

Metabolife International, Inc.

5070 Santa Fe Street

San Diego, CA 92109

(619) 490-5222

April 17, 1998

The Dockets Management Branch
(HFA-305)
Food and Drug Administration
12420 Parklawn Drive, Room 1-23
Rockville, Maryland 20857

Re: Docket No. 98N-0148
March 18, 1998 Federal Register Notice

TO WHOM THIS TOPIC IS OF CONCERN:

I. INTRODUCTION

This information is being provided as a response to the March 18, 1998, Notice which was published in the Federal Register, 63 Fed. Reg. 13258-59. We understand that this comment document will be forwarded, along with information from the Food and Drug Administration ("FDA"), the Drug Enforcement Administration ("DEA"), and other members of the public to the World Health Organization ("WHO") which will, in turn, prepare a Critical Review document for use of the Expert Committee on Drug Dependence. These comments deal only with one of the substances identified in the Notice -- Ephedrine.

Metabolife International, Inc. ("Metabolife") now responds to the above-referenced Notice. Throughout this Response, our use of the term "ephedrine" (unless otherwise noted) means ephedrine as currently used in the U.S. in both OTC drugs and in dietary supplements. But "ephedrine-containing dietary supplements" or similar language always means and includes only naturally occurring ephedrine alkaloids derived from the herb, ma huang, also known as ephedra. When used in dietary supplements, ephedrine is in the form of ephedrine-containing alkaloids. Metabolife's position is that ephedrine should not be added to any of the Schedules of the Convention on Psychotropic Substances. Metabolife urges the WHO, the Expert Committee on Drug Dependence, and the Commission on Narcotic Drugs not to add ephedrine to any of those Schedules.

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Metabolife urges this position because it believes that all the available information demonstrates that (A) ephedrine has traditionally and safely been used for medicinal purposes, and currently is being used safely for both medicinal and health purposes, and (B) that no widespread pattern of abuse of ephedrine exists in the United States or worldwide. For further reasons for our view that ephedrine need not and should not be a controlled substance, please see the Response submitted by the Dietary Supplement Science and Safety Coalition ("the Coalition"), which we support.

II. METABOLIFE AND ITS PRODUCT

[1] Our company is located at 5070 Santa Fe Street, San Diego, California 92109. Our telephone number is 1-619-490-5222.

[2] I am the president of Metabolife and am one of its founders. Metabolife markets and sells dietary supplements throughout the United States. Throughout the balance of these Comments, when I refer to "the Company" or use a pronoun such as "we", "us", or "our", I mean Metabolife. I am also the president of the Dietary Supplement Science and Safety Coalition, which is filing a separate response to the Notice.

[3] Metabolife began its business operations in August of 1995. Metabolife 356 is the Company's dietary supplement product which contains both ephedra and guarana. Metabolife 356 is sold in the form of a tablet. Its conditions of use are a suggested usage of 2 tablets per serving, not to exceed 4 servings daily. Each tablet is formulated to contain 12 mg. of ephedrine alkaloids and 40 mg. of caffeine; therefore, the maximum suggested intake each day is 96 mg. of ephedrine alkaloids and 320 mg. of caffeine. I note that there are between 100-150 mg. of caffeine in the average cup of coffee.

[4] We now sell approximately 60 million tablets per month of Metabolife 356; at 2 tablets per serving (with a maximum of 4 servings per day), this amounts to 30,000,000 servings or, from the perspective of consumers, 30,000,000 "takings" per month. At this rate, 720,000,000 tablets of Metabolife 356 are consumed annually, assuming that all tablets which are sold are actually ingested. Metabolife is purchased and consumed by persons throughout the United States.

[5] We know that Metabolife 356 provides health-related benefits to consumers. Consumers, especially repeat customers, would not buy Metabolife 356 if they did not believe it was providing benefits to them. The benefits which our customers get from Metabolife 356 are (1) effective weight management, including weight loss (2) an overall sense of well-being or feeling good and (3) a sense of empowerment or self-control over their bodies and lives.

III. PRODUCT IS SAFE AND NOT ABUSED

[6] Metabolife has never received one notice from a consumer that any serious adverse health event has occurred because of the ingestion of Metabolife 356. This claims-free history exists notwithstanding the pervasive media attention since early 1994 about dietary supplement products which contain ephedra. (Much of that attention was generated by the FDA and the Texas Department of Health.) Consequently, since there have been no serious adverse reports of any sort, there have been no such reports of overuse or abuse of the product.

[7] Metabolife has comprehensive safety monitoring procedures in place. Each label of each bottle of Metabolife 356 has a telephone number on it; when that number is called, a customer service representative carefully listens to the caller's message, manually records its principal points, and, if that call includes a medical-type complaint, refers it internally to a nurse practitioner for further review and processing. If the complaint appears to present a concern other than one of a temporary, non-serious nature or requests information about the interaction of Metabolife 356 with a prescription or OTC drug, the customer service representative is to recommend that the caller seek professional health assistance immediately. We take the health of our potential and actual customers very seriously.

[8] We have devoted a significant amount of time, energy and money to fulfill our commitment to sell only safe and effective products. Among other things, we have done the following:

(A) We were one of two companies which spent approximately \$200,000 on animal studies in 1994. The herbal compound tested was comprised of ephedra and guarana. This testing was the precursor to the key safety study identified in paragraph [8](C).

(B) In 1997, we engaged the Academy of Clinical, Environmental, Research and Informational Sciences ("ACERIS"), a non-profit, private certification company located in San Francisco, California, to review the ingredients and label of Metabolife 356 from the standpoint of safety. As a result of that review, we received a valuable quality assurance certification from ACERIS. An integral portion of that review process requires ACERIS to review the manufacturing plant of the business which manufactures Metabolife 356. Significantly, the Chemins Company, Inc. of Colorado Springs, the manufacturer of Metabolife 356, already had received an ACERIS GMP certification.

(C) We are funding a portion of a significant human study contracted for by The Ephedra Research Foundation and being carried out at two hospitals which are affiliated with Harvard University Medical School and Columbia University.

(D) We are a charter member of the Coalition. As an active member of the Coalition, we strongly insisted that ACERIS engage top clinical scientists in the United States to carry out our project.

(E) We sponsored a human clinical study on Metabolife 356 at Vanderbilt University Medical Center. The report of that study was issued to us in January of this year. The principal purpose of this study was to determine the efficacy of this product for weight loss.

The conclusions of this study are:

1. Metabolife #356 causes an increase in energy expenditure in normal, moderately obese human subjects which is independent of physical activity.

2. No adverse effects were observed or measured that affected the health of the subjects in the study. In other words, the safety profile of this compound is benign.

(F) We are sponsoring a third human clinical study. This one will be finished later this Spring. It is in progress at St. Luke's Roosevelt Hospital which is affiliated with Columbia University. This is a randomized, double blind, placebo study of approximately 75 subjects; its protocol has been primarily designed to measure the efficacy of a compound which includes ephedra and guarana. Of course, any side effects or adverse events will be reported.

IV. PRODUCT IS NEITHER A DRUG NOR A DRUG PRECURSOR.

[9] The sales statistics presented in paragraph [4] are evidence of both availability on the open market and of the legal, health-related uses of the product. The substantial consumer demand for Metabolife 356, along with the results of the metabolic tests described in paragraph [8] above, demonstrates that this product is purchased solely for a legitimate health purpose: effective weight management. The other benefit which I have identified, "a sense of well being," is a benefit recognized by the U.S. Congress and inserted into Sec. 6 of the Dietary Supplement Health and Education Act ("DSHEA"). Sec. 403(r)(6)(A) of the FDCA provides that a structure-function statement is

permitted to describe "general well-being" from consumption of a nutrient or dietary ingredient. The Congress did not restrict this state of "general well-being" to an ingredient which has caloric value. Consumers often describe this feeling as having increased energy, or simply "feeling good." However, we want to emphasize that feeling good in this context does not mean a "high" from a drug.

[10] Metabolife's ephedrine alkaloid containing product is readily available through several market channels: marketed through advertisements in newspapers and magazines, via radio and T.V. advertisements which include a 1-800 number, and at hundreds of small kiosks (i.e., small business stands or stalls) in consumer shopping malls. There is no "black market" for ephedrine-containing dietary supplement products, because there is no need for this. Ephedrine-containing dietary supplement products are widely available on the open market, and thus not trafficked on the black market.

[11] Ephedrine alkaloids in dietary supplements are not a precursor to amphetamines. As a List 1 chemical, pure ephedrine can be used in manufacturing amphetamines. However, such a scenario with a dietary supplement containing ephedrine alkaloids is highly unlikely because it is chemically impossible or, at least, extremely difficult. A recent study showed that even a professional, legitimate scientific lab trying to make amphetamines from dietary supplements containing ephedrine did not succeed. In order to respond to various U.S. and state governmental requests for information about ephedrine substances, we hired Hauser Laboratory Services and requested that they "attempt to produce methamphetamines from Metabolife #356 using the 'street' method published in The Journal of Forensic Sciences, Vol. 40, No. 4, July 1995." Each tablet contained an average of 13.1 mg. of ephedra alkaloids, with the contents of the 12 bottles of our Metabolife #356 resulting in approximately 1.3 kg of starting material.

The material was extracted into methanol and the extract was reacted with red phosphorus and hydriodic acid for five hours. The resulting mixture was basified and extracted into freon. The freon was then acidified using hydrogen chloride gas. This should have resulted in the production of methamphetamine crystals; however, it formed a black tar like material. The material was tested by Gas Chromatography/Mass Spectroscopy (GC/MS) and found to contain mostly ephedra alkaloids and caffeine; the presence of methamphetamine was not detected.

(Emphasis added.) A copy of the Hauser test results is attached.

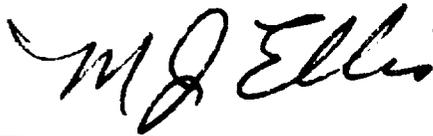
[12] Our consumer statistics, besides showing availability on the open market, also demonstrate the lack of abuse. Our in-house estimates reveal that each consumer who buys Metabolife #356 buys an average of 1.78 bottles per purchase. Each bottle contains 90 tablets. Thus, far from being overused, or leading to overdosing, our ephedrine-containing product is judiciously and moderately used -- as a health aid.

V. CONCLUSION

For these reasons, and for all the reasons cited in the Response in this Docket submitted by the Coalition, ephedrine should not be added to the Convention's schedules of controlled substances. The few cases of overuse of an ephedrine-containing product are isolated incidents, and do not demonstrate any significant or real potential for widespread abuse. In short, there is no medical, psychological, chemical, or legal reason for ephedrine to be recommended as a controlled substance, either nationally or internationally.

Yours very truly,

Metabolife International, Inc.



By: _____

Michael J. Ellis, President

HAUSER®

April 8, 1998
Test Report No. C8-0730
Page 1 of 1

CLIENT: Metabolife International Inc.
5070 Santa Fe Street
San Diego, CA 92109

Attn: Mike Ellis

SAMPLES: One case of Metabolife Dietary Supplement 356 was received March 23, 1998. The label listing the ingredients in this product is attached.

TESTS: It was requested that we attempt to produce methamphetamines from the Metabolife Dietary Supplement using the "street" method published in The Journal of Forensic Sciences, Vol. 40, No. 4, July 1995.

RESULTS: The tablets were initially analyzed for ephedra content by High Performance Liquid Chromatography (HPLC). Each tablet was found to contain 13.1 mg/tablet on average of ephedra alkaloids. The contents of the 12 bottles of Metabolife Dietary Supplement 356 were ground resulting in approximately 1.3 kg of starting material (13.7 g ephedra alkaloids). The material was extracted into methanol and the extract was reacted with red phosphorus and hydriodic acid for five hours. The resulting mixture was basified and extracted into freon. The freon was then acidified using hydrogen chloride gas. This should have resulted in the production of methamphetamine crystals, however it formed a black tar like material. The material was tested by Gas Chromatography/Mass Spectroscopy (GC/MS) and found to contain mostly ephedra alkaloids and caffeine, the presence of methamphetamine was not detected.

CONCLUSION: The procedure described above was performed according to the method published in The Journal of Forensic Sciences, Vol. 40, No 4, July 1995, titled "Ephedra's Role As a Precursor in the Clandestine Manufacture of Methamphetamine" by K.M. Andrews. Based on our analysis, it does not appear that this published method can be used to make methamphetamine from Metabolife's Dietary Supplement 356.

**REPORT WRITTEN
& ANALYSIS PERFORMED BY:**


J. Scott Moore
Technician III

REPORT REVIEWED BY:


Nicole M. Enderle
Chemist

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