and Athletic Performance Enhancement: Clinical Efficacy and Side Effects

U.S. Department of Health and Human Services
Agency for Healthcare Research and Quality

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome written comments on this evidence report. They may be sent to: Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 6010 Executive Blvd., Suite 300, Rockville, MD 20852.

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Structured Abstract

Objectives. To assess the efficacy of herbal ephedra-containing dietary supplements and ephedrine on weight loss and athletic performance, through comprehensive literature review and synthesis of evidence. We also assessed safety of these products through review of adverse events reported in clinical trials, published case reports of adverse events, reports on file with the U.S. Food and Drug Administration (FDA), and a file of reports kept by a manufacturer of ephedra products, Metabolife.

Search Strategy. We searched for studies of herbal ephedra and ephedrine using the following electronic databases: Medline, EmBase, BIOSIS, Allied & Complementary Medicine Database (AMED), MANTIS, the Cochrane Controlled Clinical Trials Register Database, International Pharmaceutical Abstracts, Pascal, and SciSearch. We were able to obtain unpublished studies by posting notices in relevant journals and through contacts on our Technical Expert Panel. The FDA provided us with copies of over 1,000 adverse event reports (AERs) related to herbal ephedra and 125 adverse event reports related to ephedrine. The Metabolife files contained 18,502 cases.

Selection Criteria. Only studies of weight loss that were controlled trials of human subjects with treatment of at least eight weeks duration were accepted to assess efficacy. For assessment of athletic performance, only controlled trials of human subjects were accepted, but no minimum follow-up was specified. Reports of adverse events from controlled trials were included regardless of treatment duration. We reviewed all available reports of death, myocardial infarction (heart attack), cerebral vascular accident (stroke), seizure, and serious psychiatric illness reported to the FDA prior to September 30, 2001 and contained in their ephedra or ephedrine files, and all case reports identified in our literature search .

Data Collection and Analysis. We found 59 articles that corresponded to 52 controlled clinical trials of ephedrine or herbal ephedra for weight loss or athletic performance. Forty-four were controlled trials assessing ephedra or ephedrine for weight loss. Of these, 18 were excluded from pooled analysis because they had treatment durations of less than eight weeks. Thirteen articles corresponding to six trials were excluded for a variety of reasons. For the outcome of weight loss the effects of ephedra/ephedrine were examined in six different types of comparisons: (1) ephedrine versus placebo; (2) ephedrine plus caffeine versus placebo; (3) ephedrine plus caffeine versus ephedrine; (4) ephedrine versus other active treatment; (5) ephedra versus placebo; and (6) ephedra plus herbs containing caffeine versus placebo. Only four placebo-controlled trials assessed the combination of ephedra plus herbs containing caffeine, and only one trial assessed ephedra without herbs containing caffeine. Because of their small number and heterogeneity, eight athletic performance trials were compared and contrasted using only a narrative review and were not synthesized statistically. We also conducted a pooled meta-analysis on those adverse event symptoms that occurred frequently in the controlled trials.

In reviewing the individual adverse event reports, we searched for documentation that an adverse event had occurred, documentation that the subject had consumed ephedra within 24 hours prior to the adverse event, or a toxicological examination revealing ephedrine or one of its associated products in the blood or urine. We also sought evidence that an adequate investigation

had assessed and excluded other potential causes. Cases that met all these criteria were labeled "sentinel events." Cases that met the first two criteria but had other possible causes of the event were labeled "possible sentinel events." Classification as a sentinel event does not imply a proven cause and effect relationship. We used clinical judgment of expert clinicians to assess whether other causes had been adequately evaluated and excluded.

Main Results. *Weight Loss.* Short-term use of ephedrine, ephedrine plus caffeine, or dietary supplements containing ephedra with or without herbs containing caffeine is associated with a statistically significant increase in short-term weight loss (compared to placebo). The addition of caffeine to ephedrine is associated with a statistically significant modest increase in short-term weight loss. The observed effects on weight loss of ephedrine plus caffeine and ephedra-containing dietary supplements with or without herbs containing caffeine are approximately equivalent: a weight loss approximately two pounds per month greater than that with placebo, for up to four to six months. No studies have assessed the long-term effects of ephedrine or ephedra-containing dietary supplements on weight loss; the longest published treatment duration was six months.

Athletic Performance. The effect of herbal ephedra–containing dietary supplements on athletic performance has not been assessed. The few studies that assess the effect of ephedrine on athletic performance have included only small samples of fit individuals (young male military recruits) and have assessed its effect only on very short-term immediate performance. These data support a modest effect of ephedrine plus caffeine on very short-term athletic performance. One study reported the addition of caffeine to ephedrine is necessary to produce an effect on athletic performance. No studies have assessed the sustained use of ephedrine on performance over time.

Safety Issues. There is sufficient evidence from controlled trials to conclude that the use of ephedrine and/ or the use of ephedra-containing herbal supplements or ephedrine plus caffeine is associated with two to three times the risk of nausea, vomiting, psychiatric symptoms such as anxiety and change in mood, autonomic hyperactivity, and palpitations. The controlled trials studied relatively few people and in aggregate were insufficient to evaluate events with a risk of less than 1.0 per one thousand.

The majority of case reports are insufficiently documented to make an informed judgment about a relationship between the use of ephedrine or ephedra-containing dietary supplements and the adverse event in question. Prior ephedra consumption was associated with two deaths, three myocardial infarctions, nine cerebrovascular accidents, three seizures, and five psychiatric cases as sentinel events. Prior consumption of ephedrine was associated with three deaths, two myocardial infarctions, two cerebrovascular accidents, one seizure, and three psychiatric cases as sentinel events. We identified 43 additional cases as possible sentinel events with prior ephedra consumption and seven additional cases as possible sentinel events with prior ephedrine consumption. About half the sentinel events occurred in persons aged 30 years or younger.

Conclusions. Ephedrine, ephedrine plus caffeine, and ephedra-containing dietary supplements with or without herbs containing caffeine all promote modest amounts of weight loss over the short term. There are no data regarding long-term effects on weight loss. Single-dose ephedrine plus caffeine has a modest effect on athletic performance. The available trials do not provide any evidence about ephedrine or ephedra-containing dietary supplements, as they are used by the general population, to enhance athletic performance. Use of ephedra or ephedrine plus caffeine is

associated with an increased risk of gastrointestinal, psychiatric, and autonomic symptoms. The adverse event reports contain a sufficient number of cases of death, myocardial infarction, cerebrovascular accident, seizure, or serious psychiatric illness in young adults to warrant a hypothesis-testing study, such as a case-control study, to support or refute the hypothesis that consumption of ephedra or ephedrine may be causally related to these serious adverse events.

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Summary

Overview

At the direction of the funding agencies (the National Institutes of Health Office of Dietary Supplements (ODS), the National Center for Complementary and Alternative Medicine (NCCAM), and the Agency for Healthcare Research and Quality (AHRQ)), and in consultation with our Technical Expert Panel, we addressed research questions regarding the efficacy of herbal ephedra and ephedrine for weight loss and athletic performance through a comprehensive literature review and synthesis of evidence. We assessed the safety of these products through review of clinical trials. Meta-analysis was performed where appropriate. In addition, we reviewed herbal ephedra- and ephedrine-related adverse events reports on file with the U.S. Food and Drug Administration (FDA), published case reports, and reports to a manufacturer of ephedra-containing products. It is expected that the results of this review will be used to direct further research.

Reporting the Evidence

The following questions were provided to us by the funding agencies and guided this evidence report.

Weight Loss

1. What is the evidence for efficacy of ephedra-containing dietary supplement products in weight loss, over a sustained period of time?
2. Can efficacy for weight loss be attributed to ephedra alone, or ephedra in combination with other ingredients (e.g., caffeine)?
3. Does ephedra have additive effects with other agents?
4. What dosage levels of ephedra are necessary to achieve weight loss?

Athletic Performance

1. What is the evidence for efficacy of ephedra-containing dietary supplement products in terms of energy enhancement and enhancement of athletic performance, over a sustained period of time?
2. Can efficacy for energy enhancement and enhancement of athletic performance be attributed to ephedra alone, or ephedra in combination with other ingredients (e.g., caffeine) that produce energy enhancement and/or enhancement of athletic performance?
3. Does ephedra have additive effects with other agents?
4. What dosage levels of ephedra are necessary to achieve energy enhancement and enhancement of athletic performance?

Safety Assessment

1. Does use of ephedra-containing dietary supplement products over a sustained period of time increase the risk of cardiovascular disease (CVD) or other serious and life-threatening events in specific populations?
2. What populations are at risk of CVD and other life-threatening events through use of ephedra over a sustained period of time?
3. Can the risk for adverse events in these populations be attributed to ephedra alone, or in combination with other ingredients (e.g., caffeine)?
4. Does ephedra have additive effects with other agents?
5. What dosage levels of ephedra produce risk of CVD or other life-threatening events?

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6. Do ephedra-containing dietary supplement products alter physiologic markers of cardiovascular function?
7. What are the metabolic actions of ephedra, so as to explain its beneficial and adverse effects?

In addition to answering these 15 questions about ephedra-containing dietary supplement products, we were also asked to synthesize the available information on the same questions for the purified alkaloid, ephedrine.

After searching published reports, journal articles, conference presentations, and various sources of unpublished studies, we identified 52 controlled clinical trials of ephedrine or herbal ephedra for weight loss or athletic performance in humans. The FDA provided us with copies of over 1,000 adverse event reports (AERs) related to herbal ephedra and 125 AERs related to ephedrine. These reports often included interviews with patients and/or family members, extensive medical records, and copies of product labels. We identified 65 case reports in the literature and received a disk of 15,951 reports containing 18,502 cases from Metabolife, a manufacturer of ephedra products.

Methodology

Efficacy. Data for the efficacy analysis were abstracted from reports of controlled trials onto a specially designed form containing questions about the study design, the number of patients and comorbidities, dosage, adverse events, the types of outcome measures, and the time from intervention until outcome measurement. We selected the variables for abstraction with input from the project's technical experts. Two physicians, working independently, each extracted data from the same reports and resolved disagreements by consensus.

In selecting studies for the meta-analysis of weight loss efficacy, we considered only those trials of at least 8 weeks treatment duration. Our technical expert panel judged that shorter treatment durations were insufficient to assess weight loss. In selecting studies on athletic performance, we found that these studies varied widely with respect to intervention. Because of this heterogeneity, we compared and contrasted these studies in a narrative review, rather than performing a statistical synthesis.

The effects of ephedra/ephedrine on weight loss were examined in six different types of comparisons: (1)ephedrine versus placebo; (2) ephedrine plus caffeine versus placebo; (3) ephedrine plus caffeine versus ephedrine; (4) ephedrine versus other active treatment; (5)ephedra versus placebo; and (6) ephedra plus herbs containing caffeine versus placebo. The last comparison subgroup contained only a single trial; thus, effect sizes were estimated only for the first five. The effect size was calculated by dividing the outcome of a study (e.g., difference in weight loss per month between the two groups) by its standard deviation, which produces a unitless measure that is useful when comparing studies that assess outcomes (such as weight) that are similar but are measured differently (e.g., weight loss in pounds versus change in body mass index). Effect sizes were pooled separately for each of the five comparison subgroups. In addition, we used meta-regression to conduct a cross-subgroup synthesis on the effect sizes of the subgroups with a placebo comparison: ephedrine versus placebo; ephedrine plus caffeine versus placebo; and ephedra plus herbs containing caffeine versus placebo.

Safety. We reviewed each report of a controlled trial (regardless of treatment duration) for data on adverse events. Adverse events were recorded onto a spreadsheet that identified each study arm, the description of the adverse event as listed in the original article, and the numbers of subjects and adverse events in each arm. We then compared event rates in the ephedra or ephedrine groups to those in the placebo groups. We conducted a meta-analysis on those adverse event symptoms for which appreciable numbers of events were noted in the controlled trials.

Adverse event reports compiled by the FDA concerning ephedra or ephedrine were also reviewed by our physician reviewers. Within the time and resource constraints of this report, we reviewed all available reports of death, myocardial infarction (heart attack), cerebral vascular accident (stroke), seizure, and serious psychiatric illness filed prior to September 30, 2001. We also reviewed published case reports as well as event reports filed with Metabolife, a manufacturer of ephedra-containing products. After screening, all case reports were subjected to a review.

Based on input from our technical expert panel and the literature on methods to assess adverse event reports, we identified three important criteria for inclusion of such reports:

1. Documentation of an adverse event that met our selection criteria.
2. Documentation that the person having the adverse event took an ephedra-containing supplement or ephedrine within 24 hours prior to the event (for cases of death, myocardial infarction, stroke, or seizure).
3. Documentation that alternative explanations for the adverse event were investigated and were excluded with reasonable certainty.

We classified cases that met all three of these criteria as "sentinel events." Cases in which the event might have had other possible causes but the pharmacology of ephedrine could have contributed were classified as "possible sentinel events." Cases of death, myocardial infarction, cerebral vascular accident, and seizure were reviewed by internists, with additional review (as indicated) by a cardiologist, neurologist, or rheumatologist. Psychiatric cases were reviewed by a psychiatrist specializing in addictions and a psychologist with expertise in substance abuse. The criterion for use within 24 hours was not required for psychiatric cases.

Findings

Efficacy for Weight Loss. We identified 44 controlled trials that assessed use of ephedra or ephedrine used for weight loss. Of these, 18 were excluded from pooled analysis because they had a treatment duration of less than 8 weeks. Six additional trials were excluded for a variety of other reasons. Of the remaining 20 trials included in the meta-analysis, only five tested herbal ephedra-containing products. Together, these 20 trials assessed 678 persons who consumed either ephedra or ephedrine. The majority of studies of both ephedra and ephedrine are plagued by methodological problems (particularly, high attrition rates) that might contribute to bias. These methodological limitations must be considered when interpreting any conclusions regarding the efficacy of these products. Nevertheless, the evidence we identified and assessed supports an association between short-term use of ephedrine, ephedrine plus caffeine, or dietary supplements that contain ephedra with or without herbs containing caffeine and a statistically significant increase in short-term weight loss (compared to placebo). Adding caffeine to ephedrine modestly increases the amount of weight loss. There is no evidence that the effect of ephedra-containing dietary supplements with herbs containing caffeine differs from that of ephedrine plus caffeine: Both result in weight loss that is approximately 2 pounds per month greater than that with placebo, for up to 4 to 6 months. No studies have assessed the long-term effects of ephedra-containing dietary supplements or ephedrine on weight loss; the longest duration of treatment in a published study was 6 months.

Efficacy for Physical Performance Enhancement. The effect of ephedrine on athletic performance was assessed in seven studies. No studies have assessed the effect of herbal ephedra-containing dietary supplements on athletic performance. The few studies that assessed the effect of ephedrine on athletic performance have, in general, included only small samples of fit individuals (young male military recruits) and have assessed the effects only on very short-term immediate performance. Thus, these studies did not assess ephedrine as it is used in the general population. The data support a modest effect of ephedrine plus caffeine on very short-term athletic performance. No studies have assessed the sustained use of ephedrine on performance over time. The only study that assessed the additive effects of these agents reported that ephedrine must be supplemented with caffeine to affect athletic performance.

Safety Issues. The data on adverse events were drawn from clinical trials and case reports published in the literature, submitted to the FDA, and reported to Metabolife, a manufacturer of ephedra-containing supplement products. The strongest evidence for causality should come from clinical trials; however, in most circumstances, such trials do not enroll sufficient numbers of patients to adequately assess the possibility of rare outcomes. Such was the case with our review of ephedrine and ephedra-containing dietary supplements. Even in aggregate, the clinical trials enrolled only enough patients to detect a serious adverse event rate of at least 1.0 per 1,000. For rare outcomes, we reviewed case reports, but a causal relationship between ephedra or ephedrine use and these events cannot be assumed or proven.

Evidence from controlled trials was sufficient to conclude that the use of ephedrine and/or the use of ephedra-containing dietary supplements or ephedrine plus caffeine is associated with two to three times the risk of nausea, vomiting, psychiatric symptoms such as anxiety and change in mood, autonomic hyperactivity, and palpitations.

The majority of case reports are insufficiently documented to make an informed judgment about a relationship between the use of ephedrine or ephedra-containing dietary supplements and the adverse event in question. For prior consumption of ephedra-containing products, we identified two deaths, three myocardial infarctions, nine cerebrovascular accidents, three seizures, and five psychiatric cases as sentinel events; for prior consumption of ephedrine, we identified three deaths, two myocardial infarctions, two cerebrovascular accidents, one seizure, and three psychiatric cases as sentinel events. We identified 43 additional cases as possible sentinel events with prior ephedra consumption and seven additional cases as possible sentinel events for prior ephedrine consumption. About half the sentinel events occurred in persons aged 30 years or younger. Classification as a sentinel event does not imply a proven cause and effect relationship.

We did not assess the plethora of additional symptoms that have been reported in the published literature and the FDA Medwatch file for ephedra-containing dietary supplements and ephedrine products.

Future Research

Our analysis of the evidence reveals numerous gaps in the literature regarding the efficacy and safety of ephedra-containing dietary supplements. First, long-term assessments of the effectiveness of herbal ephedra or ephedrine for promoting weight loss are lacking. We identified no study with a treatment duration longer than 6 months. To improve health outcomes and reduce the risk of morbidities associated with being overweight, sufficient weight loss (5 to 10 percent of body weight) and long-term weight maintenance are necessary. Therefore, the benefit of ephedrine or herbal ephedra-containing dietary supplements for health outcomes is unknown.

Evidence regarding the effect of herbal ephedra or ephedrine on physical performance that reflects its use in the general population (repeated or long-term use by a representative sample) is also needed.

In order to assess a causal relationship between ephedra or ephedrine consumption and serious adverse events, a

hypothesis-testing study is needed. Continued analysis of case reports cannot substitute for a properly designed study to assess causality. A case-control study would probably be the study design of choice.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the Southern California-RAND Evidence-based Practice Center, under Contract No. 290-97-0001. It is expected to be available in March 2003. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 76, *Ephedra and Ephedrine for Weight Loss and Athletic Performance Enhancement: Clinical Efficacy and Side Effects*. . In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.

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Evidence Report

Chapter 1. Introduction

Purpose

This evidence report details the methodology, results, and conclusions of a comprehensive literature review and synthesis of evidence on the efficacy and safety of ephedra and ephedrine, either alone or in combination with other substances, to promote weight loss or to enhance athletic performance. Meta-analysis was performed where appropriate.

Scope of Work

At the direction of the funding agencies (National Institutes of Health Office of Dietary Supplements (ODS), National Centers for Complementary and Alternative Medicine (NCCAM), and Agency for Healthcare Research and Quality (AHRQ) and in consultation with our Technical Expert Panel (see Table 2, Chapter 2), we addressed research questions regarding the efficacy of herbal ephedra and synthetic ephedrine for weight loss and athletic performance. We assessed the safety of these products through review of clinical trials. In addition, we reviewed herbal ephedra-related adverse events reports on file with the U.S. Food and Drug Administration (FDA), published case reports, and reports to a manufacturer of ephedra products. It is expected that the results of this review will be used to direct further research.

In searching for evidence of efficacy and safety, we were directed to assess studies using both the isolated alkaloid, ephedrine, and whole herb or extracts of the herb ephedra.

Background

A 2000 survey by manufacturers of ephedra-containing supplement products estimated that three billion servings of these products were consumed in the prior year; these findings were revealed during testimony at a Public Meeting on the Safety of Dietary Supplements Containing Ephedrine Alkaloids held August 8, 2000. According to Michael McGuffin, an industry spokesperson, this figure represented a 65 percent increase in sales volume over the previous five years and would correspond to approximately $6.8 billion in total sales.[1] Use of ephedrine alkaloid–containing products to promote weight loss or enhance athletic performance has garnered a great deal of media attention over the last year. This attention is due in part to a number of well-publicized adverse events reportedly associated with the use of ephedra or ephedrine alkaloid–containing products.[2-7]

Herbal ephedra has been used in China to treat respiratory conditions for over 5,000 years;[8] however, the herb is not used for weight loss or physical performance enhancement in eastern medicine. Its active alkaloid, ephedrine, was first used in western medicine as an asthma treatment in the 1930s. Since then, ephedrine and other sympathomimetic alkaloids have been used in many over-the-counter (OTC) decongestants and cold medicines. It was not until the

early 1990s that herbal ephedra and other products containing ephedrine began to be promoted as weight loss aids in the United States.

Federal regulation of dietary supplement products differs considerably from that of products that are deemed drugs. Dietary supplement products, including those that contain herbal ephedra (as distinct from the purified alkaloid ephedrine), are regulated by the Dietary Supplement Health and Education Act (DSHEA) of 1994. Under DSHEA, new products that contain only supplement ingredients that were sold in the United States before October 15, 1994 do not require FDA review before they are marketed, because they are presumed to be safe based on their history of use by humans. Manufacturers of a dietary supplement that contains a new ingredient not sold as a dietary supplement before 1994 must notify FDA of their intent to market that product and must demonstrate reasonable evidence for the safety of the product to humans. In turn, FDA can bar the new ingredient from the marketplace for safety reasons. However, manufacturers are not required to perform clinical or other studies to establish the safety of their products before marketing. Once a dietary supplement is marketed, FDA can restrict its use or order its removal from the marketplace only if it can prove that the product is not safe. In contrast to the rules for dietary supplements, before a drug product can be marketed, the manufacturer must obtain FDA approval by providing convincing evidence that it is both safe and effective.

On October 11, 1995, in response to a growing number of adverse event reports submitted to the FDA about ephedra-containing products (more than 300 at the time), the FDA convened an open meeting of the Special Working Group on Food Products Containing Ephedrine Alkaloids (a working group of the Food Advisory Committee) to assess the potential public health problems associated with dietary supplements and other food products that contained botanical sources of ephedrine alkaloids (that is, ephedra). The reported adverse events involved primarily the cardiovascular and central nervous systems. Most events occurred in young to middle-aged women, often those using the products for weight loss or to increase energy. Based on the reports and the evidence they heard, the working group found sufficient evidence to suggest that adverse effects were associated with the use of ephedrine alkaloids, that safe levels should be established and that warning labels should appear on products containing the ephedrine alkaloids, regardless of their source.

In August 1996, the FDA convened a meeting of its Food Advisory Committee to continue the discussion of the safety of ephedrine alkaloid–containing foods and supplements. By that time, the number of adverse events reported to the FDA had doubled from the year before to over 600. As a result of that meeting, some members recommended removal of dietary supplements containing ephedra from the market.[9] Other members suggested that the FDA develop rules on use that would help reduce the risk of adverse events. In 1997, the FDA published a proposed rule on use of dietary supplements containing ephedrine alkaloids. It proposed a dose limit of 8 mg ephedrine alkaloid per serving, a daily limit of 24 mg, a duration limit of 7 days, and various label warnings. After the rule was published in the Federal Register, the FDA received a large number of comments from consumers, physicians, scientists, and supplement manufacturers. In response, the General Accounting Office (GAO) audited the methods used by the FDA to develop the proposed rules. In July 1999, the GAO reported that the FDA had insufficient

evidence to support dosage and duration limits. As a result, in early 2000, the FDA withdrew a large part of the 1997 proposal.

However, the controversy over ephedra has continued. From 2000 to 2002, more than 100 people sued makers of ephedra products,[7] and from 1992 through 2002, more than 1000 health problems were reported to FDA. These reports led a nonprofit consumer group, Public Citizen, to file a lengthy petition in 2001, asking the FDA to ban the production and sale of ephedra products. In the fall of 2001, the National Football League banned the substance following the deaths of several high school and college athletes after alleged use of ephedrine-containing products, and in January 2002, the Canadian government issued a warning against use of ephedra.

On June 14, 2002, the U.S. Department of Health and Human Services proposed an expanded scientific evaluation of ephedra. The agenda for that research will be based on the findings of the current report.

The Problem of Obesity

From 1999 through 2002, the prevalence of obesity in the United States increased by 1 percent per year, reaching a level of 19.8 percent among the adult population. This increase represents a 65 percent rise in the prevalence of obesity from 1991 to 2002 (from 12 percent to 19.8 percent), although a precise comparison is difficult because of changing definitions of obesity.[10-12] Obesity is currently defined as a body mass index of 30 or greater: BMI is obtained by dividing body weight (in kilograms) by the height (in meters) squared. Overweight individuals are those whose BMI falls between 25 and 29.9. According to that definition, by the year 2000, the majority of Americans (56 percent) were overweight.[10] Moreover, according to the 1999 National Health and Nutrition Examination Survey (NHANES), 13 percent of children and adolescents are currently seriously overweight and are displaying increasing rates of obesity-related chronic diseases such as Type II diabetes, not previously seen in children.[13] Attempts to meet the body weight goal of the Healthy People 2000 Initiative[14] (reducing the prevalence of overweight among adults to less than 20 percent of the population) have failed.

The United States is not alone is facing rising rates of obesity. In Canada, between 1985 and 1998, the overall prevalence of obesity increased in adults from 5.6 percent to 14.8 percent and from 1981 to 1996, it tripled in children.[15, 16] The World Health Organization reports that there are more than 300 million obese people in the world, and the rising rate of obesity is no longer solely a problem of industrialized countries, but one that is rapidly appearing in developing countries.[17, 18]

In addition to Type 2 diabetes, other serious health risks are associated with obesity. Rates and severity of hypertension, dyslipidemia, insulin resistance (Syndrome X), coronary artery disease, stroke, sleep apnea, osteoarthritis, certain cancers, and other conditions increase with increasing weight.[19, 20] Further, obesity increases the rate of mortality as well as morbidity, especially mortality associated with heart disease and diabetes.[21] Using data from five large prospective cohorts, Allison and colleagues estimated that in 1991, 280,000 deaths were attributable to excess weight.[22] Patients with a BMI greater than 30 accounted for more than 80 percent of the obesity-attributable deaths.

The costs of obesity to the health care system are large and growing with the increasing rates of obesity. In 1986, when only 34 million Americans were clinically obese, a conservative estimate of the economic costs related to obesity was $39.3 billion.[23] By 1995, one study[24] estimated direct cost for obesity at $70 billion, although another study estimated these costs at 25 percent lower.[25] The costs of obesity are estimated to be higher than those for either smoking or excessive drinking.[26]

Intentional weight loss by obese persons leads to reductions in risk factors for disease. A minimum loss of 5 percent to 10 percent of body weight followed by long-term weight maintenance can improve health outcomes.[27] Despite this finding, only 42 percent of obese people surveyed by Galuska and colleagues reported that their doctor recommended weight loss.[28, 29] Still, much of the population reports that they are actively trying to lose weight: a 2000 survey showed that one third (38 percent) of subjects were actively trying to lose weight and another third (36 percent) were trying to maintain their weight.[11] Furthermore, among those who were overweight, 45 percent of subjects were actively trying to lose weight, and 35 percent were trying to maintain their weight. Among those who were obese, 66 percent of subjects were actively trying to lose weight, and 21 percent were trying to maintain their weight.[11] In a population-based study of 14,679 U.S. adults in 5 states using the 1998 BRFSS data, seven percent reported using nonprescription weight loss products; 2 percent reported using phenylpropanolamine and one percent reported using ephedra products from 1996 to 1998. More women used ephedra products than men; 1.6 percent of women and 0.4 percent of men reported using weight loss products containing ephedra. Extrapolated nationally, this study estimated that during 1996–1998, 2.5 million Americans used weight loss products containing ephedra. This study also has data to suggest that many individuals are not aware they are taking weight loss products that contain ephedra. Of the 183 respondents in Michigan who responded to the questions about using ephedra and reported that they took "other" nonprescription weight loss products, 33 percent reported using name-brand products that claim to contain both ephedra products and chromium picolinate.[30]

This estimate of use of ephedra-containing products may be low. Heber and Greenway state that the most widely used herbal products for weight loss contain ephedrine alkaloids.[31] Among 230 (61 percent) of 376 adults in the St. Paul/Minneapolis area who reported using an herbal product during the past 12 months, 44 (19 percent) used ephedra. Of these 44, 20 (45 percent) used ephedra for weight loss. Therefore, 5.3 percent of these adults (20 of 376) reported using ephedra for weight loss.[32]

Enhancing Physical Performance

Stimulants have a long history of use in athletic performance, dating back to the early 1900s.[33] Several serious accidents in the late 1960s, including the death of a cyclist using amphetamines, spurred the International Olympic Committee (IOC) to ban stimulants from use during competition. However, this ban was not fully enforceable until a reliable screening test became available in 1972.[34] Use of OTC stimulants is regulated somewhat differently than that of stimulants available only by prescription, because OTC stimulants are widely available in products used to treat common conditions such as colds or congestion. Therefore, these

compounds are not banned outright, but athletes whose use of these substances exceeds some reporting threshold are subject to censure.[34]

Use of dietary supplements by athletes is common and somewhat more frequent than that of the general public. In a review of 51 studies, Sobal and Marquart[35] found that 56 percent of athletes used one or more supplements. Another study of college athletes reports a 42 percent prevalence of supplement use.[36] Supplement use was higher among men than among women, and higher among elite athletes and in particular sports such as body building, weight lifting, and ultramarathon running.[35] A survey among elite Australian swimmers supports this finding: 94 percent of them reported using dietary supplements. All participants reported using vitamins and/or minerals, and 61 percent reported using herbal preparations.[37] Supplement use is prevalent even among younger athletes: 20 to 25 percent of adolescents are reportedly using supplements. For all athletes, performance enhancement is cited as a common reason for use, and multi-vitamins are the most frequently used dietary supplements.[35]

OTC stimulants, particularly ephedrine or its related alkaloids, are among the substances most frequently detected on drug screens or reported in surveys. In a series of 1,256 positive drug screens identified by IOC laboratories in 1989, 40 percent involved stimulants. Ephedrine alkaloids accounted for 75 percent of the stimulants reported.[38] Evaluation of drug use by student athletes in the most recent National Collegiate Athletic Association (NCAA) survey (2001) showed that ephedrine and amphetamine use increased from 1997 to 2001, at a time when use of many other substances was declining.[39] Ephedrine was used by 3.5 percent of responders in 1997, a figure that increased to 3.9 percent by 2001. In a survey of 511 subjects attending a gymnasium, self-reported use of ephedrine exceeded that of anabolic steroids (25 percent versus 18 percent for men; 13 percent versus 3 percent for women).[40] The authors asserted that extrapolating these figures to the general public would suggest that 2.8 million people have used ephedrine-containing products to improve athletic performance within the last three years. Further, there may be a subset of committed users of ephedrine products who take high doses for extended periods of time. Gruber and Pope[41] reported on a cohort of female weightlifters, 56 percent of whom were using doses of 120 mg ephedrine daily for over one year. Some individuals had been using such doses continuously for over five years, and the majority of these women continued to use ephedrine despite the presence of adverse symptoms.

History and Pharmacology

Ephedra species have a long history of medicinal use, documented in medical treatises from China and India. Some experts have called it the oldest medicinal plant in continuous use:[42] A species of ephedra was found in a Neanderthal grave and was presumably used medicinally.[43] Use by Dioscorides, the famous Hellenistic herbalist, has been documented, as has use in Europe from the 15th to the 19th centuries.[44] Use of ephedrine, the principal alkaloid in ephedra, gained notoriety during modern times when it was learned that the drug was given parenterally to Japanese kamikaze pilots during World War II.[45] Over 40 species of ephedra are found throughout Asia, Europe, and the Mediterranean area, as well in North and South America.

Botany

Ephedra, or ma huang, is the common name for any one of three species grown medicinally in China and recognized in the Chinese Materia Medica: *Ephedra sinica*, *Ephedra equisentina* and *Ephedra intermedia*.[46]

The branches of this small twiggy shrub have been used in the practice of traditional Chinese medicine to treat colds, fevers, and wheezing and as a diaphoretic and diuretic.[47] Botanically related species have also been used in traditional Indian and Tibetan medicine for similar indications.[48] In the modern discipline of phytomedicine, ephedra has been approved by the German Commission E to treat diseases of the respiratory tract with mild bronchospasm in patients over 6 years of age.[49] In addition to the three species mentioned above, others, such as *Ephedra distachya* or *Ephedra gerardiana* may be used for preparation of commercial products.[49] North American ephedra species, such as *Ephedra nevadensis,* commonly known as mormon tea, reportedly contain little or no ephedrine.[50, 51]

Phytochemistry

The active components of ephedra (about 1.32 percent by weight) are the phenylalanine-derived alkaloids such as (-)-ephedrine, (+)-pseudoephedrine, (-)-norephedrine, and (+)-norpseudoephedrine, which is also called cathine.[45, 52] Alkaloid content and composition may vary based on species and growing conditions such as geographic location, altitude, and soil pH.[53-56] Ephedra is harvested in the fall, when the alkaloid content is highest.[57] Even though the total alkaloid content can vary from 0.5 percent to 2.3 percent, ephedrine accounts for the majority of the alkaloids (up to 90 percent of total), followed by pseudoephedrine (generally up to 27 percent of total).[45, 58, 59] One species of ephedra, *Ephedra intermedia*, has been reported to have reversed ratios of ephedrine to pseudoephedrine, with approximately 30 percent ephedrine and up to 75 percent pseudoephedrine.[57, 60] Norephedrine content is generally very low in commercial ephedra species.[60] Ratios of the most common alkaloids vary in commercial preparations, but ephedrine and pseudoephedrine account for 90 to 100 percent of the alkaloids measured.[61] The relative potency of the alkaloids is discussed below.

Pharmacology of Ephedrine/ Ephedra

Although ephedrine was first isolated from ma huang in 1887, it was not until early in the twentieth century that the pharmacology of ephedrine and its related alkaloids was considered by Western medicine.[44, 62-64] Ephedrine is defined as a mixed sympathomimetic agent, which acts indirectly by enhancing the release of norepinephrine from sympathetic neurons and directly by stimulating alpha and beta adrenergic receptors.[65] The other, related, alkaloids have similar activities, although they are less potent than ephedrine.[62] Thus, the pharmacologic activity of a given ephedra sample depends on its alkaloid composition.

In the cardiovascular system, ephedrine increases heart rate and therefore cardiac output.[65, 66] Because of its peripheral vasoconstriction activity, ephedrine increases peripheral resistance and can lead to a sustained rise in blood pressure. As a result, parenteral ephedrine has been used to treat shock and hypotension associated with cesarean section. Elevations in blood pressure appear to be dose dependent in humans.[67] However, there appears to be a threshold effect: doses under 50 mg do not necessarily result in increased blood pressure.

In the lung, ephedrine acts via the beta (2) adrenergic receptors to relax bronchial smooth muscle.[65, 66] However, ephedrine's use as a bronchodilator (which began in 1924),[63] has largely been supplanted by more selective agents for chronic use. Currently, ephedrine is used as a decongestant and for the temporary relief of shortness of breath due to bronchial asthma.

Because of its lipid solubility, ephedrine crosses the blood-brain barrier where it acts as a central nervous system stimulant.[65, 66] Immediate effects are attributable to stimulation of dopamine release, but ephedrine also acts on central adrenergic receptors, which increases release of central norepinephrine. This combination of adrenergic and dopaminergic effects leads, in the short term, to improved mood and heightened alertness with decreased fatigue and desire for sleep. Physical activity also increases. Concern exists that because of its chemical similarity to amphetamines, ephedrine may have potential for abuse. Ephedrine has demonstrated reinforcing effects in humans that are similar to those of amphetamines but not as strong.[68] At higher doses, the release of norepinephrine causes anxiety, restlessness, and insomnia.

Ephedrine and its alkaloids may promote weight loss via several mechanisms. First, ephedrine may exert an anorexic effect via central effects of norepinephrine on satiety centers in the hypothalamus.[69] Second, stimulation of beta (3) receptors in brown fat, via release of catecholamines, leads to increased lipogenesis.[70] Third, of the three principal alkaloids of ephedra (ephedrine, pseudoephedrine, and phenylpropanolamine), ephedrine is the most potent thermogenic agent (a substance that increases the portion of ingested calories that are dissipated as heat, at the expense of energy storage).

Pharmacokinetics

Ephedrine is readily absorbed from the gastrointestinal tract, with peak concentrations of an oral, immediate-release dose achieved at approximately two to three hours.[71-73] It is distributed widely throughout the body, crossing the blood-brain barrier, as mentioned above, as well as the placenta. The half-life of ephedrine in the blood (the time required to reach half the peak concentration) is six hours.[73] Metabolism does occur in the liver, but the majority of ephedrine (60–97 percent) is excreted unchanged via the urine.[74, 75] The pharmacokinetics of pseudoephedrine and phenylpropanolamine (norephedrine) are similar.[73]

The disposition of a pharmaceutical preparation of ephedrine (25 mg) in ten healthy volunteers was compared with that of three botanical preparations that contained a roughly equivalent alkaloid dose.[76] Among the four products tested, the time to achieve peak concentration ranged from 2.61 to 3.05 hours, and the elimination half-life (time that was required for half of the ingested product to be eliminated) varied from 4.85 to 6.47 hours. None of the botanical preparations tested was found to have statistically different pharmacokinetics from the purified ephedrine. These results are not completely confirmed by a second study, which compared purified ephedrine with a botanical preparation.[77] This study found that the absorption of the botanical preparation was slower and took almost twice as long as the pharmaceutical preparation to reach maximal concentration (3.90 versus 1.69 hours). However, maximal concentration of ephedrine was actually higher for the botanical preparation. Elimination half-life was between five and six hours for both preparations.

Combination Formulas Used for Weight Loss

Pharmaceutical preparations of ephedrine for weight loss often include caffeine and/or aspirin. Caffeine alone has been shown to stimulate thermogenesis and weight loss, both as an isolated alkaloid and as a botanical tea.[67, 78, 79] Further, caffeine potentiates the thermogenic effects of ephedrine by acting as an adenosine receptor antagonist and inhibiting cellular phosphodiesterase activity.[80, 81] Botanical preparations often mimic these combined formulations by including caffeine- or salicylic acid–containing herbs or those that contain sympathomimetic amines such as *Sida cordifolia* (country mallow) or *Citrus aurantium* (bitter orange) (see Table 1). Other herbs frequently included in botanical weight loss formulas include those with diuretic or laxative actions.

Chapter 2. Methods

Original Proposed Key Questions

The topic of this report was nominated by the National Institutes of Health (NIH) Office of Dietary Supplements (ODS). The following questions were originally proposed:

Weight Loss

1. *What is the evidence for efficacy of ephedra-containing dietary supplement products for weight loss, over a sustained period of time?*
2. *Can efficacy for weight loss be attributed to ephedra alone, or ephedra in combination with other ingredients (e.g., caffeine)?*
3. *Does ephedra have additive effects with other agents?*
4. *What dosage levels of ephedra are necessary to achieve weight loss?*

Athletic Performance

1. *What is the evidence for efficacy of ephedra-containing dietary supplement products in terms of energy enhancement and enhancement of athletic performance, over a sustained period of time?*
2. *Can efficacy for energy enhancement and enhancement of athletic performance be attributed to ephedra alone, or ephedra in combination with other ingredients (e.g., caffeine) that produces energy enhancement and/or enhancement of athletic performance?*
3. *Does ephedra have additive effects with other agents?*
4. *What dosage levels of ephedra are necessary to achieve energy enhancement and enhancement of athletic performance?*

Safety Assessment

1. *Does use of ephedra-containing dietary supplement products over a sustained period of time increase the risk of cardiovascular disease (CVD) or other serious and life-threatening events in specific populations?*
2. *What populations are at risk of CVD and other life-threatening events through use of ephedra over a sustained period of time?*
3. *Can the risk for adverse events in these populations be attributed to ephedra alone, or in combination with other ingredients (e.g., caffeine)?*
4. *Does ephedra have additive effects with other agents?*
5. *What dosage levels of ephedra produce risk of CVD or other life-threatening events?*
6. *Do ephedra-containing dietary supplement products alter physiologic markers of cardiovascular function?*
7. *What are the metabolic actions of ephedra, so as to explain its beneficial and adverse effects?*

In addition to the questions related to ephedra-containing dietary supplement products, the sponsor also requested a review of the scientific literature on ephedrine (the purified alkaloid) regarding its efficacy and safety. A brief review of the mechanism of action of ephedra was also requested.

We were also asked about the gaps in knowledge about the effects of ephedra, alone or in combination with other agents, on weight loss, energy enhancement, and enhancement of athletic performance. We were asked to focus on the following categories of potential consumers: children, adolescents, young athletes (male and female), and adults (male and female).

Technical Expert Panel

Each AHRQ evidence report is guided by a Technical Expert Panel (TEP). We invited a distinguished group of basic scientists and clinicians, including individuals with expertise in cardiac electrophysiology, exercise, herbs, obesity and human nutrition, pharmacognosy (the study of developing drugs from plant and animal sources), pharmacology, and toxicology. Panel members are listed in Table 2.

Our expert panel meeting was held at RAND's Arlington, Virginia, office on Wednesday, November 28, 2001. Margaret Coopey, the Task Order Officer, represented AHRQ. Dr. Paul Coates, head of the NIH ODS, also attended. At the meeting, we discussed the focus of the report. The TEP agreed that we should review articles that discuss either ephedra or ephedrine. Studies or case reports on pseudoephedrine were not to be reviewed, except in the context of ephedra/ephedrine. We agreed to include a brief description of the other alkaloids (pseudoephedrine, norephedrine, etc.) in the introduction to our report.

The TEP also provided a number of suggestions regarding data collection. These suggestions are shown in Table 3.

Assessment of Adverse Events

With regard to adverse events, EPC staff and the TEP recognized that, even in aggregate, the number of patients included in randomized trials was likely to be too few to allow adequate statistical power to assess the rate of serious adverse events (such as death, myocardial infarction, stroke, or seizure) due to ephedra. Because of this likelihood, the EPC staff recognized the necessity of relying on case reports to help inform the sponsor regarding the key questions concerning serious adverse events. A long discussion occurred at the TEP meeting about criteria for assessing causality based on case reports. The framework for this discussion was based on an unpublished article by Cynthia Mulrow, MD (C. Mulrow, personal communication). This paper summarized the criteria used in all of the major published algorithms for establishing different levels of causality in case reports of adverse events from drugs (see Table 4). Our TEP judged that, to establish definite causality from case reports, a "de-challenge/re-challenge" test needed to be performed (that is, it had to be documented that the adverse event in question went away when the offending drug was withdrawn and reoccurred when the offending drug was reinstated). Clearly, such a de-challenge/re-challenge was not possible or feasible in the case of serious adverse events such as death or myocardial infarction.

Consequently, our TEP judged that case reports alone would be insufficient to establish definite causality between ephedra use and serious adverse events. The TEP discussed the key characteristics of a case report that would signal the need for additional study. Such characteristics would include the following:

- Documentation (preferably medical) that the adverse event occurred.

- Documentation that the patient took ephedra and that the dose and timing were consistent with the known pharmacology of ephedrine (for cases of death, myocardial infarction, stroke, or seizure). (The TEP later quantified this characteristic for acute events such as stroke or myocardial infarction to mean a dose preferably within six hours of the adverse event and in no cases greater than 24 hours before the adverse event.)

- Performance of an evaluation sufficient to rule out other potential causes for the adverse event.

The TEP and EPC staff discussed extensively the types of information necessary to satisfy this last criterion. The TEP agreed that the absence of data could not be construed as a negative result. For example, the absence of information about prior cardiac disease could not be construed as an absence of cardiac disease. Furthermore, the TEP emphasized that verbal histories indicating no prior history of serious conditions were not sufficient to rule out alternative explanations for the most serious adverse events, since unrecognized preexisting cardiac disease, congenital abnormalities, berry aneurysms in the cerebral circulation, and other such conditions occur with some frequency and are known to cause death, myocardial infarction, or stroke without warning in otherwise "healthy" individuals. Realizing that it would be very difficult to attempt to define all of the possible evaluations and interpretation of results in the abstract, the TEP left it to EPC staff to resolve these issues, guided by the three characteristics listed above.

Literature Search

Our search for controlled human studies of the effects of ephedra and ephedrine began with an electronic search of library databases in April 2001. Tables 5 and 6 show our specific search strategies. We started with Medline, which is maintained by the U.S. National Library of Medicine and is widely recognized as the premier source for bibliographic coverage of biomedical literature. It encompasses information from Index Medicus, the Index to Dental Literature, and the Cumulative Index to Nursing and Allied Health Literature (allied health includes occupational therapy, speech therapy, and rehabilitation), as well as other sources of coverage in the areas of health care organization, biological and physical sciences, humanities, and information science as they relate to medicine and health care. We also searched EMBASE, the Excerpta Medica database produced by Elsevier Science, which is a major biomedical and pharmaceutical database indexing over 3,800 international journals. EMBASE currently contains over six million records, with more than 400,000 citations and abstracts added annually. We also searched BIOSIS, the most complete database for the life sciences; the Allied & Complementary Medicine Database (AMED); the Manual Alternative and Natural Therapy Index System

(MANTIS), which is the largest index of peer-reviewed articles in the area of complementary and alternative forms of therapy; and the Cochrane Controlled Clinical Trials Register Database. AMED is produced by the Health Care Information Service library in the United Kingdom. It covers journals in allied health professions as well as complementary and alternative medicine. Similarly, MANTIS covers manual, alternative, and natural therapy. The Cochrane Collaboration is an international organization that helps people make well-informed decisions about health care by preparing, maintaining, and promoting the accessibility of systematic reviews on the effects of heath care interventions. The Cochrane Register of Controlled Trials is available on CD-ROM by subscription.

Our TEP then suggested that we search three additional databases: the International Pharmaceutical Abstracts; Pascal (produced by the Institut de l'Information Scientifique et Technique (INIST) of the French National Research Council (CNRS), whose subject areas include physics, chemistry, biology, medicine, psychology, applied sciences, technology, earth sciences, and information sciences); and SciSearch. SciSearch contains all records published in Science Citation Index and additional records from about 1,000 journals whose table of contents pages are listed and indexed in the weekly Current Contents publications. Every subject area within the broad fields of science, technology, and biomedicine is included. Mary Hardy, MD, and Margaret Maglione, MPP, reviewed a total of 1,780 retrieved titles. Of those, 452 articles were deemed relevant to our undertaking and were ordered. Thirty-four additional articles were found through mining reference lists, and 64 were contributed by the TEP or AHRQ. We reviewed the reference list of every retrieved article for additional literature we might have missed and ordered any we found. Literature was tracked using ProCite and Access software.

Additional Sources of Evidence

We obtained the report "Safety Assessment and Determination of a Tolerable Upper Limit for Ephedra," published in December 2000 by CANTOX Health Sciences and funded by the Council for Responsible Nutrition, an association of dietary supplement manufacturers. We ordered copies of all literature cited in this report. We also obtained transcripts of a public meeting, held in Washington, DC on August 8 and 9, 2000 and sponsored by the HHS Office on Women's Health, on the safety of dietary supplements containing ephedrine alkaloids. We contracted with physicians proficient in Japanese and Chinese to search for scientific literature in their native languages. These searches identified little on the use of ephedra for weight loss and exercise enhancement because ephedra is not used in that manner in Eastern cultures. In addition, we found nothing about ephedra on Phytonet, a European database. We also contacted Baptist University, Hong Kong, which has a database on herbal medicine, as well as the Taiwan Poison Control Center, but did not receive any data from either.

On January 31, 2002, we spoke to Dr. Phillip Waddington, Director of the Natural Health Products Directorate for Health Canada. He agreed to send us 60 adverse event reports regarding ephedra/ephedrine products. However, at the time of this report, we had not received anything.

In January 2002, we created an announcement regarding our project's need for any unpublished studies on the use of ephedra/ephedrine for weight loss or exercise enhancement. The announcement was submitted to both the journal *Phytomedicine* and the *Herbalgram* newsletter. The intent was to reach individuals who might know of small studies being done on

ephedra or ephedrine of which the TEP were not aware. We receive no responses to this announcement.

In March 2002, we obtained a recent monograph on ephedra, written by Dennis McKenna, from the Institute for Natural Products Research, a nonprofit research and education foundation.

Finally, Wes Seigner, an attorney for the Ephedra Education Council in Washington, D.C., agreed to send us unpublished industry studies. We developed a confidentiality agreement, and Mr. Seigner sent us several reports on then-unpublished controlled trials conducted by members of the council.

Article Review

We reviewed the articles retrieved from the various sources against our exclusion criteria to determine whether to include them in the evidence synthesis. A one-page screening review form (checklist) that contains a series of yes/no questions was created to track the articles (Figure 1). After being evaluated against this checklist, each article was either accepted for further review or rejected. Two physicians and a policy analyst, each trained in the critical analysis of scientific literature, independently reviewed each study, abstracted data, and resolved disagreements by consensus. The principal investigator resolved any disagreements that remained unresolved after discussions among the reviewers. Project staff entered data from the checklists into an electronic database that was used to track all studies through the screening process.

To be accepted for analysis, studies had to be controlled clinical trials according to the following definitions:

Randomized controlled trial (RCT). A trial in which the participants (or other units) are definitely assigned prospectively to one of two (or more) alternative forms of health care, using a process of random allocation (e.g., random number generation, coin flips).

Controlled clinical trial (CCT). A trial in which participants (or other units) are either:

> (a) Definitely assigned prospectively to one of two (or more) alternative forms of health care using a quasi-random allocation method (e.g., alternation, date of birth, patient identifier)
> OR
> (b) Possibly assigned prospectively to one of two (or more) alternative forms of health care using a process of random or quasi-random allocation.

Extraction of Study-Level Variables and Results

We abstracted data from the articles that passed our screening criteria onto a specialized Quality Review Form (QRF—see Figure 2). The form contains questions about the study design, the number of patients and comorbidities, dosage, adverse events, the types of outcome measures, and the time from intervention until outcome measurement. We selected the variables for abstraction with input from the project's TEP. Two physicians, working independently, each

extracted data from the same articles and resolved disagreements by consensus. A senior physician resolved any disagreements not resolved by consensus.

To evaluate the quality of the studies, we collected information on the study design, withdrawal/dropout rate, method of random assignment (and blinding), and method for concealment of allocation (the attempt to prevent selection bias by concealing the assignment sequence prior to allocation). We also calculated the percentage of attrition by dividing the number of persons who dropped out of the trial (i.e., the number of people who entered the trial minus the number who completed the trial) by the number of persons entering the trial. The elements of design and execution (randomization, blinding, and withdrawals) have been aggregated into a summary score developed by Jadad.[82] The Jadad score rates studies on a 0 to 5 scale, based on the answer to three questions:

- Was the study randomized?
- Was the study described as double-blind?
- Was there a description of withdrawals and dropouts?

One point is awarded for each "yes" answer, and no points are given for a "no" answer. Additional points are awarded if the randomization method and method of blinding were described and were appropriate. A point is deducted if the method is described but is not appropriate. Empirical evidence has shown that studies scoring 2 or less show larger apparent differences between treatment groups than do studies scoring 3 or more.[83]

Meta-Analysis

Selection of Trials for Meta-Analysis

In selecting trials for the meta-analysis of weight loss, we considered all weight loss trials that included a treatment duration of at least eight weeks. Our TEP suggested that shorter treatment durations were insufficient to assess long-term weight loss. Trials on athletic performance encompassed a wide variety of interventions. Because of this heterogeneity, we compared and contrasted athletic performance studies in a narrative review and did not perform a meta-analysis. This section focuses on methods used for the meta-analysis of the weight-loss trials.

Trial Inclusion

The available weight loss trials were judged to be sufficiently clinically homogeneous to support a pooled analysis. For some trials, several publications presented the same outcome data. In these cases, we picked the most informative of the duplicates; for example, if one publication was a conference abstract with preliminary data and the second was a full journal article, we chose the latter. The publications dropped for duplicate data do not appear in the evidence table but are noted in the text of Chapter 3, Results. We note that multiple citations of the same article were removed at the title screening stage of the project.

Based on input from our TEP, we chose weight loss as the most clinically relevant outcome for the included trials. In order for a trial to be included in the analysis, the associated publication

had to report on weight loss as an outcome, provide data prior to the crossover point if the trial was a crossover design, and contain sufficient statistical information for the calculation of an effect size. We calculated an effect size for every comparison of interest, e.g., ephedra versus placebo, at each relevant follow-up time-point, as described below. The effect size is calculated by dividing the difference between the weight loss in the treatment group and the weight loss in the placebo group by its standard deviation. The effect size is a unitless measure that is useful when comparing trials assessing outcomes that are similar (such as weight loss) but are measured in different ways (pounds versus body mass index). We synthesized effect sizes within comparison and follow-up subgroups. The percentage of weight lost, compared to pretreatment weight, is another clinically relevant outcome. However, we did not choose this outcome for our primary analysis for two reasons. First, pooling percentage of weight loss within a treatment group (e.g., an ephedra group) eliminates the placebo comparison from the trial and therefore does not make use of the strength of the randomized controlled design. Comparison of the treatment group to the placebo group within a trial utilizes the full strength of a randomized controlled trial, as patients who are similar in all aspects except treatment assignment are compared to each other. Thus, if one wanted to perform an analysis of weight loss percentage, we would advise pooling the difference in weight loss percentage between the treatment and placebo groups. The second, and more important, reason for not performing an analysis of weight loss percentage, regardless of whether the internal placebo comparison is made, is lack of data. The vast majority of trials did not report percentage of weight loss as an outcome. As a result, we would have had to make two assumptions in our calculations. First, to estimate mean percentage weight loss for a group in a trial, we took the ratio of mean weight loss between baseline and follow-up divided by mean baseline weight. The mean of a set of ratios does not equal the ratio of the means, but this would have been the best estimate we could obtain. Second, to estimate the standard deviation of our ratio, we would have had to use the delta method to approximate the standard deviation and furthermore would have had to estimate the correlation between the baseline and follow-up weights to be 0.5. We are unable to check either of these assumptions. In contrast, the vast majority of trials did report weight loss as an outcome, and also presented the standard deviation of this statistic. Hence, weight loss became our primary outcome for analysis.

Stratification of Interventions

The literature included 6 different types of comparisons: (1) ephedrine versus placebo; (2) ephedrine plus caffeine versus placebo; (3) ephedrine plus caffeine versus ephedrine; (4) ephedrine versus other active treatment; (5) ephedra versus placebo; and (6) ephedra plus herbs containing caffeine versus placebo. Only one trial compared the effect of ephedra alone versus placebo. If a trial had other treatment arms such as caffeine only, we dropped those arms from our analysis. Effect sizes were pooled separately within each comparison subgroup. In addition, a cross-subgroup synthesis using meta-regression was conducted on the ephedrine versus placebo; ephedrine plus caffeine versus placebo; and ephedra plus herbs containing caffeine versus placebo effect sizes as well as a direct within-study comparison for those few studies that presented data for more than one comparison, as described below.

Weight Loss Effect Size

For each trial, we calculated effect sizes for any of the six comparisons of interest for which the study provided data. The majority of trials included only one comparison—between a single treatment (e.g., ephedrine) arm and placebo. One trial[84] included both an ephedrine plus caffeine plus aspirin arm and an ephedrine plus caffeine arm. However, we combined these arms into a single ephedrine plus caffeine arm, based on the clinical reasoning that aspirin has relatively little effect on weight loss.

Nevertheless, a small number of trials contained more than one relevant comparison between arms and thus contributed more than one effect size to be considered for analysis. Double-counting patients is a concern if a trial contributed more than one effect size to an analysis, and patients were included more than once in calculating those effect sizes. For example, if a trial had one placebo arm, an ephedrine arm, and an ephedrine plus caffeine arm, it contributed two effect sizes, both based on the same placebo patients. Fortunately we encountered relatively few instances of double-counting of patients within the analyses. One trial[85] included two ephedrine doses and a placebo arm and thus contributed two ephedrine versus placebo effect sizes, that is, two effect sizes within a single comparison group.

Four trials[84, 86-88] contributed effect sizes in more than one of the six comparison groups. Since we conducted the comparison group analyses separately, the four latter trials do not double-count patients within comparison group analysis. We discuss the possible influence of multiple effect sizes per study on the meta-regression analysis below.

For each trial, we extracted the means and standard deviations of weight loss between baseline and the relevant follow-up times for each arm, if available. For example, if a trial with placebo and ephedra arms reported follow-up data at two months, we extracted the means and standard deviations of weight loss at two months for the ephedra and placebo arms. If trials did not report a weight loss mean for any arm, or this mean could not be calculated from the given data, the trial was excluded from the meta-analysis.

We initially considered four separate treatment duration measurement times: two months, three months, four months, and six months. However, only one ephedra trial[89] and two ephedrine plus caffeine trials[89, 90] reported an outcome measure for a treatment duration of six months. These numbers are too small to perform a separate pooled analysis on six-month outcomes. Thus, we considered three treatment durations: The two-month duration of treatment included only outcomes for 8 weeks of treatment. However, for the analysis of three-month treatment durations, we included data collected anytime between 12 and 15 weeks, and for the four-month analysis, we included data collected between 18 and 24 weeks. We also analyzed the rate of monthly weight loss, as described below.

The large majority of included trials reported weight loss in kilograms; some trials reported weight loss in pounds. Since an effect size is unitless, data expressed in either unit of measure could be extracted for analysis. One trial[91] reported weight loss only in terms of body mass index (BMI). Because this measure involves both height and weight, we first transformed the study data to kilograms by assuming an average height of 68 inches (within a range of reasonable values, the height that was chosen made little difference in the results).

As mentioned above, for each arm in each included trial, we also calculated the mean monthly weight loss by dividing by the number of months of treatment. Thus, using our previous example, we calculated the mean monthly weight loss for the placebo and ephedra arms respectively by dividing the associated two-month mean weight loss by two. For those trials that had more than one treatment duration time, we used the longest treatment duration time data to calculate the monthly weight loss. We extracted both weight loss at specific time points (e.g., two, three, and four months) and monthly weight loss to compare the results for both types of outcomes. This comparison allows us to check trends in weight loss, for example, whether weight loss is linear or dampens over time. Using meta-regression, we verified that weight loss was linear over the range of time for which data were available by comparing pooled monthly weight loss rates based on the two-month, three-month, and four-month data separately in each comparison group. Thus, our primary analysis focuses on monthly weight loss. We note that the included trials had relatively short-term follow-up; thus, our results address only short-term weight loss and should not be extrapolated beyond four months.

If a trial reported a standard deviation of weight loss at a relevant follow-up time, we extracted those data and used them to calculate the standard deviation of the monthly weight loss. Eight trials[84, 87, 88, 92-96] failed to report a standard deviation for weight loss at a given follow-up time, or a standard deviation could not be calculated from the given data. For these trials, we imputed the standard deviation of the monthly weight loss by using those trials and arms that did report a standard deviation. We averaged the monthly weight loss standard deviations by weighting all arms equally in the imputed value calculation. For those trials missing standard deviations, we then used the imputed monthly weight loss standard deviation to calculate the standard deviation for weight loss at the relevant follow-up time.

For each pair of arms, an unbiased estimate[97] of Hedges' g effect size[98] and a 95 percent confidence interval were calculated. A negative effect size indicates that the treatment arm (ephedrine or ephedrine plus caffeine, or ephedra plus herbs containing caffeine) is associated with a larger weight loss at follow-up (or a larger monthly weight loss) than is the comparison arm, e.g., the placebo.

Performance of Meta-Analysis

We estimated a pooled random-effects estimate[99] by combining effect sizes for comparison subgroups that contained three or more effect sizes. We also report the chi-squared test of heterogeneity p-value.[97]

Forest plots were constructed for each comparison subgroup. Each individual trial effect size is shown with confidence intervals as a box whose area is inversely proportional to the estimated variance of the effect in that trial. The pooled estimate and its confidence interval are shown as a diamond at the bottom of the plot with a dotted vertical line indicating the pooled estimate value. A vertical solid line at zero indicates no treatment effect.

For each trial, we calculated the monthly weight loss percentage for each treatment group and the placebo group. Monthly weight loss percentage is defined as the mean monthly weight loss divided by the mean baseline weight in that group. Unfortunately, we were not able to calculate monthly weight loss percentage on an individual level. To determine the standard

deviation of the monthly weight loss percentage, we used the delta method[100] and assumed a correlation of 0.5 between the baseline and follow-up weights.[101] For each comparison subgroup, we pooled monthly weight loss percentages in the treatment groups and placebo groups separately using a random effects model[99] and produced associated 95% confidence intervals. We acknowledge that combining estimates within treatment groups only, or placebo groups only, does not take advantage of the randomization and pairing of treatment and control within a trial. This lack of pairing, and the fact that the monthly weight loss percentage in the treatment group must be compared to the associated monthly weight loss percentage in the placebo group, should be kept in mind when interpreting the results of this analysis.

Sensitivity Analyses

When relevant, we conducted sensitivity analyses on subgroups of trials to determine the robustness of our conclusions. In order to assess the possible impact of attrition, we divided the trials into two groups: (1) those with less than 20 percent attrition in all arms and (2) all others. Twenty percent attrition is a commonly accepted threshold above which concerns about bias increase, due to loss to follow-up. For trials in which attrition was unknown, we assumed it was not less than 20 percent. We conducted the main analyses for the two attrition strata separately.

We also conducted further analyses on the attrition rates. To determine whether the attrition rate varied between treatment and placebo groups within a trial, we first collapsed all the treatment groups together within a trial and estimated a single attrition rate for treatment. We then conducted a paired t-test that assessed whether the difference between the treatment and placebo attrition rates within a trial was significantly different from zero. All studies were weighted equally in this analysis. We also categorized each trial as significant or not significant based on its effect size. Trials that had more than one effect size agreed in terms of significance (in other words, the trial reported consistent result with respect to significance at multiple time points). We then categorized each trial as to whether the attrition rate for the treatment group was higher than, lower than, or the same as that of the placebo group. We examined the bivariate distribution of studies into these six categories, (three relationships between group attrition rates categories, and whether each of these relationships was significant or nonsignificant), and conducted a chi-squared test of the association between significance and the relationship between group attrition rates.

When relevant, we also performed our calculations a second time, excluding the trial by Moheb and colleagues.[84] This trial was presented only in abstract form and provided only the total sample size, not the sample sizes for each arm; thus, we had to assumed equal sample sizes across arms.

For the ephedrine plus caffeine versus placebo trials, we performed two sensitivity analyses. In the first, we dropped one trial[102] that had synephrine in the ephedrine plus caffeine arm. In the second, we dropped one arm of one trial[103] in which aspirin was combined with ephedrine plus caffeine; the sensitivity analysis was performed with the ephedrine plus caffeine arm alone.

A final sensitivity analysis concerned the choice of summary statistics to pool. Instead of pooling effect sizes or "standardized mean differences," we applied a "weighted mean difference" approach. In the latter, we pooled the absolute differences in weight loss between the

treatment and placebo groups, inversely weighted by the trial variances of the differences. That is, we did not first divide the differences by their standard deviations to produce effect sizes and then weight by the inverse variances of the effect sizes. If the variances are not homogeneous and/or the variances are not well estimated, these two methods may not produce the same results. The weighted mean difference approach has the appeal of being conducted entirely in the clinical units of interest—in this case, pounds.

Analysis of Dose

We tested for a dose effect using a random-effects meta-regression model.[104] A separate model was fitted within each comparison subgroup. We defined a low dose of ephedrine as 10–20 mg; a medium dose of ephedrine as 40–90 mg; and a high dose of ephedrine as 100–150 mg. We characterized each dose level as an indicator variable in a main-effects model and chose the medium-dose group as the level to exclude. The meta-regression approach allowed us to test directly the efficacy of low and high doses versus the excluded medium dose group, as well as to estimate the effect size for each dose level.

Publication Bias

We assessed the possibility of publication bias by evaluating a funnel plot of effect sizes for asymmetry, which can result from the nonpublication of small trials with negative results. These funnel plots include a horizontal line at the fixed-effects pooled estimate and pseudo–95% confidence limits.[105] If bias due to nonpublication exists, the distribution is asymmetric or skewed. Because graphical evaluation can be subjective, we also conducted an adjusted rank correlation test[105] and a regression asymmetry test[106] as formal statistical tests for publication bias. The correlation approach tests whether the correlation between the effect sizes and their variances is significant, and the regression approach tests whether the intercept of a regression of the effects sizes on their precision differs from zero; that is, both formally test for asymmetry in the funnel plot. We acknowledge that other factors, such as differences in trial quality or true study heterogeneity, could produce asymmetry in funnel plots.

Meta-Regression

As described above, in order to compare monthly weight loss effect sizes across comparisons, we conducted a random-effects meta-regression.[104] The observations in this meta-regression were all monthly weight loss effect sizes across the ephedrine, ephedrine plus caffeine, and ephedra plus caffeine-containing herbs comparisons. The variables are indicator flags, one for each comparison. Only one trial[85] had multiple effect sizes in the regression, and we did not account for the correlation between these two effect sizes in our model.

Three trials[84, 86, 88] contained both ephedrine and ephedrine plus caffeine arms. For these trials, we were able to conduct a direct, or "head-to-head," comparison of these treatments by pooling the effect sizes for each trial together. In the estimation of an effect size in this situation, the comparison group is that group of individuals who received ephedrine alone. Thus, a negative effect size means that ephedrine plus caffeine is associated with a larger monthly weight loss than is ephedrine alone. This direct comparison is more robust than the cross-group meta-regression described above, because the former compares groups only within a trial. However, due to the small number of trials that provided more than one treatment arm and the lack of any

direct comparisons of ephedrine alone or ephedrine plus caffeine versus ephedra, we conducted both analyses.

Interpretation of the Results

To aid in interpreting our results, we back-transformed all pooled estimates to weight loss in pounds. In order to do this, we multiplied each pooled estimate by the average standard deviation across trials, and then further multiplied by 2.2 to transform kilograms to pounds. In this way, we were able to equate our unitless pooled effect size with weight loss in pounds. However, we note this back-transformation requires assuming a particular underlying standard deviation. Readers may wish to apply their own standard deviation, based on the particular patient population to which they wish to apply the results.

We conducted all analyses and drew all graphs using the statistical package Stata.[107]

Safety Assessment

Controlled Trial Adverse Events

Data Collection

Each trial that we identified was examined to determine whether it reported data on adverse events. Adverse events were recorded onto a spreadsheet that identified each study arm, the description of the adverse event as listed in the original article, the number of adverse events in each category, and the number of subjects in each arm.

Meta-Analysis

The strongest level of evidence for attributing an adverse event to an exposure comes from placebo-controlled randomized trials of the exposure in question. In this evidence report, such evidence would come from placebo-controlled trials of ephedra or ephedrine. We therefore searched all such trials that we identified and extracted from each trial the adverse events that were reported associated with it, as described above. Because each event was counted as if it represented a unique individual, and because a single individual might have experienced more than one adverse event, this method may have overestimated the number of people having an adverse event. We then compared event rates in the people who received ephedra or ephedrine with those in people who received placebo. We performed a meta-analysis on those adverse events for which there was an appreciable number of reports in the randomized trials.

We collected data on adverse events for the randomized controlled trials. For each adverse event, e.g., vomiting, and for each treatment group and for the placebo group, we abstracted either the number of events or the number of people, depending on how the trial chose to report events. The majority of trials recorded the number of events, rather than the number of unique people who experienced the event. We treated all events as if they occurred in unique individuals, which, as we stated, may overestimate the number of people apparently affected in a particular event category.

We note that some trials recorded zero events in a particular event category, and these data were thus recorded. However, some trials recorded no data for a certain event category or

recorded no adverse events at all. These trials did not enter the adverse event meta-analysis, in that we did not assume zero observed events if a trial did not mention a particular type of event. By excluding these trials, we may have underestimated the number of patients for whom a particular adverse event was *not* observed. We note that, for the power calculation (described below) for serious adverse events (deaths, myocardial infarctions, strokes, seizures, and serious psychiatric symptoms), the sample sizes of all trials were taken into account, regardless of whether they mentioned these serious events. We assumed that such serious events would have been recorded had they been observed, so that a record of zero or no mention of a serious event could both be taken to mean that no such events were observed.

After abstracting the data, we identified mutually exclusive subgroups of similar events, based on clinical expertise. When we subgrouped events, we again treated all observed events as having occurred in unique individuals. For example, we considered nausea and vomiting as a single subgroup. For a trial that reported nausea events and vomiting events separately, we assumed the events that occurred in each category were unique and occurred in different individuals. The number of individuals who were at risk of being affected is the total number of patients in the trial's relevant group (placebo or treatment).

For each event subgroup, we report the number of trials that provided data for any event in the subgroup. We also report the total number of individuals in the placebo groups in the relevant trials who were observed to have experienced the event (calculated as described above) and the total number of patients in the placebo groups in those trials. We then report the analogous counts for all applicable treatment groups (ephedrine, ephedrine plus caffeine, ephedra) in the relevant trials. We specifically do not provide crude placebo and treatment rates (total number of affected patients divided by total number of patients at risk). Such crude rates do not weight trials appropriately.

Based on clinical importance and the availability of data, we chose a limited number of event subgroups for meta-analysis. For each chosen event subgroup, we estimated the pooled odds ratio across the trials that reported on any events in the subgroup, as well as a 95% confidence interval for the pooled odds ratio. Given that many of the events were rare, we utilized exact conditional inference to perform the pooling rather than applying the usual asymptotic methods that assume normality. Asymptotic methods require corrections if zero events are observed: Generally, half an event is added to all cells in the outcome by treatment two-by-two table in order to allow estimation, since these methods are based on assuming underlying continuity. Such corrections can have a major impact on the results when the outcome event is rare. Exact methods do not require such corrections. We conducted the meta-analysis using the statistical software package StatXact.[108]

We also conducted a power calculation to determine the lowest adverse-event rate that the clinical trials we identified had at least 80 percent power to detect. That is, we assumed a sample size equal to all the trials combined, and assuming a two-sided test of level 0.05, we determined the lowest detectable adverse-event rate. This calculation was performed to assess the statistical power we actually had available to detect adverse events if few or none were observed. Even if no adverse events are observed, we cannot necessarily conclude that the rate is zero, because the sample size available may have been too small to detect a rare event.

Case Report Adverse Events

Data Collection

Because the clinical trial data had low statistical power to detect a rate of serious adverse events, we therefore assessed case reports of adverse events associated with ephedrine or ephedra-containing dietary supplement use in order to inform the sponsors regarding the Safety Assessment key questions concerning serious adverse events. We reviewed case reports from three sources: the FDA MedWatch file, published case reports, and a file kept by the ephedra supplement manufacturer, Metabolife. Published case reports were identified through our literature search process previously described.

FDA Medwatch Data

In September 2001, the FDA's Office of Nutritional Products, Labeling, and Dietary Supplements produced an Excel spreadsheet with a master list of adverse-event report case numbers and summary information, in response to our request for all herbal ephedra–related adverse-event reports from their database. After several discussions and several months of work, the dataset construction algorithm was reproduced and limited to only herbal ephedra–related adverse-events reports, because some ephedrine adverse events had mistakenly been entered into the initial Excel file. We also received several sets of compact disks containing portable document format (PDF) files of events reported in the FDA Adverse Reaction Monitoring System (ARMS) for the dates specified. Documents retrieved included MedWatch Reports (FDA form 3500); Consumer Complaint Injury Reports (FDA Form 2516); Complaint/Injury Follow-up Forms (FDA Form 2516a); Adverse Reaction Questionnaires (Form A); letters from family members, health care professionals, or lawyers; affidavits collected from witnesses during FDA-held investigations; police reports; medical records, including physician notes (both inpatient and outpatient), emergency department reports, nurse notes, and laboratory reports; product labeling and related information; and product analysis results.

The second master list of only ephedra-related adverse-event reports was created at the product level, so that adverse-event report identification numbers (IDs) were repeated if multiple products appeared in one report. Because our analysis was at the adverse-event report level, where there were multiple products per single ID, we joined those into one record. We established a cutoff date of September 30, 2001, the production date for the CDs that contained actual reports. Our analysis does not include case reports filed after that cutoff date, since these files had not been redacted of identifying information.

The data were analyzed in a series of steps. First, we coded each unique report according to type of adverse event listed in the summary information on the Excel spreadsheet. The categories into which we grouped the reports are listed in Table 7. Then, we separated those reports with events coded as most serious (death, stroke, myocardial infarction (MI), seizure, and certain psychiatric symptoms) from those considered moderately serious. Reports that contained events considered most serious were analyzed using specialized data-collection instruments called Adverse Events Analysis Forms (AEA Forms—see Figures 3a–3c). We developed these instruments to collect information from the corresponding PDF file or published case report on whether the report was actually on ephedra or ephedrine, whether the data were adequate to analyze the report, and whether or not the adverse event qualified as a "sentinel event" (see

below). When a case report dealt with more than one individual, an AEA form was completed for each individual.

To understand the other potentially serious adverse events, we reviewed all case reports that had been grouped into the categories of "other serious cardiovascular," "other serious neurological," and "psychiatric" in our initial review of the master Excel file. For this review, we used a brief data abstraction form (Figure 4). This brief form was developed to assess the evidence supporting the prior use of ephedra and to define the adverse event more precisely. Again, when a case report contained more than one subject, a brief form was completed for each subject. Then, the data collected in the brief review were used to justify including certain more-serious events into the more-detailed review described above. These more-serious adverse events included ventricular tachycardia/fibrillation, cardiac arrest, pulmonary arrest, transient ischemic attack, and brain hemorrhage. Select adverse-event reports were then reviewed a second or third time by project staff physicians to reach an implicit judgment about whether an adequate investigation of other potential causes had been performed. Internists performed the initial reviews of cases of death, myocardial infarction, stroke, and seizure, and were assisted (as appropriate) by a cardiologist, rheumatologist, or neurologist. Psychiatric events were reviewed by two experienced professionals: a psychiatrist specializing in addictions and a psychologist who leads RAND's Drug Policy Research Center. All cases were reviewed by two individuals, with differences resolved by consensus.

As part of additional work we were requested to perform, we received hard copies of MedWatch data on ephedrine, organized in the same manner as the data on ephedra. We first reviewed all these events with our short form to identify the serious adverse events. These events were then reviewed using the same methods we developed for the ephedra database. Two types of adverse events associated with ephedrine were not associated with ephedra. The first involved the intravenous use of ephedrine given during surgery; several such reports were filed by medical personnel. The second involved attempted suicide. We note these two types of case reports in our analysis.

Literature Cases

During our literature search, we identified published case reports of adverse events associated with ephedra use. These published case reports were then reviewed using the same criteria used for the MedWatch events.

Metabolife File

We received the following materials from the Food and Drug Administration (FDA), which had, in turn, received them from Metabolife:

- A CD-ROM labeled "MIPER" (described in more detail below).
- Photocopies of medical information pertaining to 43 cases (also described in more detail below).

- A two-page *Listing of Key Complaint for the Metabolife Medical Records Submitted*, which is a listing of the key complaints for 46 cases, with photocopied medical information. (Note: we received medical information for only 43 cases.)

- A two-page sheet entitled *Index of Redacted Consumer Medical Records with Corresponding MIPER Numbers,* which contained a listing of the 46 cases with additional medical record information and the file numbers for related information on the MIPER CD-ROM.

- Three reviews of the Metabolife adverse-event file, which Metabolife commissioned. Note that to prevent their assessment from biasing our own, we did not read any of these reviews prior to our assessment, but did review them briefly when our assessment was completed.

- A file entitled *77 'serious' AE's as identified by Metabolife,* which contains photocopies of reports of events that were selected by Metabolife as being the most serious in nature. Most, but not all, of these reports were contained on the MIPER CD-ROM. Again, in order to avoid bias, we did not examine this file until after our initial assessment was performed.

- Several journal articles, all of which were already in our possession.

Later, we also received a report entitled *Adverse Event Reports from Metabolife* that had been prepared for Sen. Richard J. Durbin, Rep. Henry A. Waxman, and Rep. Susan A. Davis by the Minority Staff Report Special Investigations Division, Committee on Government Reform, U.S. House of Representatives, and which consisted of an analysis of the MIPER CD-ROM.

The MIPER CD-ROM contains several thousand files of adverse event reports organized in 20 folders. The adverse-event files are numbered from 15111 to 35069, and are continuous, except for three gaps—between 21121 and 22035; 25535 and 27472; and 30627 and 35047. Each file is a TIF picture file, generally of a single sheet of paper, on which is recorded information regarding the potential adverse event or events. This information was recorded in many different ways, including an email record of a telephone conversation between a company representative and the consumer; typed or handwritten letters from the consumer to the company; handwritten notes of telephone conversations with consumers, written on either a rudimentary form or on whatever piece of paper seems to have been handy at the moment; and a form developed by Metabolife for systematically collecting information about possible adverse events. Examples of all of these types of files are presented in Figure 5. Personal identifiers had been redacted from the files we received.

Each consumer could experience one or more adverse events. We referred to a particular adverse event for a person as a "case," and our analysis was conducted at the case level, rather than at the person level. Thus, a person could contribute more than one case to our analysis. We use this terminology throughout the remainder of the report. Practically speaking, in most instances of serious adverse events such as death, heart attack, or stroke, a person contributed only a single case in this manner.

In general, each file on the MIPER CD-ROM contained only a single sheet of paper. We did identify some files that were exactly the same as other files, and we excluded these files from our analysis. The information on a case might reside in a single file or in more than one file. For example, if a letter from a consumer concerning one of the adverse events experienced by that consumer was three pages long, each page resided in a separate file. If possible, we tried to identify all files that pertained to the same case (which we called "duplicate" files), so that we would not count a case more than once. Whether we identified all such instances is unknown, since information in each file was insufficient to allow us to check for duplicate files by matching on key variables such as age, gender, and the type of adverse event. No other mechanism for checking was possible within the time and resources available to the project. Therefore, while we did our best to identify and exclude or in some other way resolve duplicate files, we cannot be certain that all such files were identified. An example of the difficulty in identifying duplicates is given in Figure 6. In this instance, Metabolife had identified in the *77 'serious' AE's* document that these two files belonged to the same case. We would not have been able to make this determination, because the files are separated by more than 7000 numbers on the MIPER CD-ROM (file 16897 and file 24209), and the notes in one file specify "seizure," whereas the other file states "no history of seizure."

In contrast to a duplicate file, a file might contain information on more than one case, either a set of adverse events all experienced by the same consumer or one or more adverse events experienced by several different consumers (see Figure 5, Example 5c). For this reason and because of duplicate files, the number of cases of possible adverse events does not equal the number of files.

In order to review this large CD-ROM dataset within the given time frame, we chose to have the initial data collected by a team of abstractors, each working on a portion of the MIPER CD-ROM. We retained six nurses, each with many years of experience in medical record abstraction. We developed a one-page data collection form to collect key variables related to age, gender, nature of the reported adverse event, and need for hospitalization, which is reproduced in Figure 7. After undergoing training by the principal investigator, each nurse abstractor completed a sample of 135 records, each of which was reviewed in a group meeting with the principal investigator to identify areas of possible misinterpretation and vague language. Based on this experience, we revised the form and developed a "codesheet" to define how certain complaints were to be coded. Formal inter-rater reliability testing was performed on a 1 percent systematic sample of the MIPER files. This sample was stratified into two parts, the larger (N = 114) portion containing only a single adverse event in each file and the smaller portion (N = 16) containing more than one case per file. Inter-rater reliability was assessed using both absolute percentage agreement among abstractors and the kappa statistic, which adjusts for agreement due to chance. Kappa varies between 0 and 1.0, with values of 0.4 to 0.6 usually indicating moderate agreement beyond chance, 0.6 to 0.8 indicating substantial agreement beyond chance, and greater than 0.8 indicating almost perfect agreement.[109] Inter-rater reliability testing demonstrated a kappa statistic of greater than 0.8 or absolute agreement of 95 percent or greater for all variables, indicating almost perfect agreement, for the "one case, one file" (N = 114) records. For the files with multiple cases, two produced disagreement over the number of multiple cases contained in the file. For the remaining 14 multiple-case files, this analysis

showed levels of reliability similar to the "one case, one file analysis." Based on these results, we concluded that the inter-rater reliability for the six nurse abstracters trained in this manner was acceptable for this project. Each nurse was then assigned approximately one-sixth of the MIPER file. Questions that arose during abstraction were posted by email or telephone to our EPC's lead physician abstracter (WAM), who answered their questions, reviewed files himself, and consulted with the principal investigator on decisions requiring nuanced judgment. He maintained the codesheet, keeping it up—to-date and redistributing it to the abstractors whenever changes or additions were made.

We reviewed the forty-three cases that included photocopies of medical information. Personal identifiers had been redacted. Some of these cases were related to cases contained on the MIPER CD-ROM. However, matching these cases was a challenge. As previously noted, we were sent a two-page *Index of Redacted Consumer Medical Records with Corresponding MIPER Numbers*, which indicated a number and the associated files on the MIPER CD-ROM. Unfortunately, the medical records we received were not numbered. Furthermore, a second table that we received entitled *Listing of Key Complaint for the Metabolife Medical Records Submitted* contained a list of main complaints, also numbered. However, the two numbering systems did not agree. We numbered the cases in the order in which we received them in the shipping box. Our numbering system and the two numbering systems we received start out in agreement, but discrepancies occur as we progress through and compare the three systems. We did our best to resolve them.

Analysis of Case Reports

In our draft report, we assigned a likelihood of causality to selected cases, based on our modification of published methods. Many of the peer review comments received for this report pertained to our attempts to assign causality. These comments varied widely, ranging from critiques of our method for being too conservative (meaning, in the opinion of some reviewers, we had excluded or assigned too low a level of causality to certain cases) to critiques for being too liberal (meaning, in the opinion of some reviewers, we had assigned too high a level of causality to certain cases). Often, these conflicting comments concerned the same cases. We believe these 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. Rather, we tried to identify those cases that would be classified medically as "idiopathic" in etiology, meaning the cause is not known. For such cases, given the known pharmacology of ephedrine, if use of ephedra or ephedrine was documented, a potential role for ephedra or ephedrine in causing the event must be considered. We classified such cases as "sentinel events."

In order to be classified as a sentinel event, three criteria had to be met:

1. Documentation existed that an adverse event meeting our selection criteria occurred.
2. Documentation existed that the person having the adverse event took an ephedra-containing supplement within 24 hours prior to the event (for cases of death, myocardial infarction, stroke, or seizure).
3. Alternative explanations were investigated and excluded with reasonable certainty.

Within the time and resources available for this evidence report, we were able to do an in-depth review of FDA case reports only for those events classified as death, myocardial infarction (which included acute coronary syndromes), stroke (which included intracerebral hemorrhage), seizures, and severe psychiatric symptoms (see below). Cases that met all three criteria were classified as "sentinel events." Cases where another condition by itself could have caused the adverse event, but for which the known pharmacology of ephedrine made it possible that ephedra or ephedrine may have helped precipitate the event, were classified as "possible sentinel events." "Probably not related" was used for events that had other clear causes discovered on detailed investigation and to which the pharmacology of ephedrine was unlikely to have potentially contributed. We also classified many cases as having insufficient information because crucial information was missing, such as the presence of ephedrine or a metabolite in the blood or documentation that the patient took ephedra within 24 hours prior to the event (for cases of death, myocardial infarction, stroke, or seizure); or other possible causes were insufficiently investigated. (We also classified as "sentinel events" a few cases that, on detailed review, led us to question whether an event meeting our inclusion criteria had actually occurred.)

We translated the criteria for identifying sentinel events into the following set of procedures:

- We required medical record documentation that an adverse event had occurred.

- For adverse events described as seizure, cases described as generalized tonic-clonic seizures underwent further review.

- For psychiatric symptoms, we reviewed cases described as psychosis, mania or severe agitation, severe depression, hallucinations, confusion or delusion, suicide attempt, paranoia, or violence.

- We required (for all but psychiatric events) that there be documentation that the subject had consumed ephedra or ephedrine within 24 hours prior to the adverse event, or that a toxicological examination revealed ephedrine or one of its associated products in the blood or urine. Cases with no such documentation were not reviewed further. For the Metabolife cases, we assumed ephedra use to have been within the prior 24 hours for all but psychiatric events.

- For psychiatric cases, we did not require documentation that the product was taken within 24 hours prior to the event. Ephedrine psychosis (as with amphetamine psychosis in general) is associated with prolonged use, which may lead to neurotoxicity, resulting in depletion of dopamine and other brain monoamines.[110]

- To be eligible for detailed review to investigate other potential causes of death, a file required evidence that an autopsy had been performed, and the results had to be available.

- To be eligible for detailed review to investigate other potential causes for cases of myocardial infarction, coronary angiography had to have been performed and the results had to be available.

- All cases of stroke that met the criterion of having consumed ephedra or ephedrine within 24 hours were reviewed in more detail. To be classified as a "sentinel event," reports of thrombotic stroke needed to have an assessment for a hypercoagulable state and vasculitis, reports of embolic stroke needed to have an embolic evaluation performed, whereas reports of hemorrhagic stroke required an examination to assess structural problems with the circulatory system of the brain.

- Other potential causes of seizure were assessed by searching cases for the results of vital signs, brain imaging (CT or MRI), serum glucose and electrolytes, blood calcium and magnesium, an EEG, and prior history of a seizure disorder or substance abuse.

- For cases with psychiatric symptoms, cases in which patients had a history of psychiatric or severe psychological problems were excluded from further review as reports of possible sentinel events. Cases where the patient reported use of or tested positive for other substances known to cause psychiatric symptoms were also excluded as possible sentinel events. For patients with a prior psychiatric history or use of other substances, these cases were classified as "inconclusive."

One of the key questions we were asked to answer by the sponsoring agencies concerned the relationship between dose and the likelihood of serious adverse events. We do not believe such an analysis is justifiable based on the case report evidence presented here, for the following reasons. First, such an analysis assumes a cause-and-effect relationship that has not been proven by conventional standards of medical science. Second, it would rely to a great extent on patients' recall of dose after having suffered an adverse event, which increases the likelihood of recall bias. Third, and most important, for more than half the adverse-event cases, no dose data were available.

Peer Review

This report was subjected to a lengthy peer review process. An initial draft report was prepared in July 2002. We received comments from 37 reviewers, including representatives from the American Herbal Products Association; Centers for Disease Control and Prevention; Consumer Healthcare Products Association; Council for Responsible Nutrition; Food and Drug Administration; National Center for Complementary and Alternative Medicine; National Institute of Diabetes and Digestive and Kidney Diseases; National Institute of Neurological Disorders and Stroke; National Heart, Lung and Blood Institute; National Institute of Health Office of Dietary Supplements; National Institute of Health Office of Research on Women's Health; National Nutritional Foods Association; Public Citizen Health Research Group; Center for Science in the Public Interest; Utah Natural Products Alliance; and members of the U.S. House of Representatives and U.S. Senate. Additional work requested, involving case report assessments, was performed during Autumn 2002. The "safety" section of the revised report, which contains the new material, was reviewed by additional experts in December 2002. A complete list of Reviewers is in Table 8.

We considered each peer review comment (more than 100 pages in total) and detail our responses in Appendix 3. Service as a reviewer of this report should not in any way be construed as agreeing with or endorsing the content of the report.

Chapter 3. Results

Results of Literature Search

Efficacy Analysis

Figure 8 displays the flow of the literature review. As a result of computerized library searches, reference mining, talking to experts, and searching government files (see Methods), we ordered 553 articles. Of those 553, we were unable to obtain 20 articles, mostly foreign or very old background articles, none of which appeared (from their titles and keywords) to be clinical trials of ephedrine or ephedra.

Of the 533 articles collected, 57 reported results from randomized clinical trials or controlled clinical trials that assessed the effects of either ephedrine or herbal ephedra on weight loss or athletic performance. The 57 articles, which corresponded to 52 unique controlled clinical trials, went on to further review and data abstraction. Articles that did not go on to initial data abstraction included 66 case reports or case series articles that reported adverse events. One hundred fifty-eight were rejected because they did not discuss ephedra or ephedrine, although they may have discussed phenylpropanolamine, pseudoephedrine, or caffeine, or provided general background on herbal medicine, weight loss, or athletic performance enhancement. One hundred twenty-four articles were rejected because they were not RCT/CCTs and did not report adverse events. Forty-eight articles were rejected because they did not study human populations. Another seven articles were duplicates of articles already on file. Fifty-four additional articles were rejected for design, including previous reviews of ephedra or ephedrine, descriptions of its chemical properties, editorials, commentaries, letters to journal editors that did not report new cases, and newspaper or trade journal stories. Eighteen RCT/CCTs were rejected because they did not concern weight loss or athletic performance.

Adverse Events Analysis

The adverse events analysis includes 52 controlled trials and 46 of the 66 case reports/case series articles (six articles were rejected because they were duplicates of articles or reports already included in the analysis).

Efficacy

Weight Loss

Of the 52 unique controlled trials that assessed the effects of either synthetic ephedrine or herbal ephedra on weight loss or athletic performance, 44 of those assessed the effects of ephedra, ephedrine, or ephedrine and other compounds on weight loss. Of these 44 trials, 18 were excluded from pooled analysis because they had treatment duration of less than eight weeks (the longest published weight loss intervention was six months, and no studies assessed post-intervention weight maintenance). Six more trials were excluded for a variety of reasons (See Table 9). We classified the comparisons made in the remaining 20 trials into six categories:

1. Ephedrine versus placebo
2. Ephedrine plus caffeine versus placebo
3. Ephedrine plus caffeine versus ephedrine alone
4. Ephedrine versus another active pharmaceutical for weight loss
5. Ephedra versus placebo
6. Ephedra plus herbs containing caffeine versus placebo

For the 16 trials that reported baseline sample sizes, the attrition rate in the treatment arms averaged 27 percent, whereas the attrition rate in the placebo arms averaged 29 percent. This difference was not statistically significant. Five trials reported more dropouts from the treatment than from the placebo group: Four of these trials reported a statistically significant benefit for the treatment, and one did not. Eight trials reported more dropouts from the placebo group than the treatment group. Five of these trials reported a statistically significant benefit for treatment, whereas three did not. Three trials reported an equivalent number of dropouts from the treatment and placebo groups. No significant association was found between the frequency of favorable results and the relative proportion of dropouts in the treatment and placebo groups.

Ephedrine Versus Placebo

We identified five trials (which contained six comparisons) that assessed the effect of ephedrine versus placebo.[84-86, 88, 94] A study by Pasquali had two comparison arms that assessed different doses.[85] The scores on Jadad's scale (0-5) for these trials were 1, 2, 2, 3, and 3, respectively. All five were described as randomized, placebo-controlled trials. Three of the trials (with four comparisons) reported results at three months, and three of the trials reported results at four months. The random effects pooled estimate of the rate of weight loss per month was an effect size of -0.50 (95% CI: -0.85, -0.15), which translates to a monthly weight loss of 1.3 pounds more than weight lost on placebo (Table 10 and Figure 9). The pooled average percent weight loss in the ephedrine-treated patients, compared to pretreatment weight, was 11 percent at 4 months.

A sensitivity analysis on only those trials that scored three or higher on the Jadad scale yielded a pooled estimate of effect substantially lower than the main analysis (effect size = -0.20); this difference was statistically significant ($p = 0.049$). All of these trials had an attrition rate greater than 20 percent; therefore, no sensitivity analysis on attrition could be performed. A final sensitivity analysis, in which the trial by Moheb[84] was dropped, did not materially change these results.

In our dose analysis, only high doses of ephedrine resulted in a weight loss that was significantly greater than zero, and the difference in weight loss between medium dose trials and high dose trials approached statistical significance ($p = 0.052$). Neither graphical nor statistical tests yielded evidence of publication bias (See Table 11 and Figure 10).

We interpret these data to indicate that the use of ephedrine is associated with a statistically significant increase in weight loss (1.3 pounds of weight loss per month) compared with that of placebo for up to four months of use.

Ephedrine plus caffeine versus placebo

We identified 12 trials that assessed the effect of ephedrine plus caffeine versus placebo for weight loss.[84, 86-88, 90-92, 95, 96, 103, 111, 112] Six trials [86, 87, 92, 95, 96, 112] had scores of three or greater on the Jadad scale, a threshold that in other settings has been associated with less bias.[83] Seven were described as randomized, double blind, placebo-controlled trials. Four of the trials measured weight loss at two months, four trials measured it at three months, and five trials measured it at four months. The random effects pooled estimate of the rate of weight loss per month was an effect size of -0.85 (95% CI: -1.1, -0.61), which translates to a weight loss of 2.2 pounds per month above that with placebo (Table 11 and Figure 11). The pooled average percent weight loss in the ephedrine plus caffeine treated patients, compared to pretreatment weight, was 11 percent at 4 months.

A sensitivity analysis on only those trials that scored three or greater on the Jadad score yielded a result similar to the main analysis. Another sensitivity analysis on only those trials that had less than 20 percent attrition yielded a similar pooled estimate effect size of -0.74 (95% CI: -1.2, -0.3). Two trials[96, 112] in this category were randomized, double-blind, placebo-controlled trials with an attrition rate of less than 20 percent. The first[112] reported an effect somewhat greater than the main analysis (effect size = -1.35; 95% CI: -2.2, 0.54). The second[96] had a smaller effect (effect size = -0.46; 95% CI: -1.3, 0.34). A fourth sensitivity analysis in which the trial by Moheb[84] was dropped did not change the result compared with the primary analysis, nor did sensitivity analyses that dropped trials that also included synephrine or aspirin.

In our dose analysis, there was a trend toward increased weight loss with higher doses (weight loss greater than placebo of 2.0, 2.2, and 2.6 pounds per month for low, medium, and high doses, respectively) but these differences were not statistically significant. Neither visual nor graphical tests revealed any evidence of publication bias (See Table 11 and Figure 12).

We interpret these data to indicate that the use of the combination of ephedrine and caffeine is associated with a significantly greater (2.2 pound) weight loss per month than is associated with placebo, for up to four months duration.

Ephedrine plus caffeine versus ephedrine

We identified three trials that included arms that compared a combination of ephedrine and caffeine to ephedrine alone.[84, 86, 88] The Jadad scores for these trials were 1, 2, and 3 respectively, and all three had attrition rates of greater than 20 percent. The random effects pooled estimate of the rate of weight loss per month was -0.31 (95% CI: -0.60, -0.02), which equates to a weight loss of 0.8 pounds per month more than with ephedrine alone (Table 13 and Figure 13). There were too few trials to perform any sensitivity analysis.

We interpret these data to indicate that addition of caffeine to ephedrine is associated with a statistically significant increase in weight loss per month of about 0.8 pounds, over that attributable to ephedrine alone.

Ephedrine versus another active weight loss therapy

We identified two trials that compared ephedrine with another active weight loss therapy (Table 14). The trials, both Danish, are briefly described here. In 1994, Breum and colleagues[113]

published the results of a randomized controlled trial comparing the effect of dexfenfluramine to a combination of ephedrine and caffeine. At 15 weeks, the dexfenfluramine group had lost an average of 6.9 kg (15.2 lb.), whereas the ephedrine and caffeine group had lost 8.3 kg (18.3 lb.), a difference that was not statistically significant. The other Danish study,[87] published in 1981, compared the effects of the Elsinore pill (a prescription that contained ephedrine and caffeine) with those of diethylpropion. At 12 weeks, the diethylpropion patients had a median weight loss of 8.4 kg (18.5 lb.), while those taking Elsinore pills lost a median of 8.1 kg (17.8 lb.), a difference that was not significant. Each of these two trials[87] included approximately 40 ephedrine and 40 other treatment patients. The approximate weight loss in the ephedrine groups was 8.4 kg (± approximately 4.0 kg SD) (18.4 ± 8.8 lb.) over three months. Based on a two-sided test of significance level 0.05 and assuming the same variance in both groups, trials of this size have only 59 percent power to distinguish between an 8.4 kg weight loss in the ephedrine group and a 6.4 kg (14.1 lb.) weight loss in the active treatment group, i.e. a difference of 30% between the groups. In order to attain 80 percent power, a study would need 67 ephedrine patients and 67 comparison treatment patients.

Ephedra versus placebo

We identified a single trial that assessed the effect of herbal ephedra versus placebo.[114] This trial was described as a randomized, double-blind, parallel group assessment of Metab-O-Lite, a dietary supplement that contains ephedra and other compounds but does not contain caffeine or herbs that contain caffeine. The duration of the trial was three months. Those in the ephedra arm lost 1.8 pounds more per month than did those in the placebo arm (95% CI: -2.7, -1.0) (Table 15). This trial scored four on Jadad's scale and had 17 percent attrition.

Ephedra plus herbs containing caffeine versus placebo

We identified four trials that assessed the effect of herbal ephedra plus herbs containing caffeine versus placebo.[89, 93, 115, 116] The Jadad scores for these four trials were 5, 5, 2, and 2 respectively; and all four were described as randomized placebo-controlled trials. Two of the trials reported outcomes at two months, one trial reported three-month outcomes, and one trial reported four-month results. The pooled random effects estimate of the rate of weight loss per month of these four trials was -0.81 (95% CI, -1.12, -0.51), which equates to a weight loss of 2.1 pounds per month more than that for placebo, for up to four months (Table 16 and Figure 14). The pooled average percent weight loss in the ephedra-treated patients, compared to pretreatment weight, was 5.2 percent at four months. A sensitivity analysis for only those trials that scored three or more on the Jadad scale yielded a result similar to the main analysis. All studies assessed medium doses of ephedra; therefore no analysis of dose effect was possible. Neither visual nor graphical tests revealed any evidence of publication bias (Table 11 and Figure 15).

We interpret these data to indicate that the use of a combination of ephedra plus herbs containing caffeine is associated with a statistically significant increase in weight loss per month of 2.1 pounds compared with that of placebo, for up to four months duration.

Meta-regression analysis

In order to assess the effects of ephedrine, ephedrine plus caffeine, and ephedra plus herbs containing caffeine on weight loss, we conducted a meta-regression analysis. The results are displayed in Table 17 and Figure 16. The table shows the pooled monthly weight loss in pounds

and its confidence interval for each comparison group versus placebo. All are significantly different from zero, indicating that all treatments are associated with an increased weight loss as compared to placebo. The last column, which compares ephedrine alone, ephedrine plus caffeine, and ephedra plus herbs containing caffeine, shows no significant differences among these treatments. Figure 16 lists the comparison groups in order of least effective versus placebo (left) to most effective (right). The individual effect sizes converted to pounds within each comparison are plotted vertically as circles, with the circle area inversely proportional to trial variance. We connect the pooled-effect sizes in pounds within each comparison group by line segments, showing the visible downward trend from left to right.

These data indicate that both ephedrine plus caffeine and ephedra plus herbs containing caffeine are somewhat more effective than ephedrine alone in promoting weight loss and that there is no difference in effect between ephedrine plus caffeine and ephedra plus herbs containing caffeine. To help put these data in context, we note that placebo-controlled trials of some FDA-approved weight loss pharmacotherapies have shown losses of 6-10 pounds more than placebo, over 6-12 months, for patients taking sibutramine[117-120] or orlistat;[121-125] or 16 pounds more than placebo, at 9 months, for patients taking phentermine.[126]

Athletic Performance

We found eight published controlled trials of the effects of synthetic ephedrine on athletic performance; most were crossover designs, and all but one also included caffeine. One trial,[127] which assessed the effect of ephedrine and exercise training on basal metabolic rate but did not report athletic performance outcomes, is not described below. The remaining seven trials were not appropriate for pooled analysis because they included various types of exercise and outcome measures. Thus, they are discussed here individually. We found no trials of the effect of herbal ephedra on athletic performance.

Six trials by Bell and colleagues assessed the exercise capacity of small groups of healthy males (all trials included 24 subjects or fewer). In their first trial,[128] healthy subjects who were not athletically trained were divided into four treatment groups: caffeine, ephedrine, ephedrine plus caffeine, and placebo. Outcome measures included oxygen consumption (VO_2), carbon dioxide production (VCO_2), and peak time to exhaustion. Ephedrine plus caffeine was reported to improve parameters of exercise performance such as oxygen consumption, time to exhaustion or carbon dioxide production by 20 to 30 percent, but neither caffeine nor ephedrine alone had significant effects. A follow up trial,[129] using a similar population and outcome measures but a lower dose of caffeine and ephedrine, showed similar effects on exercise performance and fewer side effects. Nausea and vomiting were reported in a third of subjects given 1 mg/kg ephedrine with 5 mg/kg caffeine, but none of the subjects given a lower dose (0.8 mg/kg ephedrine and 4 mg/kg caffeine) experienced symptoms. A third trial[130] assessed the effects, in a field trial, of ephedrine plus caffeine on VO_2 and time to complete a standardized exercise test, and again reported improvements in the group treated with ephedrine plus caffeine. A fourth trial[131] tested the effects of ephedrine plus caffeine on body temperature regulation and oxygen consumption during sub-maximal exercise in a hot environment and found that the combination did not increase body temperature significantly. A fifth trial[132] compared the effects of placebo, caffeine, ephedrine, and a combination of ephedrine plus caffeine on muscle endurance in men performing

weight circuit training. This trial showed an improvement in muscle endurance, but only on the first of three repetitions. The most recent trial[133] reported that, compared to placebo, ephedrine plus caffeine consistently improved exercise performance during stationary biking. The Bell trials are summarized in more detail in Table 18.

A trial by Sidney[134] assessed the effects of ephedrine versus placebo or no treatment (for baseline measures) on performance on a variety of physical function tests among 21 healthy young men. No statistical differences were seen among the groups on performance of any of the tests, including VO_2, measures of endurance and power, reaction time, hand-eye coordination, speed, and self-perceived exertion. These results agree with the finding by Bell and colleagues that ephedrine alone did not demonstrate significant effects on athletic performance.

In conclusion, the effects of ephedrine on athletic performance have not been well studied. The populations studied have been small and exclusively male, and the method of administration of ephedrine does not replicate the patterns of use reported for the general public. Effects of ephedrine on exercise performance are most often studied acutely (e.g., one to two hours after a single dose) in contrast to assessing the effects of chronic use on conditioning and performance. The one trial that did assess the effect on strength training did not find a sustained benefit of ephedrine supplementation. In addition, to show even a short-term effect of ephedrine, combination with caffeine was required. We identified no trials that assessed the sustained effect of ephedrine on aerobic conditioning or strength training and no trials that tested the effects of herbal ephedra on athletic performance.

Safety Assessment

Controlled Trials

We initially considered all 52 clinical trials of ephedra and ephedrine for the safety assessment. Two trials were excluded from the odds ratio meta-analysis because they did not contain a placebo group.[113, 138] Numerous symptoms were reported as adverse events. We grouped clinically similar symptoms as follows:

- Psychiatric symptoms: those symptoms described in the original clinical trials as “euphoria,” “neurotic behavior,” “agitation,” “neuropsychiatric,” “depressed mood,” “giddiness,” “irritability,” and “anxiety;”

- Autonomic hyperactivity: those symptoms described in the original clinical trials as “tremor,” “twitching,” “jitteriness,” “insomnia,” “difficulty sleeping,” “sweating,” “increased sweating,” and “increased perspiration;”

- Nausea/ vomiting: those symptoms described in the original clinical trials as “nausea,” “vomiting,” “abdominal pain,” “upset stomach,” “heartburn,” and “gastroesophageal reflux;”

- Palpitations: those symptoms described in the original clinical trials as “palpitations,” “irregular heartbeat,” “loud heartbeat,” “heart pounding,” and “increased or stronger heartbeat;”

- Tachycardia: those symptoms described in the original clinical trials as “tachycardia” and “slightly elevated heart rate;”

- Hypertension: those symptoms described in the original clinical trials as “hypertension,” “increased systolic blood pressure,” and “increased diastolic blood pressure;” and

- Headache.

Table 19 presents the pooled estimate of the odds ratio for those adverse events for which data were sufficient to justify meta-analysis. The odds ratio will slightly overestimate the risk ratio for these events, as they occurred in 10 to 20 percent of subjects. This analysis reports a statistically significant increase of between 2.15 and 3.64 percent in the odds for the adverse events of psychiatric symptoms, autonomic hyperactivity, nausea/vomiting, and palpitations. There is a trend toward an increase of similar magnitude in the report of hypertension, but this increase was not statistically significant. There was also a non-statistically significant trend towards an increase in headaches. There were too few trials of ephedra or ephedrine alone to support analyses specific to these products; the subgroup analysis of adverse events involving ephedrine plus caffeine was similar to the main analysis. In our dose analysis, there was a trend toward higher risk of adverse events with higher doses of ephedrine, but data were sparse, and these differences were not statistically significant (for example, adjusted odds ratios of autonomic hyperactivity were 3.0 and 12.5 for medium- and high-dose ephedrine respectively, but the 95% confidence intervals overlapped; adjusted odds ratios for the three cardiovascular outcomes combined were 2.7 and 7.9 for medium- and high-dose ephedrine, a difference that was not statistically significant). The pattern of symptoms with statistically significant increases in occurrence is consistent with the pharmacology of ephedrine.

Table 20 presents frequency data concerning the other adverse events reported in the clinical trials. Meta-analysis was not performed on these data, primarily due to small numbers of events.

No serious adverse events (e.g., death, myocardial infarction, stroke, etc.) were reported in the 52 clinical trials that reported sample sizes. Therefore, the rate for these adverse events is zero. Even in aggregate, these trials had sufficient statistical power only to detect a serious adverse event rate of 1.0 in 1000, given the small numbers of patients studied in these trials. For trials of ephedra, statistical power in aggregate was sufficient only to detect a rate of serious adverse events of 4.0 in 1000. A conventional definition of a “rare” adverse event is about 1 in 1000. We also note that these data come from patients enrolled in clinical trials: Data from the pharmaceutical literature support the contention that patients taking pharmaceuticals outside of clinical trials may have a greater risk of particular adverse events than do patients selected to participate in clinical trials.[139] Therefore, in community practice, the rate for serious adverse events may be higher than that seen in clinical trials.

Case Reports

Because, even in aggregate, the numbers of subjects enrolled in clinical trials have been too small to assess the possibility of rare but serious side effects, we assessed case reports of serious events allegedly associated with ephedra use.

FDA Medwatch Data and Literature Cases

Figure 17 is a graphical representation of the case report evidence used in the safety assessment. The first master list produced by the FDA's Office of Nutritional Products, Labeling, and Dietary Supplements contained 1,848 adverse event reports. The second master list, from which events associated with ephedrine were removed, contained 1,783 reports. When we combined event reports of identical ID number but different products, we reduced the observations by 88 to 1,695 total observations but did not lose any data. In addition, we removed 137 reports listed in the master Excel file as having been filed after our September 30, 2001 cut-off date. The master Excel list also contained 214 reports (dated before September 30, 2001) for which no PDF data files existed on the CDs. Because documentation was essential for review of each report, these reports were removed from our analysis, which left 1,344 reports in our final dataset. In Table 21, we show the result of a chi-squared test of independence, which tests the association between the type of event distribution (death; stroke; myocardial infarction; other) and the type of data (available; after September 30, 2001; not available). This test rejected the null hypothesis of no association ($p < 0.001$), indicating that the distribution of events was different for the different data types. Thus, bias may exist, because the events we included were different in type than those we had to exclude. Since more cases of death were reported, as a percentage of total cases, in the data subsequent to September 2001, it is possible that our results would be different had we had the opportunity to include the cases filed after September 2001.

To the 1,344 unique and available reports that met the cut-off date (Batch 1), the FDA added another 125 reports (Batch 2) that consisted predominately of adverse events related to ephedrine. Together, 1,469 reports from the FDA MedWatch files were reviewed. Within the 1,344 reports from Batch 1, 158 cases reported on the most serious adverse events (death, stroke, and myocardial infarction), and 1,186 reported on other adverse events according to the master Excel spreadsheet. Of the 1,186 case reports, we found 935 reports that fit the categories of "other serious cardiovascular," other serious neurological," and "psychiatric." (We did not examine the remaining 251 adverse event reports because the descriptors in the master excel spreadsheet appeared to fall outside our focus of serious adverse events.) The 935 reports contained data on 965 subjects, of which 922 reported taking ephedra. From the brief review, we determined that 158 of these subjects reported events serious enough (ventricular tachycardia/fibrillation, cardiac arrest, pulmonary arrest, transient ischemic attack, brain hemorrhage, seizure, or psychiatric symptoms) to warrant including their file in the more detailed review. Within the 125 reports of Batch 2 (reporting on 130 subjects), we found 106 subjects reporting ephedra or ephedrine use. Thirty-three of those subjects reported events serious enough (ventricular tachycardia/fibrillation, cardiac arrest, pulmonary arrest, transient ischemic attack, brain hemorrhage, seizure, or psychiatric symptoms) to warrant including their file in the more detailed review.

Of the 533 articles retrieved from the medical literature for this report, sixty-six were case reports or case series of adverse events. Six reports were rejected as duplicates, leaving 60 case reports or case series, reporting on 99 subjects. Of these, further review identified four as not reporting on ephedra or ephedrine. Of the remaining 95 subjects, 46 had adverse events that went on to detailed review, and 49 were not reviewed further.

From all sources, 84 deaths, 26 myocardial infarctions, 56 cerebral vascular accidents (strokes or cerebral hemorrhage), 30 "other cardiac" events, eight "other neurological" events, 40 cases of seizure, and 91 cases of psychiatric events. We identified two deaths, three myocardial infarctions, nine cerebrovascular accidents, three seizures, and five psychiatric cases as sentinel events with prior ephedra consumption. Three deaths, two myocardial infarctions, two cerebrovascular accidents, one seizure, and three psychiatric cases were identified as sentinel events with prior ephedrine consumption. We identified an additional 43 cases as possible sentinel events with prior ephedra consumption and an additional seven cases as possible sentinel events with prior ephedrine consumption. About half of the sentinel events occurred in persons aged 30 years or younger. Classification as a sentinel event does not imply a proven cause and effect relationship.

What follows are short descriptions of the adverse event cases that we reviewed further for other potential causes for the adverse event. Table 22 presents data abstracted from each reviewed case. Tables 23 and 24 summarize the adverse events by gender, age, and type of event. Cases classified as something other than sentinel events include, where feasible, our reasons for so classifying them. Clinical detail regarding outcome is recorded to the extent it was available in the source material.

Deaths

Sentinel Events

FDA Cases—Ephedra

A 21-year-old male collapsed and died during a physical agility run at school after taking Hydroxycut and Ripped Fuel one time to increase energy. At autopsy, ephedrine and caffeine were found in the blood at concentrations of 0.02 mg/l and 0.31 mg/l, respectively. Although the autopsy report itself was not included in the FDA documents we received, a detailed description of the autopsy was found in the police notes that were included in the FDA file. According to these notes, the autopsy report stated that the coronary arteries were normal and that the diagnosis was acute arrhythmia due to ephedrine. (13914)

A 22-year-old female who weighed 183 pounds collapsed and died while standing in line to purchase ice cream. She had a history of asthma that was characterized as "well-controlled." She had congenital hydrocephalus with a shunt placed. She was taking Slacker II. 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, except for the presence of the shunt. There was no other cause of death. The death certificate listed "cardiac arrhythmia due to ephedrine-containing diet medication." (14390)

FDA Cases—Ephedrine

A 30-year-old female died suddenly. Her husband stated that she had been taking MiniTabs in order to lose weight. She was found unresponsive by her husband and was brought to the emergency department in full cardiac arrest. Blood toxicology screen showed an ephedrine level of 24 micrograms (μg) per milliliter (ml). Examination of the heart and brain did not reveal any evidence of cause of death. Final pathological diagnosis included "acute drug toxicity–ephedrine" with the opinion that "this autopsy illustrates an instance of death due to acute drug toxicity." (3275432)

A 33-year-old male was found dead. He had been taking an over-the-counter preparation named "Max Brand Two-Way ephedrine tablets." Autopsy did not reveal any obvious cause of death, particularly with respect to the brain and heart. However, the blood ephedrine level was 13.4 μg per ml. The final pathological diagnosis was drug intoxication, with the opinion that the person died as the result of "drug intoxication with ephedrine." (3289590)

Literature Case—Ephedrine

A 28-year-old male truck driver was, according to his family, taking up to 600 mg of ephedrine per day for six years. After having consumed 250 mg of ephedrine one day, he collapsed while baling hay. Autopsy did not reveal any pathologic process to account for his death. "Specifically, the coronary arteries, valves, and myocardium, including the conduction system, were normal." Only ephedrine and guaifenesin were identified on toxicology screens. The conclusion was that death "was most likely due to a cardiac arrhythmia triggered by the combination of an excessive use of ephedrine and strenuous labor on a hot day." (348)

Possible Sentinel Events

FDA Cases—Ephedra

A 36-year-old female began taking Nature's Nutrition-Formula One in August 1993. In December 1993, she was taken to the emergency department and found to have low potassium but signed out Against Medical Advice. In May 1994, she had severe stomach cramps and later that day was found unconscious by her daughter. She was taken to the hospital, where she died five days later without having recovered consciousness. According to her husband, she had no history of heart, thyroid, or blood pressure problems. The medical record documents a past history of bulimia and anorexia. There is a brief autopsy form consisting of a series of hand-written notes and check marks. Next to the word "cardiovascular" is a handwritten check mark, suggesting the heart had been examined and found normal, but no dictation describes the heart. There is an extensive description of the brain, which was normal. Elsewhere in the medical chart is a statement that the patient was thought to have had an acute myocardial infarction with adult respiratory distress syndrome and heart failure. Her creatine phosphokinase (CPK) isoenzymes and myoglobin (MB) fractions were both elevated. The emergency department record reported a toxicology screen positive for ephedrine, phentermine, and chlorpheniramine. A cardiology note and an echocardiogram reported severe global cardiac dysfunction and a left ventricular ejection fraction of 25 percent. We classified this case as no higher than a possible sentinel event because there was no evidence available to us of an adequate examination of the heart. It is possible that this woman could have had acute myocarditis, which led to global cardiac dysfunction. (9508)

A 32-year-old male truck driver was found dead in his truck by the police. In the truck were found Nature's Nutrition-Formula One, Nature's Nutrition-Formula Three, a bottle of Tylenol with codeine, Vicks Formula 44, Nyquil, Ibuprofen, and Rexall cold tablets. The FDA files do not contain a copy of the actual autopsy report, but notes state that the autopsy report said the heart was enlarged, the coronary arteries were normal, and there was a slight case of pneumonia. The cause of death was listed as myocarditis, bronchiolitis, and pneumonia. Toxicology screen was negative for ephedrine but did show pseudoephedrine and doxylamine. We classified this case as a possible sentinel event because the myocarditis could have contributed to his death and the etiology of the myocarditis is unknown. (10276)

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. Because of this preexisting condition, we classified this as a possible sentinel event. (12485)

A 21-year-old male on his college wrestling team was trying to lose weight, perhaps as much as 17 pounds in a few days, to achieve a weight limit for an upcoming meet. He had been taking Thermogenics Plus for an unknown length of time. He began to feel weak while sitting in the sauna. He left the sauna, went to get a drink, and collapsed. On autopsy, the cause of death was listed as sudden cardiovascular collapse with rhabdomyolysis and dehydration. The heart exam revealed normal coronary arteries. We classified this as a possible sentinel event since the intense effort to lose weight likely led to dehydration, which then led to cardiac collapse. (12722)

A 15-year-old female collapsed and died while playing soccer. She had been taking Ripped Fuel for an unknown length of time. At autopsy, she was found to have a congenital abnormality: an anomalous origin of the left coronary artery from the pulmonary circulation (the Bland-White-Garland Syndrome). This condition is not usually associated with life beyond infancy, if left uncorrected. Due to this preexisting condition, the case was classified as a possible sentinel event. (12843)

A 26-year-old male had been taking Ripped Fuel for two weeks prior to his death. There is no autopsy report in the FDA files, but detailed notes state that the autopsy revealed he died of acute aortic dissection. According to the file, he had been having back pain two weeks prior to his fatal event and went to the emergency department complaining of severe chest pains. He was diagnosed with esophagitis and sent home. Four days later, he returned to the emergency room again with severe chest pains and was told the source of his pain was the chest wall. The next day, he was found dead by his girlfriend. According to his family history, several relatives had also had an aortic dissection, including a niece who had had an aortic dissection at age 18. The notes state, "This appears to have been some form of genetic connective tissue abnormality." There is also evidence of prior borderline hypertension. Toxicology screen for cocaine, ephedrine, and amphetamines was negative. Only caffeine and acetaminophen were found in the blood. This case was classified as a possible sentinel event, because it appears the patient was genetically predisposed to aortic dissection. (13906)

A 26-year-old female was found dead by her father. She had been taking a product called Diet Fuel for six months. The adverse event report stated, "Coroner felt this was a massive heart

attack." Autopsy concluded she suffered from tachycardia, high blood pressure, and restriction of the coronary artery. The death certificate stated that death was due to "dissection of the left anterior coronary artery." Ephedrine and pseudoephedrine were found in the blood. This case was classified as a possible sentinel event. (14019)

A 35-year-old male, who had been taking Hydroxycut for seven days to increase energy, came home from work early because he was not feeling well, went to the bathroom, and was later found unresponsive. At autopsy, an 80 percent stenosis of the proximal left anterior descending coronary artery was found, along with "moderate" stenosis of the right and left circumflex coronary arteries. The cause of death was listed as atherosclerotic coronary vascular disease. Because of this preexisting condition, we classified this case as a possible sentinel event. (14638)

Literature Case—Ephedra

A 23-year-old man was found dead in his apartment by his sister. He had been using Ripped Fuel. Autopsy showed "no gross evidence of a pathologic process." Microscopic examination of the heart reported "multifocal and confluent myocyte necrosis with healing of approximately 1 to 2 weeks; mild perivascular, focal endocardial, and focal epicardial fibrosis; and moderate myocyte hypertrophy and vascular congestion. There was no evidence of myocarditis." Blood toxicology screen was negative, but urine toxicology screen showed ephedrine at 1.6 μg per ml. We classified this case as a possible sentinel event. (258)

Literature Cases—Ephedrine

A 42-year-old male was found dead at home. On autopsy, he was found to have had an intracranial hemorrhage and was also found to have hypertensive cerebral vasculopathy. He had been taking a street drug ("speed") that contained ephedrine, and toxicology screen was positive for ephedrine at 2.7 μg per ml. We classified this case as a possible sentinel event due to the preexisting vasculopathy. (44)

An 84-year-old female was found in a coma and subsequently died. On clinical investigation, she was found on computerized tomography (CT) scan to have a subarachnoid hemorrhage and a right subdural hemorrhage. At autopsy, she was found to have a ruptured berry aneurysm along with cerebral atherosclerosis. She had been taking an unknown drug containing ephedrine, and her blood toxicology screen was positive for ephedrine. We classified this case as a possible sentinel event due to the preexisting berry aneurysm. (44)

A 44-year-old male was taking ephedrine as a replacement for daily coffee and cocoa. He had a sudden cardiorespiratory arrest and died. Autopsy revealed an acute thrombus in the left anterior descending coronary artery. The report states, "All other coronary lumina were patent, although calcified with focal narrowing to approximately 50 percent." Due to the preexisting coronary artery disease, we classified this case as a possible sentinel event. (224)

Probably Not Related

FDA Case—Ephedra

A 24-year-old male collapsed and died during a training run. He had reportedly taken Ripped Fuel, although none was found in his personal possessions, nor were traces of amphetamines

found on toxicology screen (which looked for ephedrine as well). At autopsy, he was found to have died of massive sickle-cell crisis. As a result, we classified this case to be probably not related to ephedra use. (13672)

FDA Cases—Ephedrine

A 40-year-old male was taking Max Alert to stay awake on the job. He had "odd symptoms that were not a recognizable illness," described as "nausea, dizziness, sweats, irritability, dehydration, respiratory problems, etc." The report then states that he was killed in a car accident while driving. We classified this case as probably not related to ephedrine use and note that it may be the same case as Case 1902493, which has a virtually identical description, both cases having been filed within one month of each other. (1859087)

A young male was killed in an automobile accident while driving home in the early morning from his night shift job at a hotel. The patient had been using Max Alert to stay awake. The cause of death at autopsy was laceration of the aorta. We classified this case as probably not related. (1902493)

A 30-year-old male was found dead. He had had chronic low back pain and a chronic pain disorder and was on numerous medications. Autopsy did not reveal any cause of death; however, the toxicology screen was positive for alcohol, fentanyl, phenylpropanolamine, ephedrine, pseudoephedrine, bupropion, nordiazepam, alprazolam, chlordiazepoxide, and nortriptyline. Cause of death was listed as mixed drug and alcohol intoxication. We classified this case as probably not related. (3491515)

A 29-year-old male died. Toxicology screens of blood and urine revealed that he was positive for morphine, hydrocodone, acetaminophen, diphenhydramine, hydromophone, promethazine, dihydrocodeine, codeine, pseudoephedrine, ephedrine, brompheniramine, phenothiazine, cannabinoids, and nicotine. We judged this case as probably not related. (3772362)

Insufficient Information

FDA Cases—Ephedra

A 37-year-old male collapsed and died after taking Metabolife for weight loss and energy. At autopsy, ephedrine was found in the blood. In addition, one coronary artery was found to be 70 to 80 percent stenosed. These data were recorded on a single page of telephone conversation notes in the file. Because there was no other documentary evidence regarding this case, we classified it as having insufficient information to judge. (13806)

A 56-year-old male who had recently started taking Thermogen Plus Liquid fat complexor tablets was found slumped over in his bathtub after a barbecue. He had a history of hypertension and was on a calcium channel blocker as well as daily baby aspirin. Within the year prior to his death, he had had a normal treadmill test. He also had elevated cholesterol for at least four years prior to his death. Four days before his death he was noted to have heartburn. No autopsy report was in the FDA records. A report of a phone conversation stated that the death certificate listed "cardiac arrhythmia of unknown etiology" as the cause of death. We counted this case as having insufficient information, because no autopsy report was available to us, and he had preexisting

hypertension and elevated cholesterol. Without the finding of the autopsy report that detailed the examination of the cardiovascular system, we can come to no other conclusion. (14465)

Myocardial Infarctions/ Acute Coronary Syndromes

Sentinel Events

FDA Case—Ephedra

A 45-year-old male took two tablets of Nature's Nutrition-Formula One prior to suffering a myocardial infarction. The patient had also smoked for 30 years and had been a practicing alcoholic until one year prior to the event. At angiography, the coronary arteries were found to be normal. (10024)

FDA Case—Ephedrine

A 23-year-old female took four Midnight Ecstasy tablets as a sexual stimulant. Shortly thereafter, she began developing symptoms of autonomic hyperactivity followed by palpitations, shortness of breath, and pink frothy sputum. She was taken to the emergency room, where she was found to be in pulmonary edema. Cardiac enzymes indicated acute myocardial injury. Urine toxicology screen was positive for marijuana and amphetamines. Ephedrine was not mentioned in the toxicology report. Coronary angiography did not reveal any sign of coronary artery disease. Her recovery was complicated by a presumed infection, but she was ultimately discharged from the hospital in good condition. (3446357)

Literature Cases—Ephedra

A 30-year-old male body builder was taking ma huang "as instructed by the product label." He presented to the emergency department complaining of chest pain. Vital signs revealed tachycardia and no hypertension. Electrocardiogram was consistent with acute inferior cardiac ischemia. Cardiac enzymes confirmed a myocardial infarction. Urine toxicology screen was negative for cocaine and amphetamines. Emergency cardiac catheterization demonstrated normal coronary arteries with mild global left ventricular hypokinesis and mild left ventricle hypertrophy. He recovered well. (244)

A 19-year-old male experienced chests pains 30 minutes after taking Dymetadrine Xtreme at the recommended dose. Vital signs revealed tachycardia and elevated respiratory rate of 22. The physical examination was described as unremarkable except for diaphoresis. Electrocardiogram was consistent with an inferolateral myocardial infarction, and myocardial necrosis was confirmed by cardiac enzymes. Toxicology test was negative for cocaine. Cardiac catheterization was reported as showing "only minimal intimal disease of the distal left anterior descending artery." The patient was reported to have recovered well. (516)

Literature Case—Ephedrine

A 35-year old woman was taking a dietary supplement containing ephedrine for weight loss. She had the acute onset of chest pain, diaphoresis (perspiration), and shortness of breath. She was admitted to the hospital, where an electrocardiogram and cardiac enzymes were consistent with acute myocardial infarction. Results of a cardiac catheterization were reported as "normal cardiac function and normal coronary arteries." She was discharged with a diagnosis of acute myocardial infarction secondary to cardiac spasm. (224)

Possible Sentinel Events

FDA Cases—Ephedra

A 37-year-old male took E'ola Amp II Pro Drops for twelve days prior to suffering an inferior myocardial infarction. At coronary angiography, his mid-right coronary artery was found to be 95 percent stenosed. The patient received percutaneous transluminal coronary angioplasty. Due to the preexisting condition, we classified this case as a possible sentinel event and note the product was later reported to include illegal doses of ephedrine. (9372)

A 54-year old-male with a history of hypertension had been taking Nature's Nutrition-Formula One for approximately three to four months prior to suffering an inferior myocardial infarction. He also had a cardiac arrest from which he was successfully resuscitated. On angiography, he was found to have an 80 percent stenosis of the right coronary artery along with total occlusion of the obtuse marginal artery. He was treated with angioplasty. Because of the preexisting condition, we classified this case as a possible sentinel event. (9504)

A 35-year-old male took five capsules of Metabolift prior to a vigorous workout. He then had an acute inferior myocardial infarction, for which he received thrombolytic therapy. At angiography, his left anterior descending coronary artery had ectasia, which is indicative of coronary artery disease. Therefore, we classified this case as a possible sentinel event. (10009)

A 38-year-old female took Herbalife Original Green for one day. The next day, she suffered an inferior myocardial infarction, for which she received thrombolytic therapy. At catheterization, the posterior descending artery was found to be totally obstructed. The left coronary artery was found to be normal except for one area with a 70 percent lesion. The toxicology screen was negative for cocaine but positive for amphetamines. Ephedrine was not mentioned in the toxicology report. The diagnosis was "presumed right coronary spasm with Prinzmetal's Angina." In the setting of coronary artery disease, we classified this case as a possible sentinel event. (13009)

A 37-year-old female with a family history of coronary artery disease was both overweight and a cigarette smoker. She was taking Metabolife 356 to lose weight. She suffered a myocardial infarction and was found on angiography to have total occlusion of the right coronary artery with diffuse disease in the left anterior descending coronary artery and the left circumflex artery. She received percutaneous transluminal coronary angioplasty with placement of a stent. Because of the preexisting condition, we classified this case as a possible sentinel event. (14114)

A 43-year-old female had a heart attack. Earlier that day, she had taken six tablets of Metab-O-Lite. She was a cigarette smoker and had a lipid disorder. At coronary catheterization, the left main coronary artery was found to be normal, the left anterior descending artery had 20–30 percent stenosis, the left circumflex artery had no disease, and the right coronary artery had 30 percent stenosis. Because of the preexisting coronary artery disease, we classified this case as a possible sentinel event. (14530)

Cerebrovascular Accident/Stroke

Sentinel Events

FDA Cases—Ephedra

A 26-year-old female began taking Thermo Slim and The Accelerator daily for weight loss. Three days later, her legs became weak, and she reported feeling like she was going to pass out. She was taken to the emergency room where she was found to have a probable basal ganglia hemorrhage on CT scan. She also had paranoid psychosis. She was a long-time intravenous drug abuser and alcohol abuser. She had also smoked cigarettes for ten years. She was not taking oral contraceptive pills. Blood pressure in the emergency room was 129/71. Toxicology screen was positive for acetone and for benzodiazapines. It was negative for cocaine, amphetamines, and a host of other substances, but ephedrine was not specifically examined. Ephedrine was not mentioned in the toxicology report. She signed out Against Medical Advice from that hospital and ended up in another hospital later that day in restraints. Another toxicology screen was positive for phenylpropanolamine and benzodiazepine. At this hospital, rheumatologic and embolic evaluation was negative. (10874)

A 42-year-old female who was taking Power Trim began having headaches. Approximately one week later, when she was scheduled to undergo a root canal procedure to treat a dental abscess, her daughter heard a “thump” on the floor and found her mother shaking, lying on the floor, unresponsive. She was taken by ambulance to the emergency room, where she was observed to have a focal seizure, which then generalized. She had no prior history of seizure. Toxicology screen was negative. Glucose was 93. CT scan revealed a possible small area of hemorrhage in the upper right parietal region. An MRI with contrast revealed a 1 by 1-1/2 centimeter area of acute hemorrhage without mass effect and without abnormal vascularity. Digital subtraction angiography did not reveal any evidence of arteriovenous malformation. The patient remained seizure-free on anticonvulsant therapy. (11062)

A 31-year-old female had been taking Trim Easy for weight loss for nine months. She occasionally took up to 6 caplets at a time and smoked 3–4 cigarettes a day. She was found in the bathroom unconscious and brought to an emergency room. Her blood pressure was 143/86. CT scan showed a large intracerebral hematoma. Cerebral angiography did not show any source of the hemorrhage, and MRI also was remarkable only for the bleed. Medical records documented improvement over a period of time, but she was left with substantial physical limitations. (11105)

A 28-year-old male who was described as a weight trainer took Ripped Fuel. He also smoked two packs of cigarettes per day. During sexual relations with his wife, he had a headache and became dizzy. He was taken to the emergency department where he was found to have a right middle cerebral artery infarction that was “suggestive of vasospastic phenomenon.” At the time of his admission, his blood pressure was 132/78. His toxicological examination was positive for benzodiazapines. Ephedrine was not mentioned in the toxicology report. Cerebral angiogram was negative. Rheumatologic and hypercoagulability evaluations were negative. There was a negative transesophageal echocardiogram. Urine screen showed ephedrine, pseudoephedrine, and caffeine, according to a discharge summary, which also described the illness as “cerebral infarction associated with ephedrine and caffeine use.” (11675)

A 39-year-old male Navy diver, who regularly took Ultimate Orange for energy, presented to the ship doctor with right hand and leg numbness. The symptoms had occurred 1½ hours after using the product, during a workout. He also reported taking omeprazole, creatine, and vitamins. CT scan and angiogram were negative except for an intracerebral hemorrhage. Blood pressure initially was 140/72. The patient made a good recovery and was able to go back to work but was prohibited from further diving. (12980)

A 29-year-old male in the Army, who was taking Ultimate Orange and had a history of migraine headaches, reported that he was running on a treadmill, when he experienced "the worst headache of his life." He was taken to the emergency department, where he had some right-sided weakness, which improved over the next 12 hours. The CT scan and lumbar puncture were normal. The following morning, most of his symptoms had resolved, but then he suddenly developed total hemiplegia. He underwent an emergency MRI and angiogram, which showed a complete occlusion of the right middle cerebral artery. The patient had a very stormy course, ultimately resulting in a right hemispherectomy to control swelling. A full hypercoagulability workup was done and was normal. Echocardiogram did not reveal an embolic source. Microscopic examination of the brain tissue did not show any sign of vasculitis. (13418)

A 53-year-old female was taking Slim Caps. In June 2000, she presented with the clumsy hand syndrome on the right. At the time, her blood pressure was 204/128. She stated that in the past, her systolic blood pressure had been 135. CT scan at the time of the event showed a lacunar infarct in the right frontal parietal region. She made a good recovery. A hypercoagulability workup was negative. Echocardiogram was done and showed no evidence of clot. (14372)

A 46-year-old female took Xenadrine for 4 days. While at work, she stood up, had a seizure, and became unresponsive. She was taken to the emergency department. A CT scan showed a left-sided frontal cortex stroke. MRI showed occlusion of the left middle cerebral artery. Blood pressure in the emergency room was 102/69. MR angiography was negative. Transesophageal echocardiogram was negative. Hypercoagulability workup was negative. (14473)

Literature Case—Ephedra

A 33-year-old male presented to the emergency department with the sudden onset of left hemiparesis and slurred speech. He smoked one pack of cigarettes a day and took bupropion for smoking cessation. He consumed Thermadrene 8 hours prior to the onset of neurologic symptoms. There was no hypertension. A noncontrast CT scan did not show any abnormalities. There was no evidence of intracerebral hemorrhage. He was treated with tissue plasminogen activator. Normal tests included a sedimentation rate, clotting studies, urine toxicology screen, homocysteine, antinuclear antibodies, Factor V level, complete hypercoagulability evaluation, echocardiogram, VDRL, and carotid and vertebral duplex studies. He was given a diagnosis of new cerebrovascular accident in the right middle cerebral artery. He was left with a permanent disability. (552)

Literature Cases—Ephedrine

A 19-year-old female with a history of anorexia/bulimia and alcoholism presented after taking 15 to 18 tablets that contained ephedrine 25 mg (along with guaifenesin). She had previously been taking this product 3 to 10 tablets at a time to lose weight, and the case report

was silent regarding whether or not this increased dose was a suicide attempt. Initial presentation was unremarkable, but while in the emergency department, she developed a severe headache and right-sided paralysis. Blood pressure was elevated at 136/98. A CT scan showed left parieto-frontal cerebral hemorrhage with extension into the left lateral ventricle. Angiography did not document a source of the bleed. She was treated with an emergency craniotomy and hematoma evacuation. No arteriovenous malformation was found. She survived but had a major residual neurologic deficit. We classified this case as a sentinel event, but also note this may have been an unrecognized suicide attempt. (184)

A 20-year-old woman took two capsules of a "purported amphetamine look-alike." Two hours after consumption, she developed a severe headache, nausea, hemiparesis, and aphasia. Ten hours later, she sought admission to a hospital. On initial evaluation, her blood pressure was not elevated and she had a right homonymous hemianopsia and a dense right spastic hemiparesis. At that time, sedimentation rate, clotting studies, rheumatologic studies, and other tests evaluating both vasculitis and the hypercoagulable state were negative. CT scan showed a left external capsular hemorrhage with shift of the midline structures. Angiography showed alternating narrowing and dilation of several branches of the middle cerebral artery. She made a slow and incomplete recovery. Analysis of the capsules demonstrated the presence of ephedrine, phenylpropanolamine, and caffeine. (514)

Possible Sentinel Events

FDA Cases—Ephedra

A 32-year-old female who was taking E'ola Amp II Pro Drops for weight loss suffered a brain stem stroke. She had been to the emergency room twice earlier in the day prior to her stroke and both times was thought to be having an allergic reaction to peanut butter. She was taking oral contraceptive pills. Evaluation of the cause of her stroke included a transesophageal echocardiogram that was negative except for an atrial septal aneurysm, but this was not thought to be the cause of the stroke. Lumbar puncture was negative. Cerebral angiography showed the basal artery was occluded with embolus. Because no hypercoagulability workup was noted, we could not judge this case as more than a possible sentinel event, and also note this product was later reported to include illegal doses of ephedrine. (9296)

A 56-year-old female who was taking E'ola Amp II Pro Drops for three months suffered a lacunar infarct. She had preexisting hypertension, total cholesterol of 238, and triglycerides of 529. She also had a 60-pack-per-year history of smoking. CT scan was negative. The MRI revealed microvascular changes. Because of her preexisting conditions, we classified this case as a possible sentinel event, and also note this product was later reported to include illegal doses of ephedrine. (9335)

A 24-year-old female had a right internal capsule stroke after taking one dose of Super Fat Burners. She was not taking oral contraceptive pills or on any other medications. Carotid arteriogram was normal, echocardiogram was normal, and drug screen was negative. She had had two miscarriages in the past. While most of the hypercoagulability evaluation was normal, one test suggested the presence of the lupus anticoagulant. Because the antiphospholipid antibody syndrome was not effectively excluded, we classified this case as a possible sentinel event. (10094)

A 64-year-old female with a history of hypertension, paroxysmal atrial fibrillation, and two transient ischemic attacks was on propranolol, isradipine, and aspirin therapy, and had taken Fit America Natural Weight Control Aid. She was found unconscious in the bathroom by her husband and taken to the emergency room, where she was found to have had an embolic stroke. She was given heparin, which resulted in a small left temporal parietal intracerebral hemorrhage. She was found to be in atrial fibrillation. Carotid ultrasound was negative. Due to the preexisting condition of atrial fibrillation, we classified this case as a possible sentinel event. (12713)

A 47-year-old male, who had a long history of hypertension but had not taken medication in 20 years, suffered a right lentiform nucleus bleed that manifested itself as left-sided paralysis. The notes stated that just prior to the event, he took Purple Blast to lose weight; however, there was no drug or alcohol use. When he arrived in the emergency department, his blood pressure was 196/94, and it later fell to 187/107. Chest x-ray revealed cardiomegaly. CT scan showed "large acute intracranial hemorrhage in mid portion of right cerebral hemisphere." His triglyceride levels were 364. Because of the history of long-standing untreated hypertension, we classified this case as a possible sentinel event. (12733)

A 41-year-old female with a history of hypertension who had been taking Diet Phen and had four stroke events over a two-month period. Blood pressure in the emergency department after one event was 170/108, and at another time, it was 158/99. She was put on coumadin and discharged home after her first stroke but then was readmitted three times in the next two months for recurrent stroke, all of which occurred while she was on anticoagulants. She suffered additional neurologic events consistent with brain stem infarction. She had numerous magnetic resonance angiograms, the first of which revealed an "irregularity of the basilar artery." Subsequent studies showed the basilar artery totally occluded. The interpretation of these angiograms was the subject of considerable discussion, with the final interpretation in the notes being "basilar artery vasculitis." Rheumatologic evaluation and hypercoagulability evaluation were negative. This case was difficult for us to assess since amphetamines have been linked to vasculitis, but her vasculitis could also have had other etiologies and therefore we classified this case as a possible sentinel event. (12888)

A 25-year-old female who was taking Natural Trim presented with slurred speech and right-sided weakness. She was not on oral contraceptives and was a nonsmoker for five months. Blood pressure recorded in the nurse's notes was 144/88. MRI revealed a lacunar stroke. Carotid duplex was negative. Echocardiogram showed a mitral valve prolapse with a patent foramen ovale with a right-to-left shunt that was described as minimal. No clot was seen. The patient had total resolution of symptoms. Hypercoagulable workup was normal, but incomplete. No tests of protein S or C (proteins involved in blood clotting) were reported in the FDA material. Therefore, we classified this case as a possible sentinel event. (14378)

A 42-year-old male who was taking Slim 'N Up awoke with paresthesia on the left and difficulty walking and talking. He was a nonsmoker for five years. The patient had a known diagnosis of hypertension, was on Diltiazem, and also had hypercholesterolemia. Emergency department blood pressure was 132/89. Lumbar puncture in the emergency room was traumatic, with 35 red blood cells in tube 1 and 0 red blood cells in tube 4. A transcranial Doppler study was negative, carotid duplex study was negative, echocardiogram was negative, and MRI

showed left cerebella infarct. Subsequent admissions were for seizure control. We classified this case as a possible sentinel event due to the prior hypertension and hypercholesterolemia and the lack of complete hypercoagulability workup. (14434)

A 55-year-old female who had been taking Metabolife 356 for 60 days developed a headache, had a seizure, and became unconscious. She was taken to the emergency department, where she was found to have a large subarachnoid hemorrhage. An emergency angiogram showed a large right posterior communicating artery aneurysm, which was subsequently clipped. She had a stormy course complicated by meningitis, hydrocephalus, and placement of a ventricular peritoneal shunt. Because of the preexisting large aneurysm, we classified this case as a possible sentinel event. (14553)

Literature Case—Ephedra

A 33-year-old man who had been taking ma huang (40–60 mg per day of ephedra alkaloids) for energy and weight training awoke with a severe Wernicke's aphasia. He had not complained of prior headache or other symptoms. He had a slight right-sided facial and arm weakness and a right Babinski sign. His blood pressure was 140/60, and his pulse was 54 per minute. Brain CT showed signs of extensive left middle cerebral artery infarct. Cervical ultrasound duplex scanning and cerebral angiography were normal. Cerebral CSF examination was normal. The report contained no coagulopathy assessment other than D-dimers (cross-linked fibrin molecules that may be a diagnostic marker for venous thromboembolism), which were within the normal range. Creatinine was in the normal range. Transesophageal echocardiography and ECG were also normal except for a patent foramen ovale. We classified this case as a possible sentinel event, because there was no additional documentation about the details of the coagulopathy evaluation. (270)

Literature Cases—Ephedrine

A 37-year-old male who ingested 10 pills of a "street drug" containing ephedrine (15.3 mg per tablet, as identified by subsequent analysis), developed sudden right body numbness and, on evaluation, was found to have pure right body sensory loss with a left thalamic infarct on MRI. Laboratory studies included normal prothrombin time and partial thromboplastin times, sedimentation rate, electrocardiogram and transthoracic electrocardiogram. The patient refused arteriography. As a result, we classified this case as a possible sentinel event. (44)

A 20-year-old man was admitted with nausea, vomiting, and headache that began one hour after he took an unknown quantity of what he called "speed." Urine drug screen on the day of admission revealed only ephedrine, in particular excluding amphetamine, phenylpropanolamine, caffeine, and other drugs. CT scan obtained on admission demonstrated blood in the subarachnoid space, which was confirmed by lumbar puncture. Angiography on the day of admission was normal, and rheumatologic evaluation was negative. A repeat angiogram seven days later showed features typical of vasculitis. We classified this case as a possible sentinel event. (438)

Insufficient Information

FDA Cases—Ephedra

A 36-year-old female who was taking Nature's Nutrition-Formula One for weight loss developed a headache. Based on CT and MRI, she was diagnosed as having had a stroke. She was a nonsmoker and was not taking oral contraceptive pills. This information was obtained from notes of a conversation with the patient herself. The notes stated that medical records were requested; however, none appeared in the FDA file. Therefore, we classified this case as having insufficient information. (9521)

A 30-year-old female who took Metabolife 356 for one week developed a headache while eating and had a stroke. A friend drove her to the hospital; en route, they encountered a paramedic, who obtained a blood pressure reading of 249/131. She stated that she was on no medications, had no hypertension, didn't smoke, and didn't drink. Unfortunately, no additional information appeared in this record. Therefore, we classified this case as having insufficient information. (13829)

A 36-year-old female who took Metabolife 356 had "respiratory failure and a possible stroke." The file contains a note stating that medical records were requested but were never received. Thus, we classified this case as having insufficient information. (13905)

FDA Case—Ephedrine

A 32-year-old female who, according to case notes, was taking over 100 "Maxi Thins" per day for five years and was "addicted to product," had three cerebral hemorrhages and two strokes and was hospitalized for two months. No additional information is available. Thus, we classified this case as having insufficient information and also note the extraordinary dose of ephedrine being consumed. (1823550)

Literature Case—Ephedrine

A 68-year-old man who had been taking an "over-the-counter anti-asthma pill" containing 40–60 mg of ephedrine per day for 10 years had a left temporal-parietal hematoma with rupture into the lateral ventricle. Angiography showed changes consistent with vasculitis, and pathological examination from material obtained during surgical evacuation of his hematoma showed necrotizing angiitis of the small vessels. The patient improved with prednisone. We classified this case as having insufficient information. (515)

Other Cardiac and Other Neurological Cases

Near Sudden Death

A 22-year-old male who regularly used Ripped Force along with a variety of other supplements collapsed while lifting weights and had a ventricular fibrillation cardiac arrest complicated by hypoxic encephalopathy. Although he had a history of asthma, this was not felt to be an asthmatic attack. Toxicological examination revealed ephedrine, pseudoephedrine, methyl ephedrine, and phenylpropanolamine. An echocardiogram ruled out asymmetric septal hypertrophy but did reveal a reduced left ventricular ejection fraction (35–40 percent) and an increased left ventricular end diastolic dimension. CT scan showed no brain tumor or bleed. A pulmonary consultant who saw him in the hospital stated that he "doubts" that this incident was related to asthma. He recovered to the point where he could feed himself but he does not

remember his friends and has substantial mental disability. We classified this as a possible sentinel event since the echocardiogram results raise the possibility that this patient could have had a cardiomyopathy, which then could be the cause of the cardiac arrest. (12851)

A 28-year-old female who took Herbalife Original Green had a cardiac arrest later that same day while playing softball. According to the affidavit, she needed to be defibrillated four times and now has a permanently implanted defibrillator. Unfortunately, other than this affidavit, no information was available. Therefore, we classified this case as having insufficient information. (13031)

A 32-year-old female had been taking Natural Trim for two weeks. On one morning, after taking Natural Trim, she ate lunch, went outside her office building to smoke a cigarette, and had a witnessed cardiac arrest. A physician bystander initiated CPR, and she was taken to the Emergency Department with decorticate posturing. Although successfully resuscitated, she was left with permanent heart and brain damage. She also had a permanent intracardiac defibrillator implanted. Notes from the FDA investigator said that her hospital records showed she had chronic obstructive pulmonary disease, ventricular fibrillation, and "cardiomyopathy versus acute myocarditis" with "possible contributing factor of cardiotoxic diet pill." She had a left ventricular ejection fraction of 35 percent with global left ventricular hypokinesia, and endomyocardial biopsy found mild focal hypertrophy and mild focal interstitial fibrosis. No medical records were available in the FDA files. Therefore, we classified this case as having insufficient information. (13643)

Cardiomyopathy

A 28-year-old female who had been taking ephedrine tablets (2000 mg per day) for eight years to lose weight presented with dilated cardiomyopathy. She denied any other chronic alcohol or drug use except tobacco. She reported that after abruptly reducing the dose of ephedrine to only 75 mg per day, she rapidly developed symptoms of dyspnea, fatigue, and orthopnea (difficulty breathing while lying flat). Exhaustive diagnostic evaluation, including cardiac catheterization and endomyocardial biopsy, revealed no specific diagnosis, and the patient's dilated cardiomyopathy was characterized as idiopathic. We classified this case as a possible sentinel event, but note the extraordinary level of ephedrine use. (110)

A 39-year-old male with a history of hypertension presented with dyspnea on exertion, orthopnea, and edema. He had been taking numerous Herbalife supplements (including Original Green) for three months, which provided a total of between 7 and 21 mg of ephedrine alkaloid daily. Exhaustive diagnostic evaluation, including endomyocardial biopsy, yielded a diagnosis of hypersensitivity or eosinophilic myocarditis. He was treated with azothioprine and prednisone, and Herbalife medications were discontinued. At six months follow-up, his heart function was normal. We classified this as a possible sentinel event. (297)

A 32-year-old housewife who was noted to be abusing ephedrine, taking up to 450 mg a day, presented with "congestive cardiac failure" and received a clinical diagnosis of congestive cardiomyopathy of unknown etiology. No coronary angiography or myocardial biopsy was performed, which may have been within the standard of practice at the time of the case (1980).

We classified this case as having insufficient information and also note the high level of ephedrine intake. (260)

A 65-year-old female who had been taking the product Thermolean for two years was hospitalized with acute congestive heart failure. Evaluation revealed cardiomyopathy with a left ventricular ejection fraction estimated at 15 percent and atrial fibrillation. It was the treating physician's opinion that the cardiomyopathy was "probably secondary to ephedrine use." There were no medical records available with this file. Therefore, we classified this case as having insufficient information. (13793)

Ventricular Tachycardia

A 48-year-old female was taking Metabolife 356 for approximately one month when she developed a rapid heartbeat that would not subside. She was taken to the emergency department and found to be in ventricular tachycardia. The file contained no information on diagnosis or treatment procedures, although the MedWatch form stated that the patient said she was taking beta-blockers. No medical records were available for this adverse event. Therefore, we classified this case as having insufficient information. (13945)

Transient Ischemic Attack

A 57-year-old female with prior history of hypothyroidism, gastroesophageal reflux disease, depression, degenerative joint disease, and fibromyalgia began having nausea and vomiting and became disoriented. She had been taking Synthroid, Oxycontin, Prozac, Trazodone, Prilosec, and one other medication whose name was illegible in the file notes. She also took Metabolife 356 for one day and a total of 48 mg of ephedrine prior to the adverse events. Her husband took her to the emergency department, where an examination was inconclusive. Laboratory values were essentially normal. A toxicology screen was positive for opiates but negative for amphetamines. A CT scan was negative. She was seen in consultation by a neurologist who told her that she had a vasospasm transient ischemic attack, possibly related to ephedrine use, and the discharge instructions were to stop using the Metabolife 356 supplement. We classified this case as a possible sentinel event, because the symptoms alone do not confirm that she had a transient ischemic attack. (13062)

Seizure

Sentinel Events

FDA Case—Ephedra

A 19-year-old female who reported using Shape Rite/Shape Fast at half the recommended dose for three to four weeks had one witnessed episode in which her "arms and legs went stiff, noticeable drool appeared, eyes rolled, [and she] appeared to black out," followed by a postictal period (period of confusion typically observed following a seizure). She had no prior history of seizures. Electrolytes were normal; complete blood work was normal; and pregnancy test was negative. She had a normal CT scan without contrast and a normal electroencephalogram. She was seen by a consultant neurologist, whose diagnosis was that she had a "single-tonic seizure, and none of the other factors which (*sic*) are normally associated with seizures, are present." (10974)

Literature Case—Ephedrine

A 38-year-old female with no prior seizure history experienced two "petit mal" seizures (the authors' description) after taking two tablets of over-the-counter ephedrine-containing dietary supplements in the morning and evening. The following day, she had a generalized tonic-clonic seizure, during which she required respiratory assistance. Over the next five days, she continued to have petit mal and generalized tonic-clonic seizures. She was diagnosed with new onset of tonic-clonic seizures with complex partial seizures. The report (in *Morbidity and Mortality Weekly*) stated, "Other possible causes of seizures were excluded." After discontinuing the ephedrine-containing dietary supplement, she had no further seizures. (224)

Possible Sentinel Events

FDA Cases—Ephedra

A 47-year-old female who had been taking Nature's Nutrition-Formula One for three weeks to lose weight (one pill twice a day) had a tonic-clonic seizure in her sleep at 2 a.m. Her husband took her to the emergency department, where some evaluation was done, but she was treated and released on no therapy. Two months later, she had another seizure, which occurred at 5 a.m. At that time, she was transported by ambulance to the emergency department and was seen by a neurologist. A random glucose was 90, electrolytes were normal, sedimentation rate was 52, MRI was normal, and EEG was described as "mildly abnormal." She had a remote history of hysterectomy and ear surgery two years prior to the event. Her only medication was Premarin, and she used alcohol only socially. It was the neurologist's opinion that the patient had new onset generalized tonic-clonic seizures, and "hypoglycemia" was suspected but could not be proved. The patient's subsequent course was complicated by rash, fever, mild pancytopenia, and increased liver function tests, which were thought due to her anticonvulsive therapy. We classified this case as a possible sentinel event, because other causes were considered and not effectively excluded. (9534)

A 37-year-old female who was taking Nature's Nutrition-Formula One was admitted to the hospital for symptoms of dizziness, shortness of breath, palpitations, and "passing out," and "intermittent episodes of confusion," with one episode of "shaking of limbs and saliva coming out of her mouth." She had no prior history of seizures. She denied using alcohol. She was seen in consultation by a neurologist. Electrolytes were normal, complete blood count was normal, arterial blood gas was normal, glucose was 179, magnesium was normal, toxicology screen was negative, pregnancy test was negative, CT scan with and without contrast was read as a "0.8 by 0.6 centimeter calcification in the frontal region, which may represent dural calcification." Subsequent MRI was normal and showed no evidence of calcification in the area seen on CT scan. Mild chronic right sinusitis was noted. EEG was interpreted as mildly abnormal due to "excessive intermittent bi-temporal slowing." No epileptogenic activity was seen. The impression of the neurologist was "complex seizures with generalization." We classified this case as a possible sentinel event. (10221)

A 62-year-old male who had been taking the product Thermo Slim for three to four months for weight loss began to have periods of memory loss, confusion, and agitation. He then had a generalized seizure with lateralizing features characterized by right sided tonic-clonic jerking and was admitted to the hospital. The patient had a prior history of heavy alcohol consumption until approximately four years before the event. In the emergency room, the patient was noted to

be normotensive and had no fever. He was characterized to be in acute delirium. Although he had no prior history of diabetes mellitus, his blood sugar on admission was 488, and he was given the diagnosis of diabetes. Toxicology screen was positive for benzodiazepines. Arterial blood gases revealed adequate oxygenation. CT scan of the brain without contrast showed atrophy but was otherwise unremarkable. MRI showed generalized brain atrophy. Electroencephalogram showed "moderate to severe abnormality, with bilateral cerebral dysfunction;" however, no epileptiform activity was identified. He was given a diagnosis of organic brain syndrome with senile dementia and also the possibility of "left temporal lobe cerebral infarct with secondary seizure." One consultant raised the possibility of acute encephalopathy of uncertain etiology. Because of the focal nature of the seizures and the multiple metabolic problems, we classified this case as a possible sentinel event. (10432)

A 23-year-old female was taking Metabolife 356, one pill two to four times a day for four months. While driving out of a parking lot, she had a generalized tonic-clonic seizure witnessed by her husband. Her husband controlled the car and prevented a crash. The seizure lasted for two minutes (during which it was noted that the patient bit her tongue) and was followed by a postictal period. She had had one seizure two years prior, which had been only partially evaluated (she had not received a CT scan at that time), and she was not treated. In addition, she had one sibling who had had a seizure at age 8, and the paternal grandparents were noted to have had seizures. She reported using alcohol only rarely. On evaluation, CT scan (non-contrast) was negative, oxygen saturation was 99 percent, toxicology screen was negative, pregnancy test was negative, and EEG was abnormal, "indicative of a potential underlying seizure disorder." Because of the prior history of seizures, we classified this as a possible sentinel event. (11649)

A 26-year-old male who had been using the product Ripped Fuel for approximately three years developed a headache that lasted approximately three days and then began experiencing seizures and was taken to the emergency room. While in the emergency department, he had a witnessed generalized tonic-clonic seizure. He had taken Ripped Fuel on the day of the event. Arterial blood gas and glucose were within normal limits. Drug screen was negative. Electrolytes were normal except for potassium of 3.2 and bicarbonate of 15.8. He had no history of medical illness, alcoholism, or serious injury. The family had no history of seizures. He had no further seizures over a three-hour period and was discharged home with referral to neurology. Two days later, he had another seizure and returned to the emergency department, where he was admitted to the hospital. Neurological consultation considered this case to be a complex partial seizure with generalized tonic-clonic seizure of new onset and to have a recent history suggestive of migraine headaches. Despite being given therapeutic doses of anti-seizure medications, he continued to have seizures to the point where he was placed in a Phenobarbital coma, requiring mechanical ventilation. After several weeks of a drug-induced coma, he was weaned off the Phenobarbital, but remained on anti-seizure medication and was left with a metabolic encephalopathy. He was transferred to a rehabilitation center. We classified this case as a possible sentinel event, because the clinical cause was quite complicated and from the records we had available we could not reach a more definitive conclusion. (13408)

A 30-year-old female was found by her husband to be moaning and making noises. She became limp and subsequently very confused. Paramedics were called and a blood glucose measured in the home was normal. She had been taking Metab-O-Lite for two to three months

for weight loss (the records are inconsistent on this point). She took one tablet before lunch and one tablet before dinner. Her last dose was on the day of the episode. She was on no medications, and had no personal or family history of seizures. She was seen in consultation by a neurologist. MRI with contrast was normal. An additional CT scan of the head, which was done without contrast, was interpreted as "negative." Serum electrolytes were normal, glucose was recorded in a dictated note as 19, but this is not commented on anywhere else in the notes and our presumption is that this is a typographical error. Serum calcium was normal, as was the complete blood count. The neurologist ordered an EEG, which showed an abnormality due to the presence of "some sharp waves emerging from the left hemisphere, mainly the parietal region." The neurologist's impression was that this was "most likely a seizure," and the patient was started and maintained on Dilantin. No further seizures were noted as of a follow-up three months after the event. We classified this case as a possible sentinel event, because it was not clear that the event was a seizure. (14275)

A 31-year-old female who was taking Thin Tabs (one tablet three times a day for approximately one month) developed a headache over her left eye, which became more severe after she took aspirin. The headache was followed by visual blurring, nausea, and vomiting, but no scintillations. She became tremulous, incoherent, and lethargic. She was taken by ambulance to the emergency room, where she had a generalized tonic-clonic seizure. In the emergency room, blood pressure was 165/107, pulse was 101, and respiratory rate was 24. Blood glucose was recorded as slightly elevated, and serum chemistries were normal. Sedimentation rate was normal. Non-contrast CT scan of the head was normal. Lumbar puncture was unremarkable. Gram stain was negative. Urine drug screen revealed amphetamines. She had no prior history of seizure. Physician's notes stated that the patient says she was "abusing" her diet pills, an assertion that was later denied in the medical record. Her medical history was remarkable for depression, for which she was being treated with Depakote (a drug used to treat seizure disorders, bipolar disorder, and schizophrenia), Trazodone, and Paxil (two antidepressants). It is also stated that she had an MRI, but those results were not in the material available for review. She had an electroencephalogram, which was normal, but which did not "entirely rule out a seizure disorder, as no Stage II sleep was seen, and a short record can miss intermittent phenomenon." Because of her EEG and in light of her taking other medications known to lower the seizure threshold, we classified this case as a possible sentinel event. (14571)

Insufficient Information

FDA Case—Ephedra

A 40-year-old female who had taken Ripped Fuel (two capsules, two times per day) for two days had a generalized tonic-clonic seizure (witnessed by her husband) while cooking dinner in her kitchen. She had no history of seizures. During the seizure, she fell, suffering a laceration to her head and was taken to the emergency department. At that time, glucose was 104, serum electrolytes were normal, and CT scan with and without contrast was normal. No report of an electroencephalogram was in the file. We classified this case as having insufficient information. (9747)

Psychiatric Symptoms

Sentinel Events

FDA Cases—Ephedra

A 21-year-old male took five to seven Nature's Nutrition-Formula One capsules in one day to stay alert while studying for final exams. He became psychotic and did not sleep for five days. A friend said he ran around campus looking like a homeless crazy person. The patient had no history of psychiatric or medical problems. (9509)

A 39-year-old female took Diet Now (tested by the manufacturer and said to contain 6 mg ephedra alkaloids per capsule, 12 mg per dose) for approximately one year at recommended doses. Her mother reports that the daughter experienced insomnia, hallucinations, psychosis, and delusions with the onset approximately one year after product initiation. She required hospitalization in a psychiatric facility for 40 days, with ongoing problems including terror, panic, and forgetfulness. She has now returned at work. (11678)

A 19-year-old female was taking Hydroxycut 2 pills twice a day to aid muscle definition and to speed metabolism. She reported dizziness and nausea two hours after use and began having violent outbursts, nightmares, poor mood, hot flashes, and fatigue. After a few days, she developed increased anger and rage and fought with boyfriend, mother, father, and sisters. She also tried to kill her boyfriend's sister and herself. After eight days of use, she developed a migraine and went to the emergency room. She then went home and picked up a knife, with homicidal intent, but was convinced to return to the hospital voluntarily. She was admitted for 18 hours and was readmitted later that day for a 72-hour involuntary hospitalization. Symptoms abated four days after Hydroxycut was discontinued. (13809)

A 29-year-old male took Xenadrine (two tablets twice per day) as a diet supplement for over six months. After six months of use, he was hospitalized three times for hyper-religiosity, paranoia, delusions, insomnia, and lack of concentration, and displayed some indication of the onset of bipolar disorder, but had no known history of prior mental health problems. Symptoms recurred twice more following use. (14529)

FDA Case—Ephedrine

A 16-year-old male took MaxAlert and Mini Thin for 11 months, often ingesting up to 40 tablets per day for weight loss and as a stimulant. The patient had episodes of aggressive behavior, irritability, tachycardia, insomnia, and violent and destructive behavior. When he visited a physician, it was noted that his symptoms coincided with an increase in dose of MaxAlert. No significant medical history and no history of other drug use were noted. We classified this as a sentinel event; however, we note the extraordinary use of product. (1855921)

Literature Case—Ephedra

A 45-year-old male who had taken an herbal dietary supplement labeled as ma huang daily for two months was brought to the emergency room by his wife when, after several weeks of using greater amounts, he began to display irritability, sleeplessness, and strange religious preoccupation. He had no medical or psychiatric history. His symptoms disappeared after brief treatment with Trazodone and discontinuation of ephedra. (48)

Literature Cases—Ephedrine

A 30-year-old female had taken Tedral (which contains ephedrine) for asthma for many years. She had no other medical problems and no history of psychiatric problems. Her mother had noticed a marked change in her behavior over the previous two years, which seemed to coincide with taking more Tedral than medically necessary. The patient became paranoid, illogical, and hallucinatory. A diagnosis of acute schizophrenic psychosis, either due to or aggravated by the abuse of ephedrine, was made. She was asked to stop taking Tedral but took it occasionally until persuaded by her family doctor to switch to cromoglycic acid. At two years follow-up, her symptoms had disappeared. (238)

A 59-year-old male who had taken ephedrine-containing products for over 25 years to treat asthma experienced auditory hallucinations, was delusional, and entered a woman's home, believing he was saving her from being tortured. At the time of the event, he had been taking ephedrine hydrochloride plus Bronchipax (ephedrine resinate 30mg; theophylline 40mg; salicylamide 250 mg) but had just doubled his daily ephedrine dose to 360 mg ephedrine plus Bronchipax. The patient had no history of psychiatric problems. The psychotic symptoms diminished 10–13 days after a reduction of the ephedrine dose. (285)

Possible Sentinel Events

FDA Cases—Ephedra

A 28-year-old female reportedly took one Slim NRG+ (ma huang) three times per day without incident for over 6 months and lost 30 pounds. After abruptly discontinuing use of the supplement, she was hospitalized for severe depression and a suicide attempt (gunshot wound to chest). She took no concomitant medications. Because no information regarding psychiatric or medical history was available, we classified this case as a possible sentinel event. (9751)

A 19-year-old man who took Ripped Fuel as directed (two capsules, three times per day) for three weeks was hospitalized with palpitations, increased blood pressure, and psychosis. He had no previous psychiatric problems or medical conditions. Because no information regarding psychiatric or medical history was available, we classified this case as a possible sentinel event. (11157)

A 13-year-old female took Nature's Nutrition-Formula One for approximately two weeks at recommended doses of approximately one tablet twice per day for weight loss. Her first symptoms were noted approximately one to two weeks after she began to use the product. She reported auditory hallucinations, disorientation to place, and withdrawal. Her symptoms endured for approximately two months. No information regarding medical or psychiatric history was included in the report, so we classified it as a possible sentinel event. (12372)

A 21-year-old male used Ripped Fuel as directed for two weeks. His parents reported personality changes such as nervousness, anger, and rage, and he went long periods without sleep. He had no previous psychiatric or medical problems. His parents reported he was sensitive to caffeine, which is included in the product. His symptoms stopped after the product was discontinued. (13005)

A 52-year-old female took Metab-O-Lite, two tablets three times per day for five months, for weight loss. She reported hallucinations, psychosis, delusions, and paranoia, which led to hospitalization in a state psychiatric facility. Her symptoms persisted for two to three days. She had a history of asthma and high blood pressure and no history of alcohol abuse. The report included a very confusing indication of a previous episode of hallucinations secondary to surgery or perhaps to Metab-O-Lite a few months earlier than the identified adverse event. (14436)

A 28-year-old female who took Metab-O-Lite (eight pills per day) for over six months for weight loss began to experience dizzy spells and headaches almost immediately after starting the supplement. She later began to experience chest tightness and a racing heart. Approximately one week after starting, she began to experience auditory hallucinations, delusions, and paranoia. Auditory hallucinations and delusions endured for over a year after discontinuing the product, thus we classified this as a possible sentinel event. (14528)

FDA Case—Ephedrine

A 31-year-old man used Max Alert for over four years, gradually increasing the dose until he was consuming 1,250 mg of ephedrine per day. He began to display psychotic behavior, including paranoia. Over four years, he was hospitalized three times, and at the time of report, was in a residential rehabilitation center for substance abuse treatment. The report states he had never used illicit substances and had no significant medical history. We classified this case as a possible sentinel event, but note the extraordinary dose of ephedrine. (1661966)

Literature Case—Ephedra

A 34-year-old male was brought to the emergency room after jumping from a second story window because he believed he was being chased. While taking ma huang over the previous nine days, he had experienced paranoid delusions and visual hallucinations. He had no history of mental illness. Medical history was not contained in the report. The patient was hospitalized for a number of weeks. After discontinuing ephedra, he remained well. The ephedrine content of the product was not noted in this case report; investigators contacted the manufacturer; however, they were unable or unwilling to disclose the amount of ephedrine in each tablet. (79)

Other Adverse Events

The FDA file contained reports of other adverse events associated with ephedra use. We briefly reviewed these reports in an attempt to more precisely establish the general nature of the adverse events, but we did not review them in more detail to determine whether they satisfied the three conditions necessary for a "sentinel event." Table 25 presents the list of other adverse events.

Metabolife File

The MIPER CD-ROMs contained 15,951 files. After removing duplicate, blank, and follow-up files, we had 18,502 cases for analysis, as indicated in Figure 18. Table 26 presents summary data regarding the key variables from our abstraction form on these cases. In 57 percent of cases, the consumer's age was not included. The majority of the remaining cases were reported by persons between the ages of 21 and 50, with a mean age of 38. In 66 percent of all cases, sex was not recorded. Of the remaining cases, 91 percent were female.

A tabulation of the symptoms showed that there were three deaths, 22 cases of myocardial infarction, three cases of cardiac arrest, 29 cases of stroke, two cases of brain hemorrhage, 46 cases of seizure, three cases of psychosis, and two cases of hallucinations. The files contained 111 cases of hospitalization in addition to those associated with the serious cases just listed. These hospitalizations were for a variety of reasons, but most were for cardiovascular-related symptoms.

The MIPER files for death, heart attack, cardiac arrest, stroke, seizure, and certain psychiatric events were all reexamined by the principal investigator and other physicians and are listed in Appendix 2 of this report. One case of death occurred as a result of "a brain hemorrhage," according to the notes. Another case involving a death contained a handwritten note that said, "wanted refund (sister's husb died)." The third case stated "cousin was taking Metabolife last yr, had stroke, died." No additional information for these cases is present. Two additional deaths, identified by Metabolife in a document entitled *77 'serious' AE's as identified by Metabolife* (see below), were not included in the MIPER CD-ROM we received. These additions bring the total number of Metabolife-related deaths to five. The cases of other serious events range in documentation from several sentences of clinical information related by the patient, letters from patients stating that they had a serious adverse event, to simply the words "heart attack" or something similar on a sheet of paper in the MIPER file. This level of documentation is insufficient to make judgments about the possible relation between ephedra use and the event. The largest proportions of case reports included symptoms of autonomic hyperactivity (14 percent of all cases) and gastrointestinal symptoms (26 percent of all cases). These data are compatible with the results of our meta-analysis of adverse events in placebo-controlled trials of ephedra and ephedrine, which demonstrated both autonomic hyperactivity and upper gastrointestinal symptoms to be causally related to use of ephedra or ephedrine.

As mentioned above, included with the material we received was a document (a sheaf of paper) entitled *77 'serious' AE's as identified by Metabolife*. This sheaf contained photocopies of the MIPER files judged by Metabolife to be the most serious in nature. These MIPER files included reports of three deaths. Two of these deaths had the MIPER number blacked out, were marked "privileged and confidential," were not found on the MIPER CD-ROM by our abstractors, and were not found using a modified MIPER CD-ROM that allowed text word searching (prepared for us by FDA).

The documentation on both cases consisted, as did many of the Metabolife files, of a printed version of an email. The first death was of a 45- to 55-year-old female, who was apparently initially healthy and continued to take Metabolife 356 for three weeks, despite symptoms of palpitations and a rapid pulse rate, until she suffered sudden death. An autopsy found "no conclusive cause of death." The email notes that toxicology studies are pending "to ascertain if ephedrine was present in her system at the time of death." No additional clinical information is available. The second case was that of a 30- to 40-year-old female who was found dead. According to her father, the autopsy "stated that the cause of death was of a cardiac nature of an unknown origin." Drug analysis found "only caffeine." No other clinical information was available.

Some cases identified by Metabolife as serious were not deemed so by us, whereas we considered a greater number of its cases to be serious than Metabolife did (we did agree on cases of death). For example, we identified six additional cases of myocardial infarction and nine additional cases of stroke. Table 27 compares the cases we identified as serious with those identified by Metabolife, along with a capsule explanation for the coding of discrepant cases.

Review of records with photocopies of medical information. The records varied greatly from detailed medical records to simply photocopies of medical bills. Table 28 contains a capsule description of each case and three numbering systems, because, as discussed in the Methods section, the medical records were numbered in three ways. The first column contains the number we assigned the records as we removed them from the shipping box. The second column contains the case number as listed on the *Index of Redacted Consumer Medical Records with Corresponding MIPER Numbers*. The third column contains the complaint case number from the *Listing of Key Complaint for the Metabolife Medical Records Submitted*. The fourth column contains the numbers for any related MIPER files that we identified or were identified by Metabolife on the Index. The column labeled "Notes" is our capsule description of what we received.

There were 12 cases with primarily cardiopulmonary symptoms (RAND ID cases 1, 13, 14, 16, 17, 20, 21, 23, 28, 29, 33, 43), two cases with neurologic symptoms (RAND ID cases 18, 38), two cases of seizure (RAND ID cases 32, 36), four cases of allergic reaction (RAND ID cases 2, 25, 26, 37), and 23 cases of miscellaneous symptoms (RAND ID cases 3, 4, 5, 6, 8, 9, 10, 11, 12, 15, 19, 22, 24, 27, 30, 31, 34, 35, 39, 40, 41, 42). There were no deaths, one case of myocardial infarction, no strokes, and no severe psychiatric events. The case of myocardial infarction (RAND ID case 23) was classified as a possible sentinel event, due to the presence of existing coronary artery disease. The two cases of seizure (RAND ID cases 32 and 36) were classified as sentinel events. Comparing these cases to the FDA Medwatch data contained in our Evidence Report demonstrates that neither the case of myocardial infarction nor the two cases of seizure are reported as sentinel or possible sentinel events in our analysis of the Medwatch file; thus, we are not double-counting these events.

Chapter 4. Limitations

We address the limitations of each set of analyses separately: meta-analysis of the weight loss and descriptive synthesis of athletic performance randomized controlled trials; analysis of the adverse events from the randomized controlled trials; and analysis of the case reports of adverse events.

The systematic reviews of the weight loss and athletic performance randomized controlled trials have the following potential limitations:

- Our search procedures for randomized controlled trials were extensive and included canvassing experts regarding studies we may have missed. In addition, we observed little to no evidence of publication bias via visual inspection or formal testing for the weight loss studies. However, we acknowledge that publication bias may still exist despite our best efforts to conduct a comprehensive search and the lack of statistical evidence of the existence of bias. Publication bias may occur for a variety of reasons, including investigators' loss of interest in the study if "negative" results are found or if results are obtained that are contrary to the interest of the sponsor or investigator.

- An important limitation common to many systematic reviews, whether or not a formal meta-analysis is conducted, is the quality of the original studies. Many of the weight loss studies suffered from an attrition rate higher than is normally allowed by FDA when assessing studies of pharmaceutical products seeking approval. However, recent attempts to define elements of study design and execution that are related to bias have shown that in many cases, such efforts are not reproducible and do not distinguish studies based on their results. Therefore, the current state of the science is to document such methodological weaknesses and perform sensitivity analyses when possible, but not to reject studies or use quality criteria to adjust the pooled outcome. We performed a sensitivity analysis on the subset of studies that had the best quality, according to the only validated scale available. The results of the sensitivity analysis did not alter the majority of our findings.

- In our meta-analysis of the weight loss studies, we did not observe significant evidence of heterogeneity. However, the chi-squared test of heterogeneity is underpowered. We did use a random effects approach to attempt to incorporate any heterogeneity and conducted sensitivity analyses to assess the robustness of our conclusions.

- We were limited by the small number of trials that provided direct comparisons between treatments of interest in the weight loss meta-analysis. Our meta-regression in this setting was an attempt to compare treatments across trials, but we acknowledge this approach does not allow for controlling for confounders within study. Direct comparisons are needed to draw more definite conclusions. In other words, while our observed results suggest that the amount of weight loss is approximately the same for ephedrine with caffeine, herbal ephedra with herbs containing caffeine, and herbal ephedra alone, the available data do not prove equivalence.

- The weight loss studies as a group had limited treatment duration; thus, we cannot draw conclusions about the association between ephedra or ephedrine and weight loss over longer and more clinically relevant intervals than about four months. Current knowledge of weight loss is that it generally ceases after six months, irrespective of treatment, and any weight loss is generally regained. Current recommendations for appropriate clinical trials in this area include a much longer treatment duration (at least one year) and an evaluation of what happens after the agent is withdrawn.

- The heterogeneity among the athletic performance studies prevented us from conducting a formal meta-analysis, so we were restricted to a descriptive synthesis.

- The results of the clinical trials are directly applicable only to the persons studied in those trials. In most cases, enrollment was highly selective to avoid certain comorbidities. Whether efficacy would be equivalent in a more representative population is unknown.

- The results of the ephedra studies regarding efficacy cannot be generalized to all ephedra-containing dietary supplements, because these may vary in their constituents from the concoctions studied and reported on here.

The analysis of the adverse events from the randomized controlled trials have the following major potential limitations:

- In this analysis, we focused only on studies that addressed weight loss or athletic performance. Although we observed no serious adverse events in these trials, we might have identified adverse events in trials that tested the efficacy of ephedra for other conditions, had we included those conditions in our search. However, we did include all controlled trials of ephedra or ephedrine for weight loss or athletic performance; therefore, our estimates are relevant to the populations taking those supplements for these reasons, which certainly constitute the majority of users of ephedrine and ephedra products in the United States.

- As with efficacy, the results of the clinical trials with respect to safety are directly applicable only to the persons studied in those trials. In most cases, enrollment was highly selective to avoid certain comorbidities. Whether safety is equivalent in a more representative population is unknown.

- As with efficacy, the results for the ephedra studies with respect to safety cannot be generalized to all ephedra-containing dietary supplements, because these may vary in their constituents from those concoctions studied and reported on here.

The analysis of the case reports of adverse events had the following major potential limitations:

- We did not have access to all adverse event files.

- Many authorities consider MedWatch case reports to underestimate the number of events, because patients need to suspect an association in order to report an event.

- This report did not review in detail other lines of evidence, such as animal studies, basic neuroscience studies, and adverse event data concerning other sympathomimetic amines that some authorities consider important when trying to assess causation.

- Many of the adverse event reports did not contain all the data that we needed to make assessments. Therefore, how the cases we classified as "insufficient evidence" might have influenced our findings had they contained appropriate documentation is unknown.

- An important limitation is that we do not have an estimate of the number of people using ephedra or ephedrine; that is, we do not have a denominator with which to calculate an event rate. An additional complication, we believe, is that the use of ephedra and ephedrine is increasing over time, as is the probability that someone will report an adverse event due to publicity.

- The most important limitation is that the study design (that is, an assessment of case reports) is insufficient for us to reach conclusions regarding causality.

The major potential limitations of the analysis of the Metabolife files can be classified into two categories: limitations of the source material and limitations of our methods.

The source material for this review differed in several important ways from source material used in other EPC projects:

- Much of what we reviewed was handwritten. Therefore, when the handwriting was poor we may not have correctly interpreted what the writer meant to say.

- The information was not recorded in an organized fashion, leaving it up to us to interpret its meaning. A good example of this was MIPER 23695 that we (but not Metabolife) classified as a "death." This file consisted of handwritten notes that stated, "migraine HA, wants refund, sister's husb died." Does this mean the customer is the sister's husband, who had a migraine headache and then died? Or did the customer have a migraine headache, perhaps in part because her sister's husband died? Without additional information it is impossible to tell.

- Each file did not attempt to collect the same information, so a recording bias probably exists.

- As already noted, we are not confident we could identify all files associated with a single case, so some double-counting may have occurred.

The methods we used to review the files also had important limitations:

- We relied on single-person review to screen cases. In the eight weeks we were given to review the files, we could not do dual review (which is standard in all our other EPC work) of over 18,000 cases. Therefore, more coding errors may have occurred than in situations where we use dual review. Mitigating this limitation is that we did do formal inter-rater reliability testing and demonstrated excellent reliability among reviewers. Also, the principal investigator reviewed all cases that were identified as serious. Furthermore, we identified nearly all the serious events identified by Metabolife, plus many more that Metabolife did not identify. So, while we acknowledge that there may still be errors in the data, we do not think they are so numerous or egregious as to threaten our conclusions.

- The Metabolife analysis did not undergo as extensive a review process as did the other sections of this report. The Metabolife analysis was reviewed by three experts and two federal agencies, in contrast to the much more extensive review process for the other sections of the report. Furthermore, because of the timeline necessary to produce the final report, the time available to the reviewers of the Metabolife analysis was shorter than we normally afford. How additional peer review may have affected our conclusions from the Metabolife analysis is unknown.

Chapter 5. Conclusions

Efficacy

The efficacy of herbal ephedra–containing dietary supplements has not been extensively studied in randomized clinical trials. We identified no clinical trials of herbal ephedra–containing dietary supplements that assessed their effect on athletic performance and only five clinical trials that assessed their effect on weight loss. Many more studies assessed the effects of ephedrine on weight loss; however, studies of the effects of ephedrine on athletic performance are still relatively sparse. The majority of studies—of both ephedra and ephedrine—are plagued by methodological problems known to be associated with bias, particularly high attrition rates. All of the conclusions on efficacy need to be considered with these methodological limitations in mind.

Given the above considerations, the evidence we identified and assessed supports the following conclusions:

Weight Loss

- The short-term use of ephedrine, ephedrine plus caffeine, or the assessed dietary supplements containing ephedra and herbs with caffeine is associated with a statistically significant increase in short-term weight loss (compared to placebo).

- There are no studies assessing the long-term effects of the use of ephedra-containing dietary supplements or ephedrine on weight loss or maintenance. In order to improve health outcomes and reduce the risk of morbidities associated with being overweight, long-term weight maintenance is necessary.

- There are no data to indicate that the effects of ephedrine plus caffeine are different from the effects of ephedra-containing dietary supplements with caffeine-containing herbs.

- The effect of either ephedra-containing dietary supplements with caffeine-containing herbs or ephedrine plus caffeine is a weight loss that is approximately two pounds per month greater than that of placebo, for up to four to six months in duration.

- As a percentage of pretreatment weight, the weight losses in these studies average between 5 percent and 11 percent in the treatment groups.

- The only two studies that compared ephedrine plus caffeine to prescription weight loss pharmaceutical products reported no differences in effectiveness between products, but these studies were statistically underpowered to detect differences of moderate size.

- The addition of caffeine to ephedrine is associated with a statistically significant increase in short-term weight loss.

- One study of ephedra without caffeine-containing herbs reported a statistically significant increase in short-term weight loss that was comparable to the effects reported by four studies of ephedra with caffeine-containing herbs.

- The data suggest a dose-response relationship with respect to ephedrine and weight loss.

- All published studies on herbal ephedra and weight loss have used a medium dose of ephedra per day; consequently, no dose-response analysis is possible.

Athletic Performance

- There are no studies assessing the effect of herbal ephedra–containing dietary supplements on athletic performance.

- The few studies that assessed the effect of ephedrine on athletic performance did so only in small samples of mostly fit individuals (young male military recruits) and only on very short-term immediate performance. This model does not reflect the use patterns in the general population. These data support a modest effect of ephedrine plus caffeine on very short-term athletic performance.

- No studies assessed the effect of the sustained use of ephedrine on performance over time.

- It is probable that ephedrine alone, without the addition of caffeine, has little or no effect on athletic performance.

- In the data we reviewed, the smallest dose of ephedrine that produced a measurable effect on athletic performance was 0.8 mg per kg of body weight. However, the effect of smaller doses has not been assessed. Higher doses produced unacceptable gastrointestinal side effects.

Adverse Consequences

The data we reviewed on adverse consequences came from both clinical trials and case reports submitted to the FDA. The strongest evidence of causality should come from clinical trials; however, in most circumstances, such trials do not enroll sufficient numbers of patients to adequately assess the possibility of rare outcomes. Such was the case with our review of ephedrine and ephedra-containing dietary supplements. For rare outcomes, we reviewed case reports. However, we could not determine definite causality from case reports.

With these considerations in mind, the evidence we identified supports the following conclusions:

- There is sufficient evidence from short-term controlled trials to conclude that the use of ephedrine and/or the use of ephedra or ephedrine plus caffeine is associated with two to three times the risk of nausea, vomiting, psychiatric symptoms such as anxiety and

change in mood, autonomic hyperactivity, and palpitations. It is not possible to separate out the contribution of caffeine to these events.

- There were no reports of serious adverse events in the controlled trials of ephedrine or ephedra, but these studies are insufficient to assess adverse events that occurred at a rate of less than 1.0 per 1000.

- A large number of adverse event reports regarding herbal ephedra–containing dietary supplements have been filed with FDA. The majority of FDA case reports are insufficiently documented to make an informed judgment about the relationship between the use of ephedra-containing dietary supplements and the adverse event in question.

- A very large number of adverse events were reported to one manufacturer of ephedra-containing dietary supplements. Nearly all of the case reports were too poorly documented to permit us to make any judgments about the potential relationship between ephedra use and the event.

- We identified two deaths, three myocardial infarctions, nine cerebrovascular accidents, three seizures, and five psychiatric cases as sentinel events with prior ephedra consumption; and three deaths, two myocardial infarctions, two cerebrovascular accidents, one seizure, and three psychiatric cases as sentinel events with prior ephedrine consumption. Classification as a sentinel event does not imply a proven cause and effect relationship.

- We identified 43 additional cases as possible sentinel events with prior ephedra consumption and seven additional cases as possible sentinel events with prior ephedrine consumption.

- About half of the sentinel events occurred in persons aged 30 years or younger.

- Scientific 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. Given the rarity of such events, a properly designed case control study would be the appropriate next step. Such a study would need to control for caffeine consumption.

Chapter 6. Future Research

Our analysis of the evidence reveals numerous gaps in the literature regarding the efficacy and safety of ephedrine and ephedra-containing dietary supplements. The most important of these gaps are the following:

- Long-term assessments of the effectiveness of ephedra or ephedrine at promoting weight loss. We identified no study having a treatment duration of more than six months. In order to improve health outcomes and reduce the risk of morbidities associated with being overweight, sufficient weight loss (5 to 10 percent of body weight) and long-term weight maintenance are necessary.

- A study of the effect of repeated use of ephedra or ephedrine on athletic performance in a variety of people including women and adolescents who are known users of these products. If use of ephedra-containing dietary supplements is going to continue to be promoted for improving athletic performance, then evidence is needed regarding their efficacy in individuals who represent the general population.

- A proper study to assess the possible association of ephedra or ephedrine consumption and the occurrence of serious adverse events. Continued analysis of case reports cannot substitute for a properly designed study to assess causality. A case-control study would probably be the study design of choice.

A partial list of other possible future research activities includes the following:

- Consider a dose-response study that would determine the minimum effective dose of ephedra and caffeine-containing herbs, or ephedra combined with other botanicals such as citrus durantium, garcinia cambogia, and other herbal diuretics and cathartics, for weight loss.

- Assess whether ephedra/ephedrine and exercise training interact in their effects on weight loss and adverse events.

- Assess adverse events for ephedrine and other prescription obesity drugs in Denmark, where doctors began prescribing an ephedrine-containing diet drug more than 20 years ago.

- Conduct studies to determine if the use of ephedrine or ephedrine-containing alkaloids increases the risk of development of heat-related conditions such as heat exhaustion, heat stroke, and rhabdomyolysis.

- Investigate further the interactions between ephedra/ephedrine and other products commonly used in the United States for weight loss and/or athletic performance.

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Table 1. Herbs containing caffeine commonly combined with ephedra in products marketed for weight loss or improved physical performance

Common Name	Botanical Name
Cocoa	*Theobroma cacao*
Coffee	*Coffea arabica*
Guarana	*Paullinia cupana*
Kola nut	*Cola acuminata* *Cola vera*
Maté leaf	*Ilex paraguayensis*
Tea (black, green, oolong)	*Camilla sinensis*

Table 2. Technical expert panel members

Name	Expertise	Institution
Awang, Dennis V. (PhD)	Natural product chemist	MediPlant Consulting Services
Benowitz, Neal (MD)	Psychiatry, pharmacology	UCSF
Farnsworth, Norman (PhD)	Pharmacognosy	University of Illinois at Chicago
Fielding, Roger (PhD)	Exercise	Boston University
Goldberger, Jeffrey (MD)	Cardiology	Northwestern Univ. Medical School
Heber, David (MD, PhD)	Weight loss	UCLA School of Medicine
Ko, Richard (PharmD, PhD)	Food and drug scientist	California Department of Health Services
Leung, Albert (PhD)	Pharmacognosy	AYSL Inc.
Mills, Simon (FNIMN)	Herbalist	Center for Complementary Medicine, Exeter, UK
Nestmann, Earle (PhD)	Toxicology	CANTOX Health Sciences, Canada

Table 3. Technical expert panel suggestions about data collection

Collection Item	Suggestions
Outcomes of interest when assessing efficacy	Weight = outcome for weight loss Long-term weight loss = at least six months Long-term exercise = at least 12 weeks Change the term “exercise enhancement” to “exercise capacity” VO2 max, metabolism, heart rate = intermediate outcomes for exercise capacity Power, strength, endurance = primary outcomes for exercise capacity
Subpopulations of interest	Age; gender; race; body composition/BMI; history of (Hx) hypertension; Hx asthma; Hx diabetes
Risk factors of interest in assessing possible harmful effects	Existing structural heart disease Renal function Use of other drugs, tobacco

Table 4. Measures used in assessing causality

Measure	Example
Temporal relationship	When the drug was consumed, dosage
De-challenge response	Do symptoms disappear when substance is removed?
Re-challenge response	Do symptoms appear again if substance is reintroduced?
Possibility of alternative explanation	Dehydration or consumption of other toxic substances
Prior reaction to same substance	
Dose response	
Objective evidence of adverse event	Witnesses or medical records
Previous conclusive reports	Has this same reaction happened when other persons consumed substance?
Definition of substance	

Table 5. Ephedra/ ephedrine search methodology

SEARCH NUMBER	#1A
Database searched and time period covered	MEDLINE Via PubMed 1965-2001
Search strategy	Ephedra AND (clinical trial OR clinical trials OR randomized controlled trials OR meta analysis OR meta-analysis OR review* OR Publication Type=Meta-Analysis OR Publication Type=Clinical Trial OR Publication Type=Review OR Publication Type=Randomized Controlled Trial)
Number of items retrieved	8
SEARCH NUMBER	#1B
Database searched and time period covered	EMBASE 1974-2001
Search strategy	Ephedra AND (clinical trial* OR randomi* OR review* OR metaanalys* OR meta analys* OR Document Type=Review)
Number of items retrieved	20
SEARCH NUMBER	#1C
Database searched and time period covered	BIOSIS 1969-2001
Search strategy	Ephedra AND (metaanal* OR meta anal* OR trial* OR review* in title or subject heading field OR Document Type=Review OR Document Type=Literature Review)
Number of items retrieved	15
SEARCH NUMBER	#1D
Database searched and time period covered	Allied & Complementary Medicine 1984-2001 MANTIS 1880-2000/Apr Cochrane Library – Controlled Clinical Trials Register Database (CCTR)
Search strategy	ephedra
Number of items retrieved	12
SEARCH NUMBER	#2A (performed 4/5/01)
Database searched and time period covered	MEDLINE via PubMed 1965-2001
Search strategy	ephedrine NOT ephedra AND (review OR meta analysis OR randomized controlled trials OR clinical trials OR Publication Type=Review OR Publication Type=Clinical Trial OR Publication Type=Randomized Controlled Trial OR Publication Type=Meta-Analysis)
Number of Items Retrieved	704
SEARCH NUMBER	#2B (performed 4/6/01)
Database searched and time period covered	EMBASE 1974-2001
Search strategy	ephedrine NOT ephedra AND (review* OR meta analys* OR metaanalys* OR random* OR trial*)
Number of items retrieved	1450

Note: *denotes truncated search term.

Table 6. Ephedra/ ephedrine search methodology – additional databases

SEARCH NUMBER	#1A (performed 6/25/01)
Database searched and time period covered	International Pharmaceutical Abstracts - 1970-2001/May Pascal - 1973-2001/June Week 4 SciSearch (Archival File) - 1974-1989 SciSearch (Current File) - 1990-2001/June Week 4
Search strategy	ephedra OR ephedrine AND trial? OR review? OR rct? OR meta analys? OR metaanal?
Number of items retrieved	167
SEARCH NUMBER	#1B (performed 6/25/01)
Database searched and time period covered	International Pharmaceutical Abstracts - 1970-2001/May Pascal - 1973-2001/June Week 4 SciSearch (Archival File) - 1974-1989 SciSearch (Current File) - 1990-2001/June Week 4
Search strategy	ephedra(IN TITLE OR SUBJECT HEADING FIELDS) OR ephedrine (IN TITLE OR SUBJECT HEADING FIELDS) AND adverse OR side effect? OR efficacy OR fail? OR succeed? OR success? OR effective? OR toxic?
Number of items retrieved	330 (NOTE – RESULTS FROM SEARCH 1A WERE “NOTTED OUT” OF THESE SEARCH RESULTS)

Table 7. Categories of adverse events

Event Type
Death
Stroke (CVA)
Myocardial infarction (heart attack)
Cardiovascular other than MI
Neurological other than stroke
Endocrine
Psychiatric
Pulmonary
Renal/urinary
Musculoskeletal
Gastrointestinal
Hepatic
Rheumatologic
Dermatological
Acid-base/electrolytic disturbances
Pain
Withdrawal symptoms
Gynecological/obstetrical
Hematological
Immunological/allergic reaction
Other rare events
Not described

Table 8. Report reviewers

Reviewer	Affiliation
Dr. David Allison	University of Alabama at Birmingham
Dr. Arne Astrup	The Research Department of Human Nutrition The Royal Veterinary and Agricultural University, Denmark
Dr. Dennis Awang	Mediplant Consulting Services
Dr. Neal Benowitz	University San Francisco, Dept. of Med., SFGH, Clin. Pharm Div.
Dr. Heidi Blanck	Centers for Disease Control and Prevention, Division of Nutrition and Physical Activity, Chronic Disease Nutrition Branch
Dr. George Bray	Pennington Biomedical Research Center
Hon Dan Burton	U.S. Representative
Mr. John Cardaro	Council for Responsible Nutrition
Ms. Beth Clay	U.S. House of Representatives, Hon Dan Burton's Office
Hon Dick Durbin	U.S. Senator
Dr. Norman Farnsworth	Univ. of Illinois Med. Center
Dr. Roger Fielding	Boston University Dept. of Health Services
Dr. Gary Franklin	University of Washington
Dr. Curt Furberg	Wake Forest University
Dr. Frank Greenway	Pennington Biomedical Research Center
Prof. Bill Gurley	University of Arkansas School for Med. Sciences, College of Pharmacy
Dr. Christine Haller	University California San Francisco, Div of Clinical Pharmacology
Dr. Robert Hart	National Institute of Neurological Disorders and Stroke
Dr. David Heber	UCLA Center for Human Nutrition, Obesity and Nutrition
Dr. Steve Heymsfield	St. Luke's/Roosevelt Hospital
Mr. Loren Israelsen	Utah Natural Products Alliance
Dr. Steven Karch	Assistant Medical Examiner, San Francisco
Dr. Steve Kimmell	Chair, Ephedra Education Council Expert Panel
Dr. Richard Ko	California Dept. of Health Services, Food and Drug Branch
Dr. Albert Leung	AYSL
Dr. Lori Love	Food and Drug Administration
Mr. Michael McGuffin	President, American Herbal Products Association
Dr. Simon Mills	Center for Complementary Health Studies, University of Exeter
Dr. Earle Nestman	CANTOX
Dr. Paul Pentel	Hennepin County Medical Center, Div. of Toxicology, Dept. of Medicine
Mr. Paul Rubin	Patton Boggs
Mr. David Seckman	National Nutritional Foods
Mr. Wes Seigner	Hyman, Phelps, & McNamara
Hon Henry Waxman	U.S. Representative
Dr. Raymond Woosley	University of Arizona Health Sciences Center
Ms. Susan Yanovski	Obesity and Eating Disorder Program National Institute of Diabetes and Digestive and Kidney Diseases
Organizations	
National Center for Complementary and Alternative Medicine	
National Institute of Diabetes and Digestive and Kidney Diseases	
National Heart, Lung and Blood Institute	
Office of Dietary Supplements	
Center for Science in the Public Interest	
Public Citizen Health Research Group	

Table 9. Weight loss trial inclusion results

Disposition of trials	**Number of Trials**
Total retained in meta-analysis	20
Total dropped from meta-analysis	24
Reasons for dropping trials from meta-analysis:	
Duration of treatment less than eight weeks	18
Ephedrine dose did not vary between study arms	1
Cross-over study without data available prior to the cross-over point	1
Insufficient statistics	3
Inappropriate outcome (weight gain)	1

Table 10. Ephedrine versus placebo

Trial	Total n	Effect Size	95% CI
Jensen[88]	17	-1.52	(-2.75, -0.29)
Lumholtz[94]	32	-1.03	(-1.78, -0.29)
Moheb[84]	64	-0.49	(-0.98, 0.01)
Pasquali[85]	19	0.00	(-0.93, 0.93)
Pasquali[85]	24	-0.42	(-1.23, 0.39)
Quaade[86]	70	-0.17	(-0.64, 0.30)
Pooled Random Effect Estimate		-0.50[1]	(-0.85, -0.15)

[1]Chi-squared test of heterogeneity p-value = 0.185

Table 11. Publication bias tests

Trials	Adjusted Rank Correlation Test p-value	Regression Asymmetry Test p-value
Ephedrine vs. placebo	0.45	0.82
Ephedrine + caffeine vs. placebo	0.30	0.12
Ephedrine + caffeine vs. ephedrine alone	N.C.	N.C.
Ephedrine vs. another weight loss therapy	N.C.	N.C.
Ephedra + herbs containing caffeine vs. placebo	0.73	0.23

N.C. = not calculated due to the small number of trials available.

Table 12. Ephedrine + caffeine versus placebo

Trial	Total n	Effect Size	95% CI
Astrup[111]	12	-0.72	(-1.88, 0.45)
Buemann[92]	32	-0.55	(-1.26, 0.16)
Daly[103]	24	-0.65	(-1.47, 0.18)
Jensen[88]	18	-1.84	(-3.10, -0.57)
Kalman[96]	25	-0.46	(-1.25, 0.34)
Kettle[90]	77	-0.40	(-0.85, 0.05)
Malchow-Moll[87]	69	-1.14	(-1.65, -0.63)
Moheb[84]	96	-0.76	(-1.20, -0.32)
Molnar[112]	29	-1.35	(-2.16, -0.54)
Quaade[86]	70	-0.50	(-0.98, -0.03)
Roed[95]	94	-1.38	(-1.83, -0.92)
Van Mil[91]	32	-1.00	(-1.74, -0.27)
Pooled Random Effect Estimate		-0.85[1]	(-1.08, -0.61)

[1]Chi-squared test of heterogeneity p-value = 0.073

Table 13. Ephedrine + caffeine versus ephedrine

Trial	Total n	Effect Size	95% CI
Jensen[88]	27	-0.32	(-1.07, 0.44)
Moheb[84]	96	-0.27	(-0.70, 0.15)
Quaade[86]	70	-0.36	(-0.83, 0.11)
Pooled Random Effect Estimate		-0.31[1]	(-0.60, -0.02)

[1]Chi-squared test of heterogeneity p-value = 0.966

Table 14. Ephedrine versus another active weight loss therapy

Trial	Total n	Effect Size	95% CI
Breum[113]	81	-0.29	(-0.73, 0.15)
Malchow-Moll[87]	70	0.08	(-0.36, 0.53)

Table 15. Ephedra versus placebo

Trial	Total n	Effect Size	95% CI
Donikyan[114]	154	-0.69	(-1.02, -0.37)

Table 16. Ephedra + herbs containing caffeine versus placebo

Trial	Total n	Effect Size	95% CI
Boozer[115]	48	-1.07	(-1.67, -0.46)
Boozer[89]	83	-0.63	(-1.07, -0.18)
Colker[93]	26	-0.87	(-1.68, -0.06)
Greenway[116]	30	-0.92	(-1.69, -0.15)
Pooled Random Effect Estimate		-0.81[1]	(-1.12, -0.51)

[1]Chi-squared test of heterogeneity p-value = 0.689

Table 17. Meta-regression results

Comparison Versus Placebo	Pooled Monthly Weight Loss Versus Placebo (lbs)	95% CI	p-value for Test Versus Ephedra + Herbs Containing Caffeine
Ephedrine	-1.3	(-2.1, -0.43)	0.17
Ephedra + herbs containing caffeine	-2.1	(-2.8, -1.3)	N.C.
Ephedrine + caffeine	-2.2	(-2.8, -1.7)	0.75

N.C. = Not calculated as this is the comparison group.

Table 18. Exercise trials by Bell and colleagues

Reference	Compounds	Type of Exercise	Results
Bell, Jacobs & Zamecnik[128]	Placebo 1 mg/kg Ephedrine 5 mg/kg Caffeine 1mg/kg Ephedrine + 5 mg/kg Caffeine (E+C)	Cycle ergometer trials to exhaustion	E+C significantly increased time to exhaustion compared to placebo. Heart rate during exercise was significantly increased for E+C, caffeine arms.
Bell & Jacobs[130]	Placebo 75 mg Ephedrine + 375 mg Caffeine (E+C)	Canadian Forces Warrior Test - 3.2 km run wearing 11 kg equipment	E+C trial run times were significantly faster than control and placebo trials.
Bell, Jacobs, McLellan, Miyazakie, and Sabiston[131]	Placebo 1 mg/kg Ephedrine + 5 mg/kg Caffeine (E+C)	Treadmill walking at 50% VO2 peak, 40 degrees celsius climate, 30% relative humidity	E+C did not significantly change tolerance times when compared to placebo. E+C did not affect skin or rectal temperature, sweat rate, or sensation of thermal comfort.
Bell, Jacobs, McLellan & Zamecnik[129]	Placebo 5 mg/kg Caffeine + 0.8 mg/kg Ephedrine 4 mg/kg Caffeine + 1 mg/kg Ephedrine 4 mg/kg Caffeine + 0.8 mg/kg Ephedrine	Cycle ergometer trials to exhaustion at 85% VO2 peak	A lower dose of E+C resulted in ergogenic effect similar in magnitude to those reported previously with a higher dose, with fewer side effects.
Pasternak, Jacobs & Bell[132]	Placebo 0.8 mg/kg Ephedrine 4 mg/kg Caffeine 0.8mg/kg Ephedrine + 4 mg/kg Caffeine (E+C)	Three supersets of leg press & bench press, to exhaustion	Ephedrine, E+C increased muscular endurance, but only in the first set. Systolic blood pressure was increase with ephedrine, E+C.
Bell, Jacobs & Ellerington[133]	Placebo 1 mg/kg Ephedrine 5 mg/kg Caffeine 1 mg/kg Ephedrine + 5 mg/kg Caffeine (E+C)	Two different cycle ergometer tests, one was to exhaustion at 125% VO2 peak	Ephedrine improved performance during Wingate test of anaerobic power. Caffeine increased time to exhaustion in second test.

Table 19. Summary table of meta-analysis of adverse events reported controlled trials

Adverse Events	# of Trials	Placebo		Intervention Groups		Pooled OR 95% CI
		# Adverse Events	Sample Size	# Adverse Events	Sample Size	
Psychiatric symptoms	8	16	273	59	351	3.64 (1.91, 7.31)
Autonomic hyperactivity	13	39	365	138	587	3.37 (2.19, 5.31)
Palpitations	11	18	386	51	563	2.29 (1.27, 4.32)
Hypertension	5	3	257	7	305	2.19 (0.49,13.34)
Upper gastrointestinal symptoms	10	46	432	88	568	2.15 (1.39, 3.38)
Headache	5	8	123	16	185	1.64 (0.62, 4.68)
Tachycardia	1	0	45	6	90	N.R.

N.R. = not reported.

Table 20. Summary table of other of adverse events reported in controlled trials

Other Adverse Events	# of Trials	Placebo		Intervention Groups	
		# Adverse Events	Sample Size	# Adverse Events	Sample Size
Bundle branch block	1	0	33	0	49
Concentration difficulties	5	17	257	18	391
Constipation	5	8	139	15	215
Diarrhea	3	3	81	3	114
Dry mouth	5	4	111	22	174
Fatigue, weakness	2	4	49	6	64
Postural hypotension	1	1	45	4	90
Syncope	1	0	45	1	90
Ventricular events	1	3	84	3	83

Table 21. Distribution of adverse events in the FDA file according to the Excel spreadsheet

Data Type	Event				
	Death	**Stroke**	**MI**	**Other**	**Total**
Available data	71 (5.3%)*	54 (4.0%)	33 (2.5%)	1,186 (88.2%)	1,344 (100%)
Data dated after Sept. 30, 2001	17 (12.4%)	15 (10.9%)	5 (3.7%)	100 (73.0%)	137 (100%)
Unavailable data	4 (1.9%)	18 (8.4%)	9 (4.2%)	183 (85.5%)	214 (100%)
Total	92 (5.4%)	87 (5.1%)	47 (2.8%)	1,469 (86.7%)	1,695 (100%)

*Number of events (row percent).
Chi-squared test of independence p-value < 0.001.
Note: summary data were available for AERs beyond Sept 30, 2001. Detailed, redacted records were only available for AERs up through Sept 30, 2001.

Table 22. Evidence table of case reports - Deaths

Event type Report date Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Investigation for Etiology	RAND Classification
Death 11/03/1999 21 yo Male Ephedra FDA Case (13914)	Hydroxycut 10.0 mg <6 hours; < 48 hours Ripped Fuel Unknown Not described; not described	Autopsy conducted: Yes	Sentinel event
Death 09/26/2000 22 yo Female Ephedra FDA Case (14390)	Slacker II Unknown Not described; 14-60 days (acute)	Autopsy conducted: Yes	Sentinel event
Death 30 yo Female Ephedrine FDA Case (3275432)	MiniTabs 250.0 mg Not described; >60 days (chronic)	Autopsy conducted: Yes	Sentinel event
Death 33 yo Male Ephedrine FDA Case (3289590)	Max Brand Two-Way 150.0 mg Not described; Not described	Autopsy conducted: Yes	Sentinel event
Death 28 yo Male Ephedrine Literature Case (348)	Insufficient information Unknown <24 hours; >60 days (chronic)	Autopsy conducted: Yes	Sentinel event
Death 05/19/1994 36 yo Female Ephedra FDA Case (9508)	Nature's Nutrition-Formula One Unknown Not described; >60 days (chronic)	Autopsy conducted: Yes	Possible sentinel event
Death 03/09/1995 32 yo Male Ephedra FDA Case (10276)	Nature's Nutrition-Formula One Unknown Not described; >60 days (chronic)	Autopsy conducted: Yes	Possible sentinel event

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – Deaths (continued)

Event type Report date Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Investigation for Etiology	RAND Classification
Death 07/25/1997 38 yo Male Ephedra FDA Case (12485)	Ripped Fuel 43.2 mg <6 hours; >60 days (chronic)	Autopsy conducted: Yes	Possible sentinel event
Death 12/19/1997 21 yo Male Ephedra FDA Case (12722)	Thermogenics Plus 23.1 mg Not described; Not described	Autopsy conducted: Yes	Possible sentinel event
Death 04/11/1998 15 yo Female Ephedra FDA Case (12843)	Ripped Fuel 40.0 mg <6 hours; Not described	Autopsy conducted: Yes	Possible sentinel event
Death 08/03/1999 26 yo Male Ephedra FDA Case (13906)	Ripped Fuel Unknown Not described; 2-13 days (acute)	Autopsy conducted: Yes	Possible sentinel event
Death 02/16/2000 26 yo Female Ephedra FDA Case (14019)	Diet Fuel 26.6 mg Not described; >60 days (chronic)	Autopsy conducted: Yes	Possible sentinel event
Death 01/09/2001 35 yo Male Ephedra FDA Case (14638)	Hydroxycut 20.0 mg 6-24 hours; 2-13 days	Autopsy conducted: Yes	Possible sentinel event
Death 23 yo Male Ephedra Literature Case (258)	Ripped Fuel 50.0 mg Not described; >60 days (chronic)	Autopsy conducted: Yes	Possible sentinel event

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – Deaths (continued)

Event type Report date Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Investigation for Etiology	RAND Classification
Death 42 yo Male Ephedrine Literature Case (44)	Street drug (“speed”) 306.0 mg Not described; >60 days (chronic)	Autopsy conducted: Yes	Possible sentinel event
Death 84 yo Female Ephedrine Literature Case (44)	Unknown Unknown Not described; Not described	Autopsy conducted: Yes	Possible sentinel event
Death Literature Case Ephedrine 44 yo Male (224)	Insufficient information Unknown <24 hours; 14-60 days (acute)	Autopsy conducted: Yes	Possible sentinel event
Death 31 yo Female Ephedrine FDA Case (313104)	Ephedrine Unknown <6 hours; <48 hours	Autopsy conducted: No	Intraoperative ephedrine
Death 30 yo Female Literature Case (17)	Insufficient information Unknown Not described; Not described	Autopsy conducted: Yes	Suicide
Death 19 yo Female Literature Case (96)	Insufficient information Unknown <6 hours; Not described	Autopsy conducted: Yes	Suicide
Death 21 yo Male Literature Case (96)	Insufficient information Unknown <6 hours; Not described	Autopsy conducted: Yes	Suicide
Death 06/11/1999 24 yo Male Ephedra FDA Case (13672)	Ripped Fuel Unknown <6 hours; < 48 hours	Autopsy conducted: Yes	Probably not related
Death 40 yo Male Ephedrine FDA Case (1859087)	Max Alert Not described Not described	Autopsy conducted: No	Probably not related

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – Deaths (continued)

Event type Report date Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Investigation for Etiology	RAND Classification
Death Not described yo Male Ephedrine FDA Case (1902493)	Unknown Not described Not described	Autopsy conducted: Yes	Probably not related
Death 30 yo Male Ephedrine FDA Case (3491515)	Insufficient information Unknown Not described; Not described	Autopsy conducted: Yes	Probably not related
Death 29 yo Male Ephedrine FDA Case (3772362)	Insufficient information Unknown Not described; Not described	Autopsy conducted: Yes	Probably not related
Death 03/10/1994 23 yo Male Ephedra FDA Case (9188)	Cybergenics Body Builder Unknown Not described; 14-60 days (acute)	Autopsy conducted: No	Insufficient information
Death 06/09/1994 44 yo Male Ephedra FDA Case (9327)	Asian Herbal High Energy Unknown Not described; >60 days (chronic)	Autopsy conducted: No	Insufficient information
Death 06/14/1994 43 yo Female Ephedra FDA Case (9395)	Nature's Nutrition-Formula One Unknown Not described; 14-60 days (acute) Nature Nutritional Complex 1 Unknown Not described; Not described	Autopsy conducted: No	Insufficient information
Death 06/20/1994 36 yo Female Ephedra FDA Case (9473)	Nature's Nutrition-Formula One Unknown Not described; >60 days (chronic)	Autopsy conducted: No	Insufficient information

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – Deaths (continued)

Event type Report date Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Investigation for Etiology	RAND Classification
Death 05/24/1994 43 yo Female Ephedra FDA Case (9506)	Nature's Nutrition-Formula One Unknown Not described; >60 days (chronic)	Autopsy conducted: No	Insufficient information
Death 09/07/1994 45 yo Male Ephedra FDA Case (9864)	Nature's Nutrition-Formula One Unknown Not described; 14-60 days (acute)	Autopsy conducted: Yes	Insufficient information
Death 04/07/1995 26 yo Male Ephedra FDA Case (10104)	Natural Trim Unknown Not described; 14-60 days (acute)	Autopsy conducted: Yes	Insufficient information
Death 01/12/1993 43 yo Male Ephedra FDA Case (10251)	Omnitrition Herbal Tea 39.0 mg Not described; >60 days (chronic)	Autopsy conducted: Yes	Insufficient information
Death 06/14/1995 61 yo Female Ephedra FDA Case (10296)	New Image Plus Unknown >24 hours; 14-60 days (acute)	Autopsy conducted: No	Insufficient information
Death 12/19/1994 20 yo Male Ephedra FDA Case (10448)	Cybertrim Unknown Not described; Not described	Autopsy conducted: Yes	Insufficient information
Death 03/15/1995 17 yo Female Ephedra FDA Case (10849)	Unknown E'ola Product Unknown Not described; Not described	Autopsy conducted: No	Insufficient information

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – Deaths (continued)

Event type Report date Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Investigation for Etiology	RAND Classification
Death 03/14/1996 20 yo Male Ephedra FDA Case (10862)	The Equillizer- Part B Unknown <6 hours; < 48 hours	Autopsy conducted: No	Insufficient information
Death 04/08/1996 67 yo Male Ephedra FDA Case (10902)	Quickshot Unknown Not described; 2-13 days	Autopsy conducted: No	Insufficient information
Death 04/12/1996 29 yo Female Ephedra FDA Case (11018)	Omni-Trim (Omni-Trim Int'l) Unknown Not described; 14-60 days (acute)	Autopsy conducted: No	Insufficient information
Death 02/16/1996 64 yo Female Ephedra FDA Case (11060)	Nature's Nutrition-Formula One Unknown >24 hours; >60 days (chronic)	Autopsy conducted: No	Insufficient information
Death 05/20/1996 Not described yo Male Ephedra FDA Case (11134)	Ripped Fuel 60.0 mg Not described; >60 days (chronic)	Autopsy conducted: Yes	Insufficient information
Death 05/13/1996 37 yo Male Ephedra FDA Case (11248)	Nature's Nutrition-Formula One 42.4 mg Not described; >60 days (chronic) Equillizer Fast Start Unknown >24 hours; >60 days (chronic) Not described Unknown Not described; Not described	Autopsy conducted: No	Insufficient information

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – Deaths (continued)

Event type Report date Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Investigation for Etiology	RAND Classification
Death 07/11/1996 59 yo Male Ephedra FDA Case (11307)	Herbalife Original Green 26.4 mg Not described; 14-60 days (acute)	Autopsy conducted: No	Insufficient information
Death 06/25/1996 34 yo Female Ephedra FDA Case (11417)	Herbalife Original Green Unknown Not described; Not described	Autopsy conducted: No	Insufficient information
Death 07/23/1996 27 yo Male Ephedra FDA Case (11441)	Ripped Fuel 51.4 mg Not described; >60 days (chronic)	Autopsy conducted: No	Insufficient information
Death 07/12/1996 24 yo Male Ephedra FDA Case (11444)	Cybergenic super anti-fatigue 3.3 mg Not described; 14-60 days (acute)	Autopsy conducted: No	Insufficient information
Death 10/07/1996 56 yo Female Ephedra FDA Case (11721)	Easy Trim Unknown Not described; Not described	Autopsy conducted: No	Insufficient information
Death 08/25/1997 32 yo Female Ephedra FDA Case (12506)	Escalation Unknown Not described; Not described	Autopsy conducted: Yes	Insufficient information
Death 10/06/1997 0 yo Female Ephedra FDA Case (12594)	Ripped Fuel 20.0 mg Not described; >60 days (chronic)	Autopsy conducted: No	Insufficient information

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – Deaths (continued)

Event type Report date Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Investigation for Etiology	RAND Classification
Death 12/19/1997 22 yo Male Ephedra FDA Case (12720)	Ripped Fuel Unknown >24 hours; Not described	Autopsy conducted: Yes	Did not meet temporal relationship criterion
Death 04/23/1998 34 yo Male Ephedra FDA Case (12859)	Herbalife Original Green 42.0 mg Not described; 14-60 days (acute)	Autopsy conducted: No	Insufficient information
Death 04/24/1998 46 yo Male Ephedra FDA Case (12871)	Diet Fuel 20.1 mg Not described; Not described	Autopsy conducted: No	Insufficient information
Death 07/11/1998 43 yo Male Ephedra FDA Case (13021)	Ripped Fuel 63.6 mg Not described; >60 days (chronic)	Autopsy conducted: No	Insufficient information
Death 09/16/1998 37 yo Female Ephedra FDA Case (13096)	Metabolife 356 Unknown Not described; 2-13 days	Autopsy conducted: Yes	Insufficient information
Death 10/08/1998 49 yo Female Ephedra FDA Case (13127)	Thin Tabs Unknown Not described; Not described	Autopsy conducted: Yes	Insufficient information
Death 02/27/1999 18 yo Male Ephedra FDA Case (13380)	Ultimate Orange Unknown <6 hours; Not described	Autopsy conducted: No	Insufficient information

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – Deaths (continued)

Event type Report date Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Investigation for Etiology	RAND Classification
Death 05/19/1999 49 yo Male Ephedra FDA Case (13634)	Metabolife 356 60.0 mg Not described; < 48 hours	Autopsy conducted: No	Insufficient information
Death 06/04/1999 40 yo Female Ephedra FDA Case (13706)	Metabolife 356 72.0 mg >24 hours; 14-60 days (acute)	Autopsy conducted: Yes	Did not meet temporal relationship criterion
Death 06/30/1999 37 yo Female Ephedra FDA Case (13762)	Thermadrene Unknown Not described; Not described	Autopsy conducted: No	Insufficient information
Death 08/06/1999 59 yo Female Ephedra FDA Case (13802)	Metabolife 356 Unknown Not described; Not described	Autopsy conducted: No	Insufficient information
Death 08/03/1999 37 yo Male Ephedra FDA Case (13806)	Metabolife 356 Unknown <6 hours; 2-13 days	Autopsy conducted: Yes	Insufficient information
Death 10/06/1999 42 yo Female Ephedra FDA Case (13901)	Herbalife Original Green Unknown Not described; 14-60 days (acute)	Autopsy conducted: Yes	Insufficient information
Death 10/13/1999 62 yo Female Ephedra FDA Case (13993)	Metabolife 356 Unknown Not described; Not described	Autopsy conducted: No	Insufficient information

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – Deaths (continued)

Event type Report date Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Investigation for Etiology	RAND Classification
Death 04/04/2000 29 yo Female Ephedra FDA Case (14113)	Metabolife 356 Unknown >24 hours; >60 days (chronic) Omnitrition Herbal Tea Unknown Not described; 14-60 days (acute) Not described Unknown Not described; Not described	Autopsy conducted: Yes	Did not meet temporal relationship criterion
Death 08/10/2000 32 yo Female Ephedra FDA Case (14323)	Metabolift 60.0 mg Not described; 2-13 days	Autopsy conducted: Yes	Insufficient information
Death 08/31/2000 46 yo Female Ephedra FDA Case (14347)	Metabomax 72.0 mg Not described; 2-13 days	Autopsy conducted: No	Insufficient information
Death 09/14/2000 40 yo Female Ephedra FDA Case (14370)	Metabolife 356 Unknown Not described; 14-60 days (acute)	Autopsy conducted: No	Insufficient information
Death 03/28/2000 56 yo Male Ephedra FDA Case (14465)	Thermogen Plus Liquid 72.0 mg Not described; 2-13 days	Autopsy conducted: Yes	Insufficient information
Death 10/16/2000 46 yo Female Ephedra FDA Case (14470)	Up Your Gas 34.2 mg Not described; Not described	Autopsy conducted: Not described	Insufficient information

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – Deaths (continued)

Event type Report date Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Investigation for Etiology	RAND Classification
Death 11/14/2000 39 yo Male Ephedra FDA Case (14498)	Xenadrine 40.0 mg Not described; >60 days (chronic)	Autopsy conducted: Yes	Insufficient information
Death 11/18/2000 45 yo Female Ephedra FDA Case (14509)	Metabolife 356 24.0 mg >24 hours; 2-13 days	Autopsy conducted: No	Insufficient information
Death 12/06/2000 49 yo Female Ephedra FDA Case (14561)	Diet 2X Unknown Not described; 14-60 days (acute)	Autopsy conducted: No	Insufficient information
Death 12/24/2000 40 yo Male Ephedra FDA Case (14585)	Metabolife 356 72.0 mg Not described; >60 days (chronic)	Autopsy conducted: Yes	Insufficient information
Death 03/18/2001 28 yo Female Ephedra FDA Case (14747)	Mini Thin 75.0 mg Not described; >60 days (chronic) Yellow Jacket Unknown Not described; >60 days (chronic)	Autopsy conducted: Yes	Insufficient information
Death 03/29/2001 31 yo Female Ephedra FDA Case (14808)	Metabolife 356 Unknown Not described; >60 days (chronic)	Autopsy conducted: Yes	Insufficient information
Death 3 yo Male Ephedrine FDA Case (1772115)	Ephedrine Unknown <6 hours; < 48 hours	Autopsy conducted: No	Insufficient information

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – Deaths (continued)

Event type Report date Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Investigation for Etiology	RAND Classification
Death 99 yo Male Ephedrine FDA Case (1874879)	Unknown Not described Not described	Autopsy conducted: Yes	Insufficient information
Death 30 yo Female Ephedrine FDA Case (3135225)	MiniTabs Unknown Not described; Not described	Autopsy conducted: Yes	Insufficient information
Death 46 yo Male Ephedrine FDA Case (3173538)	Mini 2 Way Action Unknown Not described; >60 days (chronic)	Autopsy conducted: Yes	Insufficient information
Death 32 yo Female Ephedrine FDA Case (3551127)	Metabolift Unknown <6 hours; Not described	Autopsy conducted: N/A	Insufficient information
Death 99 yo Female Ephedrine FDA Case (3623625)	Diet 2X Unknown Not described; 14-60 days (acute)	Autopsy conducted: No	Insufficient information
Death 44 yo Female Ephedrine FDA Case (3768335)	Unknown Not described Not described; >60 days (chronic)	Autopsy conducted: No	Insufficient information
Death 20 yo Male Literature Case (462)	Ultimate Xphoria Unknown <6 hours; < 48 Hours	Autopsy conducted: Not described	Insufficient information

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – MI

Event type Report date Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Investigation of Etiology	RAND Classification
MI 03/20/1995 45 yo Male Ephedra FDA Case (10024)	Nature's Nutrition-Formula One Unknown <6 hours; 2-13 days	Angiography: Yes	Sentinel event
MI 23 yo Female Ephedrine FDA Case (3446357)	Midnight Ecstacy Unknown <6 hours; < 48 hours	Angiography: Yes	Sentinel event
MI 30 yo Male Ephedra Literature Case (244)	Ma huang Unknown <24 hours; Not described	Angiography: Yes	Sentinel event
MI 19 yo Male Ephedra Literature Case (516)	Dymetradine Xtreme 48.0 . <6 hours; Not described	Angiography: Yes	Sentinel event
MI 35 yo Female Ephedrine Literature Case (224)	Product unknown Unknown <24 hours; 14-60 days (acute)	Angiography: Yes	Sentinel event
MI 04/22/1994 37 yo Male Ephedra FDA Case (9372)	E'ola Amp II Pro Drops Unknown <6 hours; 2-13 days	Angiography: Yes	Possible sentinel event Note that this product was removed from the market- it contained illegal doses of ephedrine.
MI 05/23/1994 54 yo Male Ephedra FDA Case (9504)	Nature's Nutrition-Formula One Unknown 6-24 hours; >60 days (chronic)	Angiography: Yes	Possible sentinel event
MI 03/01/1995 35 yo Male Ephedra FDA Case (10009)	Metabolift 50.0 mg <6 hours; 14-60 days (acute)	Angiography: Yes	Possible sentinel event

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – MI (continued)

Event type Report date Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Investigation of Etiology	RAND Classification
MI 06/15/1998 38 yo Female Ephedra FDA Case (13009)	Herbalife Original Green 25.6 mg <6 hours; < 48 hours	Angiography: Yes	Possible sentinel event
MI 04/18/2000 37 yo Female Ephedra FDA Case (14114)	Metabolife 356 Unknown <6 hours; 14-60 days (acute)	Angiography: Yes	Possible sentinel event
MI 11/08/2000 43 yo Female Ephedra FDA Case (14530)	Metab-O-Lite 72.0 mg <6 hours; >60 days (chronic)	Angiography: Yes	Possible sentinel event
MI 25 yo Male Literature Case (64)	Ephedrine Unknown <6 hours; Not described	Angiography: No	Intravenous injection of ephedrine
MI 04/22/1994 34 yo Female Ephedra FDA Case (9373)	E'ola Amp II Pro Drops Unknown Not described; 2-13 days	Angiography: Yes	Insufficient information
MI 06/17/1994 Not described yo Male Ephedra FDA Case (9381)	The Edge Unknown Not described; Not described	Angiography: No	Insufficient information
MI 05/24/1994 56 yo Female Ephedra FDA Case (9512)	Nature's Nutrition-Formula One Unknown >24 hours; >60 days (chronic)	Angiography: No	Insufficient information

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – MI (continued)

Event type Report date Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Investigation of Etiology	RAND Classification
MI 08/26/1994 49 yo Female Ephedra FDA Case (9572)	Nature's Nutrition-Formula One Unknown Not described; 14-60 days (acute)	Angiography: Yes	Insufficient information
MI 03/16/1995 67 yo Female Ephedra FDA Case (10065)	Nature's Nutrition-Formula One Unknown Not described; 2-13 days	Angiography: Yes	Insufficient information
MI 07/03/1997 59 yo Female Ephedra FDA Case (12452)	Omnitrition Herbal Tea 60.0 mg Not described; 14-60 days (acute)	Angiography: Yes	Insufficient information
MI 04/21/1999 39 yo Female Ephedra FDA Case (13532)	Metabolife 356 24.0 mg Not described; >60 days (chronic)	Angiography: Yes	Insufficient information
MI 08/05/1999 51 yo Male Ephedra FDA Case (13815)	Metabolife 356 Unknown Not described; Not described	Angiography: No	Insufficient information
MI 04/06/2000 30 yo Female Ephedra FDA Case (14123)	Metabolife 356 Unknown Not described; Not described	Angiography: No	Insufficient information
MI 04/15/2000 53 yo Male Ephedra FDA Case (14222)	Natural Herbal Energizer Unknown Not described; Not described	Angiography: Yes	Insufficient information

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – MI (continued)

Event type Report date Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Investigation of Etiology	RAND Classification
MI 07/05/2000 39 yo Male Ephedra FDA Case (14259)	Diet Fuel 60.0 mg Not described; 14-60 days (acute)	Angiography: Yes	Insufficient information
MI 11/15/2000 45 yo Male Ephedra FDA Case (14521)	Xenadrine Unknown Not described; >60 days (chronic) Thermocut Unknown Not described; >60 days (chronic)	Angiography: Yes	Insufficient information
MI 12/02/2000 Not described yo Not described Ephedra FDA Case (14555)	Metabolife 356 Unknown Not described; 2-13 days	Angiography: No	Insufficient information
MI 01/07/2001 50 yo Female Ephedra FDA Case (14645)	Metabolife 356 Unknown Not described; 14-60 days (acute)	Angiography: Yes	Insufficient information

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – Cerebrovascular Accident/ Stroke

Event type Report date Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Investigation of Etiology	RAND Classification
CVA 01/03/1996 26 yo Female Ephedra FDA Case (10874)	Thermo Slim Unknown <6 hours; 2-13 days	Implicit review	Sentinel event
CVA 04/12/1996 42 yo Female Ephedra FDA Case (11062)	Power Trim Unknown Not described; >60 days (chronic)	Implicit review	Sentinel event
CVA 04/17/1996 31 yo Female Ephedra FDA Case (11105)	Trim Easy 72.0 mg 6-24 hours; >60 days (chronic)	Implicit review	Sentinel event
CVA 09/04/1996 28 yo Male Ephedra FDA Case (11675)	Ripped Fuel 63.6 mg Not described; >60 days (chronic)	Implicit review	Sentinel event
CVA 06/16/1998 39 yo Male Ephedra FDA Case (12980)	Ultimate Orange Unknown <6 hours; Not described	Implicit review	Sentinel event
CVA 12/31/1998 29 yo Male Ephedra FDA Case (13418)	Ultimate Orange 62.1 mg <6 hours; 14-60 days (acute)	Implicit review	Sentinel event
CVA 09/12/2000 53 yo Female Ephedra FDA Case (14372)	Slim Caps 24.0 mg 6-24 hours; 14-60 days (acute)	Implicit review	Sentinel event

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – Cerebrovascular Accident/ Stroke (continued)

Event type Report date Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Investigation of Etiology	RAND Classification
CVA 10/20/2000 46 yo Female Ephedra FDA Case (14473)	Xenadrine Unknown <6 hours; 2-13 days	Implicit review	Sentinel event
CVA 33 yo Male Ephedra Literature Case (552)	Thermadrene Unknown 6-24 hours; Not described	Implicit review	Sentinel event
CVA 19 yo Female Ephedrine Literature Case (184)	Ephedrine Unknown <6 hours; Not described	Implicit review	Sentinel event
CVA 20 yo Female Ephedrine Literature Case (514)	"Purported amphetamine look-alike" Unknown <6 hours; < 48 Hours	Implicit review	Sentinel event
CVA 04/17/1992 30 yo Female Ephedra FDA Case (9296)	E'ola Amp II Pro Drops 75.0 mg <6 hours; 2-13 days	Implicit review	Possible sentinel event Note that this product was removed from the market- it contained illegal doses of ephedrine.
CVA 04/22/1994 56 yo Female Ephedra FDA Case (9335)	E'ola Amp II Pro Drops Unknown 6-24 hours; >60 days (chronic)	Implicit review	Possible sentinel event Note that this product was removed from the market- it contained illegal doses of ephedrine.
CVA 03/15/1995 24 yo Female Ephedra FDA Case (10094)	Super Fat Burners Unknown 6-24 hours; <48 hours	Implicit review	Possible sentinel event

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – Cerebrovascular Accident/ Stroke (continued)

Event type Report date Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Investigation of Etiology	RAND Classification
CVA 01/09/1998 64 yo Female Ephedra FDA Case (12713)	FitAmerica Natural Weight ControlAid 100.0 mg <6 hours; >60 days (chronic)	Implicit review	Possible sentinel event
CVA 12/23/1997 47 yo Male Ephedra FDA Case (12733)	Purple Blast Unknown <6 hours; 14-60 days (acute)	Implicit review	Possible sentinel event
CVA 04/27/1998 41 yo Female Ephedra FDA Case (12888)	Diet Phen 13.5 mg 6-24 hours; 14-60 days (acute)	Implicit review	Possible sentinel event
CVA 09/13/2000 25 yo Female Ephedra FDA Case (14378)	Natural Trim 44.0 mg 6-24 hours; 14-60 days (acute)	Implicit review	Possible sentinel event
CVA 10/12/2000 42 yo Male Ephedra FDA Case (14434)	Slim 'N Up Unknown 6-24 hours; >60 days (chronic)	Implicit review	Possible sentinel event
CVA/ Subarachnoid hemorrhage 11/16/2000 55 yo Female Ephedra FDA Case (14553)	Metabolife 356 Unknown 6-24 hours; 14-60 days (acute)	Implicit review	Possible sentinel event
CVA 33 yo Male Ephedra Literature Case (270)	Ma huang 40 mg 6-24 hours; 14-60 days	Implicit review	Possible sentinel event

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – Cerebrovascular Accident/ Stroke (continued)

Event type Report date Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Investigation of Etiology	RAND Classification
CVA 37 yo Male Ephedrine Literature Case (44)	"Street drug" 153.0 mg Not described; 14-60 days (acute)	Implicit review	Possible sentinel event
CVA 20 yo Male Ephedrine Literature Case (438)	"Speed" Unknown <6 hours; Not described	Implicit review	Possible sentinel event
CVA 29 yo Female Ephedrine FDA Case (3720184)	Ephedrine Unknown <6 hours; < 48 hours	Not relevant	Intraoperative ephedrine
CVA 45 yo Female Literature Case (485)	Ephedrine Unknown <6 hours; < 48 hours	Not relevant	Intraoperative ephedrine
CVA 05/12/1994 36 yo Female Ephedra FDA Case (9521)	Nature's Nutrition-Formula One Unknown <6 hours; >60 days (chronic)	Implicit review	Insufficient information
CVA 06/22/1994 52 yo Male Ephedra FDA Case (9545)	Nature's Nutrition-Formula One Unknown Not described; >60 days (chronic)	Not reviewed	Insufficient information
CVA 10/26/1994 40 yo Female Ephedra FDA Case (9749)	Equillizer Fast Start Unknown >24 hours; 2-13 days	Not reviewed	Did not meet the temporal relationship criterion
CVA 09/14/1994 49 yo Male Ephedra FDA Case (9865)	Nature's Nutrition-Formula One Unknown Not described; 14-60 days (acute)	Not reviewed	Insufficient information

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – Cerebrovascular Accident/ Stroke (continued)

Event type Report date Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Investigation of Etiology	RAND Classification
CVA 05/12/1995 53 yo Female Ephedra FDA Case (10187)	Nature's Nutrition-Formula One Unknown Not described; >60 days (chronic)	Not reviewed	Insufficient information
CVA 10/19/1995 31 yo Female Ephedra FDA Case (10477)	TriChromolean Unknown Not described; 14-60 days (acute)	Not reviewed	Insufficient information
CVA 10/12/1995 19 yo Female Ephedra FDA Case (10508)	Thermoburn Unknown Not described; >60 days (chronic)	Not reviewed	Insufficient information
CVA 02/07/1996 30 yo Female Ephedra FDA Case (10893)	Metabolift 60.0 mg Not described; 14-60 days (acute)	Not reviewed	Insufficient information
CVA 04/13/1996 34 yo Female Ephedra FDA Case (10957)	E'ola Amp II Pro Drops Unknown Not described; >60 days (chronic)	Not reviewed	Insufficient information
CVA 07/11/1996 55 yo Female Ephedra FDA Case (11306)	Natural Trim Unknown Not described; >60 days (chronic)	Not reviewed	Insufficient information
CVA 07/18/1996 39 yo Female Ephedra FDA Case (11442)	Herbalife Original Green Unknown Not described; >60 days (chronic)	Not reviewed	Insufficient information

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – Cerebrovascular Accident/ Stroke (continued)

Event type Report date Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Investigation of Etiology	RAND Classification
CVA 06/18/1996 35 yo Female Ephedra FDA Case (11619)	E'ola Amp II Pro Drops 21.5 mg >24 hours; Not described	Not reviewed	Did not meet the temporal relationship criterion
CVA 08/21/1996 33 yo Female Ephedra FDA Case (11706)	Herbalife Original Green Unknown Not described; >60 days (chronic) AP300 Unknown Not described; >60 days (chronic)	Not reviewed	Insufficient information
CVA 10/21/1996 69 yo Female Ephedra FDA Case (12340)	E'ola Amp II Pro Drops 36.8 mg Not described; 14-60 days (acute)	Not reviewed	Insufficient information
CVA 06/05/1997 64 yo Female Ephedra FDA Case (12460)	Shape Fast 30.0 mg Not described; Not described	Not reviewed	Insufficient information
CVA 08/01/1997 34 yo Female Ephedra FDA Case (12483)	Shape Fast 36.0 mg Not described; 2-13 days	Not reviewed	Insufficient information
CVA 04/22/1998 43 yo Female Ephedra FDA Case (12861)	Metabolife 356 Unknown Not described; >60 days (chronic)	Not reviewed	Insufficient information
CVA 02/11/1999 47 yo Female Ephedra FDA Case (13336)	Total Control 66.0 mg >24 hours; >60 days (chronic)	Not reviewed	Did not meet the temporal relationship criterion

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – Cerebrovascular Accident/ Stroke (continued)

Event type Report date Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Investigation of Etiology	RAND Classification
CVA 02/01/1999 48 yo Female Ephedra FDA Case (13341)	Metacut 12.3 mg Not described; 2-13 days	Not reviewed	Insufficient information
CVA 06/01/1999 16 yo Male Ephedra FDA Case (13661)	Hydroxycut (Muscle Tech R&D) 160.0 mg >24 hours; 14-60 days (acute)	Not reviewed	Did not meet the temporal relationship criterion
CVA 06/23/1999 18 yo Female Ephedra FDA Case (13779)	Metabolife 356 Unknown Not described; 14-60 days (acute)	Not reviewed	Insufficient information
CVA 08/03/1999 24 yo Female Ephedra FDA Case (13797)	Metabolife 356 Unknown Not described; >60 days (chronic)	Not reviewed	Insufficient information
CVA 08/04/1999 30 yo Female Ephedra FDA Case (13829)	Metabolife 356 48.0 mg <6 hours; 2-13 days	Implicit review	Insufficient information
CVA 07/01/1999 26 yo Female Ephedra FDA Case (13837)	Metabolife 356 Unknown Not described; 14-60 days (acute)	Not reviewed	Insufficient information
CVA 10/27/1999 36 yo Female Ephedra FDA Case (13905)	Metabolife 356 Unknown <6 hours; >60 days(chronic)	Implicit review	Insufficient information

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – Cerebrovascular Accident/ Stroke (continued)

Event type Report date Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Investigation of Etiology	RAND Classification
CVA 10/08/1998 Not described yo Female Ephedra FDA Case (14056)	Ripped Fuel Unknown Not described; Not described	Not reviewed	Insufficient information
CVA 06/13/2000 46 yo Female Ephedra FDA Case (14231)	Metabolife 356 Unknown Not described; 14-60 days (acute) Xenadrine Unknown Not described; 14-60 days (acute)	Not reviewed	Insufficient information
CVA 10/03/2000 21 yo Female Ephedra FDA Case (14431)	Slacker II Unknown Not described; 2-13 days	Not reviewed	Insufficient information
CVA 01/16/2001 48 yo Female Ephedra FDA Case (14632)	LiquiFit Exercise Drops 75.0 mg Not described; 14-60 days (acute)	Not reviewed	Insufficient information
CVA 32 yo Female Ephedrine FDA Case (1823550)	Ephedrine (“Maxi Thins”) Unknown Not described; >60 days (chronic)	Implicit review	Insufficient information
CVA 68 yo Male Literature Case (515)	“Over-the-counter anti-asthma pill” 60.0 mg <6 hours; >60 days (chronic)	Implicit review	Insufficient information

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – Other Cardiovascular

Event type Report date Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Invesigation of Etiology	RAND Classification
Cardiac/ Near sudden death 04/08/1998 22 yo Male Ephedra FDA Case (12851)	Ripped Force 20.4 mg 6-24 hours; >60 days (chronic)	Angiography: No	Possible sentinel event
Cardiac/ Cardiomyopathy 28 yo Female Literature Case (110)	Ephedrine 2000.0 mg Not described; >60 days (chronic)	Angiography: Yes	Possible sentinel event
Cardiac/ Cardiomyopathy 39 yo Male Literature Case (297)	Herbalife Original Green Unknown Not described; 14-60 days (acute)	Angiography: Yes	Possible sentinel event
Cardiac 59 yo Female Ephedrine FDA Case (3359234)	Ephedrine Unknown <6 hours; < 48 hours	Not relevant	Intraoperative ephedrine
Cardiac 99 yo Male Ephedrine FDA Case (3537599)	Ephedrine Unknown <6 hours; < 48 hours	Not relevant	Intraoperative ephedrine
Cardiac 42 yo Male Literature Case (174)	Ephedrine Unknown <6 hours; < 48 hours	Not relevant	Intraoperative ephedrine
Cardiac 07/19/1994 43 yo Male Ephedra FDA Case (9818)	Power Trim Unknown Not described; 14-60 days (acute)	Not reviewed	Insufficient information
Cardiac 06/02/1995 63 yo Female Ephedra FDA Case (10275)	Nature's Nutrition-Formula One Unknown Not described; 14-60 days (acute)	Not reviewed	Insufficient information

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – Other Cardiovascular (continued)

Event type Report date Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Invesigation of Etiology	RAND Classification
Cardiac 05/07/1996 47 yo Female Ephedra FDA Case (11133)	Natural Trim Unknown Not described; 14-60 days (acute)	Not reviewed	Insufficient information
Cardiac 05/15/1996 66 yo Female Ephedra FDA Case (11282)	E'ola Amp II Pro Drops Unknown Not described; >60 days (chronic)	Not reviewed	Insufficient information
Cardiac 06/24/1996 35 yo Female Ephedra FDA Case (11464)	Shape Fast 80.0 mg Not described; 2-13 days	Not reviewed	Insufficient information
Cardiac 01/21/1996 48 yo Male Ephedra FDA Case (11782)	Pro ripped Unknown Not described; >60 days (chronic)	Not reviewed	Insufficient information
Cardiac 01/22/1998 31 yo Female Ephedra FDA Case (12740)	Ripped Fuel Unknown Not described; 2-13 days	Not reviewed	Insufficient information
Cardiac/ Near sudden death 07/29/1998 28 yo Female Ephedra FDA Case (13031)	Herbalife Original Green 43.2 mg <6 hours; < 48 Hours	Angiography: Unknown	Insufficient Information
Cardiac 04/19/1999 57 yo Female Ephedra FDA Case (13516)	Metabolife 356 Unknown Not described; >60 days (chronic)	Not reviewed	Insufficient information

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – Other Cardiovascular (continued)

Event type Report date Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Invesigation of Etiology	RAND Classification
Cardiac/ Near sudden death 05/19/1999 32 yo Female Ephedra FDA Case (13643)	Natural Trim 88.0 mg <6 hours; 14-60 days (acute)	Angiography: Unknown	Insufficient Information
Cardiac/ Cardiomyopathy 07/23/1999 65 yo Female Ephedra FDA Case (13793)	Thermolean Unknown <6 hours; >60 days (chronic) Power Trim 84.0 mg <6 hours; >60 Days (chronic)	Not reviewed	Insufficient Information
Cardiac 07/23/1999 39 yo Male Ephedra FDA Case (13796)	Natural Trim Unknown Not described; >60 days (chronic)	Not reviewed	Insufficient information
Cardiac/ Ventricular Tachycardia 11/15/1999 48 yo Female Ephedra FDA Case (13945)	Metabolife 356 Unknown <6 hours; 14-60 days (acute)	Not reviewed	Insufficient Information
Cardiac 12/24/1999 48 yo Female Ephedra FDA Case (13992)	Unknown 45.0 mg Not described; >60 days (chronic)	Not reviewed	Insufficient information
Cardiac 11/08/1999 46 yo Male Ephedra FDA Case (14017)	Metabolife 356 Unknown Not described; 14-60 days (acute)	Not reviewed	Insufficient information

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – Other Cardiovascular (continued)

Event type Report date Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Invesigation of Etiology	RAND Classification
Cardiac 03/08/2000 26 yo Male Ephedra FDA Case (14080)	Ripped Fuel Unknown Not described; >60 days (chronic) Hydroxycut (Muscle Tech R&D) Unknown Not described; >60 Days (chronic)	Not reviewed	Insufficient information
Cardiac 03/23/2000 47 yo Female Ephedra FDA Case (14108)	Herbalife Original Green Unknown >24 hours; >60 days (chronic)	Not reviewed	Insufficient information
Cardiac 04/19/2000 41 yo Female Ephedra FDA Case (14143)	Metabolife 356 24.0 mg Not described; >60 days (chronic)	Not reviewed	Insufficient information
Cardiac 04/11/2000 43 yo Female Ephedra FDA Case (14242)	Metabolize Unknown Not described; >60 days (chronic) Unknown Unknown Not described; Not described	Not reviewed	Insufficient information
Cardiac 07/19/2000 26 yo Female Ephedra FDA Case (14284)	FitAmerica Int'l Weight ControlAid Unknown >24 hours; 2-13 days	Not reviewed	Insufficient information
Cardiac 09/14/2000 39 yo Female Ephedra FDA Case (14383)	Biolean Unknown Not described; >60 days (chronic)	I Not reviewed	Insufficient information
Cardiac/ Cardiomyopathy 32 yo Female Literature Case (260)	Ephedrine 450.0 mg Not described; >60 days (chronic)	Angiography: No	Insufficient information

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – Other Cardiovascular (continued)

Event type **Report date** **Age, Sex** **Constituent** **Source** **(ID)**	**Product** **Dose*** **Timing; Duration**	**Invesigation of Etiology**	**RAND Classification**
Cardiac/ Cardiomyopathy 35 yo Male Literature Case (271)	Insufficient information Unknown <24 hours; >60 days (chronic)	Angiography: No	Insufficient information

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – Other Neurological

Event type Report date Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Investigation of Etiology	RAND classification
Neurological/ TIA 06/29/1998 57 yo Female Ephedra FDA Case (13062)	Metabolife 356 48.0 mg 6-24 hours; < 48 hours	Implicit review	Possible sentinel event
Neurological 11/27/1995 54 yo Female Ephedra FDA Case (10573)	Thermogenic Fat Burner (Joe Weider) 48.0 mg Not described; 14-60 days (acute)	Not reviewed	Insufficient information
Neurological 08/12/1996 39 yo Male Ephedra FDA Case (11900)	Excel Energy 24.0 mg Not described; >60 days (chronic)	Not reviewed	Insufficient information
Neurological 02/10/2000 59 yo Female Ephedra FDA Case (14018)	Metabolife 356 24.0 mg >24 hours; >60 days (chronic)	Implicit review	Did not meet temporal relationship criterion
Neurological 08/31/2000 31 yo Female Ephedra FDA Case (14352)	Ripped Fuel Unknown Not described; 14-60 days (acute)	Not reviewed	Insufficient information
Neurological 11/07/2000 35 yo Female Ephedra FDA Case (14495)	Metab-O-Lite 24.0 mg Not described; >60 days (chronic)	Not reviewed	Insufficient information
Neurological 29 yo Male Ephedrine FDA Case (1535075)	Ephedrine Unknown Not described; Not described	Implicit review	Insufficient information

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – Other Neurological (continued)

Event type **Report date** **Age, Sex** **Constituent** **Source** **(ID)**	**Product** **Dose*** **Timing; Duration**	**Investigation of Etiology**	**RAND classification**
Neurological/ TIA 12 yo Female Literature Case (218)	E'ola Unknown <6 hours; < 48 hours	Implicit review	Insufficient information

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – Seizure

Event type Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Investigation for Etiology	RAND Classification
Seizure 19 YO Female Ephedra FDA Case (10974)	Shape Fast/Rite Not described Not described; 14-60 days (acute)	CT/MRI of Head: Yes Serum Electrolytes: Yes Glucose: Yes Calcium: Yes Magnesium: No Temperature: Yes EEG: Yes	Sentinel event
Seizure 38 YO Female Ephedrine Literature Case (224)	Ephedrine Not described 6-24 hours; Duration Not described	CT/MRI of Head: No Serum Electrolytes: No Glucose: No Calcium: No Magnesium: No Temperature: No EEG: No	Sentinel event
Seizure 47 YO Female Ephedra FDA Case (9534)	Nature's Nutrition-Formula One Not described 6-24 hours; 14-60 days (acute)	CT/MRI of Head: Yes Serum Electrolytes: Yes Glucose: Yes Calcium: No Magnesium: No Temperature: Yes EEG: Yes	Possible sentinel event
Seizure 37 YO Female Ephedra FDA Case (10221)	Nature's Nutrition-Formula One Not described Not described; >60 days (chronic)	CT/MRI of Head: Yes Serum Electrolytes: Yes Glucose: Yes Calcium: Yes Magnesium: Yes Temperature: Yes EEG: Yes	Possible sentinel event
Seizure 62 YO Male Ephedra FDA Case (10432)	Thermo Slim Not described Not described; >60 days (chronic)	CT/MRI of Head: Yes Serum Electrolytes: Yes Glucose: Yes Calcium: Yes Magnesium: Yes Temperature: Yes EEG: Yes	Possible sentinel event
Seizure 23 YO Female Ephedra FDA Case (11649)	Metabolife 356 Not described Not described; >60 days (chronic)	CT/MRI of Head: Yes Serum Electrolytes: Yes Glucose: Yes Calcium: Yes Magnesium: No Temperature: Yes EEG: Yes	Possible sentinel event

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – Seizure (continued)

Event type Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Investigation for Etiology	RAND Classification
Seizure 26 YO Male Ephedra FDA Case (13408)	Ripped Fuel Not described <6 hours; >60 days (chronic)	CT/MRI of Head: Yes Serum Electrolytes: Yes Glucose: Yes Calcium: Yes Magnesium: Yes Temperature: Yes EEG: Yes	Possible sentinel event
Seizure 30 YO Female Ephedra FDA Case (14275)	Metab-O-Lite Not described 6-24 hours; >60 days (chronic)	CT/MRI of Head: Yes Serum Electrolytes: Yes Glucose: Yes Calcium: Yes Magnesium: No Temperature: Yes EEG: Yes	Possible sentinel event
Seizure 31 YO Female Ephedra FDA Case (14571)	Thin Tabs Not described 6-24 hours; 14-60 days (acute)	CT/MRI of Head: Yes Serum Electrolytes: Yes Glucose: Yes Calcium: Yes Magnesium: No Temperature: Yes EEG: Yes	Possible sentinel event
Seizure 38 YO Female Ephedra FDA Case (9528)	Nature's Nutrition-Formula One Not described Not described; 14-60 days (acute)	CT/MRI of Head: Yes Serum Electrolytes: Yes Glucose: Yes Calcium: Yes Magnesium: No Temperature: Yes EEG: Yes	Insufficient Information
Seizure 47 YO Female Ephedra FDA Case (9547)	Nature's Nutrition-Formula One Not described Not described; 2-13 days	CT/MRI of Head: Yes Serum Electrolytes: Yes Glucose: No Calcium: Yes Magnesium: Yes Temperature: Yes EEG: Yes	Insufficient information
Seizure 40 YO Female Ephedra FDA Case (9747)	Ripped Fuel 25 mg Not described; 2-13 days	CT/MRI of Head: Yes Serum Electrolytes: Yes Glucose: Yes Calcium: No Magnesium: No Temperature: No EEG: No	Insufficient information

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – Seizure (continued)

Event type Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Investigation for Etiology	RAND Classification
Seizure Age Not described, Male Ephedra FDA Case (9799)	E'ola Amp II Pro Drops Not described Not described; 14-60 days (acute)	CT/MRI of Head: No Serum Electrolytes: No Glucose: No Calcium: No Magnesium: No Temperature: No EEG: Yes	Insufficient information
Seizure 34 YO Female Ephedra FDA Case (10301)	Thermogenics Plus Not described Not described; 14-60 days (acute)	CT/MRI of Head: Yes Serum Electrolytes: No Glucose: No Calcium: No Magnesium: No Temperature: No EEG: Yes	Insufficient information
Seizure 32 YO Male Ephedra FDA Case (10416)	Slim Now Not described <6 hours; >60 days (chronic)	CT/MRI of Head: Yes Serum Electrolytes: Yes Glucose: Yes Calcium: Yes Magnesium: No Temperature: Yes EEG: Yes	Insufficient information
Seizure 55 YO Female Ephedra FDA Case (10437)	Herbalife Original Green Not described <6 hours; 2-13 days	CT/MRI of Head: Yes Serum Electrolytes: Yes Glucose: Yes Calcium: Yes Magnesium: No Temperature: No EEG: No	Insufficient information
Seizure 38 YO Female Ephedra FDA Case (10570)	Thermochrome 5000 21 mg 6-24 hours; <48 hours	CT/MRI of Head: Yes Serum Electrolytes: Yes Glucose: Yes Calcium: Yes Magnesium: Yes Temperature: Yes EEG: Yes	Insufficient information
Seizure 29 YO Female Ephedra FDA Case (10964)	Diet Max/Super Diet Max Not described Not described; >60 days (chronic)	CT/MRI of Head: No Serum Electrolytes: No Glucose: No Calcium: No Magnesium: No Temperature: No EEG: No	Insufficient information

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – Seizure (continued)

Event type Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Investigation for Etiology	RAND Classification
Seizure 41 YO Female Ephedra FDA Case (11001)	Guarana Plus Not described Not described; >60 days (chronic)	CT/MRI of Head: No Serum Electrolytes: No Glucose: No Calcium: No Magnesium: No Temperature: No EEG: No	Insufficient information
Seizure 36 YO Female Ephedra FDA Case (11078)	Quick Start Not described Not described; Not described Nature's Nutrition-Formula One Not described 6-24 hours; >60 days (chronic)	CT/MRI of Head: Yes Serum Electrolytes: Yes Glucose: Yes Calcium: No Magnesium: Yes Temperature: Yes EEG: Yes	Insufficient information
Seizure 19 YO Male Ephedra FDA Case (11181)	Ripped Fuel Not described 6-24 hours; 2-13 days	CT/MRI of Head: Yes Serum Electrolytes: Yes Glucose: Yes Calcium: No Magnesium: No Temperature: Yes EEG: Yes	Insufficient information
Seizure 24 YO Male Ephedra FDA Case (11215)	Ripped Fuel Not described Not described; Not described Ripped Force Not described >24 hours; >60 days (chronic)	CT/MRI of Head: No Serum Electrolytes: No Glucose: No Calcium: No Magnesium: No Temperature: No EEG: No	Insufficient information
Seizure 20 YO Male Ephedra FDA Case (11249)	Victory Turbo Pump Not described Not described; >60 days (chronic)	CT/MRI of Head: Yes Serum Electrolytes: No Glucose: Yes Calcium: No Magnesium: No Temperature: No EEG: Yes	Insufficient information
Seizure 38 YO Female Ephedra FDA Case (11304)	E'ola Amp Pro Drops Not described <6 hours; <48 hours	CT/MRI of Head: No Serum Electrolytes: No Glucose: No Calcium: No Magnesium: No Temperature: No EEG: No	Insufficient information

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – Seizure (continued)

Event type Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Investigation for Etiology	RAND Classification
Seizure 37 YO Male Ephedra FDA Case (11316)	Nature's Nutrition-Formula One Not described 6-24 hours; 14-60 days (acute)	CT/MRI of Head: Yes Serum Electrolytes: Yes Glucose: Yes Calcium: Yes Magnesium: Yes Temperature: Yes EEG: Yes	Insufficient information
Seizure 34 YO Female Ephedra FDA Case (11594)	Fit America Intnl Weight Control Aid Not described Not described; 2-13 days	CT/MRI of Head: No Serum Electrolytes: Yes Glucose: Yes Calcium: Yes Magnesium: Yes Temperature: Yes EEG: Yes	Insufficient information
Seizure 15 YO Male Ephedra FDA Case (12477)	Up Your Gas Not described <6 hours; <48 hours	CT/MRI of Head: No Serum Electrolytes: No Glucose: No Calcium: No Magnesium: No Temperature: No EEG: No	Insufficient information
Seizure Age Not described, Female Ephedra FDA Case (12948)	Escalation Not described Not described; 2-13 days	CT/MRI of Head: No Serum Electrolytes: No Glucose: No Calcium: No Magnesium: No Temperature: No EEG: No	Insufficient information
Seizure 42 YO Female Ephedra FDA Case (13110)	E-Z Trim Tablets 24 mg Not described; 2-13 days	CT/MRI of Head: Yes Serum Electrolytes: Yes Glucose: Yes Calcium: Yes Magnesium: Yes Temperature: Yes EEG: Yes	Insufficient information
Seizure 53 YO Female Ephedra FDA Case (13514)	Metabolift Not described <6 hours; 14-60 days (acute)	CT/MRI of Head: No Serum Electrolytes: No Glucose: No Calcium: No Magnesium: No Temperature: No EEG: No	Insufficient information

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – Seizure (continued)

Event type Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Investigation for Etiology	RAND Classification
Seizure Age Not described, Female Ephedra FDA Case (13519)	Metabolife 356 Not described Not described; Not described	CT/MRI of Head: No Serum Electrolytes: Yes Glucose: No Calcium: No Magnesium: No Temperature: No EEG: No	Insufficient information
Seizure 46 YO Female Ephedra FDA Case (13625)	Metabolife 356 Not described Not described; 14-60 days (acute)	CT/MRI of Head: Yes Serum Electrolytes: Yes Glucose: Yes Calcium: No Magnesium: No Temperature: No EEG: Yes	Insufficient information
Seizure 25 YO Female Ephedra FDA Case (13715)	Diet Fuel Not described Not described; Not described Ripped Fuel Not described Not described; Not described Hydroxycut Not described <6 hours; >60 days (chronic)	CT/MRI of Head: Yes Serum Electrolytes: Yes Glucose: Yes Calcium: No Magnesium: No Temperature: No EEG: Yes	Insufficient information
Seizure 51 YO Male Ephedra FDA Case (13895)	Metabolife 356 Not described Not described; 14-60 days (acute)	CT/MRI of Head: Yes Serum Electrolytes: Yes Glucose: Yes Calcium: No Magnesium: No Temperature: No EEG: Yes	Insufficient information
Seizure 17 YO Male Ephedra FDA Case (13946)	Ripped Fuel Not described Not described; Not described Thermo-Tek Not described <6 hours; >60 days (chronic)	CT/MRI of Head: Yes Serum Electrolytes: Yes Glucose: Yes Calcium: No Magnesium: No Temperature: Yes EEG: Yes	Insufficient information
Seizure 58 YO Male Ephedra FDA Case (13972)	Metabolife 356 Not described Not described; >60 days (chronic)	CT/MRI of Head: Yes Serum Electrolytes: Yes Glucose: Yes Calcium: No Magnesium: No Temperature: No EEG: Yes	Insufficient information

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – Seizure (continued)

Event type Age, Sex Constituent Source (ID)	Product Dose* Timing; Duration	Investigation for Etiology	RAND Classification
Seizure 39 YO Female Ephedra FDA Case (14116)	Thermo-Gen Not described 6-24 hours; >60 days (chronic)	CT/MRI of Head: Yes Serum Electrolytes: Yes Glucose: Yes Calcium: Yes Magnesium: Yes Temperature: Yes EEG: Yes	Insufficient information
Seizure 23 YO Male Ephedra FDA Case (14258)	Ripped Fuel Not described <6 hours; <48 hours	CT/MRI of Head: Yes Serum Electrolytes: Yes Glucose: Yes Calcium: Yes Magnesium: Yes Temperature: Yes EEG: Yes	Insufficient information
Seizure 42 YO Female Ephedra FDA Case (14297)	Natural Trim Not described 6-24 hours; <48 hours	CT/MRI of Head: Yes Serum Electrolytes: No Glucose: No Calcium: No Magnesium: No Temperature: No EEG: Yes	Insufficient information
Seizure Age Not described, Female Ephedrine FDA Case (3549038)	Ephedrine Plus Not described <6 hours; 14-60 days (acute)	CT/MRI of Head: No Serum Electrolytes: No Glucose: No Calcium: No Magnesium: No Temperature: No EEG: No	Insufficient information

* dose reported in total daily alkaloids yo = year old

Table 22. Evidence table of case reports – Psychiatric

Event type Age, Sex Constituent Source (ID)	Product Dose* Duration Addiction Data**	Investigation for Etiology***	RAND Classification
Psychosis, Sleep disturbance, Palpitations, Dizzy 21 YO Male Ephedra FDA Case (9509)	Nature's Nutrition-Formula One Not described <48 hours Addiction: No	Psychiatric History: No Other Substances/Meds: No	Sentinel Event
Psychosis, Hallucinations, Sleep disturbance 39 YO Female Ephedra FDA Case (11678)	Diet Now 12 mg Over 1 year Addiction: No	Psychiatric History: No Other Substances/Meds: No	Sentinel Event
Mania or severe agitation, Suicidal ideation, Violent, Personality changes, Headache 19 YO Female Ephedra FDA Case (13809)	Hydroxycut Not described 2-13 days Addiction: No	Psychiatric History: No Other Substances/Meds: No	Sentinel Event
Psychosis, Mania or severe agitation, Severe depression, Suicidal ideation, Sleep disturbance, Homicidal ideation 29 YO Male Ephedra FDA Case (14529)	Xenadrine Not described 60 days to 1 year Addiction: No	Psychiatric History: No Other Substances/Meds: No	Sentinel Event
Mania or severe agitation, Ventricular tachycardia / fibrillation, Insomnia, Violent 16 YO Male Ephedrine FDA Case (1855921)	Max Alert Mini Thin Not described 60 days to 1 year Addiction: Yes	Psychiatric History: No Other Substances/Meds: No	Sentinel Event
Mania or severe agitation, Sleep disturbance 45 YO Male Ephedra Literature Case (48)	Ma huang/Ephedra Not described 14-60 days (acute) Addiction: No	Psychiatric History: No Other Substances/Meds: No	Sentinel Event

* dose reported in total daily alkaloids yo = year old

** Addiction: Yes = diagnosis or self-reported addiction to the product

*** Psychiatric history: Yes = recorded psychiatric history

Other substances/meds: Yes = patient taking other substances or medications known to cause psychiatric symptoms

Table 22. Evidence table of case reports – Psychiatric (continued)

Event type Age, Sex Constituent Source (ID)	Product Dose* Duration Addiction Data**	Investigation for Etiology***	RAND Classification
Psychosis, Paranoia 30 YO Female Ephedrine Literature Case (238)	Tedral 144 mg Over 1 year Addiction: Yes	Psychiatric History: No Other Substances/Meds: No	Sentinel Event
Psychosis, Hallucinations, Confusion/Delusional 59 YO Male Ephedrine Literature Case (285)	Bronchi Pax 360 mg Over 1 year Addiction: No	Psychiatric History: No Other Substances/Meds: No	Sentinel Event
Severe depression, Suicide attempt 28 YO Female Ephedra FDA Case (9751)	Slim NRG+ Not described 60 days to 1 year Addiction: No	Psychiatric History: No Other Substances/Meds: No	Possible Sentinel Event
Psychosis, Suicidal ideation, Palpitations, Increased hypertension, 19 YO Male Ephedra FDA Case (11157)	Ripped Fuel Not described 60 days to 1 year Addiction: No	Psychiatric History: No Other Substances/Meds: No	Possible Sentinel Event
Psychosis, Hallucinations, Memory Loss 13 YO Female Ephedra FDA Case (12372)	Nature's Nutrition-Formula One Not described 14-60 days (acute) Addiction: No	Psychiatric History: No Other Substances/Meds: No	Possible Sentinel Event
Mania or severe agitation, Sleep disturbance 21 YO Male Ephedra FDA Case (13005)	Ripped Fuel Not described 14-60 days (acute) Addiction: No	Psychiatric History: No Other Substances/Meds: No	Possible Sentinel Event
Psychosis, Hallucinations 52 YO Female Ephedra FDA Case (14436)	Metab-O-Lite Not described 60 days to 1 year Addiction: No	Psychiatric History: No Other Substances/Meds: No	Possible Sentinel Event

* dose reported in total daily alkaloids yo = year old

** Addiction: Yes = diagnosis or self-reported addiction to the product

*** Psychiatric history: Yes = recorded psychiatric history

Other substances/meds: Yes = patient taking other substances or medications known to cause psychiatric symptoms

Table 22. Evidence table of case reports – Psychiatric (continued)

Event type Age, Sex Constituent Source (ID)	Product Dose* Duration Addiction Data**	Investigation for Etiology***	RAND Classification
Psychosis, Suicide attempt, Insomnia, Ventricular tachycardia / fibrillation, Dizzy 28 YO Female Ephedra FDA Case (14528)	Metab-O-Lite Not described 60 days to 1 year Addiction: No	Psychiatric History: No Other Substances/Meds: No	Possible Sentinel Event
Psychosis, Addiction/Substance Abuse, Paranoia 31 YO Male Ephedrine FDA Case (1661966)	Max Alert up to 1250 mg / day Over 1 year Addiction: Yes	Psychiatric History: No Other Substances/Meds: No	Possible Sentinel Event
Psychosis, Mania or severe agitation, Hallucinations, Paranoia 34 YO Male Ephedra Literature Case (79)	Unknown Not described 2-13 days Addiction: No	Psychiatric History: No Other Substances/Meds: No	Possible Sentinel Event
Psychosis, Sleep disturbance, Headache 40 YO Female Ephedra FDA Case (9060)	Do-Do Tablet or Herbal Balance 100 mg 14-60 days (acute) Addiction: No	Psychiatric History: Yes Other Substances/Meds: No	Inconclusive – Prior psychiatric history
Severe depression, Suicidal ideation 47 YO Male Ephedra FDA Case (9727)	Nature's Nutrition-Formula One Not described 14-60 days (acute) Addiction: No	Psychiatric History: Yes Other Substances/Meds: Yes	Inconclusive – Prior psychiatric history
Severe depression, Suicidal ideation 38 YO Female Ephedra FDA Case (9727)	Nature's Nutrition-Formula One Not described >60 days (chronic) Addiction: No	Psychiatric History: Yes Other Substances/Meds: Yes	Inconclusive – Prior psychiatric history
Severe depression, Suicidal ideation 30 YO Female Ephedra FDA Case (9727)	Nature's Nutrition-Formula One Not described >60 days (chronic) Addiction: No	Psychiatric History: Yes Other Substances/Meds: Yes	Inconclusive – Prior psychiatric history

* dose reported in total daily alkaloids yo = year old

** Addiction: Yes = diagnosis or self-reported addiction to the product

*** Psychiatric history: Yes = recorded psychiatric history

Other substances/meds: Yes = patient taking other substances or medications known to cause psychiatric symptoms

Table 22. Evidence table of case reports – Psychiatric (continued)

Event type Age, Sex Constituent Source (ID)	Product Dose* Duration Addiction Data**	Investigation for Etiology***	RAND Classification
Psychosis, Insomnia 43 YO Female Ephedra FDA Case (9403)	Therachrome Not described 60 days to 1 year Addiction: No	Psychiatric History: Yes Other Substances/Meds: No	Inconclusive – Prior psychiatric history
Psychosis, Violent 39 YO Male Ephedra FDA Case (10042)	Diet Gel Not described Not described Addiction: No	Psychiatric History: Yes Other Substances/Meds: Yes	Inconclusive – Prior psychiatric history
Psychosis, Mania or severe agitation, Sleep disturbance 17 YO Male Ephedra FDA Case (10078)	Ripped Force Not described 60 days to 1 year Addiction: No	Psychiatric History: Yes Other Substances/Meds: Yes	Inconclusive – Prior psychiatric history
Psychosis, Severe depression, Suicide attempt, Addiction/Substance Abuse 38 YO Female Ephedra/Ephedrine FDA Case (11052)	Mini Thin 285 mg 60 days to 1 year Addiction: Yes	Psychiatric History: Yes Other Substances/Meds: No	Inconclusive – Prior psychiatric history
Psychosis, Mania or severe agitation, Violent, Addiction/Substance Abuse 17 YO Male Ephedra FDA Case (11096)	Up Your Gas Not described Not described Addiction: Yes	Psychiatric History: Yes Other Substances/Meds: No	Inconclusive – Prior psychiatric history
Severe depression, Anxiety, Headache 31 YO Male Ephedra FDA Case (11145)	Nature's Nutrition-Formula One Not described >60 days (chronic) Addiction: No	Psychiatric History: Yes Other Substances/Meds: Yes	Inconclusive – Prior psychiatric history
Violent 35 YO Male Ephedra FDA Case (11289)	Up Your Gas Not described 14-60 days (acute) Addiction: No	Psychiatric History: Yes Other Substances/Meds: Yes	Inconclusive – Prior psychiatric history

* dose reported in total daily alkaloids yo = year old

** Addiction: Yes = diagnosis or self-reported addiction to the product

*** Psychiatric history: Yes = recorded psychiatric history

Other substances/meds: Yes = patient taking other substances or medications known to cause psychiatric symptoms

Table 22. Evidence table of case reports – Psychiatric (continued)

Event type Age, Sex Constituent Source (ID)	Product Dose* Duration Addiction Data**	Investigation for Etiology***	RAND Classification
Severe depression, Addiction/Substance Abuse, Sleep disturbance 38 YO Female Ephedra FDA Case (11651)	Nature's Nutrition-Formula One Not described 60 days to 1 year Addiction: Yes	Psychiatric History: Yes Other Substances/Meds: Yes	Inconclusive – Prior psychiatric history
Psychosis 34 YO Female Ephedra FDA Case (11717)	M-80 pills Not described 60 days to 1 year Addiction: No	Psychiatric History: Yes Other Substances/Meds: No	Inconclusive – Prior psychiatric history
Severe depression, Suicidal ideation 57 YO Female Ephedra FDA Case (11828)	Herbalife Original Green Not described 14-60 days (acute) Addiction: No	Psychiatric History: Yes Other Substances/Meds: No	Inconclusive – Prior psychiatric history
Mania or severe agitation, Suicidal ideation, Cyclothymia 15 YO Female Ephedra FDA Case (13072)	Caloslim Not described >60 days (chronic) Addiction: No	Psychiatric History: Yes Other Substances/Meds: No	Inconclusive – Prior psychiatric history
Psychosis, Mania or severe agitation, Hallucinations, Sleep disturbance, Migraine 20 YO Male Ephedra/Ephedrine FDA Case (13099)	Mini Thin 75 mg Not described Hydroxycut Not described 60 days to 1 year Addiction: No	Psychiatric History: Yes Other Substances/Meds: No	Inconclusive – Prior psychiatric history
Severe depression 28 YO Female Ephedra FDA Case (14089)	Xenadrine Not described 60 days to 1 year Addiction: No	Psychiatric History: Yes Other Substances/Meds: No	Inconclusive – Prior psychiatric history
Mania or severe agitation, Severe depression, Addiction/Substance Abuse 29 YO Female Ephedra FDA Case (14276)	Up Your Gas Not described Over 1 year Addiction: Yes	Psychiatric History: Yes Other Substances/Meds: No	Inconclusive – Prior psychiatric history

* dose reported in total daily alkaloids
yo = year old
** Addiction: Yes = diagnosis or self-reported addiction to the product
*** Psychiatric history: Yes = recorded psychiatric history
Other substances/meds: Yes = patient taking other substances or medications known to cause psychiatric symptoms

Table 22. Evidence table of case reports – Psychiatric (continued)

Event type Age, Sex Constituent Source (ID)	Product Dose* Duration Addiction Data**	Investigation for Etiology***	RAND Classification
Psychosis, Severe depression, Insomnia 17 YO Male Ephedra FDA Case (14294)	Hydroxycut Not described 2-13 days Addiction: No	Psychiatric History: Yes Other Substances/Meds: Yes	Inconclusive – Prior psychiatric history
Psychosis, Severe depression, Motor vehicle accident, Paranoia, Confusion/Delusional 42 YO Female Ephedra FDA Case (14394)	Fen-Chi Not described 14-60 days (acute) Addiction: No	Psychiatric History: Yes Other Substances/Meds: Yes	Inconclusive – Prior psychiatric history
Psychosis, Suicide/Suicide attempt, Hallucinations, Anxiety, Paranoia 36 YO Female Ephedra FDA Case (14493)	Herbalife Original Green Not described >60 days (chronic) Addiction: No	Psychiatric History: Yes Other Substances/Meds: Yes	Inconclusive – Prior psychiatric history
Mania or severe agitation, Hallucinations 32 YO, Sex Not described Ephedra FDA Case (14541)	Metabolife 356 Not described 60 days to 1 year Addiction: No	Psychiatric History: Yes Other Substances/Meds: Yes	Inconclusive – Prior psychiatric history
Psychosis, Severe depression, Suicidal ideation, Hallucinations, Insomnia 22 YO Female Ephedra FDA Case (14543)	Metabolift Not described 14-60 days (acute) Addiction: No	Psychiatric History: Yes Other Substances/Meds: Yes	Inconclusive – Prior psychiatric history
Psychosis, Mania or severe agitation 20 YO Male Ephedra Literature Case (136)	Metabolife 356 Not described >60 days (chronic) Addiction: No	Psychiatric History: Yes Other Substances/Meds: Yes	Inconclusive – Prior psychiatric history

* dose reported in total daily alkaloids yo = year old

** Addiction: Yes = diagnosis or self-reported addiction to the product

*** Psychiatric history: Yes = recorded psychiatric history

Other substances/meds: Yes = patient taking other substances or medications known to cause psychiatric symptoms

Table 22. Evidence table of case reports – Psychiatric (continued)

Event type Age, Sex Constituent Source (ID)	Product Dose* Duration Addiction Data**	Investigation for Etiology***	RAND Classification
Severe depression, Suicidal ideation, Violent 27 YO Male Ephedra Literature Case (136)	Metabolife 356 Not described Over 1 year Addiction: No	Psychiatric History: Yes Other Substances/Meds: No	Inconclusive – Prior psychiatric history
Mania or severe agitation, Severe depression 40 YO Female Ephedra Literature Case (519)	Product Not described Not described Over 1 year Addiction: No	Psychiatric History: Yes Other Substances/Meds: Yes	Inconclusive – Prior psychiatric history
Psychosis, Suicidal ideation, Anxiety, Dizzy, Increased hypertension 33 YO Female Ephedra FDA Case (9516)	Nature's Nutrition-Formula One Not described 60 days to 1 year Addiction: No	Psychiatric History: No Other Substances/Meds: Yes	Inconclusive – Other meds / substances
Mania or severe agitation, Suicidal ideation, Sleep disturbance 45 YO Male Ephedra FDA Case (10233)	Nature's Nutrition-Formula One Not described 14-60 days (acute) Addiction: No	Psychiatric History: No Other Substances/Meds: Yes	Inconclusive – Other meds / substances
Psychosis, Catatonia 36 YO Male Ephedra FDA Case (12488)	Nature's Super Cap 99mg Thermadrene Just Be Natural Gorilla Nitro Plus Mega Creatine Fuel Bolt Not described Over 1 year Addiction: No	Psychiatric History: No Other Substances/Meds: Yes	Inconclusive – Other meds / substances

* dose reported in total daily alkaloids
** Addiction: Yes = diagnosis or self-reported addiction to the product
*** Psychiatric history: Yes = recorded psychiatric history
Other substances/meds: Yes = patient taking other substances or medications known to cause psychiatric symptoms
yo = year old

Table 22. Evidence table of case reports – Psychiatric (continued)

Event type Age, Sex Constituent Source (ID)	Product Dose* Duration Addiction Data**	Investigation for Etiology***	RAND Classification
Mania or severe agitation, Hallucinations, Headache, Sleep disturbance, Irregular heart rate 19 YO Male Ephedra/Ephedrine FDA Case (13370)	Metacuts Not described >60 days (chronic) Addiction: No	Psychiatric History: No Other Substances/Meds: Yes	Inconclusive – Other meds / substances
Psychosis, Mania or severe agitation, Hallucinations, Motor vehicle accident, Sleep disturbance 27 YO Female Ephedra FDA Case (13526)	Xenadrine 40 mg 2-13 days Addiction: No	Psychiatric History: No Other Substances/Meds: Yes	Inconclusive – Other meds / substances
Severe depression, Suicidal ideation, Sleep disturbance 15 YO Male Ephedra FDA Case (14082)	Ripped Force Not described 60 days to 1 year Addiction: No	Psychiatric History: No Other Substances/Meds: Yes	Inconclusive – Other meds / substances
Psychosis, Suicide attempt Age Not described, Female Ephedra FDA Case (14213)	Thermogenics Plus Not described Over 1 year Addiction: No	Psychiatric History: No Other Substances/Meds: Yes	Inconclusive – Other meds / substances
Mania or severe agitation, Severe depression, Aneurysm, ruptured cerebra, Encephalopathy Age Not described, Male Ephedra FDA Case (14287)	Diet Fuel Not described 60 days to 1 year Addiction: No	Psychiatric History: No Other Substances/Meds: Yes	Inconclusive – Other meds / substances
Psychosis, Hyperkalemia 37 YO Female Ephedra FDA Case (14300)	Metabolife 356 Not described 14-60 days (acute) Addiction: No	Psychiatric History: No Other Substances/Meds: Yes	Inconclusive – Other meds / substances

* dose reported in total daily alkaloids yo = year old

** Addiction: Yes = diagnosis or self-reported addiction to the product

*** Psychiatric history: Yes = recorded psychiatric history

Other substances/meds: Yes = patient taking other substances or medications known to cause psychiatric symptoms

Table 22. Evidence table of case reports – Psychiatric (continued)

Event type Age, Sex Constituent Source (ID)	Product Dose* Duration Addiction Data**	Investigation for Etiology***	RAND Classification
Psychosis, Sleep disturbance, Confusion/Delusional 36 YO Female Ephedra FDA Case (14546)	Metabolife 356 Not described >60 days (chronic) Addiction: No	Psychiatric History: No Other Substances/Meds: Yes	Inconclusive – Other meds / substances
Psychosis 39 YO Female Ephedra FDA Case (14575)	Up Your Gas Not described Over 1 year Addiction: No	Psychiatric History: No Other Substances/Meds: Yes	Inconclusive – Other meds / substances
Psychosis, Mania or severe agitation, Confusion/Delusional, Headache 54 YO Female Ephedra FDA Case (14582)	Metabolife 356 Not described 14-60 days (acute) Addiction: No	Psychiatric History: No Other Substances/Meds: Yes	Inconclusive – Other meds / substances
Psychosis, Hallucinations Age Not described, Female Ephedra FDA Case (10019)	Ripped Fuel Not described 60 days to 1 year Addiction: No	Psychiatric History: No Other Substances/Meds: No	Insufficient Information
Psychosis, Irregular heart rate, Insomnia, Dizzy, Gastrointestinal problems 24 YO Female Ephedra FDA Case (10614)	Diet Max Not described 14-60 days (acute) Addiction: No	Psychiatric History: No Other Substances/Meds: No	Insufficient Information
Hallucinations, Nausea, Dizzy, Headache 20 YO Male Ephedra FDA Case (11131)	Herbal Ecstasy Not described <48 hours Addiction: No	Psychiatric History: No Other Substances/Meds: Yes	Insufficient Information
Anxiety, Palpitations 25 YO Male Ephedra FDA Case (11354)	Ripped Fuel Not described 14-60 days (acute) Addiction: No	Psychiatric History: No Other Substances/Meds: No	Insufficient Information

* dose reported in total daily alkaloids yo = year old
** Addiction: Yes = diagnosis or self-reported addiction to the product
*** Psychiatric history: Yes = recorded psychiatric history
Other substances/meds: Yes = patient taking other substances or medications known to cause psychiatric symptoms

Table 22. Evidence table of case reports – Psychiatric (continued)

Event type Age, Sex Constituent Source (ID)	Product Dose* Duration Addiction Data**	Investigation for Etiology***	RAND Classification
Hallucinations Age Not described, Sex Not described Ephedra FDA Case (12368)	Power Trim Not described Not described Addiction: No	Psychiatric History: No Other Substances/Meds: No	Insufficient Information
Psychosis, Severe depression, Seizure 32 YO Female Ephedra FDA Case (14105)	Metab-O-Lite Not described 60 days to 1 year Addiction: No	Psychiatric History: No Other Substances/Meds: No	Insufficient Information
Psychosis, Seizure, Transient ischemic attack 37 YO Female Ephedra FDA Case (14615)	Metab-O-Lite Not described 60 days to 1 year Addiction: No	Psychiatric History: No Other Substances/Meds: No	Insufficient Information
Suicide attempt 15 YO Female Ephedra FDA Case (10378)	Thermogenic Fat Burner Not described <48 hours Addiction: No	Psychiatric History: No Other Substances/Meds: No	Product taken solely as suicide attempt
Suicide attempt, Headache 16 YO Male Ephedra FDA Case (13331)	Metabolife 356 Not described <48 hours Addiction: No	Psychiatric History: No Other Substances/Meds: No	Product taken solely as suicide attempt
Severe depression, Suicide attempt, Addiction/Substance Abuse 25 YO Male Ephedrine FDA Case (11103)	Ephedrine 2500 mg Over 1 year Addiction: Yes	Psychiatric History: Yes Other Substances/Meds: Yes	Inconclusive – Prior psychiatric history
Mania or severe agitation 50 YO Female Ephedra FDA Case (11780)	Ma Huang/Ephedra + Caffeine 5.6 mg 14-60 days (acute) Addiction: No	Psychiatric History: Yes Other Substances/Meds: Yes	Inconclusive – Prior psychiatric history

* dose reported in total daily alkaloids yo = year old

** Addiction: Yes = diagnosis or self-reported addiction to the product

*** Psychiatric history: Yes = recorded psychiatric history

Other substances/meds: Yes = patient taking other substances or medications known to cause psychiatric symptoms

Table 22. Evidence table of case reports – Psychiatric (continued)

Event type Age, Sex Constituent Source (ID)	Product Dose* Duration Addiction Data**	Investigation for Etiology***	RAND Classification
Mania or severe agitation, Violent, Addiction/Substance Abuse 30 YO Male Ephedrine FDA Case (185564)	Mini Thin Not described Over 1 year Addiction: Yes	Psychiatric History: Yes Other Substances/Meds: Yes	Inconclusive – Prior psychiatric history
Mania or severe agitation, Encephalopathy, Rhabdomyolysis, Hyperthermia 28 YO Female Ephedrine Literature Case (69)	Do-Do Tablet or Herbal Balance 18.31 mg <48 hours Addiction: No	Psychiatric History: Yes Other Substances/Meds: Yes	Inconclusive – Prior psychiatric history
Psychosis, Severe depression, Hallucinations 54 YO Female Ephedrine Literature Case (120)	Ephedrine Not described Over 1 year Addiction: Yes	Psychiatric History: Yes Other Substances/Meds: Yes	Inconclusive – Prior psychiatric history
Mania or severe agitation, Confusion/Delusional, Insomnia, Palpitations 21 YO Male Ephedrine Literature Case (157)	Black Beauty Not described <48 hours Addiction: No	Psychiatric History: Yes Other Substances/Meds: Yes	Inconclusive – Prior psychiatric history
Psychosis, Hallucinations, Confusion/Delusional, Violent 26 YO Male Ephedrine Literature Case (238)	Ephedrine Not described 2-13 days Addiction: No	Psychiatric History: Yes Other Substances/Meds: No	Inconclusive – Prior psychiatric history
Psychosis, Mania or severe agitation, Hallucinations, Confusion/Delusional, Violent 26 YO Male Ephedrine Literature Case (238)	Ephedrine 300 mg 14-60 days (acute) Addiction: No	Psychiatric History: Yes Other Substances/Meds: No	Inconclusive – Prior psychiatric history

* dose reported in total daily alkaloids yo = year old

** Addiction: Yes = diagnosis or self-reported addiction to the product

*** Psychiatric history: Yes = recorded psychiatric history

Other substances/meds: Yes = patient taking other substances or medications known to cause psychiatric symptoms

Table 22. Evidence table of case reports – Psychiatric (continued)

Event type Age, Sex Constituent Source (ID)	Product Dose* Duration Addiction Data**	Investigation for Etiology***	RAND Classification
Suicide attempt, Ventricular tachycardia / fibrillation 20 YO Female Ephedrine Literature Case (250)	Product Not described 22500 gm <48 hours Addiction: No	Psychiatric History: Yes Other Substances/Meds: No	Inconclusive – Prior psychiatric history
Psychosis, Hallucinations, Sleep disturbance, Confusion/Delusional 61 YO Male Ephedrine Literature Case (488)	Vicks inhaler Not described Over 1 year Addiction: No	Psychiatric History: Yes Other Substances/Meds: No	Inconclusive – Prior psychiatric history
Psychosis, Addiction/Substance Abuse 35 YO Male Ephedrine FDA Case (130741)	Ephedrine Not described Not described Addiction: Yes	Psychiatric History: No Other Substances/Meds: Yes	Inconclusive – Other substances involved
Psychosis, Mania or severe agitation 19 YO Male Ephedrine Literature Case (490)	Marax 125 mg 14-60 days (acute) Addiction: No	Psychiatric History: No Other Substances/Meds: Yes	Inconclusive – Other meds / substances
Psychosis, Paranoia, Violent, Impotence 65 YO Male Ephedrine Literature Case (120)	Ephedrine Not described Over 1 year Addiction: Yes	Psychiatric History: No Other Substances/Meds: Yes	Inconclusive – Other substances involved
Psychosis, Mania or severe agitation, Severe depression, Hallucinations 27 YO Female Ephedrine FDA Case (14542)	Thermolift Not described 14-60 days (acute) Addiction: No	Psychiatric History: No Other Substances/Meds: No	Not related – exacerbation of previously undiagnosed bipolar disorder
Psychosis, Suicide attempt, Paranoia, Confusion/Delusional 46 YO Male Ephedrine FDA Case (94799)	Mini Thin Not described 14-60 days (acute) Addiction: Yes	Psychiatric History: No Other Substances/Meds: No	Product taken solely as suicide attempt

* dose reported in total daily alkaloids yo = year old

** Addiction: Yes = diagnosis or self-reported addiction to the product

*** Psychiatric history: Yes = recorded psychiatric history

Other substances/meds: Yes = patient taking other substances or medications known to cause psychiatric symptoms

Table 22. Evidence table of case reports – Psychiatric (continued)

Event type Age, Sex Constituent Source (ID)	Product Dose* Duration Addiction Data**	Investigation for Etiology***	RAND Classification
Suicide attempt 19 YO Male Ephedrine FDA Case (1454817)	Max Alert Not described Not described Addiction: No	Psychiatric History: No Other Substances/Meds: No	Product taken solely as suicide attempt
Suicide attempt, Arrhythmia (NOS) 14 YO Female Ephedrine Literature Case (281)	RJ8 Not described <48 hours Addiction: No	Psychiatric History: No Other Substances/Meds: No	Product taken solely as suicide attempt
Psychosis, Severe depression, Palpitations 40 YO Male Ephedrine FDA Case (1761109)	Max Alert Not described 60 days to 1 year Addiction: No	Psychiatric History: No Other Substances/Meds: No	Insufficient Information
Psychosis, Severe depression, Hallucinations, Addiction/Substance Abuse 38 YO Female Ephedrine FDA Case (1834206)	Mini Thin Not described Not described Excel Energy Not described Not described Addiction: Yes	Psychiatric History: No Other Substances/Meds: No	Insufficient Information
Severe depression, Suicide/Suicide attempt 43 YO Female Ephedra/Ephedrine FDA Case (9568)	E'ola Amp Pro Drops 38 mg 14-60 days (acute) Addiction: No	Psychiatric History: Yes Other Substances/Meds: Yes	Product removed from market- Contained illegal doses of ephedrine
Mania or severe agitation, Confusion/Delusional, Jumped out of car, Cardiac Enlargement 47 YO Female Ephedra FDA Case (12486)	LiquiThin Not described Not described E'ola Amp Pro Drops 97.2 mg 2-13 days Addiction: No	Psychiatric History: Yes Other Substances/Meds: Yes	Product removed from market- Contained illegal doses of ephedrine
Psychosis, Hallucinations, Rhabdomyolysis 54 YO Male Ephedra/Ephedrine FDA Case (10894)	E'ola Amp Pro Drops Not described 14-60 days (acute) Addiction: No	Psychiatric History: No Other Substances/Meds: Yes	Product removed from market- Contained illegal doses of ephedrine

* dose reported in total daily alkaloids yo = year old

** Addiction: Yes = diagnosis or self-reported addiction to the product

*** Psychiatric history: Yes = recorded psychiatric history

Other substances/meds: Yes = patient taking other substances or medications known to cause psychiatric symptoms

Table 22. Evidence table of case reports – Psychiatric (continued)

Event type **Age, Sex** **Constituent** **Source** **(ID)**	**Product** **Dose*** **Duration** **Addiction Data****	**Investigation for Etiology*****	**RAND Classification**
Psychosis, Hallucinations, Paranoia, Confusion/Delusional 54 YO Female Ephedra/Ephedrine Literature Case (275)	E'ola Amp Pro Drops 28000 mg Over 1 year Addiction: No	Psychiatric History: No Other Substances/Meds: Yes	Product removed from market- Contained illegal doses of ephedrine

* dose reported in total daily alkaloids yo = year old
** Addiction: Yes = diagnosis or self-reported addiction to the product
*** Psychiatric history: Yes = recorded psychiatric history
Other substances/meds: Yes = patient taking other substances or medications known to cause psychiatric symptoms

Table 23. Summary of adverse events with ephedra consumption*

Demographics / Type of Event	Death	MI	Other Cardiac	CVA / Stroke	Other Neurological	Seizure	Psychiatric Symptoms
Total Events							
Sentinel Events	2	3	0	9	0	3	5
Possible Sentinel Events	9	7	2	10	1	7	7
Events by Sex							
Female							
Sentinel Events	1	0	0	5	0	3	2
Possible Sentinel Events	3	4	0	7	1	5	4
Male							
Sentinel Events	1	3	0	4	0	0	3
Possible Sentinel Events	6	3	2	3	0	2	3
Events by Age							
13–30							
Sentinel Events	2	2	0	3	0	2	3
Possible Sentinel Events	5	0	1	2	0	3	5
31–50							
Sentinel Events	0	1	0	5	0	1	2
Possible Sentinel Events	4	6	1	5	0	3	1
51–70							
Sentinel Events	0	0	0	1	0	0	0
Possible Sentinel Events	0	1	0	3	1	1	1

* includes three events from Metabolife analysis.

Table 24. Summary of adverse events with ephedrine consumption

Demographics / Type of Event	Death	MI	Other Cardiac	CVA / Stroke	Other Neurological	Seizure	Psychiatric Symptoms
Total Events							
Sentinel Events	3	2	0	2	0	1	3
Possible Sentinel Events	3	0	1	2	0	0	1
Events by Sex							
Female							
Sentinel Events	1	2	0	2	0	1	1
Possible Sentinel Events	1	0	1	0	0	0	0
Male							
Sentinel Events	2	0	0	0	0	0	2
Possible Sentinel Events	1	0	1	2	0	0	1
Events by Age							
13–30							
Sentinel Events	2	1	0	2	0	0	2
Possible Sentinel Events	0	0	1	1	0	0	0
31–50							
Sentinel Events	1	1	0	0	0	1	0
Possible Sentinel Events	1	0	1	1	0	0	1
51–70							
Sentinel Events	0	0	0	0	0	0	1
Possible Sentinel Events	1	0	0	0	0	0	0

Table 25. Summary of adverse events not reviewed in detail

Adverse Event	Number of Events Reported
Fainting/ loss of consciousness	39
Heart rate >120 or <50	45
Hypertension, systolic >180 or diastolic >120	51
Paralysis	7
Liver failure,ALT/AST >200	7
Rhabdomyolysis, CPK >400	3
Coma	1
Miscarriage	1

Table 26. Summary data of key variables from Metabolife file analysis

Age	N	%
≤ 10	5	< 1
11–20	340	2
21–30	2163	12
31–40	2369	13
41–50	1598	9
51–60	912	5
>60	343	2
No Data	10627	57

Average Age	38

Gender	N	%
Male	707	4
Female	6792	36*
No Data	11032	30

*91 percent of files with reported gender are female.

Adverse Event	N	%
No adverse event reported	2019	11
Death	3	< 1
Cardiovascular: Heart rate, >120 or <50	23	< 1
Cardiovascular: Heart rate, 50-120, or not otherwise unspecified	584	3
Cardiovascular: Hypertension, Systolic>180 or Diastolic>105	45	< 1
Cardiovascular: Hypertension, Systolic<180 or Diastolic<105, not otherwise specified	405	2
Cardiovascular: Myocardial Infarction/ Heart Attack	22	< 1
Cardiovascular: Cardiac Dysrythmia, Other/ Palpitations	630	3
Cardiovascular: Cardiac arrest	3	< 1
Cardiovascular: Ventricular Tachycardia/ Fibrillation	0	0
Cardiovascular: Chest Pain, not specified as MI	582	3
Pulmonary: Respiratory arrest	2	< 1
Neurological: Transient Ischemic Attack	5	< 1
Neurological: CVA/ Stroke, not known to be hemorrhage	29	< 1
Neurological: Brain Hemorrhage	2	< 1
Neurological: Fainting / Loss of consciousness	41	< 1
Neurological: Coma	0	0
Neurological: Seizure	46	< 1
Psychiatric: Depression	57	< 1
Psychiatric: Hallucinations	2	< 1
Psychiatric: Mania or severe agitation	1	< 1
Psychiatric: Psychosis	3	< 1
Psychiatric: Suicide attempt	0	0
Autonomic Hyperactivity (Includes: Tremor, twitching, jitteriness, insomnia, increased sweating, agitation, nervousness, and irritability)	2536	14
Changes in glucose <40 *or* >400	56	< 1
Liver failure ALT/AST >200	5	< 1
Liver abnormality, not otherwise specified	46	< 1
Rhabdomyolysis CPK >400	1	< 1
Rhabdomyolysis, not otherwise specified	0	0
Miscarriage	6	< 1

Table 26. Summary data of key variables from Metabolife file analysis (continued)

Adverse Event	N	%
Allergic Reaction	614	3
Anesthesia complication	2	< 1
Fatigue/Fever/ Chills	724	4
Abnormal lab values, not otherwise specified	216	1
Ear, Eye, Nose, or Throat	795	4
Respiratory System	374	2
Cardiovascular System	255	1
Gastrointestinal System	4680	26
Hepatobiliary System	25	< 1
Musculoskeletal System	1136	6
Genitourinary System	395	2
Gynecologic (includes breast and menstrual symptoms)	1009	5
Sexual Dysfunction	115	1
Neurological System (includes headache)	2475	13
Mental Health	462	3
Skin (Includes Pruritis)	1385	7
Hematologic System	126	1
Oncologic System	4	< 1
Other symptoms not specified above	396	2

Table 27. Comparison of serious cases identified by RAND and by Metabolife

RAND #	Metabolife #	Explanation
DEATH		
	No #	Not on our MIPER CD-ROM
	No #	Not on our MIPER CD-ROM
23695		Only notation is "migraine HA, wanted refund (sister's husb died)". Unclear if this death is the consumer or a relative
35062	35062	
MYOCARDIAL INFARCTION/ HEART ATTACK		
16006	16006	
17002	17002	
20416	20416	
20918	20918	
21010		"the man who was taking them [Metabolife 356] has now suffered a heart attack"
22492		"28 yrs old had a heart attack"
22584		"customer had a heart attack thinks it was Met"
	22779	"heart attack, gall bladder surgery, cholecystectomy"
23877		"13 heart att, 3 strokes"
24166	24166	
24236	24236	
24383		"cold sweat ht attack"
24448	24448	
24859	24859	
27941	27941	
28168	28168	
28488	28488	
28835	28835	
	35532	Not on our MIPER CD-ROM
CARDIAC ARREST		
15409	15409	
27600	27600	
35063	35063	
STROKE		
16593	16593	
	17196	"vision disturbance"
18199	18199	
	19474	"short of breath, tachycardia"
20763	20763	
22308		"pain in chest, took NTG, stood up, ?stroke, ?side won't move, CAT scan negative"
22325		"had ministroke…$50 refund…will see neurologist"
22479		"'legal' customer that had 2 strokes – lawyer"
22496		"BP and Premarin 'caffeine' → stroke"
23002	23002	
23663		"stroke that cousin suffered"
23877		"13 heart att, 3 strokes"
24825	24825	
24945	24945	
25011		"stroke" written on note, but remainder of notes are about skin and gastrointestinal symptoms.

Table 27. Comparison of serious cases identified by RAND and by Metabolife (continued)

RAND #	Metabolife #	Explanation
25147		"client had a stroke"
25482	25482	
25495	25495	
25521	25521	
27791		"wife 1997 – had stroke"
	28156	"mild stroke symptoms"
	28157	"facial numbness"
	28201	"muscle weakness"
28281	28281	
28321	28321	
29424	29424	
29469	29469	
30391	30391	
30407	30407	
BRAIN HEMORRHAGE		
27754		"brain bleeding?"
35062		Recorded by Metabolife under death
SEIZURE		
15281	15281	
15345	15345	
16461	16461	
16653	16653	
16703	16703	
16897	16897	
16970	16970	
17369	17369	
17752		"[redacted] and her sister both take Met [redacted] reports [redacted] had a seizure recently"
18335	18335	
18962	18962	
19149	19149	
20812	20812	
20864	20864	
20979	20979	
	22150	Definitely a seizure, but contained in the section of the main file that has refund requests and we inferred these cases were also recorded elsewhere in the MIPER file
	22238	"black out while driving had hot flashes also had 2 screwdrivers"
22364		"seizures like activity"
22539		"friend of a friend had seizure"
22800	22800	
23029	23029	
	23440	"s/e's → dad"
23468		"sister – grand mal seizure"
24172		"seizure"
	24209	Same case as 16897
24344	24344	
24482	24482	
24711	24711	
24839	24839	

Table 27. Comparison of serious cases identified by RAND and by Metabolife (continued)

RAND #	Metabolife #	Explanation
24947		"seizures"
25371	25371	
27487	27487	
27523	27523	
28183	28183	
28329	28329	
28442	28442	
29882		"seizure" checked off on list of symptoms on standardized form
	35568	Not on our MIPER CD-ROM

Table 28. Summary of Metabolife medical records

RAND Case #	Index Case #	Complaint Case #	MIPER#(s)	Notes
1	1	1	20867 20868	This is a 42-year-old male who took two Metabolife pills for the first time and presented with chest pain, chest-tightness and shortness of breath. He ended up in the emergency department where he was found to have a blood pressure of 140/82 with a pulse of 111. The electrocardiogram showed him to be in atrial fibrillation. A discharge summary is not included among the records received. However, the patient's note to Metabolife said that he was discharged after one day and that his doctors were "convinced" that his heart was "back to normal." Of note is that his laboratory values established that he did not have thyroid disease and did not have any evidence of a myocardial infarction.
2	2	2	20871 20872	This is a 28-year-old female who had shortness of breath, dyspnea and wheezing. She was seen in the emergency department and was said to be having an "anaphylactoid reaction." She was treated with epinephrine, steroids and Benadryl with a complete response.
3	3	3	16287 20873-75 21033 24047 24051	This is a 38-year-old female who was admitted to the hospital with acute pancreatitis. The hospital record notes that she is "quite obese." The record also notes that she had a prior total abdominal hysterectomy with bilateral salpingo-oopherectomy and at that time was found to have ovarian cancer with involvement of the bowel. This resulted in partial colectomy with a diverting colostomy, and subsequently she had a renastomosis. She also had a prior cholycystectomy. It is noted that she did not drink alcohol. Her admission records note an elevated white blood cell count with a value of 14,000 but no elevation in amylase or lipase. A subsequent note states that these laboratory tests did become elevated and then returned to normal. She was discharged after recovery. Actual laboratory values are not included with the records. There is no mention of a measurement of serum triglycerides.
4	4	4	20876-78	This case consists of a handwritten note from the patient and a medical care bill for $34. The age and gender of the patient are unknown. The complaint is of headache, dizziness and tingling.

Index Case # taken from *Index of Redacted Consumer Medical Records with Corresponding MIPER Numbers.*
Complaint Case # taken from *Listing of Key Complaint for the Metabolife Medical Records Submitted* .
MIPER #(s) taken from *Index of Redacted Consumer Medical Records with Corresponding MIPER Numbers.*
No MIPER located: this is the text from the *Index of Redacted Consumer Medical Records…* as it pertains to the Index Case #.
n/a: not available, no match found.

Table 28. Summary of Metabolife medical records (continued)

RAND Case #	Index Case #	Complaint Case #	MIPER#(s)	Notes
5	5	5	17895 20879 23365	This file consists of a single physician note of a female of unstated age who came in with the complaints of "pain over the joints, gums would bleed, veins seemed to be thrombosing, some itching, easy bruisability and pain in the back over her kidneys." The physical examination was normal, clotting studies were normal, sedimentation rate was seven, chemistry panel was normal. The patient left in good condition.
6	6	6	20880 20883-85	This is a 28-year-old female who presented with 2 weeks of stomach pain, mostly after eating food, along with explosive diarrhea. Her laboratory work-up was essentially normal with a normal white blood cell count, liver enzymes and amylase. She was diagnosed as having "acute gastritis." She had both upper and lower endoscopy that did not reveal a clear diagnosis. Stool for ova and parasites was negative. Stool was positive for occult blood. Stool culture was negative, abdominal series was negative.
7	7	7	15998 20886	This is a 53-year-old female who presented with emesis and diarrhea after eating a hamburger at a fast food restaurant. Her examination was essentially unremarkable. The diagnostic impression was acute gastroenteritis. She was treated with antibiotics and Kaopectate.
8	8	8	16166 20887 24083-84	This is a 61-year-old female with a history of asthma who presented with headaches. She was found to have a potassium of 3.3 and a sodium of 118. It was noted that she drinks eight glasses of water a day. The diagnosis given was headache, possibly due to low sodium, and a viral upper respiratory tract infection.
9	9	9	20888-89	This is a 53-year-old female who was seen for increased intraoccular pressure. She was under the care of an ophthalmologist for what she called the "iridocorneoendothelial syndrome." It was treated by her ophthalmologist.
10	10	10	20890	This is a female of unstated age who presented with a headache. The records note that she had migraines eight years ago. She had photophobia and emesis. Her blood pressure was 153/73. She was treated with Imitrex with mild relief and she also received Demerol and Phenergan.

Index Case # taken from *Index of Redacted Consumer Medical Records with Corresponding MIPER Numbers.*
Complaint Case # taken from *Listing of Key Complaint for the Metabolife Medical Records Submitted* .
MIPER #(s) taken from *Index of Redacted Consumer Medical Records with Corresponding MIPER Numbers.*
No MIPER located: this is the text from the *Index of Redacted Consumer Medical Records…* as it pertains to the Index Case #.
n/a: not available, no match found.

Table 28. Summary of Metabolife medical records (continued)

RAND Case #	Index Case #	Complaint Case #	MIPER#(s)	Notes
11	11	11	No MIPER located	This is a male of unstated age who presented with abdominal indigestion without vomiting. The records note the patient had a prior vagotomy and pyloroplasty with gastroenterostomy. He received an ultrasound, CT scan and endoscopy. There was no indication of his treatment or response. In addition, there is no mention of taking Metabolife anywhere in the medical records.
12	12	13	16995 20892 25503	This is a 53-year-old female. The complaint that is listed is hyponatremia. However there is no medical record documentation of this. All that is included is a single copy of lab tests showing normal thyroid function and normal complete blood count. Whether these data apply to this patient is unclear, as the patient age on the lab slip is listed as 33. A doctor's note in the MIPER file states she required hospitalization.
13	13	14	15996 20893-95 23828 21035-37	This is a 61-year-old female who presented with supraventricular tachycardia which required cardioversion and subsequent treatment with atenolol. This is documented in a note, possibly from her doctor, however there are no medical records included with this case.
14	n/a	12	n/a	This is a 60-year-old female who presented with palpitations and was found to be in atrial flutter. According to the discharge summary, she was electrically cardioverted and then given Digoxin and Cardizem. Subsequent clinic notes showed her to continue to be in sinus rhythm. There is no indication or records that other diagnostic studies were done.
15	14	15	16642 20897-99 21034 23859	This is a 21-year-old female. The complaint is a rash. The only documentation provided is the bill of an emergency department visit. There are no medical records.
16	15	n/a	17569 20900-01	This is a 49-year-old female, noted to weigh 160 lbs., who presented with chest pain and had an overnight hospitalization to evaluate myocardial infarction. CPK was elevated but the MB fractions were negative. The patient was discharged with the diagnosis of chest wall pain.
n/a	16	n/a	15351 23010	No medical record received

Index Case # taken from *Index of Redacted Consumer Medical Records with Corresponding MIPER Numbers.*
Complaint Case # taken from *Listing of Key Complaint for the Metabolife Medical Records Submitted* .
MIPER #(s) taken from *Index of Redacted Consumer Medical Records with Corresponding MIPER Numbers.*
No MIPER located: this is the text from the *Index of Redacted Consumer Medical Records…* as it pertains to the Index Case #.
n/a: not available, no match found.

Table 28. Summary of Metabolife medical records (continued)

RAND Case #	Index Case #	Complaint Case #	MIPER#(s)	Notes
17	17	16	17605 20904	This is a 36-year-old female who claims to be "only 20 lbs. overweight" who stated that she had elevations in blood pressure, now requiring treatment with Maxzide. However there are no medical records accompanying this complaint, only a copy of bills.
n/a	n/a	17	n/a	(Listing of Key Complaints states chest pain, shortness of breath)
n/a	n/a	18	n/a	(Listing of Key Complaints states elevated blood pressure/ racing pulse)
18	18	19 (?) (Listing of Key Complaints states Fainting)	16199	This is a 73-year-old female who was evaluated for near syncope that occurred while eating in a restaurant. In the emergency department, blood pressure was noted to be 132/37 with a pulse of 64 and glucose was 90. The discharge diagnosis was "syncope related to hypoglycemia vs. Metabolife vs. vasovagal episode." Exercise treadmill test performed later was normal but there was a submaximal heart rate achieved. Carotid ultrasound was normal. Many additional notes cover healthcare judged to be irrelevant to the use of ephedra, including a podiatry consult, breast biopsies, pap smear and an endometrial biopsy.
19	19	20	No MIPER located	This is a 24-year-old female who presented with blood in the urine for one day. The records consist of a urine culture which was negative, a urinalysis which showed 2+ blood and a hemoglobin and hematocrit of 18 and 50, respectively.
20	20	21	20905-06 25529	This is a 47-year-old male who presented in atrial fibrillilation, was shown not to have had a myocardial infarction, and who had an echo and exercise treadmill test that were both normal. There was no evidence of thyroid disease. The patient converted to sinus rhythm with medication and was then treated with Digoxin. A followup doctor's note stated that the patient was in sinus rhythm and implied that he was off Digoxin.
21	21	22	17028 20907-08 24154	This is a 31-year-old female who is noted to weigh 261 lbs. She presented with heart palpitations, shortness of breath and heart "flutter." She had a history of hypertension with pregnancy. A consultant's note reported T-wave inversions in V1 and V3 with an elevated CPK but the MB fraction was normal and the Troponin test was negative. It is unclear exactly what happened, but this apparently resolved.

Index Case # taken from *Index of Redacted Consumer Medical Records with Corresponding MIPER Numbers.*
Complaint Case # taken from *Listing of Key Complaint for the Metabolife Medical Records Submitted* .
MIPER #(s) taken from *Index of Redacted Consumer Medical Records with Corresponding MIPER Numbers.*
No MIPER located: this is the text from the *Index of Redacted Consumer Medical Records…* as it pertains to the Index Case #.
n/a: not available, no match found.

Table 28. Summary of Metabolife medical records (continued)

RAND Case #	Index Case #	Complaint Case #	MIPER#(s)	Notes
22	22	23	17277 20914-15	This is a 36-year-old female who presented with nausea, dizziness and vomiting, headache and abdominal pain. Blood pressure was noted to be 134/87 and the pulse was 85. Abdominal ultrasound was normal, pregnancy test was normal. Urinalysis showed moderate ketones. The discharge diagnosis was "abdominal pain of uncertain etiology."
n/a	23	n/a	22408 20916-17	No medical record received
n/a	n/a	24	n/a	(Listing of Key Complaints states difficulty breathing/ anxiety)
23	24	25	20918-21 21032	This is a 38-year-old female who made three visits to the emergency room over four days for epigastric and chest pain, initially being diagnosed as having esophageal reflux, then gastritis and then finally being recognized as having coronary artery disease with an 80% left anterior descending stenosis. This was treated with a coronary stent. Her cardiologist notes that she had a "very positive family history" of coronary artery disease and that her mother had an "early heart attack." There was no indication in the record that a cholesterol test was done.
24	25	26	20950 20953-54 20958-59 20961	This file contains no medical records, only medical bills documenting prescriptions for hydrochlorothiazide and phenazopyridine, along with a urinalysis. The MIPER file indicates the patient said she was diagnosed with hemorrhagic cystitis, and later hypertension.
25	26	27	20962-66 21006-07	There are no medical records in this file, only bills. On one of the bills is written "drug reaction."
26	27	28	18445	This is a 39-year-old female. The complaint is an allergic reaction. There are no medical records in this file, only bills.
n/a	28	n/a	16521 17536	No medical record received
27	29	29	20967-68	This is a 40-year-old female who developed transient elevations of liver enzymes with an ALT of 125. Albumin and bilirubin were normal. Multiple tests for possible etiologies of this were performed, all of which were negative. Metabolife was discontinued and the liver function abnormalities drifted down to normal over time; the last note said that she had recovered totally.

Index Case # taken from *Index of Redacted Consumer Medical Records with Corresponding MIPER Numbers.*
Complaint Case # taken from *Listing of Key Complaint for the Metabolife Medical Records Submitted* .
MIPER #(s) taken from *Index of Redacted Consumer Medical Records with Corresponding MIPER Numbers.*
No MIPER located: this is the text from the *Index of Redacted Consumer Medical Records…* as it pertains to the Index Case #.
n/a: not available, no match found.

Table 28. Summary of Metabolife medical records (continued)

RAND Case #	Index Case #	Complaint Case #	MIPER#(s)	Notes
28	30	30	20969 20971-75 20977-78	There are no medical records in this file. The only thing that is listed is a complaint from the patient about a heart rate being 188 and the blood pressure being high, that the patient was treated in the emergency room and that there were "blood tests to assess heart damage." The MIPER includes a long letter from the patient that relates much the same thing.
n/a	32	n/a	No MIPER located	No medical record received
n/a	33	n/a	No MIPER located	No medical record received
n/a	n/a	32	n/a	Listing of Key Complaints states nothing identified- just a bill
n/a	n/a	33	n/a	Listing of Key Complaints states nothing identified- list of medications
29	35	35	16376 21030	This is a 54-year-old male with chest pain and a headache who also complained of high blood pressure and lightheadedness. There are minimal records associated with this report of August 11, 1999, other than that the patient was diagnosed with accelerated hypertension. Of note, however, is that there are numerous clinic visit notes dating back to 1997, documenting that the patient had a history of hypertension, diabetes and hyperlipidemia, with a blood pressure on one occasion 154/92. It is noted that this was taken with a large cuff. In addition, there are clinic visits with chest pain as far back as 1997.
30	34	34	21027 21029	This is a male of unstated age, possibly 40 years old, who wrote a note saying that he had stomach problems, kidney stones, colon problems and anxiety problems. There are no medical records associated with this file, only bills.
31	31	31	21000-01	There are no medical records with this file, only some discharge instructions that say that the diagnosis was "acute nausea." The MIPER file states the patient is a 37-year-old female and that "hypoglycemia was likely."

Index Case # taken from *Index of Redacted Consumer Medical Records with Corresponding MIPER Numbers.*
Complaint Case # taken from *Listing of Key Complaint for the Metabolife Medical Records Submitted .*
MIPER #(s) taken from *Index of Redacted Consumer Medical Records with Corresponding MIPER Numbers.*
No MIPER located: this is the text from the *Index of Redacted Consumer Medical Records…* as it pertains to the Index Case #.
n/a: not available, no match found.

Table 28. Summary of Metabolife medical records (continued)

RAND Case #	Index Case #	Complaint Case #	MIPER#(s)	Notes
32	36	36	20979 24840 25498 25501	This is a 50-year-old female who had a witnessed grand mal seizure while driving. Later that day, after undergoing a CT scan in the emergency room, she had a 2nd witnessed seizure and, according to an attorney's letter, she then had a 3rd seizure at some point. An evaluation included a CT of the brain, which was normal, and an electroencephalogram, which was also normal. She had no history of alcoholism. Serum sodium was normal and glucose was normal. Pulse oximetry was 99%. Toxicology screen was positive for amphetamines. There was no prior history of seizure disorder or neurologic disease.
33	37	37	19473 23970	This is a 21-year-old female who is noted to weigh 200 pounds and on whom the MIPER file will say shortness of breath and tachycardia. There are minimal records associated with this, only a discharge diagnosis of hyperventilation, with a notation saying that a friend died two days ago. There is a listing of medications and, by implication, these are being taken by the patient. These are Darvocet (which may have been discontinued), Flexeril, Reglan, Cytotec, Dicyclomine, Viokase, Sudafed, Lopid, Citracel, Pariodel, Benadryl, DDVAP, Zantac, Trilisat, Carafate. Of note, the MIPER may also say the complaint includes aphasia, paralysis, and shortness of breath.
34	n/a	39	n/a	There are no medical records in this file, only a bill.
35	40	n/a	19350	This is a 39-year-old female who had the complaint of abdominal pain. The medical records submitted with this consist of a clinic note which says that the patient has "classic gastrointestinal illness" with mild nausea and no diarrhea, progressing to diarrhea with no vomiting.
36	38	38	20864-66	This is a 29-year-old female who had a witnessed tonic clonic seizure. There is no history of alcoholism. The grandmother had a history of seizures but was also noted to be an alcoholic. Blood pressure was normal at 120/80. Brain MRI was normal. EEG was normal. Toxicology screen by report had "large amount ephedrine and pseudoephedrines."
n/a	39	n/a	24495	No medical record received
n/a	n/a	40	n/a	(Listing of Key Complaints states lower back pain/GI)
37	n/a	41	n/a	This is a patient of unknown age and unknown gender who presented for an allergic reaction. There are no medical records and only bills and medications in this file.

Index Case # taken from *Index of Redacted Consumer Medical Records with Corresponding MIPER Numbers.*
Complaint Case # taken from *Listing of Key Complaint for the Metabolife Medical Records Submitted .*
MIPER #(s) taken from *Index of Redacted Consumer Medical Records with Corresponding MIPER Numbers.*
No MIPER located: this is the text from the *Index of Redacted Consumer Medical Records…* as it pertains to the Index Case #.
n/a: not available, no match found.

Table 28. Summary of Metabolife medical records (continued)

RAND Case #	Index Case #	Complaint Case #	MIPER#(s)	Notes
n/a	41	n/a	No MIPER located	No medical record received
38	n/a	42	n/a	There are only bills which have a diagnostic code 780.2 which is "syncope and collapse," along with indications that an echocardiogram and duplex sonography were done. There are no other medical records.
39	42	43	19604	This is a 29-year-old female, who is noted to weigh 230 lbs., who presented for menstrual irregularity, numbness and tingling. Evaluation was unremarkable and no diagnosis was given.
40	n/a	44 (?) (Listing of Key Complaints states intracranial hemo-rrhage, which is mentioned in patient history)	n/a	This is a 36-year-old female who complained of menstrual irregularity. The records document that she recently had a right posterior parietal intracranial hemorrhage with extension into the ventricular system requiring neurosurgery with a drain. This was subsequently shown by angiography to be due to an arteriovenous malformation, which was then subsequently resected. After this neurosurgery she had not had resumption of her menstrual period. In the notes available there was no work up of this symptom.
41	n/a	45	n/a	This is a 26-year-old female, who is noted to weigh 155 lbs., who had chest pains after using Metabolife for two months. She also had asthma and a brother who died of myocardial infarction at age 33. Her discharge diagnoses were asthma and chest pain.
42	n/a	46	n/a	This is a 27-year-old female who presented with sudden abdominal pain which was found to be due to a rupture of a splenic artery aneurysm which required emergency laporatomy and resection. The records note she had a history of congenital multiple ureters which had been surgically repaired at age 7 and she was left with some renal insufficiency as a result. There is no mention of the use of Metabolife in the medical records that are provided.
43	n/a	n/a	n/a	This is a 49-year-old male who had symptoms of chest pressure and pain along with shortness of breath. He had been a cigarette smoker but the record notes he quit. He had an exercise treadmill test that showed a normal electrocardiogram response but he had scintigraphic evidence of ischemia. He underwent coronary angiography that revealed normal coronary arteries. Three months later he was continuing to have unexplained chest pressure and pain.

Index Case # taken from *Index of Redacted Consumer Medical Records with Corresponding MIPER Numbers.*
Complaint Case # taken from *Listing of Key Complaint for the Metabolife Medical Records Submitted .*
MIPER #(s) taken from *Index of Redacted Consumer Medical Records with Corresponding MIPER Numbers.*
No MIPER located: this is the text from the *Index of Redacted Consumer Medical Records…* as it pertains to the Index Case #.
n/a: not available, no match found.

Table 28. Summary of Metabolife medical records (continued)

RAND Case #	Index Case #	Complaint Case #	MIPER#(s)	Notes
n/a	43	n/a	No MIPER located	No medical record received
n/a	44	n/a	No MIPER located	No medical record received
n/a	45	n/a	No MIPER located	No medical record received
n/a	46	n/a	No MIPER located	No medical record received.

Index Case # taken from *Index of Redacted Consumer Medical Records with Corresponding MIPER Numbers.*
Complaint Case # taken from *Listing of Key Complaint for the Metabolife Medical Records Submitted* .
MIPER #(s) taken from *Index of Redacted Consumer Medical Records with Corresponding MIPER Numbers.*
No MIPER located: this is the text from the *Index of Redacted Consumer Medical Records…* as it pertains to the Index Case #.
n/a: not available, no match found.

Figure 1. Screening form for literature

RAND EPC EPHEDRA PROJECT **SCREENER FORM**

1. Article ID: _____

2. First Author: _____
   (LAST NAME OF FIRST AUTHOR)

3. Reviewer: _____

4. Research topic: **CHECK ALL THAT APPLY**
   - Ephedra ..... ☐
   - Ephedrine ..... ☐
   - Pseudoephedrine ..... ☐ **(STOP)**
   - Unclear ..... ☐
   - Other (_____) .. ☐ **(STOP)**

5. Subject of article: **CHECK ALL THAT APPLY**
   - Weight Loss ..... ☐
   - Athletic Performance ..... ☐
   - Adverse Events ..... ☐
   - Other (_____) .. ☐ **(STOP)**

6. Study population: **CHECK ALL THAT APPLY**
   - Human ..... ☐
   - Animal ..... ☐ **(STOP)**
   - Unclear ..... ☐
   - Other (specify: _____) .. ☐ **(STOP)**

7. Study design: **CHECK ALL THAT APPLY**
   - Descriptive (historical, editorial etc.) ☐
   - Review/meta-analysis..... ☐
   - Randomized Clinical Trial..... ☐
   - Controlled Clinical Trial..... ☐
   - Case Series ..... ☐
   - Case Report: medical literature... ☐
   - Case Report: popular literature ... ☐
   - Other (specify: _____) .. ☐

8. Does the intervention contain caffeine or caffeine-containing herbs? **CIRCLE ONE**
   - Yes..... 1
   - No 2
   - Unclear 7
   - Not applicable..... 8

9. Language of article: **CIRCLE ONE**
   - English..... 1
   - Chinese..... 2
   - Japanese 3
   - Other (specify: _____) ... 4

Notes:

Figure 2. Quality review form for literature

RAND EPC EPHEDRA PROJECT **QUALITY REVIEW FORM**

Article ID:_____ Reviewer:_____

First Author: _____
(Last Name Only)

Study Number: ___of____Description:_____
(Enter '1 of 1' if only one) (If more than one study)

1. Design: **CIRCLE ONE**
   - RCT 1
   - CCT 2
   - Other ..... 3 **(STOP)**

(IF NOT RCT OR CCT, CHANGE STUDY DESIGN ON COVER SHEET AND STOP)

2. Were any adverse events mentioned?

	CHECK ALL THAT APPLY	
	CHECK OR CODE	**CHECK IF SERIOUS**
Cardiovascular	☐ (01)	☐
Death	☐ (02)	☐
Endocrine	☐ (03)	☐
Neurologic	☐ (04)	☐
Psychiatric	☐ (05)	☐
Pulmonary	☐ (06)	☐
Renal	☐ (07)	☐
Other:	(___ ___, ____ ___, ____ ____)	
No adverse events	☐ (96)	
None mentioned	☐ (97)	
Mentioned but not described	☐ (98)	

3. For articles on weight loss, is there a follow up of at least 8 weeks?
   CIRCLE ONE
   - Yes 1
   - No ..... 2 **(STOP)**
   - Not applicable 9

4. Is the study described as randomized? **CIRCLE ONE**
   - Yes 1
   - No 2

5. If the study was randomized, was method of randomization appropriate?
   CIRCLE ONE
   - Yes 1
   - No 2
   - Method not described 8
   - Not applicable 9

Figure 2. Quality review form for literature (continued)
RAND EPC EPHEDRA PROJECT **QUALITY REVIEW FORM**

6. Is the study described as: **CIRCLE ONE**
   Double blind 1
   Single blind, patient 2
   Single blind, outcome assessment 3
   Open 4
   Blinding not described 8
   Not applicable 9

7. If reported, was the method of double blinding appropriate?
   CIRCLE ONE
   Yes 1
   No 2
   Double blinding method not described 8
   Not applicable 9

8. If study was randomized, did the method of randomization provide for concealment of allocation? **CIRCLE ONE**
   Yes 1
   No 2
   Concealment not described 8
   Not applicable 9

9. Are withdrawals (W) and dropouts (D) described?
   CIRCLE ONE
   Yes, reason described for **all** W and D 1
   Yes, reason described for **some** W and D 2
   Not described 8
   Not applicable 9

10. Is this a cross-over study design? **CIRCLE ONE**
    Yes 1
    No 2
    Not described 8

11. Are outcome data reported separately for or primarily on over 75% of any of the following populations? **CHECK ALL THAT APPLY**
    Race:
    - African-Americans ..... ☐ (01)
    - Hispanic ..... ☐ (02)
    - Asian ..... ☐ (03)

    Gender:
    - Male ..... ☐ (04)
    - Female ..... ☐ (05)

    Age:
    - Adolescents (12-17) ..... ☐ (06)
    - Children (0-11) ..... ☐ (07)

    Misc.:
    - Athletes ..... ☐ (08)
    - Military ..... ☐ (09)

    Other:
    (Enter code: ____ ____, ____ ____, ____ ___, ____ ____)

Figure 2. Quality review form for literature (continued)
RAND EPC EPHEDRA PROJECT **QUALITY REVIEW FORM**

12. What types of comorbidities are described in the groups?

CHECK ALL THAT APPLY

Overweight/ Obesity (BMI > 27) ..... ☐ (01)
Coronary Artery Disease ..... ☐ (02)
Hypertension..... ☐ (03)
Neurological..... ☐ (04)
Psychiatric ..... ☐ (05)
Asthma..... ☐ (06)
Gastrointestinal..... ☐ (07)
Diabetes..... ☐ (08)
Renal ..... ☐ (09)
Other:
(Enter code: ____ ____, ____ ____, ____ ____, ____ ____)

Not described ..... ☐ (98)

Figure 2. Quality review form for literature (continued)
RAND EPC EPHEDRA PROJECT **QUALITY REVIEW FORM**

Arm ___ of ___ Description _____

If the study has a control/usual care arm, enter that data in arm 1.
Otherwise, enter data for the groups in order of first mention.

13. What type of arm is this? **CIRCLE ONE**
    Placebo.....1
    Usual care.....2
    Primary intervention.....3
    Other active treatment.....4

14. Is there a significant co-intervention?
    CHECK ALL THAT APPLY OR ENTER CODE
    Diet ..... ☐ (01)
    Exercise ..... ☐ (02)
    Education ..... ☐ (03)
    Other: (enter code ___ ___, ___ ___, ___ ___)
    No co-interventions..... ☐ (97)

15. What was the sample size in this arm?

    ___ ___ ___ , ___ ___ ___ Entering ___ ___ ___ , ___ ___ ___ Completing

    (ENTER 999,999 IF NOT REPORTED.)

16. What is the common, proprietary, and/or scientific (genus, genus/species) name of the product?
    ENTER CODE OR CIRCLE ONE OF THE BELOW
    Code: ____ ____
    None 97
    Not described 98
    Not applicable..... 99

17. Of which main constituents is the product made?
    ENTER CODE OR CIRCLE ONE OF THE BELOW
    Code: ____ ____, ____ ____, ____ ____
    None 97
    Not described 98
    Not applicable..... 99

18. Was chemical analysis performed on ephedrine alkaloids?
    CIRCLE ONE
    Yes..... 1
    No 2
    Not described 8
    Not applicable..... 9

Figure 2. Quality review form for literature (continued)
RAND EPC EPHEDRA PROJECT **QUALITY REVIEW FORM**

19. Intervention:

INTERVENTION	TOTAL DAILY DOSE	AMOUNT PER DOSE	UNITS	ROUTE OF ADMINISTRATION	DURATION	UNITS	EPHEDRINE ALKALOIDS
1 ____	_____	_____	_____	_____	_____	____	_____
2 ____	_____	_____	_____	_____	_____	____	_____
3 ____	_____	_____	_____	_____	_____	____	_____
4 ____	_____	_____	_____	_____	_____	____	_____
Enter code	Enter a number 998. ND 999. NA	Enter a number 998. ND 999. NA	1. μg 2. mg 3. gm 4. mg kg^{-1} 8. ND 9. NA	1. PO 2. IV 8. ND 9. NA	Enter a number 998. ND 999. NA	1. Hour 2. Day 3. Week 8. ND 9. NA	1. Included in total ephedrine alkaloids 2. In addition to ephedrine alkaloids 3. Unclear 8. ND 9. NA

20. Type of outcomes measured:

ENTER THE CODE FOR EACH OUTCOME MEASURED

____ ____
____ ____
____ ____

21. When, relative to the start of the intervention, were outcomes reported?

ENTER THE NUMBER AND LETTERS IN THE APPROPRIATE BOX

	NUMBER	UNIT
1st follow-up		
2nd follow-up		
3rd follow-up		
4th follow-up		
5th follow-up		
6th follow-up		
Additional follow-ups:		

Use the following abbreviations for units:

MI	minute
HR	hour
DY	day
WK	week
MO	month
YR	year
ND	not described
NA	not applicable

END

Figure 3a. Adverse events analysis form for death, MI, stroke cases

RAND EPC EPHEDRA PROJECT **ADVERSE EVENTS ANALYSIS FORM**

Article ID:_____ Reviewer:_____

FDA Case Number: _____

Form Number: _____of_____(Fill out one form for each subject)

1. Does adverse event form report on ephedra or ephedrine?

CIRCLE ONE

Yes..... 1
No/ Unsure.....2 **(STOP)**

(IF NOT EPHEDRA/EPHEDRINE THEN STOP)

2. Are there adequate data available to analyze this report?

CIRCLE ONE

Yes..... 1
No .....2 **(STOP)**

(IF NOT ADEQUATE DATA THEN STOP-
MUST BE A SERIOUS ADVERSE EVENT AND PRODUCT SPECIFICALLY IDENTIFIED)

3. What additional sources of data are available?

CHECK ALL THAT APPLY AND/OR ENTER CODE

FDA affidavit ..... ☐ (01)
Medical records ..... ☐ (02)
Legal documents ..... ☐ (03)
Labels ..... ☐ (04)
Other (_____)☐ (96)
None of the above ..... ☐ (97)

4. What was the adverse event? **CHECK ALL THAT APPLY AND/OR ENTER CODE**

(Start codes at 40)

Death ..... ☐ (01)
MI..... ☐ (02)
CVA ..... ☐ (03)
Other serious adverse event (enter code: _____)
Other (_____)☐ (96)
None of the above ..... ☐ (97) **(STOP)**

5. IF MI, what procedures were done? **CHECK ALL THAT APPLY**

Coronary angiography..... ☐ (01)
Revascularization ..... ☐ (02)

6. IF MI, what was(were) the outcome of the procedure(s)?

No significant CAD ..... ☐ (01)
< 3V CAD..... ☐ (02)
3V or LMD..... ☐ (03)
Low LVEF (≤ 40%) ..... ☐ (04)

Figure 3a. Adverse events analysis form for death, MI, stroke cases (continued)
RAND EPC EPHEDRA PROJECT ADVERSE EVENTS ANALYSIS FORM

7. IF STROKE, what is the outcome? **CIRCLE ONE**
   - Complete resolution 1
   - Minimally affected (still able to work) 2
   - Moderately affected (more than one limb) 3
   - Severely affected 4
   - Not described 8

8. Who completed the adverse events form? **CIRCLE ONE**
   - Physician / Health care provider 1
   - Subject 2
   - Subject surrogate 3
   - Government agency 4

9. What was the age of the subject on the date report was made?

   Enter number: _____ _____

10. What is the gender of the subject? **CIRCLE ONE**
    - Male 1
    - Female 2
    - Not described 8

11. Why was the subject taking the product?
    CHECK ALL THAT APPLY AND/OR ENTER CODE
    (Start codes at 4)
    - Weight loss ..... ☐ (01)
    - Improved athletic performance ..... ☐ (02)
    - Psychological effect ..... ☐ (03)
    - Other: … (enter code _____ , _____ , _____)
    - Not described ..... ☐ (98)

12. What was the source of the product? **CIRCLE ONE**
    - Retail market 1
    - Multi-level marketing/ out of home 2
    - Direct from manufacturer 3
    - Health care provider 4
    - Other (_____) 6
    - Not described 8

13. Was the product specifically identified? **CIRCLE ONE**
    - Yes 1
    - No 2

    (IF NO THEN SKIP TO QUESTION 18)

14. What is the common, proprietary, and/or scientific (genus, genus/species) name of the product? **ENTER CODE OR CIRCLE ONE OF THE BELOW**
    Code:_____
    - None 97
    - Not described 98
    - Not applicable 99

Figure 3a. Adverse events analysis form for death, MI, stroke cases (continued)
RAND EPC EPHEDRA PROJECT ADVERSE EVENTS ANALYSIS FORM

15. Of which main constituents is the product made?

ENTER CODE FOR EACH OR CIRCLE ONE OF THE BELOW

Code: _____ _____, _____ _____ , _____ , _____

None 97
Not described 98
Not applicable 99

16. Was chemical analysis on ephedra alkaloids data presented?

CIRCLE ONE

Yes 1
No 2
Not described 8
Not applicable 9

17. Please fill in the following information on dosage data.
This information is from **analysis: (ENTER THE NUMBER AND CODES IN THE APPROPRIATE BOXES.)**

Dosage data	Number	Unit (code)
Total daily dose of ephedrine alkaloids		
Single dose of ephedrine alkaloids		
Total daily dose of caffeine		
Ratio caffeine/ephedrine alkaloids	:	

Codes for units:

µg	1
mg	2
gm	3
$mgkg^{-1}$	4
ND	8
NA	9

18. Please fill in the following information on dosage data.
This information is from **label: (ENTER THE NUMBER AND CODES IN THE APPROPRIATE BOXES.)**

Dosage data	Number	Unit (code)
Total daily dose of ephedrine alkaloids		
Single dose of ephedrine alkaloids		
Total daily dose of caffeine		
Ratio caffeine/ephedrine alkaloids	:	

Codes for units:

µg	1
mg	2
gm	3
$mgkg^{-1}$	4
ND	8
NA	9

19. What was the duration of ephedrine use? **CIRCLE ONE**

<48 hours 1
2-13 days 2
14-60 days (acute) 3
>60 days (chronic) 4
Not described 8

Figure 3a. Adverse events analysis form for death, MI, stroke cases (continued)
RAND EPC EPHEDRA PROJECT ADVERSE EVENTS ANALYSIS FORM

20. What was the timing of the last ephedrine dose? **CIRCLE ONE**
    <6 hours 1
    6-24 hours 2
    >24 hours 3
    Not described 8

21. Was the product used again after first adverse event? **CIRCLE ONE**
    Yes 1
    No 2
    Not described 8
    Not applicable 9

22. If product was used again after first adverse event, did the adverse event reoccur? **CIRCLE ONE**
    Yes 1
    No 2
    Not described 8
    Not applicable 9

23. Was the subject actively involved in exercise at or immediately before the occurrence of the adverse event? **CIRCLE ONE**
    Yes 1
    No 2
    Not described 8
    Not applicable 9

24. Did form report on use of any other substances? **(CHECK ALL THAT APPLY AND ENTER CODE)**
    Caffeine (in addition to product) ..... ☐
    Illicit drugs: ..... ☐
    Code: _____ , _____ , _____ , _____ ,
    _____ , _____ , _____ , _____
    Other Herbs: ..... ☐
    Code: _____ , _____ , _____ , _____ ,
    _____ , _____ , _____ , _____
    Prescribed or OTC medication: ..... ☐
    Code: _____ , _____ , _____ , _____ ,
    _____ , _____ , _____ , _____
    Other substance: ..... ☐
    Code: _____ , _____ , _____ , _____ ,
    _____ , _____ , _____ , _____
    Not described ..... ☐
    None ..... ☐

Figure 3a. Adverse events analysis form for death, MI, stroke cases (continued)
RAND EPC EPHEDRA PROJECT ADVERSE EVENTS ANALYSIS FORM

25. Which of the following conditions were evaluated?

CHECK ALL THAT APPLY AND/OR ENTER CODE
(Start codes at 15)

Pre-existing condition:	PRESENT	EXCLUDED
Asthma	☐	☐
CAD	☐	☐
DM	☐	☐
HTN	☐	☐
Obesity	☐	☐
Renal disease	☐	☐
Substance abuse	☐	☐
Syncope	☐	☐
Thyroid condition	☐	☐
TIA History	☐	☐
Other vascular disease (_____)	☐	☐
Rheumatological diseases	☐	☐
Other (Enter code: _____)	☐	☐
Other (Enter code: _____)	☐	☐
Other (Enter code: _____)	☐	☐
Other (Enter code: _____)	☐	☐
Other (Enter code: _____)	☐	☐
Other (Enter code: _____)	☐	☐

26. Was a drug screen performed? **(CIRCLE ONE)**
Yes.....1
No .....2 **(STOP)**

27. Results of **URINE** screen:
(start codes at 03) **(CHECK ALL THAT APPLY)**
No substance found..... ☐ (01)
Substance(s) found and identified: (Enter code(s)):

(_____ , _____ , _____ , _____ , _____ , _____)

Not described ..... ☐ (98)

28. Results of **BLOOD** screen:
(start codes at 03) **(CHECK ALL THAT APPLY)**
No substance found..... ☐ (01)
Substance(s) found and identified: (Enter code(s) below)
(_____ , _____ , _____ , _____ , _____ , _____)

Not described ..... ☐ (98)

END

Figure 3b. Adverse events analysis form for seizure cases

RAND EPC EPHEDRA PROJECT **ADVERSE EVENTS ANALYSIS FORM**

ID/ FDA Case Number:_____ Reviewer:_____

First Author: _____
(Last Name Only)

Form Number: _____of_____(Fill out one form for each subject)

1. Does this adverse event report use of ephedra or ephedrine?

CIRCLE ONE

Ephedra only 1
No/ Unsure ..... 2 **(STOP)**
Ephedrine only 3
Ephedra and Ephedrine 4

(IF NOT EPHEDRA/ OR EPHEDRINE THEN STOP)

2. Is a generalized (tonic-clonic) seizure reported as an adverse event (synonym = grandmal seizure)? **CIRCLE ONE**

Yes 1
No, another type of seizure is reported .... 2 **(STOP)**
No, seizure unspecified is reported ..... 3 **(STOP)**
No, seizure is not reported as an adverse event ..... 9 **(STOP)**

(IF NO SEIZURE REPORTED THEN STOP)

3. For which evaluations are results reported as part of the evaluation of the seizure? **CHECK ALL THAT APPLY**

Serum electrolytes (must include Na) ..... ☐
Calcium ..... ☐
Magnesium ..... ☐
Glucose ..... ☐
CT/ MRI of head ..... ☐
EEG ..... ☐
Temperature ..... ☐

4. Were the following pre-existing conditions specifically mentioned as present or excluded?

Pre-existing condition:	NOT DESCRIBED	PRESENT	EXCLUDED
Alcoholism	☐	☐	☐
Substance Abuse	☐	☐	☐
Seizure Disorder	☐	☐	☐

5. What was the age of the subject on the date the report was made?

Enter number: _____ _____ (No Data = 99)

6. What is the gender of the subject?

Male 1
Female 2
Not described 8

Figure 3b. Adverse events analysis form for seizure cases (continued)
RAND EPC EPHEDRA PROJECT ADVERSE EVENTS ANALYSIS FORM

7. Why was the subject taking the product? .....
(Start codes at 04) **(CHECK ALL THAT APPLY AND/OR ENTER CODE)**
Weight loss..... ☐ (01)
Improved athletic performance ..... ☐ (02)
Psychological effect ..... ☐ (03)
Other:……. (enter code _____ , _____ , _____)
Not described ..... ☐ (98)

Figure 3b. Adverse events analysis form for seizure cases (continued)
RAND EPC EPHEDRA PROJECT **ADVERSE EVENTS ANALYSIS FORM**

Product: _____ of _____

Description:_____

8. What is the common, proprietary, and/or scientific (genus, genus/species) name of the product? **(ENTER CODE OR CIRCLE ONE OF THE BELOW)**

Code:_____
None.....97
Not applicable 99

.

9. Of which main constituents is the product made?
(ENTER CODE FOR EACH OR CIRCLE ONE OF THE BELOW)

Code: _____ , _____ , _____ , _____ , _____

_____ , _____ , _____ , _____ , _____
None.....97
Not applicable 99

10. Was chemical analysis on ephedra alkaloids data presented?
(CIRCLE ONE)

Yes 1
No.....2
Ordered but not reported 3
Not described 8
Not applicable 9

11. Please fill in the following information on dosage data.
This information is from **analysis: (ENTER THE NUMBER AND CODES IN THE APPROPRIATE BOXES.)**

Dosage data	Number	Unit (code)
Total daily dose of ephedrine alkaloids		
Single dose of ephedrine alkaloids		
Total daily dose of caffeine		
Ratio caffeine/ephedrine alkaloids	:	

Codes for units:

µg	1
mg	2
gm	3
$mgkg^{-1}$	4
ND	8
NA	9

12. Please fill in the following information on dosage data.
This information is from **label: (ENTER THE NUMBER AND CODES IN THE APPROPRIATE BOXES.)**

Dosage data	Number	Unit (code)
Total daily dose of ephedrine alkaloids		
Single dose of ephedrine alkaloids		
Total daily dose of caffeine		
Ratio caffeine/ephedrine alkaloids	:	

Codes for units:

µg	1
mg	2
gm	3
$mgkg^{-1}$	4
ND	8
NA	9

Figure 3b. Adverse events analysis form for seizure cases (continued)
RAND EPC EPHEDRA PROJECT ADVERSE EVENTS ANALYSIS FORM

13. What was the duration of ephedrine use? **(CIRCLE ONE)**
    - <48 hours 1
    - 2-13 days 2
    - 14-60 days (acute) 3
    - >60 days (chronic) 4
    - Not described 8

14. What was the timing of the last ephedrine dose? **(CIRCLE ONE)**
    - <6 hours 1
    - 6-24 hours 2
    - >24 hours 3
    - Not described 8

15. Was/were the product(s) discontinued after problematic symptoms emerged? **(CIRCLE ONE)**
    - Yes 1
    - No 2
    - Not described 8
    - Not applicable 9

16. If product(s) was/were used again after discontinuation, did the problematic symptoms reoccur? **(CIRCLE ONE)**
    - Yes 1
    - No 2
    - Not described 8
    - Not applicable 9

17. Did form report on use of any other substances? **(ENTER CODE OR CIRCLE)**

    Code: _____ , _____ , _____ , _____ , _____

    _____ , _____ , _____ , _____ , _____
    - None 97
    - Not described 98
    - Not applicable 99

18. Which of the following conditions were evaluated?
    (Start codes at 15) **(CHECK ALL THAT APPLY AND/OR ENTER CODE)**

Pre-existing condition:	PRESENT	EXCLUDED
Asthma	☐	☐
CAD	☐	☐
DM	☐	☐
HTN	☐	☐
Obesity	☐	☐
Prior psychiatric history	☐	☐
Renal disease	☐	☐
Syncope	☐	☐
Thyroid condition	☐	☐
TIA History	☐	☐
Other vascular disease (_____)	☐	☐
Rheumatological diseases	☐	☐
Not described	☐ (98)	

Figure 3b. Adverse events analysis form for seizure cases (continued)
RAND EPC EPHEDRA PROJECT **ADVERSE EVENTS ANALYSIS FORM**

19. Was a drug screen performed? **(CIRCLE ONE)**
    Yes 1
    No ..... 2 **(STOP)**

20. Results of **URINE** screen:
    (start codes at 03) **(CHECK ALL THAT APPLY)**
    No substance found ..... ☐ (01)
    Substance(s) found and identified: (Enter code(s)):

    (_____ , _____ , _____ , _____ , _____ , _____)

    Not described ..... ☐ (98)

21. Results of **BLOOD** screen:
    (start codes at 03) **(CHECK ALL THAT APPLY)**
    No substance found ..... ☐ (01)

    Substance(s) found and identified: (Enter code(s) below)

    (_____ , _____ , _____ , _____ , _____ , _____)

    Not described ..... ☐ (98)

END

Figure 3c. Adverse events analysis form for psychiatric cases

RAND EPC EPHEDRA PROJECT **ADVERSE EVENTS ANALYSIS FORM**

ID/ FDA Case Number:_____ Reviewer:_____

First Author: _____
(Last Name Only)

Form Number: _____of_____(Fill out one form for each subject)

1. Does this adverse event report use of ephedra or ephedrine?
(**CIRCLE ONE**)
Ephedra only 1
No/ Unsure ..... 2 **(STOP)**
Ephedrine only 3
Ephedra and Ephedrine 4
(IF NOT EPHEDRA/ OR EPHEDRINE THEN STOP)

2. Is there an adverse event? (**CIRCLE ONE**)
Yes 1
No ..... 2 **(STOP)**
(IF NO ADVERSE EVENT THEN STOP)

3. Was the product specifically identified? (**CIRCLE ONE**)
Yes 1
No ..... 2 **(STOP)**
(MUST BE A SERIOUS ADVERSE EVENT AND PRODUCT SPECIFICALLY IDENTIFIED OR STOP)

4. What was the adverse event? (**CHECK ALL THAT APPLY AND/OR ENTER TEXT**)
Psychosis ..... ☐ (06)
Mania or severe agitation ..... ☐ (07)
Severe depression ..... ☐ (08)
Suicidal ideation ..... ☐ (09)
Suicide attempt/ Suicide ..... ☐ (146)
Hallucinations ..... ☐ (138)
Other serious psychiatric events: (enter below)
_____ ..... ☐ (.)
_____ ..... ☐ (.)
_____ ..... ☐ (.)
_____ ..... ☐ (.)

Other non-serious event: _____) ..... ☐ (96) **(STOP)**
None of the above ..... ☐ (97) **(STOP)**

Figure 3c. Adverse events analysis form for psychiatric cases (continued)
RAND EPC EPHEDRA PROJECT ADVERSE EVENTS ANALYSIS FORM

5. Is there a presence or history of the following conditions?

(CHECK ALL THAT APPLY AND/OR ENTER TEXT)

	PRESENCE	HISTORY	(CODES)
Psychosis	☐	☐	(01)
Mania or severe agitation	☐	☐	(02)
Hallucinations	☐	☐	(03)
Severe depression	☐	☐	(04)
Suicide attempt	☐	☐	(05)
Suicide ideation	☐	☐	(06)
Schizophrenia	☐	☐	(07)
Acute confusion	☐	☐	(08)
Delusions	☐	☐	(09)
Aggression/threatened violence	☐	☐	(10)
Substance abuse	☐	☐	(11)
Other conditions:			
_____	☐	☐	( )
_____	☐	☐	( )
_____	☐	☐	( )
_____	☐	☐	( )
_____	☐	☐	( )
_____	☐	☐	( )
_____	☐	☐	( )
_____	☐	☐	( )
None described		☐	(98)

6. What was the outcome of the event? (CHECK ALL THAT APPLY)

- Death ☐
- Harm to self/others ☐
- Hospitalization ☐
- ER Visit ☐
- On-going adverse event/disability ☐
- Resolved ☐
- Other:_____ ☐
- Not described ☐

Figure 3c. Adverse events analysis form for psychiatric cases (continued)
RAND EPC EPHEDRA PROJECT ADVERSE EVENTS ANALYSIS FORM

7. What was intervention was prescribed after adverse event occurred?
(CHECK ALL THAT APPLY)

No procedure ☐
Discontinue Ephedra ☐
Change existing medication ☐

New medication ☐
Initiate/change frequency/intensity of outpatient visits ☐
Hospitalization ☐

Involuntary hospitalization ☐
Legal action ☐
Not described ☐
Not applicable ☐

8. What was the age of the subject on the date report was made?

Enter number: _____ _____ (No Data=99)

9. What is the gender of the subject? (CIRCLE ONE)

Male 1
Female 2
Not described 8

10. Why was the subject taking the product? (CHECK ALL THAT APPLY)

Weight loss ☐
Improved athletic performance ☐
Psychological effect ☐
Addiction ☐

Other:_____ ☐
Not described ☐

11. Did report describe the use of any other substances or medications taken prior to/or during the event?

_____ ( )

_____ ( )

_____ ( )

_____ ( )

_____ ( )

None described ☐ 98

Figure 3c. Adverse events analysis form for psychiatric cases (continued)
RAND EPC EPHEDRA PROJECT ADVERSE EVENTS ANALYSIS FORM

12. What is the common, proprietary, and/or scientific (genus, genus/species) name of the product? (ENTER TEXT OR CIRCLE ONE BELOW)

Name:_____( )
None....97
Not described....98
Not applicable....99

13. Of which main constituents is the product made?
(Enter text or circle one below)

_____( )

_____( )

_____( )

_____( )

_____( )

_____( )

_____( )

_____( )

None....97
Not described....98
Not applicable....99

14. Was chemical analysis on ephedra alkaloids data presented?
(CIRCLE ONE)

Yes....1
No....2
Ordered but not presented....3
Not described....8
Not applicable....9

Figure 3c. Adverse events analysis form for psychiatric cases (continued)
RAND EPC EPHEDRA PROJECT ADVERSE EVENTS ANALYSIS FORM

15. Please fill in the following information on dosage data.
This information is from **analysis:** (ENTER THE NUMBER AND UNITS IN THE APPROPRIATE BOXES.)

Dosage data	Number	Unit	Unit Code
Total daily dose of ephedrine alkaloids			
Single dose of ephedrine alkaloids			
Total daily dose of caffeine			
Ratio caffeine/ephedrine alkaloids	:		

Codes for units:

µg	1
mg	2
gm	3
$mgkg^{-1}$	4
ND	8
NA	9

16. This information is from **label**: (ENTER THE NUMBER AND UNITS IN THE APPROPRIATE BOXES.)

Dosage data	Number	Unit	Unit Code
Total daily dose of ephedrine alkaloids			
Single dose of ephedrine alkaloids			
Total daily dose of caffeine			
Ratio caffeine/ephedrine alkaloids	:		

Codes for units:

µg	1
mg	2
gm	3
$mgkg^{-1}$	4
ND	8
NA	9

17. What was the duration of ephedra/ephedrine use? (CIRCLE ONE)
<48 hour 1
2-13 days 2
14-60 days (acute) 3
>60 days (chronic) 4
60 days to 1 year 5
Over 1 year 6
Not described 8

18. What was the timing of the last ephedra/ephedrine dose?(CIRCLE ONE)
<6 hours 1
6-24 hours 2
>24 hours 3
Not described 8

19. Was/were the product(s) discontinued after problematic symptoms emerged? (CIRCLE ONE)
Yes 1
No 2
Not described 8
Not applicable 9

Figure 3c. Adverse events analysis form for psychiatric cases (continued)
RAND EPC EPHEDRA PROJECT ADVERSE EVENTS ANALYSIS FORM

20. If product(s) was/were used again after discontinuation, did the problematic symptoms reoccur? (CIRCLE ONE)
    Yes 1
    No 2
    Not described 8
    Not applicable 9

21. Was autopsy performed? (CIRCLE ONE)
    Yes 1
    No 2
    Not Applicable 9

22. Was drug screen performed? (CIRCLE ONE)
    Yes 1
    No ..... 2 (STOP)

23. Results of URINE screen: (CHECK ALL THAT APPLY AND/OR ENTER TEXT)
    No substance found ..... ☐ (01)
    Substance(s) found and identified:

    _____..... ( )

    _____..... ( )

    _____..... ( )

    _____..... ( )

    _____..... ( )

    _____..... ( )

    Not described ..... ☐ (98)

21. Results of **BLOOD** screen:(check all that apply and/or enter text)
    No substance found ..... ☐ (01)
    Substance(s) found and identified:

    _____..... ( )

    _____..... ( )

    _____..... ( )

    _____..... ( )

    _____..... ( )

    _____..... ( )

    Not described ..... ☐ (98)

END

Figure 4. Brief data collection form for case reports

RAND EPC EPHEDRA PROJECT **BRIEF FORM FOR CASE REPORTS**

Article ID:_____ Reviewer:_____

FDA Case Number:_____

Form Number: _____of _____ (Fill out one form for each subject)

1. Does adverse event form report on ephedra or ephedrine?

CIRCLE ONE

Yes 1
No/ Unsure ..... 2 **(STOP)**

(IF NOT EPHEDRA/EPHEDRINE THEN STOP)

2. What was the adverse event? **CHECK ALL THAT APPLY**

Death…… ☐ (01)

Cardiovascular:
- Heart rate, >120 *or* <50 ☐ (02)
- Hypertension, Systolic >180 *or* Diastolic >105 ☐ (03)
- MI ☐ (04)
- Ventricular tachycardia/ fibrillation ☐ (05)
- Cardiac arrest ☐ (06)

Pulmonary:
- Respiratory arrest ☐ (07)

Neurological:
- TIA ☐ (08)
- CVA ☐ (09)
- Brain Hemorrhage, not CVA ☐ (10)
- Fainting / Loss of consciousness ☐ (11)
- Coma ☐ (12)
- Seizure ☐ (13)
- Paralysis ☐ (14)

Psychiatric:
- Severe depression ☐ (15)
- Hallucinations ☐ (16)
- Mania or severe agitation ☐ (17)
- Psychosis ☐ (18)
- Suicide ☐ (19)

Other adverse events:
- Changes in glucose <40 *or* >400 ☐ (20)
- Liver failure ALT/AST >200 ☐ (21)
- Rhabdomyolysis CPK >400 ☐ (22)
- Miscarriage ☐ (23)
- Serious renal event ☐ (25)
- Autonomic Hyperactivity ☐ (26)

None of the above ☐ (24)

Figure 5. Examples of MIPER Files
5a. Email record of a telephone conversation

From: Redacted
Posted At: Monday, November 29, 1999 8:23 AM
Conversation: Redacted menstrual irreg
Posted To: Medical Group

Subject: Redacted menstrual irreg

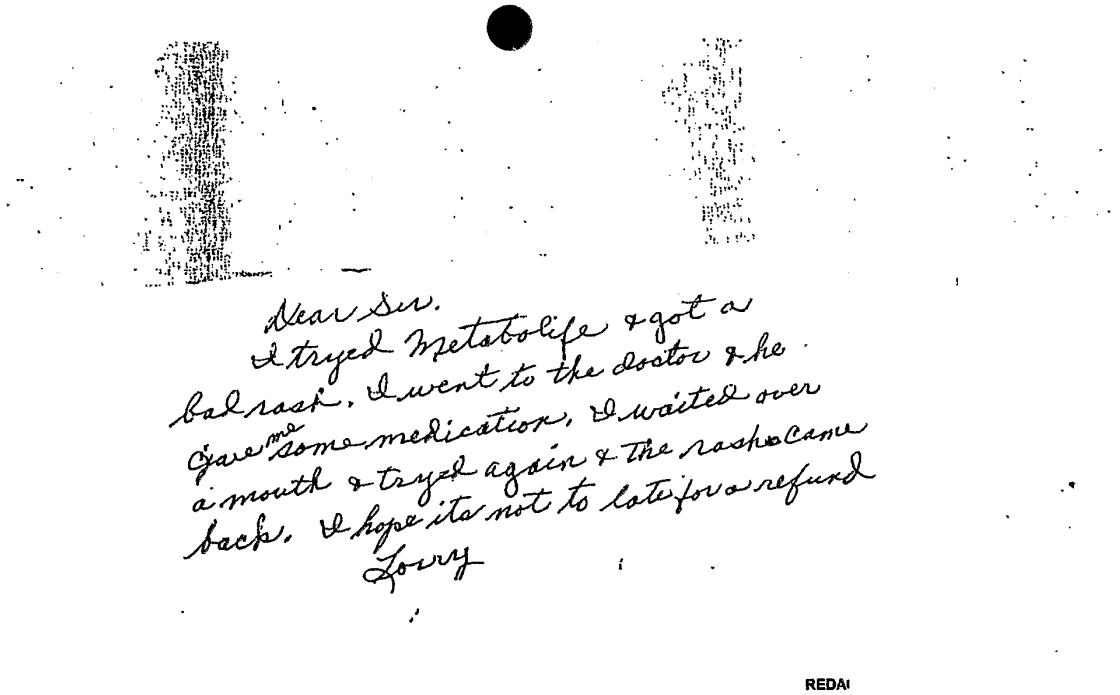
Sensitivity: Private

Categories: Menstrual Irregularity

Redacted
27 yrs 210 lbs
customer reports taking 1 1/2 caps tid ac for 1 month - eats adequate, drinks qs - now experiencing menstrual irreg an is 5 days late for her cycle
recommended contact gyn and discuss whether to continue taking- may be able to just decrease to 1 or 1 1/2 caps a day or may need to completely stop- be sure to continue to eat 3 healthy high protein meals qd and drink 64 oz of water

CONFIDENTIAL MIPER015121

Figure 5. Examples of MIPER Files (continued)
5b. Typed or handwritten letter from the consumer to the company



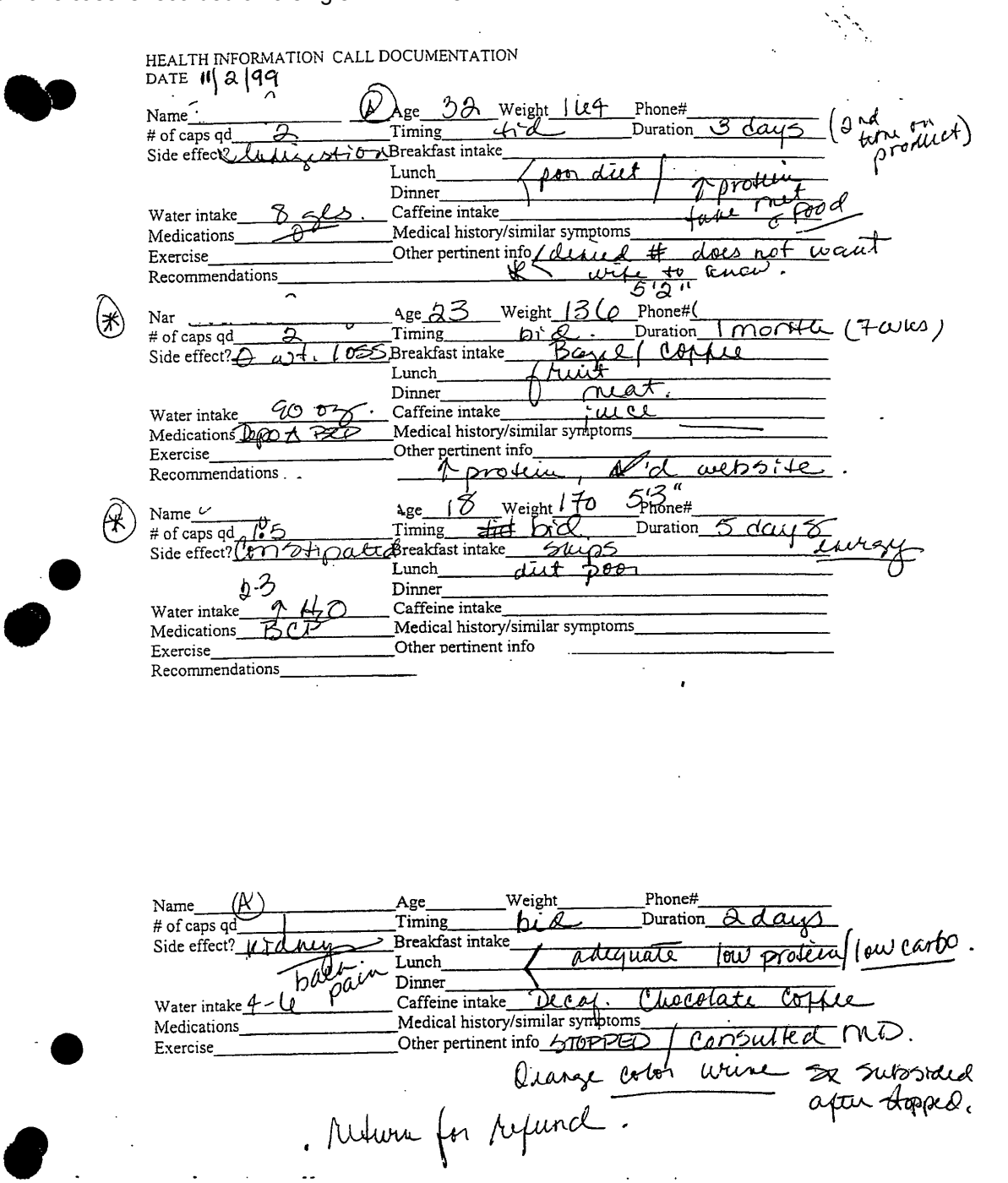
Dear Sir.
I tryed Metabolife & got a
bad rash. I went to the doctor & he
gave me some medication. I waited over
a month & tryed again & the rash came
back. I hope its not to late for a refund
Lowry

REDA

CONFIDENTIAL

MIPER020990

Figure 5. Examples of MIPER Files (continued)
5c. Handwritten note of telephone conversation with consumer written on a rudimentary form. Note more than one case is recorded on a single MIPER file.



HEALTH INFORMATION CALL DOCUMENTATION
DATE 11/2/99

Name _____ (R) Age 32 Weight 164 Phone# _____
# of caps qd 2 Timing tid Duration 3 days (2nd time on product)
Side effect? indigestion Breakfast intake _____
Lunch poor diet
Dinner
Water intake 8 qts. Caffeine intake
Medications 0 Medical history/similar symptoms
Exercise Other pertinent info desired # does not want
Recommendations wife to know.
5'2"

(*) Nar _____ Age 23 Weight 136 Phone#(
# of caps qd 2 Timing bid Duration 1 month (7 wks)
Side effect? 0 wt. loss Breakfast intake Bagel / coffee
Lunch fruit
Dinner meat.
Water intake 90 oz. Caffeine intake juice
Medications Dyaz PRN Medical history/similar symptoms
Exercise Other pertinent info
Recommendations ↑ protein, d/c website.

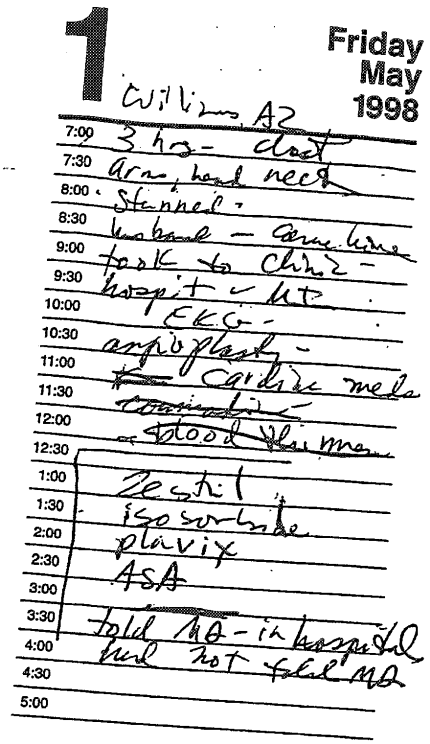
(*) Name _____ Age 18 Weight 170 5'3" Phone# _____
# of caps qd 10 5 Timing ~~tid~~ bid Duration 5 days
Side effect? constipated Breakfast intake skips energy
Lunch diet poor
Dinner
Water intake ↑ H2O Caffeine intake
Medications BCP Medical history/similar symptoms
Exercise Other pertinent info
Recommendations

Name (R) Age Weight Phone# _____
# of caps qd 1 Timing bid Duration 2 days
Side effect? kidney pain Breakfast intake
Lunch adequate low protein / low carbo.
Dinner
Water intake 4-6 Caffeine intake Decaf. Chocolate Coffee
Medications Medical history/similar symptoms
Exercise Other pertinent info STOPPED / consulted MD.
Orange color urine ~~x~~ subsided after stopped.
Return for refund.

CONFIDENTIAL
CONFIDENTIAL & NON RESPONSIVE REDACTION

MIPER022677

Figure 5. Examples of MIPER Files (continued)
5d. Handwritten note of telephone conversation with consumer written on a piece of paper



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REDACTED

MIPER024166

Figure 5. Examples of MIPER Files (continued)

5e. A form developed for systematically collecting information about possible adverse events

Nurses Database - Caller Info

First Name		*AGE(years)*	0	*Current Dose*	1	*Times per day*	1
Last Name	**Redacted**	*WT(LBS)*	180	*Suggested Dose*	0.5	*SD Times per day*	BID
		HT(INCHES)	0	*TIME ON METABOLIFE*	1	*UNITS*	DAYS

USER cela *D/C met use* ☐ *Chinac formula* ☐ *formula*

Date 11/1/199 *Time* 8:36:27 A *Refund Policy Reviewed* ☐ *356 +Chinac* ☐

Recommendations

Current Water Intake oz	*Caffeine Intake*	*Current Diet*	*Increase Water*	*High Protein*	*Other Recommendations*
64	0	low protein breakfasts	☐	☑	start slowly, inc fiber, try with meals, if sx recur, stop, see PCP

☐ *Ok to call back* ☐ *Do not call back* ☐ *Customer Understand Recommendati* ☐ *Eat w/10min to 1hr*

☐ *Usage Guidelines Sent* ☐ *Declined Usage Guidlines* ☐ *Customer to Call Meta PR* ☐ *Ate After 1hr* ☐ *Did Not Eat*

64	0	low protein breakfasts	☐	☑	start slowly, try with meals, if sx recur, stop, see PCP

☐ *Ok to call back* ☐ *Do not call back* ☐ *Customer Understand Recommendati* ☐ *Eat w/10min to 1hr*

☐ *Usage Guidelines Sent* ☐ *Declined Usage Guidlines* ☐ *Customer to Call Meta PR* ☐ *Ate After 1hr* ☐ *Did Not Eat*

☐ Abdominal Pain	☐ Dizziness	☐ Irregular Heartbeat	☐ Pregnancy on BCP
☐ Abnorm Lab Values	☐ Dry Mouth	☐ Irritability	☐ Prupitis
☐ Acne	☐ Edema	☐ Joint Pain	☐ Psychosis
☐ Addiction	☐ Elevated Liver Functions	☐ Joint Stiffness- General	☐ Rash
☐ Anesthesia Complication	☐ Excitation	☐ Joint Stiffness - Local	☐ Seizure
☐ Anxiety	☐ Eye Twitching	☐ Joint Swelling - General	☐ Sexual Disfunction
☐ Back Pain	☐ Facial Swelling	☐ Joint Swelling - Local	☐ Shortness of Breath
☐ Bloating/Gas	☐ Fatigue	☐ Kidney Stones	☐ Stroke
☐ Blood in Stool	☐ Fever	☐ Liver Enzyme Elevation	☐ Sweating
☐ Blood in Urine	☐ Fluid Retention	☐ Menstrual Irregularity	☐ Tachycardia
☐ Breast Pain	☐ Glaucoma	☐ Mood Swings	☐ Tingling Hands
☐ Briusing	☐ Hair Loss	☐ Muscle Cramps -General	☐ Tinnitis
☐ Chest Pain	☐ Headache	☐ Muscle Cramps - Leg	☑ Tremors
☐ Chills	☐ Heart Burn	☐ Myocardial Infarction	☐ Urinary Infection
☐ Cold Hands	☐ High Blood Pressure	☐ Nausea	☐ Urine Retention
☐ Constipation	☐ Hives	☐ NoseBleeds	☐ Vasodilation
☐ Cough	☐ Hypertension	☐ Numbness	☐ Vision Disturbance
☐ Death	☐ Hypoglycemia	☐ Palpitations	☐ Vomiting
☑ Diarrhea	☐ Insomnia	☐ Parestrsias	☐ Yeast Infection

Other/Comments: ☐ No Weight Loss/Gain

☐ Medical Release Form Sent ☐ Customer Denies any other signs or Symptoms

Figure 6. Example of duplicate case

From: Cela Nash
Posted At: Thursday, June 03, 1999 11:35 AM
Conversation: REDACTED Seizure
Posted To: Medical Group

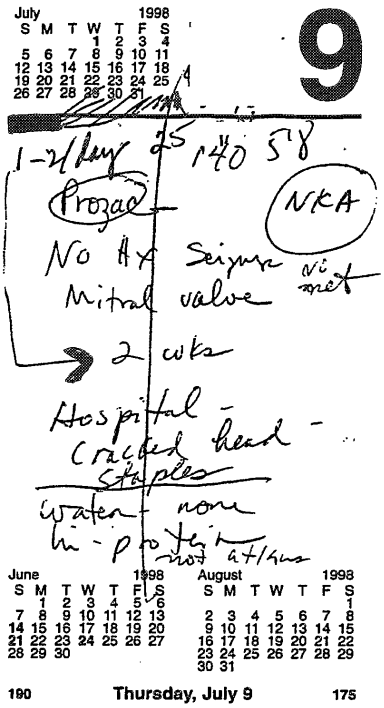
Subject: REDACTED Seizure

Categories: Seizure

25 yr old female, 5'8", 145 lbs, had been taking 1-2 met tabs per day for the last 2 weeks for energy. Had a seizure, fell and injured head, went to hospital, staples and sutures placed in head. No hx epilepsy, or family hx. Has mitral valve prolapse. Nka. Taking prozac daily; had read label, noted that met not to be taken with maos, no mention of ssris. Water, caffeine, protein intake all within guidelines. she is a nutrition/fitness professional, has taken other ephedrine products without problems, but not at the same time as prozac. Has d/c'd met. Inst that met works by stimulating cns, can lower seizure threshhold. Her eeg test is pending.

REDACTED

Figure 6. Example of duplicate case (continued)



CONFIDENTIAL
REDACTED

MIPER024209

Figure 7. Metabolife record screener form

Case Number:_____ Reviewer:_____

Form Number: _____of_____(Fill out one form for each subject)

1. Subject's age: _____ (Not Described =999)

2. What is the subject's gender? (**CIRCLE ONE**)
   - Male.....1
   - Female 2
   - Not described/ Not reported.....3

3. What was the adverse event? **(CHECK ALL THAT APPLY)**
   - No adverse event reported .....☐ (01)

   (IF NO ADVERSE EVENT THEN STOP.)
   - Death.....☐ (02)

   Cardiovascular:
   - Heart rate, >120 or <50.....☐ (03)
   - Heart rate, 50-120, or not otherwise unspecified.....☐ (04)
   - Hypertension, Systolic >180 or Diastolic >105 .....☐ (05)
   - Hypertension, Systolic <180 or Diastolic <105, or not otherwise specified .....☐ (06)
   - Myocardial Infarction/ Heart Attack.....☐ (07)
   - Cardiac Dysrythmia, Other/ Palpitations.....☐ (08)
   - Cardiac arrest.....☐ (09)
   - Ventricular Tachycardia/ Fibrillation.....☐ (10)
   - Chest Pain, not specified as MI .....☐ (11)

   Pulmonary:
   - Respiratory arrest.....☐ (12)

   Neurological:
   - Transient Ischemic Attack.....☐ (13)
   - CVA/ Stroke, not known to be hemorrhage .....☐ (14)
   - Brain Hemorrhage.....☐ (15)
   - Fainting / Loss of consciousness .....☐ (16)
   - Coma.....☐ (17)
   - Seizure .....☐ (18)

   Psychiatric:
   - Depression .....☐ (19)
   - Hallucinations.....☐ (20)
   - Mania or severe agitation.....☐ (21)
   - Psychosis .....☐ (22)
   - Suicide attempt .....☐ (23)
   - Autonomic Hyperactivity (includes: tremor, twitching, jitteriness, insomnia, increased sweating, agitation, nervousness, and irritability).....☐ (24)

Figure 7. Metabolife record screener form (continued)

3. What was the adverse event? **(CHECK ALL THAT APPLY)**
(continued)
Other adverse events:
- Changes in glucose <40 or >400 ☐ (25)
- Liver failure ALT/AST >200 ☐ (26)
- Liver abnormality, not otherwise specified ☐ (27)
- Rhabdomyolysis CPK >400 ☐ (28)
- Rhabdomyolysis, not otherwise specified ☐ (29)
- Miscarriage ☐ (30)
- Allergic Reaction ☐ (31)
- Anesthesia complication ☐ (32)
- Fatigue/Fever/ Chills ☐ (33)
- Abnormal lab values, not otherwise specified ☐ (34)

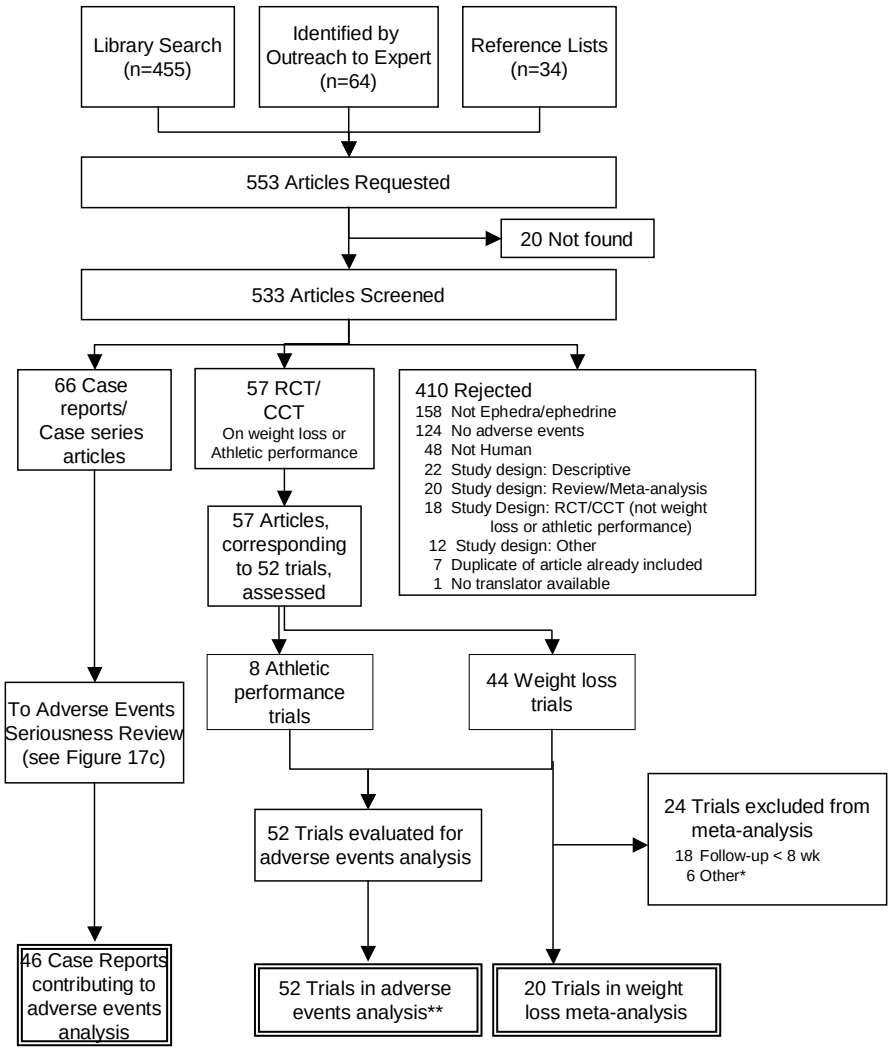
Other adverse events not already specified:
- Ear, Eye, Nose, or Throat ☐ (35)
- Respiratory System ☐ (36)
- Cardiovascular System ☐ (37)
- Gastrointestinal System ☐ (38)
- Hepatobiliary System ☐ (39)
- Musculoskeletal System ☐ (40)
- Genitourinary System ☐ (41)
- Gynecologic (includes breast and menstrual symptoms) ☐ (42)
- Sexual Dysfunction ☐ (43)
- Neurological System (includes headache) ☐ (44)
- Mental Health ☐ (45)
- Skin (includes Pruritis) ☐ (46)
- Hematologic System ☐ (47)
- Oncologic System ☐ (48)
- Other symptoms not specified above ☐ (49)

4. Did the adverse event result in a hospital stay (at least one night; do not include emergency room visits)? **(CIRCLE ONE)**
- Yes 1
- No/ No Data 2

5. Is there additional information (medical records or similar) available for more detailed review regarding past health history, current, problems, toxicology results, etc? **(CIRCLE ONE)**
- Yes 1
- No 2

END

Figure 8. Literature flow



* Various reasons, see table 9.
** Two studies had no placebo group, and therefore, contribute to the power calculations, but not to the odds-ratio meta-analysis.

Figure 9. Ephedrine versus placebo – forest plot

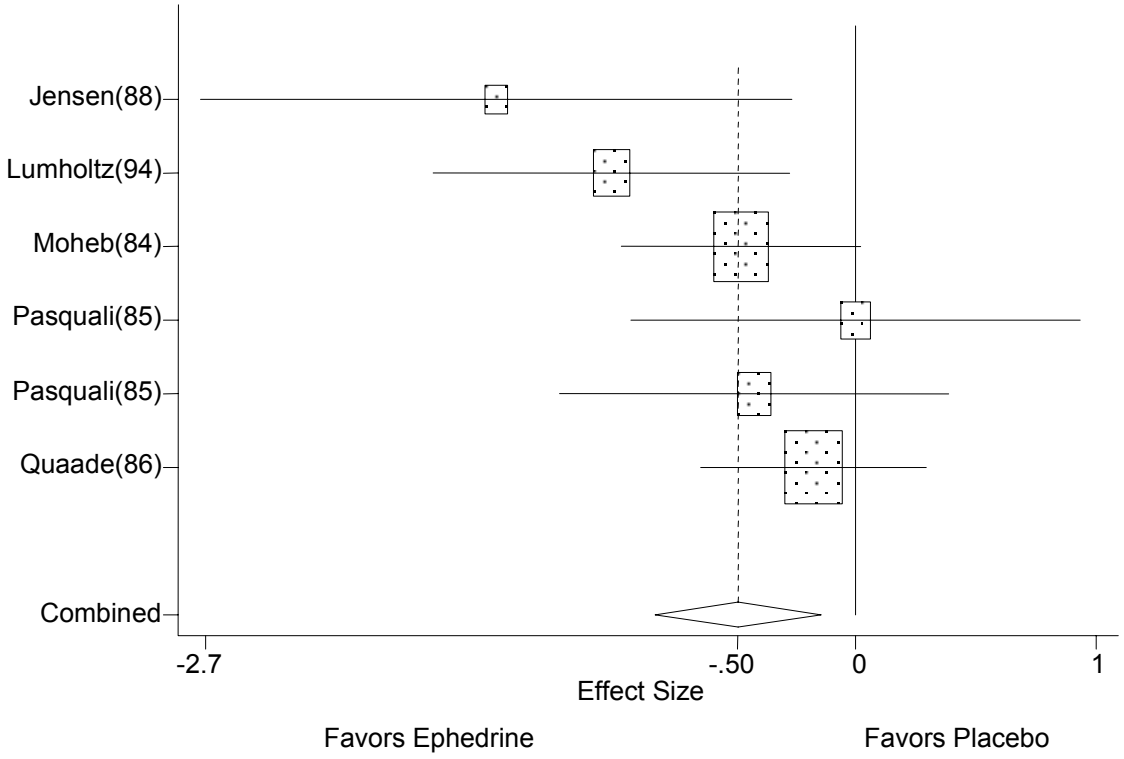


Figure 10. Ephedrine versus placebo – funnel plot

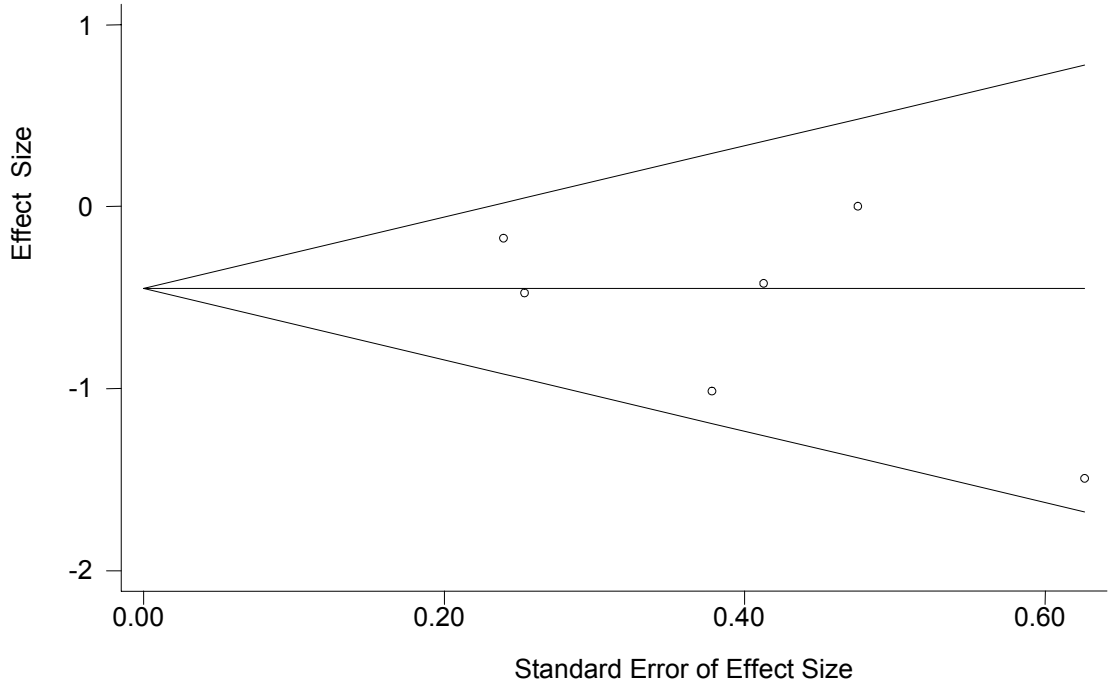


Figure 11. Ephedrine + caffeine versus placebo – forest plot

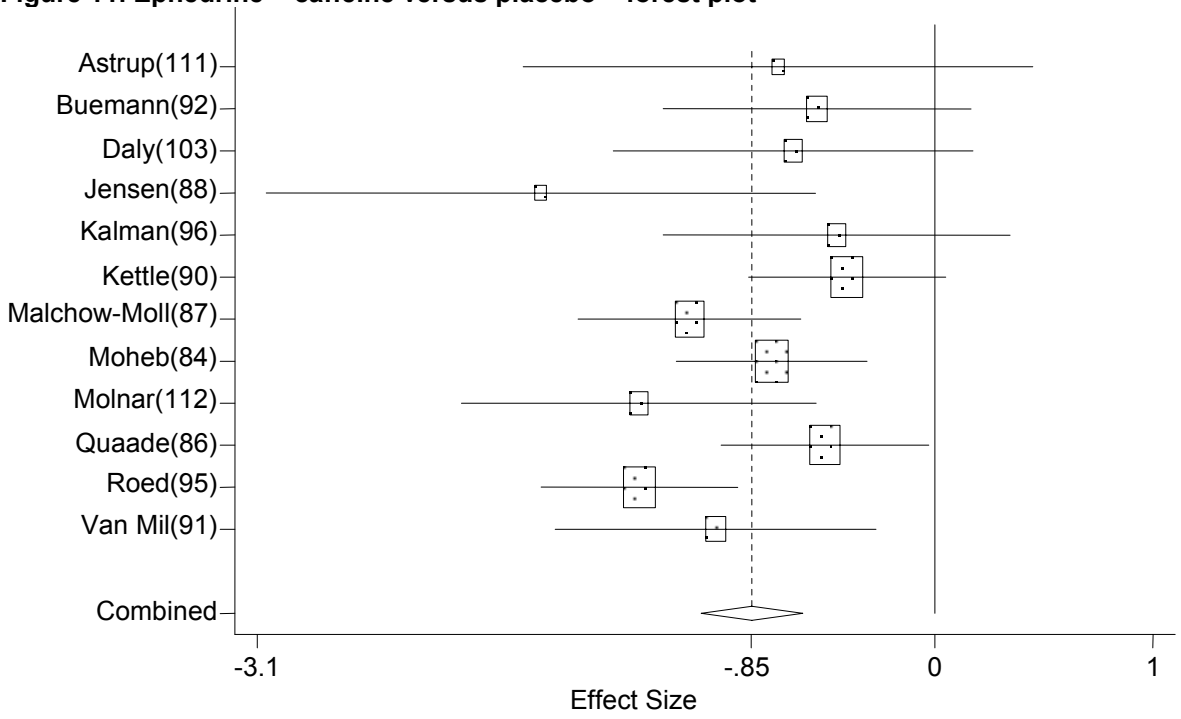


Figure 12. Ephedrine + caffeine versus placebo – funnel plot

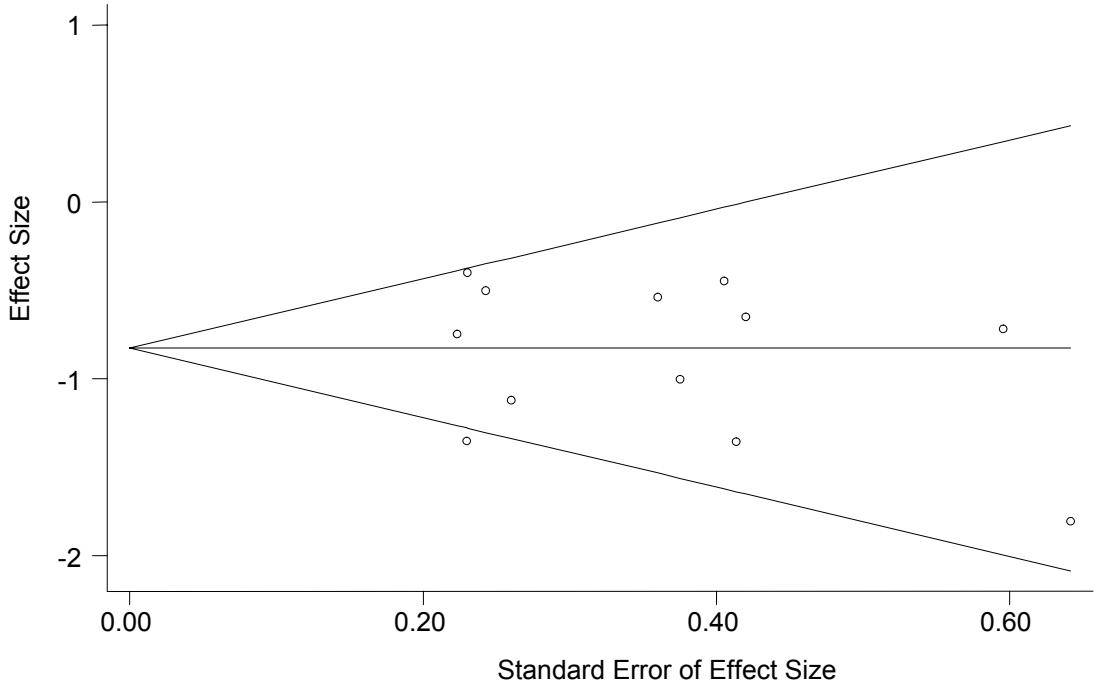


Figure 13. Ephedrine + caffeine versus ephedrine alone – forest plot

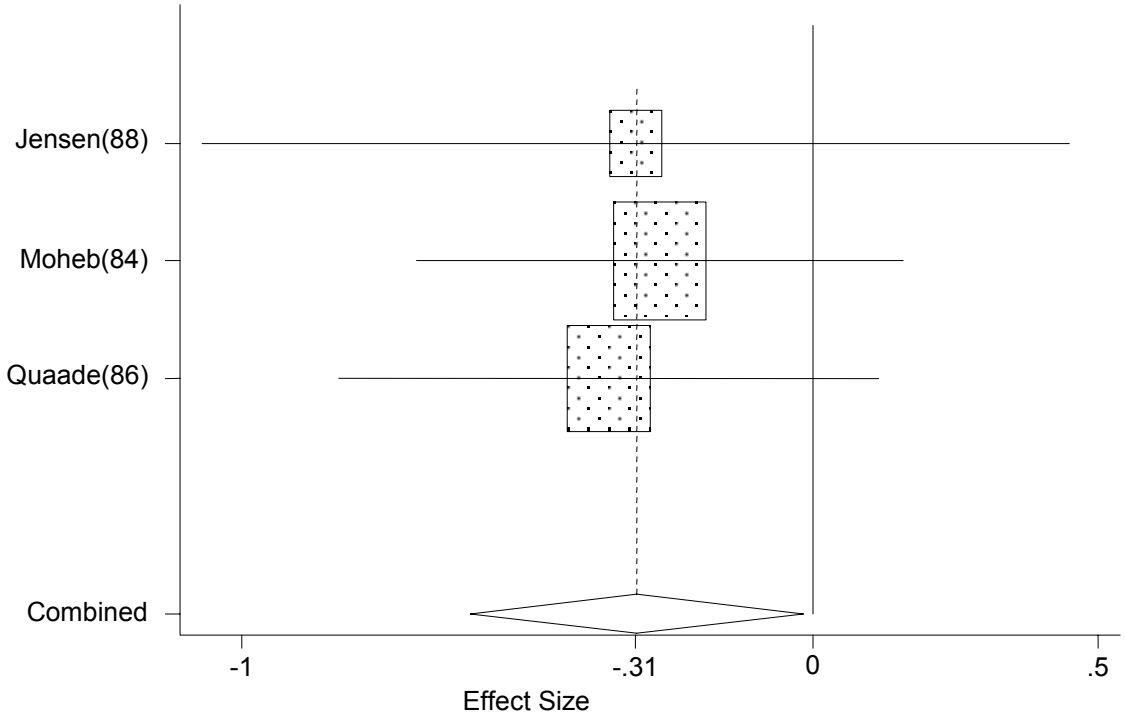


Figure 14. Ephedra + herbs containing caffeine versus placebo – forest plot

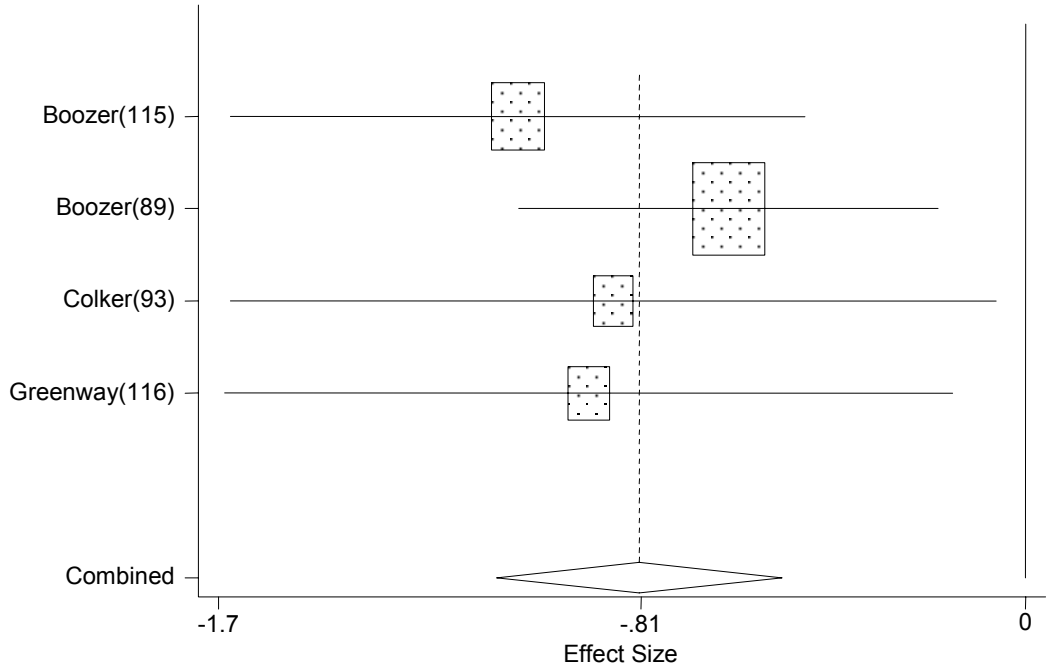


Figure 15. Ephedra + herbs containing caffeine versus placebo – funnel plot

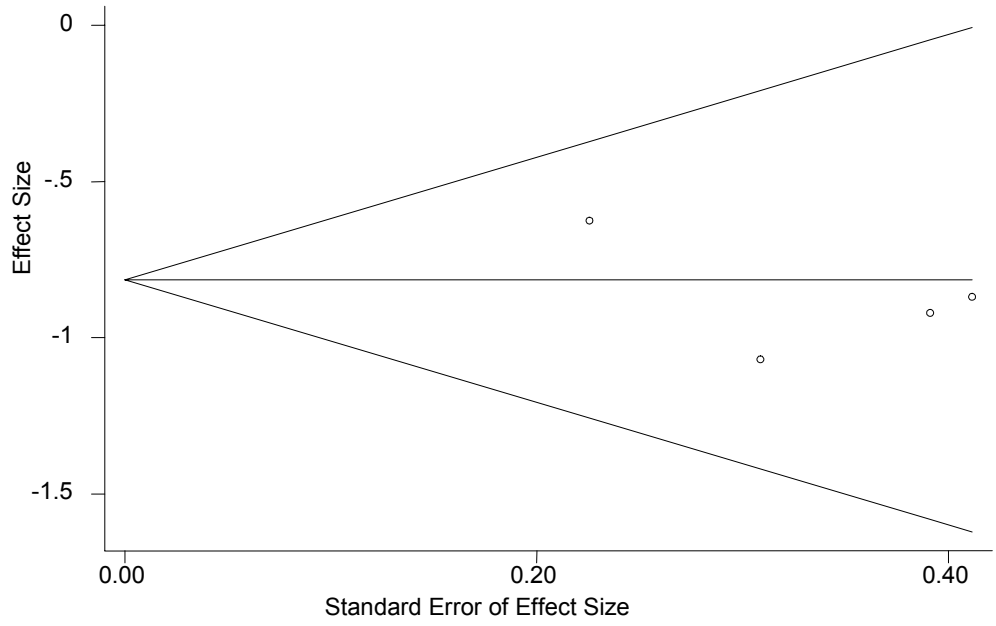


Figure 16. Effect sizes by comparison group

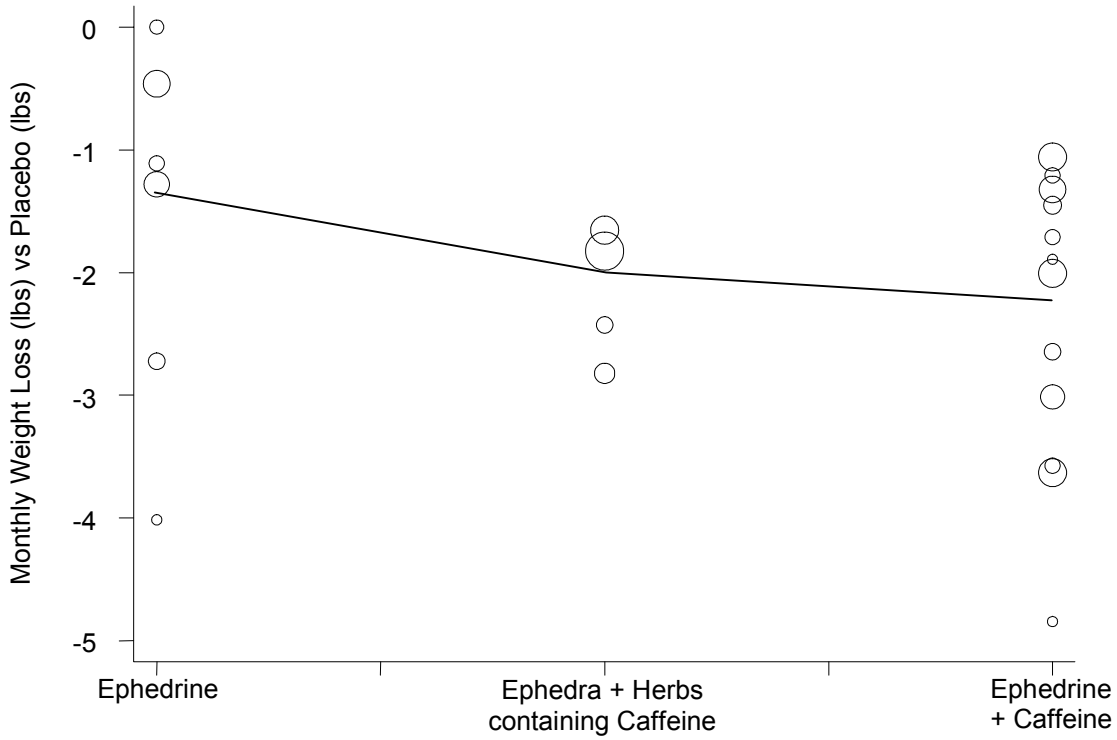


Figure 17a. Flow of evidence for adverse events analysis, part 1

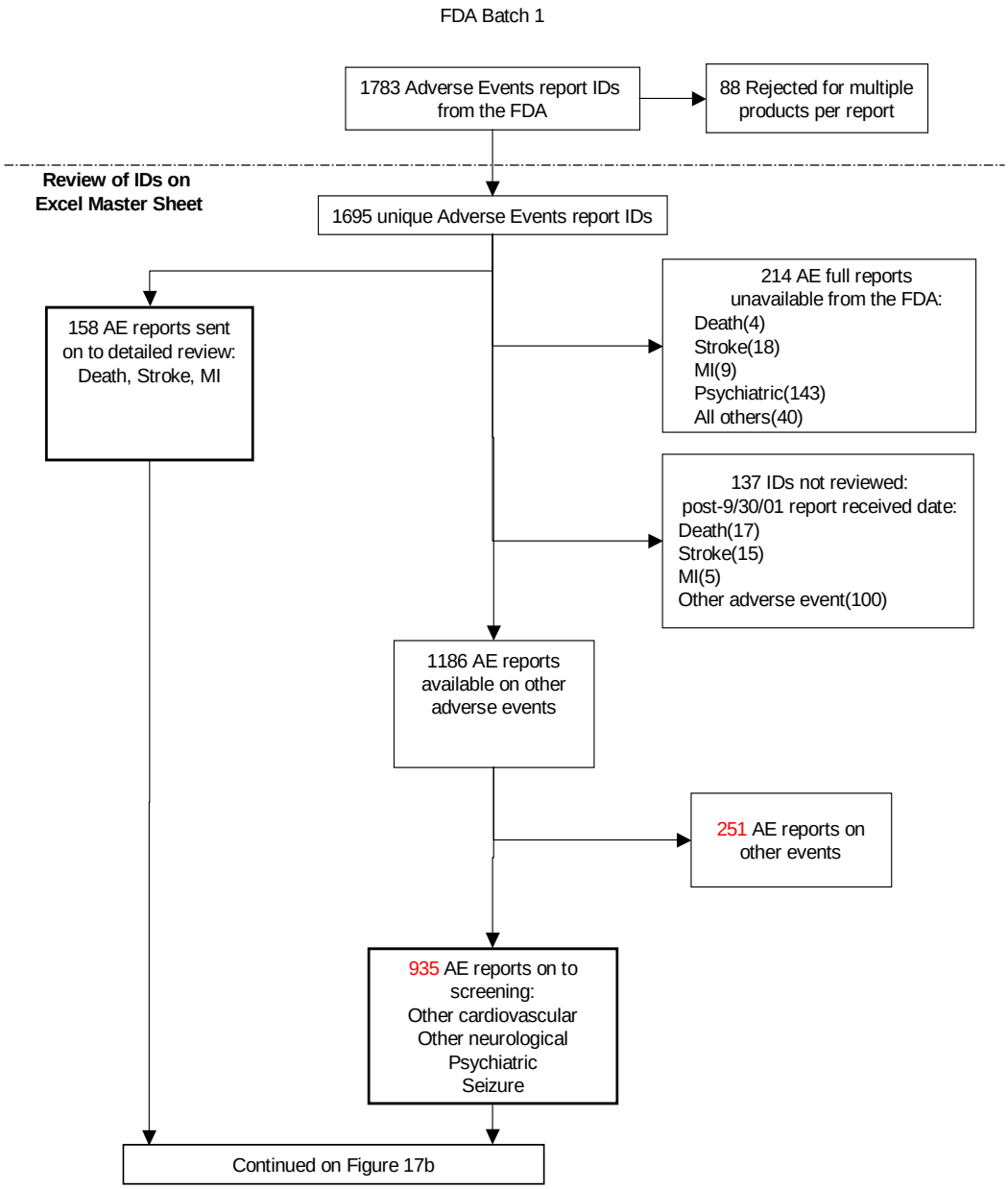


Figure 17b. Flow of evidence for adverse events analysis, part 2

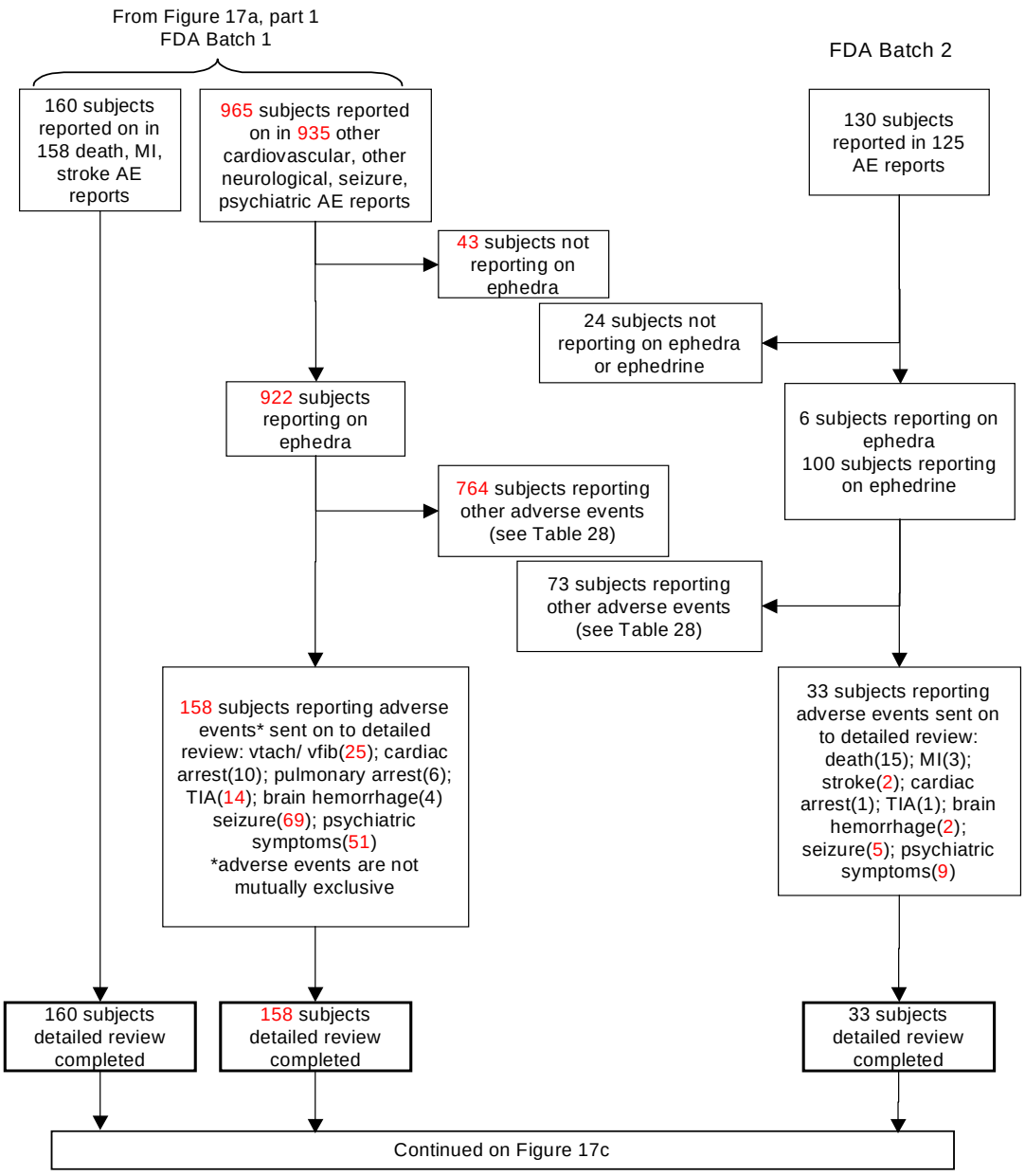


Figure 17c. Flow of evidence for adverse events analysis, part 3

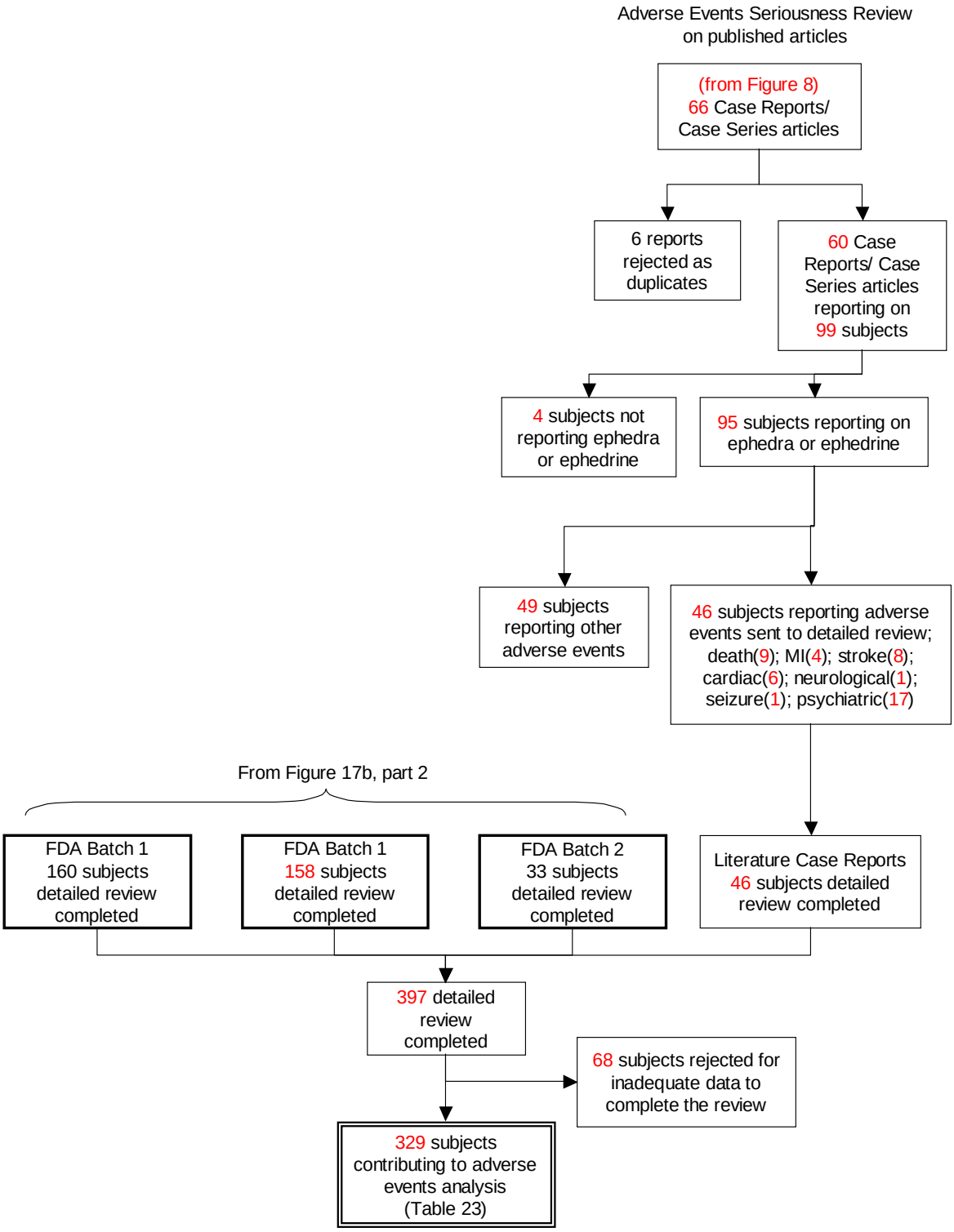
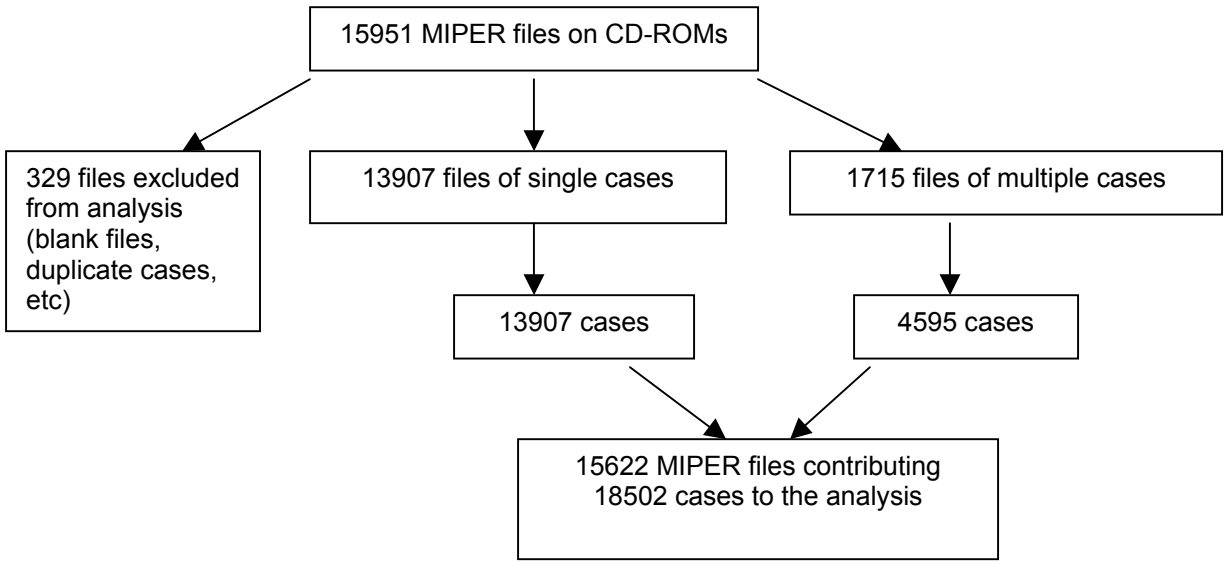


Figure 18. Flow of MIPER ID Numbers



Evidence Tables

Evidence Table 1 – RCTs and CCTs reporting on Athletic Performance Enhancement with Ephedra

First Author Year	Design Study Quality Population (>75%) Comorbidities	Arm #	Intervention Total Daily Dose Route of Administration Duration	Sample Size	Summary of Results
Bell DG & Jacobs I 1999 #24	CCT Jadad Score: 1 Population: Male athletes Comorbidities: N/A	1	Placebo Placebo for 2 days	n Entered: 9 n Analyzed: 9	VO_2 maximum during the treadmill runs, VO_2 at standard running velocities, and the relationship between the heart rate and the VO_2 were similar in both the Caffeine and Ephedrine (C+E, Arm 2) and the Placebo (Arm 1) groups. Run times of the performance test for subjects in the C+E group (Arm 2) was significantly faster ($p < 0.05$) than for subjects in the Placebo group (Arm 1).
		2	Ephedrine 75 mg orally for 2 days Caffeine 375 mg orally for 2 days	n Entered: 9 n Analyzed: 9	
Bell DG, Jacobs I, et al. 1999 #25	CCT Jadad Score: 1 Population: Male Comorbidities: N/A	1	Control No dosage data reported	n Entered: 10 n Analyzed: 10	Individuals in the Caffeine and Ephedrine (C+E) group (Arm 3) experienced a significant VO_2 increase of 7.5% compared to individuals in the Placebo group (Arm 2), but similar to individuals in the Control group (Arm 1). Tolerance times were similar for the C+E (Arm 3, 121.3 +/- 33.9 minutes) and Placebo (Arm 2, 120.0 +/- 28.4) groups, but significantly longer than the Control group (Arm 1, 106.6 +/- 24.0).
		2	Placebo Placebo for 1 day	n Entered: 10 n Analyzed: 10	
		3	Ephedrine 1 mg·kg-1 orally for 1 day Caffeine 5 mg·kg-1 orally for 1 day	n Entered: 10 n Analyzed: 10	
Bell DG, Jacobs I, et al. 2000 #26	CCT Jadad Score: 3 Population: Male Comorbidities: N/A	1	Placebo Placebo for 1 day	n Entered: 12 n Analyzed: 12	VO_2 maximum was similar among all groups. Endurance ride times to exhaustion for all Caffeine and Ephedrine groups with different dosages (Arm 2, 27.5 +/- 12.4 minutes; Arm 3, 27.6 +/-10.9; and Arm 4, 28.2 +/- 9.3) were similar, and significantly greater than Placebo (Arm 1, 17.0 +/- 3.0) with an approximated 64% improvement.
		2	Ephedrine 0.8 mg·kg-1 orally for 1 day Caffeine 5 mg·kg-1 orally for 1 day	n Entered: 12 n Analyzed: 12	
		3	Caffeine 1 mg·kg-1 orally for 1 day Caffeine 4 mg·kg-1 orally for 1 day	n Entered: 12 n Analyzed: 12	
		4	Ephedrine 0.8 mg·kg-1 orally for 1 day Caffeine 4 mg·kg-1 orally for 1 day	n Entered: N/A n Analyzed: N/A	

N/A = not available or not applicable

Evidence Table 1 – RCTs and CCTs reporting on Athletic Performance Enhancement with Ephedra (continued)

First Author Year	Design Study Quality Population (>75%) Comorbidities	Arm #	Intervention Total Daily Dose Route of Administration Duration	Sample Size	Summary of Results
Bell DG, Jacobs I, et al. 1998 #27	CCT Jadad Score: 4 Population: Male Comorbidities: N/A	1	Placebo Placebo for 1 day	n Entered: 12 n Analyzed: 8	VO_2 maximum increased progressively during exercise in all trials (Arms 1, 2, 3, and 4, $p < 0.05$), but no significant difference was found among them. Time to exhaustion was significantly longer for the Caffeine and Ephedrine trial ((Arm 2) when compared to Placebo (Arm1) and Caffeine (Arm 3) trials ($p < 0.05$).
		2	Ephedrine 1 mg·kg-1 orally for 1 day Caffeine 1 mg·kg-1 orally for 1 day	n Entered: 12 n Analyzed: 8	
		3	Caffeine 5 mg·kg-1 orally for 1 day	n Entered: 12 n Analyzed: 8	
		4	Ephedrine 1 mg·kg-1 orally for 1 day	n Entered: 12 n Analyzed: 8	
Bell DG, Jacobs I, et al. 2001 #512	CCT Jadad Score: 1 Population: Military Comorbidities: N/A	1	Placebo Placebo for 1 day	n Entered: 24 n Analyzed: 24	Accumulated VO_2 was similar between all groups. The Ephedrine (Arm 3) and Caffeine plus Ephedrine (Arm 4) treatments increased power output significantly ($p < 0.05$) early in the Wingate test compared to the Placebo (Arm 1) and Caffeine (Arm 2) treatments. Caffeine-containing treatments (Arms 2 and 4) significantly improved times to exhaustion by 8% compared to non-caffeine treatments (Arms 1 and 3).
		2	Caffeine 5 mg·kg-1 orally for 1 day	n Entered: 24 n Analyzed: 24	
		3	Ephedrine 1 mg·kg-1 orally for 1 day	n Entered: 24 n Analyzed: 24	
		4	Ephedrine 1 mg·kg-1 orally for 1 day Caffeine 1 mg·kg-1 orally for 1 day	n Entered: 24 n Analyzed: 24	
Oksbjerg N, Meyer T, et al. 1986 #214	CCT Jadad Score: 1 Population: Male Comorbidities: N/A	1	Ephedrine 40 mg orally for 1 day	n Entered: 6 n Analyzed: 6	A thermogenic effect of 4.3 +/- 1.3 watt was established for the Ephedrine group (Arm 1), the effect in the Placebo group (Arm 2) was only 1.6 +/- 1.6. The thermogenic effect in the Ephedrine group (Arm 1) increased by 100% ($p < 0.05$) following aerobic training. Overall, aerobic training increased VO_2 maximum by 7 % ($p < 0.05$).
		2	Placebo No dosage data reported	n Entered: 6 n Analyzed: 6	
Pasternak 1999 #511	CCT Jadad Score: 1 Population: Male athletes Comorbidities: N/A	1	Placebo Placebo for 1 day	n Entered: 13 n Analyzed: 13	For muscular endurance outcomes, mean number of leg and bench press repetitions only in the first set increased significantly ($p < 0.05$) for individuals in the Caffeine and Ephedrine (Arm 4) and the Ephedrine (Arm 3) groups compared to the Caffeine (Arm 2) and Placebo (Arm 1) groups. The mean number for all 3 sets of leg and bench repetitions was similar among all groups.
		2	Caffeine 4 mg·kg-1 orally for 1 day	n Entered: 13 n Analyzed: 13	
		3	Ephedrine 0.8 mg·kg-1 orally for 1 day	n Entered: 13 n Analyzed: 13	
		4	Caffeine 4 mg·kg-1 orally for 1 day Ephedrine 0.8 mg·kg-1 orally for 1 day	n Entered: 13 n Analyzed: 13	

N/A = not available or not applicable

Evidence Table 1 – RCTs and CCTs reporting on Athletic Performance Enhancement with Ephedra (continued)

First Author Year	Design Study Quality Population (>75%) Comorbidities	Arm #	Intervention Total Daily Dose Route of Administration Duration	Sample Size	Summary of Results
Sidney KH & Lefcoe NM 1977 #247	CCT Jadad Score: 2 Population: Male Comorbidities: N/A	1	Placebo Placebo for 1 day	n Entered: 21 n Analyzed: 21	No significant difference was seen between the Placebo (Arm 1) and Ephedrine (Arm 2) groups for any variable including VO_2 maximum, and endurance.
		2	Ephedrine 24 mg orally for 1 day	n Entered: 21 n Analyzed: 21	

N/A = not available or not applicable

Evidence Table 2 – RCTs and CCTs reporting on Weight Loss

First Author Year	Design Study Quality Population (>75%) Comorbidities	Arm #	Intervention Total Daily Dose Route of Administration Duration	Sample Size	Meta-analysis Data* Or Summary of Results
Astrup A, Buemann B, et al. 1992 #9	CCT Jadad Score: 2 Population: Female Comorbidities: Obesity	1	Placebo Placebo for 8 weeks	n Entered: 8 n Analyzed: 6	Average weight loss at 2 months in kg: Arm 1 = 8.4 (2.9) Arm 2 = 10.1 (1.0)
		2	Ephedrine 60 mg orally for 8 weeks Caffeine 600 mg orally for 8 weeks	n Entered: 8 n Analyzed: 6	
Belfie L, Petrie H, et al. 2001 #317	CCT Jadad Score: 1 Population: N/A Comorbidities: Obesity	1	Placebo Placebo for 12 weeks	n Entered: N/A n Analyzed: 10	Excluded from meta-analysis due to Insufficient statistics. At follow up, decreases were seen only in the Ma Huang Supplement group (Arm 2) for mass (106.0 +/-11.5 to 96.9 +/- 12.1 kg), fat mass (31.3 +/- 5.3 to 25.8 +/- 5.8 kg, $p < 0.05$), and percent body fat (29.4 +/- 3.1 to 26.4 +/- 3.0 %, $p < 0.05$).
		2	Ephedrine from Ma Huang 60 mg orally for 12 weeks Caffeine from Guarana 600 mg orally for 12 weeks	n Entered: N/A n Analyzed: 11	
Boozer CN, Daly PA, et al. 2000 #34	RCT Jadad Score: 5 Population: Female Comorbidities: Obesity	1	Placebo Placebo for 24 weeks	n Entered: 84 n Analyzed: 38	Average weight loss at 6 months in kg: Arm 1 = 2.6 (3.2) Arm 2 = 5.3 (5.0)
		2	Ephedrine from Ma Huang 86.4 mg orally for 24 weeks Caffeine from Kola nut 196 mg orally for 24 weeks	n Entered: 83 n Analyzed: 45	
Boozer CN, Nasser JA, et al. 2001 #333	RCT Jadad Score: 5 Population: Female Comorbidities: Obesity	1	Placebo Placebo for 8 weeks	n Entered: 32 n Analyzed: 24	Average weight loss at 2 months in kg: Arm 1 = 0.8 (2.4) Arm 2 = 4.0 (3.4)
		2	Ephedrine from Ma Huang 77.4 mg orally for 8 weeks Caffeine from Guarana 300 mg orally for 8 weeks	n Entered: 35 n Analyzed: 24	
Breum L, Pedersen JK, et al. 1994 #41	RCT Jadad Score: 4 Population: Female Comorbidities: Obesity	1	Dexfenfluramine 30 mg orally for 15 weeks	n Entered: 53 n Analyzed: 43	Average weight loss at 3.75 months in kg: Arm 1 = 6.9 (4.3) Arm 2 = 8.3 (5.2)
		2	Ephedrine 60 mg orally for 15 weeks Caffeine 600 mg orally for 15 weeks	n Entered: 50 n Analyzed: 38	
Buemann B, Marckmann P, et al. 1994 #45	RCT Jadad Score: 3 Population: Female Comorbidities: Obesity	1	Placebo Placebo for 8 weeks	n Entered: N/A n Analyzed: 16	Average weight loss at 2 months in kg: Arm 1 = 7.1 (2.4) Arm 2 = 8.4 (2.4)
		2	Ephedrine 60 mg orally for 8 weeks Caffeine 600 mg orally for 8 weeks	n Entered: N/A n Analyzed: 16	

N/A = not available or not applicable

* Meta-analysis data reports standard deviation in parentheses.

Evidence Table 2 – RCTs and CCTs reporting on Weight Loss (continued)

First Author Year	Design Study Quality Population (>75%) Comorbidities	Arm #	Intervention Total Daily Dose Route of Administration Duration	Sample Size		Meta-analysis Data* Or Summary of Results
Colker, Swain, et al. 2001 #548	RCT Jadad Score: 2 Population: Female Comorbidities: Obesity	1	Placebo Placebo for 8 weeks	n Entered: n Analyzed:	12 12	Average weight loss at 2 months in kg: Arm 1 = 0.49 (2.35) Arm 2 = 2.56 (2.35)
		2	Ephedrine from Ma Huang Taken orally for 8 weeks Coleus forksohlli Taken orally for 8 weeks	n Entered: n Analyzed:	14 14	
Colker, Torina, et al. 1999 #549	RCT Jadad Score: 1 Population: N/A Comorbidities: Obesity	1	Placebo Placebo for 8 Weeks	n Entered: n Analyzed:	8 8	Excluded from meta-analysis because of insufficient statistics: study reports weight loss for one group only. The Ephedra, Caffeine, Aspirin, and Exercise (E+C+A+E) group (Arm 3) had a significant reduction in body weight (-3.8 kg, p<0.01) compared to the Ephedra, Caffeine, and Aspirin (E+C+A, Arm 2) and Placebo groups (Arm 1). The E+C+A (Arm 2) group experienced a significant reduction in caloric intake (-680.2 kcal, p<0.05) compared to the other groups.
		2	Ephedrine from Ma Huang 60 mg orally for 8 weeks Caffeine from unspecified herb 600 mg orally for 8 weeks Aspirin 45 mg orally for 8 weeks	n Entered: n Analyzed:	8 8	
Daly PA, Krieger DR, et al. 1993 #68	RCT Jadad Score: 2 Population: Female Comorbidities: Obesity	1	Placebo Placebo for 8 weeks	n Entered: n Analyzed:	15 13	Average weight loss at 2 months in kg: Arm 1 = 0.7 (2.2) Arm 2 = 2.2 (2.3)
		2	Ephedrine 75 mg orally for 4 weeks Second round of previous intervention 150 mg orally for 4 weeks Caffeine 150 mg orally for 8 weeks Aspirin 330 mg orally for 8 weeks	n Entered: n Analyzed:	14 11	

N/A = not available or not applicable
* Meta-analysis data reports standard deviation in parentheses.

Evidence Table 2 – RCTs and CCTs reporting on Weight Loss (continued)

First Author Year	Design Study Quality Population (>75%) Comorbidities		Arm #	Intervention Total Daily Dose Route of Administration Duration	Sample Size		Meta-analysis Data* Or Summary of Results
Donikyan LA 2002 #509	RCT Jadad Score: Population: Comorbidities:	4 Male and female Obesity	1	Placebo Placebo for 12 weeks	n Entered: n Analyzed:	94 78	Average weight loss at 3 months in kg: Arm 1 = 3.0 (6.0) Arm 2 = excluded Arm 3 = 7.4 (6.8)
			2	Ephedrine from Ma Huang 72 mg orally for 8 weeks Chromium picolinate 450 mcq orally for 8 weeks Placebo Placebo for 4 weeks	n Entered: n Analyzed:	93 75	
			3	Ephedrine from Ma Huang 72 mg orally for 12 weeks Chromium picolinate 450 mcq orally for 12 weeks	n Entered: n Analyzed:	92 76	
Greenway F, deJonge L, et al. Unpublished #475	RCT Jadad Score: Population: Comorbidities:	2 N/A Obesity	1	Placebo Placebo for 12 weeks	n Entered: n Analyzed:	20 18	Average weight loss at 3 months in kg: Arm 1 = 0.8 (2.6) Arm 2 = 3.9 (4.0)
			2	Ephedrine from Ma Huang 72 mg orally for 12 weeks Caffeine from unspecified herb 210 mg orally for 12 weeks Phenylalanine 300 mg orally for 12 days	n Entered: n Analyzed:	20 12	
Jensen, Dano, et al. 1980 #536	RCT Jadad Score: Population: Comorbidities:	1 N/A Obesity	1	Ephedrine 100 mg orally for 16 weeks Caffeine 275 mg orally for 16 weeks	n Entered: n Analyzed:	23 14	Average weight loss at 4 months in kg: Arm 1 = 9.4 (4.7) Arm 2 = 7.9 (4.7) Arm 3 = 0.5 (4.7)
			2	Ephedrine 100 mg orally for 16 weeks	n Entered: n Analyzed:	24 13	
			3	Placebo No dosage data reported	n Entered: n Analyzed:	17 4	

N/A = not available or not applicable
* Meta-analysis data reports standard deviation in parentheses.

Evidence Table 2 – RCTs and CCTs reporting on Weight Loss (continued)

First Author Year	Design Study Quality Population (>75%) Comorbidities	Arm #	Intervention Total Daily Dose Route of Administration Duration	Sample Size		Meta-analysis Data* Or Summary of Results
Kalman DS, Colker CM, et al. 2000 #140	RCT Jadad Score: 3 Population: Male Comorbidities: Obesity	1	Placebo Placebo for 8 weeks	n Entered: n Analyzed:	14 13	Average weight loss at 2 months in kg: Arm 1 = 2.1 (2.4) Arm 2 = 3.1 (2.4)
		2	Ephedrine 40 mg orally for 8 weeks Synephrine 10 mg orally for 8 weeks Caffeine 400 mg orally for 8 weeks Aspirin 30 mg orally for 8 weeks	n Entered: n Analyzed:	16 12	
Kalman, Colker, et al. 2000 #550	RCT Jadad Score: 3 Population: N/A Comorbidities: Obesity	1	Placebo Placebo for 8 weeks	n Entered: n Analyzed:	15 15	Excluded from meta-analysis because of insufficient statistics: study only reports weight loss in percent. Subjects in the Ephedrine, Synephrine, Caffeine, and Aspirin (E+S+C+A) group (Arm 2) experienced a significant reduction in body weight (-9%, p≤0.05) as well as in percent of body fat (-16%, p<0.001) compared to the Placebo group (Arm 1, -3.8% and -1% respectively). An intragroup difference in fat free mass was seen in both groups: -0.92 kg (p<0.01) in the E+S+C+A group (Arm 2) and -3.47 kg (p<0.05) in the Placebo group (Arm 1).
		2	Ma Huang/Ephedra 20 mg orally for 8 weeks 28 5 mg orally for 8 weeks Caffeine from unspecified herb 200 mg orally for 8 weeks Aspirin 15 mg orally for 8 weeks	n Entered: n Analyzed:	15 15	
Kettle R, Toubro S, et al. 1998 #510	CCT Jadad Score: 0 Population: N/A Comorbidities: Obesity	1	Placebo Placebo for 6 months	n Entered: n Analyzed:	45 37	Average weight loss at 6 months in kg: Arm 1 = 12.8 (6.7) Arm 2 = 15.6 (7.1)
		2	Ephedrine 20 mg orally for 6 months Caffeine 200 mg orally for 6 months	n Entered: n Analyzed:	45 40	
Lumholtz IB, Thorsteinsson B, et al. 1980 #173	RCT Jadad Score: 2 Population: N/A Comorbidities: Obesity	1	Ephedrine 120 mg orally for 18 weeks	n Entered: n Analyzed:	63 18	Average weight loss at 4.5 months in kg: Arm 1 = 9.5 (5.3) Arm 2 = 4.0 (5.3)
		2	Placebo No dosage data reported	n Entered: n Analyzed:	63 14	

N/A = not available or not applicable
* Meta-analysis data reports standard deviation in parentheses.

Evidence Table 2 – RCTs and CCTs reporting on Weight Loss (continued)

First Author Year	Design Study Quality Population (>75%) Comorbidities		Arm #	Intervention Total Daily Dose Route of Administration Duration	Sample Size		Meta-analysis Data* Or Summary of Results
Malchow-Moller A, Larsen S, et al. 1981 #177	CCT Jadad Score: Population: Comorbidities:	 3 N/A Obesity	1	Placebo Placebo for 12 weeks	n Entered: n Analyzed:	33 31	Average weight loss at 3 months in kg: Arm 1 = 4.1 (3.5) Arm 2 = 8.1 (3.5) Arm 3 = 8.4 (3.5)
			2	Ephedrine 60 mg orally for 12 weeks Caffeine 150 mg orally for 12 weeks	n Entered: n Analyzed:	49 38	
			3	Diethylpropion 37.5 mg orally for 12 weeks	n Entered: n Analyzed:	50 39	
Moheb MA, Geissler CA, et al. 1998 #193	RCT Jadad Score: Population: Comorbidities:	 2 Female Obesity	1	Placebo Placebo for 12 weeks	n Entered: n Analyzed:	N/A 32	Average weight loss at 3 months in kg: Arm 1 = 6.2 (3.5) Arm 2 = 7.9 (3.5) Arm 3 = 9.6 (3.5) Arm 4 = 8.8 (3.5) Arm 5 = 8.9 (3.5)
			2	Ephedrine 150 mg orally for 12 weeks	n Entered: n Analyzed:	N/A 32	
			3	Ephedrine 150 mg orally for 12 weeks Aspirin 330 mg orally for 12 weeks	n Entered: n Analyzed:	N/A 32	
			4	Ephedrine 150 mg orally for 12 weeks Caffeine 150 mg orally for 12 weeks	n Entered: n Analyzed:	N/A 32	
			5	Ephedrine 150 mg orally for 12 weeks Caffeine 150 mg orally for 12 weeks Aspirin 330 mg orally for 12 weeks	n Entered: n Analyzed:	N/A 32	

N/A = not available or not applicable
* Meta-analysis data reports standard deviation in parentheses.

Evidence Table 2 – RCTs and CCTs reporting on Weight Loss (continued)

First Author Year	Design Study Quality Population (>75%) Comorbidities	Arm #	Intervention Total Daily Dose Route of Administration Duration	Sample Size		Meta-analysis Data* Or Summary of Results
Molnar D, Torok K, et al. 2000 #195	RCT Jadad Score: 4 Population: Adolescents (12-17) Comorbidities: Obesity	1	Placebo Placebo for 20 weeks	n Entered: n Analyzed:	16 13	Average weight loss at 5 months in kg: Arm 1 = 0.5 (4.3) Arm 2 = 7.9 (6.0)
		2	Ephedrine 10 mg orally for 1 weeks Second round of previous intervention 30-60 mg orally for 19 weeks Caffeine 100 mg orally for 1 weeks Second round of previous intervention 300-600 mg orally for 19 weeks	n Entered: n Analyzed:	16 16	
Norregaard J, Jorgensen S, et al. 1996 #210	RCT Jadad Score: 3 Population: N/A Comorbidities: Obesity, hypertension, pulmonary, AVD.	1	Placebo Placebo for 9 months	n Entered: n Analyzed:	80 73	Excluded from meta-analysis because there was no weight loss outcome, this study addressed weight gain. Subjects in the Ephedrine plus Caffeine group (Arm 2) gained significantly less weight during the first 12 weeks (Week 3 = p<0.001; Week 6 = p<0.01; Week 12 = p<0.05) than subjects in the Placebo group (Arm 1). Weight gain was similar for both groups after 1 year.
		2	Ephedrine 60 mg orally for 3 months Second round of previous intervention 40 mg orally for 3 months Third round of previous intervention 20 mg orally for 3 months Caffeine 600 mg orally for 3 months Second round of previous intervention 400 mg orally for 3 months Third round of previous intervention 200 mg orally for 3 months	n Entered: n Analyzed:	167 152	
Pasquali R, Baraldi G, et al. 1985 #220	RCT Jadad Score: 3 Population: N/A Comorbidities: Obesity	1	Placebo Placebo for 3 months	n Entered: n Analyzed:	21 12	Average weight loss at 3 months in kg: Arm 1 = 8.7 (3.5) Arm 2 = 8.7 (2.4) Arm 3 = 10.2 (3.5)
		2	Ephedrine 75 mg orally for 3 months	n Entered: n Analyzed:	19 7	
		3	Ephedrine 150 mg orally for 3 months	n Entered: n Analyzed:	22 12	

N/A = not available or not applicable
* Meta-analysis data reports standard deviation in parentheses.

Evidence Table 2 – RCTs and CCTs reporting on Weight Loss (continued)

First Author Year	Design Study Quality Population (>75%) Comorbidities		Arm #	Intervention Total Daily Dose Route of Administration Duration	Sample Size		Meta-analysis Data* Or Summary of Results
Pasquali R, Cesari MP, et al. 1987 #223	RCT Jadad Score: Population: Comorbidities:	 2 Female Obesity	1	Placebo Placebo for 2 months	n Entered: n Analyzed:	10 10	Excluded from meta-analysis because crossover study design. Patients' weight loss was significantly (p<0.05) more during the Ephedrine treatment (Arm 2, 2.41 +/- 0.6 kg.) than during the Placebo treatment (Arm 1, 0.64 +/- 0.05 kg.).
			2	Ephedrine 150 mg orally for 2 months	n Entered: n Analyzed:	10 10	
Quaade F, Astrup A, et al. 1992 #230	RCT Jadad Score: Population: Comorbidities:	 3 Male and female Obesity	1	Ephedrine 60 mg orally for 24 weeks Caffeine 600 mg orally for 24 weeks	n Entered: n Analyzed:	45 35	Average weight loss at 3 months in kg: Arm 1 = 11.7 (5.3) Arm 2 = 10.3 (4.0) Arm 3 = 9.0 (3.6) Arm 4 = 10.2 (5.7) Average weight loss at 6 months in kg: Arm 1 = 16.6 (6.8) Arm 2 = 14.3 (5.9) Arm 3 = 11.5 (6.0) Arm 4 = 13.2 (6.6)
			2	Ephedrine 60 mg orally for 24 weeks	n Entered: n Analyzed:	45 35	
			3	Caffeine 600 mg orally for 24 weeks	n Entered: n Analyzed:	45 36	
			4	Placebo No dosage data reported	n Entered: n Analyzed:	45 35	
Roed, Hansen, et al. 1980 #535	RCT Jadad Score: Population: Comorbidities:	 3 Male and female Obesity	1	Ephedrine 60 mg orally for 12 weeks Caffeine 150 mg orally for 12 weeks Phenobarbital 60 mg orally for 12 weeks	n Entered: n Analyzed:	70 49	Average weight loss at 3 months in kg: Arm 1 = excluded Arm 2 = 10.0 (3.5) Arm 3 = 5.2 (3.5)
			2	Ephedrine 60 mg orally for 12 weeks Caffeine 150 mg orally for 12 weeks	n Entered: n Analyzed:	69 52	
			3	Placebo No dosage data reported	n Entered: n Analyzed:	69 42	
Toubro S & Astrup A 1997 #261	RCT Jadad Score: Population: Comorbidities:	 2 Female Obesity	1	Ephedrine 60 mg orally for 8 weeks Caffeine 600 mg orally for 8 weeks	n Entered: n Analyzed:	21 19	Excluded from meta-analysis due to study design: ephedrine dose did not vary between arms. The mean weight loss achieved during the reduction phase was 12.6 kg (95% CI: 10.9-14.3) for the Low Energy Diet (LED) group (Arm1) and 12.6 kg (CI: 9.9-15.3) for the Conventional Diet (CD) group (Arm 2). The rate of weight loss was twice as high in the CD group (Arm 2, 1.6 kg/week, CI: 1.4 -1.8) than in the LED group (Arm 1, 0.8 kg/week, CI: 0.7-1.0).
			2	Ephedrine 60 mg orally for 17 weeks Caffeine 600 mg orally for 17 weeks	n Entered: n Analyzed:	22 19	

N/A = not available or not applicable

* Meta-analysis data reports standard deviation in parentheses.

Evidence Table 2 – RCTs and CCTs reporting on Weight Loss (continued)

First Author Year	Design Study Quality Population (>75%) Comorbidities	Arm #	Intervention Total Daily Dose Route of Administration Duration	Sample Size		Meta-analysis Data* Or Summary of Results
Van Mil E & Molnar D 2000 #272	RCT Jadad Score: 1 Population: Adolescents (12-17) Comorbidities: Obesity	1	Placebo Placebo for 20 weeks	n Entered: n Analyzed:	16 16	Average weight loss at 5 months in kg: Arm 1 = 1.5 (8.1) Arm 2 = 8.7 (5.7)
		2	Ephedrine 60 mg orally for 20 weeks Caffeine 600 mg orally for 20 weeks	n Entered: n Analyzed:	16 16	

N/A = not available or not applicable
* Meta-analysis data reports standard deviation in parentheses.

Acronyms

AEA	Adverse events analysis
AHRQ	Agency for Healthcare Research and Quality
ARMS	Adverse Reaction Monitoring System
BMI	Body Mass Index
CCT	Controlled clinical trial
CI	Confidence interval
CPK isozymes	Creatine phosphokinase isoenzyme
CPR	Cardio-plumonary resuscitation
CT scan	Computerized tomography scan
CVA	Cerebral vascular accident
CVD	Cardiovascular diseases
DF	Dexfenfluramine
DSHEA	Dietary Supplement Health and Education Act
EPC	Evidence-based Practice Center
FDA	US Food and Drug Administration
GAO	General Accounting Office
HHS	US Department of Health and Human Services
IOC	International Olympic Committee
kg	kilograms
MB fractions	Myocardial band fractions (of CPK isoenzymes)
MI	Myocardial infarction
mg	milligrams
MRI	Magnetic resonance imagery
NCAA	National Collegiate Athletic Association
NHANES	National Health and Nutrition Examination Survey
NIH	National Institutes of Health
ODS	Office of Dietary Supplements
OTC	Over-the-counter
PDF	Portable document format
QRF	Quality review form
RCT	Randomized controlled trial
TEP	Technical Expert Panel
VCO_2	Volume of carbon dioxide production
VO_2	Volume of oxygen consumption

Appendix 1. Bibliography

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Appendix 2. Metabolife Serious Adverse Events

From:	Cola Nash
Posted At:	Thursday, October 21, 1999 3:10 PM
Conversation:	Redacted Onset of Seizure disorder
Posted To:	Medical Group
Subject:	Redacted Onset of Seizure disorder
Sensitivity:	Private
Categories:	Seizure

Redacted will call back

165 lb female, took 1 tab bid for about six wks starting in april. Had first seizure in late may; no hx seizure disorder. Still having seizures at this time; working with neurologist to determine cause. md unaware of met use.

Inst to make md aware of met use; she will call us back and may have her md call when her eval is complete.

Appendix 2. Metabolife Serious Adverse Events (continued)

From: Christal Kerrigan
Posted At: Monday, October 18, 1999 4:38 PM
Conversation: Redacted
Posted To: Medical Group

Subject: Redacted

Redacted ,40yr. old female,5'2",169lbs.reports"I had a grand mal seizure,ended up with the paramedics taking me to the hospital,had a neurology consult,all negative so the Dr. thought it was from the met and the ativan I'm on. I don't want this to happen to anyone else."I questioned her further Have you had seizures before?I had them as a child [febrile] not anymore. I was on 3 servings,3x/day. for 10 days. I took it with my meals and drank lots of water. are you on any other meds?Yes,entex la and I have aThyroid problem"I told her we didn't recomend it unless she told her dr. the active ingrediants. she said she did and her dr. approved it, the dr. was suprised too!She also drank 2 sodas" a day. I let her vent awhile and said not every thing in life Can be predicted even by a dr.She agreed and stated "this was a wake up call, I'm going to a natural healer and cleanse except fof ativan. I mentioned that ativan can be addictive and she said she knew that. She was satisfied when she hung up.

CONFIDENTIAL

MIPER015345

Appendix 2. Metabolife Serious Adverse Events (continued)

From:	Bruce Carlier
Posted At:	Thursday, October 14, 1999 8:09 AM
Conversation:	cardiopulmonary arrest
Posted To:	Medical Group
Subject:	cardiopulmonary arrest
Sensitivity:	Private

Redacted , calling for a doctor from Redacted called to question whether there were any known effects from withdrawing Metabolife suddenly- I responded that usually we recommend that individuals taper off Metabolife when stopping as they may experience a decrease in energy- she responded and stated that she has a Metabolife customer who experienced cardiopulmonary arrest after apparently discontinuing suddenly from 6-8 caps a day to 1-2 caps or nothing qd- Denise states the customer works as a sheriff's officer and little else is known - she does have a bottle and list of ingredients at hand & is aware the 2 main ingredients are ephedrine and caffeine
I requested that she call us back and speak to us if there are any changes
She provide her number upon reques Redacted

Appendix 2. Metabolife Serious Adverse Events (continued)

From: Bruce Cartier
Posted At: Tuesday, September 14, 1999 1:16 PM
Conversation: *Redacted* heart attack
Posted To: Medical Group

Subject: *Redacted* heart attack

Sensitivity: Private

information provided by daughter who is attempting to get refund for 2 bottles
one purchased on April 28th and one bottle on May 17th

Redacted Redacted
customer's dgtr reports father taking unknown amt of met for approx 1 1/2 months- unknown dietary intake but states he drinks a lot of water, drinks no caffeine- no hx of heart problems- was doing mild activity on June 5th, had chest pain and went to hospital dx'd with heart attack-
instructed dgtr that will send a medical release form and to return this with as much information as possible and also purchase information (date, place, amt) and we will facilitate this process

CONFIDENTIAL MIPER016006

Appendix 2. Metabolife Serious Adverse Events (continued)

From:	Cela Nash
Posted At:	Wednesday, May 19, 1999 1:23 PM
Conversation:	REDACTED Myocardial Infarction
Posted To:	Medical Group
Subject:	REDACTED Myocardial Infarction
Categories:	Myocardial Infarction

59 yr old female, 5'7", 181 lbs, took 1 met tab tid since last summer. does not have primary physician. Has experienced no weight loss since that time. Approx 1 month after she began met, experienced some low back pain; returned to mall where salesperson inst her to drink more water. Water intake adequate, minimal additional caffeine, fair protein intake. No previous medical hx, no meds, no allergies. Experienced occ SOB during time she took met. On May 1st in the afternoon she began experiencing "fullness in the chest;" gradually became worse, extending to her arms, head, and neck. 3 hrs later her husband came home and took her to a walk-in clinic where the md there looked at the met bottle and told her, "there's lots of stuff in
here that can hurt your heart." She was admitted to a hospital where she
was dx with myocardial infarction. She was transferred to a hospital in Phoenix, AZ for angioplasty. She was d/c'd with med regime of zestril, isosorbide, plavix, asa. She does not know any of her attending md's names or phone #s. Inst to be very careful taking otc meds which also contain ephedrine.

REDACTED

Appendix 2. Metabolife Serious Adverse Events (continued)

From:	Cela Nash
Posted At:	Tuesday, August 03, 1999 4:23 PM
Conversation:	Seizure
Posted To:	Medical Group
Subject:	Seizure
Sensitivity:	Private
Categories:	Seizure

51 yr old female, 5'8", 170 lbs, took 1 tab bid for about 3 weeks, then had a seizure. Has seizure disorder; takes 5 mg clonazepam qd to control seizures. When she bought product, salesperson pointed out 1-800 health line, inst her to call if she had any medical conditions. She did not call. She also did not inform her md. Inst to be very cautious with any caffeine and/or ephedrine product; to always clear anything through her physician. She states she knows the experience was due to her actions; is not seeking any compensation.

Appendix 2. Metabolife Serious Adverse Events (continued)

From:	Cat McCollum
Posted At:	Wednesday, July 21, 1999 4:11 PM
Conversation:	*Redacted* Stroke
Posted To:	Medical Group
Subject:	*Redacted* Stroke
Sensitivity:	Private
Categories:	Stroke

Reported by Ms. Blatchford, her cousin, a Redacted

29 y.o. F, in otherwise good health, weight unknown. Taking Met 8 days, 6/day. Suffered CVA. Apparently 2 of her friends also suffered CVAs while taking Met at approximately the same time. One also had an MI. Doctors cannot attribute CVA to Met, but advised her to D/C Met as well as Depo shots. All tests WNL, cannot determine cause of CVA.

Michelle Redacted

Her cousin will request that she call us.

Appendix 2. Metabolife Serious Adverse Events (continued)

From:	Rose San Pedro
Posted At:	Monday, July 12, 1999 3:55 PM
Conversation:	*Redacted* / seizure episode and headache
Posted To:	Medical Group
Subject:	*Redacted* / seizure episode and headache
Categories:	seizure episode and headache

Redacted

Redacted

150 lbs.female reported that she started taking Met on Friday 7/9,was taking 2 caplets before breafast and 1 caplet before lunch.On Sat,appar. started having severe headache and had seizure episode.Denies having any HX of epilepsy or any seizure disorder,nor any health prob.She discont. Met yesterday Sunday,claims that she still cont.to have headaches,req.to speak to M.D.
Recom.to stop Met and not to take it ever again and see physician for check up.

Appendix 2. Metabolife Serious Adverse Events (continued)

From: Rose San Pedro
Posted At: Tuesday, July 06, 1999 10:07 AM
Conversation: ***Redacted*** / seizure exac.
Posted To: Medical Group

Subject: ***Redacted*** / seizure exac.

Categories: seizure exac.

192 lbs.on Met. was taking 1 caplet twice a day for 11 mos., she said she lost 15 lbs.,reported 4 seizure episodes for the whole month of June,claims that she's epileptic and takes dilantin 30 mg and phenobarbital daily,did'nt have any seizure episode for over a yr. until last mo, Recom.stop Met.

Appendix 2. Metabolife Serious Adverse Events (continued)

From: Cela Nash
Posted At: Thursday, June 03, 1999 11:35 AM
Conversation: REDACTED Seizure
Posted To: Medical Group

Subject: REDACTED Seizure

Categories: Seizure

25 yr old female, 5'8", 145 lbs, had been taking 1-2 met tabs per day for the last 2 weeks for energy. Had a seizure, fell and injured head, went to hospital, staples and sutures placed in head. No hx epilepsy, or family hx. Has mitral valve prolapse. Nka. Taking prozac daily; had read label, noted that met not to be taken with maos, no mention of ssris. Water, caffeine, protein intake all within guidelines. she is a nutrition/fitness professional, has taken other ephedrine products without problems, but not at the same time as prozac. Has d/c'd met. Inst that met works by stimulating cns, can lower seizure threshhold. Her eeg test is pending.

REDACTED

Appendix 2. Metabolife Serious Adverse Events (continued)

From:	Cela Nash
Posted At:	Monday, May 24, 1999 10:46 AM
Conversation:	REDACTED Seizure
Posted To:	Medical Group
Subject:	REDACTED Seizure
Categories:	Seizure

Took met approx 1 week. Had seizure while in movie theater; several mds in the theater; all said she had had a seizure; 911 was called. No hx seizure disorder. Unable to obtain further info at this time as her sister is one who called - customer is supposed to call back.

Appendix 2. Metabolife Serious Adverse Events (continued)

From:	Cela Nash
Posted At:	Wednesday, May 19, 1999 1:23 PM
Conversation:	REDACTED Myocardial Infarction
Posted To:	Medical Group
Subject:	REDACTED Myocardial Infarction
Categories:	Myocardial Infarction

59 yr old female, 5'7", 181 lbs, took 1 met tab tid since last summer. does not have primary physician. Has experienced no weight loss since that time. Approx 1 month after she began met, experienced some low back pain; returned to mall where salesperson inst her to drink more water. Water intake adequate, minimal additional caffeine, fair protein intake. No previous medical hx, no meds, no allergies. Experienced occ SOB during time she took met. On May 1st in the afternoon she began experiencing "fullness in the chest;" gradually became worse, extending to her arms, head, and neck. 3 hrs later her husband came home and took her to a walk-in clinic where the md there looked at the met bottle and told her, "there's lots of stuff in
here that can hurt your heart." She was admitted to a hospital where she
was dx with myocardial infarction. She was transferred to a hospital in Phoenix, AZ for angioplasty. She was d/c'd with med regime of zestril, isosorbide, plavix, asa. She does not know any of her attending md's names or phone #s. Inst to be very careful taking otc meds which also contain ephedrine.

REDACTED

Appendix 2. Metabolife Serious Adverse Events (continued)

From:	Cela Nash
Posted At:	Wednesday, April 14, 1999 4:22 PM
Conversation:	REDACTED calling re wife - seizures
Posted To:	Medical Group
Subject:	REDACTED calling re wife - seizures
Categories:	Numbness, Seizure

Husband called stating wife had been hospitalized 3 times with seizures, numbness on one side. She had not thought to inform any md re met use. Explained to husband that met is a cns stimulant and may lower seizure threshold; he stated wife's brain scans show no evidence of seizure disorder when off met. Matter referred to Dr. Smith.

REDACTED

CONFIDENTIAL MIPER017369

Appendix 2. Metabolife Serious Adverse Events (continued)

From: Dan Rodriguez
Posted At: Monday, February 22, 1999 7:59 AM
Conversation: siezure
Posted To: Medical Group

Subject: siezure

REDACTED and her sister both take Met REDACTED sports th REDACTED ad a siezure recently. The mother will call in the details later. REDACTED doesn't eat right or at all and is not sure how she takes it. she chose to leave the reporting to the mother.

disposition: asked for further details.

CONFIDENTIAL MIPER017752

Appendix 2. Metabolife Serious Adverse Events (continued)

Address Information

Address Line 1	*Address Line*	*City*	*State*	*Zip*
	Redacted			

Recommendations

Current Water Intake oz	*Caffeine Intake*	*Current Diet*	*Increase Water*	*High Protein*	*Other Recommendations*
8	0	diabetic	☐	☐	

☐ *Ok to call back* ☐ *Do not call back* ☐ *Customer Understand Recommendati* ☐ *Eat w10min to 1hr*

☐ *Usage Guidelines Sent* ☐ *Declined Usage Guidlines* ☐ *Customer to Call Meta 1'R* ☐ *Ate After 1hr* ☐ *Did Not Eat*

Medical History

Medications	*Medical History*	*Comments*
Glucophage	Diabetes	
Glucotrol		

☐ Abdominal Pain	☐ Dizziness	☐ Irregular Heartbeat	☐ Pregnancy on BCP
☐ Abnorm Lab Values	☐ Dry Mouth	☐ Irritability	☐ Pruritis
☐ Acne	☐ Edema	☐ Joint Pain	☐ Psychosis
☐ Addiction	☐ Elevated Liver Functions	☐ Joint Stiffness- General	☐ Rash
☐ Anesthesia Complication	☐ Excitation	☐ Joint Stiffness - Local	☐ Seizure
☐ Anxiety	☐ Eye Twitching	☐ Joint Swelling - General	☐ Sexual Disfunction
☐ Back Pain	☐ Facial Swelling	☐ Joint Swelling - Local	☐ Shortness of Breath
☐ Bloating/Gas	☐ Fatigue	☐ Kidney Stones	☑ Stroke
☐ Blood in Stool	☐ Fever	☐ Liver Enzyme Elevation	☐ Sweating
☐ Blood in Urine	☐ Fluid Retention	☐ Menstrual Irregularity	☐ Tachycardia
☐ Breast Pain	☐ Glaucoma	☐ Mood Swings	☐ Tingling Hands
☐ Bruising	☐ Hair Loss	☐ Muscle Cramps -General	☐ Tinnitis
☐ Chest Pain	☐ Headache	☐ Muscle Cramps - Leg	☐ Tremors
☐ Chills	☐ Heart Burn	☐ Myocardial Infarction	☐ Urinary Infection
☐ Cold Hands	☐ High Blood Pressure	☐ Nausea	☐ Urine Retention
☐ Constipation	☐ Hives	☐ NoseBleeds	☐ Vasodilation
☐ Cough	☐ Hypertension	☐ Numbness	☐ Vision Disturbance
☐ Death	☐ Hypoglycemia	☐ Palpitations	☐ Vomiting
☐ Diarrhea	☐ Insomnia	☐ Paresthesias	☐ Yeast Infection

Other/Comments: ☐ No Weight Loss/Gain

☐ Medical Release Form Sent ☐ Customer Denies any other signs or Symptoms

Long Comments:

[redacted] 53 yr. Oldfemale reports"I had a stroke from metabolife.Iwas on it since 1 yr. Ago last Aug., MY DR. said it was due to the met."WT.228lbs. Weight-228 lbs 1yr. Ago,now 189lbs.Customer stated she was a Diabetic when she started met

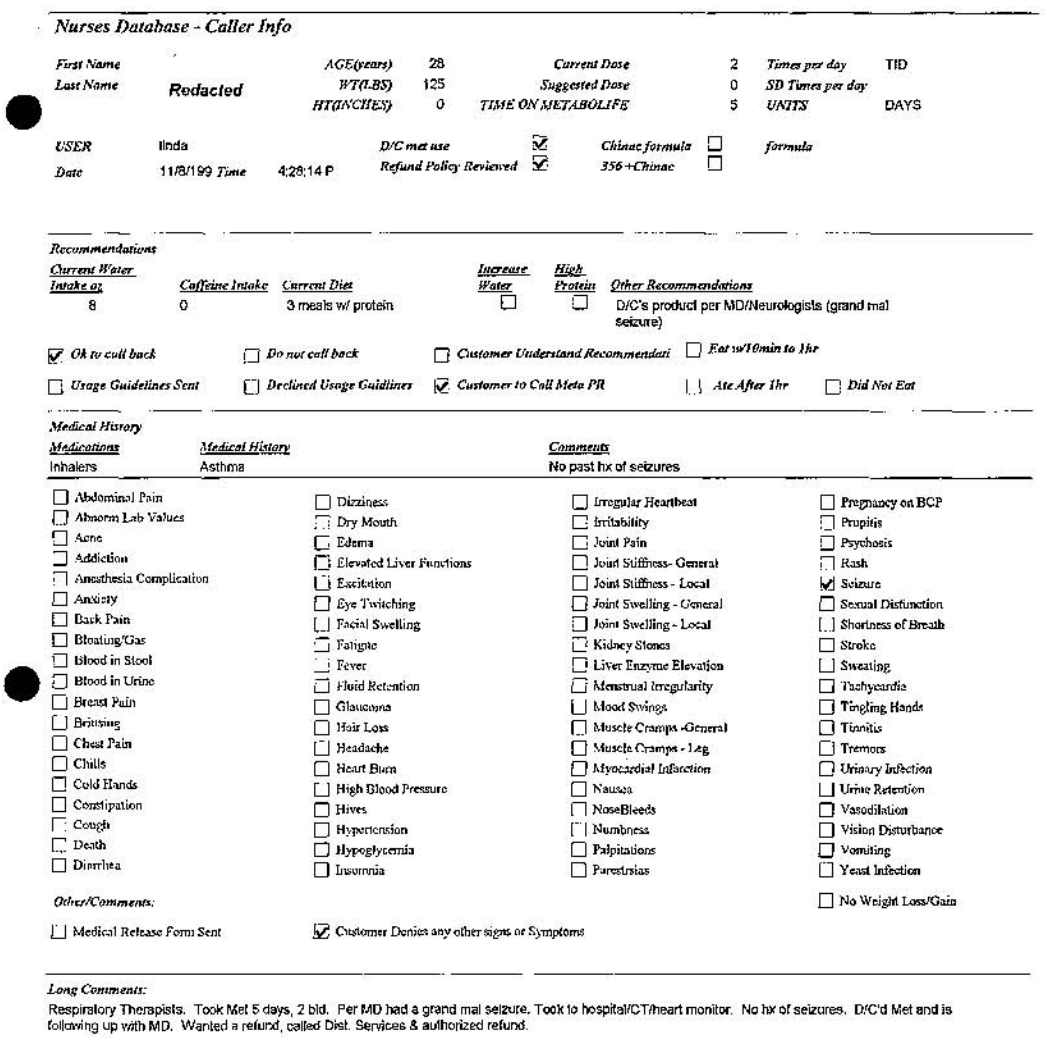
and her Dr. agreed to supervise her on it,NO hx of hypertension,both parents died of heart attacks.On Glochophage and Glucotrol,no other med's.Costomer states "I was doing well for the first few mos.The Dr. was checking my Bp and it was o.k..2 mos. Ag

o ,Istarted gaining weight and my blood sugar started going up.I was checking it at home and it went up to 168-180.I was just going to stop taking it when I started having tingling in my rt. Hand and one side of my mouth. I called the DR. went to

E.R. My bp was223/123. I got some medicine and they sent me home.I got worse and was taken to [redacted] They did a cat scan and M.R.I.The DR. Said it showed I had A minor stroke." Reports being in hospital 5 days.Residual effects-no

para'ysis,Speech not affected, experienced tingling in mouth and mild weakness Rt. Hand. Customer relayed facts in a low key manner.I told her we would be in touch with her.

Appendix 2. Metabolife Serious Adverse Events (continued)



Nurses Database - Caller Info

First Name		*AGE(years)*	28	*Current Dose*	2	*Times per day*	TID
Last Name	Redacted	*WT(LBS)*	125	*Suggested Dose*	0	*SD Times per day*	
		HT(INCHES)	0	*TIME ON METABOLIFE*	5	*UNITS*	DAYS

USER linda *D/C met use* ☑ *Chinac formula* ☐ *formula*

Date 11/8/199 *Time* 4:26:14 P *Refund Policy Reviewed* ☑ *356+Chinac* ☐

Recommendations

Current Water Intake oz	*Caffeine Intake*	*Current Diet*	*Increase Water*	*High Protein*	*Other Recommendations*
8	0	3 meals w/ protein	☐	☐	D/C's product per MD/Neurologists (grand mal seizure)

☑ *Ok to call back* ☐ *Do not call back* ☐ *Customer Understand Recommendati* ☐ *Eat w/10min to 1hr*

☐ *Usage Guidelines Sent* ☐ *Declined Usage Guidlines* ☑ *Customer to Call Meta PR* ☐ *Ate After 1hr* ☐ *Did Not Eat*

Medical History

Medications	*Medical History*	*Comments*
Inhalers	Asthma	No past hx of seizures

☐ Abdominal Pain	☐ Dizziness	☐ Irregular Heartbeat	☐ Pregnancy on BCP
☐ Abnorm Lab Values	☐ Dry Mouth	☐ Irritability	☐ Pruritis
☐ Acne	☐ Edema	☐ Joint Pain	☐ Psychosis
☐ Addiction	☐ Elevated Liver Functions	☐ Joint Stiffness- General	☐ Rash
☐ Anesthesia Complication	☐ Excitation	☐ Joint Stiffness - Local	☑ Seizure
☐ Anxiety	☐ Eye Twitching	☐ Joint Swelling - General	☐ Sexual Disfunction
☐ Back Pain	☐ Facial Swelling	☐ Joint Swelling - Local	☐ Shortness of Breath
☐ Bloating/Gas	☐ Fatigue	☐ Kidney Stones	☐ Stroke
☐ Blood in Stool	☐ Fever	☐ Liver Enzyme Elevation	☐ Sweating
☐ Blood in Urine	☐ Fluid Retention	☐ Menstrual Irregularity	☐ Tachycardia
☐ Breast Pain	☐ Glaucoma	☐ Mood Swings	☐ Tingling Hands
☐ Bruising	☐ Hair Loss	☐ Muscle Cramps -General	☐ Tinnitis
☐ Chest Pain	☐ Headache	☐ Muscle Cramps - Leg	☐ Tremors
☐ Chills	☐ Heart Burn	☐ Myocardial Infarction	☐ Urinary Infection
☐ Cold Hands	☐ High Blood Pressure	☐ Nausea	☐ Urine Retention
☐ Constipation	☐ Hives	☐ NoseBleeds	☐ Vasodilation
☐ Cough	☐ Hypertension	☐ Numbness	☐ Vision Disturbance
☐ Death	☐ Hypoglycemia	☐ Palpitations	☐ Vomiting
☐ Diarrhea	☐ Insomnia	☐ Paresthesias	☐ Yeast Infection

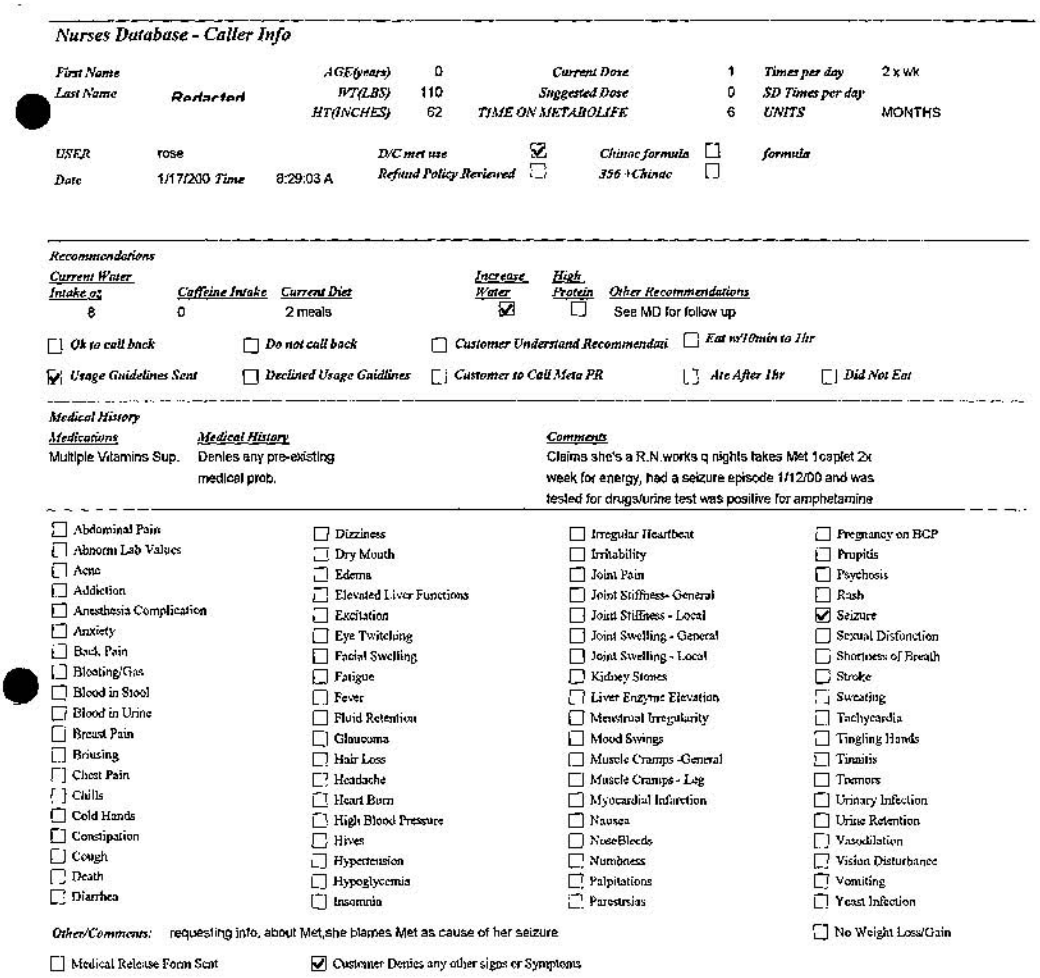
Other/Comments: ☐ No Weight Loss/Gain

☐ Medical Release Form Sent ☑ Customer Denies any other signs or Symptoms

Long Comments:

Respiratory Therapists. Took Met 5 days, 2 bid. Per MD had a grand mal seizure. Took to hospital/CT/heart monitor. No hx of seizures. D/C'd Met and is following up with MD. Wanted a refund, called Dist. Services & authorized refund.

Appendix 2. Metabolife Serious Adverse Events (continued)



Nurses Database - Caller Info

First Name		*AGE(years)*	0	*Current Dose*	1	*Times per day*	2 x wk
Last Name	Redacted	*WT(LBS)*	110	*Suggested Dose*	0	*SD Times per day*	
		HT(INCHES)	62	*TIME ON METABOLIFE*	6	*UNITS*	MONTHS

USER rose *D/C met use* ☑ *Chinae formula* ☐ *formula*

Date 1/17/200 *Time* 8:29:03 A *Refund Policy Reviewed* ☐ *356 +Chinae* ☐

Recommendations

Current Water Intake oz	*Caffeine Intake*	*Current Diet*	*Increase Water*	*High Protein*	*Other Recommendations*
8	0	2 meals	☑	☐	See MD for follow up

☐ *Ok to call back* ☐ *Do not call back* ☐ *Customer Understand Recommendati* ☐ *Eat w/10min to 1hr*

☑ *Usage Guidelines Sent* ☐ *Declined Usage Guidlines* ☐ *Customer to Call Meta PR* ☐ *Ate After 1hr* ☐ *Did Not Eat*

Medical History

Medications	*Medical History*	*Comments*
Multiple Vitamins Sup.	Denies any pre-existing medical prob.	Claims she's a R.N.works q nights takes Met 1caplet 2x week for energy, had a seizure episode 1/12/00 and was tested for drugs/urine test was positive for amphetamine

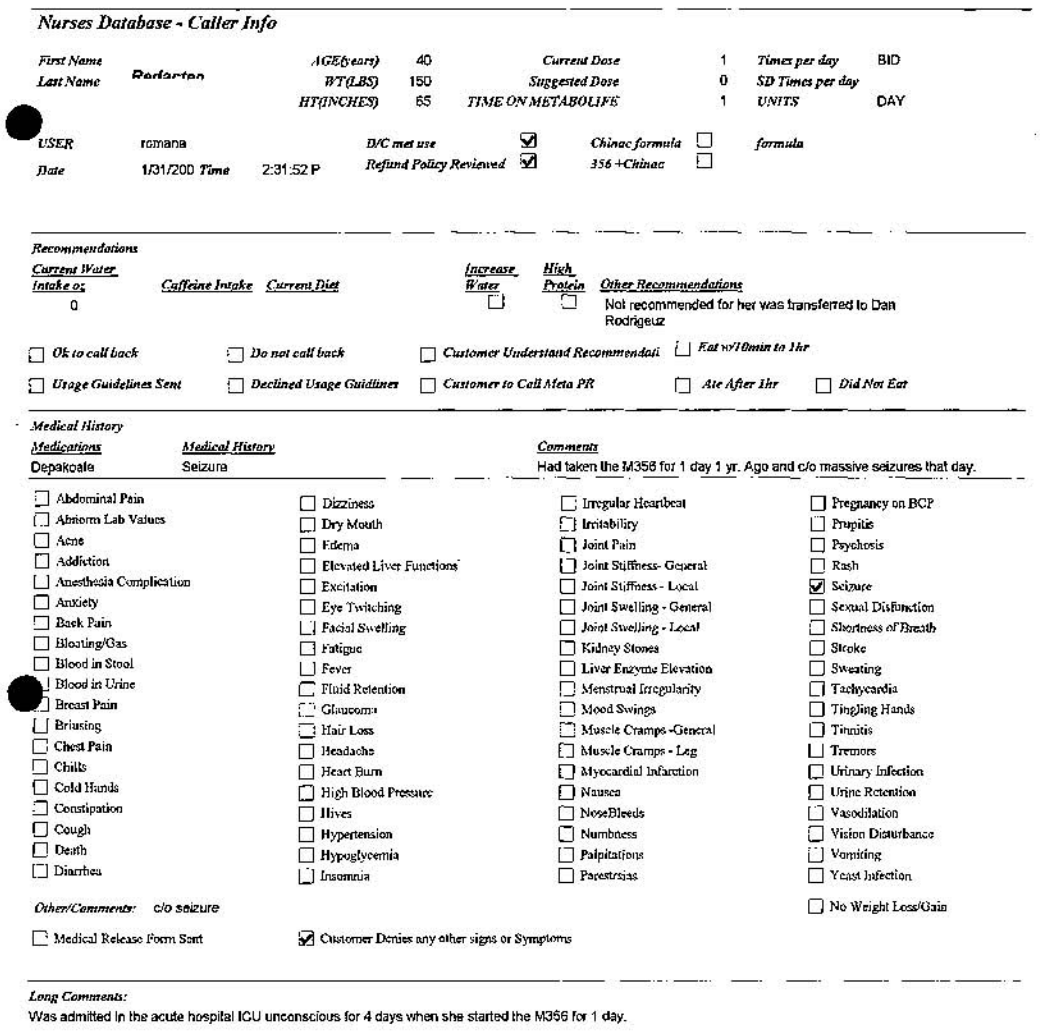
☐ Abdominal Pain	☐ Dizziness	☐ Irregular Heartbeat	☐ Pregnancy on BCP
☐ Abnorm Lab Values	☐ Dry Mouth	☐ Irritability	☐ Pupitis
☐ Acne	☐ Edema	☐ Joint Pain	☐ Psychosis
☐ Addiction	☐ Elevated Liver Functions	☐ Joint Stiffness- General	☐ Rash
☐ Anesthesia Complication	☐ Excitation	☐ Joint Stiffness - Local	☑ Seizure
☐ Anxiety	☐ Eye Twitching	☐ Joint Swelling - General	☐ Sexual Disfunction
☐ Back Pain	☐ Facial Swelling	☐ Joint Swelling - Local	☐ Shortness of Breath
☐ Bloating/Gas	☐ Fatigue	☐ Kidney Stones	☐ Stroke
☐ Blood in Stool	☐ Fever	☐ Liver Enzyme Elevation	☐ Sweating
☐ Blood in Urine	☐ Fluid Retention	☐ Menstrual Irregularity	☐ Tachycardia
☐ Breast Pain	☐ Glaucoma	☐ Mood Swings	☐ Tingling Hands
☐ Bruising	☐ Hair Loss	☐ Muscle Cramps -General	☐ Tinnitis
☐ Chest Pain	☐ Headache	☐ Muscle Cramps - Leg	☐ Tremors
☐ Chills	☐ Heart Burn	☐ Myocardial Infarction	☐ Urinary Infection
☐ Cold Hands	☐ High Blood Pressure	☐ Nausea	☐ Urine Retention
☐ Constipation	☐ Hives	☐ NoseBleeds	☐ Vasodilation
☐ Cough	☐ Hypertension	☐ Numbness	☐ Vision Disturbance
☐ Death	☐ Hypoglycemia	☐ Palpitations	☐ Vomiting
☐ Diarrhea	☐ Insomnia	☐ Paresthesias	☐ Yeast Infection

Other/Comments: requesting info, about Met,she blames Met as cause of her seizure ☐ No Weight Loss/Gain

☐ Medical Release Form Sent ☑ Customer Denies any other signs or Symptoms

CONFIDENTIAL MIPER018962

Appendix 2. Metabolife Serious Adverse Events (continued)



Nurses Database - Caller Info

First Name: Redacted
Last Name: Redacted
AGE(years): 40
WT(LBS): 150
HT(INCHES): 65
Current Dose: 1
Suggested Dose: 0
TIME ON METABOLIFE: 1
Times per day: BID
SD Times per day:
UNITS: DAY

USER: romana
Date: 1/31/200 Time: 2:31:52 P
D/C met use: ☑
Refund Policy Reviewed: ☑
Chinac formula: ☐
356 +Chinac: ☐
formula:

Recommendations

Current Water Intake oz:	Caffeine Intake	Current Diet	Increase Water	High Protein	Other Recommendations
0			☐	☐	Not recommended for her was transferred to Dan Rodrigeuz

☐ Ok to call back ☐ Do not call back ☐ Customer Understand Recommendati ☐ Eat w/10min to 1hr
☐ Usage Guidelines Sent ☐ Declined Usage Guidlines ☐ Customer to Call Meta PR ☐ Ate After 1hr ☐ Did Not Eat

Medical History

Medications	Medical History	Comments
Depakoate	Seizure	Had taken the M356 for 1 day 1 yr. Ago and c/o massive seizures that day.

☐ Abdominal Pain	☐ Dizziness	☐ Irregular Heartbeat	☐ Pregnancy on BCP
☐ Abnorm Lab Values	☐ Dry Mouth	☐ Irritability	☐ Pruritis
☐ Acne	☐ Edema	☐ Joint Pain	☐ Psychosis
☐ Addiction	☐ Elevated Liver Functions	☐ Joint Stiffness- General	☐ Rash
☐ Anesthesia Complication	☐ Excitation	☐ Joint Stiffness - Local	☑ Seizure
☐ Anxiety	☐ Eye Twitching	☐ Joint Swelling - General	☐ Sexual Disfunction
☐ Back Pain	☐ Facial Swelling	☐ Joint Swelling - Local	☐ Shortness of Breath
☐ Bloating/Gas	☐ Fatigue	☐ Kidney Stones	☐ Stroke
☐ Blood in Stool	☐ Fever	☐ Liver Enzyme Elevation	☐ Sweating
☐ Blood in Urine	☐ Fluid Retention	☐ Menstrual Irregularity	☐ Tachycardia
☐ Breast Pain	☐ Glaucoma	☐ Mood Swings	☐ Tingling Hands
☐ Bruising	☐ Hair Loss	☐ Muscle Cramps -General	☐ Tinnitis
☐ Chest Pain	☐ Headache	☐ Muscle Cramps - Leg	☐ Tremors
☐ Chills	☐ Heart Burn	☐ Myocardial Infarction	☐ Urinary Infection
☐ Cold Hands	☐ High Blood Pressure	☐ Nausea	☐ Urine Retention
☐ Constipation	☐ Hives	☐ NoseBleeds	☐ Vasodilation
☐ Cough	☐ Hypertension	☐ Numbness	☐ Vision Disturbance
☐ Death	☐ Hypoglycemia	☐ Palpitations	☐ Vomiting
☐ Diarrhea	☐ Insomnia	☐ Parestesias	☐ Yeast Infection

Other/Comments: c/o seizure

☐ No Weight Loss/Gain

☐ Medical Release Form Sent ☑ Customer Denies any other signs or Symptoms

Long Comments:
Was admitted in the acute hospital ICU unconscious for 4 days when she started the M356 for 1 day.

Appendix 2. Metabolife Serious Adverse Events (continued)

Nurses Database - Caller Info

First Name		*AGE(years)*	46	*Current Dose*	2	*Times per day*	TID
Last Name	REDACTED	*WT(LBS)*	200	*Suggested Dose*	0	*SD Times per day*	
		HT(INCHES)	0	*TIME ON METABOLIFE*	2	*UNITS*	WEEKS

USER bruce *D/C met use* ☑ *Chinac formula* ☐ *formula*

Date 4/10/200 *Time* 7:17:04 P *Refund Policy Reviewed* ☑ *356+Chinac* ☐

Address Information

Address Line 1 *Address Line* REDACTED *City* *State* *Zip*

Recommendations

Current Water Intake oz	*Caffeine Intake*	*Current Diet*	*Increase Water*	*High Protein*	*Other Recommendations*
6	2 cups coffee	toavt for brkfst, adequate lunch /dinner	☑	☑	stop do not take again

☑ *Ok to call back* ☐ *Do not call back* ☑ *Customer Understand Recommendati* ☐ *Eat w/10min to 1hr*

☐ *Usage Guidelines Sent* ☐ *Declined Usage Guidlines* ☑ *Customer to Call Meta Pit* ☐ *Ate After 1hr* ☐ *Did Not Eat*

☐ Abdominal Pain	☐ Dizziness	☐ Irregular Heartbeat	☐ Pregnancy on BCP
☐ Abnorm Lab Values	☐ Dry Mouth	☐ Irritability	☐ Prupitis
☐ Acne	☐ Edema	☐ Joint Pain	☐ Psychosis
☐ Addiction	☐ Elevated Liver Functions	☐ Joint Stiffness- General	☐ Rash
☐ Anesthesia Complication	☐ Excitation	☐ Joint Stiffness - Local	☐ Seizure
☐ Anxiety	☐ Eye Twitching	☐ Joint Swelling - General	☐ Sexual Disfunction
☐ Back Pain	☐ Facial Swelling	☐ Joint Swelling - Local	☐ Shortness of Breath
☐ Bloating/Gas	☐ Fatigue	☐ Kidney Stones	☐ Stroke
☐ Blood in Stool	☐ Fever	☐ Liver Enzyme Elevation	☐ Sweating
☐ Blood in Urine	☐ Fluid Retention	☐ Menstrual Irregularity	☐ Tachycardia
☐ Breast Pain	☐ Glaucoma	☐ Mood Swings	☐ Tingling Hands
☐ Bruising	☐ Hair Loss	☐ Muscle Cramps -General	☐ Tinnitis
☐ Chest Pain	☐ Headache	☐ Muscle Cramps - Leg	☐ Tremors
☐ Chills	☐ Heart Burn	☑ Myocardial Infarction	☐ Urinary Infection
☐ Cold Hands	☐ High Blood Pressure	☐ Nausea	☐ Urine Retention
☐ Constipation	☐ Hives	☐ NoseBleeds	☐ Vasodilation
☐ Cough	☐ Hypertension	☐ Numbness	☐ Vision Disturbance
☐ Death	☐ Hypoglycemia	☐ Palpitations	☐ Vomiting
☐ Diarrhea	☐ Insomnia	☐ Parestrasia	☐ Yeast Infection
Other/Comments:			☐ No Weight Loss/Gain

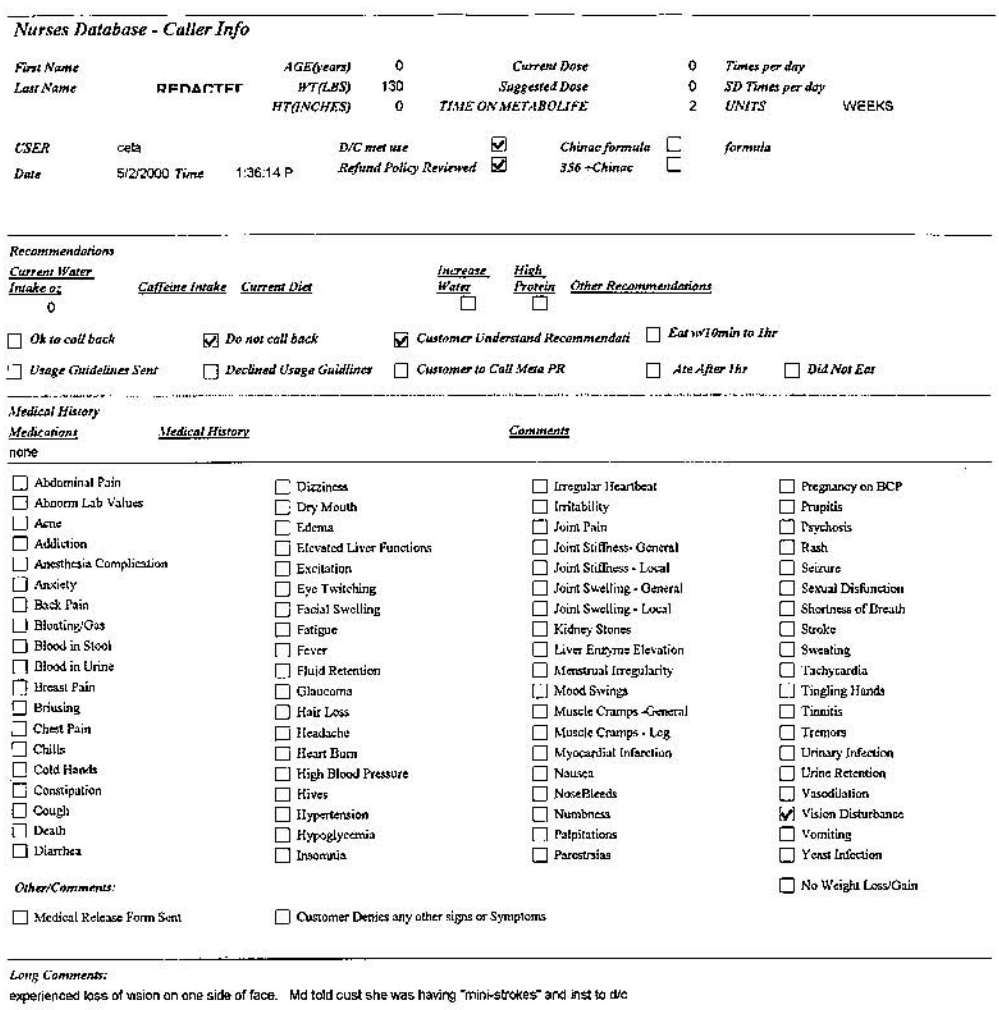
☐ Medical Release Form Sent ☐ Customer Denies any other signs or Symptoms

Long Comments:

wife calling to get refund, husband in hospital secondary MI

CONFIDENTIAL MIPER020416

Appendix 2. Metabolife Serious Adverse Events (continued)



Nurses Database - Caller Info

First Name		*AGE(years)*	0	*Current Dose*	0	*Times per day*	
Last Name	REDACTED	*WT(LBS)*	130	*Suggested Dose*	0	*SD Times per day*	
		HT(INCHES)	0	*TIME ON METABOLIFE*	2	*UNITS*	WEEKS

USER ceta *D/C met use* ☑ *Chinac formula* ☐ *formula*

Date 5/2/2000 *Time* 1:36:14 P *Refund Policy Reviewed* ☑ *356 +Chinac* ☐

Recommendations

Current Water Intake oz	*Caffeine Intake*	*Current Diet*	*Increase Water*	*High Protein*	*Other Recommendations*
0			☐	☐	

☐ *Ok to call back* ☑ *Do not call back* ☑ *Customer Understand Recommendati* ☐ *Eat w/10min to 1hr*

☐ *Usage Guidelines Sent* ☐ *Declined Usage Guidlines* ☐ *Customer to Call Meta PR* ☐ *Ate After 1hr* ☐ *Did Not Eat*

Medical History

Medications	*Medical History*	*Comments*
none		

☐ Abdominal Pain	☐ Dizziness	☐ Irregular Heartbeat	☐ Pregnancy on BCP
☐ Abnorm Lab Values	☐ Dry Mouth	☐ Irritability	☐ Pruritis
☐ Acne	☐ Edema	☐ Joint Pain	☐ Psychosis
☐ Addiction	☐ Elevated Liver Functions	☐ Joint Stiffness- General	☐ Rash
☐ Anesthesia Complication	☐ Excitation	☐ Joint Stiffness - Local	☐ Seizure
☐ Anxiety	☐ Eye Twitching	☐ Joint Swelling - General	☐ Sexual Disfunction
☐ Back Pain	☐ Facial Swelling	☐ Joint Swelling - Local	☐ Shortness of Breath
☐ Bloating/Gas	☐ Fatigue	☐ Kidney Stones	☐ Stroke
☐ Blood in Stool	☐ Fever	☐ Liver Enzyme Elevation	☐ Sweating
☐ Blood in Urine	☐ Fluid Retention	☐ Menstrual Irregularity	☐ Tachycardia
☐ Breast Pain	☐ Glaucoma	☐ Mood Swings	☐ Tingling Hands
☐ Bruising	☐ Hair Loss	☐ Muscle Cramps -General	☐ Tinnitis
☐ Chest Pain	☐ Headache	☐ Muscle Cramps - Leg	☐ Tremors
☐ Chills	☐ Heart Burn	☐ Myocardial Infarction	☐ Urinary Infection
☐ Cold Hands	☐ High Blood Pressure	☐ Nausea	☐ Urine Retention
☐ Constipation	☐ Hives	☐ NoseBleeds	☐ Vasodilation
☐ Cough	☐ Hypertension	☐ Numbness	☑ Vision Disturbance
☐ Death	☐ Hypoglycemia	☐ Palpitations	☐ Vomiting
☐ Diarrhea	☐ Insomnia	☐ Parestrsias	☐ Yeast Infection

Other/Comments: ☐ No Weight Loss/Gain

☐ Medical Release Form Sent ☐ Customer Denies any other signs or Symptoms

Long Comments:

experienced loss of vision on one side of face. Md told cust she was having "mini-strokes" and inst to d/c

CONFIDENTIAL MIPER020763

Appendix 2. Metabolife Serious Adverse Events (continued)

Nurses Database - Caller Info

First Name		*AGE(years)*	18	*Current Dose*	0	*Times per day*
Last Name	REDACTED	*WT(LBS)*	0	*Suggested Dose*	0	*SD Times per day*
		HT(INCHES)	0	*TIME ON METABOLIFE*	0	*UNITS*

USER	cat	*D/C met use*	☐	*Chinac formula*	☐	*formula*
Date	5/4/2000 *Time* 9:46:02 A	*Refund Policy Reviewed*	☐	*356+Chinac*	☐	

Medical History

Medications	*Medical History*	*Comments*
none	none	

Long Comments:

Mother , REDACTED states REDACTED had gand mal seizure last night CT scan (-). Was taking Met, but mother has no details. Instr her to bring bottle to hospital, show it to attending doctor.

CONFIDENTIAL

MIPER020812

November 23, 1999

Dear Sirs:

My name is REDACTED and my distributor number is REDACTED As per your request I am writing you this letter to inform you that I wish not to be affiliated with your company or product line in no way shape or form .

on November 21, 1999 I suffered a grand mal seizure and had to be transported to the hospital by ambulance . after undergoing a CAT scan, EKG, MRI, & EEG. and finding no apparent reason for me to start having seizures out of the blue, and the fact that my physician Has on average treated at least 5-6 new patients per week (ALL OF WHOM ARE TAKING METABOLIFE) ,and all of whom are taking your products are led to believe that it is directly caused by them.

I am 29 years old and am a non-drinker and do not use any drugs prescription or otherwise. I have no prior medical history which could account for the collapse.

as requested I am writing to let you know that I would like a full refund for all the enclosed metabolife. and would like to resign as a distributor . It is against my better judgment to continue to disperse that which could cause such terrible repercussions. I feel that I have ethic and moral responsibility to step down

I would also request that after I receive all of the rest of my test results ,and let you review them that you would do the right thing and compensate me for my pain and suffering also. I hope that we can come to some civil compromise and resolve this matter without ,bringing in outside parties (which I am Prepared to do) in a fast and courteous manner

After re-reading the label several times The only warnings I could find were if you were pregnant or nursing , high blood pressure ,heart or thyroid disease , diabetes, or prostate problems. At no place does it mention any warning to people epilepsy or any other kind of seizure

CONFIDENTIAL MIPER020864

Appendix 2. Metabolife Serious Adverse Events (continued)

METABOLIFE INTERNATIONAL, INC. ™

REPORT OF ALLEDGED EFFECT

PERSON REPORTING _____ RELATION TO CLIENT Self

CLIENT [redacted] AGE 38 WT 172# HT 5'3" PHONE [redacted]

ADDRESS [redacted]

HOSPITAL _____ ADDRESS _____

DATES OF SERVICE 9/1/99 PHYSICIAN _____

saying 9/10/99 PHONE _____

STATEMENT OF EXPERIENCE
80% "collapsed" Cor. Art main - was having chest pains → to ER → card cath. → 2 days w/ home stent placed. RN in Hosp. said other pts. had problems also + heart. Angioplasty. She has considered putting out an ad for other pts. c negative exp.

PAST MEDICAL HISTORY
PHx. PMEDS -

MEDICATIONS ANAPROX PRN MOUSES (now on numerous heart and anticoag. meds)

HERBS _____ CAFFEINE _____

VITAMINS _____ OTC _____

PRODUCT USE HISTORY tried 2 1st started in April - lost 13#

#CAPS 1-2 tbsp TIMING 1 BID DURATION 3-4 wks. WATER INTAKE 8 glasses

BREAKFAST ate fruit, LUNCH sandwich DINNER chicken ↓ appetite

PREVIOUS RECOMMENDATIONS BY: DISTRIBUTOR _____ HEALTHLINE _____ OTHER _____

REPORT TAKEN BY [signature] DATE 10/11/99 TIME 1500

FAX MED. RELEASE FOR DOCS. : call her back w/ wk of docs recd.

CONFIDENTIAL

MIPER020918

REDA

ATTORNEYS AT LAW
A Professional Corporation

REDA

To Anorita / From Glenn Pack

REDA

REDA

May 13, 1998

Metabolife International, Inc.
5070 Santa Fe Street
San Diego, CA 92109

CERTIFIED MAIL RETURN
RECEIPT REQUESTED

REDA

Makes Cents
Metabolife Independent Distributors

CERTIFIED MAIL RETURN
RECEIPT REQUESTED

REDA

REDA

Dear Sir or Madam:

Please be advised that I have been hired by REDA to represent her in regard to a claim for personal injuries arising out of her use of the Metabolife product which she purchased from the REDA , location on May 6, 1998. The drug caused REDA to have a series of seizures. The first seizure occurred while REDA REDA REDA control of her automobile and it left the roadway injuring REDA her daughter-in-law and her grandchild. REDA subsequently had two additional seizures. REDA has received medical care and is off work and prohibited from driving. According to REDA REDA physicians, REDA may have further seizures in the future.

REDA has no history of seizures and no significant medical history. According to REDA physicians, it was your drug that caused her to go into seizure.

Please have your attorney, claims representative or insurance company contact me in regard to this matter.

Sincerely,

REDA

REDA

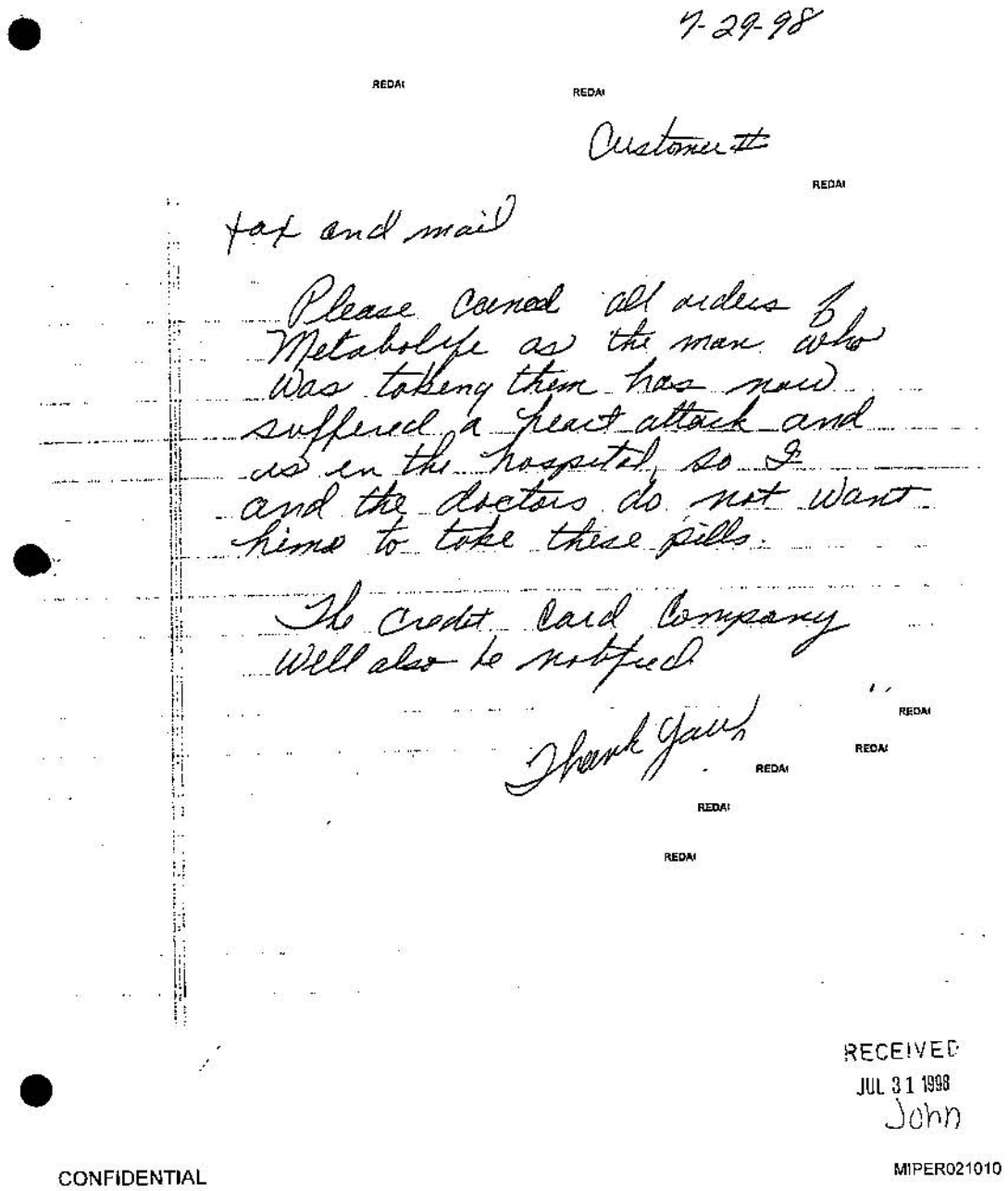
REDA

REDA

To Anorita, This is very upsetting to He tried to get someone to return his call at 2 o'clock yesterday Nobody called him back Can we please talk to him

CONFIDENTIAL MIPER020979

Appendix 2. Metabolife Serious Adverse Events (continued)



7-29-98

REDAI

REDAI

Customer #

REDAI

fax and mail

Please cancel all orders for Metabolife as the man who was taking them has now suffered a heart attack and is in the hospital so he and the doctors do not want him to take these pills.

The credit card company will also be notified

Thank you

REDAI

REDAI

REDAI

REDAI

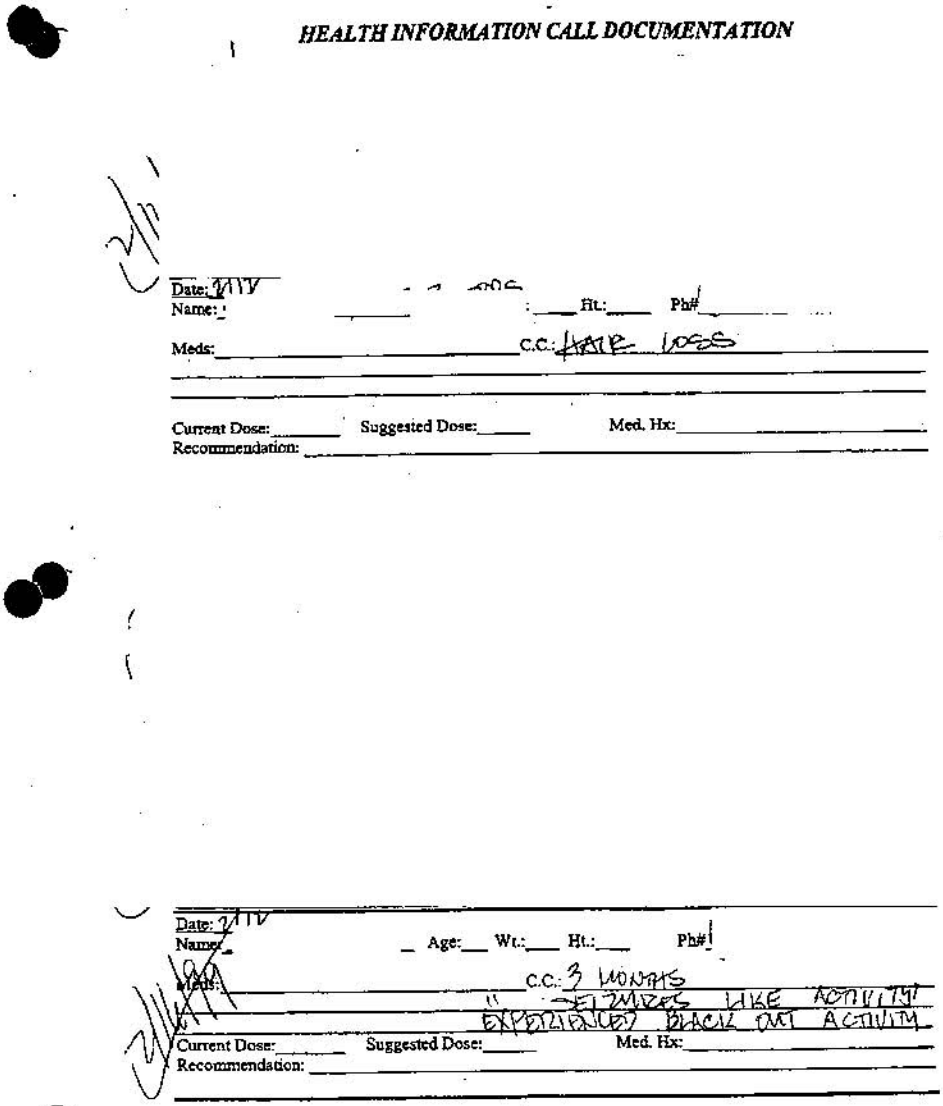
REDAI

RECEIVED
JUL 31 1998
John

CONFIDENTIAL

MIPER021010

Appendix 2. Metabolife Serious Adverse Events (continued)

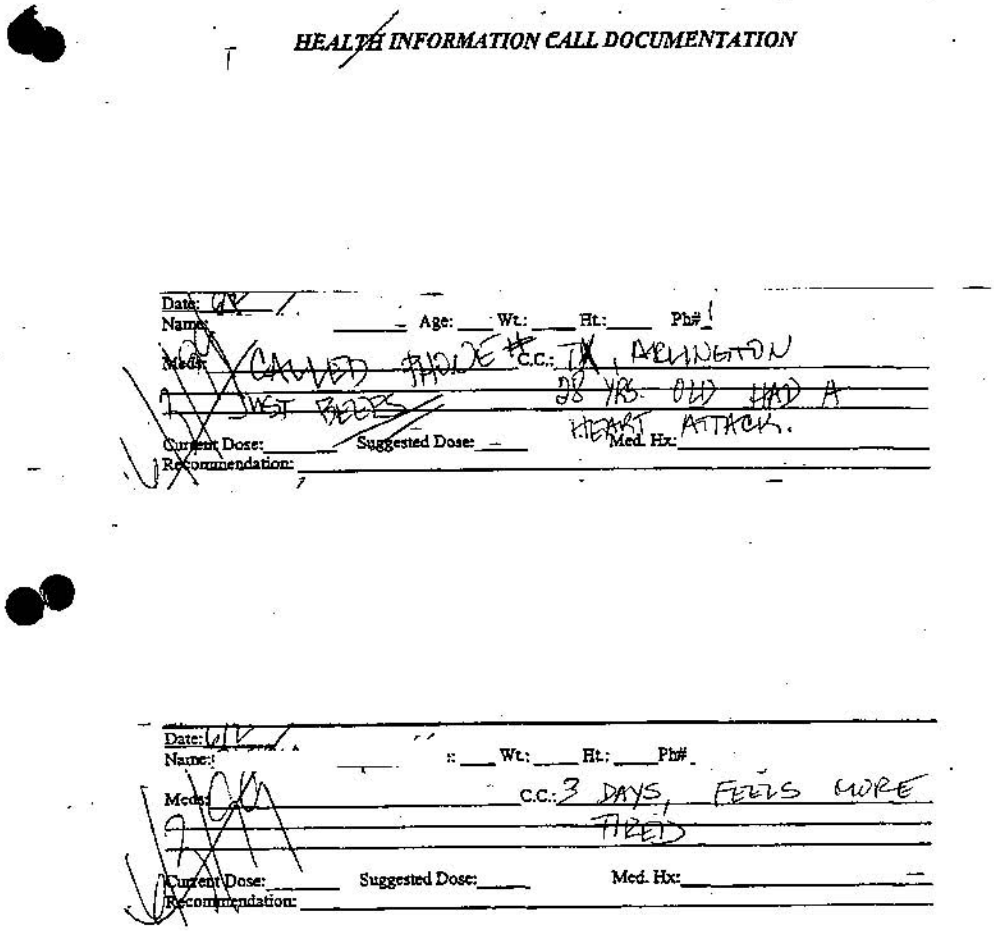


HEALTH INFORMATION CALL DOCUMENTATION

Date: 2/11/
Name: _____ Ht.:____ Ph#_____
Meds: _____ C.C.: HAIR LOSS
Current Dose:_____ Suggested Dose:_____ Med. Hx:_____
Recommendation: _____

Date: 2/11/
Name: _____ Age:___ Wt.:___ Ht.:___ Ph#:
Meds: _____ C.C.: 3 MONTHS
" SEIZURES LIKE ACTIVITY
EXPERIENCED BLACK OUT ACTIVITY
Current Dose:_____ Suggested Dose:_____ Med. Hx:_____
Recommendation: _____

Appendix 2. Metabolife Serious Adverse Events (continued)



HEALTH INFORMATION CALL DOCUMENTATION

Date: 4/8/
Name: _____ Age: ___ Wt: ___ Ht: ___ Ph#
Meds: CALLED 911 C.C.: TX, ARLINGTON
1 JUST FEELS 28 YRS. OLD HAD A
HEART ATTACK.
Current Dose: _____ Suggested Dose: ___ Med. Hx: _____
Recommendation: _____

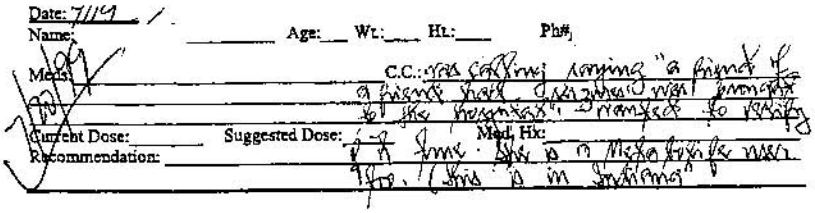
Date: 4/8/
Name: _____ Age: ___ Wt: ___ Ht: ___ Ph#
Meds: C.C.: 3 DAYS, FEELS MORE
TIRED
Current Dose: _____ Suggested Dose: ___ Med. Hx: _____
Recommendation: _____

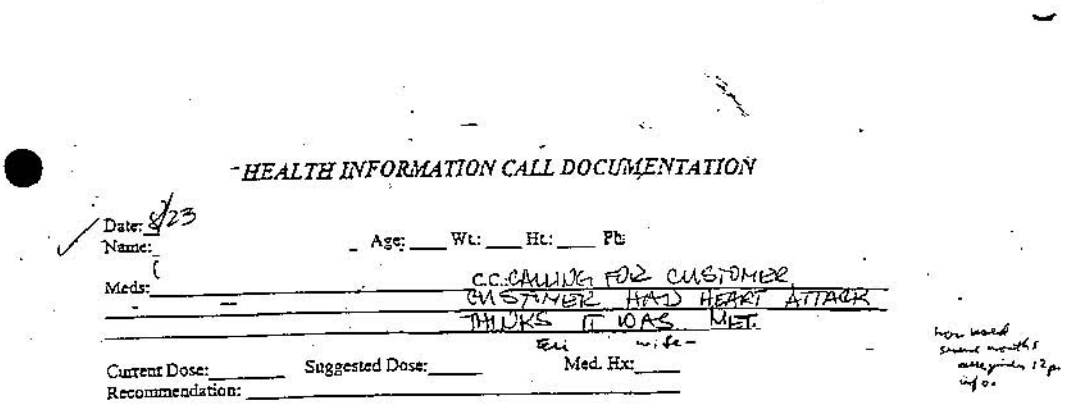
CONFIDENTIAL
CONFIDENTIAL & NON RESPONSIVE REDACTION

MIPER022492

Appendix 2. Metabolife Serious Adverse Events (continued)

HEALTH INFORMATION CALL DOCUMENTATION





HEALTH INFORMATION CALL DOCUMENTATION

Date: 8/23
Name: _____ Age: ___ Wt: ___ Ht: ___ Ft:
Meds: C.C. CALLING FOR CUSTOMER
CUSTOMER HAD HEART ATTACK
THINKS IT WAS MET.
Eri wife
Current Dose: _____ Suggested Dose: _____ Med. Hx: ____
Recommendation: _____

how much
same months
ago
info.

CONFIDENTIAL
CONFIDENTIAL & NON RESPONSIVE REDACTION

MIPER022584

Appendix 2. Metabolife Serious Adverse Events (continued)

1-20-99

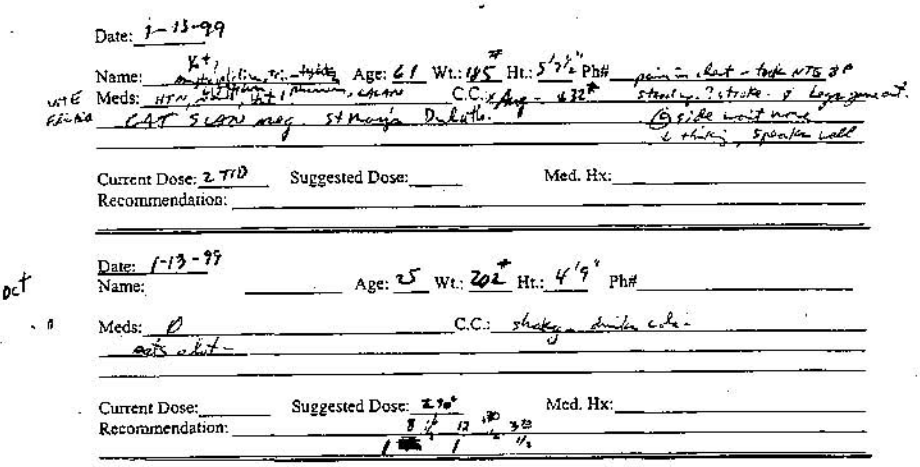
HEALTH INFORMATION CALL DOCUMENTATION

Date:__
Name:_ Age: ___ Wt.: ___ Ht.: ___ Ph#_
Meds:_ C.C.: Mo Hearing - (seizures)
Current Dose:_____ Suggested Dose:_____ Med Hx:_____
Recommendation:_____

CONFIDENTIAL
CONFIDENTIAL & NON RESPONSIVE REDACTION

MIPER022800

Appendix 2. Metabolife Serious Adverse Events (continued)



Date: 1-13-99
Name: [redacted] Age: 61 Wt.: 185# Ht.: 5'7½" Ph#
Meds: [redacted] C.C.:
CAT SCAN neg. St Marys Duluth.

Current Dose: 2 TID Suggested Dose: Med. Hx:
Recommendation:

Date: 1-13-99
Name: [redacted] Age: 25 Wt.: 202# Ht.: 4'9" Ph#
Meds: 0 C.C.:

Current Dose: Suggested Dose: Med. Hx:
Recommendation:

Appendix 2. Metabolife Serious Adverse Events (continued)

HEALTH INFORMATION CALL DOCUMENTATION

Recommendation: _____

Date: 1-22-
Name: _____ Age: ___ Wt.: ___ Ht.: ___ Ph _____
Meds: on b/p meds Thyroid #CT2 C.C.: 6/98 had mini stroke b/p & KL DT cycled.
$50 refund
Ka# 122 DJR will see neurologist
1 otc submitted bugs.
Current Dose: _____ Suggested Dose: _____ Med. Hx: _____
Recommendation: _____

CONFIDENTIAL
CONFIDENTIAL & NON RESPONSIVE REDACTION

MIPER022325

Appendix 2. Metabolife Serious Adverse Events (continued)

HEALTH INFORMATION CALL DOCUMENTATION

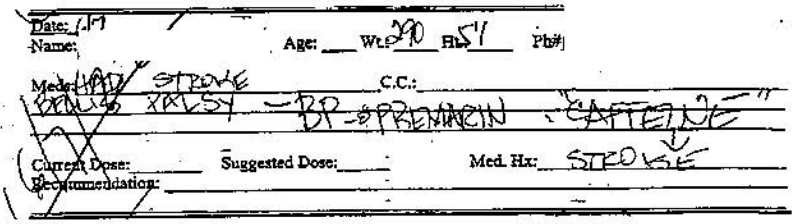
Date: 1/25/
Name: Age: ___ Wt: ___ Ht: ___ Pt
DOB: 35194
Med: C.C.: TRANSFERRED TO DAN
LEGAL HISTORY THAT HAD
1 STROKES - LAWYERS
Current Dose: _____ Suggested Dose: _____ Med. Hx: _____
Recommendation: _____

CONFIDENTIAL
CONFIDENTIAL & NON RESPONSIVE REDACTION

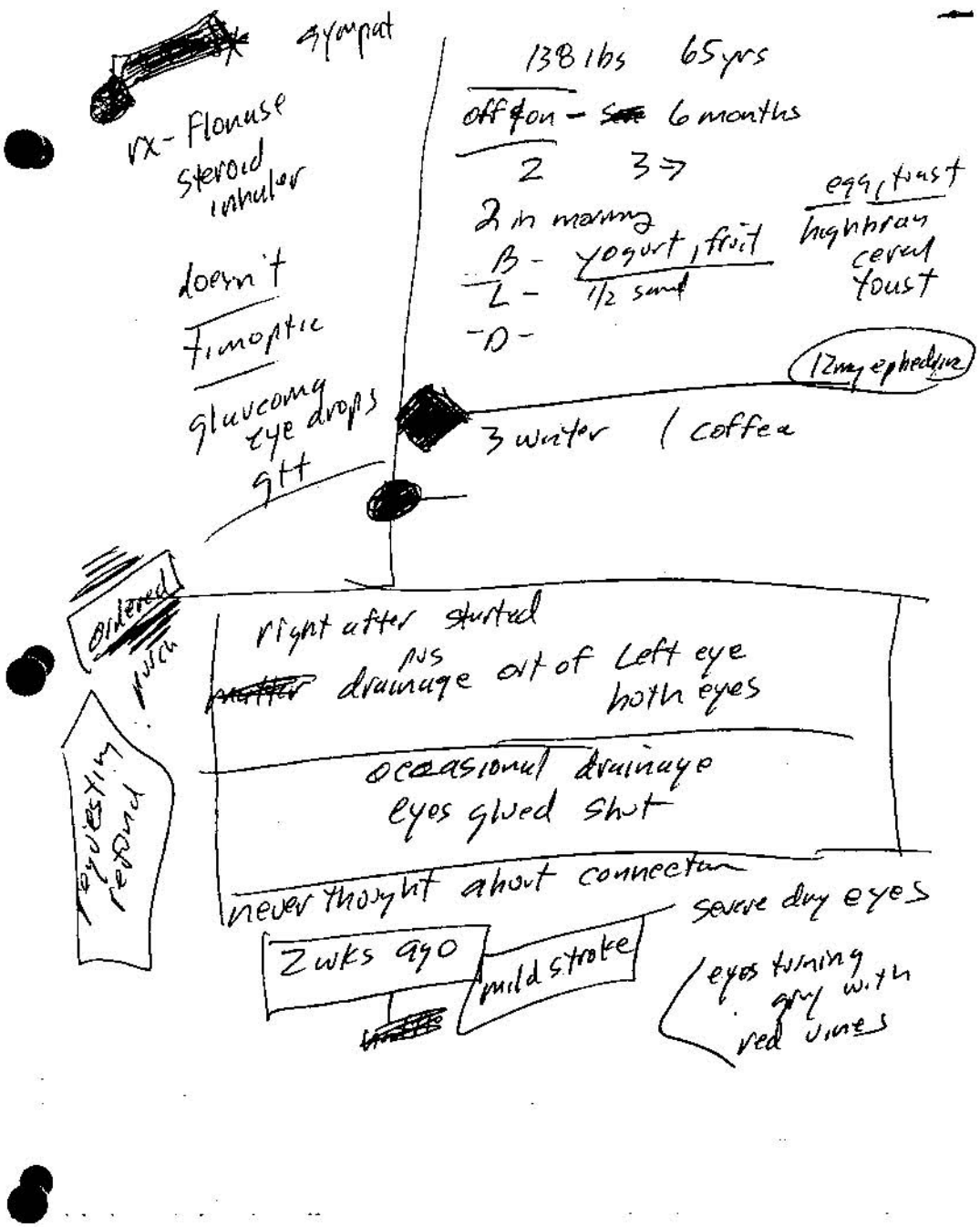
MIPER022479

Appendix 2. Metabolife Serious Adverse Events (continued)

HEALTH INFORMATION CALL DOCUMENTATION



Appendix 2. Metabolife Serious Adverse Events (continued)



HEALTH INFORMATION CALL DOCUMENTATION

5/2/00

Date: 5/18

Name:

Age: ___ Wt: ___ Ht: ___

Meds: TRANSFERED TO DAN

DAUGHTER HAD A SEIZURE, SAW THE SEGMENT ON 20/20 AND SHE

Current Dose: ___ Suggested Dose: ___

Recommendations: ___

Med. Hx: CALLED 20/20 GAVE HER PHONE NUMBER.

Sent

MIPER023029

1/14

HEALTH INFORMATION CALL DOCUMENTATION talked c̄

Date:
Name: Wt.: Ht.: Ph.

Meds: C.C.: off Met x 2 wks

sister - grand mal seizure this eve - Met since Sept. MD say drug-related.

Current Dose: Suggested Dose: Med. Hx:
Recommendation: took ~~ Metabolite same day of seizure

UA

Meds: C.C.: heartburn

Current Dose: Suggested Dose: Med. Hx:
Recommendation:

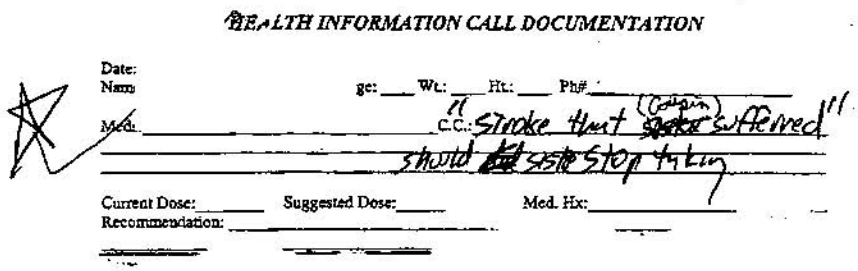
Date:
Name: Age: Wt.: Ht.: Ph#

Meds: C.C.:

Current Dose: Suggested Dose: Med. Hx:
Recommendation:

MIPER023468

Appendix 2. Metabolife Serious Adverse Events (continued)



HEALTH INFORMATION CALL DOCUMENTATION

Date:
Name ge: Wt.: Ht.: Ph#
Med: C.C.: "Stroke Hurt (Cousin) suffered"
should stop taking

Current Dose: Suggested Dose: Med. Hx:
Recommendation:

CONFIDENTIAL
REDACTED

MIPER023663

Appendix 2. Metabolife Serious Adverse Events (continued)

Joe

HEALTH INFORMATION CALL DOCUMENTATION
DATE

Name_____ Age_____ Weight_____ Phone#_____
# of caps qd_____ Timing_____ Duration 1 ER
Side effect? migraine HA Breakfast intake_____
Lunch_____
Dinner_____
Water intake_____ Caffeine/alcohol intake_____
Medications_____ Medical history/similar symptoms_____
# of bottles_____ Lot #_____
Recommendations_____ united airlin (sister's husb died)

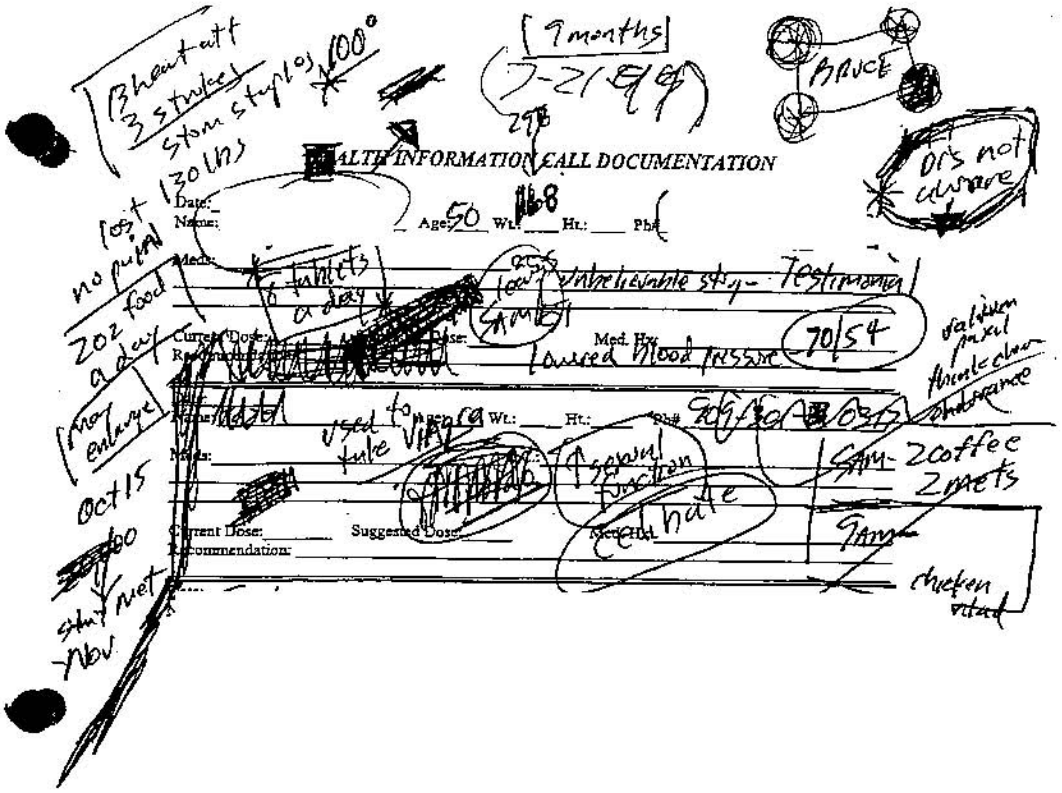
Name_____ Age_____ Weight_____ Phone#_____
# of caps qd_____ Timing_____ Duration_____
Side effect?_____ Breakfast intake_____
Lunch_____
Dinner_____
Water intake_____ Caffeine/alcohol intake_____
Medications_____ Medical history/similar symptoms_____
Lot #_____ # of bottles_____
Recommendations_____

Name_____ Age_____ Weight_____ Phone#_____
# of caps qd_____ Timing_____ Duration_____
Side effect?_____ Breakfast intake_____
Lunch_____
Dinner_____
Water intake_____ Caffeine/alcohol intake_____
Medications_____ Medical history/similar symptoms_____
Lot #_____ # of bottles_____

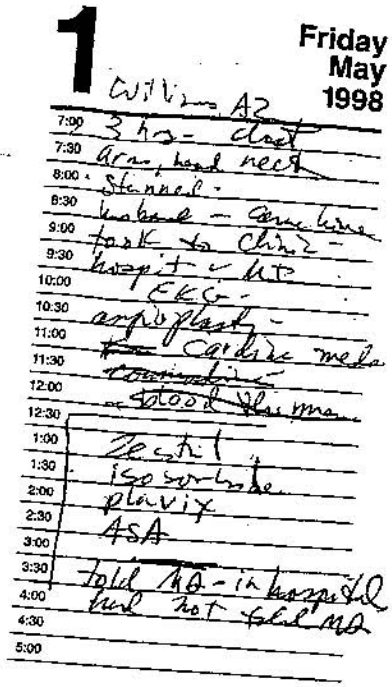
CONFIDENTIAL
CONFIDENTIAL & NON RESPONSIVE REDACTION

MIPER023695

Appendix 2. Metabolife Serious Adverse Events (continued)



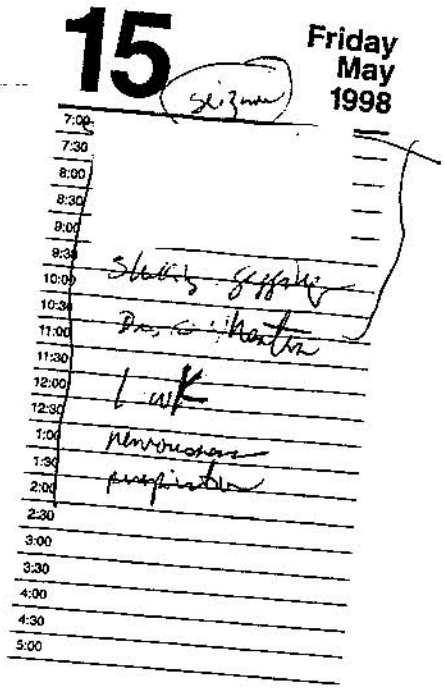
Appendix 2. Metabolife Serious Adverse Events (continued)



CONFIDENTIAL
REDACTED

MIPER024166

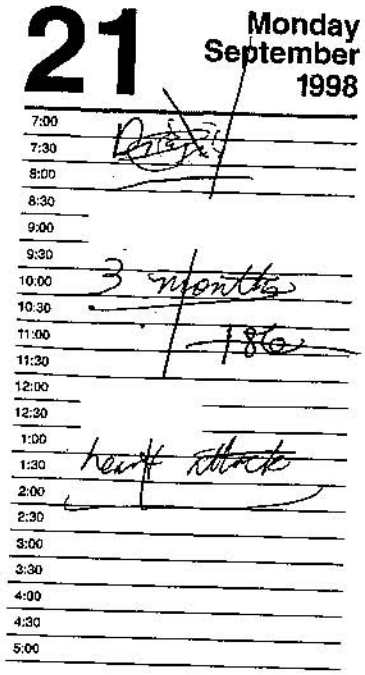
Appendix 2. Metabolife Serious Adverse Events (continued)



CONFIDENTIAL
REDACTED

MIPER024172

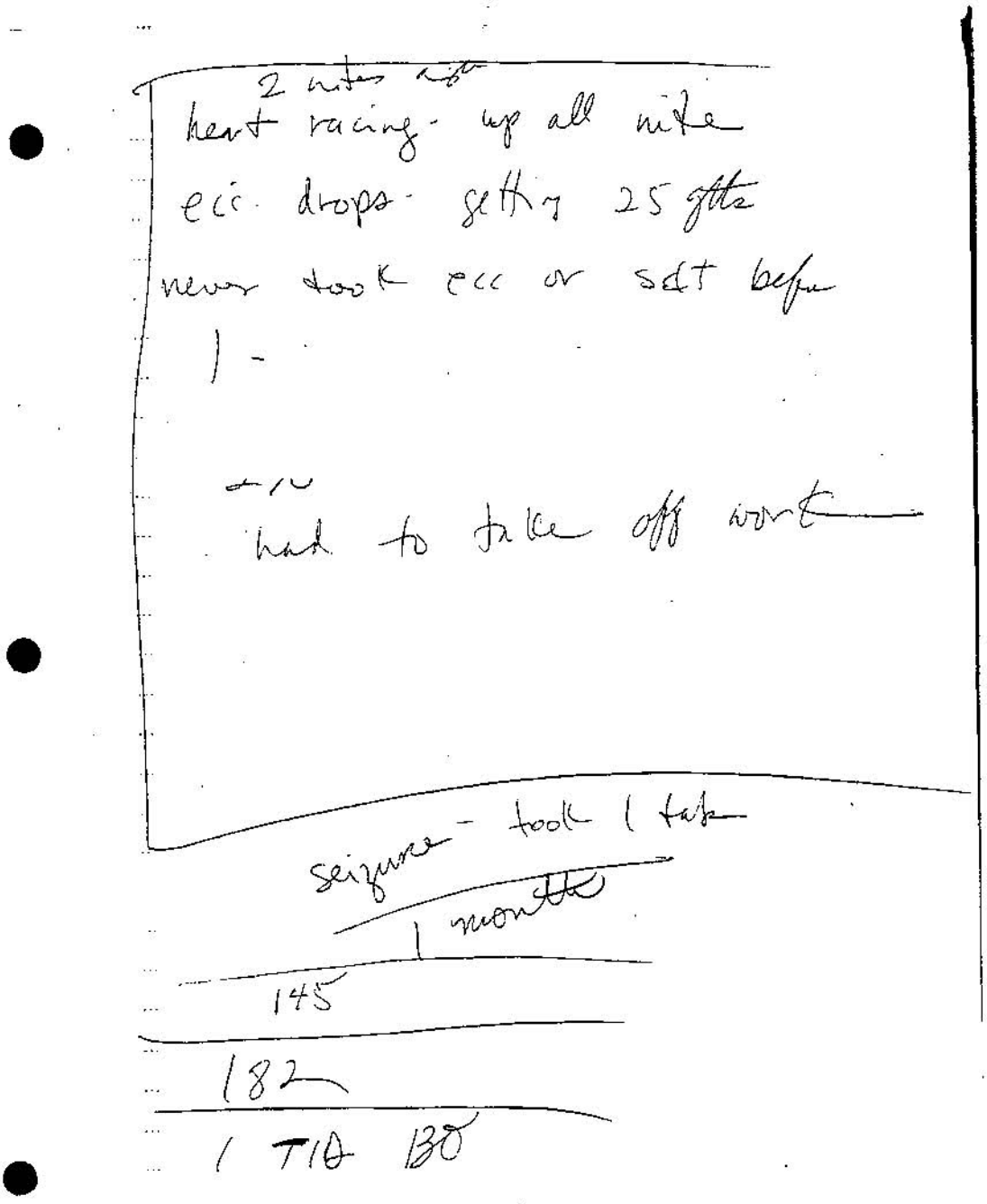
Appendix 2. Metabolife Serious Adverse Events (continued)



CONFIDENTIAL
REDACTED

MIPER024236

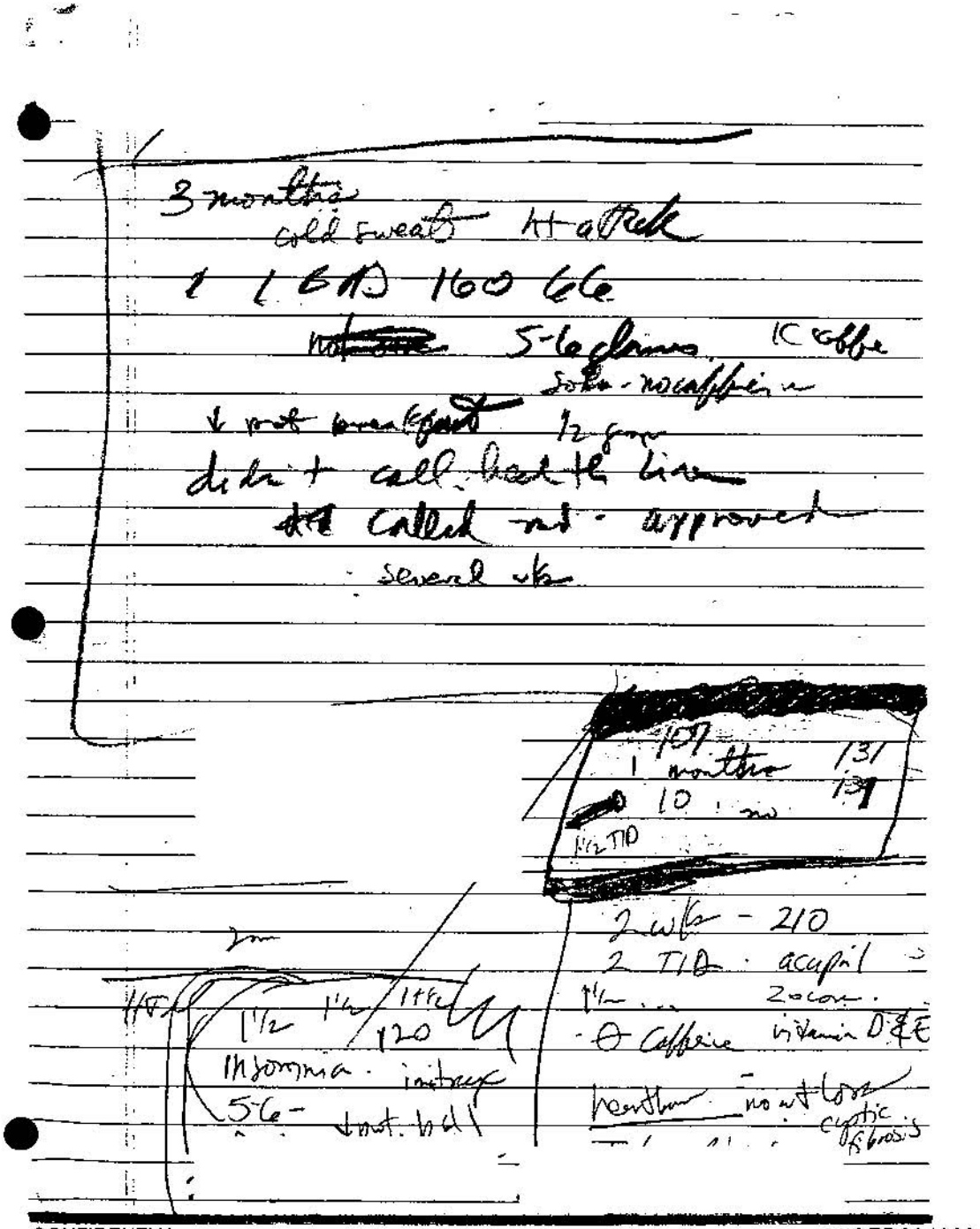
Appendix 2. Metabolife Serious Adverse Events (continued)


2 mths ago
heart racing - up all night
ecc drops - setting 25 gifts
never took ecc or sat before
1 -

-10
had to take off work

seizure - took 1 tab
1 month
145
182
1 TID 130

Appendix 2. Metabolife Serious Adverse Events (continued)



CONFIDENTIAL
CONFIDENTIAL & NON RESPONSIVE REDACTION

MIPER024383

Appendix 2. Metabolife Serious Adverse Events (continued)

HEALTH INFORMATION CALL DOCUMENTATION
DATE

Name_____Age_____Weight_____Phone#_
Chief complaint Heart attack?
#of caps qd_____Timing_____D
Meals/snacks_____
Water intake_____Caffeine intake_____
Medications_____Medical history/similar symptoms_____
Exercise_____Other pertinent info_____
Recommendations_____

CONFIDENTIAL
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MIPER024448

Appendix 2. Metabolife Serious Adverse Events (continued)

HEALTH INFORMATION CALL DOCUMENTATION

Date: 6-1
Name:
Age: 56 Wt: 151 Ht: 5'2" F/M
5/16 Meds: Estrin [illegible] Propulsid [illegible] C.C.: bloating, constipation x 4 days
water 3-4 [illegible] caffeine 3 meals
Current Dose: 1 B/D Suggested Dose: Med. Hx: Hiatal hernia MD is aware
Recommendation: decrease the amount or [illegible] take with food [illegible]
-1 C.A.M.

Date: 6
Name:
Age: 29 Wt: 170 Ht: 5'4" F/M
Meds: ∅ C.C.: convulsion [illegible] 2 day
water [illegible] ∅ caffeine 3 meals
— wants refund
Current Dose: 1 TID Suggested Dose: Med. Hx: ∅ MD not aware
Recommendation: refer to requests [illegible] [illegible]

Date: 6
Name:
Age: 32 Wt: 198 Ht: 5'7" F/M
4/21 Meds: BCP C.C.: [illegible] [illegible] [illegible]
water 2 liters ∅ caffeine 3 meals [illegible]
stop [illegible] 4 days [illegible] [illegible]
Current Dose: 2-1-1 Suggested Dose: d/c [illegible] Med. Hx: ∅ MD is aware [illegible]
Recommendation: [illegible] d/c [illegible] [illegible]
[illegible] until further test done [illegible]

Date: 6
Name:
Age: 59 Wt: 140 Ht: 4'10" F/M
Meds: Coumadin, Lipitor C.C.: [illegible] level low was hospitalized
water 1/2 gallon, coffee 2 soda 1 3 meals
[illegible] refund
Current Dose: 2 TID Suggested Dose: Med. Hx: [illegible] MD not aware
Recommendation: [illegible] is 30 days. Refund requests submitted to [illegible]

Appendix 2. Metabolife Serious Adverse Events (continued)

HEALTH INFORMATION CALL DOCUMENTATION

Date: 4/19

Name: Age: ___ Wt: ___ Ht: ___

Med: TRANSFERED TO DAN — C.C: HER HUSBAND TOOK MET. 2 MONTHS - OCT. 99 — EVER SINCE THEN HE HAS SUFFERING FROM SEIZURES. HEMATOLOGIST SAYS IT RAMBLE MET. — OK.

Current Dose: ___ Suggested Dose: ___

Recommendation: ___

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MIPER024711

Appendix 2. Metabolife Serious Adverse Events (continued)

Date 9/28/98 **Medical Log Notes**

(1873)

Name [redacted]
Phone _____
Age 23
Weight 135#
Height 5'6
Medications Ø

Gender ☐ Male ☒ Female

Chief Complaint

1. No Weight Loss
☐ Underdosing ☐ Med. Conflict
☐ Dehydration ☐ Other _____

2. Side Effects
☐ Jitteriness/Nervousness ☐ Insomnia
☐ Cramping ☐ GI Disturbance
☐ Other _____

Medical History 6mo's - Stroke - last week - MD's said Methuang.
lost 30-35#

Conclusion/Recommendations: _____

Current Dosage 6/D Recommended Dosage _____

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MIPER024825

Appendix 2. Metabolife Serious Adverse Events (continued)

Glenda Aspholm

From:
Sent: Monday, April 27, 1998 6:39 PM
To: info@metabolife.com
Subject: Medical Complication

Importance: High

At 4:30 am on 4/27/98 my wife had a grand mal seizure. After admission to the emergency room of a near by hospital and several test the doctors came to the conclusion that your product was the only likely factor since she had no history of seizures or head injuries. I cannot stress enough the fear I experienced from her sudden convulsions that awakened me in the early morning hours, for I was sure she was experiencing a fatal stroke or cerebral hemorrhage. Another alarming revolation at the hospital was that Metabolife showed up as an amphetamine in her urinalysis. Please help us by providing any detailed testing on your product and any know side effects that have been reported, especially any similar to our experience. I'm am well aware of the legality of your product so please don't hide behind this, help us, her experience could occur again.

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REDACTED

MIPER024839

6-23-98

I took your products
for six weeks &
landed up having a
Heart attack. Doctor
took the label off
to check it out &
said it speeds up
your Heart & don't
take it again. Can
I get a Refund

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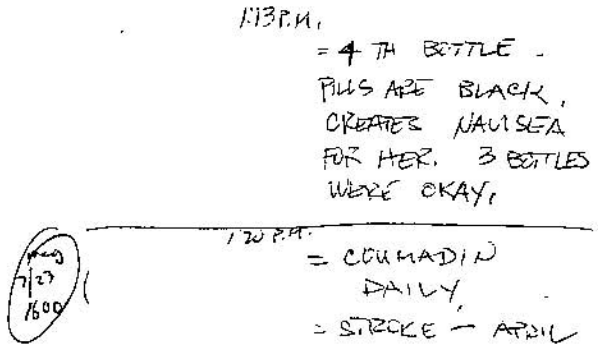
MIPER024859


1:13 P.M.
= 4 TH BOTTLE -
PILLS ARE BLACK,
CREATES NAUSEA
FOR HER. 3 BOTTLES
WERE OKAY,
1:20 P.M.
= COUMADIN
DAILY,
= STROKE — APRIL
7/27
1600

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MIPER024945

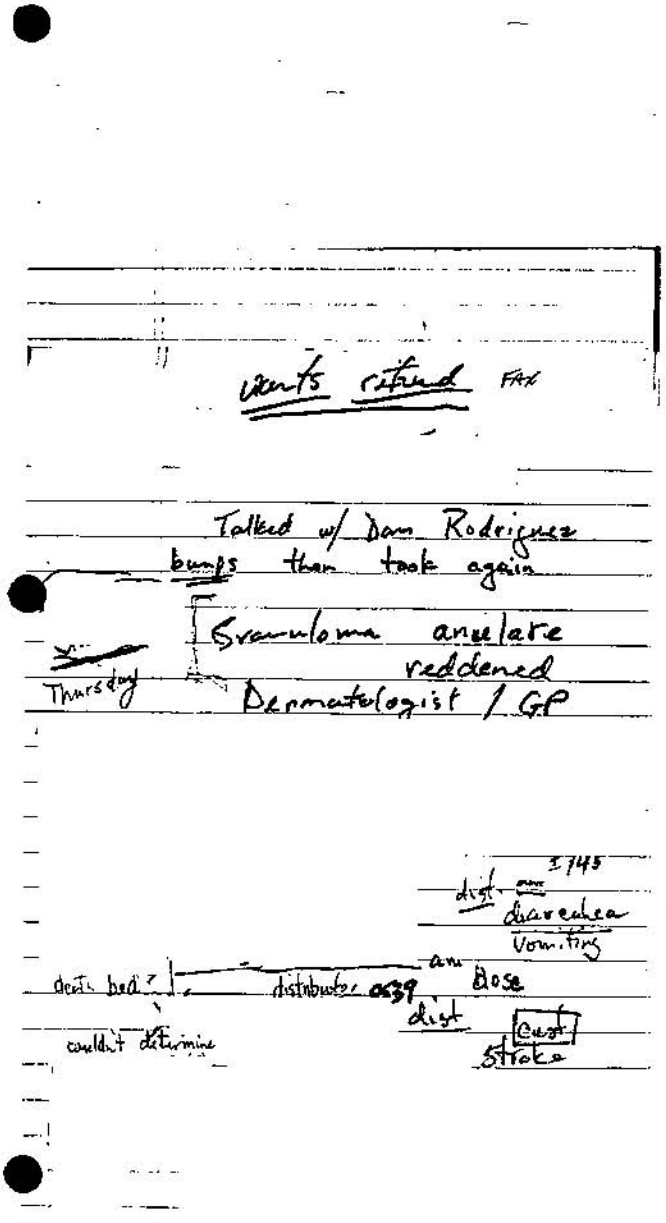
seizures

↓ energy ↓ wt loss

CONFIDENTIAL
CONFIDENTIAL & NON RESPONSIVE REDACTION

MIPER024947

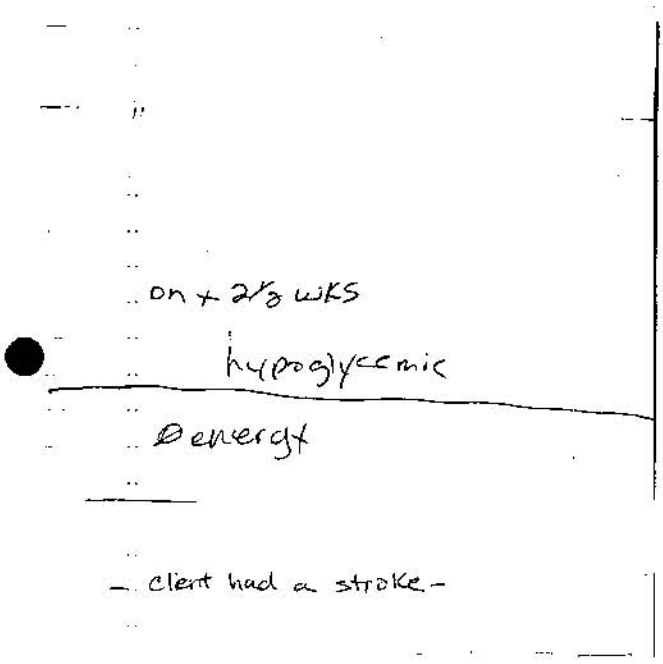
Appendix 2. Metabolife Serious Adverse Events (continued)



CONFIDENTIAL
CONFIDENTIAL & NON RESPONSIVE REDACTION

MIPER025011

Appendix 2. Metabolife Serious Adverse Events (continued)



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MIPER025147

3/20/98

✓ ?doment. seizure – BCP – anti dep.
seizure disorder – Passed out.

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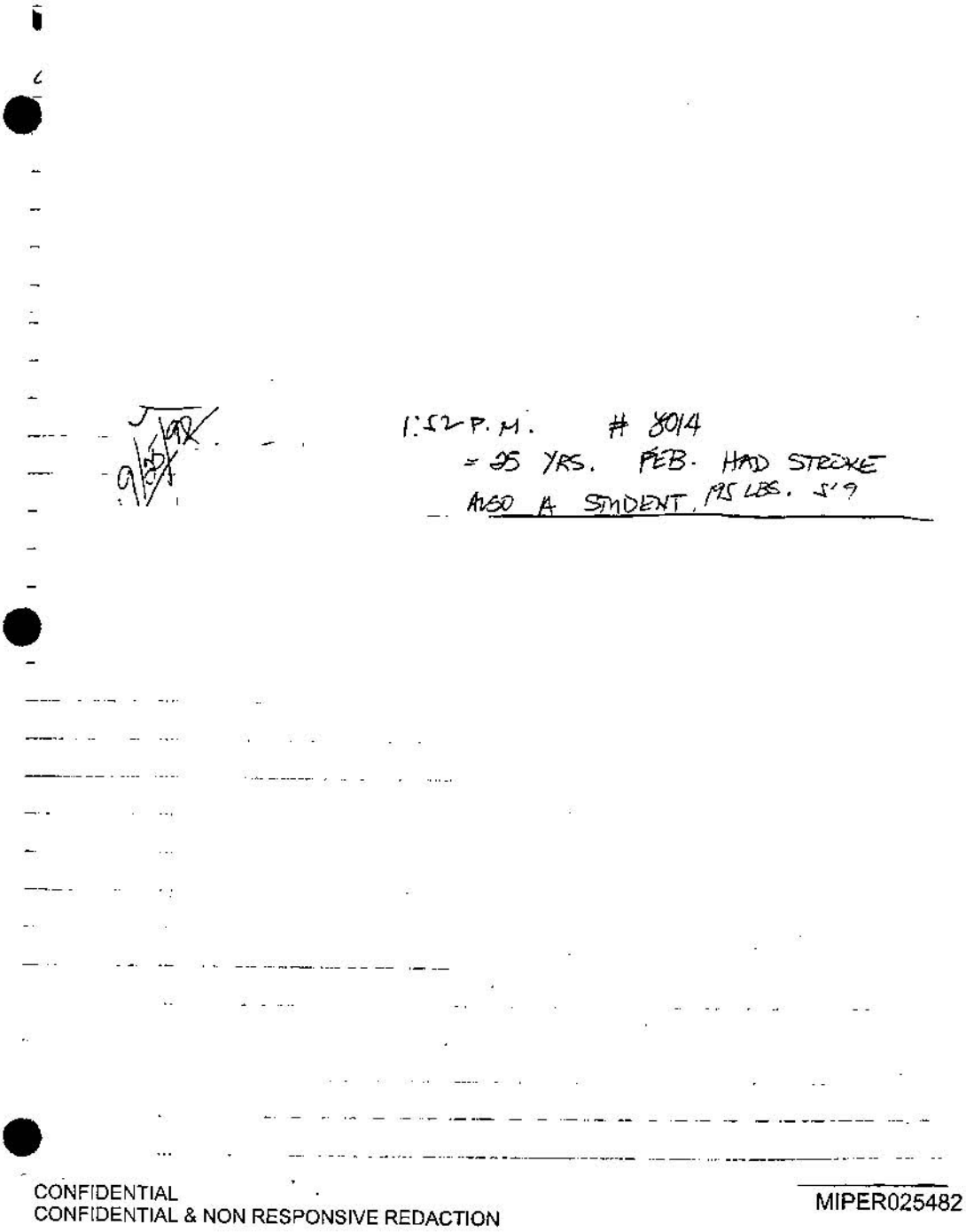
CONFIDENTIAL & NON RESPONSIVE REDACTION

MIPER025371

Appendix 2. Metabolife Serious Adverse Events (continued)


1:52 P.M. # 8014
= 25 YRS. FEB. HAD STROKE
ALSO A SMOKER, 195 LBS. 5'9

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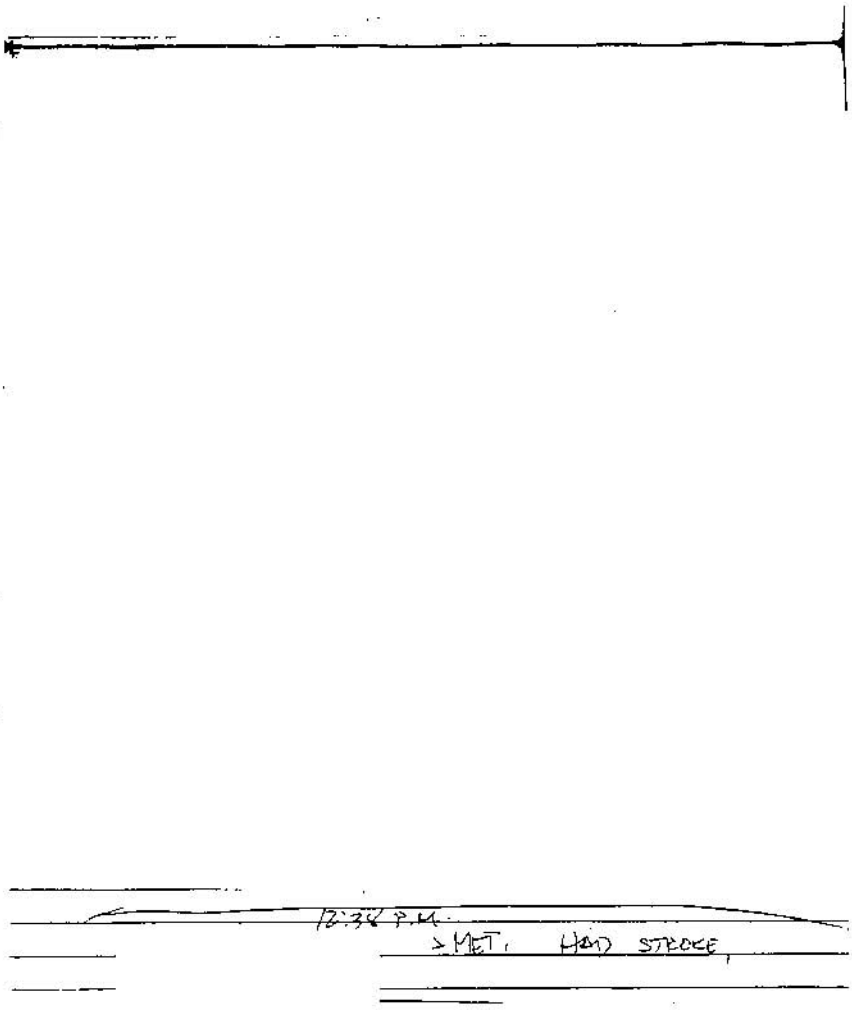
CONFIDENTIAL & NON RESPONSIVE REDACTION

MIPER025482

Appendix 2. Metabolife Serious Adverse Events (continued)



CONFIDENTIAL
CONFIDENTIAL & NON RESPONSIVE REDACTION

MIPER025495

O'CONNOR
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Attorneys at Law

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Marissa L. Godby
Jim L. Hardin
Michael A. O'Hara*
Elizabeth M. Zucker
Scott A. Greiner
Jon J. Lieberman*
Lynn A. Lape
Cliff G. Linn**
Tammy D. Gifford

*also admitted in Kentucky
*Also admitted in W. Virginia
**also admitted in N. Carolina

November 30, 1999

Metabolife International, Inc.
5070 Santa Fe St.
San Diego, CA 92109
Attn.: Risk Management

RE: Our Client:
Date of Loss: 9-2-99

Dear Sir/Madam:

Please be advised that the undersigned has been retained to represent the interest of . was injured on 9-2-99 when she suffered a rare stroke which is attributed to the ingredients in your product of which she was not warned..

Please have either your authorized legal representative or insurance carrier contact me at their earliest convenience to discuss this situation.

Sincerely yours,
O'CONNOR, ACCIANI & LEVY

Jim L Hardin

JLH/jj
cc:

CONFIDENTIAL

MIPER025521

Appendix 2. Metabolife Serious Adverse Events (continued)

HEALTH INFORMATION CALL DOCUMENTATION

Date: 1/7
Name: _____ Age: ___ Wt: ___ Ht: ___ Phone:

RECEIVED 2 DAYS AGO.

Meds: _____ C.C.: WHILE TAKING THE PRODUCT SHE HAD SEIZURE
Left message on answering machine to call Back
Current Dose: _____ Suggested Dose: _____ Med Hx: _____
Recommendation: Client called back 1-3 & Spoke to Janine

Date: 1/3 6'2 290
Name: _____ Age: ___ Wt: ___ Ht: ___ Phone:
Spoke to mother to C.C.: 7 MONTHS ON MET. WENT TO
be explained MD wants DOCTOR DIAGNOSED AS HAVING
her son to stop all caffeine HIGH BLOOD PRESSURE. CAN HE
Sodas, coffee, meat etc STILL TAKE THIS.
Current Dose: _____ Suggested Dose: _____ Med Hx: _____
Recommendation: Follow MD orders

Appendix 2. Metabolife Serious Adverse Events (continued)

Metabolife International, Inc.

From: John Macaulay
Sent: Monday, July 06, 1998 3:39 PM
To: 'toxinfo@aol.com'
Subject: FW: Possible side effect/seizure

Mike:

Per our conversation, Mike Ellis agrees that we need to assemble the same type of response as we developed in the seizure case. I will call you tomorrow @ 9 am in your hotel: (

John

-----Original Message-----
From: John Macaulay
Sent: Monday, July 06, 1998 10:34 AM
To: Bob Bradley; Michael Blevins; Mike Ellis; Larry Miller
Cc: Dan Rodriguez
Subject: FW: Possible side effect/seizure

Best Herbal Library "CriminiPoison Control Center"

Gentlemen;

I have conferred with Dr. , an ER physician with the University of Hospital, who is treating a patient who suffered a seizure. Dan Rodriguez in our department originally fielded this call. Apparently the woman was taking Metabolife 356 and this physician is convinced that the ephedrine's (amphetamine-like effect caused) this woman's seizure. Also he has some confusion concerning tableting agent Methocel misinterpreting it as Methamphetamine. She definitely suffered a seizure based upon the EEG tracings showing severe generalized slowing. It is my feeling that she had a preexisting condition that predisposed her to this seizure. The ER physician does not share my views on this in spite of the patient having no previous EEG tracing record history to prove this point. Perhaps it would be prudent to enlist the help of Mike Scott/Dr. Dash to interface with the physician to prevent this from digressing.

John

Dilantin

Wayne Snodgrass
Wallace Winters 3 top minds

3x

potential teratogenic effect
pharmakinetics
pharmacology
toxicology

Adverse Effect Report

pull literature seizures
statistical evidence
in population in general

Stanford researcher
Utah Ecpals Library
director Tom Stoddard
Health & Medical Science

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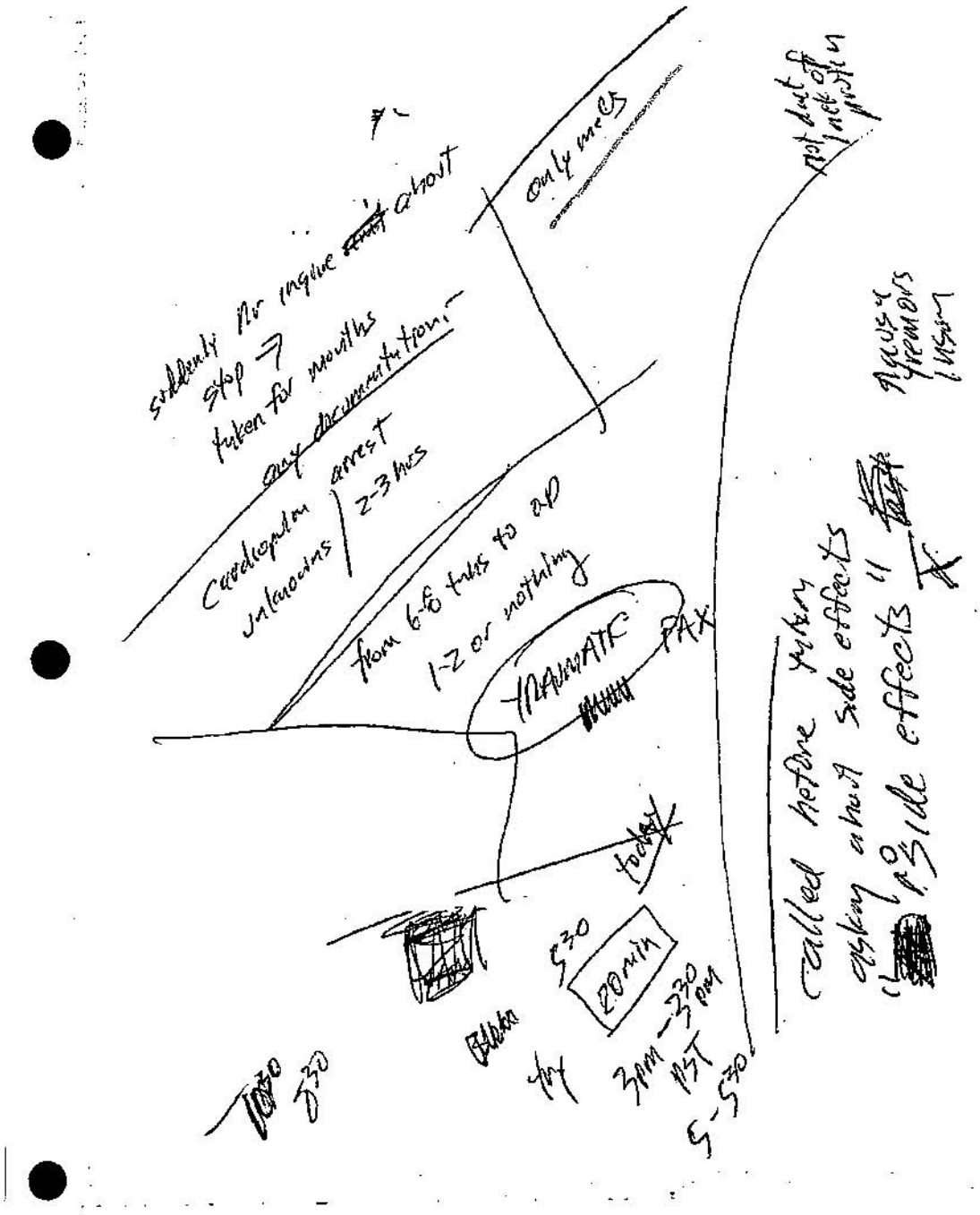
Appendix 2. Metabolife Serious Adverse Events (continued)



CONFIDENTIAL MIPER27600

Appendix 2. Metabolife Serious Adverse Events (continued)

5/21

HEALTH INFORMATION CALL DOCUMENTATION
DATE

Name_____ Age_____ Weight_____ Phone# Brain bleed?
Chief complaint Dist
#of caps qd_____ Timing_____ Duration_____
Meals/snacks_____
Water intake_____ Caffeine intake_____
Medications_____ Medical history/similar symptoms_____
Exercise_____ Other pertinent info_____
Recommendations Call MSC

CONFIDENTIAL MIPER27754

Appendix 2. Metabolife Serious Adverse Events (continued)

HEALTH INFORMATION CALL DOCUMENTATION

Non-Responsive Redaction

Non-Responsive Redaction

Non-Responsive Redaction

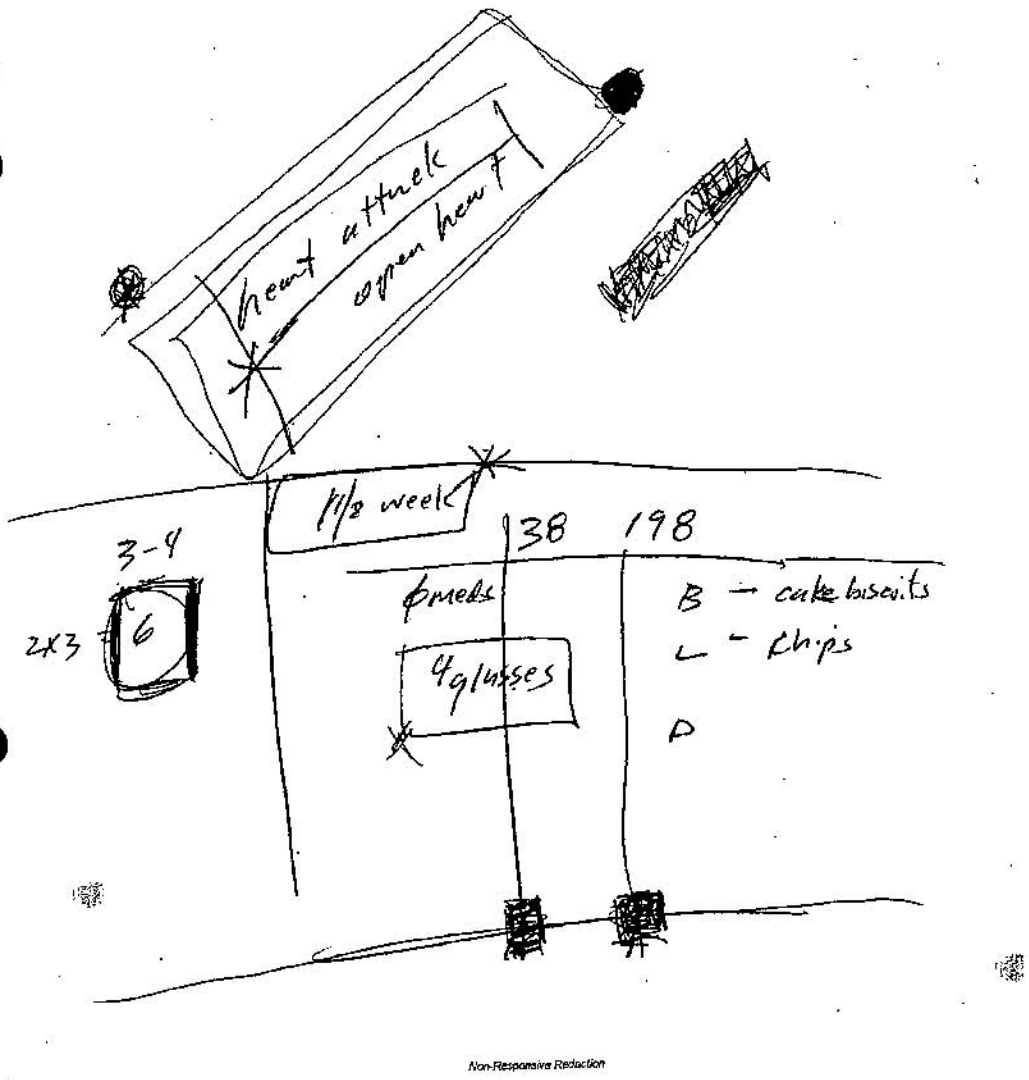
Non-Responsive Redaction

Date: 11/99
Name: Non-Responsive Redaction Age:___ Wt.:___ Ht.:___ Ph#: Non-Responsive Redaction
Meds: COUMADIN c.c.: WIFE PMT HAD STROKE
Rx
Current Dose:_____ Suggested Dose:_____ Med. Hx:_____
Recommendation:_____

Non-Responsive Redaction

CONFIDENTIAL MIPER27791

Appendix 2. Metabolife Serious Adverse Events (continued)



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MIPER27941

Appendix 2. Metabolife Serious Adverse Events (continued)

8/23/99 - T.C. 1700 n/A

8/29/99 0950 voice mail from dist.

customer came in for 4 more bottles & mentioned that his wife had "heart attack" for which MD says Met responsible.

Customer is-

dist. reports they are repeat customer and were given "12 pages of info repeating how to safely take Met."

0935 8/24 - msg on Mark

CONFIDENTIAL

NON-RESPONSIVE REDACTION

MIPER028168

Appendix 2. Metabolife Serious Adverse Events (continued)

This is an e-mail I just received today via an internet server for renal dietitians. Thought you would be interested in it as well...

Subj: **Metabolite**
Date: 8/10/99 11:35:05 PM Eastern Daylight Time
From:
Sender:
Reply-to:
To:

Yesterday one of our ESRD on HD pts was admitted to the ICU with n/o seizures. It was discovered that he was taking Metabolite. Per the lable it contains: Magnesium, Zinc, Chromium, Guaarana Concentrate (seed), Ma Huang Concentrate, Bee Pollen, Ginseng (root), Ginger (root), Lecithin, Bovine Complex, Damiana (leaf), Sarsaparilla (root), Golden Seal (arial part), Nettles (leaf), Gotu Kola (arial part), Spirulina Algae, and Royal Jelly. Is anyone familiar with these herbs? Would any of them cause seizures?
TIA

---------- Headers ----------
Return-Path:
Received: from

Received: from
..., 10 Aug 1999 23:34:51 -0400
Received:

for
Received:
by
for
From:
Received:
by
for
Message-ID: <69183aa1.24e248a1@aol.com>
Date: Tue, 10 Aug 1999 23:23:13 EDT
Subject: Metabolite
To:
MIME-Version: 1.0
Content-Type: text/plain; charset="us-ascii"
Content-Transfer-Encoding: 7bit
X-Mailer: AOL 2.7 for Mac sub 3
Content-Transfer-Encoding: 7bit
Sender:
Precedence: bulk
Reply-To:
Content-Transfer-Encoding: 7bit

Appendix 2. Metabolife Serious Adverse Events (continued)

Danielle For your Follow up
THANKS

call id 315

long comments: 1.53 yr. Old female reports"I had a stroke from metabolife.was on it since 1 yr. Ago last Aug.. MY DR. said it was due to the met."WT.225lbs. Weight-228 lbs 1yr. Ago,now 189lbs.Customer stated she was a Diabetic when she started met

long comments: and her Dr. agreed to supervise her on it.NO hx of hypertension,both parents died of heart attacks.On Glochophage and Glucotrol,no other meds.Costomer states "I was doing well for the first few mos.The Dr. was checking my Bp and it was o.k..2 mos. Ag

long comments: o ,I started gaining weight and my blood sugar started going up.I was checking it at home and it went up to 168-180.I was just going to stop taking it when I started having tingling in my rt. Hand and one side of my mouth. I called the DR. went to

long comments: E.R. My bp was223/123. I got some medicine and they sent me home.I got worse and was taken to the university hospital.They did a cat scan and M.R.I.The DR. Said it showed I had A minor stroke." Reports being in hospital 5 days.Residual effects-no

long comments: paralysis,Speech not affected, experienced tingling in mouth and mild weakness Rt. Hand. Customer relayed facts in a low key manner.I told her we would be in touch with her.

MRF Sent 11/10/99

ONFIDENTIAL

NON-RESPONSIVE REDACTION

MIPER028281

Health

May 1, 2001

Dear Sir!

This is the second letter I have written. I have since called and was told the supervisor was out so call Back. I called Back But Dan never picked up on his line. I'm not giving up Writing again.

In August 1999, my husband & I were Walking the mall for exercise. We passed a Booth that sold only Metabolife. My husband & I purchased it. My husband took it maybe 5 days then he just quit. I continued to take it. In Oct of 1999 I had a stroke. It was Oct, 18, 1999. At the time I was 57 years old. I did not have high Blood Pressure & my level was fine. Then suddenly I had a stroke. The first of Nov. I tried to go Back to Work but I had a hard time. So in Jan 2000 I quit Work & took time off to recover. I had a hard time & took off for one Year. When I wrote to you

CONFIDENTIAL MIPER028321

NON-RESPONSIVE REDACTION

June 15, 2001

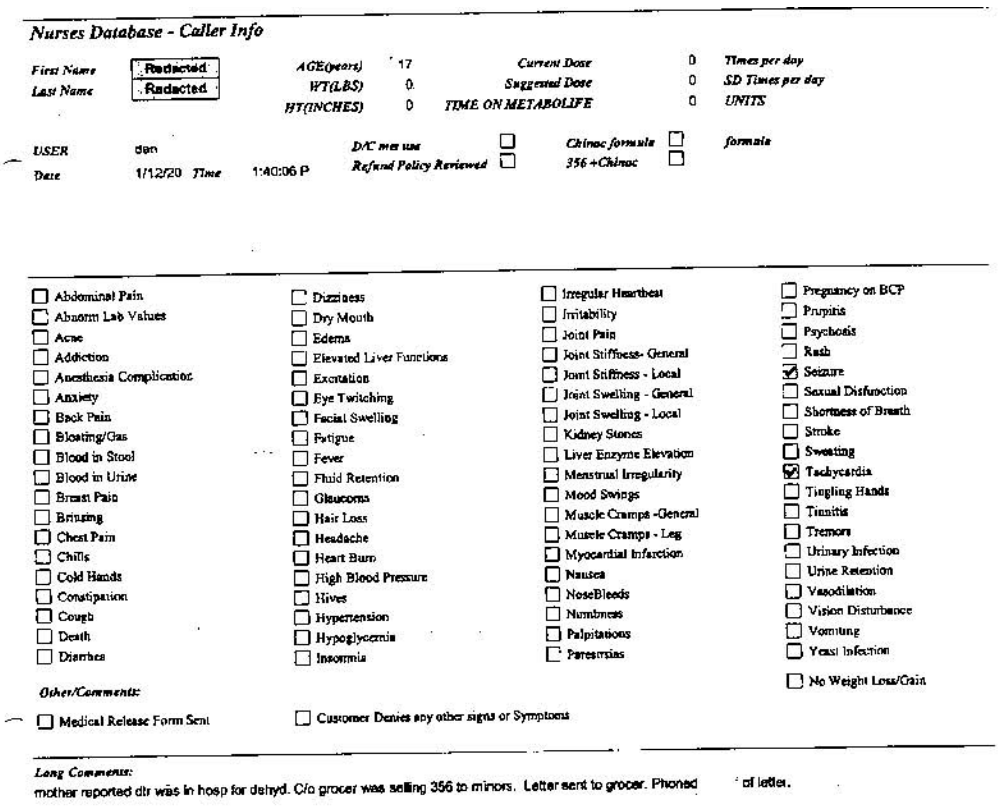
To:

Metabolife: This letter is to inform you that on 2-19-01 me and my daughter took a trip to Texarkana, Ark. to visit my sister. My daughter is some what over weight so we brought (Met.) because of it supposedly to be all natural + my daughter is 20 years old but because of all the things you hear about diet pills, I would never allow her to take anything + and I myself put her on Metabolife, 4 pills a day, not even the full dose! She nearly died after going into comatal states and completely stopped breathing! We thought she would die before a ambulance team arrived. They immediently loaded her and took her to Christus St. Michaels Hospital in Texarkana Texas. It was determined that the Metabolife drug was definitly the cause. As her doctor reported to me if she had been using the full dose she may not of survived. I am still very upset over this matter, this is the second letter We

CONFIDENTIAL MIPER028329

NON-RESPONSIVE REDACTION

Appendix 2. Metabolife Serious Adverse Events (continued)



Nurses Database - Caller Info

First Name: Redacted
Last Name: Redacted

AGE(years): 17
WT(LBS): 0
HT(INCHES): 0

Current Dose: 0 Times per day
Suggested Dose: 0 SD Times per day
TIME ON METABOLIFE: 0 UNITS

USER: dan
Date: 1/12/20 Time: 1:40:06 P

D/C mes use ☐ Chinoc formula ☐ formula
Refund Policy Reviewed ☐ 356 +Chinoc ☐

☐ Abdominal Pain	☐ Dizziness	☐ Irregular Heartbeat	☐ Pregnancy on BCP
☐ Abnorm Lab Values	☐ Dry Mouth	☐ Irritability	☐ Pruritis
☐ Acne	☐ Edema	☐ Joint Pain	☐ Psychosis
☐ Addiction	☐ Elevated Liver Functions	☐ Joint Stiffness- General	☐ Rash
☐ Anesthesia Complication	☐ Excretion	☐ Joint Stiffness - Local	☑ Seizure
☐ Anxiety	☐ Eye Twitching	☐ Joint Swelling - General	☐ Sexual Disfunction
☐ Back Pain	☐ Facial Swelling	☐ Joint Swelling - Local	☐ Shortness of Breath
☐ Bloating/Gas	☐ Fatigue	☐ Kidney Stones	☐ Stroke
☐ Blood in Stool	☐ Fever	☐ Liver Enzyme Elevation	☐ Sweating
☐ Blood in Urine	☐ Fluid Retention	☐ Menstrual Irregularity	☑ Tachycardia
☐ Breast Pain	☐ Glaucoma	☐ Mood Swings	☐ Tingling Hands
☐ Bruising	☐ Hair Loss	☐ Muscle Cramps -General	☐ Tinnitis
☐ Chest Pain	☐ Headache	☐ Muscle Cramps - Leg	☐ Tremors
☐ Chills	☐ Heart Burn	☐ Myocardial Infarction	☐ Urinary Infection
☐ Cold Hands	☐ High Blood Pressure	☐ Nausea	☐ Urine Retention
☐ Constipation	☐ Hives	☐ NoseBleeds	☐ Vasodilation
☐ Cough	☐ Hypertension	☐ Numbness	☐ Vision Disturbance
☐ Death	☐ Hypoglycemia	☐ Palpitations	☐ Vomiting
☐ Diarrhea	☐ Insomnia	☐ Paresthesias	☐ Yeast Infection
			☐ No Weight Loss/Gain

Other/Comments:

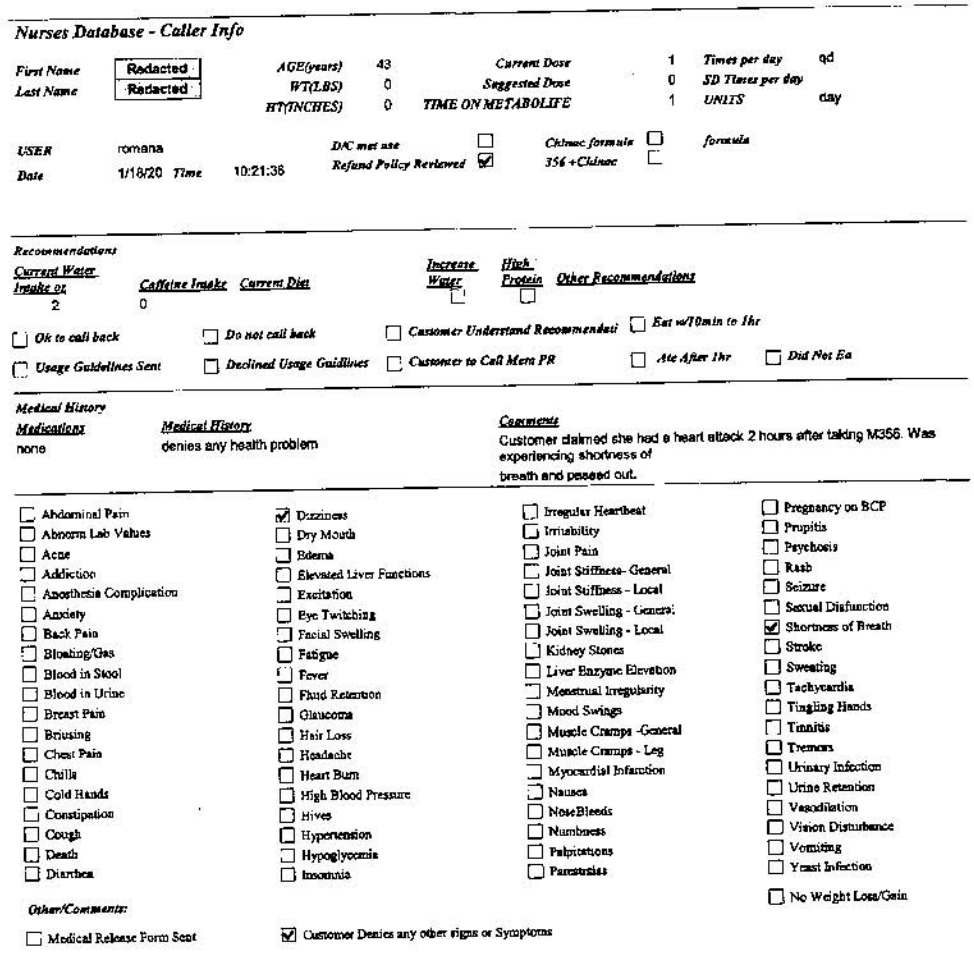
☐ Medical Release Form Sent ☐ Customer Denies any other signs or Symptoms

Long Comments:
mother reported dtr was in hosp for dehyd. C/o grocer was selling 356 to minors. Letter sent to grocer. Phoned of letter.

CONFIDENTIAL MIPER028442

NON-RESPONSIVE REDACTION

Appendix 2. Metabolife Serious Adverse Events (continued)



Nurses Database - Caller Info

First Name: Redacted
Last Name: Redacted

AGE(years): 43
WT(LBS): 0
HT(INCHES): 0

Current Dose: 1 — Times per day: qd
Suggested Dose: 0 — SD Times per day:
TIME ON METABOLIFE: 1 — UNITS: day

USER: romana
Date: 1/18/20 Time: 10:21:38

D/C met use ☐ — Refund Policy Reviewed ☑
Chitosc formula ☐ — formula
356 +Chitosc ☐

Recommendations

Current Water Intake oz	Caffeine Intake	Current Diet	Increase Water	High Protein	Other Recommendations
2	0		☐	☐	

☐ Ok to call back ☐ Do not call back ☐ Customer Understand Recommendati ☐ Eat w/10min to 1hr
☐ Usage Guidelines Sent ☐ Declined Usage Guidlines ☐ Customer to Call Mem PR ☐ Ate After 1hr ☐ Did Not Ea

Medical History

Medications: none

Medical History: denies any health problem

Comments: Customer claimed she had a heart attack 2 hours after taking M356. Was experiencing shortness of breath and passed out.

☐ Abdominal Pain	☑ Dizziness	☐ Irregular Heartbeat	☐ Pregnancy on BCP
☐ Abnorm Lab Values	☐ Dry Mouth	☐ Irritability	☐ Pruritis
☐ Acne	☐ Edema	☐ Joint Pain	☐ Psychosis
☐ Addiction	☐ Elevated Liver Functions	☐ Joint Stiffness- General	☐ Rash
☐ Anesthesia Complication	☐ Excitation	☐ Joint Stiffness - Local	☐ Seizure
☐ Anxiety	☐ Eye Twitching	☐ Joint Swelling - General	☐ Sexual Disfunction
☐ Back Pain	☐ Facial Swelling	☐ Joint Swelling - Local	☑ Shortness of Breath
☐ Bloating/Gas	☐ Fatigue	☐ Kidney Stones	☐ Stroke
☐ Blood in Stool	☐ Fever	☐ Liver Enzyme Elevation	☐ Sweating
☐ Blood in Urine	☐ Fluid Retention	☐ Menstrual Irregularity	☐ Tachycardia
☐ Breast Pain	☐ Glaucoma	☐ Mood Swings	☐ Tingling Hands
☐ Bruising	☐ Hair Loss	☐ Muscle Cramps -General	☐ Tinnitis
☐ Chest Pain	☐ Headache	☐ Muscle Cramps - Leg	☐ Tremors
☐ Chills	☐ Heart Burn	☐ Myocardial Infarction	☐ Urinary Infection
☐ Cold Hands	☐ High Blood Pressure	☐ Nausea	☐ Urine Retention
☐ Constipation	☐ Hives	☐ NoseBleeds	☐ Vasodilation
☐ Cough	☐ Hypertension	☐ Numbness	☐ Vision Disturbance
☐ Death	☐ Hypoglycemia	☐ Palpitations	☐ Vomiting
☐ Diarrhea	☐ Insomnia	☐ Paresthesias	☐ Yeast Infection
			☐ No Weight Loss/Gain

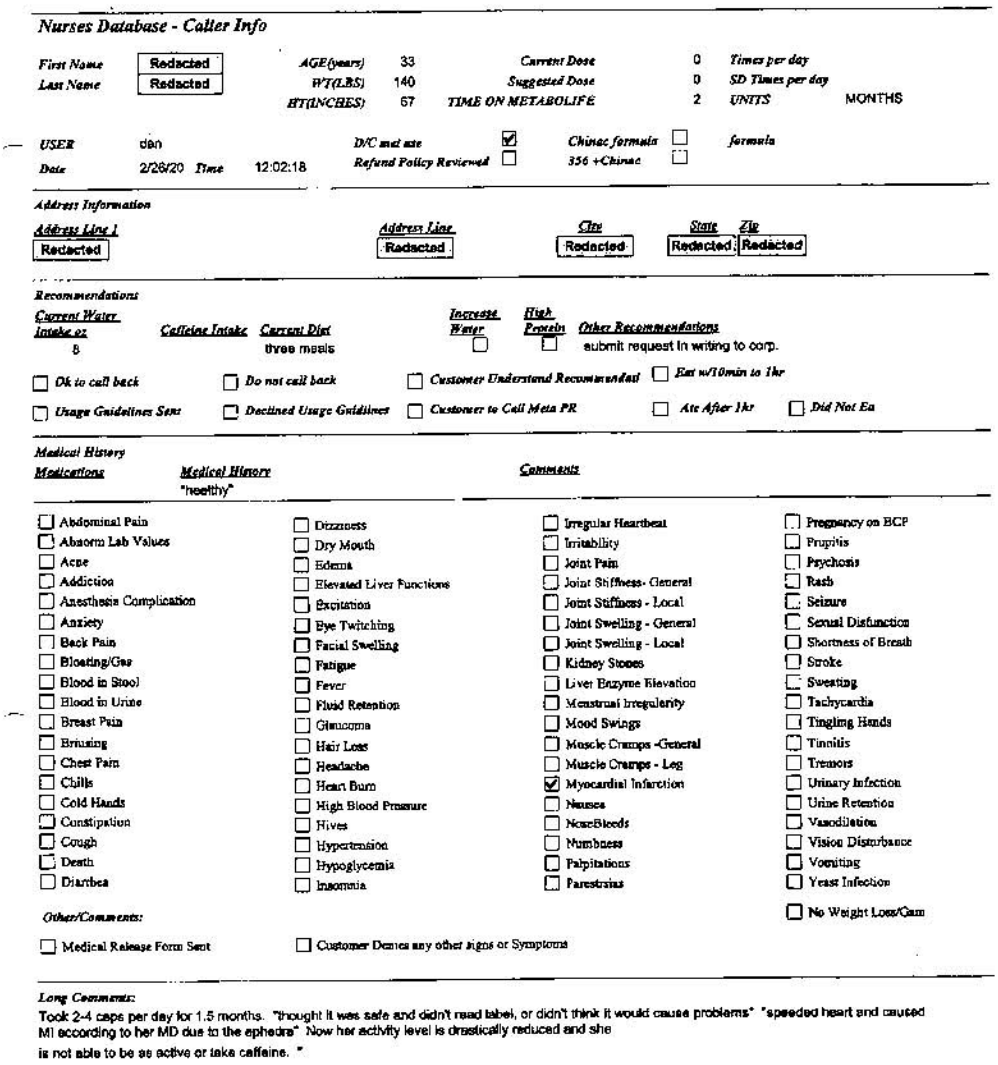
Other/Comments:

☐ Medical Release Form Sent ☑ Customer Denies any other signs or Symptoms

CONFIDENTIAL MIPER028488

NON-RESPONSIVE REDACTION

Appendix 2. Metabolife Serious Adverse Events (continued)



Nurses Database - Caller Info

First Name: Redacted
Last Name: Redacted
AGE(years): 33
WT(LBS): 140
HT(INCHES): 67
Current Dose: 0
Suggested Dose: 0
TIME ON METABOLIFE: 2
Times per day
SD Times per day
UNITS: MONTHS

USER: dan
Date: 2/26/20 Time: 12:02:18
D/C and ate ☑
Refund Policy Reviewed ☐
Chinac formula ☐
356 +Chinac ☐
formula

Address Information

Address Line 1: Redacted
Address Line: Redacted
City: Redacted
State: Redacted
Zip: Redacted

Recommendations

Current Water Intake oz: 8
Caffeine Intake
Current Diet: three meals
Increase Water ☐
High Protein ☐
Other Recommendations: submit request in writing to corp.

☐ Ok to call back ☐ Do not call back ☐ Customer Understand Recommendati ☐ Eat w/10min to 1hr
☐ Usage Guidelines Sent ☐ Declined Usage Guidlines ☐ Customer to Call Meta PR ☐ Ate After 1hr ☐ Did Not Ea

Medical History

Medications
Medical History: "healthy"
Comments

☐ Abdominal Pain	☐ Dizziness	☐ Irregular Heartbeat	☐ Pregnancy on BCP
☐ Abnorm Lab Values	☐ Dry Mouth	☐ Irritability	☐ Pruritis
☐ Acne	☐ Edema	☐ Joint Pain	☐ Psychosis
☐ Addiction	☐ Elevated Liver Functions	☐ Joint Stiffness- General	☐ Rash
☐ Anesthesia Complication	☐ Excitation	☐ Joint Stiffness - Local	☐ Seizure
☐ Anxiety	☐ Eye Twitching	☐ Joint Swelling - General	☐ Sexual Disfunction
☐ Back Pain	☐ Facial Swelling	☐ Joint Swelling - Local	☐ Shortness of Breath
☐ Bloating/Gas	☐ Fatigue	☐ Kidney Stones	☐ Stroke
☐ Blood in Stool	☐ Fever	☐ Liver Enzyme Elevation	☐ Sweating
☐ Blood in Urine	☐ Fluid Retention	☐ Menstrual Irregularity	☐ Tachycardia
☐ Breast Pain	☐ Glaucoma	☐ Mood Swings	☐ Tingling Hands
☐ Bruising	☐ Hair Loss	☐ Muscle Cramps -General	☐ Tinnitis
☐ Chest Pain	☐ Headache	☐ Muscle Cramps - Leg	☐ Tremors
☐ Chills	☐ Heart Burn	☑ Myocardial Infarction	☐ Urinary Infection
☐ Cold Hands	☐ High Blood Pressure	☐ Nausea	☐ Urine Retention
☐ Constipation	☐ Hives	☐ NoseBleeds	☐ Vasodilation
☐ Cough	☐ Hypertension	☐ Numbness	☐ Vision Disturbance
☐ Death	☐ Hypoglycemia	☐ Palpitations	☐ Vomiting
☐ Diarrhea	☐ Insomnia	☐ Parestrains	☐ Yeast Infection

Other/Comments:

☐ No Weight Loss/Gain

☐ Medical Release Form Sent ☐ Customer Denies any other Signs or Symptoms

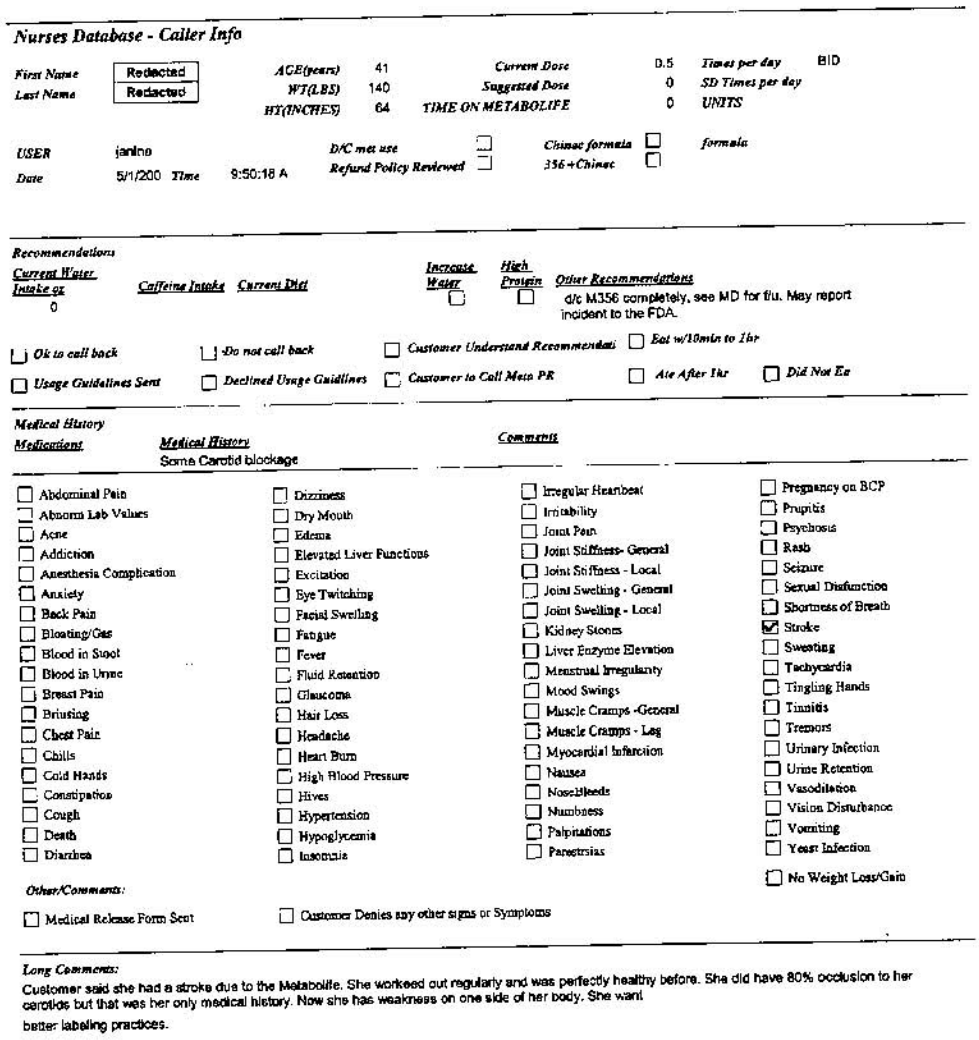
Long Comments:

Took 2-4 caps per day for 1.5 months. "thought it was safe and didn't read label, or didn't think it would cause problems" "speeded heart and caused MI according to her MD due to the ephedra" Now her activity level is drastically reduced and she is not able to be as active or take caffeine. "

CONFIDENTIAL MIPER028835

NON-RESPONSIVE REDACTION

Appendix 2. Metabolife Serious Adverse Events (continued)



Nurses Database - Caller Info

First Name: Redacted
Last Name: Redacted
AGE(years): 41
WT(LBS): 140
HT(INCHES): 64
Current Dose: 0.5
Suggested Dose: 0
TIME ON METABOLIFE: 0
Times per day: BID
SD Times per day:
UNITS:

USER: janine
Date: 5/1/200 Time: 9:50:18 A
D/C met use ☐
Refund Policy Reviewed ☐
Chinese formula ☐
356+Chinese ☐
formula:

Recommendations

Current Water Intake oz: 0
Caffeine Intake
Current Diet
Increase Water ☐
High Protein ☐
Other Recommendations: d/c M356 completely, see MD for f/u. May report incident to the FDA.

☐ Ok to call back ☐ Do not call back ☐ Customer Understand Recommendati ☐ Eat w/10min to 1hr
☐ Usage Guidelines Sent ☐ Declined Usage Guidlines ☐ Customer to Call Meta PR ☐ Ate After 1hr ☐ Did Not Eat

Medical History

Medications
Medical History: Some Carotid blockage
Comments

☐ Abdominal Pain	☐ Dizziness	☐ Irregular Heartbeat	☐ Pregnancy on BCP
☐ Abnorm Lab Values	☐ Dry Mouth	☐ Irritability	☐ Pruritis
☐ Acne	☐ Edema	☐ Joint Pain	☐ Psychosis
☐ Addiction	☐ Elevated Liver Functions	☐ Joint Stiffness- General	☐ Rash
☐ Anesthesia Complication	☐ Excitation	☐ Joint Stiffness - Local	☐ Seizure
☐ Anxiety	☐ Eye Twitching	☐ Joint Swelling - General	☐ Sexual Disfunction
☐ Back Pain	☐ Facial Swelling	☐ Joint Swelling - Local	☐ Shortness of Breath
☐ Bloating/Gas	☐ Fatigue	☐ Kidney Stones	☑ Stroke
☐ Blood in Stool	☐ Fever	☐ Liver Enzyme Elevation	☐ Sweating
☐ Blood in Urine	☐ Fluid Retention	☐ Menstrual Irregularity	☐ Tachycardia
☐ Breast Pain	☐ Glaucoma	☐ Mood Swings	☐ Tingling Hands
☐ Bruising	☐ Hair Loss	☐ Muscle Cramps -General	☐ Tinnitis
☐ Chest Pain	☐ Headache	☐ Muscle Cramps - Leg	☐ Tremors
☐ Chills	☐ Heart Burn	☐ Myocardial Infarction	☐ Urinary Infection
☐ Cold Hands	☐ High Blood Pressure	☐ Nausea	☐ Urine Retention
☐ Constipation	☐ Hives	☐ Nosebleeds	☐ Vasodilation
☐ Cough	☐ Hypertension	☐ Numbness	☐ Vision Disturbance
☐ Death	☐ Hypoglycemia	☐ Palpitations	☐ Vomiting
☐ Diarrhea	☐ Insomnia	☐ Paresthesias	☐ Yeast Infection
			☐ No Weight Loss/Gain

Other/Comments:

☐ Medical Release Form Sent ☐ Customer Denies any other signs or Symptoms

Long Comments:

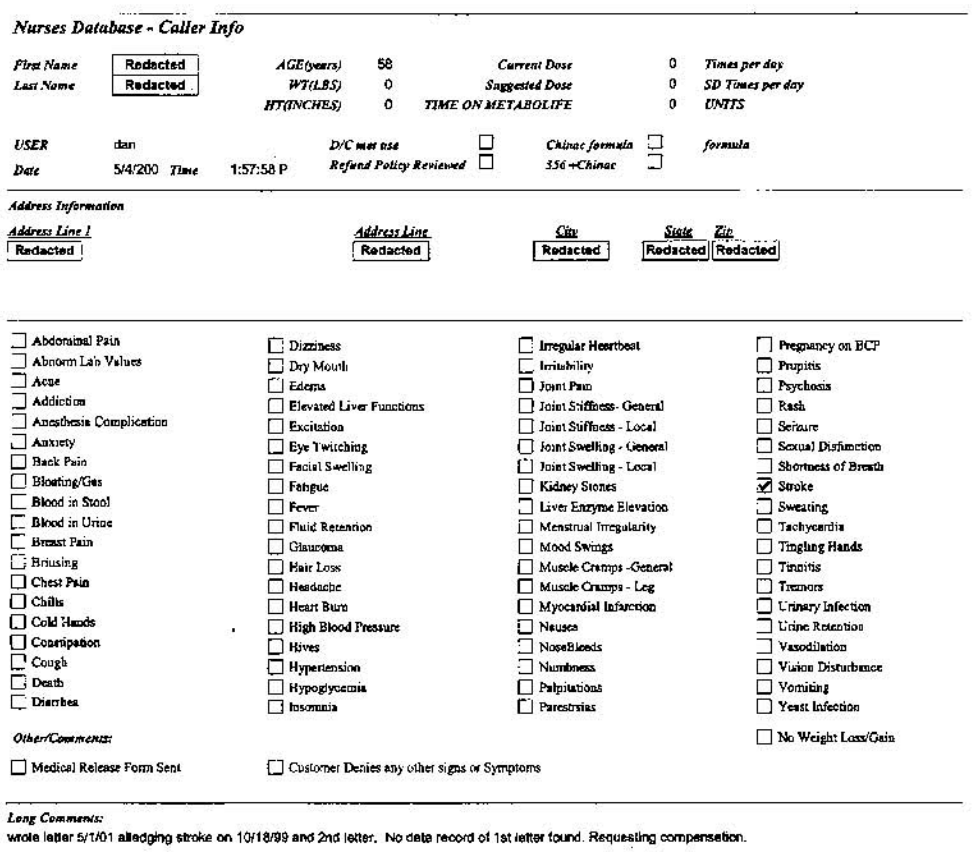
Customer said she had a stroke due to the Metabolife. She worked out regularly and was perfectly healthy before. She did have 80% occlusion to her carotids but that was her only medical history. Now she has weakness on one side of her body. She want better labeling practices.

CONFIDENTIAL

MIPER029424

NON-RESPONSIVE REDACTION

Appendix 2. Metabolife Serious Adverse Events (continued)



Nurses Database - Caller Info

First Name	Redacted	*AGE(years)*	58	*Current Dose*	0	*Times per day*	
Last Name	Redacted	*WT(LBS)*	0	*Suggested Dose*	0	*SD Times per day*	
		HT(INCHES)	0	*TIME ON METABOLIFE*	0	*UNITS*	

USER dan *D/C met use* ☐ *Chinac formula* ☐ *formula*

Date 5/4/200 *Time* 1:57:58 P *Refund Policy Reviewed* ☐ *356 +Chinac* ☐

Address Information

Address Line 1	*Address Line*	*City*	*State*	*Zip*
Redacted	Redacted	Redacted	Redacted	Redacted

☐ Abdominal Pain	☐ Dizziness	☐ Irregular Heartbeat	☐ Pregnancy on ECP
☐ Abnorm Lab Values	☐ Dry Mouth	☐ Irritability	☐ Pruritis
☐ Acne	☐ Edema	☐ Joint Pain	☐ Psychosis
☐ Addiction	☐ Elevated Liver Functions	☐ Joint Stiffness- General	☐ Rash
☐ Anesthesia Complication	☐ Excitation	☐ Joint Stiffness - Local	☐ Seizure
☐ Anxiety	☐ Eye Twitching	☐ Joint Swelling - General	☐ Sexual Disfunction
☐ Back Pain	☐ Facial Swelling	☐ Joint Swelling - Local	☐ Shortness of Breath
☐ Bloating/Gas	☐ Fatigue	☐ Kidney Stones	☑ Stroke
☐ Blood in Stool	☐ Fever	☐ Liver Enzyme Elevation	☐ Sweating
☐ Blood in Urine	☐ Fluid Retention	☐ Menstrual Irregularity	☐ Tachycardia
☐ Breast Pain	☐ Glaucoma	☐ Mood Swings	☐ Tingling Hands
☐ Bruising	☐ Hair Loss	☐ Muscle Cramps -General	☐ Tinnitis
☐ Chest Pain	☐ Headache	☐ Muscle Cramps - Leg	☐ Tremors
☐ Chills	☐ Heart Burn	☐ Myocardial Infarction	☐ Urinary Infection
☐ Cold Hands	☐ High Blood Pressure	☐ Nausea	☐ Urine Retention
☐ Constipation	☐ Hives	☐ NoseBleeds	☐ Vasodilation
☐ Cough	☐ Hypertension	☐ Numbness	☐ Vision Disturbance
☐ Death	☐ Hypoglycemia	☐ Palpitations	☐ Vomiting
☐ Diarrhea	☐ Insomnia	☐ Parestrias	☐ Yeast Infection

Other/Comments: ☐ No Weight Loss/Gain

☐ Medical Release Form Sent ☐ Customer Denies any other signs or Symptoms

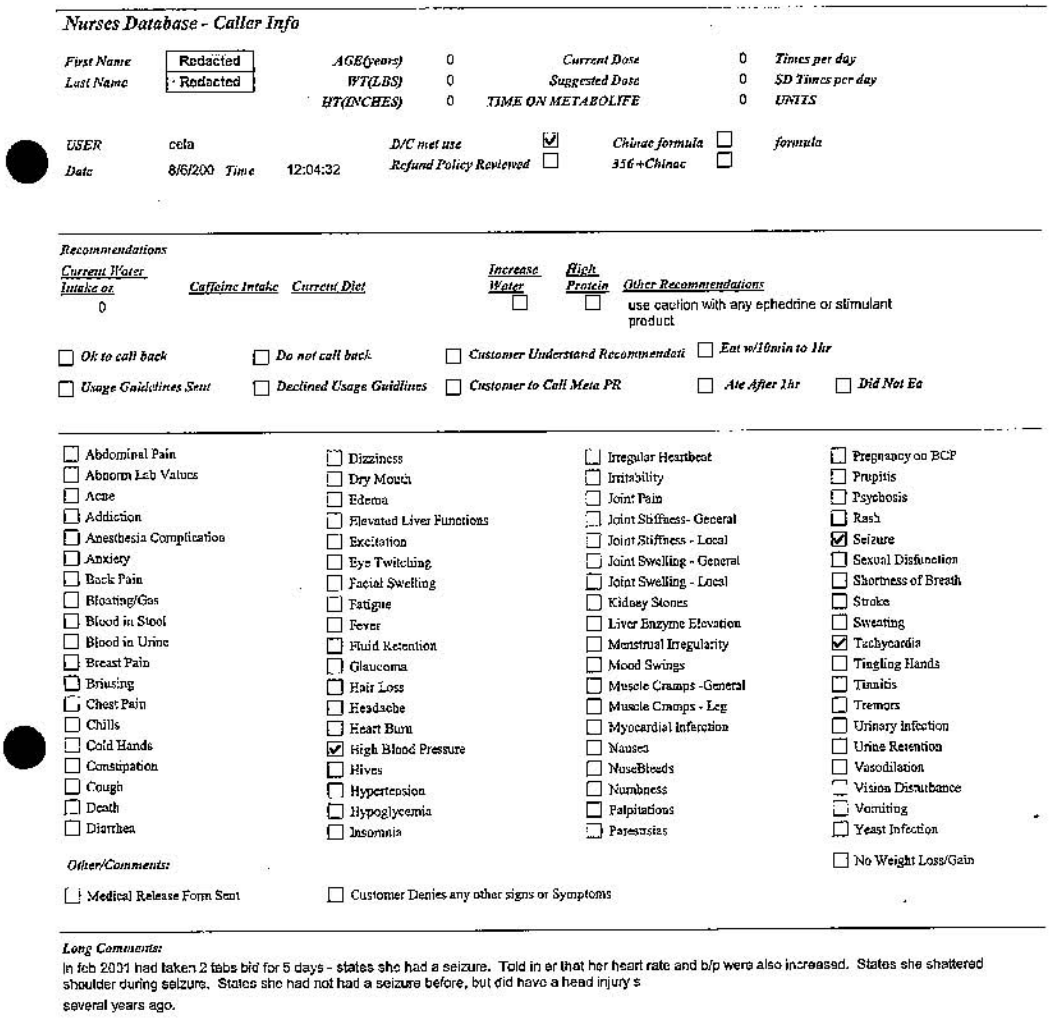
Long Comments:

wrote letter 5/1/01 alledging stroke on 10/18/99 and 2nd letter. No data record of 1st letter found. Requesting compensation.

CONFIDENTIAL MIPER029469

NON-RESPONSIVE REDACTION

Appendix 2. Metabolife Serious Adverse Events (continued)



Nurses Database - Caller Info

First Name: Redacted
Last Name: Redacted
AGE(years): 0
WT(LBS): 0
HT(INCHES): 0
Current Dose: 0
Suggested Dose: 0
TIME ON METABOLIFE: 0
Times per day: 0
SD Times per day: 0
UNITS:

USER: celia
Date: 8/6/200 Time: 12:04:32
D/C met use: ☑
Refund Policy Reviewed: ☐
Chinac formula: ☐
356+Chinac: ☐
formula:

Recommendations

Current Water Intake oz: 0
Caffeine Intake:
Current Diet:
Increase Water: ☐
High Protein: ☐
Other Recommendations: use caution with any ephedrine or stimulant product

☐ Ok to call back ☐ Do not call back ☐ Customer Understand Recommendati ☐ Eat w/10min to 1hr
☐ Usage Guidelines Sent ☐ Declined Usage Guidlines ☐ Customer to Call Meta PR ☐ Ate After 1hr ☐ Did Not Ea

☐ Abdominal Pain	☐ Dizziness	☐ Irregular Heartbeat	☐ Pregnancy on BCP
☐ Abnorm Lab Values	☐ Dry Mouth	☐ Irritability	☐ Pruritis
☐ Acne	☐ Edema	☐ Joint Pain	☐ Psychosis
☐ Addiction	☐ Elevated Liver Functions	☐ Joint Stiffness- General	☐ Rash
☐ Anesthesia Complication	☐ Excitation	☐ Joint Stiffness - Local	☑ Seizure
☐ Anxiety	☐ Eye Twitching	☐ Joint Swelling - General	☐ Sexual Disfunction
☐ Back Pain	☐ Facial Swelling	☐ Joint Swelling - Local	☐ Shortness of Breath
☐ Bloating/Gas	☐ Fatigue	☐ Kidney Stones	☐ Stroke
☐ Blood in Stool	☐ Fever	☐ Liver Enzyme Elevation	☐ Sweating
☐ Blood in Urine	☐ Fluid Retention	☐ Menstrual Irregularity	☑ Tachycardia
☐ Breast Pain	☐ Glaucoma	☐ Mood Swings	☐ Tingling Hands
☐ Bruising	☐ Hair Loss	☐ Muscle Cramps -General	☐ Tinnitis
☐ Chest Pain	☐ Headache	☐ Muscle Cramps - Leg	☐ Tremors
☐ Chills	☐ Heart Burn	☐ Myocardial Infection	☐ Urinary Infection
☐ Cold Hands	☑ High Blood Pressure	☐ Nausea	☐ Urine Retention
☐ Constipation	☐ Hives	☐ NoseBleeds	☐ Vasodilation
☐ Cough	☐ Hypertension	☐ Numbness	☐ Vision Disturbance
☐ Death	☐ Hypoglycemia	☐ Palpitations	☐ Vomiting
☐ Diarrhea	☐ Insomnia	☐ Paresusias	☐ Yeast Infection
			☐ No Weight Loss/Gain

Other/Comments:

☐ Medical Release Form Sent ☐ Customer Denies any other signs or Symptoms

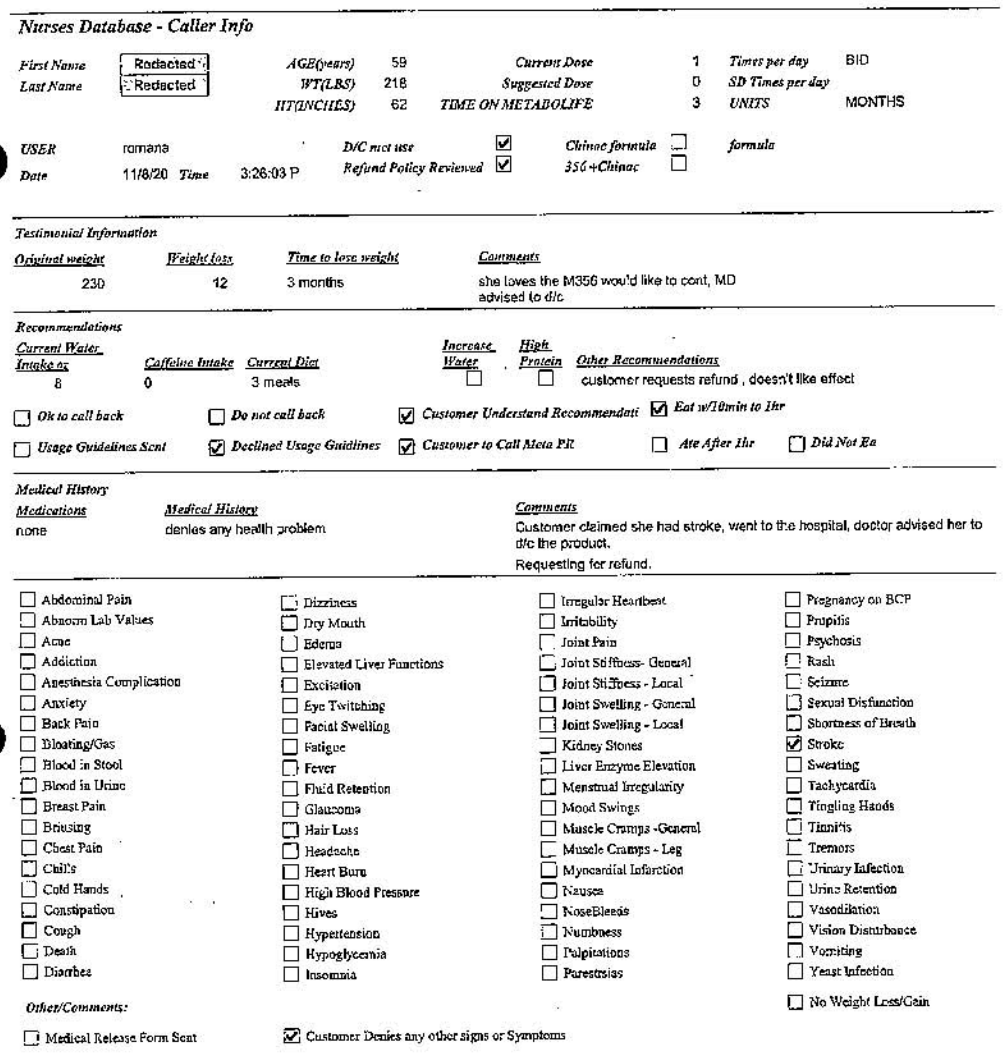
Long Comments:

In feb 2001 had taken 2 tabs bid for 5 days - states she had a seizure. Told in er that her heart rate and b/p were also increased. States she shattered shoulder during seizure. States she had not had a seizure before, but did have a head injury s several years ago.

CONFIDENTIAL MIPER029882

NON-RESPONSIVE REDACTION

Appendix 2. Metabolife Serious Adverse Events (continued)



Nurses Database - Caller Info

First Name	Redacted	*AGE(years)*	59	*Current Dose*	1	*Times per day*	BID
Last Name	Redacted	*WT(LBS)*	218	*Suggested Dose*	0	*SD Times per day*	
		HT(INCHES)	62	*TIME ON METABOLIFE*	3	*UNITS*	MONTHS

USER romana *D/C mct use* ☑ *Chinse formula* ☐ *formula*

Date 11/8/20 *Time* 3:26:03 P *Refund Policy Reviewed* ☑ *356+Chinac* ☐

Testimonial Information

Original weight	*Weight loss*	*Time to lose weight*	*Comments*
230	12	3 months	she lowes the M356 would like to cont, MD advised to d/c

Recommendations

Current Water Intake oz	*Caffeine Intake*	*Current Diet*	*Increase Water*	*High Protein*	*Other Recommendations*
8	0	3 meals	☐	☐	customer requests refund , doesn't like effect

☐ *Ok to call back* ☐ *Do not call back* ☑ *Customer Understand Recommendati* ☑ *Eat w/10min to 1hr*

☐ *Usage Guidelines Sent* ☑ *Declined Usage Guidlines* ☑ *Customer to Call Meta Fit* ☐ *Ate After 1hr* ☐ *Did Not Ea*

Medical History

Medications	*Medical History*	*Comments*
none	denies any health problem	Customer claimed she had stroke, went to the hospital, doctor advised her to d/c the product. Requesting for refund.

☐ Abdominal Pain	☐ Dizziness	☐ Irregular Heartbeat	☐ Pregnancy on BCP
☐ Abnorm Lab Values	☐ Dry Mouth	☐ Irritability	☐ Pruritis
☐ Acne	☐ Edema	☐ Joint Pain	☐ Psychosis
☐ Addiction	☐ Elevated Liver Functions	☐ Joint Stiffness- General	☐ Rash
☐ Anesthesia Complication	☐ Excitation	☐ Joint Stiffness - Local	☐ Seizure
☐ Anxiety	☐ Eye Twitching	☐ Joint Swelling - General	☐ Sexual Disfunction
☐ Back Pain	☐ Facial Swelling	☐ Joint Swelling - Local	☐ Shortness of Breath
☐ Bloating/Gas	☐ Fatigue	☐ Kidney Stones	☑ Stroke
☐ Blood in Stool	☐ Fever	☐ Liver Enzyme Elevation	☐ Sweating
☐ Blood in Urine	☐ Fluid Retention	☐ Menstrual Irregularity	☐ Tachycardia
☐ Breast Pain	☐ Glaucoma	☐ Mood Swings	☐ Tingling Hands
☐ Bruising	☐ Hair Loss	☐ Muscle Cramps -General	☐ Tinnitis
☐ Chest Pain	☐ Headache	☐ Muscle Cramps - Leg	☐ Tremors
☐ Chill's	☐ Heart Burn	☐ Myocardial Infarction	☐ Urinary Infection
☐ Cold Hands	☐ High Blood Pressure	☐ Nausea	☐ Urine Retention
☐ Constipation	☐ Hives	☐ NoseBleeds	☐ Vasodilation
☐ Cough	☐ Hypertension	☐ Numbness	☐ Vision Disturbance
☐ Death	☐ Hypoglycemia	☐ Palpitations	☐ Vomiting
☐ Diarrhea	☐ Insomnia	☐ Paresthesias	☐ Yeast Infection
			☐ No Weight Loss/Gain

Other/Comments:

☐ Medical Release Form Sent ☑ Customer Denies any other signs or Symptoms

CONFIDENTIAL MIPER030391

NON-RESPONSIVE REDACTION

Appendix 2. Metabolife Serious Adverse Events (continued)

Nurses Database - Caller Info

First Name	[redacted]	*AGE(years)*	48	*Current Dose*	0	*Times per day*	
Last Name	[redacted]	*WT(LBS)*	0	*Suggested Dose*	0	*SD Times per day*	
		HT(INCHES)	0	*TIME ON METABOLIFE*	0	*UNITS*	

USER janine *D/C met use* ☐ *Chinac formula* ☐ *formula*

Date 11/13/2 *Time* 4:29:03 P *Refund Policy Reviewed* ☐ *356+Chinac* ☐

☐ Abdominal Pain	☐ Dizziness	☐ Irregular Heartbeat	☐ Pregnancy on BCP
☐ Abnorm Lab Values	☐ Dry Mouth	☐ Irritability	☐ Pupitis
☐ Acne	☐ Edema	☐ Joint Pain	☐ Psychosis
☐ Addiction	☐ Elevated Liver Functions	☐ Joint Stiffness- General	☐ Rash
☐ Anesthesia Complication	☐ Excitation	☐ Joint Stiffness - Local	☐ Seizure
☐ Anxiety	☐ Eye Twitching	☐ Joint Swelling - General	☐ Sexual Disfunction
☐ Back Pain	☐ Facial Swelling	☐ Joint Swelling - Local	☐ Shortness of Breath
☐ Bloating/Gas	☐ Fatigue	☐ Kidney Stones	☑ Stroke
☐ Blood in Stool	☐ Fever	☐ Liver Enzyme Elevation	☐ Sweating
☐ Blood in Urine	☐ Fluid Retention	☐ Menstrual Irregularity	☐ Tachycardia
☐ Breast Pain	☐ Glaucoma	☐ Mood Swings	☐ Tingling Hands
☐ Bruising	☐ Hair Loss	☐ Muscle Cramps -General	☐ Tinnitis
☐ Chest Pain	☐ Headache	☐ Muscle Cramps - Leg	☐ Tremors
☐ Chills	☐ Heart Burn	☐ Myocardial Infarction	☐ Urinary Infection
☐ Cold Hands	☐ High Blood Pressure	☐ Nausea	☐ Urine Retention
☐ Constipation	☐ Hives	☐ NoseBleeds	☐ Vasodilation
☐ Cough	☐ Hypertension	☐ Numbness	☐ Vision Disturbance
☐ Death	☐ Hypoglycemia	☐ Palpitations	☐ Vomiting
☐ Diarrhea	☐ Insomnia	☐ Parestesias	☐ Yeast Infection

Other/Comments: ☐ No Weight Loss/Gain

☐ Medical Release Form Sent ☐ Customer Denies any other signs or Symptoms

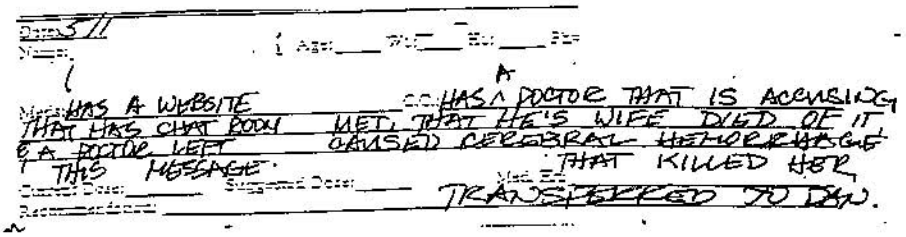
Long Comments:

Father called to say son had a stroke and is now I a Nursing Home. He took the product for 8 mths but father does not know any other history. Requests some compensation. Caller referred to supervisor Dan Rodriquez.

CONFIDENTIAL MIPER030407

NON-RESPONSIVE REDACTION

Appendix 2. Metabolife Serious Adverse Events (continued)


HAS A WEBSITE THAT HAS CHAT BOOM & A DOCTOR LEFT THIS MESSAGE.

HAS A DOCTOR THAT IS ACCUSING ME, THAT HE'S WIFE DIED OF IT CAUSED CEREBRAL HEMORRHAGE THAT KILLED HER.

TRANSFERRED TO DAN.

MIPER035062

Appendix 2. Metabolife Serious Adverse Events (continued)

From: [redacted]
To: [redacted]

Date: Thursday, May 20, 1999 8:41 AM
Subject: Fw: MetaboLife - Weight Loss product warning

Subj: MetaboLife - Weight Loss product warning
Date: 5/13/99 7:13:58 PM Central Daylight Time

Hello Friends,

I wanted to write an addendum to this to let you know that just this week, [redacted] got their second patient with cardiac arrest who was using MetaboLife. She was without a pulse for 16 minutes. She is currently in critical condition at [redacted] This information comes from [redacted] who is a nurse at [redacted] and who has a mutual friend of the young woman who is in critical condition. MetaboLife contains the active ingredient Ma Huang, which is a central nervous system stimulant. When ingested on a regular basis it can cause elevated heart rate and blood pressure, ultimately resulting in cardiac arrhythmias and arrest. It is marketed as a weight-loss product - what a way to lose, perhaps even your life!

Trust Shaklee not to market anything like this product, even though there are those ready to put this kind of stuff into their bodies, not realizing the danger. Herbal products are unregulated in this country. I personally rely on Shaklee's impeccable research -- if Shaklee doesn't make it, I don't take it, because I know there's a good reason why they don't!

[redacted] RN

5/21/99

[redacted] 2/4

MIPER035063

Appendix 3. Reviewer Comments

Reviewer Comment	Rand Response
Title is not very informative. Should include something about the conditions under study. Example: Efficacy and Safety of Ephedra for Weight Management and Athletic Performance Enhancement.	Change Made
Since the stated overall objective is "to assess he efficacy of herbal ephedra and synthetic ephedrine on weight loss and athletic performance ……" and since there is stated too few studies and data available to conduct an analysis of herbal ephedra on athletic performance, should not the title of the study be altered or the reported at least noted to reflect this limitation?	We think this is more appropriate for the text, and the title reflects the uses for which we attempted to find evidence.
I think you did an excellent job. Having reviewed this subject in more superficial fashion in the past, I can appreciate, more than most, what fine job you have done.	No Response
The overall purpose of the evaluation, including the questions, methods, findings and conclusions are clearly and succinctly written and easy to understand.	No Response
The search for relevant data appears to have been thorough and encompassed a broad range of literature resources.	No Response
The study selection appears to be appropriate for an evidence-based review of this type.	No Response
Data collection and data synthesis appear to be reasonable.	No Response
This is an excellent comprehensive review, and it will make an important contribution to the literature. Strong points are a clear description of review criteria, rigorous assessment methods, and straightforward data presentation. The questions formulated are relevant and appropriate, search strategies seem reasonable, and study selection is well justified. The meta-analyses are useful.	No Response
The Evidence Report utilizes modern methods of meta-analysis of clinical trials. However, it ignores a great deal of scientific evidence that can augment the interpretation of data from the clinical trials and has a major structural flaw and several weaknesses that are discussed below.	No Response. A specific response to the "great deal of scientific evidence ignored" is presented where such evidence is specifically referred to.
In my area of expertise (clinical studies of obesity), the findings were consistent with my understanding of the literature.	No Response
The overall evaluation is clear, and the purpose of the report is well stated.	No Response
Overall I found the report well-researched and written.	No Response
The questions were adequately formulated and easily understood.	No Response

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
Reasons for inclusion or exclusion of studies were clear.	No Response
In evaluating the obesity weight loss clinical studies, the report acknowledges some of the problems [small numbers of subjects, short durations of treatment, etc.] and states that long-term assessments of effectiveness are lacking. It would be useful to put these statements in the context of current knowledge in this area: that weight loss generally ceases after about 6 months irrespective of the treatment and any weight lost is generally regained. Current recommendations for appropriate clinical trials in this area include a much longer duration of treatment [1 – 2 years] and an evaluation of what happens after the agent is withdrawn . Both of these are very important in evaluating the efficacy and the risk to benefit ratio of a particular substance. Although ephedrine plus caffeine combinations [pharmaceutical and dietary supplement sources] are being compared to certain prescription drugs, to date no ephedrine plus caffeine product has undergone the equivalent types of efficacy and safety studies that are required prior to marketing of a prescription drug in the US.	This information was added to the limitations.
The purpose of the study and the means for arriving at its conclusions were clear and relatively easy to follow. The Meta analysis approach was appropriate and the criteria well defined. I believe some discussion should be given to the purported mechanisms of action (i.e. anoretic versus thermogenic) behind the " statistically significant "weight loss attributed to synthetic ephedrine/caffeine/ or ephedra-containing dietary supplements. The impression given by the meta analysis results is that, while statistically significant, these types of products also provide clinically relevant weight reductions. Given the results of the case report analyses, I don't believe the benefit of minimal weight loss (e.g. 1 to 3 pounds per month) outweighs the potential risk of serious adverse health effects exemplified by the case report analysis. Despite the study's inability to assign causality to most, if not all, of the serious adverse events, the authors, in their conclusion, seem to downplay the "potential" risks associated with these products.	This communicates a value judgment about the balance of evidence that is beyond the scope of the EPC. The concern about the report “downplaying” the potential risks is, as later peer review comments will indicate, shared by some other reviewers, but directly contradicted by others.
The appraisal of ephedra studies for weight loss could include a stronger statement about the unusually high attrition rates as compared to many drug studies. Although this is mentioned in the Limitations section, it also might be included in the results section where the data is interpreted. Can you expand on whether attrition rates differed between treatments a placebo groups? In my view, this is a major weakness of the recent efficacy studies involving ephedra.	Attrition rates did not differ between treatment and placebo groups. This has now been added to the results.
It is stated under Findings [p4] and elsewhere “that in aggregate the clinical trials only enrolled a sufficient number of patients to detect a serious adverse event rate of one per one thousand” or “three per thousand “ in the case of	Change Made

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
botanical sources of ephedrine It would be useful to put these numbers in the context of the frequencies of adverse events [common, infrequent, rare, etc.] Using commonly accepted definitions , all of the current clinical trials in aggregate, irrespective of source, lack the power to detect any rare adverse event [defined as greater than 1 per 1000 rate or frequency].	
Throughout the report, reference is made to "synthetic ephedrine". I suggest deleting "synthetic", since ephedrine is ephedrine. Some is extracted from plants and some is synthesized.	As these contradictory comments indicate, there is no agreement among experts about standardized terminology. In this report, for simplicity's sake, we use the term "ephedra" to mean the herb or herb abstract, and "ephedrine" to mean the chemical, regardless of source.
The term "synthetic ephedrine" is ambiguous due to the meaning of the terms "natural" and "synthetic" with respect to natural products chemistry. What could be meant are synthetically derived ephedrine alkaloids because these are natural products by virtue of their existence as naturally occurring compounds regardless of how they are produced. Ephedrine is by definition always a natural product unless one is referring to the racemate that is produced during some synthetic production processes because the specific optical isomer that is identical to naturally occurring ephedrine is itself is itself often synthesized through chiral specific processes. The fact of the matter is that what the draft means when referring to "synthetic ephedrine" could be either naturally or synthetically derived. It may be preferable then, in the interest of clarity throughout the document, to use some consistent terminology, such as: "ephedra" as the name of the crude raw material (with parenthetical identification of the pinyin name: ma huang one time, but not as a substitute common name) which consist of the dried stem of the plant; "ephedra extract" when referring to raw materials or ingredients that are processed extracts of ephedra; "ephedrine " when referring specifically to those one alkaloids as found in the plant or wherever the term "synthetic ephedrine" now occurs in the draft.	
I would place "synthetic" in front of all mention of ephedrine, or ephedrine alkaloids; for policy experts and others it is important to make the distinction between herbal and synthetic. I would use "herbal" ephedra when possible. I would also state more directly and more often why the synthetic ephedrine use is not reviewed as part of the AERs.	
Also, contrary to the phytochemical section of the report, ephedra is know to contain (-)-norephedrine but not (+)-norephedrine. Phenylpropanolamine consists of (-/+)-norephedrine, while ephedra does not contain (+)-norephedrine. The parenthetical identification of norephedrine as phenylpropanolamine should therefore be removed.	Change made

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
A minor point in phytochemistry (page 13) is that only (-)-norephedrine occurs naturally in ephedra, whereas the synthetic drug, phelypropanolamine is the racemic mixture of (+/-) -norephedrine. So, it is more precise to state that ephedra contains norephedrine, as opposed to containing PPA.	
After reading the RAND report, my first impression is the following: What are we evaluating – ephedrine or herb ephedra? The latter is not a single-chemical entity and cannot be assumed to be ephedrine. Even assuming the herb ephedra in the literature is defined to contain specific dosage levels of 'ephedrine,' what efforts were made to ascertain that this 'ephedrine' is indeed ephedrine and not a mixture of ephedrine-type alkaloids, or, worse, different types of alkaloids that are also present in ephedra? Any study or report on a natural product (not just a single-chemical compound) must clearly define what the material under study or being reported is. I don't see such a definition in this report. Despite the limited availability of useful data, this report's conclusions regarding the efficacy of ephedrine (the single-chemical drug), in the presence and the absence of caffeine, in short-term weight loss and athletic performance, appears to be sound. However, this cannot be said of the herb ephedra that contains ephedrine but is not equivalent to ephedrine. Hence, the conclusion regarding ephedra's efficacy "Ephedrine, ephedrine + caffeine, and ephedra-containing dietary supplements + herbs containing caffeine all promote modest amounts of weight loss over the short term..." lacks supporting data, unless all the limited number of clinical studies employing "ephedra-containing dietary supplements" had clearly defined ephedra, including amounts of ephedrine and related alkaloids (not just ephedrine and inert herb carrier).	We agree that the lack of specificity is a problem. We have modified the conclusions to be more specific to only these herbal combinations studied. In the RCTs of herbal ephedra included in the efficacy analysis, the dose of ephedrine alkaloid was stated.
The ODS and AHRQ contracted with RAND (Dr. Paul Shekelle as Task Director) to conduct a thorough synthesis of the clinical efficacy and adverse effects of ephedra. It was clear to me that the objective of this contract was met. The review was complete and the researchers used the systematic review/meta-analysis tool to review the published controlled clinical studies on ephedra-containing dietary supplements.	No Response
There was a mention of 157 articles that were case reports of adverse events published in medical journal, however, they are not included in the case report and there are no mention of the finding in the Limitation section on page 110. Would those case reports provide more information than what are available from FDA? Should a statement be made on why those published case reports not included in the analysis (e.g. potential duplication with FDA, time and	These case reports are now included in this revision.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
resources...etc.)?	
The report has been carried out and is free from bias. It is objective. I cannot comment on some areas of the report that are not my expertise.	No response
The draft report is incomplete since it does not include a review of studies of two types: Toxicology in laboratory animals, and published case reports.	Published case reports are now included. Toxicology and animal studies were not included, as this (and most all EPC reports) focus on clinical studies in humans.
This draft emphasizes the subjective judgments of the authors over the objective findings of the clinical studies and therefore appears from the outset to have a slant against the safety of ephedra products.	We disagree that the report is slanted against the safety of ephedra products, and note the peer review comments we received with exactly the opposite opinion (i.e. that we were too conservative in our conclusions regarding possible adverse events from ephedra).
Given the observations and comments above, one is left with the impression that this draft report has a tone or tenor that leans toward an apparently preconceived conclusion that ephedra supplements are not safe. The tone is established in the abstract by reference to the FDA's AERs "related to herbal ephedra" and "available reports of herbal ephedra-related death, myocardial infarction (heart attack) and cerebral vascular accident (stroke)." the abstract goes on to describe "our causality algorithm" and later to use terms "probably causally related" and "possibly casually related". Nowhere in the abstract is it suggested that these purported AERs were looked at objectively and found (to quote page 112) that "definite causality cannot be determined from case reports". The statements in the abstract strike the reader as definite scientific conclusions rather than subjective observations that is not consistent with other objective data. Nowhere in the abstract are the major limitations described, nor is there any mention that "scientific studies (not additional case reports) are necessary" (from page 113). On page 5 it is stated that "Continued analysis of case studies cannot substitute for a properly designed study to assess causality", yet this is precisely what this draft report has done. Additional statements and references point to a lack of objectivity and a bent toward sensationalism. For example, page 5 a comparison is drawn with phenylpropanolamine and it's "reported association and cerebral hemorrhage" without nothing that the report at issues is highly controversial, or that the report found no association between ephedrine as an over-the-counter drug. The mention of cerebral hemorrhage at the conclusion of the abstract is presumably also a result of some unfounded	We have endeavored to keep the language of the report as factual as possible. We note that other reviewers criticized the report for exactly the opposite reason – being "too soft" and "down playing" the risks of ephedra use. We do not think we can revise the report to reconcile these two divergent opinions. With regard to format, this report adheres to EPC format requirements. With regards to phenylpropanolamine, we note other reviewers critiqued us for not making more of possible similarities. In this case, we deleted the phenylpropanolamine sentence.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
conclusion that phenylpropanolamine have been conclusively tied to cerebral hemorrhage when this is not the case. In counterpoint to a description of the extent of present use and to the long history of use in China, references are made to media attention, lawsuits, a citizens' petition, and a ban by the National Football League, and a Canadian Warning. These references are not helpful in a scientific review that should be evidence based, but instead give an impression of the slant toward a view that ephedra products are not safe.	
Although the draft report contains much factual information about both the benefits and risks of ephedra, ephedrine, and combinations of one or the other with caffeine sources, certain critical components of a full analysis are missing. Specifically, there is much proper emphasis on examining the data for evidence of causality, but little or no attention to the dose-response relationship within any possible causal case. This is a critical limitation that prevents the safety component of the report from being fully useful.	A dose response analysis has been added to the RCT analysis. We indicate that we do not feel such an analysis is justified on the case report data.
The strength of this report is that it is not only comprehensive, but also objectively performed. Another strength of this report is defining the areas that need further research. The limitations are those imposed by the data.	No response
It is clear what was done.	No response
The major strength of study was the statistical approach utilized for assessment of efficacy and the incidence of minor adverse effects.	No response
The major limitation was the coupling of conservative causality assessment criteria with limited medical records and toxicology data while interpreting the case reports. While the case reports do not offer mechanism for assessing the incidence of serious adverse events, they shouldn't be dismissed completely owing to an overly conservative set of exclusion criteria. Case control studies are definitely warranted, but it would be especially tragic if their outcome, when determined three of four years from now, confirm what is strongly suspected at the moment.	We acknowledge our criteria are conservative. We note the great deal of discussion among peer reviewers regarding whether a case report analysis was biased toward or against the safety of these products.
There are some nomenclature issues in the draft that should be corrected or clarified. The term "herbal ephedra" contains a redundancy, as by definition, all ephedra is herbal or herbally derived. Also, and this goes beyond nomenclature to ingredient definition, the term ephedra is often used in the draft when in fact what is being discussed is an extract of ephedra with a specified percentage of ephedrine alkaloids. This sort of misrepresentation of material identity leads to confusion between ephedra as a crude botanical, an extract of ephedra (the form most often used in dietary supplements) with a specified percentage of constituent ephedrine alkaloids, (usually 8%), and the	We have endeavored to keep the nomenclature clear.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
ephedrine alkaloids themselves.	
Perhaps it could be made clearer that, overall, a very small number of people have been studied in controlled trials of any duration. This is an issue as regards to safety, rather than efficacy where the studies, though small, are quite consistent.	We emphasize the limited power of the RCTs to assess safety.
This review reflects my perspective as a neurologist and stroke researcher. It is a very valuable collection of data assembled to address clear, relevant clinical questions.	No response
It was clear how the report was developed.	No response
The major strength of this report is its collection of data systematically on one report for review and assessment.	No response
The major limitation is the way in which the conclusion are stated and failure to distinguish for the lay reader the difference in strength of evidence of adverse reports vs. intervention studies.	We have tried to make this distinction clearer in this revision.
This well-done report takes a conservative approach without extrapolating the interpretation beyond the available data . It clearly describes the methods used, limitations of the methodology, and results. The text under Future Research describing identification of gaps in knowledge is particularly useful. The presentation of the analysis of adverse events reports (AERs) might be made clearer by using different terminology or a narrative explanation of the causality designations.	No response, other than causality has been removed from this revision.
Quality of Life. As I view the field of obesity, there are two reasons people want to lose weight. One is for the health-related benefits. For most physicians, of whom I am one, this is often the major focus of our support for efforts to lose weight. However, over the years, I have come to realize that the major reason people want to lose weight is because obesity is a "stigmatized" condition. The fact that 75% or so of the people volunteering for treatment are women, and that obesity carries such a negative social view stimulates people, particularly women, to use over-the-counter medications. Yet there is no mention that I can find of quality of life in this report.	We agree this outcome is important. However, we did not find it reported in the clinical trials we identified.
Body Composition. One of the interesting responses to treatment with ephedrine and caffeine in the reports of Astrup and his colleagues is the increase in lean body mass, or loss of less lean body mass. The implications of this for use of these medications and in the future research is not even mentioned that I can find.	This distinction is not one that was included as an outcome of interest by our TEP. We agree it is a potential area for future study.
Performance. There is quite a literature on caffeine and performance that certainly plays into the ephedra/caffeine use by athletes. Yet none of this literature is dealt with here.	We were not requested to assess the literature on caffeine and performance.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
Drop Outs. The issue of drop-outs is considered with the <20% vs. >20%. From a therapeutic effect, the "completers" in a trial are much more informative to me than using the data on those who drop-out in a last observation carried forward analysis. We are certain that drop-outs are likely to regain weight - We aren't curing obesity and weight gain during the adult life is the "expected". Moreover, if we do not use the LOCF approach, the impact depends strongly on when people drop out. If they drop-out at month 5 of a 6 month trial it has essentially no effect. If they drop out in the first month it has a major effect.	We agree that knowing when dropouts occurred might make it possible to better understand the results of weight loss trials. However, when dropouts leave a study is not routinely reported and hence we did not have access to these data.
On page 3 there is mention that the studies have "particularly high attrition rates." What is considered a high attrition rate? How do these studies compare to other studies on obesity? There is no explanation as to whether there is a particular challenge in all obesity studies or research in general, or whether this attrition rate appears to be unique to the ephedra studies.	The attrition rate issue is explained in more detail on page 27, where 20% is identified as a threshold. A high attrition rate is not unique to studies of ephedra, but regardless of study question a high attrition rate increases the concern regarding bias.
Long-Term Trials. In the Future Research area you call for "longer" term trials. For all reported drugs the maximal weight loss is achieved by 6 months. Continuing treatment usually maintains an effect, but because weight losses of 10% (20 lbs for someone weighing 200 lbs) does not often get them to a satisfactory weight, people drop-out because of perceived "failure" of the medication. I thus have limited enthusiasm for long term studies with agents that don't produce weight losses of more than 10%. On p. 4 you indicate that there are "no long term" studies. As noted above, I think the 6 month studies that reach a plateau tell us about all we can expect from these trials. Do you disagree?	We clarified this to indicate both longer duration of treatment and maintenance of weight loss.
The report should be reorganized to focus on the conclusions about the need for further research. The section on safety should address expected effects at intended doses and comment on adverse effects of higher doses. The transient nature of the events observed in the clinical studies should be discussed. The FDA AER database unfortunately is not of sufficient quality to comment on either of these issues related to safety.	We do not know if the events observed in the clinical studies were all transient and would not characterize them as so. A dose analysis is now included in this revision.
There should be another draft report issued to the TEP to ensure that these issues are addressed to the satisfaction of the TEP before a report is finalized.	This is not EPC practice, and there is no requirement that the TEP be “satisfied” before the report is finalized. We intentionally recruit TEP members holding differing views in order to be made aware of all viewpoints. Trying to get all such people to be “satisfied” with the final report is an impossibility as demonstrated by the wildly diverging comments we received from TEP members regarding the causality analysis.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
Para 1 I would use the word treatment duration, intervention length, or other terms designating the duration for which the participants were on ephedra/ephedrine instead of using "follow up". I would not use follow-up as it denotes a passive time post-intervention for which participants were followed to measure outcomes. e.g. 19 were excluded from pooled analysis because their intervention periods were less than 8 weeks.	Change Made
The term "follow-up" can have a number of meanings in the context of obesity/weight loss trials. In addition to referring to the duration of treatment with a test agent during which a research subject is evaluated, it can also refer to patient evaluation after treatment has been discontinued. From my reading of this report, you are using "follow-up" to only refer to the time during which treatment is administered. It might be useful to clarify this in the text as 8 weeks of treatment, etc so as to avoid any confusion in meaning.	Change Made
I was slightly troubled by the exclusion of studies with less than eight weeks' follow-up. While I agree that studies with less than eight weeks' follow-up are undesirable, if a large number of such studies exist, it does seem unfortunate to exclude them. I would rather have seen them included and have separate analyses for a very short-term weight loss and slightly longer term weight loss. I think that the exclusion of such studies, if there are many, opens up the report to allegations from companies who have done such short term studies that their important data were not included and that the report is biased. I am not stating that I believe the report is biased, but only by any exclusion of such studies if there are many, opens up the report to this allegation. Moreover, while as I said previously, I do not favor studies less than eight weeks' duration, I still think that while such studies exist there is something we can learn from them.	The exclusion of studies less than 8 weeks duration was made by the TEP and not something we can change at this stage. The key question specified "a sustained period of time" for efficacy and this was judged by the TEP to be at least 8 weeks.
Page 2, para 4: It would be useful to give the reason that the Technical Expert Panel (TEP) gave for suggesting that follow-up of less than 8 weeks is insufficient to assess weight loss. It is because the original charge was to assess long-term weight loss and the TEP thought 8 weeks could not be considered long-term?	Yes, and furthermore even short term weight loss would not be useful below 8 weeks. Explanation made in the Methods.
Follow-up of 8 weeks. This term used on p. 2 and then many other places is confusing. As a clinical investigator, follow-up usually means the time after treatment is complete. You appear to be using it only for the treatment period. It would confuse me less if you said "duration of treatment".	Change Made
This review excluded 19-controlled trials that assessed ephedra or ephedrine for weight loss because there was follow up of less than 8 weeks in each of these. This	These studies were included in the safety assessment.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
exclusion is rational from the perspective of evaluating the evidence for efficacy. Information obtained from these trials about short term adverse effects, or the lack thereof, would be valuable however in the overall evaluation of safety. We strongly encourage the inclusion of all such data from these trials.	
The statement, "In order to improve health outcomes, long term weight loss is necessary" is not accurate. Usually in pharmacotheraphy for weight loss, long-term means one year or more. I am not aware of studies that have used time in place of percent body weight loss as the important measure. Because your point is that the studies were short (<=4 months) I would change loss to maintenance because Yanovski et al. (2002) states that most nonsurgical obesity treatments lead to weight loss for the first four to six months followed by regain. It is not only that the ephedra interventions did not extend beyond 4 months but also that there was not sufficient follow-up to determine if individuals were able to maintain their loss. See review by Yanovski et al., 2002 New Engl Journal Med.	Change Made
Rewrite last sentence to say "In order to improve health outcomes and reduce the risk of morbidities associated with being overweight, sufficient weight loss (5 to 10% of body weight) and long term weight maintenance is necessary.	Change Made
See comments on page 3 and 5 regarding use of term follow-up; treatment duration, ephedra intervention, etc.	No Response
Small weight losses (5 to 10%) of body weight reduce the risk of morbidities associated with being overweight (Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. National Heart, Lung, and Blood Institute (NHLBI), Clinical guidelines for obesity, 1998.)	Reference Added
This first paragraph seems to blend intervention duration and follow-up post intervention. Please rewrite to reflect data. Longest intervention: 4 months (this is not "follow up").	Change Made
You do not address whether individuals lost a certain percent of their pre-ephedra weight. This measure is important when it comes to defining weight loss success.	Percent of weight loss in the treatment group is now included in this revision.
Maybe the key points of DSHEA needs to be stated in the overview or somewhere else to emphasize herbal supplements versus supplements containing synthetic alkaloids. Maybe place a sentence after the "In addition to the questions related to ephedra-…safety. Because synthetic ephedrine alkaloids….	We revised the text to try and improving clarity.
On page 3 the report mentions that an algorithm for assessing causality was developed by the authors. Was the	This algorithm was deleted from this revision

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
algorithm unique to this study, or is there already significant scientific agreement to its accuracy and validity? If it is a new algorithm, who suggested its use? How was "reasonable certainty" determined?	
The Draft identifies question that guided this Report, both in relation to weight loss and energy enhancement, as "Does ephedra have additive effects with other agents?" Specific emphasis was placed on caffeine and caffeine-containing botanicals, but in Table 1 herbal "agents" were listed as "Herbs commonly combined with ephedra," presumably (though not stated) in products marketed for weight loss.	Change Made
It is stated that “the majority of ephedrine (up to 97%) is excreted unchanged by the urine.” The 97% seems too high. The recent paper by Christine Haller et al (Clin Pharmacol Therap 2002;71:421-32) indicates that about 60% of ephedrine is excreted unchanged in the urine. This is important because the other 40% can be metabolized to other pharmacologically active alkaloids.	Change made
In places, particularly the introduction , the report focuses more on ephedrine than ephedra. Since there were only 5 trials assessing ephedra for weight loss (actually 4, since one is reported twice) and many more synthetic ephedrine, the ephedrine trials would seem to have greater weight than the ephedra trials. Not clear how this influences the results.	We present the results stratified by agent. The efficacy results for ephedrine & ephedra were similar.
There are several problems with Table 1. No references were given to inform as to how the herbs included in this Table were identified as "commonly combined with ephedra" and in fact it is our belief that several of the listed herbs are either uncommonly found in products containing ephedra and marketed for weight loss or are not found in the market. For example, although the aloe resin is known to be a cathartic laxative, we are not aware that it exists as an ingredient in any ephedra product (or in any dietary supplement product), and if it does it is certainly not common. Without attempting to be exhaustive, the same is true for at least the following: cocoas, coffee, scotch broom, jalap bark, and mayapple root. In addition, several of the ingredients are at best questionable for the described categories, and follow-up should be undertaken to find references to support that yellow dock root is a cathartic laxatives. These examples are again not exhaustive; references should be given to support each herb in its classification. An additional oversight is that some listings do provide the part of the plant that is purportedly a commonly combined with ephedra, though very nearly 50% do not. The federal law requires that botanical ingredients in dietary supplements identify the plant part and this Table should do the same.	We greatly shortened this Table to include just the caffeine-containing herbs, as suggested by this reviewer.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
Finally, the Table does not appear to provide any information that is useful toward answering any of the questions proposed by the funding agencies or those that guided the Report. While the question of the additive effect of other agents was proposed and reportedly guided the report, there is no attempt in the Report to actually do this, except in the case of caffeine containing herbs. In summary, it might be best to eliminate the Table to reduce it to consist of just the caffeine containing herbs. If the table is maintained, some effort should be made to actually find each of the listed ingredients in one or more products in the market. This is especially true for hers with significant toxicity potential, such as Scotch broom to mayapple as the final report should not communicate that these ingredients are "commonly" sold. Preferably, such market information would be provided in the form of references. The part of the plant that is used should be including for any plant listed in this Table. References should be provided as to how classifications are made if the categories in the Table are maintained. Notwithstanding the above comments the question whether all of these herbs should be included in the Table, there are several spelling errors in the botanical names: Coffea is correct, as in the 1st such listing but Caffea is not; Camellia is correct as in the 2nd such listing, but Camilla is not; the correct spelling of the species name for Mate is paraguariensis; the references species of mayapple is P. peltatum while Rheum palatum us correctly recorded as rhubarb, R tanguticum (misspelled in the Table) is considered to be a variety of R. palmatum (so R. palmatum var.tanguticum) and R. officinale is misspelled in the Table; the correct spelling of the botanical name for flax ends in "m" rather than "n" (so Linum usitatissium);Irish moss is in the genus Chondrus, not Chrondrus; contemporary authorities accept the name of the slippery elm to be Ulmus rubra rather than Ulmus fulva, these corrections may not be exhaustive.	

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
The characterization of DSHEA in the Background section of Chapter 1 is inaccurate, biased, unnecessary and badly written!! It should either be removed -It has nothing to do with the assignment-or expanded, to include other elements of the law. For example:" The DSHEA was passed unanimously in 1994 based in part of Congressional displeasure with the federal governments 'adhoc, patchwork regulatory policy on dietary supplements.' Under these regulations, herbal dietary supplements are not necessarily required to be tested for safety prior to marketing, although marketers are required to assure all of their products are free of significant or unreasonable risks. Also, as with over-the-counter drugs, there is not a requirement to report health problems that resulted from their use. The federal regulations that govern this class of goods are different from this that control either foods or drugs, but as with both of these classes, FDA and FTC maintain significant authority to regulate the manufacture, labeling and claims for dietary supplements and to remove unsafe products."	We have included some, but not all, of this additional material when describing the DSHEA.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
The Dietary Supplement Health and Education Act of 1994 (DSHEA) The brief mention of Public Law 103-417 is inadequate. In 1994, Congress passed the Dietary Supplement Health and Education Act (DSHEA) amending the Federal Food, Drug, and Cosmetic Act. In DSHEA, the term "dietary supplement" is defined as: 1. A product other than tobacco intended to supplement the diet that bears or contains one or more of the following dietary ingredients: * a vitamin; * a mineral; * an herb or other botanical; * an amino acid; * a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or * a concentrate, metabolite, constituent, extract, or combination of the above listed dietary ingredients. 2. A product that is intended for ingestion is not represented as food or as a sole item of a meal or diet, and is labeled as a dietary supplement. 3. It includes an article that is approved as a new drug, or licensed as a biologic, and was, prior to such approval, certification, or license, marketed as a dietary supplement or as a food unless the Secretary has issued a regulation, after notice and comment, finding that the article, when used as or in a dietary supplement under the conditions of use and dosages set forth in the labeling for such dietary supplement, is unlawful. 4. It excludes articles that are approved as a new drug, certified as an antibiotic, or licensed as a biologic, or an article authorized for investigation as a new drug, antibiotic, or biological for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, which was not before such approval, certification, licensing, or authorization marketed as a dietary supplement or as a food, unless the Secretary, in the Secretary's discretion, has issued a regulation, after notice and comment, finding that the article would be lawfully marketed as a dietary supplement. 5. It deems a dietary supplement to be a food. 6. It excludes a dietary supplement from the definition of the term "food additive." Important safety measures were included in DSHEA. A food could be deemed to be adulterated if it was a dietary supplement or contained a dietary ingredient that: 1. presents a significant or unreasonable risk of injury; 2. is a new dietary ingredient for which there is inadequate information to provide assurance that such ingredient does not present such risk; 3. poses an imminent hazard to public health or safety; or 4. contains an ingredient that renders it adulterated. Important clarifications were included in the law regarding labels and labeling. Section 5 of DSHEA provides that a publication shall not be defined as labeling when used in connection with the sale of dietary supplements when it: 1. is not false or misleading; 2. does not promote a particular manufacturer or brand of supplement; 3. is displayed so as to present a balanced view of the available scientific information; 4. is displayed physically separate from such supplements; and 5. does not have appended to it any information by sticker or other method. 6. places the burden of proof on the United States in establishing that such matter is false or misleading. Additionally DSHEA: 1. Set forth conditions under which nutritional claims may be made with respect to such supplements. 2. Deemed a dietary supplement misbranded unless its labeling meets specified guidelines. 3. Deemed a dietary supplement which contains a new dietary ingredient adulterated unless: A	

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
The draft sites in it's Chapter 1 the findings of a 1996 meeting of the FDA's Food Advisory Committee (FAC), stating that "over half of the members recommended removal of dietary supplements containing ephedra on the market" and gives as it's reference Dr. Lori Love's testimony in August 2000 at another meeting. To assure that the findings of this meeting are most accurately reported it would be best to add a statement such as "a finding that was in direct contravention to the recommendation of the Special Working Group of experts that had been empanelled to offer guidance to the FAC. "The transcript of the 1995 meeting of this Special Working Group can be seen at http://www.cfsan.fda.gov/~dms/ds-ephe1.html . The more important factor with regard to this statement, however, is that it is false. The transcript of this meeting is available on the FDA's website in two PDF files (see http://www.fda.gov/ohrms/dockets/ac/cfsan96.htm). Regardless of how Dr. Love characterized the recommendations of the FAC members, the record shows that only 4 of the eleven voting members of the FAC stated that ephedra products should be removed; even when calculating the opinions of all the meeting's participants, well under half made statements to that effect. The statement in the Draft could be corrected either by changing "over half of" to "a minority of" or by reversing the two sentences (At this time over half of the members recommended that the FDA develop rules on use that would help reduce risk over adverse events, a recommendation that trade groups had made two years earlier". Finally, the use of the word "Thus", at the beginning of the next sentence in this section implies a direct relationship between the reported advice of the FAC and FDA's imposed rule. This is a reinvention of the historical facts. FDA stated in its proposal was based on information that included, but was not limited to the opinions of the FAC. More detail should be added to this section if the report is to be an accurate record of facts. If the only limitation accessible about the history of the controversy regarding the use of ephedra in dietary supplements was from the Background in the Draft's Chapter 1, one would conclude that federal health officials, consumer groups and National Football league had been actively attentive to this issue while industry stood by. This is not the case. The Background information should be expanded to include some or all of the facts: that AHPA adopted labeling guidelines in 1994 that were substantially familiar to those later proposed by FDA; AHPA adopted dosage limits (25mg/servind; 100mg/day of ephedra alkaloids) in 1995; AHPA and others specifically requested in public hearings in 1995 and 1996, and in a meeting with FDA in 1999 that the industry policies be adopted by rulemaking; AHPA and others submitted a Citizen petition in October 2000 (prior to the Public Citizen petition identified in the background) to make the same request in a more formal manner.	

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
Many scientists would disagree with the statement [page 4, and elsewhere] that “definite causality cannot be determined for case reports when the adverse event is very serious” [or various iterations of this statement]	We note this comment, and also note that many scientists would agree with it. At any rate, we have deleted from this revision the causality assessment.
p.9 Background states “Three billion servings of ephedra containing products were consumed during 1999” This is a misstatement , as in the transcript Mr. McGuffin indicates “servings sold” rather than servings consumed. As a separate comment, it is unclear as to whether the data on the number of servings actually represents servings manufactured by a particular company or some other measure.	We have revised this statement to make clear this is the industry’s contention.
D. Finally, the report should not repeat the industry assertion that three billion servings of ephedra were consumed in 1999, unless this is based on hard facts. It's a self-serving statement that has the effect of diminishing the safety concerns over ephedra by perhaps inflating the frequency of exposure. Is the three billion estimate based on quantities sold? Surely not all dosages were consumed.	Change made to reflect this is an industry assumption.
p.10 FDA concerns about the safety of ephedrine alkaloid containing products sold as supplements preceded the passage of DSHEA, which changed how FDA could deal with safety in the context of supplements.	We revised the text to reflect this.
Two references in the background section should, in my opinion, be changed. On page 11, you state that "weight loss has been associated with decreased morbidity and mortality" and cite ref. 26, the Williamson et al study. Actually, the literature on this point is quite controversial, and despite the Williamson study, much of the literature shows an increase in mortality with weight loss. All of these studies are observational, and subject to serious limitation. This is why NIDDK is undertaking a very large study (Look AHEAD) to answer questions about morbidity/mortality with voluntary weight loss. The DPP does suggest that intentional weight loss in persons at risk can delay or prevent the onset of type 2 diabetes in persons at high risk. I suggest that you state instead that "intentional weight loss in obese persons leads to reductions in risk factors for disease" and cite the NIH guidelines: Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. Obes Res 1998; 6 Suppl 2:51S-209S.	Change made
Also, on page 14, ref. 69--when discussing the role of ephedrine in humans, its role in stimulation of beta three adrenergic receptors in brown fat is noted. There is very little brown fat in adult humans, and I'm unsure that this would play any role in ephedrine's thermogenic effect. The reference cited is an old one (1982). Someone should be sure that this citation represents current thinking on the role	We deleted this comment.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
(if any) of brown fat in the thermogenic effects of ephedra compounds.	
The definition of overweight is >=25-29.9 (not in excess of 25 but also inclusion of 25) and the definition of obesity is >=30 (not greater than 30 but inclusion of 30) See NHLBI, Clinical guidelines for obesity, 1998	Change made
The attempted intentional weight loss data is only for 1996. The 1998 data you reference is a paper that only includes a subset, only 5 states. The latest national data on attempts for weight control is the 2000 data that is in Reference 10. Therefore, you may want to delete reference to the 1996 data and instead use the 2000 or just edit the sentences to say "The same survey when administered in 2000 showed that one third (38.5%) of subjects were actively trying to lose weight and another third (35.9%) were trying to maintain their weight.ref 10 Furthermore, among those who were overweight 45.0% of subjects were actively trying to lose weight and 34.9% were trying to maintain their weight. Among those who were obese, 65.7% of subjects were actively trying to lose weight and 20.8% were trying to maintain their weight" ref 10. I then go on to reference 29 data. The would suggest using the estimates from Reference 29 to determine a denominator for use. I would suggest also using the Michigan data from this paper to support claims that consumers are not aware of the ingredients in their herbal supplements. Ref 29 –"In a population-based study of 14,679 U.S. adults in 5-states using the 1998 BRFSS data, 7% reported using nonprescription weight loss products; 2% reported using PPA and 1% reported using ephedra products from 1996 to 1998. More women used ephedra products than men; 1.6% of women and 0.4% of men reported using weight loss products containing ephedra. Extrapolated nationally, this study estimated that during 1996-1998, 2.5 million Americans used weight loss products containing ephedra. "This study also has data to suggest that many individuals are not aware they are taking weight loss products that contain ephedra. Of the 183 respondents in Michigan who responded no to the questions about using ephedra and reported to have taken "other" nonprescription weight loss products, 33% reported using name-brand products that claim to contain both ephedra products and chromium picolinate. "	Change made
I would rewrite the sentence regarding Harnack et al. (2001) to be the following (inclusion of small n and previous of ephedra specific for weight loss). It is hard to follow what the 12% of the total is when you don't give the original total usage (61.2%); and, it is really 5.3% that used ephedra for weight loss. This is larger than Ref 29, but Ref 29 has	This change was made consistent with previous reviewers comments.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
14679 individuals whereas the Harnack study has only 376. Among 230 (61.2%) of 376 adults in the St. Paul/MSP area who reported using an herbal products during the past 12 months, 44 (19.1%) used ephedra. Of these 44, 20 (45%) used ephedra for weight loss. Therefore, 5.3% of adults (20 of 376) reported using ephedra for weight loss. --Taking these estimates, you find that 20 (5.3%) of 376 individuals used ephedra for weight loss during the past 12 months (1998/1999).	
Some of the herbs mentioned in the last sentence are not listed in Table 1. Many of the latest formulations also contain bitter orange. I would add these to the Table.	This Table has been greatly shortened and this part has been deleted.
On page 9, the following key information is provided: Ephedra has been used for over 5,000 years. Three billion doses have been sold. Even after the FDA's campaign to advertise the AERs and to have more AERs reported, there has been a 65% increase in volume of sales over the previous five years. Even after the FDA's campaign, there are only 1,500 AERs out of 3 billion servings. That calculates to about 1 adverse event in every 2 million servings. By anyone's standards that is very safe.	This is a judgment and not a statement of evidence, which is what the Evidence Report presents.
On page 10, the statement, "Still, the controversy over ephedra continues," and a reference to litigation have no place in a scientific analysis. It is doubtful that such information was garnered from a review of the published scientific literature. Inclusion of this type of information takes away from the science.	We disagree that these sentences take away from the science, we think they are necessary to put the science in context.
Information from the scientific literature on ephedrine (the purified alkaloid) regarding it mechanism of action. There is a fair amount of literature (1910 to 1930) about ephedrine. For example, Chen KK, Schmidt CF. Ephedrine and Related Substances, Medicine volume 9, number 1, 1930.	This section of the report was not intended to be exhaustive, but to provide context for the reader. Many relevant references may not be included.
Page 10 paragraph 1: Obesity, The definition of obesity had changed since 1991. A result of this change was that in the mid-1990's many more people were considered obese than previously. So, although the incidence of obesity had been increasing since 1991, the change in definition makes it seem more dramatic than it actually was. As a result, this statement may need to be qualified.	This is probably true, but by most standards the incidence is increasing. At any rate we did qualify the statement.
Page 12, paragraph 2: It is appropriate to extrapolate figures from 511 subjects attending a gymnasium to the general public? Suggest qualifying this statement.	We indicated this is the authors' extrapolation.
The RAND Corporation has drafted a document entitled "Ephedra: Clinical Efficacy and Side Effects" in order to assess the efficacy of herbal and synthetic ephedrine on weight loss and athletic performance and to assess the safety of herbal ephedrine products through review of adverse events reported in clinical trials and in reports on	No specific response to these general comments. Specific responses to specific comments below.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
file with the U.S. Food and Drug Administration (FDA). This report will focus on the safety assessment in the RAND report. Prior to commenting on this assessment, however, it is important to note that the RAND report includes a formal meta-analysis that concludes that products containing herbal ephedra and caffeine produce significant weight loss over a 4 to 6 month period. This weight loss is similar to that documented from synthetic ephedrine plus caffeine. Given the epidemic of obesity in the United States and the associated morbidity and mortality from obesity, it must be emphasized that weight loss may play a large role in reducing morbidity and mortality. In fact, several studies have shown that weight loss associated with herbal ephedra and synthetic ephedrine are associated with significant reductions in parameters associated with cardiovascular disease among the obese (e.g., reductions in triglycerides, 1, ApoB, 1 and LDL-cholesterol;2 and increases in HDL-cholesterol2).The evidence for weight loss is quite robust because it is derived from controlled randomized trials. The best data for safety would also be derived from randomized trials. RAND reports on adverse events within randomized trials, noting that there were "no serious adverse events (e.g., death, myocardial infarction, stroke) reported in these clinical trials." Because of the limited numbers of subjects studied in these trials, these studies could only detect a serious adverse event rate of one in a thousand. That is the studies can exclude a rate of serious adverse events of greater than one in a thousand. This should not be inferred to mean that the rate is one in a thousand nor that ephedra even causes adverse events. In the absence of additional controlled studies, RAND then turned to adverse event reports (AERs) filed with the FDA up to September 30, 2001. The limitations of AERs in proving causality, especially when viewed in isolation of the totality of evidence, are well known and have been discussed extensively in the literature and basic textbooks of pharmacoepidemiology. Causality cannot be proven by AERs because there is no comparison control group. Authors of other reviews of AERs in the ephedra database have noted that a collection of AERs "does not prove causation, nor does it provide quantitative information with regard to risk."3 There are several reasons for this which will be discussed briefly.	
To what end was this inquiry directed? Most exogenously ingested chemicals that are thought to enhance athletic performance are banned from competitive sports. To what end will the results of such an inquiry be applied?	This report was commissioned by AHRQ & ODS to assess the state of the science regarding ephedra.
Given the most contradictory recommendations of the CANTOX report regarding the safety of the ephedra supplements, why was a member of CANTOX included as a	We believe that every person on the TEP has a bias. Our goal in selecting the TEP was to try and get a balanced set of

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
part of the Technical Expert Panel? Some bias may have been imparted from a member of an organization with such close ties with the ephedra industry.	biases. We judged it important to include in the TEP a member with close ties to the industry who was also scientifically credible.
Of note, no neurologists (and particularly no stroke experts) were included on the Technical Expert Panel.	While true, a neurologist was included in the group assessing the case reports and a neurologist was included in the peer reviewers.
The group was charged with assembling and evaluating the evidence that ephedra and its congeners favorably affected "energy enhancement", affected weight loss and improved athletic performance. "Energy enhancement" is a vague term and it is not clear how it can be measured or tested.	Our TEP defined this for us as indicated in Table 3.
A basic problem in the method adopted for the pooling of studies rests with the false assumption that these herbal preparations have been standardized and are similar enough in constituents, potency and purity that they can be assumed to have sufficient homogeneity to justify pooling of results. In fact, there is much evidence that this is not the case. Yet much of the report rests on the results of the pooling of many under-powered studies of herbs or ephedra where potency and constituents are vaguely described or even unknown. The herbs are mixtures of many chemicals with various actions so it is doubtful merging or pooling such studies represents a scientifically legitimate exercise.	We disagree with this opinion, and point out the chi-square test of heterogeneity did not reject the null hypothesis of no difference in the effects reported in the four ephedra studies.
In sum, this report addresses two questions that are not relevant to the public health: "energy enhancement" and "improved athletic performance". The public health question it does address, obesity or weight loss, is not answered due to the heterogeneity of the products examined and pooled and the lack of long-term follow-up studies. The case reports of adverse events possibly due to ephedra or ephedrine are not well described and the algorithm adopted is too rigid and is being applied to a data collection system that is unable to obtain the data required for causality in the algorithm.	The key questions were given to us by Federal Agencies and defined by our TEP. Causality was removed from this revision.
There is no reason to engage in further research concerning ephedra or ephedrine. Enough is known about its benefits and risks to remove the drug from the market. More research is merely a stalling device to delay the removal of the product from the market.	This is an opinion and not a comment about evidence to which we can respond.
That ephedra has efficacy for weight loss seems to be true, though people can quibble over how much. The key question, as I see it, is: Is there credible evidence that ephedra poses a significant or unreasonable risk of harm, even when taken at recommended dosages? This report so far is inadequate for addressing this question.	No response as there is no specific critique of methods or analysis.
Page 23, paragraph 3: This paragraph is not clearly written.	Change Made

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
What about: To be accepted for pooled analysis, studies were required to be controlled clinical trials according to the following definitions [insert definitions].	
Page 26, first sentence: Not sure about the implications for BMI of assuming an average height 5'8". Where did this number come from? Does it affect the outcome significantly is this number is off?	We chose this number arbitrarily. The results do not change across a range of potential heights.
Because study ref 87 is in adolescents, I question whether transformation of the data using a height of 5' 8" is a good decision. I would suggest contacting the study authors and request the actual individual height data.	A sensitivity analysis using 5'4" made little difference in the results. Therefore we do not feel it necessary to contact the original authors.
Page 27, Paragraph 1: Less than 20% attrition is a commonly accepted threshold below which concerns about bias increase due to loss of follow up. Should this read greater than 20% would be concern for bias.	The reviewer is correct, change made.
Page 28: Meta-Analysis. Will the two Danish trials be included in the final analysis?	Yes.
Update literature searches past December 2001, if appropriate.	Done
The questions guiding the evidence report were relevant, well formulated and easy to understand. The only problem I saw were questions 3, 7 and 12 were the same (Does ephedra have additive effects with other agents?) Most of the questions were related to the herbal ephedra, but much of the data reviewed was based on synthetic ephedrine.	These questions are the same but refer to, respectively weight loss, athletic performance, and safety.
"Of the 517 articles collected, 56 were controlled clinical trials of either synthetic ephedrine or herbal ephedra..."If the number of articles are added together (56+146+84+19+47+4+3+157), there are only 516 articles. According to page 53 of the Evidence Report, there are 48 controlled trials identified. It is unclear if the two Danish trials are included or not. Even if it is, there are still discrepancies with the number.	These numbers have been reconciled.
In reading the objectives, one assume that synthetic ephedrine was also part of the study objectives. However, this is not the original intent (see page 19 on Original Potential Key Questions). Should the changed in objectives be explained in the evidence report (rather than just a statement of agreement by TEP on page 20)?	It is explained in the text why this change was made, and we also changed the title to reflect this.
It will be more corrected to state that, "Forty-eight were controlled trials assessing ephedra/ephedrine for weight loss."	Change Made
Most likely the only detailed analysis of all the trials of ephedrine in the literature. The detailed explanation of the method with tables and graphs are helpful to the reader.	No Response

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
Should the same list of questions applicable to ephedrine as this is listed in the Objectives, or does ephedrine serve only as information (if that is the case, the objectives need to be reworded)?	We listed the question as received from AHRQ, and then describe how these were modified for the task order.
Page 20, paragraph 2, last sentence:… categories of patients: children, adolescents, young athletes, and adults. These are not generally patients, but rather potential consumers of ephedra or ephedrine products.	Change Made.
Page 22: Additional sources of evidence. Readers may think it unusual (as did several of our reviewers) that RAND would place an announcement seeking unpublished studies in Phytomedicine and Herbalgram. They would wonder why such announcements were not put into more mainstream medical journals such as JAMA and Lancet. It might be useful to mention that the intent in choosing Phytomedicine and Herbalgram was to reach individuals who might know of small studies being done on ephedra or ephedrine the TEP may not have been familiar with.	Change Made.
It is quite evident that a concerted effort was put forth by the authors to search all relevant databases and literature sources for clinical studies assessing the efficacy of the ephedrine/caffeine and ephedra containing dietary supplements. I was somewhat surprised that advertisements were placed only in Phytomedicine and HerbalGram. Phytomedicine is a relatively obscure journal while HerbalGram is targeted more toward the layperson. Were other journals considered?	
On page 26, the authors state that when a standard deviation was missing they imputed an average standard deviation from all other available data. They further state that they weighted all other standard deviations equally (IF I understood them correctly). It was unclear to me why they would weight all the standard deviations equally rather than weighting them by same size.	We weighted each study equally in the imputation procedure, i.e. we did not weight each study by its sample size (we assume the reviewer meant “sample size” not “same size”). Neither approach (weighting equally or weighting by sample size) is entirely consistent with our assumed random effects model. The approach we did take is simply applied, and we have found in practice that the results are fairly insensitive to weight choice.
On page 42, the authors indicate that in their reporting form, BMI greater than 27 was defined as obesity. This seems an odd choice given that both the NIH and the World Health Organization have now reached a consensus that a BMI greater than or equal to 30 should represent obesity and this information was available prior to the initiation of the current project.	The form has been correct to read “overweight/obese”.
On page 55 the authors describe some power analyses. It was not crystal clear to me what null hypothesis was under consideration in the power analyses the described. I think	This text was revised to try and increase clarity.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
greater clarity in this section could be achieved.	
In the weight loss category, of the 24 trials listed in Evidence Table 2, 4 were excluded, 2 because of study design, the other 2 because of "insufficient statistics" and lack of "weight loss outcome" (addressed weight gain). However, 4, available only as abstracts, were rated using the Jadad system, scoring 0,1,2, and 2. Of the 20 trials included in this weight loss panel, only 5 used herbal ephedra, the other 15 employing the pure alkaloid ephedrine. Interestingly the highest scores (5) on the Jadad scale were to the two Boozer studies, which combined herbal caffeine (kola and guarana, respectively).	No Response
Regarding the efficacy aspect of ephedra/ ephedrine use, the rejection of 19 of the identified 48 controlled trials on the basis of a lack of 2 month follow-up, appears reasonable, but assessment of the 19 terms of safety indication may add to the pool of data.	These were included in the safety analysis. The text has been changed to reflect this.
The literature search seems to be appropriate, with the relevant publications being identified. The study selection for efficacy analysis seems justified, whereas the selection of studies for safety is not appropriate. This reviewer finds it justified including only the controlled trials with a placebo arm for efficacy analysis. But for safety evaluation is obvious that all trials should be included. The safety information collected during a clinical trial has much better value and validity than the cases received through the FDA. I suggest therefore that the analysis of safety in terms of adverse effect dropouts and side effects should be re-examined with inclusion of all the available trials.	We did include all available trials in the safety analysis and have clarified the text to reflect this.
Could you estimate the average amount of weight loss per month in each of the ephedrine groups and in the placebo weight loss groups. For the lay press and political readers this may mean more to them than the difference in weight loss between the active intervention and the placebo.	This revision now contains the percent weight loss in the treated group.
It is clear there are data gaps with respect to ephedra use and effects which are apparent in this study. However, I did not identify any evidence of bias in the data collection process.	No Response
It appears that the researchers made every effort to reduce bias in the data collection process. The data collection process was systematic and thorough. Problems were identified and explained in the Limitations section of the report. The researchers did acknowledge that missing information did exist and also described this in the Limitations section. It seems as if the researchers did the best they could have done with the literature captured in the meta-analysis.	No Response
Is there a minimal amount of missing information regarding	We conducted sensitivity analysis on

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
outcomes and other variables considered key to the interpretation of results? The fact that the studies that were found has 6 month or less treatment duration. That is too short a period of time to fully analyze safety or efficacy.	attrition rate greater or less than 20%, and the results are reported in the text. We acknowledge in the limitations that the short duration of the identified studies limits the conclusions that can be drawn.
I believe you did a fine job in synthesizing the data. There was one inconsistency that I think might have been a typographical error. In table 15 you state that the pooled monthly weight loss in pounds is 2.7. In the text on page 55 and 56, you state that the same monthly weight loss is 2.1 pounds. You my want to check this apparent conflict.	This discrepancy has been corrected.
Reasonable decisions were made concerning whether and how to combine data. Precisions of results were indicated. Limitations and inconsistencies were also stated.	No Response
All study designs were considered in the synthesis and reasonable decisions were made as to combining the data. Precision was reported and limitations described. Limitations and inconsistencies were stated along with limitations of the review process. The meta-regression was used in an attempt to compare treatment across trials.	No Response
At one or more points the authors used the term "cathartic". I am not certain I know what they mean by that . Do you mean laxative?	Yes.
I believe that there are at least three major reviews related to this topic to varying degrees that merit mention. I believe the authors have mentioned at least two of these three. The three of these are: the CANTOX Report; Frank Greenway's recent review, and a review by Allison and colleagues which appeared in critical reviews in Food Science and Nutrition in 2001. Each of these reports addressed the use of ephedrine products for weight loss in part or in whole. I do not think any of them need to be discussed at great length, but it should be mentioned an the authors of the current report should briefly mention whether their conclusions largely agree or do not agree with those prior reports. The authors are probably also aware that, subsequent to their producing this draft document, there was a Senate hearings on the use of dietary supplements for weight loss, at which a number of experts provided testimony. The written testimony from several of these experts are available on the Senate's website. The authors may wish to briefly mention this in their report and cite any key relevant information that appeared in that testimony that was not available to them this report was written.	In this revision we do not review previous reviews, therefore we did not act on this comment.
I think that as it intimated above, any studies excluded must be carefully accounted for. The exclusion of studies opens up the reports to potential allegations of bias. Therefore, I would advocate that the authors include a very detailed table of all excluded studies giving the reason for their	We considered doing so, but felt the report had so many tables already that this table was of marginal extra benefit.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
exclusion and a full reference to the study. If the authors have already done that and I missed it (the tables were quite extensive and I confess that I did not go through them with a fine toothed comb), I apologize.	
I was confused on one point. I thought that the authors only included studies that were randomized, double-blind, placebo-controlled trials. If I understand the scoring of the Jadad system correctly, a study that is randomized would get at least one point, and a study that was placebo-controlled (and therefore presumably double-blind) would get a second point. Therefore, all studies should receive a score of at least 2 on the Jadad scale. However, I thought that I saw some point that some of the studies received scores less than 2. Can this be clarified?	Studies were included if they were controlled clinical trials. Such studies can score zero on the Jadad scale.
I was somewhat disappointed by the authors discussion and use of effect sizes. First, the discussion is slightly simplistic at points. For example, it seems to imply that the particular effect size metric they use is "the" effect size rather than "a" specific metric of effect size. Moreover, it is generally well-recognized that when the outcome measure in a field of study is something that had intrinsic or accepted meaning it is perfectly reasonable to use this outcome measure rather than the particular effect size metric the authors used, which scales things relative to within group standard deviations. This is the case with body weight, where most investigators and people in general understand pounds and kilograms. There is no reason to standardize by the standard deviation, which makes the data less interpretable. In fact, several meta analyses have appeared in the literature on obesity and simply use pounds or kilograms. I agree that several meta analyses have as appeared in the obesity field that have used the standardized effect size that the authors use, but I personally see it as unnecessary. It is not only unnecessary but it can create situations in which there is less clarity. For example, two studies can achieve the same absolute weight loss and yet one study because it is much more tightly controlled may have a smaller standard deviation. This latter study would achieve a larger effect size and yet I do not think that most people would see it as more efficacious if the same number of pound or kilograms were lost. The authors themselves seem not to accept this metric of effect size because they later back transform if two pounds as a way to help the reader interpret the results. Finally, although a minor point, the authors should use metric units of weight (kilograms) rather than pounds. The metric system is the accepted system in current scientific practice and the authors report will be perceived as less professional otherwise.	The effect sizes were transformed back to changes in weight loss in pounds. We also assessed whether conducting the analysis entirely in pounds changed the results. It did not. We also continue to report the results in pounds because US audiences are more familiar with this unit of measurement.
Being not a statistician, I do not understand certain parts in	The methods text has been revised to

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
the Methodology. For example, effect size is not defined in the section “Weight Loss Effect Size” (page 25), the paragraph in the Safety Assessment, Controlled Trial Adverse Events, Meta-Analysis section on exact conditional inference methods versus asymptotic methods (page 29) was not very clear.	improve clarity.
On p. 2 you describe the "effect size" determination. Although it becomes clear later that you are comparing them with placebo, this one sounds like it is only for single treatments. I am confused.	An effect size is calculated for any comparison of two groups.
In general I think that this a reasonable objective, and have little doubt that this will make a useful contribution to the field. That being said, I think there are a number of points that, if carefully addressed, could improve the document. I detailed specific comments below. In the main summary (I.e. pages V and VI) the authors made no mention of dose. I think that this is a marked oversight. It could inappropriately be taken as an indication that they statements they make apply to all doses. Clearly this is not the case as the statements they make can only apply at best to the doses for which they observed the data. I believe the authors should consider substantially softening several of their statements. The first one to catch my eye was the statement on page VI that "the effects on weight loss of synthetic ephedrine plus caffeine and Ephedra-containing dietary supplements with herbs containing caffeine are equivalent..." As I am sure the authors are well aware, lack of evidence for an effect is not the same as evidence for lack of an effect. We can never marshal sufficient evidence to unequivocally prove the null hypothesis. We can only fail to reject a null hypothesis. If the authors had access to multiple, very well controlled studies comparing herbal and non-herbal ephedrine, this conclusion might be warranted. However, based on the data they have observed, a far softer statement such as "We observed no statistically significant difference between the effects of herbal and non-herbal sources of ephedrine and caffeine" would be much more appropriate. The authors may perceive me to be a stickler on this point. I am suggesting that the authors try to particularly cautious throughout this report in framing their conclusions because of the highly contentious nature of the topic they are studying. Even if these authors never enter a courtroom, it is highly probable that they will "speak" in one or more courtrooms through this document. That is, lawyers and expert witnesses representing multiple diverse interests are likely to cite this document in court cases. For this reason, it is crucial that the authors say exactly what they mean and state exactly what can be supported by data and be vary catious about making statements that could be	A dose analysis is included with this revision. We also tried to make sure our statements were accurate.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
misinterpreted or overextended	
On page 11of the report, the authors state some numbers regarding how many billions of dollars obesity costs. Although I do not think these numbers are especially relevant to the report and could easily be eliminated without any loss, if the authors are going to cite them they should cite the most accurate information available. My colleagues and I published a report in the American Journal of Public Health in 1999 in which we showed that prior estimates of the costs of obesity were almost certainly inflated by a fact of approximately 25%. If the authors are going to cite cost figures they should probably cite our paper and lower costs showed therein.	We stated that the reported value is only one estimate. The point, we think, is that obesity has an enormous cost in terms of health. We also included this reference stating that another estimate was 25% less.
On Page 14 under Pharmacokinetics, I thought the authors may wish to consider softening their statements about the lack of difference between herbal and non-herbal sources of ephedrine in terms of Pharmacokinetics. It seemed to me that the studies they reviewed did not fully support what appeared to be their conclusions, namely that there were no important differences in pharmacokinetics between herbal and non-herbal ephedrine.	We made this modification.
The authors state that two physicians working independently extracted data in duplicate and resolved disagreements by consensus. It would be interesting to know how often such disagreements occurred. That is, can the authors present any indication of the reliability of their coding scheme.	We did not assess in this project (or any similar project) a measure of disagreements, such as Kappa, and therefore cannot report this.
With respect to the search strategy, the authors seem to have been quite thorough. However, there are two sources they did not mention using that, in my experience can be extremely useful for this type of work. The first is the United States Patent and Trade Office which now has all patents on line. The online data base is searchable. One can often obtain quite a bit of additional information on this topic by finding companies' patents. Second, although, in my experience a less important source, Dissertation Abstracts International, Which also had on line searchable databases can occasionally help uncover additional studies. I can certainly understand the last thing the authors probably wish to hear at this point is a suggestion they go back and search for more literature. Whether they ultimately choose to do so is obviously up to them. However, at minimum they might want to do a type of "sensitivity search" to see if it seems likely that they would have missed a great deal of information by not searching these databases.	We did not go back and search these databases. No reviewers identified any missed trials, so while we can never be sure, we judge it unlikely that there are significantly large and well done RCTs that were not included in our analyses.
Regarding herbal ephedra for weight loss: There are apparently no studies addressing whether weight loss is maintained after ephedra use is discontinued. This is a very important gap in our knowledge and should be explicitly	An addition was made to the limitation section.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
pointed out. With all other weight loss medications, weight is regained after their use is discontinued, suggesting that life-long use (whether continuous or intermittent) is likely needed to maintain weight loss. If this is also true for ephedra, adverse events must be considered from the perspective of chronic ephedra use rather than episodic use. This has important implications for clinical use, public health, and study design to detect adverse effects.	
The HHS requested this analysis to evaluate the safety and efficacy of ephedra/caffeine products when used for weight loss or exercise enhancement used in the absence of medical supervision. However, the reports that have been analyzed have all been performed on subjects that were screened for pre-existing medical conditions and were followed during the trials with medical supervision. For example, in the most recent study by Boozer et al., the investigators excluded one of every ten subjects they screened for medical history or for conditions that made ephedra/caffeine, in their estimation, to be unsafe. The only trials that could have adequately addressed the question posed by HHS would be any that enrolled an unscreened population and followed them with little, if any, medical supervision. Such studies are not feasible or ethical because of the general knowledge that ephedrine-containing products are dangerous. An Institutional Review Board would not accept this study design. The report should note that the clinical trials reviewed (at least the ones with which I am familiar) had strict criteria for medical exclusion and require careful monitoring for safety during the study. This is the result of the general understanding of the medical community that these products are dangerous and therefore requires medical supervision during their use	The issue of studying select populations was added to the limitations.
The other major flaw in the analysis is that it failed to adequately consider the pharmacology and clinical pharmacology of sympathomimetic amines. The consistency of the evidence across a range of chemically related substances must be considered. The relative safety and efficacy of other drugs that have similar pharmacologic actions is absolutely relevant. Every drug with sympathomimetic actions that have been studied adequately has been associated with serious cardiovascular and neurological adverse events. Likewise, the actions of drugs that antagonize the effects of ephedrine should be considered. For example, adrenergic antagonists reduce the incidence of strokes and heart attacks.	These are topic areas that may be worthy of review but were outside our scope of work.
The questions are clearly formulated, but some of the answers are difficult to find. For example, the answer to question 7 on page 19 was buried in paragraphs on page 14. I might suggest adding to the summary chapter, brief answers to the questions you posed that are based on your	We reported the questions as we received them. We tried to reword our conclusions to better match the questions.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
analysis. Although the summary does address many of the questions, it would be nice to see the answers lined up with the questions. For example, the answer to questions 7 may be something short like this: " Ephedrine releases norephedrine from nerve terminals stimulating alpha and beta adrenergic receptors. Caffeine magnifies this effect by slowing the breakdown of cyclic-AMP inside the cell through the inhibition of phosphodiesterase." This is not an attempt to suggest text, but just to give an idea of how it might be possible to address the questions you posed in a two or three sentence answer. The questions are understandable but not well formulated. The questions should be specific for the way the ephedrine/caffeine products are being used. To ask whether they are safe without specifying how they are used ignores the potential selective bias.	
The selection of 24 hours as a window for exposure to ephedra is conservative. It is quite possible that ephedra could cause coronary or cerebral vasospasm that could persist much longer. This certainly has been described for other sympathomimetic drugs such as cocaine.	The 24 hour criterion was set by the TEP and not something we can change.
In evaluating the adverse events, why was documented use of ephedra with 24 hours made a criterion? This timing interval is far shorter than that used in the PPA epidemiology study [use ~72 hours]. Furthermore, this criterion tends to exclude those adverse events that are not necessarily time or dose dependent or whose effects are not ascertained until some critical threshold is exceeded [e.g., immunological reactions; hemorrhagic stroke with symptoms of an antecedent headache not considered “typical”].	This criterion was set by the TEP
Requiring documentation of ephedra exposure within 24 hours of the acute event may be biased against the most serious cases when a patient cannot provide a history of recent use because of death, coma, aphasia, or other sever impairment. In the absence of toxological results a reliance proxy history by a household or family member should be adequate.	We did count as satisfying this criterion a report of the subject consuming ephedra or ephedrine within 24 hours.
Most likely the only detail analysis of all the trials of ephedrine in the literature. The detail explanation of the method with tables and graphs are helpful to the reader.	No response
Is the FDA data on the products that contain ephedra based on label claims that it is ephedra or there are lab analysis confirmation? This should be stated as many of the products tested claim to contain “ephedra only” contain ephedrine and pseudoephedrine and no other ephedra alkaloids. This is likely due to a non-naturally occurring source.	It could be based on the label or on direct analysis.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
"In September 2001, the FDA's Office of Nutritional Products, Labeling, and Dietary Supplements produced an excel spreadsheet...for the dates specified" What is the inclusive date of the requested report?	From inception to September 2001.
The literature on herbal supplements/medicines is replete with reports based on undefined or poorly defined research materials. This occurs at least one of three levels: (1) research, (2) reporting research findings in journals, and (3) abstracting/indexing journal articles for database entry. Unless serious efforts are made immediately to set criteria for researchers at all three levels to follow, further research in the herbal supplements/medicines field will only continue to generate data that will continue to lead to ambiguous conclusions and hence, controversy. Ephedra and ephedrine are no exception.	No response
Ephedra herb (defined as the green herbaceous stem) sometimes contains up to 30% root material, which has different types of chemical constituents than those of ephedra herb. The root has completely different traditional uses than the stem as well (e.g., antiperspirant vs. diaphoretic). And the root contains macrocyclic spermine alkaloids (ephedradines) that are hypotensive, as opposed to the hypertensive effect of ephedrine in ephedra herb. Also, ephedra herb from different sources (Ephedra sinica, E. intermedia, E. equisetina, etc.) contains widely different levels of ephedrine among the ephedrine alkaloids (30%-90%) present in the herb.4 We can't assume the results from ephedra herb containing 'ephedrine' are equivalent to those based on the single-chemical drug ephedrine unless both the following two conditions are met: (1) the efficacy and safety evaluation is only based on ephedrine and (2) the concentration of ephedrine in ephedra has been specifically defined by definitive chemical analyses. Otherwise this 'ephedrine' could only be 30% ephedrine, with the rest (70%) being made up of other phenethylamines (e.g., pseudoephedrine, norephedrine, etc.) as well as ephedradines (from root material present as adulterant in the raw material used for extraction); the latter have different pharmacological activities and toxicities than ephedrine.	We added to the limitations the lack of standardized products for ephedra.
Line 3 should read this: "Less than 20 percent attrition is a commonly accepted threshold above which concerns about bias increase due to loss to follow up.	Change made.
The cases of seizures (n=70) and fainting/loss of consciousness (n=63) may represent serious cardiovascular events such as syncope due to cardiac arythmia.	The seizure cases are now included in this report.
You may want to add to table 1, Bitter orange extract (Citrus aurantium) and Garcinia Combogia.	This portion of this Table was deleted in this revision.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
In contrast to the Rand draft report, the relation of the potential of consumption of ephedra to the dosage involved was the central point of the ephedra risk assessment contracted by the Council for Responsible Nutrition and performed by Cantox Health Sciences International, Mississauga, Ontario (http://www.crnusa.org/CRNCantoxreportindex.html). The Cantox report reflects a true risk assessment that includes (1) evaluation of the evidence for a hazardous effect, (2) dose response relationship evaluation, (3) uncertainty assessment, and (4) identification of a dose that does not carry significant risk under specified conditions of use. The Rand report includes one important topic not addressed by Cantox—the benefits of ephedra.	No response
Given the animal toxicology data that includes well-documented toxicity at high doses, as well as many anecdotal cases from the drug and dietary supplement literature that point toward ephedrine or ephedrine alkaloid toxicity, examination of the ephedra adverse event report (AER) dataset for possibly, likely, or even "definite" causality seems to be a moot point unless the dosage that produced that causal case is identified and put into context with the recommended dosages. There are abundant examples among the essential nutrients of the absolute necessity of applying this principle. For a comparative example, a conclusion that vitamin A can cause liver damage may be true but is misleading, and actually harmful, as a generality. Clearly, scientists should recognize the critical importance of dose in any evaluation of causality, but not all policymakers or legislators, much less the general public, can be expected to do so. Thus, it is critically important to recognize and evaluate the dosage involved in any possibly or likely causal cases of adverse effects by ephedra. The Rand evaluation of risk stops a major and critical step short of the Cantox risk assessment in that little attention was paid to the dosage involved in adverse effects that might be casually related to ephedra ingestion. The absence of any significant dose-response consideration in the evaluation and conclusions is very clear in the Structured Abstract sections Main Results and Conclusions (page vi). This omission inexplicably occurs even though in the Methodology section (page 19), the Safety Assessment list of considerations asks the appropriate dosage question. This virtual absence of dose-response assessment in the entire report is reflected in the section on Attribution of Adverse Events (pages 20-21). In that section, the "dose question" is asked mainly in relation to the temporal relationship, not a dose-response quantitative relationship. Likewise, in the section on Causality Analysis of Case Reports, the three key points of the causality algorithm do not include any evaluation of the dose that produced the	A dose analysis is now included in this revision and this revision no longer assigns causality.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
adverse effect. A complete evaluation requires an answer to the following question: If the answer is affirmative on all three key points, what dose was involved? Paracelsus got it right some 500 years ago—"the dose makes the poison." Without consideration of dose, we can justifiably conclude that anything, indeed everything, is a poison. The necessity of adequate information to answer the dose-response question is exemplified by AER 13408, released by the Food and Drug Administration (FDA). In contrast to the labeled dosage of up to six capsules per day, the wife of the 26 year-old male in this case acknowledged to the FDA investigator that he "took a handful at a time, several times a day." This case is mentioned only to illustrate actual dosage may bear no resemblance whatever to labeled or expected dosage. Regardless of oral reports of specific dosage, the actual dosage should be assumed to be completely unknown, without confirming pharmacokinetic information or other objective information.	
Pharmacokinetics. There are two published studies of the pharmacokinetics of ephedra, both from the same laboratory (Gurley, references 74, 75). Unfortunately, the results are not consistent, but rather conflicting. It is strongly recommended that future research include a carefully designed comparison of the pharmacokinetics of ephedrine and two ephedra formulations, one comprised of powdered whole herb and the other powdered extract of the whole herb, in human volunteers. This should resolve the issue of a potential difference between purified ephedrine and the herbal products.	We agree this is an important line of research, but think this falls somewhat lower in priority than our first three listed recommendations.
The report notes the similarity between ephedrine and phenylpropanolamine (PPA) but fails to consider the relevance of the data with PPA to ephedrine. The suggestion that a trial similar to the one with PPA should be performed ignores the fact that most would consider the study to be unethical. The only ethical way to do the study would be to exclude patients at risk for cardiovascular events but that would make it impossible to accurately define the safety in an unscreened population of patients. Again, it would not be ethical to conduct a case control trial to quantify the magnitude of harm from a drug known to have the ability to cause strokes and heart attacks. The only reasonable recommendation from this analysis is that the drug (ephedrine/caffeine) has modest short-term efficacy and probable safety when used under medical supervision. If it is to remain available to the public it should only be used under medical supervision, i.e. dispensed only by prescription.	The case control study suggested is an observational study design that does not compel subjects to take anything, and in most situations starts after exposure has already occurred. We do not think it any more unethical to conduct this study than the PPA study.
The review of the safety of a drug with potentially rare adverse events must include a complete consideration of the polymorphisms of adrenergic receptors that have been	We judged this beyond the scope of our report.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
identified that could explain variable response and idiosyncratic reactions (Am. J. Human Genetics 2002: 70; 935-42). The polymorphisms that result in failure to develop tolerance are especially important to be considered. The section on metabolism should include some mention of the metabolic polymorphisms that result in deficient metabolism and accumulation of excessive drug levels.	
The evidence report questions were easily understandable.	No response
There was a paper published several years ago in the American Statistician, Unfortunately, I do not recall the authors' names. However they presented a particular method as a way of analyzing MedWatch Report data from the FDA. In brief, the method entailed creating a contingency table between types of events on the one hand, and drugs or substances ingested on the other hand. By looking for cells with larger than expected frequencies, one can potentially identify drugs with particular hazards. The authors might consider adapting this method to their data, or at least mentioning it.	We could not find this paper so we could not include this.
On page 54, the authors state that "a sensitivity analysis on only those studies scoring 3 or greater on the Jadad scale yielded a pooled estimate of effect size substantially lower than the main analysis…this difference…did not quite reach the conventional levels of statistical significance (p=.053)." In my opinion this is an extremely important finding. The literature on supplements for weight loss is riddled with a large number of trials of a very dubious quality. It is often difficult to know how to interpret such trials. It is easy to point out the flaws in these trials, but the obvious question is do these flaws matter? No study is perfect, and defenders of the claims companies make based upon these flawed trials are quick to point this out. The finding from the current authors suggest that such flared trials may be giving misleading answers. I believe that the authors should much more carefully describe this result and its implications and portray it much more prominently in the report.	We do note this prominently in the text but also note this effect was only observed for studies of ephedrine without caffeine.
On page 58 the authors state that there are data from the pharmaceutical literature that support the contention that patients taking pharmaceuticals outside of clinical trials may have a greater risk of certain adverse events than do patients selected to participate in clinical trials. The authors should supply one or more references supporting this statement.	Reference added.
On page 59 the authors state "Thus bias may exist, as the events we included were different in terms of type vs. those we had to exclude." It is unclear to me exactly what they meant by this. I suggest that they describe exactly what bias they are referring to.	We revised the text to try and clarify this point.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
Health Canada discourages its citizens from using ephedra for weight loss. They say they have at least 60 reports of adverse events. It's not enough to say that you haven't received them. You must get them and include them in your analysis. The US military discourages its people from using ephedra. A Col Mike Health, identified as an Army pharmacy consultant, states on the armymedicine.army.mil website: "There were 25 documented active-duty deaths of soldiers, sailors, airmen or Marines who had died and were coincidentally taking ephedra-containing products." You must get these and include them in your analysis. The American Association of Poison Control Centers collects information on human poison exposure cases, including cases attributed to dietary supplements. In 2000, 2.2 million cases of poisoning were reported to 63 centers. The Los Angeles Times reported on September 2, 2002, that the nation's Poison Control Centers collected 9,000 cases of ephedra poisoning since 1993. Where are these? You must include them in your analysis. E'Ola, a manufacturer of ephedra products, admitted in a lawsuit deposition in 1999 that it had received 3,500 complaints about ephedra from its customers that it had not forwarded to FDA. Where are these? They should be included in your analysis. There are at least 25,585 reports of adverse events associated with ephedra that you have not included	The EPC did request adverse event reports from most of these sources. We did not receive any. The EPC does not have the power to compel organizations to provide any data. Furthermore, the adverse events that were assessed leave us unable to conclude anything about causation. Therefore, our expectation is that the inclusion of additional case reports is unlikely to increase our certainty about a causal relationship between ephedra use & serious cardiovascular or neurologic events.
This report must deal better with the issue of dosages. Some people dismiss reports of ephedra-induced reactions as the consequences of over-dosing. Which events among the likely or possibly associated with ephedra use involved subjects taking only the recommended dosages?	It is not possible to tell which patients were taking the recommended doses.
Why were the criteria for high blood pressure set at systolic BP > 180 or diastolic > 105 mm Hg? More reasonable measures for serious or clinically significant hypertension would be to capture all cases of hypertension where pharmacologically management is indicated [class 2 and 3 hypertension] . This would be consistent with the definitions of serious adverse event as defined by MedWatch and in CIOMS [required intervention to prevent serious outcome….] Ascertainment of the rate and risk of clinically significant hypertension would be particularly critical in any safety assessment of ephedrine alkaloid containing products for use the general population where a “learned intermediary” is not required.	The criteria were set at a level sufficiently high that treatment would be warranted that day.
p. 50 Figure 4 brief data collection form for case report: what criteria were used to establish the categories under psychiatric [e.g., severe depression, psychosis]	The implicit review of experienced clinicians.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
On page 59 it is stated that "we did not examine the remaining 251 adverse events because the descriptors in the master excel spreadsheet were of conditions less severe….." The descriptors mentioned in the listing were of the 'adverse event as reported' [usually by a consumer] rather a diagnosis or precise description of signs and symptoms. Consequently, this description may be an unreliable or inadequate characterization of the adverse event, its severity or seriousness. It may be better to state that the remaining 251 AERs appeared to fall outside the focus of serious adverse events [deaths, cardiovascular, CNS, etc.].	We changed the text to reflect this.
Were other measures of variation included, e.g. confidence intervals or limits? Could these be used instead of having to impute standard deviations?	If possible we back calculated the standard deviation from other information include din the report. Otherwise, we reported the standard deviation.
The questions were clearly formed.	No response
The search methods were appropriate and resources were clearly documented.	No response
Inclusion of Non-Scientific Adverse Event Reports Invalidate the Integrity of the Study There is a potentially fatal weakness in the report in that there is no inclusion of a discussion on the peer-reviewed animal and laboratory research but extensive discussion of the non-peer-reviewed, non-scientific FDA Adverse Event Reports (AERs). The inclusion and heavy dependence on data that the General Accounting Office has already concluded was flawed is likely to nullify the scientific integrity of the report. The GAO report stated:	Animal and laboratory data were outside our scope.
While FDA's conclusions regarding the desirability of the proposed action may be valid, we believe these conclusions are open to question because of limitations and uncertainties associated with the agency's scientific and economic analyses. The GAO found that the AERs were poorly documented; that the FDA did not perform a causal analysis to determine if, in fact, the adverse events reported in the 13 AERs it used to set dosing levels were caused by supplements containing ephedrine alkaloids; and that the FDA indicated in its proposed rule that 10 to 73 percent of reported adverse events might not be related to consumption of dietary supplements containing ephedrine alkaloids.	We do not see how this critique of FDA is applicable to our report.
Have AERs ever been included in an AHRQ or RAND Evidence-based Center review before? An important hallmark of the evidence-based review or meta-analysis is the establishment of strict criteria prior to the review and an adherence to the established criteria once the review begins. Any deviation from criteria once the study begins may result in a flawed analysis and a loss of credibility	Case reports have certainly been included as a course of evidence in other AHRQ evidence reports, for example our own report on a "Best Case Series for CAM Treatments of Cancer".

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
The inclusion of AERs as part of this review appears to be a serious deviation both from what AHRQ requested and from the standard criteria used in conducting a meta-analysis. On page 4 of the draft, the authors conclude, "the majority of FDA case reports are insufficiently documented to make an informed judgment about the relationship between the use of ephedra-containing supplements and the adverse event in question." Devoting approximately 50 pages to AER reports in the report seems incongruent with the space devoted to descriptions of the peer-reviewed scientific data.	
There is also no explanation in the AER evaluation of products that were found to be illegally marketed as dietary supplements, which in fact were misbranded. Some of the early and most serious adverse events were from products that were adulterated with high doses of synthetic ephedra.	In fact, as our analysis shows, there were more deaths as a percentage of total AERs reported in the more recent data compared to the older data.
Several of the preliminary questions provided to RAND have not been addressed in the report. We expected a review of the literature to be included in the report: Questions about Dosage: What dosage of ephedra produce risk of CVD or other life threatening events? This may be because there is little or no data available. If so, it should be made clear in the report. The CANTOX report drew conclusions about a safe upper limit. While these were based on the results of a single study, they were somewhat corroborated by others. This is not to say that the CANTOX report is definitive.	A dosage analysis is included in this revision.
Also not addressed: Do ephedra-containing dietary supplement products alter physiologic markers of cardiovascular function?	This was addressed to the extent that RCT data in humans was identified. Blood pressure and ventricular tachycardia were two physiologic measures of cardiac function included in the analysis.
Adding AER analyses of ephedra AERs in the published literature, ephedrine AERs from the FDA's Adverse Event Database, and those for seizure and would make the report more complete and well balanced.	These have been included in this revision.
While it's useful to analyze the controlled trials for evidence of adverse effects, we're not likely to find significant effects in them because if adverse events were that common the studies wouldn't have been permitted in the first place. We must rely instead on case reports and adverse event reports for evidence. Therefore, every effort should be made to assemble all the credible case reports and adverse event reports associated with ephedra use. That was not done.	We disagree strongly with the contention that we did not expend every effort to obtain case reports. We have extensive documentation of our efforts to identify and obtain case reports for this analysis. Within the resources available to this project every possible effort was made.
The report should also make a better attempt at comparing the commonly reported adverse symptoms with those symptoms observed upon exposure to ephedra/ephedrine in controlled experiments. If the symptoms are consistent, or inconsistent, that's important to know.	This has been done in this revision.
The case reports cited are difficult to evaluate as they	We were limited by what was available in

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
contain clinical terms incorrectly used, incomplete descriptions and use an algorithm for causality that is impractical and unrealistic when using FDA reports. A vigorous documentation and search for better records at the time the case-reports were received would have improved the utility of the case reports. We regard the handling of adverse consequences as incomplete and unrealistic. The review by the Clinical Research and Review staff of the Center for Food Safety and Applied Nutrition of the Food and Drug Administration represents a more comprehensive and scientifically valid approach to reviewing adverse events associated with ephedra and ephedrine.	the files sent to us. It is not within the EPC scope to "search for better records at the time the case reports were received." We disagree that clinical terms are incorrectly used; in most circumstances we are reporting the clinical terms used in the source documents. Finally, if there was agreement about the best "scientifically valid approach to reviewing adverse events" then there would exist standardized methods for so doing and we would not have received the same level of peer review comments that we did.
Overall Evaluation. (i)The means used to evaluate the AERs is not clear. It is difficult to determine what role, if any, the TEP actually played in the review process. From the description given in the text, it would appear that most members of the TEP never even saw the AERs. (ii) It is not clear why an eight-week exclusion criteria was chosen the review of earlier safety studies. The exclusion of double-blind placebo control studies of less than 8 weeks duration resulted in the loss of valuable information about acute toxicity (and excluded most of the existing data not demonstrating toxicity). (iii) Important epidemiologic and scientific data has been omitted. This omission severely limits the value of this study.	The trials of less than 8 weeks duration were not excluded from the safety analysis and epidemiologic studies were outside our scope of work.
Question Formulation. Questions are well formulated and easily understood. All of the defects in the study, and there are many, stem from the methods used to answer the questions.	No response
Study Identification. Appropriate search criteria were not used. Not all episodes of ephedra/ephedrine toxicity are a consequence of chronic exposure. The exclusion of all studies of less than eight weeks duration may strengthen conclusions about effectiveness, but it weakens conclusions about safety. There are, for example, dozens of double blind placebo control studies where clinically relevant doses of ephedrine were found to have no effect on blood pressure or cause arrhythmias, even in asthmatics with heart disease. There is no reason to exclude such highly relevant data. Studies where ephedrine was compared to placebo should not be excluded just because they were not about weight loss or athletic performance. The scientific credibility of the report was weakened by the search strategy that was chosen. Clearly, the authors of the report assume that (1) all episodes of ephedra/ephedrine toxicity are a consequence of chronic exposure, and that (2) clinical trials of ephedrine have been limited to studies assessing the effect of ephedrine on weight loss. All these assumptions are easily shown to be incorrect.	There is no assumption that chronic exposure is necessary and we did not assume that trials of ephedrine have been limited to studies of weight loss. We do not agree that studies of safety in healthy adults are necessarily relevant to studies in obese individuals who are at greater risk for comorbid conditions.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
Data Synthesis. The analysis of the weight loss achieved by ephedrine versus placebo, and ephedrine plus caffeine versus placebo etc., is very problematic because one has assumed that the weight loss rate is high initially and subsequently lowers, so that the weight loss from months 3 to 6 is typically very small. It is therefore invalid to simply calculate the mean rate of weight loss as pounds weight loss per month when trials of very different duration are included. Those who are familiar with placebo controlled weight loss and weight maintenance trials know that most of the difference between the active and placebo arms is achieved during the first 3 to 4 months, and that the difference is subsequently maintained even up to 2 years. The way the data are handled in this report has therefore produced projections that severely underestimate the real efficacy of ephedrine and ephedrine plus caffeine. This has been carried over into the conclusions, where it is stated that ephedrine/caffeine is not as effective as other anti-obesity medications currently on the market.	We disagree. We tested whether weight loss was linear over this time period and we could not prove that it was not.
Data Synthesis. This must refer to Orlistat (the pancreatic lipase inhibitor from Roche) and Sibutramine (the centrally acting compound from Abbott). If one looks at the long-term of Orlistat ones sees that the mean weight loss difference between Orlistat and placebo after 6 months to 2 years are of the order of between 2-5 kg in all the large trials. Ephedrine plus caffeine produces at least an equivalent effect. For example: If the weight loss on an active compound after 3 months is 10 pounds more than on placebo, and this result is maintained also after 6 months, it is clear that rate of weight loss would be calculated as 10 pounds divided by 3 (=3.33) if the trial is stopped at 3 months. Whereas the result from a 6 month trial would give 10 pounds divided by 6 months (=1.67), which is exactly half of the weight loss. This issue should be addressed and the efficacy section should be revised accordingly. The way the panel has calculated the weight loss rate actually assumes that the weight loss rate is linear and that it continues at the same rate with prolonged use. Obviously, this is not the case.	We were careful to state in the text that our results could not be extrapolated beyond 4-6 months. We added data on other weight loss products for comparison.
Data Synthesis. I note that Astrup et al. International Journal of Obesity 1992;16:269-77, listed in the bibliography (accepted articles) as number 1, is not included in the analysis! The Danish double publication of this is the Quaade et al., listed as number 48 in the same bibliography. It is hard to see why the panel quotes the Quaade et al. publication in Danish, which a condensed version of the Astrup et al. paper, which I assume must be the paper the panel had taken the study information from in English. The panel has used pounds in the analysis of weight loss, but it would be more appropriate to use weight loss in percent of initial body weight, because the weight loss in pounds in not	We identified these two trials as reporting identical data, and the inclusion of either (but not both) should make no difference in the results. Our practice is to include the most informative article. For these reasons we note, a percent weight loss analysis has several limitations.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
independent of initial body weight. This may introduce a bias if the initial body weight and body mass index in the 2 arms were not comparable.	
Page vi. , paragraph 3; page vi, paragraph 4; page;4, paragraph 4; and page 30 last paragraph: Some may not classify anxiety, change in mood as psychiatric symptoms. Emotional/ mood adverse effects might be more appropriate.	Psychiatrists may disagree with the statement that anxiety and change in mood are not psychiatric symptoms. No change made.
On page 55, the authors state "the effects of ephedrine and caffeine appear to be additive. I do not understand the basis for the authors statement. Unless there is a 2 x2 design in which to have the opportunity to observe an interaction between ephedrine and caffeine and observe that no such interaction occurs, how can the make a statement of additivity? I believe what they mean to state is that there is an effect of the combination of ephedrine and caffeine combined that is greater of the effect of either alone. This is not that same thing as stating that the effect is additive.	The reviewer is correct. We clarified the language so that we do not imply the effects are “additive” in the arithmetic sense.
On page VI, the authors state that there are no data from studies of herbal ephedra-containing dietary supplement products without caffeine. This is not correct. There is at least one study. My colleagues and presented an abstract at the 2002 Experimental Biology meeting from suck a trial. Unfortunately, we did not present efficacy data. Moreover, I had thought the community sponsoring the study had provided the safety data to the NIH for this review. Although, it is not within my authority to release the data themselves, I can certainly provide the authors a copy of the poster presented if they do not have access to it.	Without efficacy data we cannot include this in the analysis. We did not receive this study in response to our requests to industry for unpublished studies.
There is no published study of the efficacy of ephedra without caffeine, but a large, industry-sponsored study was done by Coffey et al. at the 2002 Experimental Biology Meeting the authors reported that there had been no adverse events, but did not report on efficacy.	
I think you did an excellent job in collating the important available data.	No Response
The Danish study reports a 100% increase on post-exercise O2 consumption by 100%. Was that immediately after exercise and for how long, this seems like a very big increase are you sure this is correct? If you are unclear have Mary Hardy send me this paper and I will have a look at it.	On further review, we determined the Danish study was not relevant to the report since it did not report differences in performance between groups.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
As far as athletic performance goes, no studies were available on herbal ephedra and only a modest affect on "very short-term immediate performance" was observed with ephedrine, only when caffeine was co-administered. The report states that there was one study that assessed the effect of "sustained use of ephedrine on performance over time", an " reported that the addition of caffeine to ephedrine necessary to produce an effect on athletic performance." But in the structured abstract it is not made clear what the extent of the effect was. The report text states on pg. 57, however, that "a study116 published in Denmark concluded that aerobic training enhanced the effect of ephedrine on energy expenditure. After, 8 weeks of aerobic conditioning, ephedrine increased post-exercise energy expenditure by 100%. N. B. The reference numbers in the section are incorrect e.g. ref 116 cited above should be 43, 115:52	
Regarding the 1986 Denmark study – do you mean that ephedra increased energy expenditure during exercise, or that it increased energy expenditure after the completion of exercise? Please clarify.	On re-examination we determined this study should have been excluded, as it did not measure the effect of ephedrine on physical activity but rather on basal metabolic rate.
Were there a disproportionate number of case reports of adverse events that occurred during or after the performance of exercise training or physical activity?	Not assessed, and probably not possible to assess.
The conclusions regarding herbal ephedra for weight loss are reasonable and defensible as far as they go, but are too conservative. Saying that there is no evidence for sustained weight loss with use of these preparations for more than 3-4 months is true, but does not translate into conclusions that are useful for the clinician or regulatory agencies. The data presented and summarized support the use of herbal ephedra or ephedra + caffeine for weight loss.	Our charge was to present the evidence. Translating the evidence into clinical recommendations or regulatory decisions is specifically beyond the scope of the EPC.
Important parameters were properly identified and addressed, such as study population and design.	No Response
In general, the appropriate study parameters were examined. However, I would have liked more data on dose-response, especially with the efficacy trials	A dose response analysis is included in this revision
Most of the important parameters were systematically addressed.	No Response
Should a descriptive statement be made on possible non-statistical publication bias. For example, funding source for the published clinical trials may also bias the quality of the results (see BMJ 2002;325 (August 3):249).	This was added to the limitations.
There should be an expanded general statement regarding the medical exclusion criteria that are used in all the published clinical trials. This needs to be emphasized in the analysis and should specifically point out that many patients	This was added to the limitations.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
with underlying diseases (hypertension, heart failure...etc) were excluded from trials. The emphasis is needed due to common argument that safety data from clinical trials do not support the potential serious adverse reactions collected by FDA.	
None of the information provided addressed analytical methods with the ephedrine or herbal ephedra products used (e.g., certificate of analysis verification that the product used in the study met label claim) and other issues of quality.	We included this information where it was available.
I think you did a good job in defining the methods you would use in appraising the studies. Open label treatment following a controlled clinical trial is often thought to be a way to screen for safety, but I understand how incorporating that into your assessment might inject bias due to lack of a control group. Although caffeine and ephedrine has been evaluated in a controlled clinical trial for 6 months followed by an additional 6 months of open label treatment, I understand the statement that trials do not last more than 6 months refers to the double blind period.	No Response
The studies that were obtained for review were evaluated carefully. Objective criteria were established prior for inclusion into the planned meta-analyses. The evaluation of the case studies provided by FDA was also performed in an objective manner. The limited number of studies on exercise and athletic performance are presented objectively. The limitations of these studies is accurately noted.	No Response
It appears that a thorough search for relevant data was undertaken. I can find no evidence of bias or intentional inclusion/omission of data or search strategies.	No Response
Criteria for clinical study inclusion and exclusion were well defined and adhered to. Little bias seemed to be introduced by the selection process, at least for the clinical studies. All important relevant studies were evaluated.	No Response
The inclusion and exclusion criteria for the selection of articles is adequate. I am unaware that any crucial data is lacking; however, it would be helpful if Dr. Phil Waddington's data from Canada could be included in the final report.	We contacted Dr. Waddington but did not receive any data from him.
Should the search term "adverse reaction" be part of the strategy? If not, why not? Please see my comments on funding source of the clinical trial. In an ideal situation, a trial funded by a neutral party will probably yield the most un-bias information.	Generally, these terms act as "limiters" and would exclude studies if they were not tagged in this fashion. We prefer not to limit the search in this way. Since tagging articles is not always accurate and we did not want to prematurely exclude potentially relevant studies. We did include "adverse events" as text search terms.
There were appropriate inclusion and exclusion criteria for	This revision includes the results of a few

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
the studies selected for the meta-analysis and these were clearly stated and explained. There may have been some bias based on the studies selected, even though the inclusion criteria were clearly spelled out. This was mentioned in the Limitations section of the report. Efforts were made to identity unpublished studies and several studies were missed in the evaluation as they had not been received. The researchers indicated that they will be considered for future assessment. When this will occur is unclear.	additional studies that are relevant. We do not judge that any of the handful of requested but unretrieved articles are RCTs.
The discussion of the results of the weight loss trials makes no mention of doses. Doses should be mentioned either in the text or in the table. It is stated that "all of these studies had an attrition rate of greater than 20%…" Was the attrition rate higher in the active vs. placebo treatment group? This should be clarified. If the rates were higher in the active group, which I suspect, then a specific analysis should be done as to the cause of attrition.	The mean attrition rate was not higher in the active treatment group. This has been added to the results
Athletic Performance, second paragraph. Please clarify the duration of the exercise test. This is important because some drugs (like creatine) may produce benefit with short duration exercise (a few seconds) but not longer duration exercise.	The exercise tests varied in duration from short (weight lifting) to an hour or more (endurance).
The originally proposed key questions included inquiries regarding dosage levels if ephedra with respect to weight loss, athletic performance, and safety. The Report does not address dosage levels with respect to weight loss, athletic performance, and safety assessment (except for the mention of possible future research study). Clearly this is an extremely important concept, and issue, regarding to these materials, especially with respect to the review of case reported obtained from the passive AE reporting system. It is our view that the general omission of dosage considerations should be mentioned with regard to the AER case report reviews and that it receive some attention in weight loss and athletic performance assessments.	A dose analysis was added to the RCT portion of the report. We did not judge analysis to be possible in the case report portion of the report.
Are all of these studies single dose studies? What was the interval between taking the dietary supplement and the performance of the exercise test?	This has been clarified in the results.
The meaning of this sentence is obscure. What is meant by "enhanced mechanisms of heat loss?"	This sentence has been reworded.
See page 26: none of the weight loss studies were beyond 4 months. Therefore, I would rewrite the first paragraph of the Main Results to say the "longest published weight loss intervention was 4 months". If there was a study with a post-intervention follow-up then this should be stated as well. (See comments for page 5)	Three studies had 6 months of treatment, which was too few to perform meta-analysis on this time period specifically. For studies that reported only 6 month data, we included these in the "4 month" time point, and specified in the methods section in the report that this could include data out to 6 months. Hence the "4 - 6

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
	months" statements in the text.
On page 3 there is mention that 19 of the 48 controlled trials were excluded from pooled analysis because they had follow up of less than eight weeks. There should be some description of the findings of these studies in this report.	These studies were excluded as evidence on the advice of our TEP. To discuss them as evidence of efficacy would be inappropriate in our view. We did include them in our safety analysis.
It may not be standard format for the EPC's to cite patient numbers at this early point in a report, but to make sure readers understand what a small number of people have actually been studied in controlled trials, it would be helpful to include this near the beginning of the report.	This was added to the report in the safety assessment, where the possibility of a type II error is increased due to low numbers of studied patients.
Figure 2, question 18: Chemical analysis of ephedrine alkaloids was part of the quality review form, but data for individual studies are not provided. Given the variability of herbal ephedra, if chemical analysis was not performed in a particular study, does that call into question the results of the study?	We do not think so since the results for the ephedra studies were remarkably consistent.
"In order to improve health outcomes, long-term weight loss is necessary." Do you really mean that long-term follow-up would be necessary to determine health outcomes?	No, we meant maintenance of weight loss, since the relationship to health outcomes is known. We have clarified this.
Page 53: Results Section. Weight loss. It might be helpful to provide a table of 5 types of comparison studies indicating sample size in each trial and the power calculations for each. It is important to highlight when sample sizes are small and individual power calculations are insufficient.	Considering that we pooled data, we do not think the addition of our assessment of power of individual studies is very useful. We did include this in specific circumstances where it seemed warranted.
"Use of ephedrine, ephedrine + coffee, or dietary supplements containing Ephedra and herbs with caffeine is associated with a statistically significant increase in weight loss (compared to placebo) over relatively short periods of time (no more than a few months)." Please Clarify "(no more than a few months)". We assume you are not saying that the data show loss of effect after a few months, just that the studies don't extend beyond a few months.	The data cannot be extrapolated beyond a few months. We have clarified this. We earlier explained the reason for the "4 – 6" month designation.
It would be helpful to define what is meant by "sufficient evidence."	This is defined as statistically significant.
Several of the preliminary questions provided to RAND have not been addressed in the report. We expected a review of the literature to be included in the report: Questions about Dosage: I. What dosage levels of ephedra are necessary to achieve weight loss?	We now include a dose analysis in this revision.
When describing the efficacy studies, it might be helpful to include a table delineating the key elements of the weight loss studies: Dietary prescriptions, Description of subject characteristics, Mean weight or BMI at initiation of study, and inclusion and exclusion criteria for studies.	We considered this change or addition but decided there were already a great deal of tables and therefore we did not add this table.
Although ephedrine is the chemical drug that has been	We are sympathetic to this comment but

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
found to be effective in short-term weight loss and athletic performance, this result cannot be extrapolated to the herb ephedra that contains multi chemical components. In order to study the efficacy of herb ephedra, the amount of ephedrine present in the herb ephedra being tested must be precisely defined. This 'ephedrine' must be pure ephedrine and not, say, 50% ephedrine with 25% pseudoephedrine and 25% norephedrine or other related or unrelated alkaloids, as are normally present in herb ephedra. Ephedra is not ephedrine and vice versa, even though ephedrine is one of ephedra's active components. I personally don't see how one can generate meaningful results from a study using a material, such as ephedra, which is not clearly defined. There are just too many variables. Good science requires a well-defined test material. For example, we would never accept a single-chemical drug like cortisone with even 25% impurities when performing a clinical trial on cortisone. Why should we accept the chemical drug, ephedrine, present in herb ephedra, whose concentration can vary by 300% (from 30% to 90%, with the balance composed of other alkaloids)!? Until this problem (which is not insurmountable, as product definition criteria have been and can be set)5 is resolved, any studies on herb ephedra for weight loss or athletic performance (both based on ephedrine) will not yield meaningful results. It is possible that some of the papers the RAND report selected do clearly define the ephedrine content in the herb ephedra (though I seriously doubt it), the fact still remains that there are related and unrelated alkaloids also present in addition to ephedrine. For example, if a product containing an ephedra extract has been analyzed to contain specifically 20mg ephedrine per tablet/capsule to conform to the required amount of ephedrine for efficacy, what happens to the other alkaloids also present, which could easily be twice the ephedrine amount, or 40mg, making the total alkaloids content 60mg? This is a natural scenario unless made 'unnatural' by manufacturers or suppliers who take spent ephedra herb (from which all alkaloids have been extracted) or a token amount of ephedra herb and add the prescribed amount of ephedrine, thus rendering the product basically a single-component drug (ephedrine), formulated with inert spent ephedra or token ephedra herb as carrier/excipient. In this 'unnatural' case, the 'ephedra' product is basically an ephedrine drug dosage form and has nothing to do with the herb ephedra. I doubt there is any published scientific information on herb ephedra based on sound scientific definition of the test products containing ephedra. Furthermore, whatever reports available most likely have not clearly identified and characterized their test materials	believe that the consistency of our findings supports the decision to pool studies of weight loss and compare ephedra to ephedrine.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
hence rendering their findings of little value to us. Based on the current state of published information in this field, I don't believe we will be able to obtain meaningful conclusions relating to herb ephedra's toxicity through adverse events analysis alone or based on modern published experimental data. In case of the former, since no precise standards are required for commercial ephedra products, few if any of the reported adverse events can be reasonably traced to ephedra herb. In case of the latter, there are simply too few useful published reports whose findings are based on work that used well characterized and well-define ephedra. Modern medicine and traditional Chinese medicine are two parallel and distinctly different healthcare systems, each has its own merits and defects. While modern medicine is based on scientific experimentation, TCM is based on empirical practice and trial and error in humans over time. The latter has accumulated a vast amount of recorded information, including cautions and contraindications. This has been an ongoing process and it continues to accumulate data as TCM practice continues to generate them. It would be our loss if this valuable resource was not somehow utilized. Since herb ephedra has a long use history in traditional Chinese medicine with an extensively documented record (safety, cautions, contraindications, etc.) over a 2000-year period, this should be taken into consideration. Also, common TCM traditional practice should be heeded. For example, some of the adverse events reportedly due to herb ephedra alone may not be so at all, but rather due to the concurrent and inappropriate use of other common herbs such as Asian ginseng which is traditionally cautioned against use in healthy persons with a vigorous (yang) constitution and which has been known to cause serious toxicity, including death when used improperly. 6 If one combines the indiscriminate use of even such common herbal tonics as Asian ginseng with a relatively potent herbal drug like ephedra as dietary supplements, to be used daily with no prominent warnings or precautions, serious adverse effects are bound to occur. In order to meaningfully study or evaluate the safety and efficacy of traditional medicines such as ephedra (not ephedrine, the chemical), apart from ensuring that the ephedra has been well characterized and defined, we should also consider taking its historical record and its traditional use context into consideration as well as keeping an eye open to the simultaneous but inappropriate (outside of tradition) use of tonics such as Asian ginseng. Furthermore, we should keep an open mind to the possibility that the efficacy and safety of herbal medicines simply cannot be determined by Western 'hard' science alone. Common sense and well-documented historical use and safety data should constitute	

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
part of the evaluation protocol.	
Regarding safety or adverse effects of ephedrine and herb ephedra, the two drugs need to be evaluated separately. With ephedrine, there should not be much of a problem because there must be copious amounts of data on the drug ephedrine, which can be accessed in various databases. However, with ephedra herb, it is quite different. Since ephedra has not entered the market through the usual drug-development-and-approval route, which would have generated toxicity data during that process, evaluating its safety as if it were a standard pharmaceutical (the single-chemical drug ephedrine) is not appropriate. There are few modern scientific or clinical reports published in the field.	For the RCT data, the numbers of patients studied with ephedra have been too small to assess adverse events without a high probability of a type II error. For the case report analysis, we did separate ephedrine from ephedra.
You are to be commended for the comprehensive search you conducted. Your methods seemed well-defined and unbiased.	No response
I think you did an excellent job of selecting articles using specific criteria and limiting bias. I know that one of the major issues prompting this review was concern regarding the safety profile of caffeine and ephedrine. In the United States this combination is sold in an unregulated fashion, so the only estimate of the denominator for adverse events is the number of doses manufactured. In Denmark, caffeine and ephedrine is a prescription preparation for the treatment of obesity. Orlistat and, before 1997, dexfenfluramine were approved prescription drugs in Denmark competing with caffeine and ephedrine. I assume that sibutramine is also approved in that country, but I do not know that for sure. It may be too late to at this point to include in this report, but information must exist for the incidence of reported adverse events to obesity drugs in Denmark. Although this is not a perfect way to assess safety, it might be useful to determine the relative incidence of serious adverse events reported with various prescription obesity drugs in Denmark. Based on conversations with individuals familiar with the Danish experience, I suspect that the safety of caffeine and ephedrine would compare favorably with sibutramine. One advantage of such an analysis is that one would be comparing alternative drugs for treatment of obesity in the same population. The second advantage would be a better estimate of the denominator based on prescriptions written rater than manufactured pills.	It was beyond our resources to obtain safety data (other than published data) from Denmark. We added to the future research that this would be a good study to undertake.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
Denmark Experience. Ephedrine/caffeine combinations are used extensively in Denmark for weight control purposes. There is a long history and experience that should be considered by RAND. Dr. Astrup has indicated that there are very few adverse event reports associated with such products in Denmark. RAND should contact the Denmark health authority, and/or Dr. Astrup, in order to obtain more information regarding these reports - and should include this information and Denmark experience in the final report.	
With regard to the adverse event reports, significant amounts of information were often missing; however that was not the fault of the authors, but rather a shortcoming of the MEDWATCH program. If anything the study highlights the inadequacy of voluntary reporting systems for adverse health effects and the confusion that results when a "systematic" analysis is attempted on such data. It is well known among the legal community and the FDA that thousands of adverse events have been reported to ephedra supplement manufacturers. Access to these reports might have affected the outcome of the present study. If anything these additional reports would have magnified the gravity of the public health threat attributable to ephedra-containing supplements. Moreover, Poison Control Centers throughout the country also log calls on ephedra supplements. Were attempts were made to access these additional resources?	We did not contact Poison Control Centers. We did include in this revision an assessment of the reports made to one manufacturer.
There was a thorough search of relevant articles using 9 electronic databases. Both national and international journals were included and the searches appeared to capture most of the relevant studies. The majority of the accepted articles for the meta-analysis were from the U.S. It seemed that 3 were from Germany. There were no studies from Asian journals.	No response
Table 19, I do not understand the point of this table or the conclusions being drawn. Please clarify for the simple minded.	We have added text to explain this table. The point is the later cases, that we did not have access to, contained proportionately more deaths.
Timing of last ephedrine (ephedra) dose? If it was > 24 hours, because of the relatively short half life, one would not expect to detect much or any in the blood at autopsy. Is timing of last dose with a tox screen negative test taken into consideration when determining causality?	Such cases were not reviewed, so a negative toxicology screen would not even have been assessed.
Insert percentage next to the # of adverse events for easier direct comparison of the placebo and intervention groups	We do not feel this comparison is justified due to small sample sizes, that is why we did not perform meta-analysis.
Instead of the 5x4 (nxn) test, it may be better to perform the chi-square test on event type vs. data type, ie. death (vs. other) x data type (2x3), stroke x type, etc.	We are not sure what this comment applies to.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
There were clear criteria used to select studies for inclusion in the report.	No response
The appropriate criteria were used to assess the studies on efficacy of weight loss with ephedra or ephedra/caffeine.	No response
The initial draft failed to include a review of the published case reports of adverse events. Given that these case reports were published in peer-reviewed medical journals and are prepared by medical professionals, they are likely to contain data that is more complete, accurate, and of scientific merit. It would seem more appropriate for these reports to have been evaluated and included in this report, especially since no other entity has conducted a review of them, than to once again include an evaluation of the FDA's evaluation.	These published case reports are now included in this revision.
Currently one must read to page 54 to get an answer to the key question, "We interpret this data as indicating the use of ephedra is associated with a statistically significant 1.3 pounds of weight loss per month more than is associated with placebo for up to four months of use" and "We interpret these data as indicating that the use of ephedrine and caffeine is associated with a statistically significant 2.2 pound weight loss per month more than is associated with placebo up to four months duration." This should be in the very beginning of the report.	This information is in the appropriate place for an EPC evidence report.
The 19 efficacy studies not pooled in the analysis because they had a duration of less than 8 weeks, and the 9 studies eliminated for a variety of reasons should be accounted for in the document, and any serious adverse event reports described should be included in the report.	These studies were included in the safety analysis.
“Even in aggregate the clinical trials only enrolled sufficient number (how many?) of patients to detect a serious adverse event rate of one per one thousand.” And again on page 58: “For studies of ephedra, there was only sufficient statistical power in aggregate to detect a rate of serious adverse events if three in one thousand.” For the reader, it would be helpful to know how these event rates, 1/1000 and 3/1000 compare with those reported in the literature for drugs in the same usage category as ephedra (three billion servings in 1999), i.e. to HRT (approx, 3.8/1000 women has an MI or developed breast cancer), or to event rates for aspirin and GI bleed.	We added that these events would be classified as “rare.”
References 104 and 108: The Nasser study (ref.108) is the same as the first Boozer study (ref.104).	This duplicate study has now been removed from the pooled analysis.
Under Bibliography Accepted Articles, pp 135 –137, references 12 and 41 are the same study [12=published study, 41 = published abstract], leaving 4 studies that assessed the effect of ephedra + herbal caffeine. Data reported in Chapter 3, Results, including Table 14, will need	This duplicate study has now been removed from the pooled analysis.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
to be corrected and re-analyzed.	
Monthly Weight Loss. In your results section you report the data as "Monthly" weight loss. The rationale for this escapes me. Weight loss with all medications slows with time and a plateau is reached between 4 and 6 months. Thus, the most rapid weight loss occurs in the first month. In trials that last 6 months, the only weight loss will be slower than one that lasts 2 months. How do we compare them with this criterion?	We tested, given the data available in these trials, whether weight loss differed across the different months. We could find no evidence that it did. Therefore, within the limited time frames of these trials (4 months), we included all relevant data points, as it increased our statistical power.
Miscellaneous Comments. On page 11, the draft report acknowledge that the "estimate of use of ephedra containing products may be low." Despite this, the report fails to emphasize denominator-related concerns associated with adverse event report reviews. This major scientific weakness needs to be acknowledged as part of the adverse event report analysis in a manner similar to that used in prior AHRQ studies (such as the Garlic Report). On page 29, the draft report indicates that although certain studies did not record any data for certain even category or indeed any adverse events at all, such studies were not included in the adverse event meta-analysis as RAND did not assume zero observed events if a study did not mention a particular type of event. Is this approach consistent with most scientific reviews?	We did assume zero events for serious events like death or stroke even if they were not recorded in the RCT. We did not do so for other events because we could ever know whether those events were sought by the investigators if they were not recorded. In other words, we did not assume zero for the entire universe of adverse events, only for those specifically mentioned and sought and recorded as zero. This is consistent with most high quality scientific reviews.
The Garlic Report. The draft report, as noted above, is in many ways inconsistent with prior AHRQ reports that address adverse event case reports. The AHRQ Garlic Report (Garlic: Effects on Cardiovascular Risks and Disease, Protective Effects Against Cancer, and Clinical Adverse Effects), and statements contained in the Garlic Report, should be reviewed by RAND as a potential model for the ephedra report - particularly in the manner case reports are assessed and described. For example, the Garlic Report provides the following with regard to adverse event reports and confounding factors: Adverse effects of oral ingestion of garlic are "smelly" breath and body odor. Other possible, but not proven, adverse effects include flatulence, esophageal and abdominal pain, small intestinal obstruction, contact dermatitis, rhinitis, asthmas, bleeding, and myocardial infarction...The frequency of adverse effects with oral ingestion of garlic and whether they vary by particular preparations are not established...Furthermore, the causality of the adverse effects was not clear, except for the breath and body odor, and the expected frequency of adverse effects was not determined... In addition to the RCTs, 73 studies were found that addressed diverse effects. Most (97 percent) were case reports or small case series (Evidence Table 9). The literature reviewed gives a limited picture of adverse effects	The inclusion criteria and reporting of studies in the Garlic Report were shaped by their TEP and their Partners. The inclusion criteria and reporting of studies in our ephedra report were shaped by our TEP and our Partners. There is no requirement that these reports be the same in inclusion and reporting.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
attributable to garlic for many reasons. First, searching for studies that report adverse effects is difficult. Many studies may mention adverse effects in passing, but do not use adverse effects as a key index word or in their abstracts. If these studies do not otherwise meet selection criteria in a review, they will be missed. Second, in most case reports and case series, adverse effects cannot be directly attributed to garlic because chance, coincidence, or confounding factors could have been responsible for the adverse effect. For example, alternative causes of reported adverse effects were possible in 22 percent of the reviewed studies and could not be excluded definitively in 69 percent. Third, case reports and case series may miss delayed adverse reactions because such associations are more difficult to make than those that occur immediately after garlic is administered. Fourth, although case reports and case series can provide qualitative information about the nature of an adverse effect, incidence cannot be estimated from such evidence... The frequency and severity of adverse effects that are related to garlic should be quantified. Whether adverse effects are specific to particular preparations, constituents, and doses of garlic should be elucidated. Whether certain adverse effects are unique to particular types of garlic exposure (e.g. inhaled, oral, or topical) should be clarified. The most serious potential adverse effects of garlic that have been cited are complications related to bleeding. Whether particular preparations and constituents of garlic affect physiological parameters related to bleeding such as platelet adhesiveness, prothrombin time, and partial thromboplastin time, as well as whether particular preparations lead to clinically significant bleeding, warrants more study. (emphasis added).	
The limitations of the review process are not stated. You have adverse reactions and inconclusive studies on the effectiveness of ephedra/caffeine. That leaves us with insufficient information to make an assessment of either safety or efficacy. In the data synthesis, the impression is given that there is more precision than can be justified based on the nature of the data.	We disagree with regard to the reviewers comments on precision. Precision is determined mostly by sample size and number of studies. We believe our pooled results adequately reflect the degree of precision the data allow.
Possible bias of the report due to members of the TEP and literature captured. Limitations and quality of the studies and short-term studies used in the systematic review. Combining the systematic review by meta-analysis with the analysis of AERs. No conclusions for herbal ephedra and weight loss. The AERs evaluated were limited to those provided by FDA. AERs from the studies were not reviewed. Report did not emphasize any potential benefits of ephedra/ephedrine and weight loss.	The AERs from other sources are now included in this revision. We disagree that the report did not emphasize the potential benefits of ephedra/ ephedrine use and weight loss. The other limitations are noted.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
Reference 29 can provide a national estimate of 2.5 million individuals using ephedra wt loss products (during 1996-1998), which is probably an underestimate since 33% of one-states respondents did not know that their nonprescription weight loss product contained ephedra.	The imprecision noted by the reviewer even in this one estimate is, we believe, good reason to avoid its use in trying to calculate a rate using case reports.
Some of the questions guiding the evidence report were not answered but are available in the literature search and data collection. For example, the question regarding the dosage level of ephedra necessary to achieve weight loss was not answer. There is no summary statement on the dose of ephedra or ephedrine other than Evidence Table 1 and 2.	A dose analysis is included in this revision.
Conclusions regarding the efficacy of ephedra-containing supplements in promoting weight loss and the enhancement of exercise performance were supported by the available data.	No Response
The conclusions are clearly and concisely laid out and are consistent with the evidence presented.	No Response
The conclusions of the efficacy of ephedrine and related compounds are valid for the short term studies evaluated and conclude that longer term studies need to be conducted. The remaining conclusions are valid and appropriate.	No Response
For the efficacy and minor adverse effect evaluations, the evidence does support the conclusions.	No Response
Finally, there was no demonstrable effect of sustained ephedrine supplementation on strength training.	No Response
According to the report, caffeine appears to enhance the effect of ephedrine yet there is no mention of assessing caffeine in the diet. This would have to be done in a case-control study. It may be appropriate to add this separate bullet under conclusions.	The need to control for caffeine intake was added to a bullet in the conclusion.
Bullet 1: Conclusion of "sufficient evidence" should be tempered with reference doses used and duration of treatment in the studies.-Bullet 2: This is just a statement not a conclusion. It would become a conclusion by adding that out of 1848 cases known, 1344 were selected for review and of these, 158 showed serious adverse events. Within this subset of 158 reports, 11 were identified in which ephedra was possibly causal. Conclusions section should be able to stand alone. This would require adding more detail including doses and duration.	Changes made to bullets.
It is generally acknowledged in the field of obesity research that any study with less than a 2-year follow-up is misleading and not relevant to the evaluation of the anti-obesity modality under investigation. The reason for this is that most individuals regain lost weight on any diet, drug or weight loss program after 24 months. There were no long-	We believe the text is clear that these results cannot be extrapolated beyond four months. The data support a linear relationship for weight loss over 4 months in these studies.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
term weight loss studies of ephedra or ephedrine reviewed in this report, yet a mathematical formula for weight loss associated with ephedra was presented. This seems highly speculative and hard to defend. The conclusion that short-term weight loss can be achieved with herbal ephedra and caffeine rest on studies of herbal concoctions that are not adequately characterized, chemically and pharmacologically, to permit pooling of studies; The attempt to quantitate the weight loss per month attributed to the use of ephedra-containing herbs is invalid. Further, the model assumes constant weight loss over time, an unlikely outcome.	
The need to add caffeine to ephedrine to produce any measurable degree of enhanced athletic performance suggests caffeine alone may suffice to achieve this effect, which, in any event, is evident for only short time periods.	The reviewer is incorrect, since one study reported in the athletic performance section compared ephedrine, caffeine, and their combination, and reported only the ephedrine/caffeine combination produced an effect. This result refutes the reviewer's hypothesis that caffeine alone may suffice.
It seemed that the decision to review FDA adverse event reports produced very little useful information and was almost a duplicate effort given Haller and Benowitz study. It may be more useful to use the same strategy on the case studies reported in the literature.	The literature cases are now included in this revision.
The bullet point "Scientific studies (not additional case reports) are necessary..." should be deleted as this is not the conclusion of the Adverse Consequences but rather Future Research, which has been stated already.	We think it important to also include this as a conclusion.
Dr. Leung made the point that there were thousands of Chinese literature on the Ma Huang, and if it wasn't safe the literature would say so. The literature comments that some people should not take it, but there is a lot of information to show that it is safe. Dr. Leung also made a point on the credibility of this information by stating that for other herbs the literature shows they are not safe.	We do not disagree that there may be extensive Chinese literature on MaHuang but we did not find controlled trials in our literature search, nor was this literature offered to us by any of the many reviewers of this report. Furthermore, we believe that there is ample evidence to support that the most valid conclusions come from properly designed hypothesis testing studies, not a collection of anecdotal literature, either supporting or refuting safety.
I disagree with the safety conclusion of this report for two reasons: 1. The clinical trials excluded patients at risk, thereby reducing the study's ability to detect harmful effects of the drugs. 2. The totality of prior pharmacologic information was ignored in the analyses of the FDA cases. The consistency between the type of events reported and the known actions of ephedrine to increase heart rate and blood pressure must contribute to the assessment of causality. The similarity of	We added to the limitations the issue of select patient populations. It was outside our scope to assess other chemicals.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
the reports seen with similar chemicals, e.g. phenylpropanolamine, must be given consideration. The cases that the authors classify as "possibly caused" by ephedrine/caffeine I would classify as "probably caused by" ephedrine/caffeine.	
I believe the second bullet under "Adverse Consequences" (page 112) is unclear and unqualified. This statement reads, "There have been a great number of adverse event reports filed with FDA regarding herbal ephedra-containing dietary supplements." I find this statement unqualified and unhelpful. A great number of reports compared to what? – Total dietary supplements sales? The number of AER's reported for other dietary supplements? The statement should be better qualified, in my judgment.	We believe 2000 is "a great number" by most people's definition and have not made any changes.
The first bullet on page 113 is a very key issue and I believe deserves further comments. I agree with the conclusion that, given the rarity of serious adverse events associated with ephedra, properly designed case controlled studies would be appropriate. However, I believe it will be difficult to develop such a properly designed case controlled study, as the underlying factors (that appear to be idiosyncratic) are not well understood. How, then, would a case controlled study be designed to take such unquantifiable factors into account? This is precisely the continuing problem in deciding how best to approach both the regulation of and further scientific research into ephedra	It is beyond the scope of an EPC evidence report to go into such details of study design. We note, however, that others have made detailed proposals to governmental agencies for just such a study.
The conclusions seemed fair and stated appropriately. I would suggest adding a section answering the questions you posed at the start of the report in a summary fashion.	We organized our bullets to follow the order of the questions.
Most of the studies reviewed were on synthetic ephedrine and weight loss, therefore, a relationship between herbal ephedra and weight loss cannot be made and this appears problematic. The clinical data that were examined only included ephedra in combination with another herbal stimulant. While it is true that many weight loss products contain a combination of ingredients, not all do (NNFA's database of ma hang or ephedra reveals that almost half of the products do not contain another stimulant). A concern is that the conclusions drawn in the report may be applied to all ephedra products, regardless of use and regardless of whether other ingredients are present.	We now include one RCT of ephedra without caffeine. We have limited the conclusions to only those concoctions studied.
It seems important to mention that apparently healthy individuals have died from the use of these products, possibly related to exacerbation of previously undetected disease. And, because these products are available without prescription, and not even regulated as OTC drugs, the risk associated with unsupervised use are potentially greater than with drug formulations of ephedrine.	We have added to the conclusions and limitations both of these points.
The conclusions of adverse consequences are internally	We disagree, since the finding of serious

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
inconsistent. Once the limitations are listed, then the number of serious adverse events (death, stroke, and myocardial infarction) should not be enumerated. This is the same thing as saying that results of a scientific study are not statistically significant and then still enumerating them in the conclusion. The most important conclusion is listed second to last on Page 113 and should be moved up to the front of the conclusion section of the report. That is, scientific studies (not additional case reports) are necessary. I disagree that a case-control study would be the next step. Rather I would recommend strongly a prospectively randomized controlled study design with appropriate data safety and monitoring in place. A population-based study will have the same drawbacks as the phenylpropanolamine study and will have the same risk of spurious associations rather than cause and effect relationships. An intervention study and not an epidemiologic study is needed to clarify the situation. As already stated, it is clear that the evidence does not support the conclusions. The adverse event reports are that they are. The attempts to connect them to the use Ephedra/Caffeine remain unconvincing both in this report and in the New England Journal of Medicine article.	adverse events in otherwise healthy young people is a cause for concern. We also disagree that the phenylpropanolamine study found a “spurious” association. We note that a case control study is the accepted study design to quickly assess a possible relationship between an exposure and rare adverse events.
Specific issues related to ephedra are not addressed adequately, and notions for which there is no proof are presented as if they were accepted scientific fact. For example, in the Pharmacology section, the report states "ephedrine increases peripheral resistance and can lead to a sustained raise in blood pressure...Elevations in blood pressure appear to be dose dependent in humans. However, does under 50 mg do not always result in increased blood pressure." The report fails to state that the sustained raises seen in hypotensive patients occur after the intravenous, not oral administration of ephedrine. The only citation for the dose dependency of an ephedrine-related rise in pressure is a review article, and that article does NOT say that ephedrine causes hypertension! It says, ephedrine and caffeine cause a greater increase in systolic pressure than ephedrine alone, that there is no effect on diastolic pressure, and that hemodynamic effects are transient. The statement is quoted out of context and is therefore misleading. The way the sentence is written, readers would be likely to assume that, even though "doses under 50 mg do not always result in increased blood pressure, a series of double-blind, placebo control trials have shown that at most the effects of oral ephedrine on blood pressure are negligible (as opposed to intravenous dosing used b anesthesiologists). A partial listing of some of these studies is cited here [10-23]. The lack of effect on blood pressure is even supported by the list of TEP "accepted articles" cited in	We clarified that the use of ephedrine to raise blood pressure intraoperatively is with parenteral use.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
the bibliography. All of the cited articles were from controlled clinical trials, and none reported clinically significant blood pressure elevations. These studies should be included as part of the RAND review, and the statements regarding increases in blood pressure should be substantially revised. Indeed, if the authors of the report cannot cite published, double-blind placebo control studies showing that taking oral ephedra/ephedrine significantly increase blood pressure, that that claim should not be included in the report.	
Suggested directions for research were provided, but they are narrow in scope and may suggest "gaps" that do not really exist. To date, more than 2000 ephedra/ephedrine users have been enrolled in clinical trials. Given the consistently benign results of all the previous trials, are still more trials needed before the issue is put to rest? On the other hand, cutting edge issues in obesity-related research are completely ignored. Does ephedrine interact with uncoupling protein? Does use of ephedra supplements have any effect on the production of inflammatory cytokines by adipose tissue? Or upon lepton homeostasis? On Lipotoxicity? If supplement manufacturers are to be believed, they have thousands of testimonials from satisfied users reporting weight losses of 50 pounds or more. Why not study these individuals and compare them with other product users who were unable to achieve weight loss? Having identified a population of proven ephedra responders, and non-responders, comparing the two groups medically, chemically, or genetically, may provide some truly useful insights.	We would ask the reviewer whether 2000 successful airplane flights mean that airplanes never crash. The point is that 2000 studied patients is insufficient to detect a rate of 1/1000 events, and even rare events, when multiplied by the millions of people who may be consuming ephedra, add up to numerous serious adverse events, if such an association exists.
The report draws conclusions about efficacy and safety that are not sufficiently supported by the data. As I have pointed out below the efficacy of ephedrine/caffeine is underestimated due to the incorrect method of analysis. In addition, in my view a number of shortcomings in the safety assessment tend to exaggerate the adverse events. My overall conclusion is that in several aspects the report needs some important revision. This includes the identification of studies, selection of studies for efficacy and safety. The data handling is also inadequate in some aspects. Consequently the report's overall conclusions are not supported in the current version and I believe that the revision suggested below will produce a substantially changed conclusion.	No response to this general comment. Specific response made to specific comments. We disagree that the identification of studies, selection of studies, data handling, etc. are inadequate. We also disagree that our results underestimate the efficacy of ephedrine/ caffeine, or that our analysis is incorrect.
Weight Loss. In the first bullet it is stated that compounds produce weight loss over relatively short periods of time (no more than a few months). This is misleading as there are trials for a duration of 6 months. The same applies for the 3rd bullet where the expression "short-term weight loss" is used. Bullet 6 is outrageous, here it is concluded that	Six months is still “a few months” when one year data are considered necessary by FDA to assess pharmaceuticals. The data about phentermine are taken directly from the graph in the cited reference. We have added data about weight loss using

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
ephedrine and ephedrine plus caffeine produce a weight loss somewhat less than the effect reported for FDA approved pharmaceuticals for weight loss. The panel has used phentermine as an example and state that the effect is "reported at about 20 pounds of weight loss at 6 months". This is certainly not the weight loss produced by phentermine above placebo, the weight loss produced by phentermine from baseline including a diet. For comparison one can take the Astrup et al. study from 1992 where the weight loss in the ephedrine plus caffeine arm was about 16 kg. But of course, the weight loss in the placebo arm must be subtracted, giving an additional weight loss produced by the compound of 3.6 kg.	other pharmaceuticals.
Adverse consequences. Again, this reviewer suggests that the open trials should also be included. In the first bullet it is stated that it is not possible to separate out how caffeine contributes to the side-effects. This is actually possible. In the Astrup et al. in International Journal of Obesity in 1992 there was a separate caffeine arm in the 6 months trial. Side-effects are shown in one of the tables in this paper, and here it is clear which side-effects can be attributed to caffeine.	Our statement refers to the data included in our review, which was restricted to RCTs and CCTs.
A long-term study of comparing ephedra + caffeine with ephedrine + caffeine at promoting weight loss and adverse reactions. Expand the pharmacokinetic study of ephedrine (pharmaceutical preparation) and ephedra (botanical preparation) absorption (as part of the dose response studies).	We think this is already subsumed under the first bullet point.
The most basic and important aspect of any research in natural products and in the reporting of findings is the characterization and clear definition of the products or materials being studied. Without this, research findings cannot be reproduced and thus are meaningless. In our case with ephedra evaluation, we not only need to set criteria for selecting articles for study, but also be sure to clearly understand what it is that we want to study – ephedra herb or ephedrine. The whole field of 'ephedra' in weight loss and athletic performance is twisted backwards. The herb ephedra has never been traditionally used for either function, nor has it been first clinically reported (before ephedrine) to have these effects. Only the drug ephedrine has. Yet ephedra is being used for these effects and is touted as natural ephedrine and thus safer. So far, there has been no credible clinical evidence that ephedra itself (and not synthetic ephedrine in an inert 'ephedra' carrier) has these actions, despite the conclusion reached in this report. It is worthwhile to reevaluate references 104-108 to determine whether the 'ephedra' used in those studies was actually natural ephedra containing the total complements of	The included ephedra studies said they assessed herbal ephedra. We agree with the reviewer that a future study of ephedra should adhere to these recommendations.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
ephedrine alkaloids in their natural proportions. If not, was it composed mainly of synthetic ephedrine formulated with carriers (e.g., token ephedra or exhausted ephedra marc) into an 'ephedra' dietary supplement that contains little or none of the usual complements of other ephedrine alkaloids? If it is the latter, then this 'ephedra' herb has no place as a dietary supplement in weight loss or athletic performance. Such 'ephedra'-containing products should then be more appropriately placed under the OTC-drug category which would eliminate much of the problems currently associated with its abuse and also would save us taxpayers much money trying to resolve these problems. In order to show ephedra herb (not synthetic ephedrine) to also have efficacy in weight loss and/or athletic performance, it is necessary to first characterize and standardize ephedra products to specific amounts of ephedra's alkaloids in their natural proportions, before subjecting them to clinical trials. This would eliminate the drug ephedrine being formulated into a dietary supplement to bypass the OTC-drug regulations. Unless ephedrine-containing products (whether natural or synthetic) for weight loss and athletic performance are all considered OTC drugs, adulterated, poorly characterized, and undefined dietary supplements containing ephedra herb will continue to be sold and abused. We need to set standards for manufacturers to meet and follow in order to be able to label and market their ephedra-containing products as dietary supplements. As I have repeatedly stressed, the most important aspect of any research in herbal medicines/supplements is characterization and precise definition of the test materials, without which no meaningful and reproducible results can be achieved, no matter how well designed and how well executed the rest of the research. In order to reduce the continued accumulation and dissemination of ambiguous, meaningless, and useless research data in the natural products field, we urgently need to set criteria for the characterization and precise definition of test materials at three levels: (1) research; (2) publication; and (3) abstracting, indexing, and data input into databases. Such criteria have been published and are available.	
The conclusion that "a properly designed case control study would be the appropriate next step" would require a study so large, lengthy and expensive it is unlikely to ever be funded or completed. (If one assumes a prevalence of use of ephedra of 1%, an alpha of 0.05, a power of 80% and if one seeks to detect a doubling of risk, then 2,400 stroke cases and 2,400 unaffected controls would be required. See Schlesselman, Case-Control Studies, Oxford University Press, 1982). The presumed benefits of ephedrine, should they exist, (improved athletic performance, enhanced	We agree that a properly designed case control study would need to be large (perhaps not as large as this reviewer conjectures). However, the PPA case control study was also large and was successfully completed, and we do not favor substituting opinion for science when the scientific study is feasible.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
energy, short-term weight loss) are likely due to the sympathomimetic effects of the drug and the adverse consequences are predictable as they were with isoproterenol, amphetamines and fenfluramine. Since sympathomimetic drugs have never been shown to result in safe and sustained weight loss, it is highly unlikely that this will be the result of long-term controlled trials of ephedrine and weight loss. But the known adverse effects of the drug and its congeners are now well characterized.	
First, you need to organize your listing of sources of adverse event information better so that readers can see which sources you have included and which you have not. Right now, it's difficult to follow what you have gathered. A table would be ideal, with each row specifying the source, the number of complaints, the number of deaths, serious injuries, non-serious injuries, and the numbers of each of these you concluded are likely or possibly related to ephedra use.	All of the serious adverse events came from FDA data, so in the draft report such a table would have no meaning. In the revised report, such a table is included.
You do not provide clear evidence of the pharmacological and pharmacokinetic equivalences in the use of the herb or of ephedrine alone. The complexity of the Phytochemistry of Ephedra (p 13) reinforces the point that the whole herb contains other alkaloids that are likely to be active or to qualify the effect of ephedrine. More should be made of this deficit at various points in the text.	We agree that there is likely heterogeneity in the herbal concoctions, but note the striking consistency of our findings relative to amount of ephedrine alkaloid and weight loss.
There is insufficient evidence that dietary supplements made up of the herb Ephedra spp. have any of the effects or risks identified for the alkaloid ephedrine.	We disagree and believe the data speak for themselves.
The future research directions proposed are reasonable. One addition may be to recommend examining the interaction of ephedrine and exercise training on weight loss and adverse events. Is there some interaction between physical activity and ephedrine?	This was added to the future research.
If the majority of ephedra users are seeking long-term weight loss, it would be very helpful to better understand the age, gender, race, temporal use patterns, concomitant drug use and other risk factors associated with ephedra usage. These points are underdeveloped and are, I believe, central to understanding safe and appropriate use of ephedra in the general population.	We agree in principle with this comment, but think it might wait until there is better evidence of sustained weight loss in any population.
I agree with the suggestion to analyze and compare the adverse events reported for ephedrine to ephedra. I would also add PPA.	This report now includes an assessment of ephedrine so this bullet has been eliminated.
The suggestion to consider a dose response study to determine a minimum effective dose of ephedra would be difficult, at best. Effectiveness criteria should be identified in these comments.	While it may be difficult, it is certainly feasible and consistent with the way FDA evaluates pharmaceuticals for weight loss.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
There remain open questions whether there is a difference between synthetic ephedrine and naturally extracted ephedrine alkaloids. It would be a very useful research activity to analyze the branded products which are identified in AER's using both AOAC and USP methods to try and determine whether synthetic or naturally occurring ephedrine alkaloids are present.	Agreed.
Future Research. The "numerous gaps" in the literature regarding the efficacy and safety of ephedra is a central point.	No response
FDA has recently taken action against six companies selling synthetic ephedrine as dietary supplements. This is not permitted under current law but, unfortunately, synthetic ephedrine dietary supplements are being sold to the general public.	No response
As a final thought, the inadequacy of FDA's adverse event reporting system is clear as it relates to ephedrine. I believe it is appropriate for RAND to recommend that, with respect to ephedra products, FDA/CFSAN's process and systems to evaluate and capture ephedra-related AER's be thoroughly reviewed, as it is likely that continued reliance will be placed on this system, despite its weaknesses.	This is not a proper role for an EPC evidence report and we decline to make such recommendations.
A chapter was devoted to future research. The researchers addressed the gaps in a variety of areas and suggested meaningful recommendations for further research. Most significant is the need for long-term studies of ephedra/ephedrine and weight loss and athletic performance including both anaerobic and aerobic exercise. This was emphasized in this chapter.	No response
It might be beneficial to explain the pathophysiology of how ephedra/ ephedrine can contribute to an acute cardiovascular event in the setting of mild-moderate underlying disease. For instance, in individuals with non-critical coronary artery disease, ephedrine alkaloids can produce platelet aggregation with resultant thrombus, increased myocardial oxygen demand, and cause vasospasm, all of which can result in decreased perfusion and ischemia. The same contributory actions could be expected in individuals with congenital cerebral aneurysms, and other underlying abnormalities in the cardiovascular system.	While we agree that biologic rationale is an important criterion when assessing causality, we think that direct evidence of an association is most important, and therefore recommend a hypothesis-testing study.
The implications for future research are fairly stated. I would suggest adding the analysis of safety or adverse events reports in Denmark comparing available prescription obesity drugs, since Denmark uses caffeine and ephedrine as one of it's approved prescription drugs for obesity.	This was added to the Future Research Section.
Are implications for research discussed? Not adequately. The major implication of the research is whether the	The role of the EPC is to report the evidence, which we believe we have done

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
analysis will be adequate to advise the FDA and HHS on whether they should take action to protect the public. This aspect of the analysis is ignored.	The judgment about the adequacy of the evidence to make a judgment is not a role for the EPC.
What directions for future research would you recommend based on this report that we have not covered? As I discuss in the following general statement, the missing ingredient in this (in addition to the issue of how the products are being used by the public) is the need for an analysis of the complete pharmacology of ephedrine/caffeine products. This must include consideration of the modern science of pharacogenomics and genetic polymorphisms of receptors for these products. This type of analysis adds relevance and credibility to adverse events that occur in low frequencies. It explains how some patients can have little or no change in blood pressure or heart rate and how some can be placed at risk of stroke, seizures or heart attacks.	A good suggestion, but one that we feel is probably some years off, as opposed to the three studies listed first. A genetic analysis could conceivably be added to a case control study and used as an effect modifier in the analysis.
Implications for future research were discussed. Physicians and most pharmacologists seem to want to lay the blame for problems associated with ephedra supplements at the feet of ephedrine/ caffeine. This narrow view excludes the pharmacological activity or potential interactions with other phytochemicals present in these products. In the opinion of this reviewer, the problem is more complex than simply ephedrine and caffeine.	This is a good point. An assessment of ephedra use may be able to take advantage of the heterogeneity in concoctions to perform subgroup analyses looking for ingredients other than ephedrine and caffeine.
Regarding future research aimed at stroke aspects, it would seem valuable to pursue case-control studies along the lines of that by Kernan and colleagues cited above but considering both hemorrhagic and idiopathic ischemic stroke in relatively young adults.	Agreed. The proposed case control study should assess all of the serious outcomes we assessed.
Page 5, paragraphs 3 and 4 would it be appropriate to mention ethical considerations for case-controlled studies in the summary?	We do not think so. The exposure has already occurred.
Page 5, paragraph 4: “Pre-clinical studies should also be considered to determine the use of ephedrine or ephedrine containing the alkaloids increases the risk of development of heat related conditions such as heat exhaustion, heat stroke, and rhabdmyolysis, if an appropriate animal model can be found.” What specifically would be learned from this? Could it be extrapolated to humans?	It might help establish a biologic rationale, but in this discussion we have deleted the “animal model” and “pre-clinical aspect” to this and suggest it be included in a study of adverse outcomes in humans.
Rewrite to redirect emphasis of sentence by placing, “If an appropriate animal model can be found, pre-clinical studies should be….and rhabdomyolysis.”	We actually eliminated the “preclinical studies” part of this and suggest a study assessing this as a potential adverse event.
I would suggest come additions to the section of future research including an interaction study to investigate the effects of ephedra with not just caffeine-containing herbs, but also combined with botanicals such as citrus aurantium, garcinia cambogia, and the herbal diuretics and cathartics	These suggestions have been added.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
as listed in Table 1. Also, I would specifically suggest that studies on athletic performance be conducted in women and adolescents, since these populations are known users of these products. Finally, I would recommend that the association between ephedra and seizures be formally explored.	
Future Research Section. You favor a case-control study. The case-control trial with phenylpropanolamine was sufficient to remove the drug from the market, but it was a pretty poor study. The controls and cases had very different lifestyle habits. There was a no-dose-response to PPA. The effect was only detected in women. Because of the large number of things used in the many products on the market, and the relatively high rate of deaths and disability from heart disease and stroke, it is not clear that a useful answer would emerge.	We disagree. We think such a study would tell us something useful about ephedra products. We do not think the heterogeneity in the components of the products will be any greater impediment to the analysis of safety than it was to efficacy. Our data are consistent with the hypothesis that the only active components with respect to efficacy and safety are ephedrine and caffeine.
Another point that might be useful to make is that from the available data it is not possible to determine which populations are at greatest risk for serious adverse events, and that this could only be determined by additional research.	This point has been made in our suggestion for a hypothesis testing study.

CAUSALITY COMMENTS

The remaining reviewer comments from the first review concern an attempt in our draft document to assess causality for some adverse events. We did so using our own modification of published methods. These comments varied widely, ranging from critiques of our method for being too conservative (meaning, in the opinion of some reviewers, we had excluded or assigned too low a level of causality to certain cases) to critiques for being too liberal (meaning, in the opinion of some reviewers, we assigned too high a level of causality to certain cases). Often, these conflicting comments concerned the same cases. We believe these 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. Rather, we tried to identify those cases that would be classified medically as "idiopathic" in etiology, meaning the cause is not known. For such cases, given the known pharmacology of ephedrine, if use of ephedra or ephedrine was documented, a potential role for ephedra or ephedrine in causing the event must be considered. We classified such cases as "sentinel events." Other than correct typographical errors and respond to questions of fact, we do not provide a response to the numerous criticisms of the causality algorithm or suggestions to change our interpretation of these case reports based on the reviewer's opinion or "additional information" they posses that we did not have in the documents available to us to review.

Reviewer Comment	Rand Response
Although the present study was compared to that report by Haller and Benowitz (New England J Med), why was a comparison not made to the Samenuk et al. study (Mayo Clin. Proc.)? Were individual case numbers not available from Dr. Samenuk? On page 51, in Level 2 of the Causal Flow Model, what is meant by "in more than minimal dose"? What constitutes a minimal dose? Are you talking about ephedrine, ephedrine/caffeine, or ephedra supplements? It must be emphasized that ephedrine and caffeine in conjunction potentially hundreds of other pharmalogically active phytochemicals constitute an ephedra supplement? Accordingly, the pharmacodynamic effects for ephedra supplements are not directly comparable to synthetic ephedrine or ephedrine/caffeine combinations. Furthermore, given the heterogeneity of ephedra supplement formulations, the pharmacodynamic effects of individual ephedra supplements are expected to vary.	
It should also be acknowledged in the final report that there is very little consistency in the results of any expert attempts at assessing causality with this same set of AERs. The draft touched on this issue in discussing comparison with other reports and in presenting information in Table 22. The language of the draft is not, however, consistent with the data in the table. The draft states that the current judgments "are more conservative than those of Drs. Haller and Benowitz" but that there was agreement that some cases cannot otherwise be explained. It is difficult to understand how such statements, with their implication that any differences are either minimal it immaterial, can possibly be associated with the actual information in the table. The table identifies 24 cases, 20 of which were evaluated by both this	

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group and by Haller and Benowitz. In only 5 of these is there full agreement. Twelve of the 20 cases are cases where Haller and Benowitz report possible or probable causality while the current reviewers reported insufficient information! It is curious that the Table does not note that, of the 11 cases reported by the draft as probably and the 26 cases identified as possibly related to the use of ephedra, Haller and Benowitz only classified 2 of the first and 7 of the second as either probably or possibly related. Information is not provided to assist in understanding whether Haller and Benowitz had classed these as not associated with ephedra of whether they had not evaluated these cases. If the first case, it should be disclosed if the second, there should be some mention that the current causality assessment is preliminary and subject to review by other qualified experts.	
It is also curious why reviews with different conclusions by other parties were not acknowledged. For example, in at least one case where both this group and Haller and Benowitz agreed that there was a possible causal relation between use of ephedra and death, the local coroner ascribed the unfortunate incident to congenital problem. In addition testimony was given by Theodore Farber, Ph.D. on August 8, 2000 at the HHS Office of Women's Health to discuss the issue of inconsistency at length and in detail. As Dr, Farber noted " There was a sufficient lack of concordance between the FDA's causality analysis and the causality analysis performed by it outside experts." Other presenters at this meeting provided analyses of these AERs that found quite different conclusion that have been drawn in the Draft. It must be assumed that the record of this meeting and possibly more specific information, was accessible as the draft was being prepared but it does not appear that any attention was paid to any other commentary on causality reviews to date. This must be corrected.	
In discussing the case reports the Draft states that "events related to synthetic ephedrine" were removed. Notwithstanding out earlier attempt to clarify that synthetic ephedrine probably means ephedrine in isolation (or its salts, e.g. ephedrine hydrochloride), at least 8 of the cases reported on were associated with a product that was labeled to contain ephedrine hydrochloride (the E'OLA product) or was subsequently found, or at least has come out to be assumed to have been manufactured with undisclosed ephedrine salts (Formula One). At lease two cases do not identify the brand so it is not known how this determination was made from these cases.	
Almost every 'Probable" case and "Possible" case had either a preexisting condition that could have contributed to the adverse event or exhibited unhealthy behaviors	

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(excessive drinking, smoking, "intense effort to lose weight") which should be noted.	
On p 69 and Table 22 there is a comparison of the results of Rand evaluation of FDA AER with those of Dr. Benowitz – the specific criteria to meet definite, probably or possible causality are explicitly stated for the Benowitz evaluation [as was the case with other expert evaluations of these data in the FDA docket]. It would be useful to specifically list the criteria used for the Rand Evaluation for their classification. It is stated that the Rand evaluation is more conservative than the analysis by Benowitz, but what about comparisons with other expert reviews of these data [2 FDA reviews, Woosley, Benowitz, Ricaurte and Stoll]?	
Table 22 Summary of comparision with other reports of ephedra adverse events there is an error in the table for FDA case number 12720 and 12722. According to information elsewhere in the report, the following appear to be the correct data entries: Case# Adverse event Benowitz EPC 12720 Death Possible Insufficient information 12722 Death Possible Possible	
What was the classification of the CanTox study commissioned by CRN?	
Do you have information as to how soon an autopsy was performed? Could this have any impact on the toxicological screen results?	
I would assume that the prevalence of pre-existing coronary artery disease is very high. Therefore, when interpretations are made as to causality and risk for most Americans, it may be important to have some reference numbers as to how many Americans have pre-existing CAD.According to the Am Heart Association (using NHANES III data), 1 in 5 males and females has come form of cardiovascular disease, see this website for details about CAD.See American Heart Association. 2002 Heart and Stroke Statistical Update. Dallas, Texas: American Heart Association, 2001.http://www.americanheart.org/downloadable/heart/1014832809466101319099012 3HS_State_02.pdf	
My prior bias about ephedra and stroke was based on influential case-control study of the relationship between the use of phenylpropanolamine, a compound with related physiological effects, and hemorrhagic stroke (Kernan WN et al. NEJM 2000;343:1826-32). I believe that it is likely, re-enforced by the data in this draft report, that ephedra use occasionally leads to stroke. However, for the purpose of this review, I have elected to play the devils advocate in considering the specific question: "how strong is the existing	A neurologist was included in the review process in this revision. "Grand mal" seizure was the description of the event in the original source material.

Appendix 3. Reviewer Comments (continued)

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evidence that use of ephedra can cause a stroke?" Because determining the cause of strokes among young people is not that often straightforward, it would have been optimal to have the stroke cases reviewed and classified by a stroke expert with experience in evaluation of young stroke. The case reports (p.63) suggest a lack of neurological sophistication (i.e. grand mal seizure in case 11062 is not technically correct; generalized convulsive seizure is probably what was intended). OK,so this is an irrelevant elitist comment, but in the absence of hard evidence, credibility is a subjective issue. Case 10874 is categorized as "probably causal" : along time intravenous drug abuser with phenylpropanolamine on toxicology screen. Case 9335 is classified as "possibly causal": 56 year old woman with hypertension, tabacco use, elevated cholesterol and triglicerides, an MRI with microvascular changes and whose event was lacunar infarct. Case 12713 was "possibly causal": a 63 year-old woman with artificial fibrillation with acute loss of conscious and embolic stroke. It would be easy to take issue with classification of likelihood of causality in each case. In short, I agree with the appropriately cautious conclusion that "there is sufficient evidence to suggst a possible causal role of ephedra-containing dietary supplements in rare, but serious adverse events, particularily cerebral hemorrhage." (p.vi) Support for this statement would be better served by have a stroke expert review the case reports and perhaps tossing our the marginal cases (such as noted above). Further, since this authoratative report may eventually be used for medical-legal purposes, it would seem responsible to include a caveat that it is not sensible to consider all strokes of idiopathic cause in people taking ephedra as caused by the agent. These comments are not meant to disparage the overall quality of this impressive report. As noted at the outset, I have elected to play the devil's advocate concerning this specific aspect.	
The criteria for determining causality were arbitrary and did not address the true causality. In fact, the term "causality" is misleading in this connection. Rather, the term "association" should be used as in "guilt by association". Lay people will read this report and "probable causality" will be interpreted as a cause-effect relationship which is not warranted by the data available from medical record reviews.	
The limitations of the data collection are not emphasized enough in this report. Adverse reactions reports by definition have no denominator and are subject to reporting bias. In the famous Phen-Fen debate, initial reports on which the FDA took action suggested at 35% incidence of valvular abnormalities. Subsequently, this was found to be less than 8% and reversible following discontinuation of the	

Appendix 3. Reviewer Comments (continued)

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medications.	
It is very important to the integrity of this report that the basic questions asked in the contract are answered, that the report is well ordered, and that only scientifically valid information is included. If the AER information, which is not scientifically valid is included, it should be included as an appendix, not in the body of the report, as this takes away from the science.	
Use of the terms probably and possibly causally related may make the causality assessment sound more objective than it is. Would be the subjective natures of the assessment be more effectively conveyed by changing those AERs currently designated as probably causal to possibly causal, such as events if uncertain relationship? Instead of specific designations it might be adequate to describe the results in narrative form. The narrative could explain that although in some cases cofounders make it difficult to attribute causality, there is a subset of cases in which cofounders make it difficult to attribute causality, there is a subset of cases on which cofounding factors are minimal or absent as far as can be determined, and it is these cases that raise concern over safety. Whatever terms or phrases are used, defining them early in the document will help even those unfamiliar with adverse event causality analyses understand their meaning.	
Should make it clear that it is not possible to determine the actual level of risk for people taking ephedra or ephedrine because the number of people who actually take it is not known.	
It would be helpful to provide possible reasons for the differences between the RAND causality assessment and the one done by Haller and Benowitz, this could be done by adding text to point out that: I. Each group used different criteria. II. The same group of experts would come to different conclusions of they were using different sets of criteria for evaluating the same set of AERs, and III. The RAND report use more stringent/restrictive criteria for assigning causality than were used in the Haller and Benowitz review, resulting in more conservative assessment.	This table has been dropped from this revision since causality is no longer assessed.
Requirement of angiography for assigning causality for M.I.s to Ephedra (similar comments from two reviewers): Page V Paragraph 5:" for cases of myocardial infarction, we required coronary angiography to have been performed and the results available." This seems like a very restrictive set of myocardial infarction cases. What would be the effect on the results if angiography had not yet been done? Why was this restriction used? Results section explains this better, Assume all such cases would have been classified as	

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possibly causal , so the data is still listed. Pages 3 and 32: While we understand the importance if documenting the occurrence of myocardial infarction by restricting the documentation of the event so that the cardiac characterization is required to assign causality to ephedra, are the number of MI events being underestimated? Why not also use enzyme changes in laboratory specimens and Q-wave changes on the EKG to assign causality?	
"'Probably not causal' was used for events that had clear other causes discovered on detailed investigation." This assumes all events had a single cause. But can't someone with known atherosclerosis die suddenly because of superimposed effects of a substance.	
This sentence is confusing " In the 935 reports, there were data in 968 subjects of which 925 reported taking ephedra." Not clear how there can be more subjects than reports.	A single FDA MedWatch report can contain information on more than one person.
A case presented (#12843, 15-year-old female) without any reference to ephedra exposure. Absent that information, it would be hard to make this even a possibly causal classification.	
A couple of reviewers were confused by the mention of AERs that took place after September 30, 2001. Perhaps a footnote on the table would be informative to remind readers if the timeframe for the AERs analyzed.	We added text to try and help explain this.
Table 20 provides a lot of useful information, but it might be easier for readers to interpret the data if another table were added. This table would have 5 columns across the top, labeled Product, #Probably Causal, #Possible Causal, # Insufficient Information, and Total (terminology may change based on other comments).	We considered but did not make any changes to this table. A different kind of Summary Table is included with this revision.
Data from the case report of the death of a 28-year-old female indicates that the MiniThin was one of the products that she was taking. MiniThins were shown to contain synthetic ephedrine, not ephedra, and the FDA required the company stop marketing it for weight loss and change the name and marketing focus (product name was subsequently changed to MiniTwoWays and was marketed for use on people with bronchial asthma). Should this AER be included there?	This case was included in the ephedra FDA MedWatch file. The patient was also taking Yellow Jacket.
Specific cases. Page 60, Deaths, Probably Causal: A 21-year-old male collapsed…": This patient has been taking hydroxycut, which I assume is hydroxy citrate. Hydroxy citrate is probably quite toxic, though it has not been systematically assessed in clinical trials. Biochemically it may be assumed to have a substantially liver toxic effect. I think it is therefore very difficult to attribute the case to ephedrine. I think that there are too many examples of patients with many other risk factors, such as those included	

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under the "probably causal" myocardial infarctions, e.g. a 54-year-old, who has smoked for 30 years and been an alcoholic.	
Specific cases. Page 62, Deaths, Probably Causal (cont'd): Page 62: Another example is the "Stroke, Probably Causal": "She was a long-time intravenous drug abuser and alcohol abuser. She also smoked cigarettes for 10 years." She tested positive for benzodiazapines and phenylpropanolamine, whereas there was no positive test for ephedrine. I strongly disagree with the conclusion that this case can be classified as probably causal with respect to ephedra use. It is more likely, with the given history and the positive test of the patient, that the stroke was caused by other vaso-active drugs taken by the patient. These weaknesses apply to several of the other stroke cases, and I think this is particularly interesting in light of the meta-analysis of adverse events reported from control trials (Table 17, page 80) where it is found that there is no statistically significant increased risk of hypertension. This also quite clear from the control study by Ingerslev et al. on hypertensive patients treated with ephedrine/caffeine. One should therefore be cautious about drawing conclusions on the causality with respect to stroke.	
HHS and GAO Statements Regarding the Same AERs that RAND Reviewed. The draft report attempts to ascribe degrees of causality to the ephedra AERs, thereby ignoring recent statements by the Department of Health and Human Services and the General Accounting Office ("GAO"). HHS and FDA recently reviewed the same AERs that RAND reviewed, and issued a response to Public Citizen on June 14 that provides the following: The primary purpose of a voluntary adverse event reporting system is to generate 'signals' of potentially related events, rather than assessing product safety. While a 'signal' has been generated by these reports, FDA has determined that questions remain on the likelihood and strength of association between ephedrine alkaloids and the adverse events reported to the FDA... There are situations when background rates of the observed event are so rare or unusual that, in combination with physiologic responses and biologic plausibility, a significant relationship between the events is self-evident from the reports in a voluntary reporting system. However, the FDA has advised me that the types of observed outcomes reported in relationship to the ingestion of ephedrine alkaloids are not uncommon in the general population and therefore the reports alone do not provide a scientific basis for assessing the safety of ephedrine alkaloids or establish a link between the reported adverse events and the ingestion of ephedrine alkaloids. (emphasis added). The draft report should mention and cite the above-	

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mentioned letter and FDA's and HAS' position with regard to the AERs and attempts to ascribe causality. The draft report also does not acknowledge the GAO report on ephedra AERs, which reviewed the same AERs and determined that they were "poorly documented," further weakening RAND's reliance upon reports for causation analysis. GAO also noted that the AERs have "inherent weaknesses" and lacked or had inconsistent information...such as the amount of the product used, how often it was used, or for how long it was used. These limitations were not prominently identified in the RAND report - nor were the general limitations associated with attempts to ascribe causality based upon review of information obtained from a passive surveillance system. GAO also noted that, based upon its review of specific AERs, it was not possible to draw conclusions regarding the "causal relationship between ingestion of the implicated product and the adverse event observed." Potential Product Variation. As noted above, the draft report does not even acknowledge the possibility that certain ephedra supplements may not be standardized and/or manufactured according to GMPs. Accordingly, even assuming causation (which is a major assumption), it is conceivable that certain adverse events may have been caused by problems with a specific product (such as having more ephedrine alkaloids or caffeine than stated on the label). Although it is my understanding that most manufacturers of ephedra employ stringent quality controls, this is still nevertheless a significant possibility that should be reflected in the report. Attachment B contains an article prepared by Dr. Gurley entitled "Content versus label claims in ephedra-containing dietary supplements." Although this article reviewed only a small subset of ephedra products, and only reviewed a small sample-size of bottles, it nevertheless supports the conclusion that it may be inappropriate to assume that all ephedra products are identical with regard to product quality. Accordingly, even assuming causation, it should be noted that there is no assurance that any potential adverse health events were not caused as a result of consumers ingesting non-standardized products that contain too much ephedrine or caffeine. It would be inappropriate for RAND to assume that consumption of ephedrine and caffeine within labeled amounts is a potential problem if the possibility exists that certain incidents may have been caused by consuming non-standardized products. Accordingly, my strong opinion is that as part of its review, RAND should call for FDA to finalize dietary supplement GMPs and impose stringent quality control requirements on ephedra manufacturers to ensure that such products contain what they are claimed to contain. Haller/Benowitz Review of AERs. The draft report places	

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great importance of the review of ephedra adverse events reports conducted by Dr. Haller and Benowitz. In fact, the draft report compares RAND's assessment of AERs with the Haller/Benowitz assessment. The draft report, however, fails to mention that Drs. Haller and Benowitz subsequently wrote a letter to the editor of the New England Journal of Medicine (Attachment C) indicating that their review did NOT prove causation or provide quantitative information with regard to risk. Specifically, their letter provides the following: Finally, our report describes a series of cases in which the use of ephedrine-containing dietary supplements was associated with a diverse cardiovascular events. Our report does not prove causation, nor does it provide quantitative information with regard to risk. A large-scale case-control study similar to the Hemorrhagic Stroke Project for phenylpropanolamine is needed to determine the risks associated with these dietary supplements. Based upon this letter and clarification, it is unclear why the Haller/Benowitz review of the AERs is used as a baseline for purposes of comparison. Moreover, it is unclear why their statement regarding causation and the recommendation of a case-control study is not highlighted - as this would appear to be information that RAND should consider as a recommendation for further research. Importance of Background Risk - Kimmel Study. This draft report fails to cite favorable analyses of FDA AERs - including a detailed study conducted by Dr. Steven Kimmel that was presented before the Office of Women's Health (Attachment D). Dr. Kimmel reviewed the AERs and determined that the number of events was consistent with background rates in the general population. His report highlights the importance of background risk - an issue that should be highlighted in the RAND report. He concludes that the AERs - even assuming significant under-reporting - are not suggestive of causation. In this regard, he quoted FDA" "it is possible that the reported serious adverse events are reflective of coincidental background spontaneous occurrences in the population and are not necessarily causally related..." OTC Drugs Containing Ephedrine and Caffeine. The draft report does not prominently refer to the wide usage in the United States of ephedrine in OTC drug products. The report should include use-data for OTC drugs, and should explain that FDA has already determined - under the OTC Drug Review - that ephedrine is safe and effective (as a bronchodilator) in does well over 100 mg per day (the maximum dose level for the vast majority of ephedra supplements on the market). In addition, the FDA does not require such products to contraindicate caffeine ingestion (i.e. consumers routinely ingest such products along with coffee, tea, and other beverages that contain caffeine). This	

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information must be factored into the final report, as they have a direct bearing on any safety assessment of ephedrine and caffeine. OTC drug use-data indicates that the combination of ephedrine and caffeine is safe. Scientific Data and the Landmark Six-Month Harvard-Columbia Trial. The draft report acknowledges that "there were no serious adverse events reported in these clinical trials." Despite this, the report barely addresses this issue. Rather, the vast majority of the report reviews and subjectively interprets AERs that GAO, HHS, and FDA have already reviewed. Even though the number of subjects in the clinical studies is limited, and therefore it is conceivable that small subsets of the population may have some susceptibility, the clinical data is far more reliable than the anecdotal adverse event reports and should receive greater prominence than the AERs. In addition, the report does not place enough significance upon scientific data such as the Cantox Report and the landmark six-month Harvard-Columbia trial (published in the International Journal of Obesity). The Harvard-Columbia trial addresses the review of adverse event reports, and makes suggestions regarding future research. The RAND report should contain a more detailed discussion of this landmark trial - including the researchers assessments regarding product safety and efficacy. For ease of review, sections of the report addressing adverse event reports, product safety and efficacy, and future research are included below: In a FDA-sponsored analysis, Haller and Benowitz categorized 140 adverse-event reports based on how likely they believed the reported events to have resulted from the use of ephedra supplements. The difficulty in making such judgments is illustrated by the controversy regarding their conclusions. With millions of American consuming ephedra-containing products it is obvious that some number of adverse events is expected each year regardless of consumption of these products. The real question is not whether adverse events occur in a population undergoing treatment, but whether these occur at a rate that is higher than that of a matched, untreated group. This is impossible to determine from adverse event reports alone. The randomized, placebo-controlled trial allows evaluation of cause and effect relationships vs. coincidental events. Most clinical trials purposely exclude individuals with pre-existing medical conditions to avoid confounding of results. It is therefore not justified to extrapolate results from such trials to individuals with such exclusionary medical conditions or to extrapolate results beyond amounts or time periods that have been studied. The possibility of unfavorable interactions between herbal combinations and other medications, either prescription or	

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illicit, should be recognized and warning labels present on herbal products should be adhered to. Some have expressed the theory that adverse event reports may reflect an unusually high degree of sensitivity in a small fraction of individuals. Because of the low suspected incidence, this type of sensitivity might not be revealed in a clinical trial, but requires a case-control study of a very large number of individuals. Such a study would be difficult to conduct, but may be the only way to address the question of rare hypersensitivity. In total, these [ephedra studies] suggest that herbal ephedra/caffeine herbal supplements, when used as directed by healthy overweight men and women in combination with healthy diet and exercise habits, may be beneficial for weight reduction without significantly increased risk of adverse events. In total, these [ephedra studies] suggest that herbal ephedra/caffeine herbal supplements, when used as directed by healthy overweight men and women in combination with healthy diet and exercise habits, may be beneficial for weight reduction without significantly increased risk of adverse events. The current widespread usage of herbal products and the increasing incidence of obesity warrant additional clinical trials to confirm and extend these results. (emphasis added). Finally, it should be noted that the Harvard-Columbia Trial researchers, and Drs. Haller and Benowitz appear to agree that in order to evaluate the safety of ephedra, a long-term control study would be beneficial.	
The draft report in the end recognizes the futility of trying to reach scientific conclusions from the AER's, recommending that a case control study be done to assess risk and recommending against further AER analysis. Nevertheless, a detailed causality assessment was performed and included in the draft report, and conclusions of this assessment are presented without context. Further, the draft report describes the involvement of the TEP in a way makes it appear this assessment was done on the recommendation of the TEP., when I and others thought that there was a general agreement within the TEP and RAND further assessing causality based on the AER's was not recommended and would not be part of the ephedra review. The draft report on page 21 states that the "Highest level if causality that could be ascribed. Was "probably" causal". This is not a position taken by the TEP at the November meeting; in fact it is contradictory to the TEP's position as quoted above. There was a discussion of the characteristics of the case reports, but not in the context as stated on Page 21..."that would be necessary in order to assign a classification of "probably causal." The criteria quoted were of causality. The report not only implies (also	The causality analysis was dropped from this revision. Regarding the involvement of the TEP, there was a lengthy discussion of the criteria by which we would assess case reports, so we are surprised this TEP member concluded "the TEP" agreed that such a review was not warranted. We did not receive any such comment from any other TEP member, all of whom reviewed this report.

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on page 31) but also states that the TEP agreed with this causality classification categorization, which was not the case. The classification scheme was developed after the November meeting, and any category such as "possible causal" or "probably causal" that suggests a causal relationship is in contrast to the position of the TEP at the November meeting. Terminology of "possibly" or "probably" causal is too strong and more than suggestive of causality, and to suggest that these terms are less than "definitely" causal is too fine a point for readers of this report and also an incorrect representation of the TEP's position. If the causality assessment remains in the final report, I suggest that all reference to this classification scheme be changed accordingly, to omit the word "causal". The conclusions could be characterized as weak evidence or possibly suggestive evidence, but the words causality and causal are too strong. The draft report notes correctly about the AERs that "The most important limitation is that the study design, that is an assessment of case reports, is insufficient to warrant definite conclusions regarding causality." Yet when it came to assessment of individual case reports, there were definite conclusions that the AERs prove ephedra to be unsafe. The result is a misleading presentation of the available information. For the reasons explained above, I feel the report requires major revision and subsequent further review by the TEP. Because I have been focused on the fundamentals of the reports as described above, I haven't even considered the comments on details that are included in the draft report. The weakness of the FDA AER database must be better addressed, and the causality analysis should either be removed from the report or substantial revised to, among other things, provide the necessary context and to change the classification of the AERs to avoid using the terms "causal" and "causality". The fact that the safety section is dominated buy the AER analysis reduces the credibility of the section and indeed the whole part of the report.	
However, in the opinion of the reviewer, those conclusions regarding the case reports are limited by a combination of the conservative causality assessment criteria and the limited medical records and toxicology data available for most case reports. For example, hypertension was defined as a systolic pressure in excess of 180 and a diastolic pressure in excess of 105. Also, no consideration appeared to have been given to the contribution multi-component ephedra-containing dietary supplements might have had in those individuals with underlying cardiovascular or cerebrovascular disease. I think it is generally accepted among the medical and scientific community the presence	

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of sympathomimetic agents could potentially exacerbate the likelihood of adverse events in such populations? I would think most clinicians would factor such information into their differential diagnosis rather than dismiss them altogether.	
Adverse Events Reports: One limitation with your approach taken in evaluation of the adverse events reports made to the FDA is that your causality algorithm does not include an assessment of whether ephedra played a contributory role on the adverse event. Because ephedra is available as a dietary supplement, it is likely that many persons taking these products are not using them under doctor's supervision, and may have medical contraindications to their use. Therefore, the role of underlying disease becomes a crucial factor in causation assessment, particularly when a potential risk factor often goes undetected (i.e. essential hypertension, structural heart defect), or when a condition is omitted from the ephedra product label warning (i.e. family history of premature CAD, sickle cell trait).	
Two AERs that you assess as no higher than possibly causal illustrate this point. AER 12485 did indeed have a moderate degree of coronary artery disease detected at autopsy. However, he was reportedly in good health without history of angina, and had been jogging regularly without adverse effects. Because he collapsed suddenly after returning from jogging, we felt this was a primary arrhythmic event due to ephedra. Similarly AER 12843 was a healthy, adolescent who had participated in competitive sports for many years. She had appeared to have been well-compensated for a serious underlying coronary artery abnormality that was clinically undetected since birth. Only with use of Ripped Fuel, did she suffer a catastrophic cardiac event resulting in death. We felt that the cardiac stimulant effects of ephedra resulted in myocardial ischemia in this case.	
It would be helpful to specify what degree of pre-existing coronary artery disease would constitute a significant risk factor to result in myocardial infarction or sudden death in the absence of stimulant use, thereby ruling out ephedra in the causation assessment. (page 32 of chapter 2 methodology). In the case of AER 14530 (page 63), I would disagree that 20-30% stenosis would be significant enough to result in acute M.I. in a 43-year-old female smoker without a significant contributory effect from the ephedra alkaloids in Metabolife.	This case was reviewed by a cardiologist who made this judgment.
On page 59 I suggest the authors be slightly cautious with their use of language such as "probably causal" and "no other possible explanation." The latter phrase is particularly troubling. What they mean is no other explanation that they could identify. Similarly, on page 69 they state that there are a certain number of cases of serious adverse events that	We have revised this language.

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"cannot be explained by causes other than ephedra use." While I do not deny that it is extremely likely that many cases of adverse events happen due to ephedra use, simply because we do not have in our hand an explanation of why an event occurred other than a particular explanation under consideration, does not mean that the particular explanation under consideration is the correct one.	
Because of the paucity of large randomized trials, evidence concerning stroke and ephedra by necessity consists of analysis of case reports. "…An assessment of case reports is insufficient to warrant definite conclusions regarding causality." (p.110) Nevertheless, arbitrary criteria are used to define "probably cause": documentation that a stroke occurred, that ephedra was used, and that there was exclusion of other potential causes. The definition may be too liberal. Of ischemic strokes in relatively young adults (i.e. those <50 years old), perhaps 20-35% are "idiopathic" despite thorough evaluation. The definition implies that all idiopathic strokes would be classified as "probably causal" if ephedra was used in any dose in proximity to the event. Given the frequency of idiopathic stroke, many (perhaps most) neurologists would consider "possibly causal" to be a better designation in this situation. Are there specific clinical circumstances in which the relationship of ephedra use and idiopathic stroke could be certain? Perhaps if acute, striking elevation of blood pressure were known to precede the stroke onset of of angiographic features characteristic of vasospasm were present in the abscence of migrane? Arbitrary to be sure, and not very helpful.	
The evidence for effectiveness supports the conclusion. Except for AERs, however, little evidence of toxicity is actually provided, and evidence of safety has been largely ignored. No evidence is provided to even suggest "a possible causal role of ephedrine-containing dietary supplement in rare, but serious events," let alone extremely common events such as heart attack and stroke. Even critics of ephedra have concluded that the clinical effects of pharmaceutical ephedrine, and the ephedrine contained in herbal preparations, are indistinguishable. Gurley states that the increased incidence of ma huang toxicity does not stem from differences in the absorption of botanical ephedrine compared with synthetic ephedrine." Haller and Benowitz, in their most recent publication, conclude, "Botanical stimulants have disposition characteristics similar to their pharmaceutical counterparts..." The Cantox Report, and the Report of the Expert Panel of the EEC reached similar conclusions. Since there are no real differences, studies demonstrating the safety of pharmaceutical ephedrine and pharmaceutical ephedrine in combination with pharmaceutical caffeine, should not be	

Appendix 3. Reviewer Comments (continued)

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excluded when considering the safety of herbal equivalents. The explanation most frequently offered for alleged cases of ephedrine-related stroke is drug-induced blood pressure elevation, this in spite of the fact that no clinical trial, of any duration, has ever demonstrated that a clinically significant effect on blood pressure exists. Indeed, the studies that have addressed this question. including the most recent paper by Drs Haller and Benowitz, have shown diminishing cardiovascular effects over time. In other words, if dangerous blood pressure elevations do not occur with the first dose ephedrine, they are even less likely to occur with prolonged dosing. These studies should be included in the RAND review of ephedra and should be used to address the question of potential increases in blood pressure and other safety issues. Ephedrine has been studied in more than 50 double blind, placebo-controlled clinical trials, some of long duration. A far from exhaustive literature search produced the attached list of peer-reviewed, published, clinical trials. Most have compared ephedrine to placebo, and to other sympathomimetic drugs used to treat asthma. However, others have involved smoking cessation, sexual function and athletic performance. Nearly a dozen of these trials involved caffeine/ephedrine combinations using does exceeding those found in herbal supplements. In total, more than 2000 individuals have been enrolled in these trials. In several studies there was even continuous cardiac monitoring in middle-aged patients with known heart disease; no effect was observed. No clinically significant episodes of toxicity were reported. Including these and other studies on ephedrine that have been excluded from the RAND review will increase the power of the safety calculations that can be derived from clinical data. One of the major limitations of the report was the composition of the TEP and the reviewers who made subjective assessments of the AERs. Given the importance placed on assessment of AERs, it is unfortunate that no pathologist was included in the view or on the panel. The lack of expertise is obvious from the comments made about the individual AERs. The failure to provide information about any potential conflicts of reviewers also detracts from the study. Why were the findings of Expert Panel of the Ephedra Education Counsel not considered? The analysis of this panel was in some ways unique, as it is the only consensus opinion on ephedra safety. In addition, this panel conducted the most comprehensive review of the ephedra AERs to date, and yet the causality assessment, which conflicted the findings of the draft report, are not even mentioned. If RAND believes that the EEC review and analysis was, in some way scientifically flawed, then the reasons for that belief should be stated.	

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The danger of drawing conclusions from AERs without a control group can be illustrated by examining data from randomized trials in which participants are blinded to whether they are receiving the study treatment or inactive placebo. In the placebo group of a recent randomized trial,2 there was an increase in ventricular couplets (extra heart beats) at the 4th week of the study 9from 3% at baseline to around 14% at week 4). This is, of course, not due to the placebo, which is inactive, but rather just spontaneous ventricular couplets that occurred by chance. However, if these participants had been given ephedrine alkaloids in an uncontrolled study (without placebo), this change could have been attributed, incorrectly, to the ephedra. That is, these could be AERs that were attributed to ephedra. In fact, in the controlled trial, a similar increase in ventricular couplets was not seen in the ephedra/caffeine arm. Another example is the 15-year-old female (case 12843) with Bland-White-Garland syndrome who died while playing soccer. This disorder has been associated with sudden death after physical exertion. In the absence of a unique pathologic process, it is almost never possible to establish a causal association on the basis of adverse event reports. There is nothing pathologically or diagnostically unique about the adverse events noted in the ephedra database (e.g., myocardial infarction, stroke) that allow one to distinguish a spontaneous event from one caused by use of Ephedra products. In fact, a review of all autopsy data from ephedra AERs by Dr. Grover Hutchins, a Professor of Pathology at the John Hopkins University School of Medicine and member of the Expert Panel of the EEC, concluded that "The pathology data available do not show any pattern consistent with ephedrine alkaloid-containing dietary supplements as a cause of death."5 Similarly, 10 participants in the ephedra/caffeine group (12% of these participants) withdrew because of cardiovascular symptoms (palpitations, elevated blood pressure, arrhythmias). If there were no control group, these also might have been attributed to the ephedra/caffeine combination. However, the same proportion of participants in the placebo group (13%) withdrew for the same reasons. The withdrawal rate in the ephedra/caffeine group thus was consistent with the background rate of these events in a placebo group unrelated to ephedra use. A second limitation of adverse event reports is that other potential causes of the event are often present, making it extremely difficult to determine if an event truly is related to the exposure. As an example, it is well established that physical exertion can trigger myocardial infarctions and cardiac arrest (up to a 74-fold increase in the risk of sudden death, according to a recent report in the New England Journal of Medicine6)	

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Therefore, a case such as the 38-year-old man with three vessel coronary disease and a dilated heart who died after jogging could very well have been related only to the physical exertion and not the ephedra. According to his wife, his heart problems had been known for at least five years. In addition, this man had been taking an ephedra product for one year without apparent ill effect. The third limitation of AERs is that their interpretation remains subjective. Even experts in the field will disagree about the possibility that an event may or may not be due to an exposure. The RAND report (Table 22) displays a comparison of the causality assessment between their review panel and a published report by reviewers for the FDA.3 In only two out of 20 cases that both groups reviewed was their agreement about the highest level of possible causality. For example, with respect to the 38-year-old discussed above, the Haller and Benowitz review recorded this event as "Definitely or probably related" to ephedra while the RAND report classified it as only "Possibly causal." Another review of AERs performed by Dr. Theodore Farber and Dr. Norbert Page, members of the Expert Panel of the EEC, reveals similar disagreements. The two "probable" cases reviewed by EPC were rated as "Low Possible" (case 12980) and "Improbable" (case 13418) by Drs. Farber and Page. The fact that the etiology of events can be debated simply illustrates the substantial limitation of case reports that lack a comparison control group. This echoes reviews done by FDA and its consultants in which agreement about causality was poor. For example, two consultants from FDA, Drs. Ricaurte and Stoll, reviewed 28 AERs related to neurological events. Dr. Ricaurte classified eleven cases as "attributable" while Dr. Stoll classified only five as "attributable."5 Only two of the consultant's findings overlapped - that is, there were only two cases that both Dr. Ricaurte and Dr. Stoll agreed should be categorized as "attributable."5 This disagreement is not a flaw of the reviewers, but rather a flaw of AERs. A fourth limitation of AERs is that ingestion of the substance in question cannot always be substantiated. For example, case 10276 is a 32-year-old with an enlarged heart who was found dead in his truck. Although a product that contains herbal ephedra was found in his truck, so were several bottles of cold medications, including Nyquil. Toxicology revealed no ephedrine, but did identify pseudoephedrine and doxylamine, both components on Nyquil. Thus, there is no evidence that this person even ingested the herbal ephedra. A similar case (13096) revealed no ephedrine in a toxicology screen again suggesting that the man had not ingested ephedrine around the time of death. Equally importantly, this man died of a disease that appeared to run	

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in his family (aortic dissection), including an 18-year-old niece. In summary, AERs cannot be used to assess causality. As stated by several authors with experience in interpreting adverse event reports for the FDA: "It is probably impossible to do comparative analyses employing ADE [adverse drug event] reports for drugs that have received extensive publicity in the mass media for an adverse event..."7 In fact, the FDA's Center for Drug Evaluation and Research pointed out, in a February 10, 2000 memorandum concerning ephedra products, that "it is possible that the reported serious adverse events are reflective of coincidental background spontaneous occurrences in the population and are not necessarily causally related to [the use of dietary supplements containing ephedrine-type alkaloids]." The RAND review notes this as well, stating that "The most important limitation [of their assessment of adverse events] is that the study design, that is an assessment of case reports, is insufficient to warrant definite conclusions regarding causality." They list this limitation as one of the "most important...gaps" in the current knowledge-base. The RAND review also states that "Disentangling the relative importance of the pre-existing condition and the ephedra use is not possible." They state further that "Continued analysis of case reports cannot substitute for a properly designed study to assess causality. A case control study would probably be the study design of choice." Their Technical Expert Panel also "judged that case reports alone would be insufficient to establish definite causality between ephedra use and serious adverse events." Because of these limitations, terms such as "probably causal" and "possibly causal" in AER reviews are potentially misleading (see, in particular, the "Conclusions" section of the "Structured Abstract," page vi, and the "Conclusions" section, page 112). They represent only reviewers' assessment of causality based on uncontrolled data and subjective assessments. Although these terms are often used in scientific publications, their use in the RAND report may suggest a level of evidence that does not exist from the current data. These statements, therefore, should not be taken out of context. RAND's stated limitation that "Definite causality cannot be determined from case reports" must be kept in mind when interpreting this report. It is also critically important to remember that case reports can produce false signals of cause and effect.8,9 Most importantly, because of the limitation of AERs, it is unclear why the RAND report states, in the Structured Abstract, that "These [sic] is sufficient evidence to suggest a possible causal role of ephedra-containing dietary supplements in rare but serious adverse	

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events, particularly cerebral hemorrhage." With respect to a possible causal role of ephedra in adverse events, RAND acknowledges that AERs are not sufficient to draw conclusions about causality, consistent with the known limitations of AERs discussed above. In addition, this comment is puzzling given that their "Conclusions" section (ages 112-113) does not state this at all. With respect to cerebral hemorrhage, the only comment in the body of the report on cerebral hemorrhage refers to a case-control study of phenylpropanolamine (PPA) and cerebral hemorrhage.10 However, the RAND report refers to this study only as an example of case-control methodology that could be applied in the future to ephedra. The report does not discuss the PPA study further. In fact, this study has been heavily criticized. Despite this, there was not a formal review of this study by RAND (and there were no members of the technical expert panel listed with expertise in epidemiology to perform such a review). In addition, PPA and ephedra have different chemical structures and different pharmacological activities. Finally, the RAND report does not mention that the PPA report also presented data on non-PPA, ephedrine-alkaloid containing products. These agents included medications that contained pseudoephedrine hydrochloride, phenylephrine, ephedrine, and epinephrine. In the report, there was similar prevalence of use of these products among those with and without hemorrhagic strokes. Although this is not a definitive analysis, it suggests that there was no association between these ephedra-containing products and hemorrhagic stroke. Therefore, the statement in the Conclusions section of the Structured Abstract of the RAND report is inconsistent with currently available scientific data. In summary, the RAND review supports the use of herbal ephedra and caffeine for weight loss, an effect that may have beneficial health consequences. The report also suggest, from controlled studies, that adverse events following ephedra use are, at most, rare. (The should not imply that the events are even causally related to ephedra us.) Most importantly, because of the reliance on AERs, the report cannot establish a causal effect of ephedra on serious adverse events.	
Review of Anecdotal Adverse Event Reports - Limitation of Review. On pages 109-110, the report identifies potential limitations associated with the review of anecdotal adverse event reports. These limitations are buried at the end of the report, rather than being incorporated into the appropriate sections of the report (as per prior AHRQ reports, such as the Garlic Report - see Section IX, herein). Moreover, a number of limitations are not prominently identified, including but not limited to: a) The poor quality of the data and information contained in the anecdotal adverse event	

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reports; b) Inherent problems associated with voluntary reporting systems; c) The number of individuals in the general population who experience the adverse events identified (i.e. background risk); d) The possibility that certain products may not have been standardized and/or manufactured according to Good Manufacturing Practices ("GMPs") - resulting in potential adverse events that have nothing to do with ephedra or caffeine when consumed in recommended amounts. Specifically, in the absence of standardization and quality control, it is conceivable that certain products may contain far more ephedra or caffeine (or other constituents) than indicated on the product label. This possibility must be considered when evaluating anecdotal adverse event reports. In the absence of identical product identity, any general conclusions regarding ephedra and caffeine are inappropriate and highly suspect based upon adverse event reports (see the AHRQ Garlic Report for an appropriate way to address this issue). In my opinion, RAND should strongly support immediate issuance by the FDA of dietary supplement GMPs and should endorse stringent quality control measures to ensure that all ephedra supplements contain what they are claimed to contain; e) The possibility that the consumer abused or misused a product by ingesting more than the recommended amount - or that the consumer ignored detailed product warnings and contraindications. RAND should emphasize the detailed warning label contained on the vast majority of ephedra supplements - and should acknowledge that there is little way to know from anecdotal data whether a consumer abused a product (either intentionally or more likely inadvertently); f) The possibility that the anecdotal adverse event reflects chance, coincidence , or confounding factors - including but not limited to the possibility that ingestion of a different product or substance led to the stated event. I I. Review of Anecdotal Adverse Event Reports - B. Ascribing Causality to Adverse Event Reports - 1. Reliance on Unpublished Article. In order to establish a framework for analyzing the adverse event reports, the draft report relies upon an unpublished article written by Cynthia Mulrow, M.D. Reliance upon an unpublished, non peer-reviewed article to establish the framework for a critical portion of the report is entirely unacceptable. AHRQ studies have not, to our knowledge, ever relied upon an unpulished article to establish the framework for this type of analysis. In addition, reviewers such as myself have no way of analyzing the article - thereby defeating one of the primary reasons for review of the draft report. II. Review of Anecdotal Adverse Event Reports - B. Ascribing Causality to Adverse Event Reports - 2. Failure to Review Factors Critical to the Interpretation of Anecdotal Adverse Event Reports. Table 4 of the draft report	

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summarizes the various methods researchers use to assess causality from adverse event reports. The following nine factors are identified: a. Temporal relationship. b. Dechallenge response. c. Rechallenge response. d. Could there be an alternative explanation? For example, dehydration or consumption of other toxic substances. e) Prior reaction to same substance. f) Dose response. g) Objective evidence of adverse event. h) Previous conclusive reports. i) Definition of substance. Despite the report's reference to these nine factors, it is my understanding that the report concludes that events are "probably causal" based upon a review of only two factors - a and g. The draft report does not explain why RAND believes only two factors out of nine can be used to ascribe degrees of causation to anecdotal adverse event reports. II. Review of Anecdotal Adverse Event Reports - B. Ascribing Causality to Adverse Event Reports - 2. Failure to Review Factors Critical to the Interpretation of Anecdotal Adverse Event Reports (cont'd). The draft report also indicates that three factors are used to determine if an event is "probably causal": a) Reasonable certainty that the adverse event occurred. b) Reasonable certainty that the patient took ephedra in a dose and timing compatible with the known pharmacology of ephedrine. c) An adequate evaluation must have been done to rule out other potential causes for the adverse event. The third factor (factor c, above) is exceptionally problematic from a scientific perspective. The report acknowledges that the third factor is subjective. Specifically, in an effort to rule out other potential causes, the report indicates that such a determination was made by determining if the subject had a pre-existing condition that was identified in the adverse event report.	
Adverse Event Reports. While CRN acknowledges that the judgments made about the AERs were, overall, much more conservative than those made by other reviewers, there is concern that, in some cases, a much more likely explanation was evident, but still possible causality was assigned. Some examples follow, although they are not all-inclusive: 1. Case 10276. A deceased truck driver was found with cold tablets, Nyquil and Vick's Formula 44, in addition to ephedra-containing supplements. The toxicology screen was negative for ephedrine, but positive for pseudoephedrine. The much more obvious and likely culprit here would be one of the pseudoephedrine-containing cold formulas, since ephedrine is the dominant alkaloid by far in ephedra products, and the clearance rates for the alkaloids are roughly the same. 2. Case 12843. A 15 year old died of a congenital abnormality of the left coronary artery. No ephedrine was	

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reported in her system. How could this possibly be causal? 3. Case 10874. A woman with considerable substance abuse problems and some use of ephedra supplements for weight loss tested positive for phenylpropanolamine (PPA), but not for ephedrine or pseudoephedrine. The former is but a minor constituent of ephedra and products derived there from, but were a common primary component of a number of OTC weight loss products until recently. Such products are a much more likely source of the PPA than the "possibly causal" ephedra supplements.	
We have several concerns about the way the information is presented in the sections related to safety. It is AHPA's position that the report's safety assessment section reviews case reports from a passive event reporting system without fully and redundantly disclosing what has already been determined about the nature of the FDA's current AER system. Appropriate disclosures include, at a minimum, a reference to the GAO report on the subject and recognition that the Special Working Group of the office of Special Nutritional (FDA: Food Products Containing Ephedrine Alkaloids, Washington D.C., October 11th-12th, 1995) explicitly stated that such a system cannot, by it's nature, show causality.	We acknowledge that the case reports cannot show causality. We do not need to discuss the findings of other with respect to the adequacy of the FDA AER system. We assessed the information we did receive using explicit criteria, and our findings are reported.
AHPA recognizes that limitations in the clinical trial data lead one necessarily to consider case reports for an assessment of serious adverse events. The fact that there are no serious adverse events reported in any of the clinical study should however be stressed, even as it is identified as of insufficient statistical power to detect a rate of serious adverse events. This fact should be repeated at the Structured Abstract and in the Conclusions, for example, and the total number of patients in these studies (is that 2319 in the intervention groups?) should be identified. In addition, Table 17 should be expanded to include each of the serious adverse events that are subject to safety review in the draft (e.g. death, myocardial infarction, and stroke) and the number "zero" should be entered in both the placebo and intervention columns, if that was in fact the published observation.	We do not favor, as a general rule, adding rows or columns to a Table when all the entries in each cell will be the same. Such information can more expeditiously be conveyed in the text.
The Draft contains an extensive review of the specific AER case reports. This inherent emphasis presents an unbalanced appearance with respect to the intent of the original key questions. In comparison, assessment of efficacy is presented in a much more summarized fashion.	We cannot change the amount of space needed to describe what we did.
In arriving at criteria for judging the causal relationship in case reports of adverse effects from ephedra, the concept of biological plausibility is conspicuously absent. All else bring equal, adverse events that are biologically plausible (consistent with the mechanism of action of the drug in question) are more likely to be causally related to drug use	

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than those, which are not. Sudden death, myocardial infarction, and stroke are biologically plausible toxic effects of ephedra. This should be taken into account when interpreting the data.	
Clearly there is no right or wrong answer with regard to how much data is needed to judge the causality of an adverse event case report as "probable" or "possible" but I believe that the criteria used in this review have resulted in conclusions that that are understated. There is nothing wrong with the criteria per se, but using the term "probable" for a death that has fulfilled every review criteria (except re-challenge which is by definition impossible) understates the quality of the data and implications of the case. Similarly, the term "possible" for cases that have satisfied several but not all criteria makes it sound like these importance of these cases should be minimized, which I do not think is the intent of the report. For example, requiring negative angiographies to support causality for myocardial infarction has a rationale, but will necessarily exclude many or most cases because not all patients have this procedure.	
The importance of this wording is illustrated by the comparison of the Benowitz ephedrine data and your group's reanalysis of it, which would have downgraded so many case reports as to make the report unpublishable. Instead, It was published and shows a remarkable similarity in adverse event profile with the current report. This congruence of findings is in fact some of the strongest literature support for the conclusions of the current report regarding toxicities from ephedrine and ephedra, and these two reports suggest just that.	
The alternative to changing the terminology of the report is to provide additional commentary on the interpretation of the findings; that, in a view of 1) biological plausibility, 2) the considerable number of case reports emanating form a spontaneous reporting system, 3) similar toxic effects of pharmaceutical ephedrine, and 4) similar toxic effects of phenylpropanolamine, the findings of the current review are highly suggestive of a relationship between herbal ephedra and serious adverse events such as sudden death, myocardial infarction, and stroke.	
Discussion at the NIH requested that the title "possibly causal" was misleading and should be retitled to indicate more accurately the Rand staff interpretation that there is no proof of causality and while causality is possible, it is not probable.	
Study Selection. Study selection was not appropriate. Partly for the reasons stated above, but also because of the reliance placed upon passively collected anecdotal data. The mere fact that existing clinical trials contained "too few	

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(subjects) to allow adequate statistical power to access the rate of serious adverse events," does not make AER analysis any more reliable or probative. In fact, case reports cannot be "relied upon to assess serious adverse events," except, perhaps for the occurrence of rare disorders such as coronary artery dissection. The decision to include an analysis of AERs is particularly puzzling, given that the TEP chose to reject the Haller and Benowitz analyzing the same AERs (see "rejected articles" #195, record #116)! Heart attack and stroke are common disorders in our society, and thousands of ephedra product users would be expected to experience vascular events, even if ephedra did not exist. Analysis of AERs for common disorders, which are even more frequent among the overweight, is virtually guaranteed to show a connection with ephedra use, even if no such connection exists (for example, see the August 1 article, "Obesity and the Risk of Heart Failure" in the New England Journal of Medicine).	
Appraisal of Studies. Important parameters that could alter study results have not been systematically addressed. The brief discussion of obesity is confined to generalities. Obesity is a prothrombotic disease. [1]. Overweight people, presumably the majority of ephedra supplements users, are at greater risk for sudden cardiac death (SCD), and heart disease [2]. The report fails to provide any sort of epidemiologic prospective, leaving the false impression that the occurrence of these disorders among ephedra product users is somehow surprising or unanticipated. In fact, when the GAO wrote its highly critical analysis of the FDA's proposed rule on ephedra products, one of the issues raised was FDA failure to account for the reality that "there is almost always an underlying background rate for any clinical event in a population, regardless of whether there was exposure to a particular product..." The RAND report states that 3 billion servings of ephedra were sold in 1999. Assuming that 3 servings are used per day for 12 weeks (as Haller and Benowitz do in the NEJM paper), then there were 12 million users. The accepted rate for sudden death, heart attack, and stroke in the U.S. is 0.1, .5, and .2 percent per year respectively [3]; which means that even if ephedra/ephedrine has absolutely no relationship to any of these disorders, 12,000 cases of SCD, 60,000 cases of myocardial infarction, and 24,000 cases of stroke would still be expected among ephedra users each year. Not providing this information to general readers paints a completely misleading picture and leads to a misinformed, if not false, impression of relative risk. It also repeats the same FDA error already criticized by the Government Accounting Office.	
Data Collection. No effort is made to reduce bias in the	The reviewer is incorrect. The autopsy was

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data collection, or even to assure that the data is valid. This is immediately apparent in the discussion of the first AER. The history given for AER #13914 is simply incorrect. The autopsy was, in fact, included in the docket (copy attached). The heart was actually examined by a consultant cardiac pathologist, and that report states "the cause of death may be attributed to myocarditis in the absence of other demonstrable cause." The summary in the report misstates the data available and misrepresents the conclusion in the report.	not included in the docket we received.
Data synthesis. Limitations of the review process are not adequately stated. Many, if not most, of the interpretative problem seem to be the result of the medical experts on whom RAND relied upon the review the AERs (it is not clear from the draft report who reviewed which AERs). Medical-legal death investigation is customarily performed by pathologists with specific training and expertise in sudden death investigation, yet it appears that not a single pathologist was included among the reviewers. As a consequence, many of the AERs were almost certainly misinterpreted. I do not have access to many of the AER files that RAND reviewed, so I cannot comment specifically on RAND's subjective assessments of causality in most of the cases. However, the errors and misinformation in the AERs that I can check show clearly this experienced death investigators were not involved in the project. For example, Case #14390, classified by the panel as "probably causal", was said to have had a "shunt" in place. It follows that the brain could not, as the report states, possibly have been "normal". For one thing, there would have been a shunt in place, which is decidedly not normal. There would have been tissue reaction around the shunt, both the heart and brain. If the shunt had been placed for traumatic injury, trauma residuals would have present. If the shunt had been placed for traumatic injury, trauma residuals would have been present. If the shunt was for congenital hydrocephalus, it is quite likely that the abnormalities associated with the Arnold-Chiari malformation would have been present. Sudden cardiac death secondary to acute obstructive hydrocephalus is well recognized by forensic pathologists [4, 5]. Even if a pathologist was on the AER review panel, the methods section is so vague that it is not clear whether the pathologist would have been asked to review this AER. One can only conclude that the panel of reviewers do not know the accepted causes of sudden death in young people with ventriculatrial shunts. Evidence of potential bias in the AER reviews is provided by the AERs chosen as "probable" and "possible" as well as by the summaries of the AERs contained in the draft report. For example, Case #12485 was classified as "possible causal," and the presence of	

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"mild cardiomegaly," noted. The autopsy report in the docket shows a heart weight of 490 grams, two standard deviations above predicted [6]. No one with training in vascular pathology and sudden death investigation would call that degree of enlargement "mild." Cardiac enlargement is a recognized risk factor for SCD [7], over and above the severe coronary artery disease that was also present [8]. Referring to such an important pathologic finding as "mild" can only be explained in two ways: either the reviewers were unaware of the significance of this abnormality, or they were trying to minimize the finding because it did not fit a bias towards finding evidence of ephedrine toxicity. Preconceived bias is strongly suggested by the inclusions of AER #12722, a child who died of a type of congenital heart disease where the left coronary artery arises from the left pulmonary artery (not vein, as stated in report). No ephedrine was detected in tissues analyzed by the FDA, and there was extensive scarring of the myocardium, reflecting early episodes of healed myocardial infarction. By their very nature, the morphologic changes detected, which almost certainly were the cause of death, antedate by weeks or months the alleged history of ephedrine ingestion. Classification of this case as "possibly causal", violates the report's own stated criteria, which specifically reserve the "possible" category for those cases where "another condition by itself could have caused the adverse event, but ephedra use may have helped precipitate the event." No ephedrine was detected at autopsy, and anatomic changes were present that had to have occurred weeks or months before the first use of any ephedra product is even alleged. Bias is also suggested by the discussion of phenylpropanolamine. The section on Phytochemistry correctly states that the phenylpropanolamine (PPA) content of ephedra is low. But then in the discussion of AER #10874, the report also states "there is a described association between PPA and cerebral hemorrhage, PPA is also a component of some herbal ephedra." Had a balanced presentation been intended, the report would have provided the additional information that the most PPA ever detected in a serving of an ephedra supplement was half a milligram, and that in studies with volunteers, 50 mg of PPP is needed just to modestly raise blood pressure [9]. The emphasis of the potential linkage between PPA and ephedra in the report is distressing for three reasons. Firstly, it reiterates the same unproven argument propounded by Drs. Haller and Benowitz in their most recent publication (Haller, et al., Clin Pharmacol Ther 2002; 71:421 432). The unquestioning repetition of an unproven hypothesis tends to lend legitimacy to that hypothesis, even in the absence of evidence, thereby detracting from the value of the report. Secondly, and quite improperly, the	

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report nowhere discloses that this unproven mechanism of toxicity is, in fact, an unproven theory propounded by one of the TEP members. Thirdly, the report makes no mention of the dispute between professional epidemiologists over the validity of the study that lead to the withdrawal of PPA in the first place. Indeed, the entire discussion of PPA in this report, the failure to mention the PPA content of the average herbal supplement, the failure to mention the fact that ephedrine is minimally metabolized to (-) norephedrine, and the failure to mention existing disagreements among epidemiologists about PPA, is simply not scientifically supportable. A consumer would have to simultaneously ingest 100 servings of an ephedra supplement in order to receive enough PPA to minimally raise blood pressure, and probably twice that amount to cause a clinically significant increase. In AER #14019, death was attributed to "dissection of a left anterior coronary artery" in a 26-year-old woman. This is not a supportable conclusion. Coronary artery dissection has never been reported in an ephedrine user, or even in amphetamine abusers (a drug to which ephedrine has frequently been compared). Almost all reported cases of spontaneous coronary artery dissection involved young women following childbirth, or in cocaine users. Had the decedent just delivered? Was she a cocaine user, or both? Was toxicology testing performed? This case and others classified as probable and possible are examples where "crucial information is missing" and they should have been classified as "insufficient".	
Safety assessment. As mentioned above, the panel should also include the non-placebo controlled and non-randomized trials in the safety assessment. The information obtained from such trials is superior to that from case reports. Page 58, 4th section: Here it is stated that patients taking pharmaceuticals outside of clinical trials may have a greater risk of certain adverse events than patients selected to participate in clinical trials. I strongly disagree. In all the clinical trials we have conducted, which have been conducted in Denmark, it is quite normal that the patients are referred by general practitioners or hospital departments because they have a high degree of overweight (are typically obese, with a body mass index of 29-40) and suffer from complications to the obese state. This may not necessarily be ischemic heart disease, heart failure or type 3 diabetes, because these subjects will typically be excluded, but patients with pre-diabetes, dyspnoea, osteoarthrosis in knee or hip, etc. In addition, one of the large trials was conducted on the hypertensive obese patients (Ingers, et al.). In contrast, individuals in the community taking preparations containing ephedrine will typically be less overweight and be	

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generally healthier. They will be less likely to experience serious adverse events than subjects in clinical trials I think the conclusion reached by the panel should therefore be reversed.	
The Danish Experience. It is quite natural that the panel has received the list of case reports from FDA's office of nutritional products, labeling and dietary supplements. However, why did the panel not ask the Danish FDA for their full report of collected adverse events during the 12 years from 1990 to 2002 where an ephedrine/caffeine prescription compound has been on the market in Denmark? This is a substantial body of experience that could give more valid conclusions than those received the American FDA alone. During the last 8 years, the defined day doses have ranged between 3.6 and 4.6 per 1,000 inhabitant/day in Denmark. It also means that the Danish Drug Administration has, in its surveillance program, obtained anecdotal data regarding reported side effects from General Practitioners and other Doctors in Denmark. The post market surveillance program is very effective in Denmark and there are 134 reports of side effects, but they are all very mild side effects and the all the well-known side effects we know from the pharmacological action of ephedrine/caffeine. They include tremor, insomnia, palpitations; side effects from the use of ephedrine/caffeine even though Denmark has had a substantial amount of sales and ten years experience.	
First there is no control group. Because there is often an underlying baseline risk of disease unrelated to exposure to a product, there will be events reported in people exposed to that product that are in no way associated with use of the product. Given the large number of users of ephedra to a product, there will be events reported in people exposed to that product that are in no way associated with use of the product. Given the large number of users of ephedra-containing products,4 there will be events among users that are coincidental with the use of ephedra (i.e., not causally related) even in the absence of other explainable causes of these events. In an analysis performed by the Expert Panel of the Ephedra Education Council (EEC), an estimate of the rate of serious events in ephedra users was compared with the rate of events expected in the general population. 5	
Although this analysis was not designed to rule in or out a possible cause-and-effect relationship between ephedra and the outcomes evaluated, it did suggest that the adverse events reported among ephedra users may very well represent simply the background rate of events expected among such a large number of users of ephedra-containing products, unrelated to ephedra itself. This was true even under assumptions that inflated the risk from ephedra and	

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even assuming the events reported to FDA represented a small percent of the adverse events occurring among ephedra product consumers.	
I. Research Parameters - Overview. Based upon my review of the draft questions provided to RAND, it is my understanding that RAND was asked to provide a science-based review in order to identify gaps in the data relating to ephedra safety and efficacy. Identification of these data gaps was deemed essential to prepare an agenda for future research. Despite this charter, RAND instead acknowledged that it engaged in a subjective review of anecdotal adverse event reports in order to ascribe potential causality to such reports. As explained below (see Section II, herein), the inherently subjective nature of such a review by definition reduces the objectivity of the report and may lead one to question the proposed research agenda. It is my strong belief that RAND should issue a report that is entirely objective and science-based. A subjective review of anecdotal adverse event reports that attempts to ascribe potential causality to such reports in my opinion provides no meaningful benefit with regard to identifying data gaps and developing a research agenda.	
I. Research Parameters - Overview (cont'd). If the goal of RAND's review is to identify data gaps, RAND should address this issue by reviewing the scientific studies and the types of anecdotal adverse events that have been reported - which should be used as a signal to identify additional research projects. Ascribing degrees of causality to poor data is not helpful in this regard. Moreover, by including a subjective component to the review, and indeed emphasizing this component, one does not control for potential inadvertent reviewer bias. One of the reasons placebo controlled double-blind trials are considered to be the gold-standard for scientific research is that researcher bias must be accounted for and eliminated to the greatest degree possible. It is understood in the scientific community that despite the best of intentions, inadvertent bias can impact researcher conclusions.	
I. Research Parameters - Overview (cont'd). RAND acknowledged that its review of FDA's AERs was subjective, and even focused on potential publication bias by certain researchers and organizations, yet failed to even acknowledge the possibility that inadvertent bias could potentially impact its own report based upon the subjective nature of the review of adverse event reports. I am not in any way alleging that the draft report is actually biased - either intentionally or inadvertently. Rather, my point is that a subjective review is subject to inherent inadvertent bias and therefore the report should focus on objective information. If the goal of RAND's report is to identify data	

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gaps and suggest areas for additional research, ascribing degrees of potential causality to anecdotal adverse event reports appears to be entirely counter-productive. Finally, the General Accounting Office and Department of Health and Human Services (along with the FDA) have already acknowledged that it is not possible to determine causation based upon a review of these anecdotal adverse event reports.	
I. Research Parameters - Overview (cont'd). In light of this determination, it is difficult to comprehend the benefit that can result from RAND attempting to ascribe degrees of causation to such reports. From an objective perspective, the adverse event reports should not be used to ascribe degrees of causation - but also should not be ignored. Rather, as noted, the reported adverse events should be documented and identified and then used to help target endpoints for future research.	
The draft report's causality assessment is not consistent with how other Agency for Healthcare Quality and Research (AHRQ) reports have addressed dietary supplement adverse events. From our review of other reports, the draft reports causality assessment is unprecedented. The central question is why RAND conducted a causality assessment of the AERs and prominently reported it admittedly subjective attributions of causality. RANDs causality assessment obscures the objective findings of the report to such a degree that the research agenda RAND recommends will not be achievable. Further. Rends subjective attributions do little or nothing to answer the questions that RAND has been asked to address. In a broader context, the final report, if published with the causality assessment, as it now exists, will threaten future support for similar reviews of other dietary supplements. Despite serious concerns, the draft report contains a very worthwhile and comprehensive review of the objective data on ephedra and ephedrine, and the recommendations for future research are commendable and attainable, and will serve the valuable function of answering important questions concerning ephedra products. The final report can become a monument for how to address controversial safety issues such as those that exist for ephedra, provided the final report focuses on objective science rather than subjective assessments of the AERs. The purpose of the RAND review is to perform an objective review of the science pertaining to ephedra in order to answer specific questions from the current data, and to identify research gaps and recommended additional research to answer the questions where the current data are insufficient or do not exist. All parties to the ephedra discussion agree that the AERs raise serious questions that	

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deserve serious attention. Industry has enthusiastically supported the concept of the RAND review for that reason. However, as the draft report recognizes, the AERs do not represent the objective data. RAND's review of ephedra is necessary in large part to resolve the controversy that has been created by widespread reporting of the subjective assessments of the AERs on ephedra and the conflicting opinions as to what the AERs mean. Informed critics and supporters of the ephedra agree that the AERs cannot be used to assess safety, to establish whether there is in fact a risk of serious adverse events, or to quantify that risk if the risk exists. These limitations on the use of the AERs for ephedra were the focus of the HHS and the Food and Drug Administration's (FDA's) recent statements on ephedra on June 14, 2002 1) and have also been noted by critics such as Drs. Haller and Benowitz, as well as industry-supported panels such as the Expert Panel of the Ephedra Education Panel. 1)"The primary purpose of a voluntary adverse event reporting system is to generate 'signals' of potentially related events, rather than assessing product safety...There are situations when background rated of the observed event are so rare or unusual that, in combination with physiologic responses and biologic plausibility, A significant relationship between the events is self-evident from the reports in a voluntary reporting system. However, the FDA has advised me that the types of observed outcomes reported in relationship to the ingestion of the ephedrine alkaloids are not uncommon in the general population and there for the reports alone do not provide a scientific basis for assessing the safety of ephedrine alkaloids or establish a link between the reported adverse events and the ingestion of ephedrine alkaloids #2 "[O]ur report describes a series of cases which the use of ephedrine-containing dietary supplements was associated with adverse cardiovascular events. Our report does not prove causation, not does it prove quantitative information with regard to risk. A large-scale case-control study similar to the Hemorrhagic Stroke Project for phenylpropanolamine is needed to determine the risks associated with these dietary supplements" Christine A, Haller & Neal L. Benowitz, Dietary Supplements Containing Ephedra Alkaloids: Letter to Editor, 344 New Eng. J. Med 1095,1096-1097 (2001). #3 the consensus conclusions of the EEC Expert Panel, as well as extensive reviews of the published literature and the most comprehensive review of the AERs that has been conducted to date, were submitted to the FDA's published docket on ephedra in October 2000 and were made available to RAND. Since the Expert Panel Report is nowhere mentioned is referenced in RAND's draft report, a copy is included with these comments. The Expert Panel	

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concluded that the available data and information including the AERs, "do [] not demonstrate an association between the use of dietary supplements containing ephedrine alkaloids and serious adverse events when used according to the American Herbal Products Association (AHPA) trade recommendation for ephedra products." Expert Panel, Ephedra Educ. Council, Comments of the Ephedra Education Council on the Safety of Dietary Supplements Containing Ephedrine Alkaloids and on the AERs and Health Assessment Released by the FDA on April3, 2000 on 6 (2000) (on file in FDA docket 00N-1200 as C30) RAND has also concluded that, because of the subjectivity of assessing causality from AERs, further analysis is additional case reports will not lead to any objective scientific conclusions and would not be useful to establish whether there is any causal connection between ephedra and the type of serious adverse events. Continued analysis of case reports cannot substitute for a properly designed study to assess causality." Draft Report at 5. Nonetheless, RAND has conducted a causality assessment of some of the AERs deemed to report serious adverse events and has described the results of this review in terms of "probable" and "possible" causal relationships between ephedra, death and other serious events. RAND's findings are presented in a way that will expand the controversy surrounding the AERs on ephedra rather than resolve it through objective analysis and recommendations for additional research. Further, the draft report is open to the inappropriate interpretation than RAND has concluded, based on the AERs, that ephedra causes serious adverse events, and that is exactly how the ephedra critics will interpret the draft report. This interpretation is a result of the wording of RAND's findings as well as the presentation of the causality findings without necessary context. The headlines that will result concerning RAND's findings on causality will make is difficult if not impossible to justify the research agendas that RAND recommends at the very end of the draft report. Again, given the lack of any scientific value to RAND's analysis, the ability to discuss the "signal" that the reports raise without reporting subjective attributions of causality, and the importance of the report as a means to resolve the controversy that the AERs have created, the best solution is to remove the causality from the assessment report. The problems created by the RAND causality assessment are aggravated by a number of factors: 1) The vast majority of the draft report's text and tables relating to safety address AERs (10 pages of text, 20 pages of tables) rather than clinical data (one page of text, three pages of tables), even though RAND acknowledges that clinical data are if much greater value, and even though in the end of the report	

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RAND concludes that causality assessments do not provide objective, science-based answers to the questions that it was asked to address. Although the draft report discusses a review of selected AERs that was conducted under the contract with FDA by Drs. Haller and Benowitz, and the draft report compares the results of this review to the RAND review, the draft report excludes any mention of an extensive review by Cantox Health Sciences International, and the most comprehensive review of the AERs to date by the Expert Panel of the EEC. A copy of the Expert Panels Report is enclosed with a hard copy of these comments. While the issues of publication bias and other coursed of bias were carefully analyzes in the draft report for published studies, other than a brief mention of the subjectivity of RAND's causality assessment, the draft report does not adequately address the potential for reviewer bias in RAND's causality findings. Because the AER files that RAND reviewed not the same as those that FDA had provided to the public, and RAND has not made its AER files available to the technical expert panel or the peer reviewers, none of these reviewers will have the ability to do an in-depth analysis of RAND's causality assessments. Some reviewers may have their own files on some of the AERs, but this will not permit the type of analysis that would be needed for a thorough peer review. There is a simple solution to the problems that the RAND causality assessment, and the manner in which the assessment is presented in the draft report, have created. The causality assessment should be removed from the report. The final report will then be focused on the objective assessment of the data and answering the questions that RAND was asked with addressing. In addition, dropping the causality assessment will permit the recommended research agenda to proceed as intended. To do otherwise places the whole RAND ephedra project in jeopardy, as well as future support for similar projects. If RAND does not remove the causality assessment from the report, RAND should drop the attributions assigned to specific reported as either probably causally" or "possibly causally" related to ephedra consumption. Instead, RAND should state the certain reports were reviewed for causality and that those reports raise a "signal" that additional research is needed to address that signal. This would be a neutral and objective statement that would be accepted by parties, and would be consistent with the recent statements of HHS and FDA on the inability to make safety determinations or regulatory decisions based on the AERs for ephedra.	
However, in the opinion of the reviewer, those conclusions	

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regarding the case reports are limited by a combination of the conservative causality assessment criteria and the limited medical records and toxicology data available for most case reports. For example, hypertension was defined as a systolic pressure in excess of 180 and a diastolic pressure in excess of 105. Also, no consideration appeared to have been given to the contribution multi-component ephedra-containing dietary supplements might have had in those individuals with underlying cardiovascular or cerebrovascular disease. I think it is generally accepted among the medical and scientific community the presence of sympathomimetic agents could potentially exacerbate the likelihood of adverse events in such populations? I would think most clinicians would factor such information into their differential diagnosis rather than dismiss them altogether.	
Adverse Events Reports: One limitation with your approach taken in evaluation of the adverse events reports made to the FDA is that your causality algorithm does not include an assessment of whether ephedra played a contributory role on the adverse event. Because ephedra is available as a dietary supplement, it is likely that many persons taking these products are not using them under doctor's supervision, and may have medical contraindications to their use. Therefore, the role of underlying disease becomes a crucial factor in causation assessment, particularly when a potential risk factor often goes undetected (i.e. essential hypertension, structural heart defect), or when a condition is omitted from the ephedra product label warning (i.e. family history of premature CAD, sickle cell trait).	
Two AERs that you assess as no higher than possibly causal illustrate this point. AER 12485 did indeed have a moderate degree of coronary artery disease detected at autopsy. However, he was reportedly in good health without history of angina, and had been jogging regularly without adverse effects. Because he collapsed suddenly after returning from jogging, we felt this was a primary arrhythmic event due to ephedra. Similarly AER 12843 was a healthy, adolescent who had participated in competitive sports for many years. She had appeared to have been well-compensated for a serious underlying coronary artery abnormality that was clinically undetected since birth. Only with use of Ripped Fuel, did she suffer a catastrophic cardiac event resulting in death. We felt that the cardiac stimulant effects of ephedra resulted in myocardial ischemia in this case.	
It would be helpful to specify what degree of pre-existing coronary artery disease would constitute a significant risk factor to result in myocardial infarction or sudden death in the absence of stimulant use, thereby ruling out ephedra in the causation assessment. (page 32 of chapter 2	This case was reviewed by a cardiologist who made this judgment.

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methodology). In the case of AER 14530 (page 63), I would disagree that 20-30% stenosis would be significant enough to result in acute M.I. in a 43-year-old female smoker without a significant contributory effect from the ephedra alkaloids in Metabolife.	
On page 59 I suggest the authors be slightly cautious with their use of language such as "probably causal" and "no other possible explanation." The latter phrase is particularly troubling. What the mean is no other explanation that they could identify. Similarly, on page 69 they state that there are a certain number of cases of serious adverse events that "cannot be explained by causes other than ephedra use." While I do not deny that it is extremely likely that many cases of adverse events happen due to ephedra use, simply because we do not have in our hand an explanation of why an event occurred other than a particular explanation under consideration, does not mean that the particular explanation under consideration is the correct one.	We have revised this language.
Because of the paucity of large randomized trials, evidence concerning stroke and ephedra by necessity consists of analysis of case reports. "…An assessment of case reports is insufficient to warrant definite conclusions regarding causality." (p.110) Nevertheless, arbitrary criteria are used to define "probably cause": documentation that a stroke occured, that ephedra was used, and that there was exclusion of other potential causes. The definition may be too liberal. Of ischemic strokes in relatively young adults (i.e. those <50 years old), perhaps 20-35% are "idiopathic" despite thorough evaluation. The definition implies that all idiopathic strokes would be classified as "probably causal" if ephedra was used in any dose in proximity to the event. Given the frequency of idiopathic stroke, many (perhaps most) neurologists would consider "possibly causal" to be a better designation in this situation. Are there specific clinical circumstances in which the relationship of ephedra use and idiopathic stroke could be certain? Perhaps if acute, striking elevation of blood pressure were known to precede the stroke onset of of angiographic features characteristic of vasospasm were present in the abscence of migrane? Arbitrary to be sure, and not very helpful.	
The evidence for effectiveness supports the conclusion. Except for AERs, however, little evidence of toxicity is actually provided, and evidence of safety has been largely ignored. No evidence is provided to even suggest "a possible causal role of ephedrine-containing dietary supplement in rare, but serious events," let alone extremely common events such as heart attack and stroke. Even critics of ephedra have concluded that the clinical effects of pharmaceutical ephedrine, and the ephedrine contained in	

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herbal preparations, are indistinguishable. Gurley states that the increased incidence of ma huang toxicity does not stem from differences in the absorption of botanical ephedrine compared with synthetic ephedrine." Haller and Benowitz, in their most recent publication, conclude, "Botanical stimulants have disposition characteristics similar to their pharmaceutical counterparts..." The Cantox Report, and the Report of the Expert Panel of the EEC reached similar conclusions. Since there are no real differences, studies demonstrating the safety of pharmaceutical ephedrine and pharmaceutical ephedrine in combination with pharmaceutical caffeine, should not be excluded when considering the safety of herbal equivalents. The explanation most frequently offered for alleged cases of ephedrine-related stroke is drug-induced blood pressure elevation, this in spite of the fact that no clinical trial, of any duration, has ever demonstrated that a clinically significant effect on blood pressure exists. Indeed, the studies that have addressed this question. including the most recent paper by Drs Haller and Benowitz, have shown diminishing cardiovascular effects over time. In other words, if dangerous blood pressure elevations do not occur with the first dose ephedrine, they are even less likely to occur with prolonged dosing. These studies should be included in the RAND review of ephedra and should be used to address the question of potential increases in blood pressure and other safety issues. Ephedrine has been studied in more than 50 double blind, placebo-controlled clinical trials, some of long duration. A far from exhaustive literature search produced the attached list of peer-reviewed, published, clinical trials. Most have compared ephedrine to placebo, and to other sympathomimetic drugs used to treat asthma. However, others have involved smoking cessation, sexual function and athletic performance. Nearly a dozen of these trials involved caffeine/ephedrine combinations using does exceeding those found in herbal supplements. In total, more than 2000 individuals have been enrolled in these trials. In several studies there was even continuous cardiac monitoring in middle-aged patients with known heart disease; no effect was observed. No clinically significant episodes of toxicity were reported. Including these and other studies on ephedrine that have been excluded from the RAND review will increase the power of the safety calculations that can be derived from clinical data. One of the major limitations of the report was the composition of the TEP and the reviewers who made subjective assessments of the AERs. Given the importance placed on assessment of AERs, it is unfortunate that no pathologist was included in the view or on the panel. The lack of expertise is obvious from the comments made about	

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the individual AERs. The failure to provide information about any potential conflicts of reviewers also detracts from the study. Why were the findings of Expert Panel of the Ephedra Education Counsel not considered? The analysis of this panel was in some ways unique, as it is the only consensus opinion on ephedra safety. In addition, this panel conducted the most comprehensive review of the ephedra AERs to date, and yet the causality assessment, which conflicted the findings of the draft report, are not even mentioned. If RAND believes that the EEC review and analysis was, in some way scientifically flawed, then the reasons for that belief should be stated.	
The danger of drawing conclusions from AERs without a control group can be illustrated by examining data from randomized trials in which participants are blinded to whether they are receiving the study treatment or inactive placebo. In the placebo group of a recent randomized trial,2 there was an increase in ventricular couplets (extra heart beats) at the 4th week of the study 9from 3% at baseline to around 14% at week 4). This is, of course, not due to the placebo, which is inactive, but rather just spontaneous ventricular couplets that occurred by chance. However, if these participants had been given ephedrine alkaloids in an uncontrolled study (without placebo), this change could have been attributed, incorrectly, to the ephedra. That is, these could be AERs that were attributed to ephedra. In fact, in the controlled trial, a similar increase in ventricular couplets was not seen in the ephedra/caffeine arm. Another example is the 15-year-old female (case 12843) with Bland-White-Garland syndrome who died while playing soccer. This disorder has been associated with sudden death after physical exertion. In the absence of a unique pathologic process, it is almost never possible to establish a causal association on the basis of adverse event reports. There is nothing pathologically or diagnostically unique about the adverse events noted in the ephedra database (e.g., myocardial infarction, stroke) that allow one to distinguish a spontaneous event from one caused by use of Ephedra products. In fact, a review of all autopsy data from ephedra AERs by Dr. Grover Hutchins, a Professor of Pathology at the John Hopkins University School of Medicine and member of the Expert Panel of the EEC, concluded that "The pathology data available do not show any pattern consistent with ephedrine alkaloid-containing dietary supplements as a cause of death."5 Similarly, 10 participants in the ephedra/caffeine group (12% of these participants) withdrew because of cardiovascular symptoms (palpitations, elevated blood pressure, arrhythmias). If there were no control group, these also might have been attributed to the ephedra/caffeine combination. However, the same	

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proportion of participants in the placebo group (13%) withdrew for the same reasons. The withdrawal rate in the ephedra/caffeine group thus was consistent with the background rate of these events in a placebo group unrelated to ephedra use. A second limitation of adverse event reports is that other potential causes of the event are often present, making it extremely difficult to determine if an event truly is related to the exposure. As an example, it is well established that physical exertion can trigger myocardial infarctions and cardiac arrest (up to a 74-fold increase in the risk of sudden death, according to a recent report in the New England Journal of Medicine6). Therefore, a case such as the 38-year-old man with three vessel coronary disease and a dilated heart who died after jogging could very well have been related only to the physical exertion and not the ephedra. According to his wife, his heart problems had been known for at least five years. In addition, this man had been taking an ephedra product for one year without apparent ill effect. The third limitation of AERs is that their interpretation remains subjective. Even experts in the field will disagree about the possibility that an event may or may not be due to an exposure. The RAND report (Table 22) displays a comparison of the causality assessment between their review panel and a published report by reviewers for the FDA.3 In only two out of 20 cases that both groups reviewed was their agreement about the highest level of possible causality. For example, with respect to the 38-year-old discussed above, the Haller and Benowitz review recorded this event as "Definitely or probably related" to ephedra while the RAND report classified it as only "Possibly causal." Another review of AERs performed by Dr. Theodore Farber and Dr. Norbert Page, members of the Expert Panel of the EEC, reveals similar disagreements. The two "probable" cases reviewed by EPC were rated as "Low Possible" (case 12980) and "Improbable" (case 13418) by Drs. Farber and Page. The fact that the etiology of events can be debated simply illustrates the substantial limitation of case reports that lack a comparison control group. This echoes reviews done by FDA and its consultants in which agreement about causality was poor. For example, two consultants from FDA, Drs. Ricaurte and Stoll, reviewed 28 AERs related to neurological events. Dr. Ricaurte classified eleven cases as "attributable" while Dr. Stoll classified only five as "attributable."5 Only two of the consultant's findings overlapped - that is, there were only two cases that both Dr. Ricaurte and Dr. Stoll agreed should be categorized as "attributable."5 This disagreement is not a flaw of the reviewers, but rather a flaw of AERs. A fourth limitation of AERs is that ingestion of the substance	

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in question cannot always be substantiated. For example, case 10276 is a 32-year-old with an enlarged heart who was found dead in his truck. Although a product that contains herbal ephedra was found in his truck, so were several bottles of cold medications, including Nyquil. Toxicology revealed no ephedrine, but did identify pseudoephedrine and doxylamine, both components on Nyquil. Thus, there is no evidence that this person even ingested the herbal ephedra. A similar case (13096) revealed no ephedrine in a toxicology screen again suggesting that the man had not ingested ephedrine around the time of death. Equally importantly, this man died of a disease that appeared to run in his family (aortic dissection), including an 18-year-old niece. In summary, AERs cannot be used to assess causality. As stated by several authors with experience in interpreting adverse event reports for the FDA: "It is probably impossible to do comparative analyses employing ADE [adverse drug event] reports for drugs that have received extensive publicity in the mass media for an adverse event..."7 In fact, the FDA's Center for Drug Evaluation and Research pointed out, in a February 10, 2000 memorandum concerning ephedra products, that "it is possible that the reported serious adverse events are reflective of coincidental background spontaneous occurrences in the population and are not necessarily causally related to [the use of dietary supplements containing ephedrine-type alkaloids]." The RAND review notes this as well, stating that "The most important limitation [of their assessment of adverse events] is that the study design, that is an assessment of case reports, is insufficient to warrant definite conclusions regarding causality." They list this limitation as one of the "most important...gaps" in the current knowledge-base. The RAND review also states that "Disentangling the relative importance of the pre-existing condition and the ephedra use is not possible." They state further that "Continued analysis of case reports cannot substitute for a properly designed study to assess causality. A case control study would probably be the study design of choice." Their Technical Expert Panel also "judged that case reports alone would be insufficient to establish definite causality between ephedra use and serious adverse events." Because of these limitations, terms such as "probably causal" and "possibly causal" in AER reviews are potentially misleading (see, in particular, the "Conclusions" section of the "Structured Abstract," page vi, and the "Conclusions" section, page 112). They represent only reviewers' assessment of causality based on uncontrolled data and subjective assessments. Although these terms are often used in scientific publications, their use in the RAND report may suggest a level of evidence that does not exist from the	

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current data. These statements, therefore, should not be taken out of context. RAND's stated limitation that "Definite causality cannot be determined from case reports" must be kept in mind when interpreting this report. It is also critically important to remember that case reports can produce false signals of cause and effect.8,9 Most importantly, because of the limitation of AERs, it is unclear why the RAND report states, in the Structured Abstract, that "These [sic] is sufficient evidence to suggest a possible causal role of ephedra-containing dietary supplements in rare but serious adverse events, particularly cerebral hemorrhage." With respect to a possible causal role of ephedra in adverse events, RAND acknowledges that AERs are not sufficient to draw conclusions about causality, consistent with the known limitations of AERs discussed above. In addition, this comment is puzzling given that their "Conclusions" section (ages 112-113) does not state this at all. With respect to cerebral hemorrhage, the only comment in the body of the report on cerebral hemorrhage refers to a case-control study of phenylpropanolamine (PPA) and cerebral hemorrhage.10 However, the RAND report refers to this study only as an example of case-control methodology that could be applied in the future to ephedra. The report does not discuss the PPA study further. In fact, this study has been heavily criticized. Despite this, there was not a formal review of this study by RAND (and there were no members of the technical expert panel listed with expertise in epidemiology to perform such a review). In addition, PPA and ephedra have different chemical structures and different pharmacological activities. Finally, the RAND report does not mention that the PPA report also presented data on non-PPA, ephedrine-alkaloid containing products. These agents included medications that contained pseudoephedrine hydrochloride, phenylephrine, ephedrine, and epinephrine. In the report, there was similar prevalence of use of these products among those with and without hemorrhagic strokes. Although this is not a definitive analysis, it suggests that there was no association between these ephedra-containing products and hemorrhagic stroke. Therefore, the statement in the Conclusions section of the Structured Abstract of the RAND report is inconsistent with currently available scientific data. In summary, the RAND review supports the use of herbal ephedra and caffeine for weight loss, an effect that may have beneficial health consequences. The report also suggest, from controlled studies, that adverse events following ephedra use are, at most, rare. (The should not imply that the events are even causally related to ephedra us.) Most importantly, because of the reliance on AERs, the report cannot establish a causal effect of ephedra on	

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serious adverse events.	
Review of Anecdotal Adverse Event Reports - Limitation of Review. On pages 109-110, the report identifies potential limitations associated with the review of anecdotal adverse event reports. These limitations are buried at the end of the report, rather than being incorporated into the appropriate sections of the report (as per prior AHRQ reports, such as the Garlic Report - see Section IX, herein). Moreover, a number of limitations are not prominently identified, including but not limited to: a) The poor quality of the data and information contained in the anecdotal adverse event reports; b) Inherent problems associated with voluntary reporting systems; c) The number of individuals in the general population who experience the adverse events identified (i.e. background risk); d) The possibility that certain products may not have been standardized and/or manufactured according to Good Manufacturing Practices ("GMPs") - resulting in potential adverse events that have nothing to do with ephedra or caffeine when consumed in recommended amounts. Specifically, in the absence of standardization and quality control, it is conceivable that certain products may contain far more ephedra or caffeine (or other constituents) than indicated on the product label. This possibility must be considered when evaluating anecdotal adverse event reports. In the absence of identical product identity, any general conclusions regarding ephedra and caffeine are inappropriate and highly suspect based upon adverse event reports (see the AHRQ Garlic Report for an appropriate way to address this issue). In my opinion, RAND should strongly support immediate issuance by the FDA of dietary supplement GMPs and should endorse stringent quality control measures to ensure that all ephedra supplements contain what they are claimed to contain; e) The possibility that the consumer abused or misused a product by ingesting more than the recommended amount - or that the consumer ignored detailed product warnings and contraindications. RAND should emphasize the detailed warning label contained on the vast majority of ephedra supplements - and should acknowledge that there is little way to know from anecdotal data whether a consumer abused a product (either intentionally or more likely inadvertently); f) The possibility that the anecdotal adverse event reflects chance, coincidence , or confounding factors - including but not limited to the possibility that ingestion of a different product or substance led to the stated event. I I. Review of Anecdotal Adverse Event Reports - B. Ascribing Causality to Adverse Event Reports - 1. Reliance on Unpublished Article. In order to establish a framework for analyzing the adverse event reports, the draft report relies upon an unpublished article written by Cynthia	

Appendix 3. Reviewer Comments (continued)

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Mulrow, M.D. Reliance upon an unpublished, non peer-reviewed article to establish the framework for a critical portion of the report is entirely unacceptable. AHRQ studies have not, to our knowledge, ever relied upon an unpulished article to establish the framework for this type of analysis. In addition, reviewers such as myself have no way of analyzing the article - thereby defeating one of the primary reasons for review of the draft report. II. Review of Anecdotal Adverse Event Reports - B. Ascribing Causality to Adverse Event Reports - 2. Failure to Review Factors Critical to the Interpretation of Anecdotal Adverse Event Reports. Table 4 of the draft report summarizes the various methods researchers use to assess causality from adverse event reports. The following nine factors are identified: a. Temporal relationship. b. Dechallenge response. c. Rechallenge response. d. Could there be an alternative explanation? For example, dehydration or consumption of other toxic substances. e) Prior reaction to same substance. f) Dose response. g) Objective evidence of adverse event. h) Previous conclusive reports. i) Definition of substance. Despite the report's reference to these nine factors, it is my understanding that the report concludes that events are "probably causal" based upon a review of only two factors - a and g. The draft report does not explain why RAND believes only two factors out of nine can be used to ascribe degrees of causation to anecdotal adverse event reports. II. Review of Anecdotal Adverse Event Reports - B. Ascribing Causality to Adverse Event Reports - 2. Failure to Review Factors Critical to the Interpretation of Anecdotal Adverse Event Reports (cont'd). The draft report also indicates that three factors are used to determine if an event is "probably causal": a) Reasonable certainty that the adverse event occurred. b) Reasonable certainty that the patient took ephedra in a dose and timing compatible with the known pharmacology of ephedrine. c) An adequate evaluation must have been done to rule out other potential causes for the adverse event. The third factor (factor c, above) is exceptionally problematic from a scientific perspective. The report acknowledges that the third factor is subjective. Specifically, in an effort to rule out other potential causes, the report indicates that such a determination was made by determining if the subject had a pre-existing condition that was identified in the adverse event report.	
It is stated, "With regard to adverse events, it was recognized by EPC staff and the TEP that, even in aggregate, the number of patients included in randomized trials was likely to be few…. Because of this, it was recognized that case reports would have to be relied upon to assess serious adverse events." It was Dr. Shekelle who	The causality analysis has been removed from this revision. We revised the sentence to indicate EPC staff recognized assessing case reports was going to be required to meet the terms of the contract. Our notes from the TEP meeting are clear

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
advanced his position to this question, but it is not correct to state that this was recognized by the TEP. In my remarks I made it clear that the clinical trials were the most useful clinical data available, and that the FDA AER database was to flawed and incomplete to be able to draw any conclusions. Dr. Shekelle introduces Cindy Mulrow's criteria as Rand's position in the assessment of adverse medical events. My point was that these criteria would be useful in assessing adverse events in the course of controlled, conventional, pharmaceutical trials, not the poor quality of the voluntary AERs in the FDA database was shocking in contrast. We did the best analysis possible in the circumstances for the CRN report and found that even the most complete subset was not sufficient quality to draw any conclusions. Dr. Benowitz agreed that the AERs did not have all the elements of an AER analysis. Therefore, the statement on page 21of the draft report is a reasonable summary of the discussion, i.e., "Consequently our TEP judged that case reports alone would be insufficient to establish definite causality…" Dr. Shekelle also agreed that the FDA AER could not be used to assess causality. He said that the adverse event issue would be the hardest to deal with, because it is front page and gets wide attention, but he was not worried about disagreeing with the FDA. Stating that not all the AERs were true or false, he acknowledged that the gold standard was lacking to link exposure and outcome, there is no basis for a conclusion.	that the majority of the TEP agreed.
The assessment of probability/ possibility respecting causality between use of ephedra-containing dietary supplements and adverse health events seems shaky based as noted mainly on FDA case reports, "insufficiency documented". It is not clear to me where the margin is between probably and possibly. and whether there is a clear basis for location on either side of the margin.	Causality has been removed from this revision.
It is not clear why you require coronary angiography for cases of myocardial infarction. Clearly MI can be diagnosed on the basis of EKG and enzyme changes. Coronary angiography does address the severity of underlying coronary artery disease, but that does not address whether or not ephedra played a causative role. It is well known that coronary spasm is most likely to occur at the site where there is some underlying coronary artery disease. If ephedra can cause coronary spasm, a person with underlying coronary artery disease would be most vulnerable to this occurring.	We clarified that coronary angiography was required in cases of myocardial infarction in order to evaluate other causes, such as coronary artery disease, not to make diagnosis. In the presence of coronary artery disease, the occurrence of an MI could be classified no higher than a possible sentinel event.
The criteria in our causality algorithm may be too conservative. Requiring coronary angiography in cases of M.I. would exclude cases diagnosed by cardiac enzymes and ECG changes alone.	Angiography was required to assess the possibility of alternative explanations, not the presence of a myocardial infarction. The text has been revised to reflect this.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
The interpretation of co-existing cardiovascular disease with respect to causation is an important issue. It is quite likely that underlying cardiovascular disease would predispose to ephedra causing a serious cardiovascular event. This has been well shown to be the case for cocaine. I think this issue needs to be made quite clear, especially since this is the reason why many of the adverse events are classified as possible in your evaluation, while they were judged to be probable in the evaluation done by Christine Haller and myself.	In this revision we no longer deal with causality.
What is meant by "more than the minimal dose?" How do you know what a "minimal dose" is? Were any cases excluded because of this criterion? In the same figure on level 3, the question comes up again about the difference between probably causal and possibly causal. The box above possibly causal says "interaction with ephedrine likely." If you say that the interaction is likely, then why do you say it's possibly causal?	We no longer use this criterion or assign causality in this revision.
"A 41-year-old female has four stroke events over a 2-month period between December and February." This case seemed to have incomplete description as there was no mention of the product (Diet Phen) that the patient was taking and when and for how long (14-60 days).	This text has been revised.
According to Table 20, Ripped Fuel was also involved but there is no mention of the product in the description (which is probably important information for the reader).	This change was made.
If the date of death is May 1994, she cannot be admitted to the Emergency Room in December of 1994. Should it be 1993?	This typo has been corrected.
I found that Table 20, column titled as "Key Determinants of Causality" rather confusing, incomplete and unclear. Delete "Timing<24 hours" from all cases as this does not contribute any additional information but rather add confusion to the interpretation (reader may interpret a "no" to Timing <24 hours means ingestion did not occur within 24 hours, which is not the case as many times tox screen is "yes".) Change "Tox screen**:" to "Tox screen was done:" and eliminate "**Ephedrine/amphetamines found in toxicology screen" as this is not true in all cases. Add "Ephedrine alkaloid detected: Yes or No" to the column since tox screen may not include detection of ephedrine or its alkaloid.	This table has been revised to improve clarity.
Does Nature's Nutrition Formula Three contain ephedrine (see p. 60 case description)? Should this be included in the table? In the description on p.60, it stated that "Toxicology screen was negative for ephedrine...", however, table 20 indicated that ephedrine was found The footnote may be	Change made.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
misleading and it may be more appropriate to footnote tox screen with“Tox screen was done” rather than “Ephedrine/amphetamines found in toxicology screen”.	
The case description stated that “Toxicology screen for cocaine, ephedrine and amphetamines was negative.” However, the Table indicated that ephedrine / amphetamines were found (same problem as #15).	Change made.
The age of the patient is different (37 y.o. or 36 y.o as described on page 62)?	Change made.
Should the product be Metabolife (as described on page 63) or Metab-O-Lite as indicated in the table.	Change made.
Does Accelerator also contain ephedrine? Should this be included in Table 20? Footnote of tox. screen is inconsistent with the description on p.63 (same problem as #15).	Change made.
The ages are different between the table and the description on page 64.What is the tox. screen results for this patient?	Change made.
The ages are different between the table and the description on page 64-66.	Change made.
There is no description of the case on page 66 under Stroke, possibly causal section but it is found under Subarachnoid Hemorrhage on page 68. Yet, it is grouped together with all the other cases of Stroke (CVA) in table 20. Should this be separately described or should this be described under Stroke section?	The grouping of the cases has been changed to better improve clarity.
For AER 13672 described as "probably not causal" on page 62, There are toxicology results that showed 280 ng/ml ephedrine in the blood. These results were reported by the Medical Examiner on 2/12/02, which may be after the FDA report was finalized.	
Metabolife recently admitted (after this draft was issued) that it has received 13,000 complaints about its ephedra products. These should be included in your analysis.	These are now included.
p 47, question 18: what was the rationale for dividing the durations of use into the listed classes? Because tachyphylaxis generally occurs after about 14 days of continuous use of ephedrine, the evaluation of acute use or for acute effects is commonly limited to days 1-14, with durations longer than 2 weeks considered “chronic” use.	Because we wanted to distinguish dosing within 24 hours, we divided the categories in the Table in this fashion.. In the actual data, we recorded the exact time.
Regarding adverse event adjudication -- you make your reasoning clear for exclusion of individual events due to insufficient information or downgrading attribution due to pre-existing conditions; however, the point could be made more clearly that this may tend to underestimate the number of serious adverse events	We have emphasized in the text that our methods of case report analysis are conservative and may underestimate the number of events.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
A concern is that in the case studies there was no analysis and no sufficient emphasis place on the evaluation of dosage amount, which in many cases appeared to be excessive.	In the majority of case reports the dose was not even reported, preventing any dose analysis of the case reports.
To demonstrate how additional data could affect the outcome of the present study, consider case 13672, which was designated "probably not causal". This reviewer has access to additional data on this particular case, specifically that the decedent did not have a toxicological examination that revealed a postmortem ephedrine blood concentration of 280 ng/mL and a pseudophedrine level of 100ng/mL. Given this additional information, is the causality level assigned to this specific case still valid? More thorough investigations like those pursued during the discovery process of specific lawsuits almost always yield additional information that would likely modify the causality assessment of specific cases submitted via the MEDWATCH program. Also, were those case reports described in the medical literature used in the case report assessment? They do not appear to have been utilized.	We did include the medical literature case reports in this revision. The additional information about a specific case, as provided by this reviewer for this case and other reviewers for other cases, we unfortunately cannot include or assess in our report, as we have no access to the original information.
I wasn't clear as to why only case reports documenting death, myocardial infarction, and/or cerebrovascular accidents were evaluated. To me this made the comparison to the Haller and Benowitz study less meaningful.	We have included additional case reports in this revision. We have deleted the comparison to the Haller and Benowitz study since we no longer assess causality.

Appendix 3. Reviewer Comments (continued)
Second Review of Safety Analysis including Metabolife Data

Reviewer Comment	Rand Response
Meta-analysis. This study was sent to me for information purposes only. The analysis is well done and meets the highest standard. The efficacy of Ephedra is very modest in terms of weight loss. Treatment causes significant adverse effects with RRs ranging from 2 to 3. Statistical power is inadequate to rule out severe adverse events occurring at a rate of 1.1/1000. The severity of the adverse effects can not be determined (my assumption). Likewise, the dose-response relationship can't be estimated.	No response
Metabolife analysis. The database is extremely messy and does not allow many meaningful analyses and conclusions. Your approach in terms of coding rules, data extraction and event classification is good. If a pharmaceutical company had kept records in this sloppy way my assumption is that it would be in deep trouble with the FDA. You conclusion is weak in my view. I would say that the "Findings are consistent with an increase in rare serious adverse events. What troubles me is that the population is so young. I would not expect serious cardiovascular events occurring so often. I realize that we don't have a denominator so any attempt at even guessing what the event rates might be are probably too speculative. In summary, you have from an analytic point of view done what can be done.	No response
Evidence Report. This is another well-done study. My interpretation is colored by two facts. When people complete a MedWatch form they suspect an association. There is a marked underreporting ranging from 90 to 99 %. This means that what appears to be rare may not be very rare. The temporal relationship between use of Ephedra and the occurrence of an event may exist even if it isn't documented. Again, I think your conclusion is too mild. I am fairly convinced that Ephedra causes serious events but I can't give a rate. Moreover the benefit-risk ratio is unfavorable (minor benefit for sure), so I would question the wisdom of leaving the compounds) on the market. My position is also influenced by the age of the victims.	We added to the limitations that MedWatch may underestimate the number of events.
The AERs presented in this report appear to be consistent with the known pharmacologic actions of ephedrine. Would it be appropriate to include a statement to this effect in the report?	We included such a statement.
When the summary text under Results and Conclusions is updated to include the analysis of the ephedrine AERs, care should be taken to present results for ephedra and ephedrine separately.	This was done.
For the case descriptions of the cerebrovascular accident/stroke events, it would be helpful to include the individual's functional status in the text (it is already included in the Table 20).	We included this information to the extent that we identified it in the source documents.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
We've seen a comment from NCCAM regarding the tables. We agree with that comment.	These tables are now incorporated into this revision.
Page 5, paragraph 3, last line: "Subject" should be defined. Page 7, paragraph 2: Second sentence: Text would read better as follows, "…seizure, only those cases described as generalized toxic-clonic seizures underwent further review." Sentence beginning at end of line 5: Text notes requirement that there be documentation that the individual had consumed ephedra or ephedrine within 24 hours of the event, but that this was not a requirement for psychiatric events. It would be helpful to explain why this decision was made. "Sentinel case" was not defined previously or used subsequently in the report. If it means "sentinel event", should change wording. Page 24, paragraph: Should "doses" be changed to "dosage?" Page 27 Paragraph 1, under FDA Cases Ephedra: The dates aren't correct. It appears as if the patient was taken to the hospital in December 1994 where she signed out AMA even though she had died in May 1994. What is "chlophoramine?" Paragraph 2, line 3: Change "toxicology" to "toxicology screen." Page 28, Paragraph 3 (case# 12722): Text doesn't mention ephedra exposure – what product was used? Paragraph 4 (case# 12843): Text doesn't mention ephedra exposure – what product was used? Paragraph 7 (case# 14638): Text notes that individual had been taking Hydroxycut for seven days, but Table 20 (page 52) says 2-13 days. Page 29 Paragraphs 2 and 3 (case# 44): Text doesn't mention ephedra exposure – what products were used? Paragraph 5: Case# 258 is not included in Table 20. Paragraph 6 (case# 13672): Change "rain" to "run." "Soldier" does not indicate gender. Although from the text the individual is apparently a male, wording should be changed. Should indicate whether the toxicology screen looked for ephedrine or that ephedrine was not mentioned in the report. Paragraph 7 (case# 1859087): Text says this individual was taking Max Alert, but Table 20 says the product is unknown Page 30: Paragraphs 5 and 6 (case# 13806 and case# 14465) are not included in Table 20. Paragraph 6 (case# 14465), last line: Change "not conclude anymore" to "come to no other conclusions." Page 31: Paragraph 1: Product names in text and Table 20 do not match. Paragraph 2: Product names in text and Table 20 do not match. Indicate whether the toxicology screen looked for ephedrine or that ephedrine was not mentioned in the report. Paragraph 6: Text notes that this individual was taking E'ola Amp II Pro drops for 12 days but Table 20 indicates that he took them for 2-13 days.	We corrected typographical errors. We made suggested changes in language. We stated whether ephedrine was looked for in the toxicology screen. We made the product names match, e.g. "Ripped Fuel (Twin Labs)" was changed to "Ripped Fuel." The reviewer is incorrect about cases being in the text but not in Table 20 (now table 22); all were present.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
Page 32: Paragraph 2 (case# 9504): Product names in text and Table 20 do not match. Paragraph 3 (case# 10009): Is (was) there such a product as "Metabolift?" Paragraph 4 (case# 13009): Text indicates that the individual described is a male, but Table 20 notes that it was a female. Indicate whether the toxicology screen looked for ephedrine or that ephedrine was not mentioned in the report. Paragraphs 5 and 6 (case# 14114 and case# 14530): Product names in text and Table 20 do not match. After case# 14530, the last one in the text under "Myocardial Infarction", Table 20 continues with many more case reports of MIs (pages 64-66) and then lists "other cardiac " (pages 67-71) starting with three "possible sentinel events." Why aren't the descriptions in the same order in both text and table? Page 33: Paragraph 1: Indicate whether the toxicology screen looked for ephedrine or that ephedrine was not mentioned in the report. Paragraph 2, line 1 (case# 11062): Paragraph 2: Text indicates individual was 44 years old, but Table 20 says she was 42. Insert "was" between "and" and "a" in "was taking Power Trim and a cigarette smoker." Paragraph 4: Indicate whether the toxicology screen looked for ephedrine or that ephedrine was not mentioned in the report. Page 34: Paragraph 1: Product names in text and Table 20 do not match. Paragraph 5: Sedimentation is misspelled. Page 35: Paragraph 1: Product names in text and Table 20 do not match. Line 2: editorial - change "here" to "her". Line 7: editorial – change "with embolus" to "with an embolus" Paragraphs 3 and 4 (case# 10094 and case# 12713): Product name in text and Table 20 do not match. Paragraph 6 (case# 515): Text doesn't mention ephedra exposure – what product was used? Page 36: Paragraph 2: Text indicates individual is 25 years old while Table 20 indicates she is 26. Paragraphs 2, 3, and 4 (case# 14378, case# 14434, and case# 14553): Product names in text and Table 20 do not match. Paragraph 5: Thoracic is misspelled Page 37: Paragraph 2: Product name in text and Table 20 do not match. Paragraph 3: Delete either "other" or "additional." Paragraphs 3 and 4 (case# 13829 and case# 13905): These cases are not listed in the same order in the text and in Table 20 making them difficult to find (they are located on page 78). Paragraph 4 (case# 13905): Text notes individual is a female of unknown age while Table 20 indicates she is 36 years old. Paragraph 6: Text notes that individual was taking 40-60 mg of ephedrine for 10 years. Was this 40-60 mg per day? Some indication of amount per unit time should be provided, or a note should be made that the information is not available. Page 38, paragraphs 1, 2, 3, and 4 (case # 12851, case# 13031, case# 13643, and case# 13793): These cases are	

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
not included in Table 20. Page 39: Paragraphs 1, 2, 3, and 4 (case# 110, case# 297, case# 260, and case# 13945): These cases are not included in Table 20. Paragraph 1 (case# 110): This case was classified as a "possible sentinel event" but is listed in the middle of a list of cases with "insufficient information." Paragraph 2 (case# 297): Change "taken" to "taking." Should indicate whether or not there was any information on how long he had been taking Herbalife supplements? This case was classified as a "possible sentinel event" but is listed in the middle of a list of cases with "insufficient information." Paragraph 3, last line (case# 260): Delete "intake." Paragraph 5 (case# 13062): Product name, duration, and dose are not included in the text, but are given in Table 20 and should be included here. This case was classified as a "possible sentinel event" but is listed in the middle of a list of cases with insufficient information. Page 40: Paragraph 3: "5am in the morning" is redundant. Paragraphs 3 and 4: Product names in text and in Table 20 do not match. Page 41: Paragraph 2 (case# 10432): Product name in text and Table 20 do not match. What is "encepholophy?" Change "focality" to "focal nature." Paragraph 3 (case# 11062): Product name in text and table do not match. Change "taking" to "taken." The last line notes that because of the possible structural abnormality, this event was classified as a possible sentinel event. However, it is not clear from the text what the possible structural abnormality was. Paragraph 4 (case# 11649): Product name in text and Table 20 do not match. Indicate whether or not there was information regarding how long this individual had been taking Metabolife prior to the event. Page 42: Paragraph 1 (case# 13408): Product name in text and Table 20 do not match. Paragraphs 1 and 4 (case# 10874 and case# 11675): Indicate whether the toxicology screens looked for ephedrine or that ephedrine was not mentioned in the report. Paragraph 2: Text indicates individual in case# 14275 was 38 years old, but Table 20 says she was 30. Paragraph 3: Text indicates individual in case# 11105 was 31 years old, but Table 20 says she was 30. Paragraphs 3 and 4 (case# 11105 and case# 11675): Product names in text and Table 20 do not match. Pages 43 Paragraph 2 (case# 9747): This case is not included in Table 20. Paragraph 3 (case# 9509): Product name in text and in Table 20 do not match. Paragraph 5, last sentence (case# 13809): Text indicates the individual described was intent on doing harm to others, but Table 20 describes her as suicidal. Suggest changing "alleviated" to "subsided." Page 44: Paragraph 2 (case# 1855921): Text notes that this individual was taking Minithin but this information is not	

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
included in Table 20. Text notes that there was no history of other drug use, but Table 20 says this individual had a history of substance abuse. Paragraphs 3 and 4 (case# 48 and case# 238): Change "psyc" to "psychiatric." Paragraph 4 (case# 238): Provide composition of Tedral as is done for Bronchipax in paragraph 5. Also note that this drug is listed as "Bronchi Pax" in Table 20. Paragraph 6 (case# 9751): Product name in text and in Table 20 do not match. Should note in Table 20 that problem resulted from discontinuation of product use as described in the text. Page 45: Paragraph 3 (case# 12372): Product name in text and Table 20 do not match. Last line: Change "classified as" to "classified it as." Paragraph 4, first line Case# 13005): Change "also" to "used." Paragraph 4 (case# 14436): Delete "(tid)." Paragraphs 5, 6 and 8 (case# 14436, case# 14528, and case# 79): Product names in text and in Table 20 do not match. Paragraph 6 (case# 14528): Clarify "very soon" vs. "approximately 1 week after." Paragraph 7 (case# 1682426): End of line 3: Change "in residential" to "in a residential." Last line: "Note" is misspelled. Page 46: Paragraph 1 (case# 79): Text notes that product name is not given, but that investigators contacted the manufacturer – is the name of the manufacturer known? Paragraph 2: Should term "causality" be used here after the discussion about not trying to determine causality on page 6? Page 63, Table 20, row 6, and Page 73, Table 20, rows 5 and 6: Care should be taken to provide full product name. E'ola is the manufacturer name and E'ola makes some diet products that are laxative-based which would be inappropriate for inclusion in this report.	
Page 72 and elsewhere in Table 20: What does "implicit review" mean?	This was defined in the report.
Page 91 and elsewhere: Replace "psyc" with "psychiatric."	This change was made.
Page 103: Paragraph 1: Use of term "causality" should be reconciled with discussion on page 6 regarding the intent of the report. Last two sentences would be more accurate if changed to: "Definite causality for adverse events cannot be determined from case reports. When an adverse event is very serious it may be infeasible or unethical to conduct a de-challenge/re-challenge test for causality."	Causality has been removed from this revision.
Given the short time frame RAND has to fulfill its contractual obligations, the peer review process also has necessarily been severely time-constrained, not to mention coincidental with the year-end holiday period. This is regrettable but I have had the opportunity to review these drafts and reflect upon what they say in general and how it is said. I have not had sufficient time to review the details of the reports and tables for accuracy, which is almost certainly true for the	We indicate in the report that this section did not receive the same level of peer review as the other portion of the report.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
other peer reviewers. Any claim that the Metabolife Report in particular has been "peer-reviewed" should be qualified, as a true peer review was not possible under the circumstances.	
The Metabolife Report spends a large proportion of its content describing the poor quality of the reports, limitations of the records and methods, the short time frame, the many thousands of files, etc., making it difficult to see a scientific value to this review under these circumstances.	We were requested to do this review as part of the contract.
A major criticism of the Metabolife Report is the disconnect between the final limitation listed on p7, which clearly states that ". . . case reports are in general not considered sufficient evidence to draw conclusions about causality", and the overall tone of the report. Any reader will be led to believe that this report links the occurrence of adverse events to the consumption of ephedra, despite the limitations listed at the end. Even though the words "possible" and "may" do appear in the report, the terms and phrases used in the methodology, the detailed and repetitious descriptions of the case reports, and the results, are all written with such a factual tone that there can be no doubt that this report will be interpreted to mean that these events were caused by ephedra. The report should be rewritten to state the study's major limitations (p7) at the beginning, i.e., that these case reports cannot be ". . . considered sufficient evidence to draw conclusions about causality". Then the report should state at the outset in clear terms that the purpose of the analysis was not to establish or prove that there is a risk of serious adverse events, since AERs are not suitable to that task. The purpose was to determine whether or not this database might be useful to "generate a" (rather than "support the") "hypothesis that ephedra may cause rare serious adverse events", to quote conclusions on p7. The introduction should also state the fact, which is not a conclusion of the study but was included as the final statement of conclusions (p7), that "A hypothesis-testing study, such as a case-control study, is necessary to prove or disprove this hypothesis". Each statement in all sections should be carefully examined and rewritten if found to be interpretable as drawing a link between ephedra and effects. Phrases such as "instances of serious adverse events such as death, heart attack, or stroke" are repeated several times which undoubtedly will lead to the impression that these are caused by ephedra. It should be made more clear that the Metabolife Report, as well as the review of the FDA AERs and published case reports, are part of the effort to explore the hypothesis that ephedra may cause rare serious adverse events. Common sense and a rudimentary understanding of pharmacology will lead to the conclusion that this clearly is possible, depending principally upon the dose. Anything at a	RAND did not generate the hypothesis that ephedra causes serious adverse events, that hypothesis was already generated and one reason why our report was commissioned. Certainly the existence of serious adverse events in otherwise healthy young adults must be considered “support” for this hypothesis, just as the lack of such events would be considered a lack of support. It is not proof of a causal relationship, and we say so, repeatedly. We also note that the concern about out report being overly suggestive that the case reports imply a cause and effect relationship is not shared by numerous other reviewers, who believe just the opposite, that our report downplays the possibility of a causal relationship.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
sufficiently high exposure can cause adverse events. Continued analysis of deficient and flawed adverse event databases cannot and will not lead to any conclusions about causality, but hurried evaluation, suggestive language, and imprecise wording can lead to perceptions of cause and effect that are not scientifically supported. Turning to the revised RAND Report, it is difficult to comment on the "Safety Assessment Excerpt" without seeing and understanding how it is used and referenced in the rest of the report. Most of the comments that I made previously still apply to this draft because 99% of the safety assessment deals with adverse event reports which are flawed and inconclusive. Some limited peer review of the introduction and conclusion sections of the completed report should be permitted to assure that the wording of these sections avoids the continuing problem of implications that a cause and effect relationship can be established from the number of AERs, or the exhaustive treatment given to the AERs, in the report. The language in the previous draft has been changed to reflect the fact that the "causality scale" leads to erroneous and exaggerated conclusions. Nevertheless, the new scheme of classification, using the terminology "sentinel" instead of causal, is still suggestive that these reports can be used for interpreting cause and effect. To help avoid this problem, there should be added to the explanation of the term "sentinel" on p7 of the Metabolife Report and on p6 of the Safety Assessment Excerpt that adverse events, even serious events, are commonly idiopathic in etiology, and that therefore the lack of any known cause combined with known consumption of ephedra is not meant to imply that ephedra was the cause -- the intent is simply to show which events could potentially have been caused by ephedra, given the lack of a known cause, with the understanding that a cause and effect relationship for ephedra cannot be established from such reports. I have not been able to review in any detail the descriptions of events categorized in the Metabolife Report or in the Safety Assessment Excerpt. Nonetheless, a cursory review indicates that the criteria established for "sentinel" events in particular has not been met in a significant number of these cases, and these reports should be reviewed with this in mind. For example., RAND did not have access to the results of the autopsy in the first death listed as a sentinel event on p26, and availability of autopsy results is appropriately listed as a criterion for qualification as a sentinel event on p7. Also, there are a number of cases described as sentinel events where the individuals are also described as long-term smokers, alcoholics, or drug abusers. These and other cases do not appear to meet the criterion that sentinel events be idiopathic when these conditions are known to be risk factors for events at issue.	

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
The revised report on p7 states that the Office of Dietary Supplements had given RAND a key question concerning "the relationship between dose and the likelihood of serious adverse events". The authors, however, ". . . do not believe such an analysis is justifiable on the case report evidence. . . ." It seems to me, if evidence is insufficient to be evaluated for dose relationship, then any such evaluation is unjustifiable, which speaks to the point I made in my previous review that reliance on flawed case reports can only lead to flawed analysis and conclusions. Similar to previous comments on the Metabolife report above, the limitations and lack of ability to draw conclusions from AERs should be stated clearly up front in the Safety Assessment Excerpt. The language used to describe the large number of reports clearly suggests causality, even if not intended. The preponderance of the description in the safety section leads the reader to conclude early on that ephedra must be responsible for these effects. The very brief description of controlled trials is dismissive of strong evidence for ephedra safety, and the extensive toxicology database is completely ignored. Therefore, the safety section continues to be unbalanced by the absence of objective evidence in contrast to the voluminous treatment given to the case reports. I agree with the statements in the revised report (p6) concerning the variability and subjectivity of interpretation of case reports. This is a principal reason for my objection to their consideration being the centerpiece of the report's safety assessment. It is an important exercise, and RAND has done as thorough a review as could be expected. It is extremely important, therefore, that readers of this report not be led to an impression that the repetitive descriptions of large numbers of case reports can be interpreted as evidence for cause and effect. Clearly this is and will be the message unless the introduction, methods and language throughout are consistent with the messages about limitations, insufficiency for causality, and the need for a conclusive study of a different kind, i.e., a case-controlled study to add to the existing objective clinical evidence. As a final point in this regard, the "Conclusions" section on p103 of the Safety Assessment Excerpt should be revised to remove the implication that RAND has concluded that the case reports are useful to establish causation or that the case reports establish that there is in fact a risk of serious adverse events. The reports generate a hypothesis, and whether a risk of serious events exists as well as the estimate of the level of any risk needs to be determined through scientific studies, not review of additional case reports. In particular, the sentence beginning with "For rare outcomes" in the first paragraph should be revised to make	

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
it clear that the review of case reports was to assess whether these reports generate a hypothesis that ephedra might cause rare outcomes.	
In addition, the third bullet should be revised to avoid the implication that the lack of other identifiable causes combined with ephedra consumption establishes causation.	We added this important qualifier.
RAND's conclusion that further analysis of case reports is pointless is the key to moving forward with a scientific evaluation of ephedra and the resolution of a controversy that has been created by over-focusing on case reports. This point should, therefore, be made in clear terms at the very beginning of the completed Ephedra Report.	The “Conclusions” is the appropriate place for this conclusion.
We would like to see summary tables of the sentinel and possible sentinel events by ephedra use, by ephedrine use; by gender; by broad age groups; by category of AER. The long tables listing each event are not sufficient.	These tables are now added.
As to the adverse consequence conclusions it would seem appropriate to summarize the events for ephedrine as they are 'bulleted' for ephedra. Right now, it looks as if there is no conclusion on the sentinel and possible such events for ephedrine.	This change was made.
A recommendation is made for scientific studies of ephedra risk. No comment is made on whether it would be appropriate to also do this for ephedrine. For the present data, one could argue that PPA-like case-control studies should be generated for other ephedra and ephedrine products.	These changes were made.
Adverse Event Data from Randomized Trials. Methods. RAND identified 44 randomized, controlled studies, and a pooled meta-analysis was conducted of the risk of adverse events in treated vs. placebo groups for the most commonly reported adverse events. Risk was significantly elevated for psychiatric symptoms (OR 3.24, 95% CI 1.67-6.58), autonomic hyperactivity (OR 2.91, 95% CI 1.84-.70), nausea and vomiting (OR 2.37, 95% CI 1.51-3.78), and palpitations (OR 2.11, 95% CI 1.16-4.02). The risk was elevated, but not significantly, for hypertension (OR 1.86, 95% CI 0.39-11.74). Tachycardia was reported in only one study. The methods used are standard; the analyses appear appropriate.	No response
Adverse Event Data from Randomized Trials. Methods. The subgroup analyses of adverse events of ephedrine (+) caffeine were said to be “similar to the main analysis”. This data may be important and should be presented in greater detail. The reason for this is that caffeine can potentiate the CNS stimulant effects of this class of drugs (sympathomimetic aminies).	The results are the same because the ephedrine plus caffeine studies contribute the vast majority of the data to this analysis. So we have said as much as we can about this.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
Adverse Event Data from Randomized Trials. Methods. A second recommendation is to conduct the pooled analysis combining similar adverse event groups in an attempt to reanalyze for a dose-response effect from ephedra or ephedrine (+) caffeine. For example, it would make sense to combine palpitations, tachycardia, and hypertension in such an analysis, since all are cardiovascular, sympathomimetic events.	We did this analysis and included it in the results.
Adverse Event Data from Randomized Trials. Methods. I would also like to see a pooled analysis of headache, and add this to Table 17. The reason for this is that headache may be a prodrome to more serious neurologic events, and was present in all three cases I reported at the 1996 meeting of the American Academy of Neurology.	This adverse event analysis was added.
Adverse Event Data from Randomized Trials. Potential for Bias. Since this data is a meta-analysis, there is little opportunity for bias.	No response
Adverse Event Data from Randomized Trials .Clarity of Reporting. The writing is clear. The report (I) would flow better if the meta-analysis section was stand-alone and separate from the case report analysis.	It is separate in the final version of the report.
Adverse Event Data from Randomized Trials. Conclusions. The conclusions are to the point. However, I find the meta-analysis conclusion somewhat lacking in methodologic content and discussion. To be more useful, expansion of the author's critical point in ¶1, page 25, should be added to the Conclusion section (p.103). The conclusions would more properly read: 1."There is sufficient evidence"…. (same). 2. Safety data from relatively small clinical trials of ephedra/ephedrine are unlikely to reveal rare but serious adverse events, those that may occur at a rate of less than 1/1000. Thus, such data cannot be used to conclude that ephedra/ephedrine does not cause such serious adverse events. In addition, it is likely that, in some of these trials, differential drop out of treated patients related to a higher rate of milder adverse events could have removed subjects at higher risk for more serious events.	We reworded this to try and improve clarity.
Adverse Even Data from Reported Cases. Methods. It is important to point out that the authors utilized a very much more conservative method to identify the likelihood of association with ephedra/ephedrine than that reported by both Haller and Benowitz5 for cardiovascular and central nervous system events, and by Samenuk et al for cardiovascular events. The authors should point out the differences with these studies, and how these differences may have led to different counts of adverse events in the main categories in Reports I and II. A table highlighting the differences with Haller and Benowitz would allow clearer comparison of categories. One important difference is that	Since we dropped a "causality" assessment from this revision, we don't think such a comparison is valid. We do acknowledge in the limitations that our methods are more conservative than those used by some other groups.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
RAND dropped all cases with any alternative explanation or competing cause to "probably not related". Haller and Benowitz, however, considered events at least possibly related, even in the face of co-existing or pre-existing condition, if those conditions themselves could be severely exacerbated by ephedra alkaloids (e.g., hypertension, some psychiatric conditions).	
Adverse Even Data from Reported Cases. Methods. One table should summarize all of the reviewed cases by adverse event type (e.g., death, seizure) and by author's conclusions regarding category (sentinel, possible sentinel, probably not related, and insufficient information). For example, of 41 reported seizure cases, only two were deemed "sentinel" cases. This may highlight the insufficiency of available data with which one may judge likelihood of association. For example, I have detailed knowledge of seizure case 13408. Even with the author's criteria, this case should be classified as "sentinel".	These tables are now included. We acknowledge that limitations of the source documents limit our ability to draw conclusions.
Adverse Even Data from Reported Cases. Potential for Bias. With the conservative approach described under "Methods", there is potential for serious misclassification of cases, primarily in the direction of "probably not related" or "insufficient data". It is much less likely that misclassification substantially went in the other direction.	This limitation was acknowledged in the appropriate section.
Adverse Even Data from Reported Cases. Clarity of Reporting. As mentioned above, at least one or two other summary tables would be helpful to the reader.	These tables are now included.
Adverse Even Data from Reported Cases. Conclusions. The conclusions reached on p.103 regarding the case report assessment are not very helpful in moving things forward on this issue. There is an underlying assumption that, if causality cannot be proven from passively reported cases with poor documentation, then it may take a case control study to do so. There are several problems with these conclusions: (1) If ephedra were an FDA-approved drug, its use would have likely been banned related only to the sheer number of serious adverse events reported. Even if one accepts only the "sentinel" and "possible sentinel" events reported here, or those reported by Haller and Benowitz, or the cases from Texas or Rochester6, the likelihood of association, to most clinicians, would be overwhelming. (2) There should be substantial discussion added to the report related to other converging lines of evidence one would normally wish to include in an assessment of causal relations. These would include: (a) Expected actions of sympathomimetic amines, including effects on the peripheral vascular system, and the biologic plausibility of association with milder and severe adverse events. (b) A summary of the extensive literature on the potential for the "look alike" drugs such as PPA to cause similar serious	We note there is a great deal of controversy among experts about whether case reports are sufficient to conclude cause and effect relationship with serious adverse events. The other kinds of evidence cited by this reviewer were outside our scope. We do think a case control study is possible, and that the controversy is likely to continue to rage until such a hypothesis-testing study is performed.

Appendix 3. Reviewer Comments (continued)

Reviewer Comment	Rand Response
adverse events. For example, both PPA and ephedrine are known to be associated with angiitis. (c) Evidence from animal studies or basic neuroscience studies related to adverse events of ephedrine. (3) If one of the problems relates to poor reporting to the FDA or from the manufacturers, it would seem that, at a minimum, clearer reporting standards should be established. (4) It would be extremely difficult to conduct the type of case control study recommended. The serious events are rare, and among the major event categories (e.g., seizures), ephedra is not likely a frequent cause. I have thought about how to conduct such a study, either via emergency departments or poison control centers. However, there would be serious methodologic issues in proper case and control specification. Can we really afford to wait for such an imperfect study to be conducted? Is there really any justification whatsoever not to ban unfettered use and marketing of these sympathomimetic amines in pharmacologic doses?	