

**Tab 96**

Food and Drug Administration  
Rockville MD 20857

**DATE:** March 28, 2000

**TO:** Joseph A. Levitt  
Director, Center for Food Safety and Nutrition

**FROM:** Director, Center for Drug Evaluation and Research

**SUBJECT:** Office of Postmarketing Drug Risk Assessment (OPDRA) Analysis of Adverse Event Reports for Ephedrine Alkaloid-Containing Dietary Supplements (EADS)

I have reviewed OPDRA's analysis of the adverse event reports for EADS. The core of the OPDRA analysis focused on 139 detailed adverse events reported between June 1997 and March 1999. This set of reports generally included detailed information that permitted OPDRA to conduct a rigorous analysis of the strength of the association between the adverse events and EADS. Of the 139 reports, OPDRA excluded from further analysis 31 reports that lacked sufficient information to infer a meaningful association with EADS.

Of the remaining 108 reports, most were characterized as clinically significant cardiovascular and central nervous system (CNS) adverse events. Seven of the nine deaths in this group were from sudden cardiac death, cardiac arrest, or stroke. The subjects of the 108 adverse events were generally young (median age of 35), and most had no underlying medical condition or disease. In addition, most appeared to have taken the EADS "as directed" without evidence that the recommended dosages had been exceeded.

OPDRA also reviewed summary information on 1164 unduplicated adverse event reports from 1990 to November 1999, which included summary information on the 139 adverse events analyzed in detail. This set of reports associated with products known or suspected to contain EADS provides summary data on demographics, reported product use information, reported adverse events, and the outcomes of those events. OPDRA concluded that the pattern of the 1164 reports was similar to the 139 cases that were reviewed in greater depth with respect to the age, gender, duration, adverse events and outcomes.

OPDRA's in-depth analysis is very cautious in evaluating the strength of the association with the EADS because it is extremely difficult to establish a causal relationship based solely on adverse event report data. However, at least 108 of the reports OPDRA analyzed provide very strong evidence in support of a causal relationship between EADS and the adverse events, particularly in light of the known pharmacodynamic effects of ephedrine alkaloids.

First, even though we do not have good data on background occurrence of these adverse events in the populations consuming EADS, we nevertheless believe it is most likely that EADS are causing these adverse events. The primary reasons for our belief are: (1) the temporal

proximity between EADS consumption and the adverse events, (2) the generally young age of the subjects of most of the adverse event reports and the fact that the subjects generally had no other predisposing factors, and (3) the similarity between the adverse events and the known pharmacodynamic properties of ephedrine alkaloids.

Second, although many EADS also contain other constituents, the most cogent interpretation of these data focuses on the common denominator, which is the presence of ephedrine alkaloids. In other words, the fact that adverse events are associated with ephedrine alkaloids containing a variety of other constituents, taken with the fact that we are not aware of the same level of adverse events associated with any of the other constituents in EADS (or with other products containing those constituents), supports the causal relationship between ephedrine alkaloids and the adverse events.

Third, although there was, for some subjects, a medical history that may have contributed to these adverse events, particularly in some of the most severe adverse events, there were also many cases in which such potentially confounding risk factors were absent. These preexisting risk factors do not preclude establishing EADS as a primary cause of the adverse events. In fact, synergy with the underlying medical conditions may have been a factor in several of the most severe adverse events.

In conclusion, upon consideration of issues of background rates, confounding medical risk factors, and multiplicity of substances in the various supplements, I believe that the most plausible and likely interpretation is a causative association between EADS and the cardiovascular and CNS adverse events. This is compellingly supported by the known pharmacodynamic actions of ephedrine alkaloids, which are concordant with the nature of the adverse of the adverse events.

  
Janet Woodcock, M.D.

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES  
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DATE: FEB 10 2000

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TO: Center for Food Science and Applied Nutrition

SUBJECT: OPDRA Postmarketing Safety Review:  
Evaluation of Adverse Event Reports Associated with  
Ephedrine Alkaloid-Containing Dietary Supplements

#### INTRODUCTION AND EXECUTIVE SUMMARY

CFSAN provided OPDRA the following databases on November 12, 1999 to review and analyze adverse events associated with the use of ephedrine alkaloid-containing dietary supplements (EDS):

1. One hundred thirty-nine adverse event case reports received and previously reviewed and followed-up by CFSAN (on two CDs) dated between June 1, 1997 and March 31, 1999. This June 1, 1997 date was chosen by CFSAN because it was near the time of the Agency's publication of proposed regulation concerning ephedrine alkaloid-containing dietary supplements (June 7, 1997).
2. Summary tabulations of 1176 report data files including the above 139 case reports on 3 CDs dated between 1990 and November 3, 1999.

Many of the 139 case report records contained extensive follow-up investigations and some contained only limited information. It was not our intention to make further attempts to follow-up when information or clinical data were incomplete. Therefore, evaluation and assessment for EDS association was made based on available information. The case tabulations contained some patient demographics but very limited clinical information, which was not verified against all available records. Accordingly, causality could not be assessed in the majority of the total available case tabulations of 1176 reports.

Of the 139 adverse event reports, 31 were considered not likely to be associated with the EDS product for the following reasons: insufficient information or no certainty that consumer was on an EDS (9), unevaluable reaction or unsubstantiated reaction (6), no identifiable consumer (2), confounded by multiple-suspect products (11), or confounded by underlying disease (3).

The remaining 108 adverse event reports were either probably or possibly related (defined in Method) to the use of the suspected EDS product(s). The report year distribution was 1997 (36), 1998 (50), and 1999 (20). Overall most of the adverse events were reported in women (female-67, male-40, unknown-1). The ages ranged from six days to 67 years of age with a mean and median age of 35. There were five reports in 15 year olds and one in a 16 year old. The serious outcomes included nine deaths, 49 hospitalizations or emergency room treatment, and 16 consumers that required outpatient intervention from a health care provider.

Of the nine deaths, the consumers were generally young with ages ranging from six days old to 43 years old. Seven of the deaths were cardiovascular-related deaths (cardiac arrest or sudden cardiac death-5, cerebrovascular accident-2). One was an infant exposed in utero and one consumer died from complications of rhabdomyolysis and multiple organ system failure. Four consumers were exercising at the time of their death. Of the cardiovascular deaths, one had a past medical history of unspecified "heart problems," one had a heart murmur (not thought to be significant), and one had borderline hypertension.

Many of the adverse events were consistent with the known sympathomimetic pharmacological effects from ephedrine, particularly those involving the cardiovascular and central nervous system. In some cases, the mechanisms of the injury or alternative etiology of reported events were not apparent. Idiosyncratic hypersensitivity to the product remains a possibility. However, since these products contain numerous ingredients, there is no certainty that the ephedrine alkaloid component was solely or primarily responsible.

At least 45 different EDS product names were identified. The most reported products included Metabolife (21) and Ripped Fuel (15). Most of these products were combination products that also contained caffeine from a variety of sources, including Guarana Extract, Green Tea Extract, Cola Nut, or Yerba Mate Leaf. Most consumers appeared to be taking the EDS products as directed without apparent over use or misuse. We did not attempt to determine the daily ephedra or ephedrine-alkaloid dose in these cases, because of the large number of different products and because many of the reports did not provide that information. Several products indicated approximately 300 mg of Ma Huang or ephedra extract containing 12-24 mg of ephedrine.

#### Summary of reports by major body system

- Cardiovascular events (46) included cardiac arrest or sudden cardiac death (7), cerebrovascular events (12), cardiac ischemic events (9), dysrhythmias (9), and hypertensive events (9). Overall, age did not appear to be an independent risk factor in the cardiovascular cases. There were more female consumers, however, in the death cases the distribution was more equal between male (4) and female (3). Half of the cases occurred within the first month of use. Possible contributing factors identified included previous or newly diagnosed underlying cardiovascular disease (17), hypokalemia (3), concomitant medication-DHEA (1),

and inappropriate use (2). Of note, five consumers suffered cardiac arrest and four suffered from stroke during or after vigorous exercise.

Two cardiac arrests, seven cerebrovascular events, six cardiac ischemic events, five hypertensive events, and three cardiac rhythm disturbance cases were probably related to use of an EDS and appeared to have no contributing factors. The remaining cases with possible contributing factors were considered possibly related to the use of an EDS product.

- Central nervous system events (41) included central stimulant effects (22), psychiatric disorders (11), and seizures (8). Consumers reported the majority of these events, but many reports contained medical records or other form of documentation of the adverse event. Approximately half of the subjects had visited an emergency room (ER) or health care provider after experiencing the adverse events. The stimulant effects involved heart palpitations, insomnia or nervousness mostly shortly after EDS use. The psychiatric events were behavior changes, manic reaction, or withdrawal reaction with months of use. These were reported from mostly younger adult consumers without underlying medical conditions or any concomitant prescription medications (11). However, some were on multiple dietary supplements or stimulants to enhance the intended usage of the EDS. Four had serious psychiatric events and were hospitalized with a confirmed or newly diagnosed underlying psychiatric disorder.

Eight cases of seizure occurred in adults with age 21-51 after seven days to intermittent use over several years. Six were hospitalized. Two probable cases occurred within a month of use. The amount of ephedrine alkaloid and the mechanism are unknown. Potential contributing factors in other six cases included possible underlying seizure disorder (2), hypoglycemia and multiple concomitant products (1), and concomitant or suspect medication.

- There were 21 adverse event reports involving the gastrointestinal, musculoskeletal, renal, hematological, or miscellaneous systems associated with the use of an EDS. These were isolated reports with the following diagnoses: necrotizing enterocolitis (NEC) in an infant, pancreatitis, hepatitis, urinary retention, acute renal failure with diabetes insipidus, hypokalemia with rhabdomyolysis, thrombocytopenia, and allergic reaction. Except for possible NEC and urinary retention, these events are not well recognized pharmacological properties of ephedrine. We cannot exclude the possibility that an EDS product with multiple ingredients might have contributed to these adverse reactions.

The entire tabulation listings of 1164 unduplicated reports were analyzed. Except for the 139 cases, the remaining 1025 cases in a line listing format provided only some patient demographic information but little clinical details. Most of the adverse event reports were submitted between 1994 and 1996 with a concentration of reports in 1996 (486). Other notable report characteristics included: adult consumers (49%) ranging from 16 to 65 years of age, female gender (54%), one or more months in duration of use (47%), and many received health provider care (39%). While clinical data were not included in the tabulations, most had cardiovascular and/or nervous system events. The most frequently reported products were Nature's Formula One (179), Metabolife (72), Ripped Fuel (69), and Thermojetics (51).

There were 34 reports in pediatrics (< 16 years old) but there was limited information on which to assess the use of these products, especially for children under the age of six. There were 65 listed deaths, but the limited information contained in the line listing did not permit evaluation of the adverse event or cause of death in 31 of the deaths. Certain reports listed associated aneurysm, heart attack, or stroke. Of the more recently dated reports (89 after 3/31/99), similar patterns were noted in age, gender and reported cardiovascular events. None were in children under 16 years of age. Five of the nine recent deaths listed events of heat stroke, ruptured aorta, intracerebral hemorrhage, heart attack, or massive coronary events.

In conclusion, our quantitative evaluation of the 139 case reports and 1164 tabulated summary listings from 1990 to 11/3/1999 associated with ephedrine alkaloid-containing dietary supplements indicates that the majority involved cardiovascular and nervous system events. Most of the adverse events in 139 reviewed reports were possibly related to the use of ephedrine alkaloid-containing products. Generally, these reports described a young population using EDS for weight loss and other related indications. Many consumers did not have any apparent underlying risk factors contributing to the adverse events, but certain serious events or outcomes appeared to have occurred in those that had a history of underlying medical conditions or previously undiagnosed diseases.

However, the majority of the EDS products contained other herbal or chemical ingredients as well as ephedrine alkaloid. This has contributed to the difficulties in assessing the direct association of the adverse events to the EDS products in most of the reports. Additionally, 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 EDS product uses. The availability of additional information, including product market or usage data, would be useful to further characterize the potential risks associated with the use of these products.

## TABLE OF CONTENTS

<b><u>Selection Of Cases</u></b>	6
<b><u>Evaluation Method</u></b>	6
<b><u>Results</u></b>	7
<b>I. Evaluation of 139 Cases</b>	7
A. Cases not related to EDS (31)	7
B. Overall Summary of 108 Probable and Possible Cases	8
C. Cardiovascular Adverse Event Cases (46)	9
1. Overall summary and demographics	9
2. Cardiac arrest and sudden cardiac death (7)	11
3. Cerebrovascular events (12)	11
4. Cardiac ischemic events (9)	12
5. Hypertensive events (9)	13
6. Dysrhythmias (9)	13
D. Central Nervous System Adverse Event Cases (41)	14
1. Central stimulant adverse event cases (22)	14
2. Psychiatric adverse event cases (11)	15
3. Seizure (8)	16
E. Gastrointestinal Events (7)	16
F. Musculoskeletal Events (6)	17
G. Renal Events (4)	18
H. Hematological Events (4)	18
I. Miscellaneous Events (2)	19
<b>II Summary Information of All CFSAN Reports (1164)</b>	19
A. Report year distribution	20
B. Age	20
C. Gender	20
D. Duration of EDS use	20
E. Outcome	20
F. Most reported events	20
G. Most reported EDS products	21
H. 448 Hospitalization or Receiving Health Care Reports	21
I. 34 Pediatric Reports	21
J. 65 Death Reports	22
K. 89 Most Recent Reports Information Between 4/1/99 and 11/3/99	22
<b><u>Conclusion</u></b>	23
<b>Attachments</b>	
1. Table of cases not likely associated with an EDS product	
2. Table of 108 Evaluable Cases	
3. Table of Cardiovascular Cases	
4. Table of Central Nervous System Cases	
5. Table of other cases	

## SELECTION OF CASES

We received two CDs from CFSAN on November 12, 1999, which were used to retrieve the images of 139 adverse event case reports and the respective investigative and medical records. These cases were reported to CFSAN's Special Nutrition Adverse Event Monitoring System (AEMS) between June 1, 1997 to March 31, 1999. The first date was chosen by CFSAN because it followed the publication of FDA's proposed regulation on ephedrine alkaloid-containing dietary supplements on June 7, 1997. These reports were evaluated for the association to EDS.

Three CDs, one in SAS and two in Excel files, contained demographic data fields in a summary tabulation format of a total of 1176 AEMS reports between 1990 and 11/3/99. As detailed follow-up information was not available, attribution and causality assessment could not be performed. There was no certainty that listed adverse events including many deaths were related to the listed products. These data files were electronically reviewed and analyzed to identify any pattern of characteristics in the reports including pediatric use, and deaths.

## EVALUATION METHOD

Hands-on review of 139 case report records revealed that many contained extensive follow-up investigations from the field office and some contained only limited information. It was not our intention to make attempts to follow-up further at this time when the information was not complete.

There is no standard international or U.S. nomenclature in describing the degree of causality between the suspect product and an event. Terms of association are in use such as certainly, definitely, probably, possibly or likely related, or not related. There are many factors we can apply to define cases if information is available. For the purpose of this evaluation, the temporal or causal relationship to EDS administration was established according to the following primary criteria:

### Probable association

- Adverse event is product related or temporally associated and not thought to be consistent with progression of underlying disease.
- Event occurs after product administration in a reasonable time frame.
- There is no underlying medical disease or condition confounding the reported events.
- Dechallenge and rechallenge information may be present in the report to support the association.

### Possible association

- Adverse event is product related or temporally associated.
- History of related or relevant medical disease or condition may confound the event, but the event occurs, or is aggravated, after the suspect product administration.
- Other drugs may confound the event, but there is no medical supportive information indicating that the adverse event exists or is ongoing prior to the suspect drug administration. The event only occurs after the newly administered suspect product.

- An association to the suspect product cannot be excluded when an adverse event is either within the expected spectrum of pharmacological effect of a product, or no other etiology can be identified.

#### Likely no direct association

- Event is confounded by concurrent disease condition.
- Event is confounded by concomitant drug or other product.
- Lack of information to make an association.

As stated earlier, the line listed data have not been verified against all available records, according to CFSAN. Review of the summary listings from the collapsed data files revealed that they contained some of the following demographics in each report: case number, report date and year, age, gender, duration, adverse event or body system, hospitalization, whether the patient received health care provider treatment, product name, ingredients, and manufacturer name. No description of any medical information was entered in these line listings. Duration of product use was not always available. No regulatory defined outcomes were listed except for hospitalization (hosp) or received treatment from a health care provider (HCP). Duplication of records might exist. There was no certainty that listed adverse events including many deaths were related to the listed products. Nevertheless, analysis of the demographic information was provided to give an overview of any pattern or trend of demographic characteristics from the total of 1176 reports.

## RESULTS

### I. EVALUATION OF 139 CASE REPORTS

#### A. CASES UNLIKELY ATTRIBUTABLE TO AN EDS (31)

Thirty-one cases were not further analyzed for the following reasons:

- Insufficient information or no certainty consumer was on EDS during the event (9) - Most of these cases reported a severe event such as death or stroke, however, in all cases, use of EDS product could not be ascertained and in four cases no other information was listed except death.
- Unevaluable or unsubstantiated reactions (6) - These were all consumer-reported events and not medically substantiated. An example of this includes a patient that reported a "burning acid sensation on her pancreas and liver."
- No identifiable subjects (2) - Two reports reported events in numerous subjects (none that were uniquely identified). The first involved a EDS salesman who reported that he knew of a number of people (8 to 38 people) that became ill. The second physician reported five women who developed post-menopausal bleed requiring dissection and curettage.
- Multiple suspect products/concomitant dietary supplements or other suspect products (11) - Eleven subjects were receiving concomitant or other suspect agents that may have caused the event. An example includes one case of respiratory depression confounded by concomitant GBL use. Respiratory depression is a known adverse event associated with the use of GBL.

- **Confounded by underlying disease (3)** – Three cases involved events that appeared to be more consistent with underlying disease. An example includes a consumer with a past medical history of fibrocystic breast disease who was diagnosed with breast cyst during three weeks' use of a EDS.

A summary tabulation of these cases is provided in a table format for your review (Attachment 1).

**B. OVERALL SUMMARY OF PROBABLE OR POSSIBLE CASES ATTRIBUTABLE TO AN EDS (108)**

We summarized 108 cases of adverse events probably or possibly associated with the use of an ephedrine alkaloid-containing dietary supplements by the reported major event category: cardiovascular, central nervous system, gastrointestinal, musculoskeletal, renal, hematological, and miscellaneous adverse events. The breakdown of counts of cases and the association category by body system are:

	CV	CNS	GI	MS	Renal	Hem	Misc	Total
Probable	23	24	5	2	1	0	0	48
Possible	23	17	2	4	1	2	2	59
Total	46	41	7	6	2	4	2	108

The adverse events mostly involved the cardiovascular and central nervous systems and are consistent with the known pharmacological effects of ephedrine alkaloids. The remaining cases were also potentially associated with the use of the EDS, however most of these events are not consistent with the known pharmacological properties of the ephedrine and therefore there is no certainty that the ephedrine alkaloid component of the dietary product was responsible for the events.

Of the 108 cases evaluated, there were nine deaths. The subjects were generally young with ages ranging from six days old to 43 years old. Although there were more reports in females overall, the gender distribution in those individuals that died was more balanced (male-5, female-4). Seven of the deaths were cardiovascular-related deaths (cardiac arrest or sudden cardiac death-5, cerebrovascular accident-2). One was an infant exposed in utero to an EDS who was born prematurely and died on day six of necrotizing enterocolitis, and one consumer died from complications of rhabdomyolysis and multiple organ system failure. Four subjects were exercising at the time of their death. Of the cardiovascular deaths, one had a past medical history of unspecified "heart problems," one had a heart murmur (not thought to be significant), and one had borderline hypertension.

Most consumers appeared to be taking the EDS product "as directed" or without apparent over use of the products. There were five cases that reported greater than the recommended doses (6-12 tablets at one time-4, or 20-25 per day-1). Dosage information was not known in 13 cases and possibly estimated in several of the death cases. Although these products may contain certain warnings for high-risk individuals, they are promoted as products that help improve the health

and well being of an individual. Many of these products actually suggest the use of the product in conjunction with an exercise and diet program.

A summary tabulation of the 108 evaluable cases by ARMS number is provided in a table format for your review (Attachment 2). They are also provided in a line-listing format (including a brief summary) by body system (Attachments 3 through 5).

### C. CARDIOVASCULAR ADVERSE EVENT REPORTS (46)

Forty-six cases reported cardiovascular events probably (23) or possibly (23) related to EDS product use. The major categories of cardiovascular events included cardiac arrest or sudden cardiac death (7), cerebrovascular events (12), cardiac ischemic events (9), dysrhythmias (9), and hypertensive events (9). Demographic information of all cardiovascular cases is provided below.

#### Demographics

Age in years:	Range 15 to 64 (mean 40, median 39) < 16 (2), 16-65 (41), >65 (0), not reported (3)
Gender:	Male (15), Female (31)
Outcome:	Died (7), Life threatening (9), Hospitalization (29), Required surgery (6), Disability (10), Required intervention (6), Not reported or resolved (3)
Time to Onset:	Ranged 1 dose to > 1 year (not reported-7) ≤ 1 day (7), > 1 day, ≤ 1 week (10), > 1 week, ≤ 1 month (9), > 1 month (13)
Indication:	Weight loss (30), Energy booster or stimulant (4), improve exercise performance (4), not reported (8)
Reporter:	Health care provider (26), consumer or patient (20)

Age did not appear to be an independent risk factor in the cardiovascular cases. The consumers were generally young with ages ranging from 15 to 64 years old. The mean and median ages were 40 years old. All of the events were reported to have occurred during use of EDS; a specific length of drug use was not reported in seven cases. The mean and median length of drug use was 55 days and 14 days, respectively, with a range of one dose to greater than one year. Approximately half of the cases occurred within the first month of use. Overall, there were more reported events in females, however in the death cases, the distribution was more equal between male (4) and female (3).

The serious outcomes included seven deaths all of these from sudden cardiac death, cardiac arrest, or stroke. Twenty-nine subjects required hospitalization, 12 of which required surgery or suffered permanent disability. Many of the more serious events (cardiac arrest and sudden cardiac death, myocardial infarction, stroke and subarachnoid hemorrhage) occurred in those individuals that either reportedly had a previous history or undiagnosed cardiac disease, or those individuals were using the EDS product in conjunction with vigorous exercise and/or dieting. None of the hypertensive and dysrhythmia cases occurred during vigorous exercise, however some did have a previous cardiac history.

Twenty-five different EDS were associated with the cardiovascular events with most reported events occurring in association with Metabolife 356 (13) and Ripped Fuel (5). Most consumers appeared to be taking the recommended doses that appeared on the label. There were three cases that reported greater than the recommended doses (6-12 tablets at one time). Dosage information was not known in six cases and possibly estimated in several of the death cases.

### **Narrative Summaries of Representative Cases**

Several of the very severe cardiovascular cases occurred in young (< 40 years old), otherwise healthy individuals in whom no underlying cardiovascular diseases or other contributing factors could be identified. These six cases are described below.

1. #12483 (1997) A 34-year-old female collapsed during an aerobics class approximately one week after starting Shape-Fast TID. Hospital workup revealed a subarachnoid hemorrhage thought to be secondary to hypertension from ephedra and a "small" anterior MI with subsequent pulmonary edema. There was aneurysm by angiography. She had no pre-existing medical condition and was on no other medications. She had reportedly been doing aerobics and working on a treadmill for several years. She appeared to be improving however, final outcome regarding cardiac and neurological status was not provided. She was still on mechanical ventilation at time of follow up.
2. #12722 (1997) A 21-year-old male suffered sudden cardiovascular collapse following training for wrestling. He had reportedly been wearing "plastic" for several days in order to make weight class and had possibly been taking Thermogenics Plus (duration and dose unknown). Shortly after the paramedics arrived, he went into ventricular fibrillation. He was pronounced dead on arrival in the ER. Toxicology screen was positive for ephedrine and pseudoephedrine. An autopsy was performed and the report suggests that ephedra containing product in conjunction with extreme sweating activities may have contributed to cardiac events and death. He had no past cardiovascular history. His only complaint prior this event was recent muscle weakness and numbness.
3. #12740 (1997) A 31-year-old female was admitted to the hospital with a chief complaint of chest pressure in the chest and nervousness. She had started taking Ripped Fuel (one capsule TID). One day prior to admission, she increased to two capsules TID. She was diagnosed with bigeminy and a short run of ventricular tachycardia. Her past medical history was non-contributory and she was not receiving concomitant medication. She was discharged on atenolol. No further information was provided.
4. #12851 (1998) A 22-year-old male suffered ventricular fibrillation leading to cardiac arrest and anoxic brain injury after consuming Ripped Force Drink during a workout. His past medical history was significant for asthma. His concomitant medication included theophylline, Ventolin inhaler and various other dietary supplements. His serum theophylline level on admission was 11mcg/ml (WNL). Testosterone levels were within normal limits. His best friend stated that he exercised regularly six days per week and estimated his use of Ripped Force between 1 to 3 bottles (532mL) (three times per week). He had a prolonged

hospitalization and at the time of follow up, he was being treated at a rehabilitation hospital. Other medications might have been contributing factors to these events.

#12980 (1998) A 39-year-old male suffered a hemorrhagic stroke during a workout, 1.5 hours after consuming Ultimate Orange 1 to 1.5 scoops. The report did indicate the length of therapy (i.e., after first dose or chronic use). His past medical history was significant for gastroesophageal reflux. He was on concomitant multivitamins, creatine, vitamins A and E, and Prilosec as needed. He was unaware that he suffered a stroke until he noticed he lost a shoe (sometime after workout). He also noticed right upper and lower extremity numbness. Computerized tomography revealed a left intracranial hemorrhage. Hospital workup was negative for evidence of a vascular anomaly in the region of the hemorrhage. At the time of the report, he was able to resume most of his normal activities but he was unable to return to his previous profession.

6. #13380 (1999) This case involves a poorly documented report of an 18-year-old male who ingested an unknown amount of Ultimate Orange prior to going to a gym. He reportedly noted a headache during a workout and then had a seizure. One reporter stated that he suffered the stroke in his automobile on the way to gym (as opposed to during his workout). He was admitted to an intensive care unit and diagnosed with massive subarachnoid hemorrhage. The neurologist suspected an aneurysm, however, evidence of this was not provided in the case report. He had no significant past medical history and concomitant drugs were not reported. He was declared brain dead, and life support was withdrawn one day after admission.

#### Cardiac Arrest and Sudden Cardiac Death (7)

There are seven cases of cardiac arrest or sudden cardiac death (male-4, female-3). The ages ranged from 15 to 43 years of age, with a mean and median of 28 and 25, respectively. The outcomes associated with these events included six deaths and two hospitalizations with permanent disability. One suffered anoxic brain injury and the other required surgical placement of a defibrillator. The time to onset in the other cases ranged from one day to one year of use of EDS and all cases had reportedly used the product on the day of the event.

Several common characteristics or risk factors were identified in this case series. Potential cardiac risk factors were identified in three cases. Autopsy results revealed coronary atherosclerotic disease in a 38-year-old male. Two cases had a history of heart murmur, which were not felt to be significant. Six subjects were reportedly exercising just prior or during the event. Four were dieting or trying to lose weight prior to the event; two were trying to make weight for wrestling, and two had documented low serum potassium levels (2.7 and 1.7). Two cases that were probably related to use of an EDS because there appeared to be no other contributing factors such as underlying disease or other suspect medication. Five cases were possibly associated with an EDS product, three of which had a past medical history of "heart murmur" (2) and unspecified "heart problems" (1), and two had hypokalemia.

#### 2. Cerebrovascular Events (12)

There are twelve cases of cerebrovascular events associated with an ephedra-containing dietary supplement (male-6, female-6). The reported diagnoses included cerebrovascular accident (CVA)-4, intracerebral hemorrhage-3, subarachnoid hemorrhage (SAH)-2, transient ischemic attack (TIA)-1, pontine infarction-1, and stroke-1. The ages ranged from 18 to 64 years of age, with a mean and median of 43. The time to onset after initiating the ephedra alkaloid-containing product ranged from one day to approximately nine months of use. Four cases developed the cerebrovascular event during or just following vigorous exercise.

The outcomes associated with these events included three deaths, eight hospitalizations, one reported as life threatening, and one required emergency department treatment. Of those hospitalized individuals, eight suffered permanent disability (four requiring surgical intervention).

Seven cases were probably related to use of an EDS because there appeared to be no other contributing factors such as underlying disease or other suspect medication. Five cases were possibly associated with an EDS product, four of which had a past medical history or underlying hypertension as previously discussed, and one had concomitant use of dehydroepiandrosterone (DHEA).

### 3. Cardiac Ischemic Events (9)

Nine cases involved myocardial ischemic events potentially associated with an ephedra-containing product (female-7, male-2). The diagnoses included myocardial infarction (MI)-2, possible MI and cardiomyopathy-1, unstable angina-1, and chest pain-5. The ages ranged from 20 to 59 years of age, with a mean and median of 36. One case of MI and SAH was discussed in the previous section and will not be included in this summary.

Six cases (chest pain-6, unstable angina-1) were probably related to use of an EDS because there appeared to be no other contributing factors such as underlying disease. Three cases were possibly associated with an EDS product, two were diagnosed with coronary artery disease at the time of the event and one had possible MI of uncertain age.

These events were reported to occur from one day to three months of initiating the ephedrine alkaloid-containing product. The outcomes associated with these events included five hospitalizations (two considered life threatening), three requiring emergency room treatment or medical attention from a health care provider, and one outcome unknown.

Two cases were diagnosed with coronary artery disease during their hospitalization for a MI. One case had cardiac catheterization, which was suggestive of coronary vasospasm. At the time of the event she was also receiving concomitant pseudoephedrine in addition to the ephedra-containing product. It is not clear in the other case whether the consumer had superimposed vasospasm in the face of arteriosclerosis.

The most complicated case (#13110) involved a 42-year-old female who presented with seizure-like activity and cardiogenic shock. She underwent cardiac catheterization that revealed normal coronary arteries and an ejection fraction of <15%. ECG showed some evidence of a MI the age

of which could not be determined. She had started an ephedrine alkaloid-containing product one week prior to this event.

#### **4. Hypertensive Events (9)**

Nine cases involved hypertensive events associated with an ephedrine alkaloid-containing product (male-2, female-7). The ages ranged from 22 to 61 years of age, with a mean and median of 47. The hypertensive events were reported to occur from one day to four months of initiating the EDS. The outcomes associated with these events included four events that were considered life threatening (three reported hospital admission), three requiring treatment with an antihypertensive medication, and two that appeared to resolve with only discontinuation of the ephedra-containing product.

The severity of the events varied. Three had a reported diagnosis of hypertensive emergency/crisis and hypertensive urgency. Four might have suffered symptoms associated with the hypertensive event including non-specific ECG changes, motor changes (of right hand and wrist), infarction of tips of toes, and diplopia. Blood pressure measurements were reported in five subjects and ranged from 140-220 and 86 to 120 for systolic and diastolic pressures, respectively. Two had a past medical history of hypertension and one had previously taken antihypertensive medication many years prior to the event. None of the subjects were on an antihypertensive medication at the time of their hypertensive event.

Based on the information provided, there were six cases of hypertension that were probably related to use of an EDS because there appeared to be no other contributing factors such as underlying disease or other suspect medication and the patients recovered or improved after discontinuation of the EDS. Three cases were possibly associated with an EDS product but were somewhat confounded by a past medical history of hypertension.

#### **5. Dysrhythmias (9)**

Nine cases involved rhythm disturbances potentially associated with an ephedra-containing product (male-2, female-7). The reported events included tachycardia (1), "racing heart" (1), "heart beat irregularities" (1), ventricular tachycardia (2), supraventricular tachycardia (1), atrial fibrillation (1), unspecified arrhythmia (1), and arrhythmia with prolonged QT interval (1). The ages ranged from 15 to 53 years of age, with a mean and median of 34. These events were reported to occur from one day to six months of initiating the ephedra alkaloid-containing product. The outcomes associated with these events included six requiring hospitalization or emergency room treatment and two requiring intervention (physician office visit).

Six cases may have had predisposing factors that put them at risk for a dysrhythmia after an EDS product was initiated. Two subjects who developed ventricular tachycardia and supraventricular tachycardia had a past medical history of their respective events. One developed a "racing heart" and sought medical attention, and echocardiography revealed trivial mitral and tricuspid regurgitation. Another subject who developed QT prolongation had a previous syncopal episode one year prior to this event. This subject also took six Metabolife capsules at one time instead of TID and consumed two caffeinated products that day. One developed atrial fibrillation and was

newly diagnosed at the time of his event with cardiomegaly. The sixth subject had been dieting (40 lbs weight loss) and taking Thermolift prior to the onset of unspecified arrhythmias. On admission she had low serum potassium and magnesium levels (K 2.7, Mg 1.6).

Based on the information provided, there was three cases (tachycardia, heart beat irregularities, VT and bigeminy) that were probably related to use of an EDS because there appeared to be no other contributing factors such as underlying disease or other suspect product. Six cases were possibly associated with an EDS product because of possible contributing or predisposing factors as previously discussed.

## D. CENTRAL NERVOUS SYSTEM

### 1. Central Stimulant-Related Events (22)

Twenty-two cases reported central stimulant adverse events probably (19) or possibly (3) related to EDS product use. Most cases were in young female consumers reporting events occurring within one week of use of the products. The events generally involved one or more body system:

CNS - dizziness, nervousness, anxiety, panic attack, blurred vision, wide-eyed, restless sleep or insomnia, shaky, tremors, tingling;  
CV- palpitations, increasing heart beats, feeling of black out;  
Respiratory - shortness of breath.

The events were all within the known pharmacological effects of ephedrine. At least four reported caffeine or synephrine in the product ingredient list that might have contributed to or aggravated the events. Demographics and summary of one case follows.

#### Demographics

Age in years:	Range 15-37
Gender:	Female (16), Male (5), Unknown (1)
Time to onset:	≤ 1 day (4), < 1 week (7), < 1 mo (4), > 1 mo (3), unknown (1)
Outcome:	ER visit or medical attention (8)
Medical history:	None (3), Cardiovascular-heart murmur (1), leaky heart valve (1), hypertension and/or diabetes (2), stress-related seizure (1)
Report source:	Health care provider (4), consumer (17)
Indications:	weight loss, super fat burner or metabolic enhancer for body-building
Reported products:	Ripped Fuel (2), Rip fuel, Rapid fuel, Diet Fuel, Thermodrene, Natural Trim Thermogen, Thermo-Lift, Thermogenics Plus (2) (8% MA Huang=14 mg ephedrine), Thermo-Slim Thermo-Genenis (2), Fit America (2), Metabolift

#12669 (1997) A 21-year-old female used Herbal Balance Quick Weight Loss according to directions. During the second week after increasing doses, she experienced insomnia, heart palpitations, difficulty breathing, hot flashes, sweating and increased heart rate. A technician, at the Quick Weight Loss Center told her, that she must be under a lot of stress and the product was

natural and safe. She discontinued the product after hearing from relatives about the product containing ephedra (Ma Huang). She recovered.

#### 6. Psychiatric-related Event Reports with or without Central Stimulant Effects (11)

Eleven cases had psychiatric events probably (2) or possibly (9) associated with the EDS use. The psychiatric events included euphoria, personality or behavior changes, mood swing, erratic manner, delusional, depression, severe withdrawal symptoms, addiction. The reported events also involved many central stimulant effects such as CV: heart beat increase, chest pain; Nervous: insomnia, shaky, nervousness, tremor.

The psychiatric events appeared to occur in individuals with months of use. Additionally, in four cases, an underlying disease might have been triggered or aggravated by the use of EDS, of which two were hospitalized and treated extensively with psychiatric medications, one was a recovering cocaine addict. Of note, one patient was also diagnosed with having thyroid nodules while experiencing anxiety and panic disorder, symptoms lasted eight weeks after discontinuing two different Ma-Huang-containing products. It is uncertain how the underlying developing of thyroid disorder might have contributed to the reported events. Demographics and a brief summary of four cases follow.

#### Demographics

Age in years:	Range 15 - 41
Gender:	Male (7), Female (4)
Time to onset:	< 1 mo (1), 2 mo (3), 3 mo (2), 6 mo to 1 yr (3), > 1yr (2)
Outcome:	Hospitalized (4), ER or physician visits (3)
Medical history:	Depression (1), recovering cocaine addict (1), borderline manic depressive (1), caffeine sensitive (1)
Indication:	weight loss, body builder, workout enhancer, reducing body fat, stimulant
Report source:	health care provider (3), consumer (8)
Reported products:	Ripped Fuel (3), Metabolife (1), Unspecified ephedra-containing products (2), Metaform Metacuts (1), Calor Slim (1), Diet Health (1), Be Thin Again (1), Infernal Blast (1)

1. #13005 (1998) A 21-year-old male with a history of caffeine sensitivity since 8 years of age, reported personality change, nervousness, loss of memory, euphoria, depression and insomnia diagnosed as bipolar disorder after 2 to 3 weeks use of Ripped Fuel.
2. #13072 (1998) A 15-year-old female was hospitalized for two months after one month use of Calor Slim for erratic manner, heart palpitations, tremor and suicidal behavior. Was diagnosed "cyclothymic disorder" and treated with depakote.
3. #12608 (1997) A male patient (age unknown) reported severe withdrawal symptoms and signs of depression after discontinuing the use of Ripped Fuel for 1½ yrs.
4. #12837 (1998) A 31-year-old male recovering cocaine addict took 20-25 tablets daily within a month of starting ephedra-Ma Huang. Became manic, tense, aggressive, addictive and starting using cocaine again and committing crimes.

## 5. Seizure Cases (8)

There are eight cases that involved seizure or seizure-like activity potentially associated with the use of an ephedra alkaloid-containing product (male-4, female-4). The ages ranged from 21 to 51 years of age, with a mean and median of 36 and 34, respectively. The time to onset occurred from seven days to intermittent use over several years after initiating the EDS. The outcomes associated with these events included six hospitalizations, one that required intervention (multiple physician visits), and one whose outcome was not reported. Of the six hospitalizations, one was considered life threatening and the other resulted in permanent disability.

Two individuals had a possible underlying seizure disorder. One had not experienced seizure activity for 18 years prior to initiating therapy with the EDS and the other was diagnosed with possible underlying convulsive disorder. Three cases listed concomitant medication or other drugs that potentially confounded or contributed to the development of seizures. One had taken TheraFlu and Advil four days prior to the event for the flu, however he was not on the medication when the seizure occurred. Another had been receiving Paxil, which is labeled for seizure, however, it was not listed as a suspect product, so it is assumed that she had been receiving this medication chronically. The third had a history of possible previous marijuana and cocaine use, and he was also on other concomitant dietary supplements (XTC, GHB, Creatine). It is not clear when these products were taken in relation to the event.

Based on the information provided, two were probably related to use of an EDS because there appeared to be no other contributing factors such as underlying disease or other suspect medications and they recovered after discontinuation of the EDS product. Six cases were possibly associated with an EDS product. Possible contributing factors include possible underlying seizure disorder (2), hypoglycemia and multiple concomitant products (1), and concomitant or suspect medication (2). Two cases lacked medical documentation (medical history, concomitant medications) to make a clear association.

## E. GASTROINTESTINAL EVENTS

Seven cases reported gastrointestinal events. Three had necrotizing enterocolitis (NEC) (1), pancreatitis (1), or hepatitis (1) resulting in one death and two hospitalizations. Four mentioned gastrointestinal symptoms associated with the use of the ephedrine alkaloid-containing multi-ingredient products. GERD was diagnosed in one case after 17 days of use, however, GERD improved after Prilosec was added, so it is not clear if discontinuation of the EDS alone resulted in improvement of the GERD symptoms. The other three cases reported a variety of symptoms to include stomach or abdominal pain or burning, anorexia, stomach "sickness," and "gastrointestinal problems." No serious outcomes were reported. The time to onset or duration of EDS products use was reported in six patients ranging from one week to nine months. The case involving an infant with NEC is described below.

#12594 (1997) An infant female was born at 34 weeks gestation to a 32-year-old that had consumed Ripped Fuel throughout her pregnancy. The infant was diagnosed with NEC on day three of life and underwent surgery at five days old. Surgical findings consisted of a completely necrotic colon and her small bowel was entirely necrotic except for six inches of jejunum. She

died at six days of age. The mother had a positive smoking history during pregnancy but denied ETOH or illicit drug use. The neonatologist felt that the EDS possibly reduced blood flow to the intestine and might have contributed to the pathogenesis of NEC.

The hepatitis and pancreatitis cases appeared to be temporally related to Metabolife use with symptoms occurring within 2-8 weeks of initiating the product and symptoms quickly subsiding with discontinuation. Neither patient had past medical history, underlying disease, or other contributing factors such as concomitant or other suspect products.

In summary, five cases (GI symptoms-3, hepatitis-1, pancreatitis-1) were probably related to use of an EDS because there appeared to be no other contributing factors such as underlying disease or other suspect medications and the subjects recovered after discontinuation of the EDS product. Two cases were possibly associated with an EDS product. Possible contributing factors include prematurity of the infant that developed NEC.

#### **F. MUSCULOSKELETAL EVENTS (6)**

Six cases involved musculoskeletal events, rhabdomyolysis (2), myopathy (1), and three characterized as muscle cramps, muscle/joint pain, or transient loss of muscle control in neck, arms, and hands. Ages ranged from 15 to 47 years old, with a mean and median of 34. All cases appeared to be temporally associated with the use of an ephedrine alkaloid-containing product, however, two were also receiving numerous other dietary supplements. The time to onset was reported in four cases and ranged from one dose to two to three months of EDS product use.

One case of rhabdomyolysis was fatal. The other rhabdomyolysis and the myopathy cases resulted in hospitalization and intensive care treatment. One developed myopathy following the use of 12 products for unknown times. This individual continued to decline despite stopping the products; three to four months later she required mechanical ventilation. The remaining subjects recovered.

Predisposing factors for the rhabdomyolysis could include hypokalemia, which occurred in both patients. The fatal case had also been dieting several weeks prior and was exercising (running) at the time he collapsed. It was not clear if the rhabdomyolysis was secondary to the hypokalemia or the result of an ingredient in the dietary product. There have been published case reports of hypokalemia and rhabdomyolysis associated with the use of inhaled beta agonists.<sup>1-4</sup>

In summary, two cases of muscle cramps were probably related to the use of an EDS because the patient improved with discontinuation in one case and there were no other contributing factors reported. Four cases were possibly associated with an EDS product. Possible contributing factors included hypokalemia in two that developed rhabdomyolysis, and multiple dietary supplement use in the other that developed myopathy. One cases lacked medical documentation (medical history, concomitant medications) or dechallenge information to make a clear association.

## G. RENAL EVENTS (2)

There were two cases involving adverse events of the renal system. The first involved acute renal failure (ARF) with diabetes insipidus (DI) in a 22-year-old female who developed ARF with nephrogenic DI approximately one month possibly associated with the use of PhenSafe. She had also been taking Advil 800mg per day, however, acute interstitial nephritis and glomerulonephritis were ruled out. She had discontinued the PhenSafe approximately two weeks prior to admission. Renal function reportedly recovered. The labeling for PhenSafe contains an ingredient called 'Sida Cordifolia' which is thought to contain ephedra alkaloid. The nephrologist thought that the combination of this ingredient with licorice (another ingredient in PhenSafe) could cause chemical changes similar to lithium. Although there was a good temporal relationship with the product, implication of the ephedra alkaloid-like substance as the causative agent could not be determined.

The second case involved a 54-year-old male who developed urinary retention probably related to the use of Herbalife diet plan. His symptoms progressively worsened and he was referred to an urologist. He was scheduled for a Uroflow and cystoscopy workup, however, his symptoms improved upon discontinuation of the product. Urinary retention is a known side effect of ephedrine. The onset of his symptoms coincided with the initiation of therapy with the dietary supplement. Although he required intervention from an urologist, the outcome of this did not appear to be serious.

## H. HEMATOLOGICAL EVENTS

There were four cases involving hematological events including thrombocytopenia (2) and nose bleeding (2) associated with the use of ephedra-containing DS. The ages ranged from 36 to 50 years old and all were reported in females. All cases appeared to be temporally associated with the use of an ephedrine alkaloid-containing product, however the sequence of events (nose bleed, vision problems, and pain) in one case was not well described. Consumers were also receiving numerous other dietary supplements. The time to onset was reported in three cases and ranged from 3.5 weeks to approximately three months of EDS product use. It is uncertain how ephedrine alkaloid played a role in these cases. The outcome of two cases appeared to be fairly serious and they are summarized below.

1. # 13381(1999) One 41-year-old female used Natural Trim for weight loss. After 3.5 weeks, she experienced a petechial rash over her hands, face, and back and was found to have a platelet count of 2000. She took no other medications and had no contributory medical history. She was treated with tapering doses of prednisone; the platelet count rebounded rapidly and remained normal after discontinuation of prednisone. A hematologist made the diagnosis of "drug-induced ITP" suspecting an immunological etiology from the multiple components of the product, Thermogenic Natural Trim. It contains bladderwrack, goldenrod leaf, parsley leaf, Uva Urso leaf, ephedra sinica, comsilk pistils, hathorn berries, fumitory herb, cascara sagrada bark, licorice root, chromium and many other ingredients.

2. #12906(1997) A 36-year-old female reported severe nose bleeding after 2 ½ months use of AMP II Pro and Liqua Thin with caffeine. She was sent to ER and undergone emergency surgery to stop the hemorrhaging. The consumer used the product according to direction for weight loss. No medical records or CBC counts were available to document the etiology of bleeding.

## **I. MISCELLANEOUS EVENTS (2)**

The last two cases could not be characterized in any of the above organ systems. Both events appeared to be temporally associated with the use of the EDS product, however there is no certainty that the ephedrine alkaloid component was responsible for the reported events. They are summarized below.

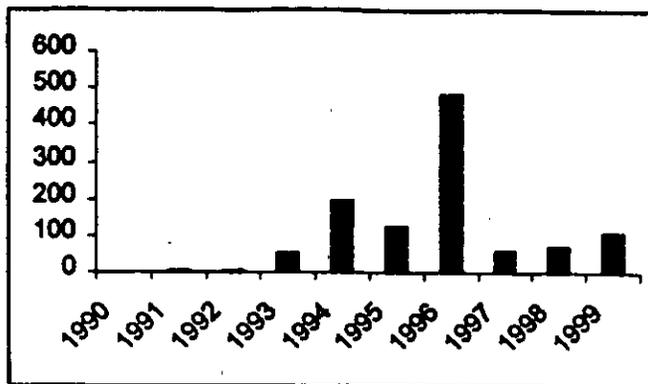
1. #13041 (1998) A 62-year-old female experienced symptoms of swollen face and ankle plus an 8 lb weight gain after one month use of Metabolife. Medical conditions included hypertension, chronic migraine, irritable bowel, and UTIs. No peripheral edema or other abnormalities was noted. Symptoms subsided two weeks after stopping the use per doctor's advice. Potentially allergic reactions to any of the EDS ingredients occurred in this patient with multiple underlying medical conditions.
2. #13266 (1998) A 19-year-old male was found unconscious in bathroom floor. He used "Hydroxycut" for about three months and had become extremely thirsty and urinated frequently. He was in a coma for ten days and diagnosed with diabetic ketoacidosis related encephalopathy, pancreatitis, hepatitis, acute renal failure, rhabdomyolysis, GI bleeding, hypokalemia. Etiology was not determined in the available records, but mother did relate that there was some family history of diabetes. Hydroxycut listed ingredients as hydroxagen 2000 mg (1000 mg hydroxycitric acid), Ma Huang extract 334 mg, guarana extract (caffeine), willow bark extract, carnitine and chromium picolinate. It appeared that the patient suffered severe dehydration resulting in DKA and multi-organ failure.

## **II. SUMMARY INFORMATION OF ALL CFSAN REPORTS (1176)**

We compressed all available data files from CFSAN and eliminated duplicates by using ARMS identification number, which resulted in a total of 1164 reports in case summary tabulation format. Because 139 case reports were reviewed in details, they contained more of the following demographics in each report: case number, report date and year, age, gender, dose, duration, adverse event or body system, hospitalization, received health care provider, product name, ingredients, manufacturer name or source of reports. The remaining 1025 reports in tabulations contained only some of the above demographics, and, specifically, dose and duration of use, or source of report information were not generally available. Nevertheless, for completeness, we included the missing data fields in the following analyses to reflect the actual data.

**A. Report year distribution**

1990-	1
1991-	8
1992-	8
1993-	54
1994-	196
1995-	128
1996-	486
1997-	63
1998-	71
1999-	111



**B. Age in years**

<16	34 (2.9%)
16-65	571 (49.1%)
>65	20 (1.7%)
Missing	539 (46.3%)

**C. Gender**

Female	809 (69.5%)
Male	307 (26.4%)
Missing	48 (4.1%)

**D. Duration of EDS use**

< 1 day	72 (6.2%)
< 1 week	110 (9.5%)
< 1 month	124 (10.7%)
> 1 month	239 (20.5%)
Missing	619 (53.2%)

**E. Outcome**

Deaths	65 (5.6%) (included death term as one of the events)
Received health care	403 (34.6%)
Report year	Mostly in 1994 (124, 27.7%), 1996 (105, 23.4%)

**F. Most reported events**

Palpitations	164	Weakness	34
Dizziness (exc vertigo)	152	Convulsions NOS	33
Heart rate increased	137	Vomiting NOS	32
Headache NOS	107	Diarrhea NOS	31
Nausea	94	Feeling jittery	30

Insomnia NEC	87	Myocardial infarction	30
Chest pain	79	Sweating increased	30
Nervousness	71	Syncope	30
Dyspnoea NOS	65	Paraesthesia NEC	28
Hypertension NOS	57	Abdominal pain NOS	26
Hypoesthesia	47	Depression NEC	25
Euphoric mood	40	Dermatitis NOS	25
Tremor NEC	36	Fatigue	25
Cerebrovascular accident NOS	35	Feeling abnormal	22
Tachycardia	35	Amnesia NEC	20
Anxiety NEC	34		

#### G. Most reported EDS products

Nature's Formula 1	179
Metabolife	72
Ripped Fuel	69
Thermojetics	51
AMP II Pro Drops, E'Ola	28
Natural Trim	27
Trichromaleane	27
Unspecified ephedra product	26
Shape-Fast	20

#### H. 448 Hospitalization or Receiving Health Care Reports

There were 448 (38.5% of all) reports flagged with either hospitalization or received health care. The demographics are:

Age in years: <16 (16), 16-65 (209), >65 (8), unknown (215)  
 Gender: Female (206), Male (100), Unknown (142)  
 Duration: < 1 day (36), < 1 week (55), < 1 month (83), > 1 month (176),  
 Unknown (98)  
 Events: Cardiovascular (118), Nervous (94)  
 Report year: 1991 (1), 1992 (3), 1993 (26), 1994 (124), 1995 (74), 1996 (105),  
 1997 (27), 1998 (54), 1999 (19)

#### I. 34 Pediatric (<16 years old) Reports

Age in years: 0-1 (3), 2 (5), 3-12 (10), 13-15 (13), unknown (1)  
 Gender: Female (23), Male (9), unknown (2)  
 Report year: 1993 (1), 1994 (2), 1995 (1), 1996 (18), 1997 (5), 1998 (4)  
 Duration: <1 day (5), < 1 week (2), < 1 month (2), > 1 month (9),  
 Unknown (6)  
 Events: Cardiovascular (2), Nervous (7)  
 Outcome: Deaths (3), hospitalized (16), received health care (15)

Due to limited tabulated case information, the circumstances of using EDS were unknown in this population. In the three deaths, two listed age as 0 (one as premature baby with necrotizing enterocolitis), and one 15 year old had no events listed. Of the 16 that had hospitalization flagged, two had no event information and the remaining listed the following events:

- 0-1 yo (3)- unexplained death, dizziness & epistaxis, heart rate increased & nervousness
- 2 yo (5)- behavior changes, palpitations, seizure, anxiety
- 3 yo (1)- psychiatric & hypoglycemia, drug dependence
- 4 yo (1)- chest pain
- 5 yo (1)- dizziness
- 15 yo (3)-palpitations, abnormal behavior, unexplained death

The most reported products were Ripped Fuel (9), Metabolife (5), and Thermogetics (3).

#### **J. 65 Death Reports**

There were a total of 65 deaths. Forty-one were reported between 1/93 to 2/97 (1993-1, 1994-9, 1995-6, 1996-24, 1997-1). Fifteen were reported between 6/97 and 3/99 and the actual case reports have been reviewed in the earlier sections. Nine were more recently reported between 3/99 and 11/99. One 6-day-old infant had necrotizing enterocolitis. The remaining 64 were in age range of 15-61 years old (mean 36) and the genders were female (20), male (32), and unknown (13).

Summary of 41 tabulated case information indicated that 31 had no causes/events listed. Ten listed the following events: aneurysm, heart attack (2), unconsciousness, stroke (3), hyponatremia, heart arrest, or hyperthermia. Products included unspecified EDS (12), Nature's Nutrition Formula One (9), Ripped Fuel (2), Thermogertics (2), Cybergetics (2), Slim & Trim, Natural Trim, Chromoslim, Quick Shot, New Image Plus, and First Course.

The recently reported nine deaths had the following reported events: heat stroke, ruptured aorta, intracerebral hemorrhage, heart attack or massive coronary events, or unknown (4). Reported products included Metabolife (3), Ripped Fuel (2), Thermodrene, Thermojetics, and Hydroxycut.

#### **K. 89 Most Recent Reports Information Between 3/31/99 and 11/3/99**

These 89 were identified from one data file and had report dates after CFSAN's assessment of the 139 reports. There were 9 deaths. The demographics are:

- Age: 17 (4), 17-64 (70), >64 (4), unknown (11)
- Gender: Female (57), Male (27), unknown (5)
- Events: Dizziness (11), nausea (9), palpitation (9), convulsion (7), headache (7), chest pain (6), CVA (4), MI (4)
- Products: Metabolife (44), Hydroxycut (4), Ripped Fuel (4)

Four reports involved 16-year-old males but none were in children under the age of 16. The listed events in the four 16 year olds were stroke, collapse, hyperactivity, and amnesia.

## **CONCLUSION**

Overall summary evaluation of all the information provided by CFSAN follows:

- EDS products mostly with multiple ingredients were used for purpose of weight loss, fat burner, bodybuilding, metabolic enhancer or central stimulant. Generally, daily consumption was according to labeled direction or instruction.
- Of those containing information on gender, majority of the reports involved young female adults, but deaths occurred more equally between male and female.
- Cardiovascular and nervous systems adverse events constituted most of the events in the 108 probable or possible case reports and the 1164 summary tabulated reports.
- Many cases occurred in young consumers with no apparent underlying medical condition or disease. The more serious events, cardiac arrest, sudden death, myocardial infarction, stroke or CVA, seizure and psychiatric disorder occurred in those individuals that reportedly had either a previous history or undiagnosed disease.
- Seven of the 9 deaths were cardiovascular-related (cardiac arrest or sudden cardiac death-5, cerebrovascular accident-2) and three had past cardiac history.
- The pattern of the overall 1164 reports was similar to the 108 probable and possible cases in age, gender, duration, adverse events and outcomes.
- The 89 recently dated reports (4/99-11/99) in tabulations had a similar pattern including 9 deaths.

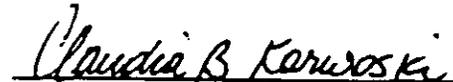
**In conclusion**, our quantitative evaluation of the 139 case reports and 1164 tabulated summary findings from 1990 to 11/3/1999 associated with ephedrine alkaloid-containing dietary supplements indicates that the majority involved cardiovascular and nervous system events. Most of the adverse events in 139 reviewed reports were possibly related to the use of ephedrine alkaloid-containing products. Generally, these reports described a young population using EDS for weight loss and other related indications. Many consumers did not have any apparent underlying risk factors contributing to the adverse events, but certain serious events or outcomes appeared to have occurred in those that had a history of underlying medical conditions or previously undiagnosed diseases.

However, the majority of the EDS products contained other herbal or chemical ingredients as well as ephedrine alkaloid. This has contributed to the difficulties in assessing the direct association of the adverse events to the EDS products in most of the reports. Additionally, 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 EDS product uses. The availability of additional information, including product market or usage data, would be useful to further characterize the potential risks associated with the use of these products.

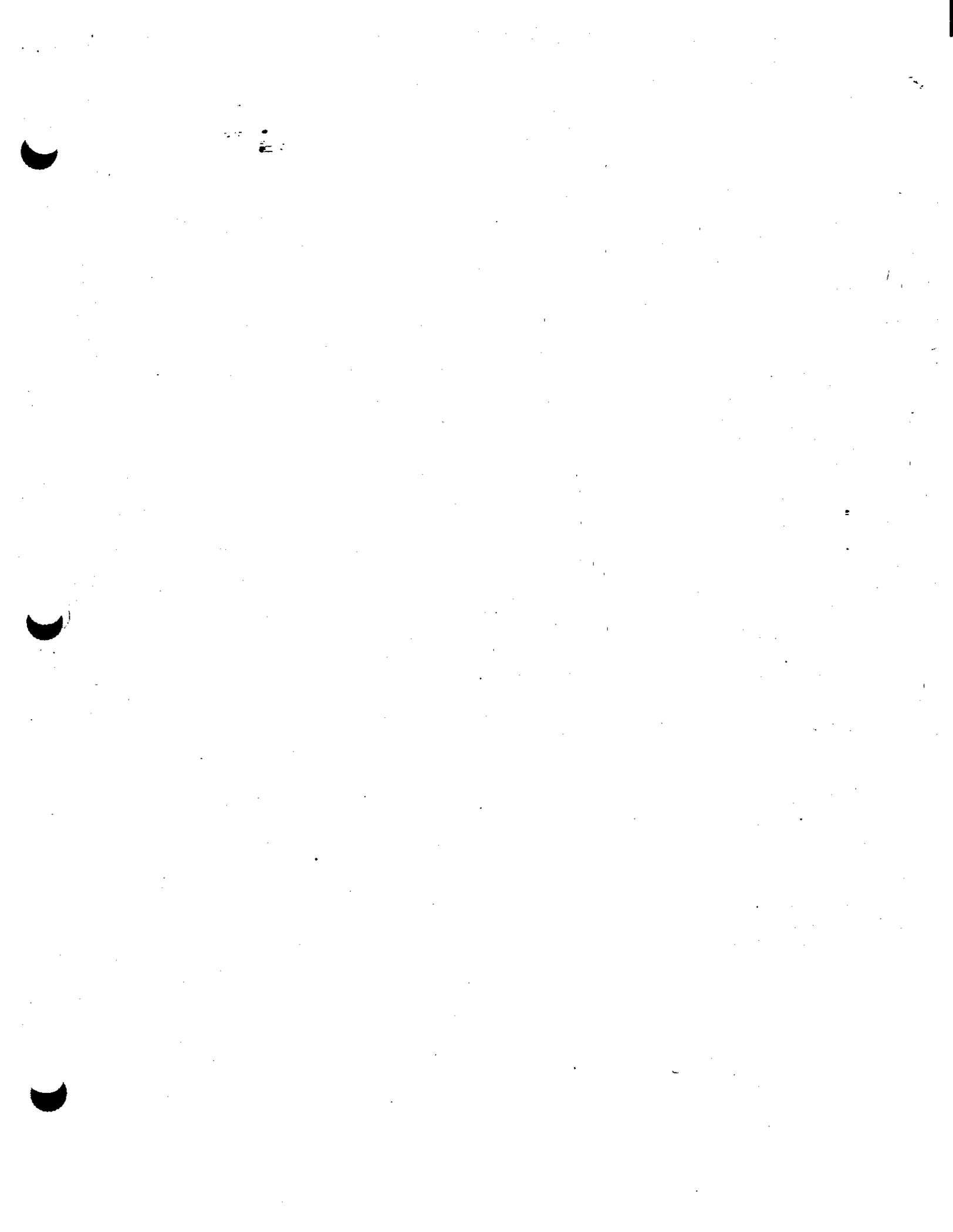
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Cc:  
HFD-1 Woodcock/Lumpkin  
HFD-430 Honig/Trontell/Chen/Karwoski/Guinn  
12/27/1999, 1/2/2000



**ATC (MUSC) CARDIOVASCULAR**

Case #	DOB	Sex	Height	Weight	Event	Diagnosis	Time to Event	Medications	Activities	Comments	Outcome
12485	87	M	38	170	Cardiac arrest	1 yr	Ripped Fuel			Collapsed and died after taking product, striking coffee and consuming a morning bag. Cause of death: acute myocardial infarction, due to atherosclerotic cardiovascular disease, years. Toxicology: epinephrine 0.11 mcg/ml	Died
12772	87	M	21	170	CV collapse, cardiac arrest, tachycardia	NR	Thermonics Plus			Summarized in document, page 10. Tox 0.04mg/L, pseudophedrine 0.02mg/L, other products: cyclobenzaprine, caffeine, lisdexine, naproxen, sulicylate	Died
12843	88	F	15	110	sudden death	post 7-10 days	Ripped Fuel			She collapsed while playing soccer. She had apparently taken 2-4 fuel day. The events was described as seizure type activity, hypocalcemia (2.7), acute respiratory distress, elevated CPK 37K, cerebral hypoxia, limb ischemia. Autopsy revealed cardiac scarring and capillaries in stomach contents. She was declared brain dead and died 3 days later.	Died
12851	88	M	22	170	MI cardiac arrest, anoxic encephalopathy	NR	Ripped Fuel			Experienced Vfib cardiac arrest during workout. Consumed product prior to workout - usually worked out 6 d/wk.	hosp. DS
13021	88	M	43	170	MI with sudden cardiac death	7 mos	Ripped Fuel			Early on included initially, frequent urination/changes in sleeping pattern, wt loss. Collapsed after going to dinner with family. CPR initiated, in Vfib when EMT arrived, arystole in ER, never regained consciousness.	Died
13031	88	F	28	110	cardiac arrest	1 day	Herbals Thermonics Original Green			Approx. 1 hr after initial use, heart "racing". - 7 hr later had cardiac arrest while playing softball with ventricular fibrillation. No etiology found for Vfib on cardiac cath. Defibrillator implanted.	hosp. surgery
13088	88	F	37	110	sudden cardiac death hypocalcemia	1 wk	Metabolite 356			Sudden death, was dying 8 mo postpartum. Autopsy: cardiac arrhythmia due to profound hypocalcemia (1.8) due to electrolyte imbalance secondary to dialysis. One day prior to sudden death had 60 shery anterior pelvic pain and of being lightheaded. Husband stated that pt had probably been taking the product for - 1 wk.	Died

**ATC (MUSC) CARDIOVASCULAR**

Case #	DOB	Sex	Height	Weight	Event	Diagnosis	Time to Event	Medications	Activities	Comments	Outcome
12480	87	F	64	170	MI CVA	NR	Shape Fuel			no risk factors	none
12483	87	F	34	110	SAH, and MI	1 wk	Shape-Fuel & Shape-Fuel Plus			Summarized in document, page 10.	negative
12487	87	M	28	110	stroke	9 mos	Ultimate Nutrition Products			Woke up after late workout and collapsed. Medical records not provided only copies of deposition.	hosp. possible DS
12713	87	F	64	170	central intracerebral hemorrhage	2 mos	Fit America			experienced L.CVA, started on heparin and der. minor intracerebral bleed, also in AIB which converted to NSR prior to discharge.	hosp. surgery DS
12733	87	M	47	170	intracerebral hemorrhage	3-4 wk	Purple Blast			Found unresponsive in bed w/ paralysis. BP 180/110. CT: R basal ganglia hemorrhage.	hosp. DS
12851	88	F	43	110	intracerebral hemorrhage	4-6 mos	Metabolite 356			R basal ganglia hemorrhage w/ intraventricular extension, requiring V-P shunt. In coma for 4 wks. Has conf cognitive impairments. Hypertension difficult to control during hospitalization, question of renal artery stenosis.	hosp. surgery DS
12858	88	F	41	110	positive infarctions	1 mo	Diet-Phen			Recurrent positive infarctions, w/ MRI showing progression of peduncular suggested as chv vasculitis, vascular spasm, and later thrombosis. Final dx was basilar artery vasculitis with basilar artery thrombosis resulting in recurrent positive and brain stem stroke events. Reported to have died secondary to "blood vessel in the brain bursting".	hosp. DS later reported to have died

**Admitted Cardiovascular (continued)**

MRN	DOB	Sex	Race	Admission Date	Discharge Date	Diagnosis	Procedure	Location	Comments	Medications	Other
1200	88	M	White	11/15/01	11/15/01	Intracerebral hemorrhage	Ultimate Orange	Hosp, DB	Developed R sided numbness during workout, 1.5 hr after using product. CT(Angiogram) revealed intracerebral hemorrhage, but no aneurysms. Persisting deficit.	creatinine, multivitamin VIA, VRE, Phososec pm	negative
1302	88	F	White	1 day		TIA	Metabolic 358	ER	New onset TIA one day after starting product. MCP attribution to product. Underlying health conditions and on multiple medications	Symfrel, carbocystin Prozac, Robaxin Phobic, Anapax NSAIDs, pain meds	hypothyroidism, GERD DJO depression, anorexia
1308	88	F	White	9 mos		Stroke	Total Control	Hosp, DB	Used product for ~ 8-9 mo until 2 d prior to stroke. Had stopped pro because of "weakness in legs", leg weakness & difficulty in walking. Seen in ER without definitive Dx. That evening was in hot tub. ~ 1.5 hr later noted L-sided weakness. Seen in ER & admitted. Dx: lacunar stroke (MCA), (R-L) related to small vessel disease. Hypertensive at time of admission 185/92 (previously noted to be non-hypertensive). Dx with hypercholesterolemia (212) and hypertension.	none	obesity recurrent numbness of fingers & hands w/o id cause
1309	88	M	White	NR		subarachnoid and intraventricular hemorrhage	Ultimate Orange	Died	He reportedly ingested an unknown amount of product prior to going to the gym. On the drive over, he experienced a seizure. Neurologist note suggested SAH and ICH was probably from an aneurysm. The patient had no brain stem reflexes and it was decided to withdraw care.	NR	NR
1319	88	M	White	2 wks		stroke	Ultimate Orange	Hosp, surgery DB	Collapsed while running on a treadmill. Severe headache persisting (different from typical migraines) and complete left-sided paralysis at hospital. CT unremarkable. Labs: AST 48, T Bil 2.4 and K 3.3. Transiently required feeding on left side, but subsequently suffered massive stroke to R brain, with total L hemiplegia. Emergent MRI and MR angiography chr complete occlusion of R middle cerebral artery, w/ early infarction also noted in R putamen and caudate. Multiple brain surges to control swelling and pressure prior to remove necrotic tissue. VP shunt placed during the last brain surgery. Rocky course (coma, pneumonia, ventilator dependent), but eventually transferred to rehab hospital.	dehydroepiandrosterone (DHEA), Naproxen (for migraines)	migraines
<b>Admitted Cardiovascular - Exits</b>											
12432	87	M	White	1 mo		ant. MI	Ormetin Powder Tea	Hosp, surgery	Cardiac cath: severe 3 vessel disease (70-90% stenosis) w/ CABG(3).	Captopril	HTN, CRF, high cholesterol, metastatic stroke, CAD
12832	88	M	White	1 d		chest pain	Tricium Loro-4	NR	poorly documented, itchy head, nausea, events	NR	NR
12880	88	F	White	5 days		chest pain, SOB	Chiesse Phen-ON	ER	ECG and CXR performed but results not known. Treated with Advair and discharged	NR	NR
13008	88	F	White	2 days		acute MI	Herbals Thermolytics Original Green	LT, hosp	Started product 1 day before hospitalized w/ EKG changes chr acute inferior wall MI. On day of event took product as directed in AM. Also took 2 Sudafed(30 mg) in AM, and 2 more at 3 PM in hospital given thrombolytic therapy and St improved. Cardiac cath indicative of presumed R coronary artery spasm and some coronary dx.	Sudafed	obesity, GERD, gastritis, knee and back surge
13110	88	F	White	1 wk		cardiomyopathy, post MI (myocysteam)	EZ Film Tablets	Hosp R	Onset HA, dizziness and radiating chest pain, and tonic clonic seizures ~ 1 wk after starting product BP 150/100. Extensive w/ in hospital: negative CT and LP, drug screen positive for amphetamine. Cardiac cath: rt coronary, but markedly depressed cardiac ejection fraction <10%. Other w/ for cardiomyopathy negative. Hosp course chr resp failure, rhabdo. Gradually recovered. Follow up echo showed much improvement with only mild hypertrophy and normal LV function.	Alimta	obesity refractive for cardiac risk factors or other significant illness

**Aluminum Sulfate Tablets (continued)**

Case No.	Date	Age	Sex	Product	Duration	Site	Signs/Symptoms	Course	Diagnosis	Comments
13228	88	38	F	Melabothol 356	3 mos	ER	chest pain			Started taking product 6/68. By 8/68 did not feel well and experienced pleuritic chest pain, w/ pain down L arm. CO2, ECG and labs in ER w/ T1 symptomatically and released. D/C product on MD recommendation in Oct and 8x improved. Re-started the product in mid-Dec and experienced 8x which included joint pain. D/C product and 8x have resolved. Also on Propylthiouracil for hyperthyroidism (Graves Disease) and has been evaluated for anti-cardioid syndrome assoc w/ miscarriages. ANA and ACA positive while on product. Thers decreased when off product.
13414	88	18	F	Melabothol 356	2 wks	RI	chest pain			19 yr F used product for 2 wks when experienced chest pain, pounding heart, dizziness, and was sweaty and jittery. Over-the-counter took to MD, where EXG showed T wave inversion in III only. Sx resolved 3-4 d. Noted to be also consuming caffeinated beverages.
13463	89	62	F	Melabothol 356	1 day	LT, hosp	unstable angina			Took 1 tab before lunch and became jittery. Took an additional tablet before dinner. ~11 PM experienced sharp pain in chest and L arm. Did not take additional product the next day, but experienced more chest pain ~3 PM. Called MD, then went to ER where was kept overnight. EKG, stress test. Dx unstable angina. No epinephrine → epinephrine. Normal stress test 2 mo prior to event.
13503	89	20	M	unspecified EDS	NR	hosp	possible seizure, SOB, chest pain			During intercourse he experienced SOB and CP. Pt became unresponsive, reflexes and complete. HR 110, resp 20, BP 148/72. A1 hosp HR 117, BP 180/102. Observed overnight. Cardiac wks negative. Test was negative.
<b>ADVERSE REACTIONS</b>										
12813	87	45	F	Thermogenics Plus	NR	LT	severe HTN			Hypertensive emergency, BP reported as 240/180, no previous Hx HTN. Positive discharge
12878	88	22	M	Ripped Fuel	1 day	RL, LT	HTN, tachycardia			Pt presented to the student health clinic with a cc of racing heart and inability to sleep during the night. He had taken 6-7 tablets in 18 hours to stay awake. His pulse was 120, BP 140/104. He was given valium
12882	88	NR	F	Melabothol Nutrition Center	5 days	NR	increased BP			poorly documented
12878	88	65	M	Melabothol 356	several wks	hosp, RI	severe HTN infarction lips of nose			Severe HTN with microvascular changes in lower extremity. Partially recovered after dx of Melabothol BP on admission 192/06, not sure what baseline is.
12978	88	61	F	Melabothol 356	3 wks	RI	HTN, tachycardia			BP 180/108, HR 100. Treated with Procardia. Not clear if she was still taking the medication at the time of the visit. On subsequent visit was RI for MI, underwent CABG (cannot attribute to product bc she was off ~1 wk) 1.5 mo prior to MI)
13167	88	45	F	Melabothol 356	5 days	LT, hosp	hypertensive crisis, non-specific ECG changes			Took 2 doses of product and presented to ER with headache and high BP. Hospitalized, by 220/120. BP returned to normal after stopping product. Also Dx w/ hypothyroidism
13203	88	46	F	Melabothol 356	2 mos	LT, hosp	hypertensive emergency			Took products because of mild depression and wanted to lose weight. Admitted 11/13/98 for dyspnea, fever 102 F, and BP 200/130. Extensive work-up essentially negative (CT, MRI, cultures, labs). Normal BP in April 1999.
13341	88	48	F	Melabothol Melabothol	3 days	RI	HTN w/ motor changes			Took product ~3 d, and experienced "extreme hypertension". Stopped product. Next morning experienced loss of motor function of R hand and wrist. Originally thought to be pinched nerve, but BP in ER was 130/104. CT scan stated to reveal no signs of stroke. Treated with Zoc. Cardiflon has improved, but BP remained elevated for several days. PE in 11/98 was normal. BP was 120/82.
13438	88	65	F	Melabothol 356	4 mo	received	HTN heart pounding			Developed HTN and pounding heart (baseline 115/65 up to 155/95). BP returned to normal after stopping product.

**Atypical Cardiovascular Cases (Continued)**

Case #	DOB	Sex	Age	Presenting Complaint	History	Physical Exam	ECG	Investigations	Diagnosis	Management	Outcome
12572	97	NR	f	Stickers	1 d	tachycardia	hoop	poorly documented	NR	obesity	
12630	97	32	f	Diet Fuel, X-mid, Zolam	6 mo	Heart murmur, heart block	R	She underwent echocardiography which showed "MVA" mitral and bicuspid aortic valve.	NR	negative	
12698	97	63	f	Herbals Therapeutic Original Galen	NR	heart beat irregularities	R	sought medical attention. Other nutritional products: Bulga, Caliboss, original yellow, Herbal Loss, Protein Drink.	Promethin, Percocet	NR	
12740	97	31	f	Ripped Fuel	1 wk	VT, bigeminy	hoop	Hospitalized for chest pressure & nervousness. In bigeminy w/ short duration of VT which resolved 2 d.	none listed	negative	
12944	98	47	m	Fen-Chi Herbal	6 wks	ventricular tachycardia	hoop	PI was admitted to ER with sustained VT with spontaneous conversion. He has had similar problems over the previous 18 mos and was treated up by cardio with the ultimate conclusion that his VT was non-inducible. The onset of this event occurred while he was loading horses. With straining he apparently had a sudden onset of palpitations. He was admitted again with negative ECG, serum K 3.1. Discharged after 3 days.	HGTZ, tylenol 3	HTN, family hb HD, VT each 18 mos prior	
13168	98	21	f	Thermodil	2 mos	arrhythmias	hoop	poorly documented. Patient took product for approximately 2 months, had 40 lbs and admitted to ER with cardiac arrhythmias. Eventually required pacemaker. Serum K 2.7, Mg 1.6	NR	OTC cold medication	
13229	98	15	f	Metaboli	6 wks	arrhythmia w/ prolonged QT	LT, hoop	16 yo developed chest pain after taking product. Missed directions and took 6 capsules at once in am. Also had consumed 2 double-shot lattes. EKG showed unusual T-waves and prolonged QT interval (corrected up to 800msec). No evidence of ischemia. Resolved w/ 24 hr.	Prozac	negative	7 Depression, syncope episode 1 Long QT syndrome
13325	99	38	m	Metaboli 358	7.3 days	ABs	hoop	Obese M has taking product as directed on package for weight loss when diet scale onset of A-As w/ fast ventricular response (200). Was admitted and treated (Lanoxin, Coverit Cardiom drip). Leds all w/ 2D echo unremarkable. Die on Accupril, Lanoxin, Rhythmol. PI stopped Rhythmol and Cardiom in 3/99. Fx exam in 6/99 showed pt to be in HRS.	Accupril Timoptic Cardium vitamins Aurbien pm hs	obesity HTN glaucoma asthma, poor cardiomyopathy	
13408	99	38	f	Metaboli 358	2 wks	SVT	LT, ER	PI drank popai and took capsule of Metaboli for breakfast. Within 30 min she had an episode of SVT. She arrived in the ER with HR 190, BP 154/116. Was subsequently again seen in ER for SVT (3 months later) reportedly not on Metaboli.	NR	SVT, enlarged thyroid	



**Aluminum Chloride Solution Case Collection**

Case #	Date	Sex	Age	Weight	Height	Product	Indication	Response	Adverse Effects	Notes	Outcome	
13548	89	27	f	Medicall 358				received	stimulant effects	Used product for ~ 3 wks for weight loss-energy booster. Each time she used product developed heart palpitations ~ 1-1.5 hr later. Parent also noted mood swings. She stopped after stopping product. Did not see HCP.	none reported	
<b>247-012 (12) Cases</b>												
11918	97	38	f	Be Thin Again			throughout course 1995-2008	NR	personality changes, depression, and others	Insomnia, addiction, depressed, mood swings, heart racing and skipping beats.	NR	
12464	97	NR	m	Ripped Fuel			NR	NR	stomach, addiction withdrawal syndrome	poorly documented	NR	
12529	97	41	m	Infernal Blast			2 mo	LT, DS	Chest pain, withdrawal syndrome	Alongly stopped product after using 30K. Experienced withdrawal, including severe panic type attacks w/ chest pain (during attack had auto accident)	NR	
12608	97	nr	m	Ripped Fuel			1.5 yrs	NR	severe withdrawal	Severe withdrawal Sx, including depression and caffeine fatigue on stopping product.	lethargic	
12609	97	28	f	Diet Health			8 mos	hoop, DS	panic disorder	Developed insomnia, irritability, extreme wt loss, thyroid nodules, and severe panic dis. Hoop for 8 mos. Had 5 weeks of rest.	Synthroid	
12637	98	31	m	unspecified EDS			1 mo	NR	addicted	receiving cocaine whilst took 20-25 tablets daily within a month of starting ephedra-like Huang. Became manic, lachry, aggressive, addictive and starting using cocaine again and committing crimes.	escalating doses	
12660	98	29	m	unspecified EDS			? Sev mos	NR	behavior change	Described as leaving his wife, excessive alcohol, job performance problems, excessive wt loss, stopped attending church.	NR	
13005	98	21	m	Ripped Fuel			2-3 wks	R	mood disorder	Severe personality changes attributed by psychiatrist to supplement. Sx resolved on stopping. Noted to be "caffeine sensitive." Symptoms included nervousness, wt loss, loss of memory, inability to reason, euphoria, depression	NR	
13072	98	16	f	Color Slim			1 mo	hoop	stomach behavior palpitations, subtidal behavior	Hospitalized for 2 months after 1 month use of Color Slim for erratic manner, heart palpitations, tremor and suicidal behavior. Was diagnosed "bipolar disorder" and treated with depotolol.	NR	
13228	98	38	f	Medicall 358			14 weeks	NR	behavior change, aggression, addiction	Described as marlet rifle and dissociation. Denial of addiction to EDS, insomnia, memory loss, agitated, aggressive	NR	
13370	99	19	m	Medicall Medicall			3 mos	hoop	psychotic	19 yrs M had used product on and off for 3 months at recommended dose for energy during exercise. After using ~ 2 mos, experienced sleeplessness, which progressed to include agitation, shortness of breath, rapid heart rate and hallucinations. Was hospitalized several times for extreme agitation and psychotic behavior. Dx: bipolar disorder, manic, with psychotic features, most likely triggered by "mefedrin".	Colored Viagra Medicall	

**Atacombi (007) Central Nervous System Drugs (continued)**

ATC Code	Product	Class	Subclass	Drug	Strength	Form	Quantity	Indication	Adverse Reaction	Outcome	Notes
11912	Dial Fuel	NR		seizure							NR
11919	Neural Trim	NR		seizure							NR
12027	unspecified EDS	7 days		seizure							Depression
12040	Excitation	1 mo		seizure							self-carried tablets
12075	Dial Fuel	11 mos		seizure							starting spells for 1 year
13001	Melabolite 358	NR		seizure							negative
13408	Ripped Fuel	-3yr		seizure, toxic encephalopathy							headaches
13344	Hydroxyd	6 mos		seizure							usual hospital repair

Patient was taking product for 2 years and experienced a number of symptoms to include HA, tremor, muscle fasciculation, myoclonus, cognitive deficits, GI problems, and dysfunction. Patient self diagnosed osteoporosis-myopia syndrome or additive photorefractive Dystrophia Syndrome

poorly documented

She had no previous seizure disorder. There were no medical records follow up information recorded for consultation.

Positive discharge. She was discharged from the hospital on phenytoin for 7-10 days. She did a use of Escalation and phenytoin and had no recurrent seizures.

Began experiencing rising spells after starting product to enhance exercise performance. After seizure witnessed by mother, was transported to ER and admitted. Negative head CT. Discharged on Dilantin. Outpatient evaluation - 1 set later: MRI - within normal limits and EEG - abnormal, due an underlying convulsive disorder.

Near onset seizure after ingesting product. Negative diagnostic workup for seizures. Discharged after 48h with no recurrence of seizures. Unable to get further FU from MD.

Took Ripped Fuel for stress on and off for 3 years. Complained of headaches for 3 days prior to event, Tx with Tylenol. On day of event, had taken 2 caps of Ripped Fuel at 7 PM. Seized while talking on phone with wife. In the ER experienced grand mal seizure. Work up in ER negative drug screen (Ephedrine not specifically evaluated), K 3.2, and low blood glucose. He was treated (D50 and Advren) and released. Had additional seizure next day and was hospitalized. Condition progressed to status epilepticus, refractory to treatment. Placed in drug-induced coma - prolonged hospitalization. Outcome not known at time of table-up, but condition grave.

21 yo M had been using product - 8 mo to build muscle and reduce body fat. Apparently had not been feeling well on day of AE (note in chart of 7 URO). Had also been noted by friends as being short-tempered and not acting like himself. Had gone on a day old trip, but had not eaten much secondary to not feeling well. On the bus home, he experienced a seizure-like episode, and was combative. Taken to the ER for presumed drug overdose where he was sedated, intubated and admitted. Admit labs: K of 3.2. Tox screen was negative for any drugs of abuse (does not indicate that epinephrine was tested). Family noted that pt esp headaches for 1 week after discharge (7 related to withdrawal).

Therapy 4 d PTE

headaches

recurrence use of marijuana and cocaine, otherwise healthy, weakness, Creatine, XTC, and GH8

**Anticholinergic Overdoses**

Case #	DOB	Sex	Product	Duration	Presenting Complaint	History	Course	Outcome	Notes
1284	97	64	F	Ripped Fuel	9 mo	premature birth respiratory emphysema	None temporarily died	NR	At school age she was born at 34 weeks gestation to a 32-year-old mother. She had a congenitally dilated fundus throughout her pregnancy. The infant was diagnosed with NEC on day 3 of life and underwent surgery at 8 days old. Surgical findings consisted of a completely necrotic colon and two small bowel segments entirely necrotic except for six inches of jejunum. She died at 8 days of age. The necrotoxicologist felt that the EDS product reduced blood flow to the intestine and might have contributed to the pathogenesis of NEC.
1277	97	NR	M	Natural Herbal Energizer	1 wk	stomach pain	NR	NR	Used product for approximately one week when his stomach began to hurt. He discontinued product and felt better.
1280	98	30	M	Metabolic 358	17 days	GERD	NR	NR	Took product - 2 wk, when dev chest pain (ix as GERD). Rx resolved on stopping (started on Protonix).
13010	98	34	M	Ripped Fuel	6 mo	Abdominal pain withdrewn on stopping	RE	NR	Used product 6 mo and developed stomach upset, deorientation and loss of appetite. Endoscopy revealed mild hernia, distal mild enteritis w/ erosions. MD felt DR contributed to illness. After product stopped, GI gradually resolved, but pt developed headache, mild depression, and anxiety lasting for 3-4 wk. MD suggested that product contained caffeine and may have contributed to GI symptoms.
13044	98	66	F	Metabolic 358	2 wks	hepatitis	hoop	NR	Hospitalized for chest pain. Labs: increased SGOT, BIL 2.1, increase alk phos, normal EKG and cardiac enz. Negative viral screen. LFTs improved after stopping product
13187	98	68	F	Metabolic 358	2.5 mos	acute pancreatitis	hoop	NR	- 1 mo after re-starting product, experienced general nervous Sx, bloating, and abd pain, indigestion and nausea. Admitted to hospital 10/12/98 US of gallbladder and common bile duct normal. WBC 13.3, amylase 1238, AST 60, normal GGTP and Triglycerides. Resolved with supportive care. Used a variable dose < recommendation; was off prod - 12 d, then re-started, but at lower dose
13277	98	32	M	Metabolic 358	NR	GI symptoms	NR	NR	HA, upset stomach

**Muscle/Neurological Cases**

Case #	DOB	Sex	Product	Duration	Presenting Complaint	History	Course	Outcome	Notes
11916	97	47	F	Per-Form Perfect Herbal Formula, Root-to-Health, Diverse Natural Tea	2 mo	progressive muscle weakness, dysphagia, diarrhea, hyponatremia, proteinuria, pulmonary edema	hoop	NR	Patient initially presented with progressive muscle weakness, dysphagia, and diarrhea. She underwent GI biopsies and was treated empirically C. diff. Symptoms progressed and she was worked up by neurology with muscle biopsy which showed an active neurotoxic myopathy. During her hospitalization she was diagnosed with hyponatremia. Also found to have a CPK 13,000. Immunological, infectious, and metabolic workup were negative.
12477	97	15	M	Up Year Gas	1 dose	MS	NR	NR	lost muscle control of neck, arms, hands
12616	98	34	F	Thermoff	NR	muscle cramps	resolved	NR	Patient started taking Thermoff. She was also on Demerol for endometriosis. Started having muscle cramps. Stopped both and cramps resolved. Restarted Demerol w/o recurrence
12659	98	34	M	Herbal Tea, Thermoflex original green	3 wks	myoglobinuria	hoop, died	NR	multiple products

**ADVERSE REACTIONS (continued)**

Case No.	Age	Sex	Product	Onset	Signs	Symptoms	Course	Outcome
13085	88	31	f	HELIP.	2-3 mo	hypotension thrombocytopenia	LT, hosp	Presented to ER with 2-3 d Hx of generalized weakness, K 1.8, increased UFTs, positive urine myoglobin, CK - 2k U/L. Dx with rhabdomyolysis. She initiated EDG dietary product HELIP. for 2-3 months prior to the event. She did not have a history of diabetic use or fasting prior to the event. Positive dechallenge.
13264	47	m	M	Diet Fuel	NR	Muscle and joint pain	R	47 yo M started esp muscle pain, followed by joint pain, which started after using product. On no other meds at time. Saw HCP - normal labs, incl UFTs. SSRs abated after stopping product.

**SKIN REACTIONS**

12853	54	m	M	Herbals Therapies original green	2 mos	difficulty breathing	R	Unhappy (slow flow, inability to empty bladder), began - 2-3 wk after starting product. Pt developed urinary retention 1 month after starting Herbals diet plan. His symptoms progressively worsened and he was referred to an urologist. He was scheduled for a Uroflow and cystoscopy workup. However, he Sr received - 1 wk after stopping product.
13202	22	f	F	PhenSafe	1 mo	ARF and DI	hosp	Presented w/ RLQ pain, increased thirst, polydipsia, polyuria and w/ increasing BUN/Cr. Hospitalized. Dx nephrotic disease (nephritis with acute renal failure. Last dose of product was 1 d PTA. Slowly received after - 8 wk, with no treatment.

**HEMATOLOGIC REACTIONS**

13208	98	38	f	Amg II Pro Drops	2.5 mo	hemorrhage	hosp	bleeding from nose and mouth, required surgery.
13328	99	60	f	Tyzane	NR	Nose bleed	NR	NR
13365	99	49	f	Metabolic Nutrition System	3 mo	anemia thrombocytopenia	required intervention, recovered	Used product line with multiple components for ~6 mo and developed anemia (hgb 12.1) and thrombocytopenia (pl 85K). Sr received over 2.5 mo after stopping product.
13381	99	41	f	NaturalTRM	3.5 wks	thrombocytopenia	LT, RI, recovered	Developed facial ecchymoses - 3.5 wk after starting product. Stopped the supplement on medical advice. Platelet count of 200 on CBC obtained the next day. Three days later, she was evaluated by a specialist, who noted the ecchymoses and found her platelet count on repeat to be 10,000. Dx: Drug-induced thrombocytopenia. Improved with treatment for ITP on a prednisone taper. Six weeks later (3 wks after prednisone dx) platelet count remained at 300K.

**MISCELLANEOUS REACTIONS**

13041	98	62	f	Metabolic 358	2 wks	anxiety and face edema	recovered	swollen ankles and face, 8 lb wt gain. Resolved 2 wks after d/c'd.
13266	98	19	m	Hydroxyol	NR	DKA, acute pancreatitis, metab acidosis, rhabdo	LT, hosp, surgery, Dx	Dx polyuria and polydipsia - 1 wk prior to event. Found unresponsive to ER hypotensive & unresponsive to painful stimuli, with minimal respiratory drive. Assessment: hypotensive, DKA, respiratory insufficiency. Labs also indicated hypotension, elevated glucose, BUN, Cr, WBC and ketonuria. Multiple complications: esophagitis with GI bleed, renal failure, anemia and hypocalcemia. Later transferred to rehab hospital for con't care (total - 2 mo following initial event). His discharge summary does not note diabetes (glycohemoglobin and Hgb A1c, both wmf), only med. was Metoprol. He con'ts to receive outpatient care for neurological deficits.









**ADVERSE DRUG REACTIONS**

Case No.	Yr	Sex	Age	Product	Reaction	Onset	Duration	Outcome	Notes	Ref
12572	97	M	41	Stactura	tachycardia	14		CV		NR
12588	97	M	41	Infrared Blast	Chest pain, withdrawal syndrome	2 mo		psych-CNS		NR
12594	97	M	41	Ripped Fuel	premature birth recurrently enterocolitis	9 mo		GI		NR
12608	97	M	41	Ripped Fuel	severe withdrawal	1.5 yrs		psych-CNS		NR
12609	97	M	41	Diet Health	panic disorder	8 mo		psych-CNS		NR
12613	97	M	46	Thermogenics Plus	severe HTN	NR		CV		NR
12620	97	M	32	Diet Fuel, X-rated, telomo	Heart murmur, "heart racing"	6 mo		CV		NR
12688	97	M	20	Herbal Balance	stimulant effects	2 wks		central stimulant-CNS		NR
12696	97	F	16	Herbolic 355	numbness, numbness, ataxia	NR		central stimulant-CNS		NR
12698	97	F	53	Herbolic Original	heart beat irregularities	NR		CV		NR
12713	97	F	64	FI America	central infarct, intracerebral hemorrhage	2 mo		CV		NR
12717	97	M	NR	Natural Herbal	stomach pain	1 wk		GI		NR
12722	97	M	21	Thermogenics Plus	CV collapse, cardiac arrest, rhabdomyolysis	NR		CV		NR
12733	97	M	47	Purple Blast	intracerebral hemorrhage	3-4 wk		CV		NR
12740	97	F	31	Ripped Fuel	VT, lighthead	1 wk		CV		NR
12761	97	F	15	unsupplied ED8	rapid heart beat, nausea	NR		central stimulant-CNS		NR
12816	98	F	34	Thermo LR	muscle cramps	NR		MS		NR
12832	98	M	NR	Truckers Love-4	chest pain	1 d		CV		NR
12837	98	M	31	unsupplied ED8	edematous	~ 1 mo		psych-CNS		NR
12843	98	F	15	Ripped Fuel	sudden death	post 7-10 days		CV		NR
12844	98	M	47	Fen-Chi Herbal	ventricular tachycardia	6 wks		CV		NR
12851	98	M	22	Ripped Force	rib cardiac arrest arrest encephalopathy	NR		CV		NR
12859	98	M	34	Herbolic Thermogenics original	rhabdomyolysis	3 wks		MS		NR
12860	98	M	25	unsupplied ED8	behavior change	7 Sev mo		psych-CNS		NR

**Abacrimon 2121EVALUABLE CASES (Continued)**

Case No.	Sex	Age	Product	Onset	Signs	Diagnosis	Course	Path	Report	Outcome
12611	M	43	Metaboils 358	4-6 mos	intracerebral hemorrhage	CV	hoop, surgery, DS	not significant	HCP	Y, no more than 1 pill qd, for 8-9 mo
12676	M	22	Ripped Fuel	1 day	HTN, tachycardia	CV	LT, RI	negative	HCP	6-7 tablets, one time
12680	M	30	Metaboils 358	17 days	GERD	GI	NR	NR	consumer	3 tab qd x 2 wk
12686	M	17	Ripped Fuel	1 day	acute stimulant effects	central stimulant-CNS	RI	R lines segment strain	consumer	took 4 caps in am on empty stomach, at 11 am took additional cap had used 90 caps in 30-45 d PTE
12687	M	32	Thermajex	1 day	recurrent stimulant effects	central stimulant-CNS	resolved	none	HCP	1 cap po qd on 3 separate days
12688	F	41	Diet-Phen	1 mo	parosmia infections	CV	hoop, DS, Died	negative w/ visual disturbances, borderline LDM	consumer	Y, 1-2 tabs in am, 1 in pm for 2 mo PTE
12696	F	36	Amp II Pro Drops	2.5 mo	hemorrhage	hem	hoop	None	consumer	Y (not to exceed 30 drops/day) x 2.5 mo
12697	F	61	unspecified EDS	7 days	seizure	seizure-CNS	hoop	Depression	HCP	NR
12699	M	54	Herbalife Thermojex original	2 mos	difficulty swallowing	renal	RI	High cholesterol	consumer	Y, 2 tabs bid x 1 mo, then 3 tabs bid, used 2 mo
12942	M	NR	Metabolic Nutrition	5 days	increased BP	CV	NR	HTN, obesity, DM	HCP	as directed
12946	F	37	Castor	5 days	stimulant effects	central stimulant-CNS	resolved	negative	HCP	1 po bid 11/19-20th
12948	F	44	Excitation	1 mo	seizure	seizure-CNS	LT, hoop	slp cervical fusion	consumer	1 qd
12950	F	28	Chinese Phen-Cl	5 days	chest pain, SOB	CV	ER	NR	consumer	2 BID
12974	NR	NR	unspecified EDS	2 d	hypertension	central stimulant-CNS	RI, recovered	NR	consumer	NR
12975	M	23	Diet Fuel	11 mos	seizure	seizure-CNS	hoop	starting spells for 1 year	consumer	began taking 1 bid, then gradually increased this to 3 bid
12978	M	66	Metaboils 358	several wks	severe HTN infracture tips of toes	CV	hoop	HTN obesity anxiety negative	HCP	Y, AEG: 8 pills x 6 wk, but MPH: 1 qd
12979	F	61	Metaboils 358	3 wks	HTN, tachycardia	CV	RI	negative	HCP	Y, week one 1-2 tabs qd, then inc dose to 4-5/day (no more than 2 tabs at one time) had taken higher dose no more than 3-4 d. Total duration of product use - 3 weeks
13000	M	39	Ultimate Orange	1.5 hr	intracerebral hemorrhage	CV	hoop, DS	negative	HCP	Y, 1 scoop po before exercise, duration unknown
13001	M	61	Metaboils 358	NR	seizure	seizure-CNS	hoop	negative	HCP	7 Dose, freq & duration unknown
13005	M	21	Ripped Fuel	2-3 wks	mood disorder	psych-CNS	RI	negative	consumer	Y, 2 caps bid x 3 wk (AEG), 2-3 wk (MPH)
13009	F	39	Herbalife Thermojex original	2 days	acute MI	CV	LT, hoop	obesity, GERD, gastritis, loose and back surgery	HCP/Consumer	Y, 2 bid x 1 d, 2 in am
13070	M	34	Ripped Fuel	6 mo	Abdominal pain subdiaphragmatic ascites	GI	RI	at over weight, otherwise unremarkable	HCP	Y, 4-4 capsid x 6 mo
13071	M	43	Ripped Fuel	7 mos	MI with sudden cardiac death	CV	Dead	heart murmur at birth, post op valve, irregular heart beat-10 yrs earlier	consumer	not sure, wife believed he took at least 6 caps per day (Y, 2 tabs bid x 7 mos)

**Atenolol 25mg Tablets (continued)**

Case #	Age	Sex	Product	Dose	Onset	Signs/Symptoms	Diagnosis	History	Concomitant	GI	Response	Disposition
13071	66	F	Metabolite 356 Therapeutic original	1 day		cardiac arrest	CV	Heart, surgery	Herbals: raspberry program	Heart murmur in child	consumer	Y, 3 tabs x 2 - 8 hr apart for 1 day only wt loss
13041	62	F	Metabolite 356	2 wks		ankle and face edema	renal	recovered	Regitin, Enox, Tenormin, Pernitin, V/E and C, Ornidol Dua D, MM	IBO, HTN	consumer	Y, 2 caps bid x 1 mo wt loss
13044	66	F	Metabolite 356	2 wks		hepatitis	GI	hoop	Tranzione Prozac (x 6 y) Estron	depression cholelithiasis hypertension	HCP	Y, 1 cap BID wk wt loss
13062	66	F	Metabolite 356	1 day		TIA	CV	ER	Syntrod, enyulysh Prozac, Robax Pibotic, Anapax NSAIDs, pain med, anti/peribiotic	hypertension, GERD DUO depression, Bromocriptine	consumer	Y, 2 caps am & pm, duration appears to be one day energy booster
13072	66	F	Oral 50m			blurred behavior palpitations, sublethal behavior	psych-CNS	hoop	None	None	consumer	NR, - 2-3 mo duration wt loss
13086	66	F	H.E.L.P.	2-3 mo		hypotension dizziness headache	MS	LT, hoop	Lodine	allergic rhinitis Isoniazid, I.P.T.A		Y, 1 bid x 3 mo (can take up to 2 bid) wt loss
13098	66	F	Metabolite 356	1 wk		sudden cardiac death hypotension	CV	dead	none recently Phen Fen (previous yr)	Obesity 6 mo post perium, dizziness	consumer	Y, husband states had typically taken 3 tablets x 1 wk wt loss
13110	66	F	EZ 75m Tablets	1 wk		cardiomyopathy, post MI dizziness	CV	hoop	vitamins	obesity	HCP	Y, 1 tab bid x 7 d wt loss
13146	66	F	Ripped Fuel	< 2 days		central stimulant	central stimulant-CNS	NR	none	heart murmur, MVP	consumer	2 pills bid, duration < 1 wk wt loss and body building
13166	66	F	Thermax	2 mos		arrhythmia	CV	hoop	NR	OTC cold medication	HCP	NR
13167	66	F	Metabolite 356	5 days		hypertensive crisis, non-specific ECG changes	CV	LT, hoop	Estradiol	GI/epg hypertension, obesity, previous TIA, BP read in early 1980s, Hepatitis B-	HCP	1 tab bid x 5 d vs 2 tabs bid x 3 d wt loss
13167	66	F	Metabolite 356	2.5 mos		acute pancreatitis	GI	hoop	minocycline [1996] Pernitin [1993]	nausea	HCP	Y, used variable doses < recommended, was off product for 12 day, had restarted at lower dose wt loss
13202	66	F	PhenSafe	1 mo		ARF and GI	renal	hoop	Tiphenil Aval (Morph)	obese coronary cyst, otherwise negative	HCP	Y, 3 caps bid x - 3 wk wt loss
13203	66	F	Metabolite 356	2 mos		hypertensive urgency	CV	LT, hoop	St John's wort Aval, ASA	mild depression	HCP	4 Metabolite caps daily in am, and 1 BR which was also x 2 mo wt loss
13229	66	F	Metabolite	6 wks		arrhythmia of prolonged QT	CV	LT, hoop	Prozac	1 Depression, syncope obesity	HCP	N, took 6 caps at once in am x 6 wk wt loss
13238	66	F	Metabolite	14 wks		behavior change	psych-CNS	NR	NR	NR	consumer	Y, 6 tabs x 4 mo wt loss
13256	66	F	Metabolite 356	3 mos		chest pain	CV	ER	Propylthiouracil	hypertension, infarction positive	consumer	2 bid, some days none [see Hq] wt loss
13264	66	M	Dial Fuel	NR		Muscle and joint pain	MS	R	NR	NR	HCP	1-3 caps bid x - 2 mo. NR
13268	66	M	Hydrocod	3 mos		DKA, acute pancreatitis, melib acidosis, chills	renal	LT, hoop surgery, DS	none	negative	HCP	Y, 4 caps bid (morning & afternoon) for - 3 mo wt loss
13271	66	F	Xanax (R/M)	1 day		stimulant effects	central stimulant-CNS	hoop	none	over weight	HCP	Y, 2 caps once wt loss
13272	66	F	Thermax	< 1 wk		dizziness, HR, nervousness	central stimulant-CNS	NR	NR	NR	consumer	2 caps/d energy booster

