UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF NEW YORK

PAUL HARABEDIAN, individually on behalf of himself and all others similarly situated,

Plaintiff,

v.

HAMMER NUTRITION, LTD.,

Defendants.

CV-14 0459

Case No.

WEXLER, J

CLASS ACTION COMPLAINT

JURY TRIAL DEMANDED

LINDSAY, M

Plaintiff, individually and on behalf of all others similarly situated, by his attorneys, alleges the following upon information and belief, except for those allegations pertaining to Plaintiff, which are based on personal knowledge:

NATURE OF ACTION

1. Plaintiff Paul Harabedian ("Plaintiff") brings this action against Hammer Nutrition, Ltd. ("Hammer" or "Defendant") on behalf of himself and a class consisting of all consumers in the State of New York who purchased any of the following Hammer products at any time during the applicable statute of limitations period up to and including the present (the "Class Period"):

a) Appestat capsules

b) Perpetuem powder

(the "Hammer products").

2. Hammer claims to be a leading, high-end dietary supplement manufacturer in the United States. On Hammer's website, its owner, Brian Frank, states:

"Brian Frank's uncompromising commitment to superlative customer service, unlimited free educational resources, and providing the highest quality, *all-natural* products specifically engineered for endurance athletes has allowed him to achieve his goal of helping serious endurance athletes reach their highest level of performance and health, safely and naturally, since 1987." (emphasis added) *See*, http://www.hammernutrition.com/about/experts/.

3. Notwithstanding Mr. Frank's express statements, Hammer has in the past and continues to make material misrepresentations and engage in deceptive business practices in violation of New York law.

4. The Hammer products in question prominently display on the front of the packaging that they are made with "natural ingredients." *See*, **Exhibits A & B.**

5. United States regulatory organizations have clearly delineated between natural ingredients and synthetic ingredients. They have not, however, adopted a formal definition of the term "natural."

6. The FDA, which is charged with regulating dietary supplements, declared in 2012: "From a food science perspective, it is difficult to define a food product that is 'natural' because the food has probably been processed and is no longer the product of the earth. That said, the FDA has not developed a definition for use of the term natural or its derivatives. However, the agency has not objected to the use of the term if the food does not contain added color, artificial flavors, or *synthetic substances*." (emphasis added). *See*, **Exhibit C**. This declaration reiterated and reaffirmed the policy that the FDA articulated in 1993. 58 Fed. Reg. 2302, 2407 (Jan. 6, 1993).

7. On January 6, 2014, the FDA issued a letter to Judges Yvonne G. Rogers and Jeffrey S. White of the United States District Court, Northern District of California and to Judge Kevin McNulty of the District of New Jersey. In essence, the FDA declined the courts' invitation to comment on whether food containing substances derived from genetically modified seeds could be labeled "natural." Notably, the FDA declared: "The agency has, however, stated that its policy regarding the use of the term 'natural' on food labeling means that 'nothing artificial or synthetic (including color additives regardless of source) has been included in, or has been added to, a food that would not normally be expected to be in food." *See*, **Exhibit D**.

8. The FDA has included dietary supplements within the definition of "food." For instance, the FDA explained that:

> The Dietary Supplement Health and Education Act (DSHEA) places dietary supplements in a special category under the general umbrella of "foods," not drugs, and requires that every supplement be labeled a dietary supplement. Because dietary supplements are under the "umbrella" of foods, FDA's Center for Food Safety and Applied Nutrition (CFSAN) is responsible for the agency's oversight of these products. *See*, **Exhibit E.**

9. The Dietary Supplement Health and Education Act provides:

> **Definition of Certain Foods as Dietary Supplements.** Section 201 (21 U.S.C. 321) is amended by adding at the end the following:
>
> "(ff) The term "dietary supplement" -
>
> "(1) means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:
>
> i. "(A) a vitamin;

ii. "(B) a mineral;

iii. "(C) an herb or other botanical;

iv. "(D) an amino acid;

v. "(E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or

vi. "(F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E). *See*, Dietary Supplement Health and Education Act of 1994, Public Law 103-417.

10. In 2013, the USDA issued a Draft Guidance Decision Tree for Classification of Materials as Synthetic or Nonsynthetic (Natural). In accordance with this decision tree, a substance is natural – as opposed to synthetic – if: a) it is manufactured, produced, or extracted from a natural source (i.e. naturally occurring mineral or biological matter); b) it has not undergone a chemical change (i.e. a process whereby a substance is transformed into one or more other distinct substances) so that it is chemically or structurally different than how it naturally occurs in the source material; or c) the chemical change was created by a naturally occurring biological process such as composting, fermentation, or enzymatic digestion or by hearing or burning biological matter. *See*, **Exhibit F**.

11. The term "synthetic" is also defined by federal statute as "a substance that is formulated or manufactured by a chemical process or by a process that chemically changes a substance extracted from naturally occurring plant, animal, or mineral sources, except that such term shall not apply to substances created by naturally occurring biological processes." 7 U.S.C. § 6502 (21).

12. Hammer's claim that its products are made with natural ingredients are false and

misleading. During the class period, Hammer has been misrepresenting to New York consumers that the ingredients found in its products are natural. In fact, Hammer products contain synthetic ingredients, and ingredients that are not even identified on its label.

13. Testing of the Hammer products revealed, *inter alia*, that they do not fit within the USDA's "natural" classification, and the products contain ingredients that would prompt objection by the FDA when used in connection with the term "natural." More specifically, testing revealed that the Hammer products contain synthetic ingredients such as Magnesium stearate; Zinc monomethionine; Chromium polynicotinate; and Choline bitartrate. *See*, **Exhibit G**, Mr. Rigler's Preliminary Expert Report.

14. Magnesium stearate is a white powder synthesized by the reaction of sodium stearate and magnesium sulfate. Magnesium stearate is used as a lubricant for pharmaceutical preparations and as an anti-sticking agent in medical devices. There have been reports that this synthetic ingredient could pose hazards to one's health, specifically suppressing cells in the body that fight off cancer. *See*, **Exhibit H**.

15. In addition, Zinc monomethionine is the combination of metal zinc with amino acid methionine. It is another synthetic compound which is synthesized in large quantities by numerous chemical manufacturers for agricultural feed and animal supplements. Studies concerning this synthetic ingredient reveal that increased consumption can cause prostate cancer. *See*, **Exhibit I**, Leitzmann MF, Stampfer MJ, Wu K, Colditz GA, Willett WC, Giovannucci EL. Zinc supplement use and risk of prostate cancer. *J Natl Cancer Inst*. 2003;95(13):1004-07.

16. Further, Chromium polynicotinate is elemental chromium coupled to more than

one molecule of niacin. Hammer describes this compound as "ChromMate brand of trivalent niacin bound chromium polynicotinate." Chromium polynicotinate is a synthetic compound. *See*, **Exhibit G**.

17. Choline bitartrate is a white powder manufactured by reacting ethylene oxide with trimethylamine in water or in an acid if one of the salts is required. This process can be performed in a batch mode or in a continuous manufacturing process. The precipitated powder is dried and stored. Choline bitartrate is a synthetic compound. *See*, **Exhibit G**.

18. Besides misleading and deceiving consumers that its products are natural when in fact its products contain synthetic ingredients, the Hammer products also contain ingredients that are not even identified on the labeling. For instance, Plaintiff's testing revealed that the Appestat capsules contain caffeine. *See*, **Exhibit G**. Nowhere on its labeling does Appestat identify caffeine as an ingredient, and caffeine is not a "natural flavor" under 21 CFR 101.22. Defendant's failure to identify a potent ingredient like caffeine can create catastrophic health consequences to an end-user who is, for example, sensitive to and/or allergic to caffeine.

19. Apparently, Hammer is notorious for failing to disclose ingredients in its products. For instance, in 2008, three endurance athletes filed suit against Hammer Nutrition, Ltd. in the Orange County Superior Court, California, alleging that their positive drug tests were caused by the use of Hammer Nutrition Enduroly te supplements contaminated with the steroid precursor norandrostenedione. Hammer resolved that matter confidentially prior to trial.

20. Hammer's actions are part of a growing epidemic affecting consumers. According to a recent New York Times article, the supplement industry is "riddled with questionable practices." Moreover, a well-known senior nutritionist from the Center for Science in Public Interest stated that "the problems [with mislabeling] are widespread and that quality

control for many companies, whether through ignorance, incompetence, or dishonesty, is unacceptable." **Exhibit J**.

21. Given that the FDA has a broad mandate and limited resources, the dietary supplement industry is largely unregulated. In the January 6, 2014 FDA letter (**Exhibit D**), Assistant Commissioner Leslie Kux writes "at present, priority food public health and safety matters are largely occupying the limited resources the FDA has to address food matters."

22. Furthermore, the FDA has explained that: "In that FDA has limited resources to analyze the composition of food products, including dietary supplements, it focuses these resources first on public health emergencies and products that may have caused injury or illness. Enforcement priorities then go to products thought to be unsafe or fraudulent or in violation of the law." *See*, **Exhibit E.**

23. Accordingly, dietary supplement manufacturers are held accountable for their false advertising and deceptive practices by way of consumers filing lawsuits and availing themselves of state statutes that have been promulgated to protect consumers.

24. In addition to Hammer misleading and deceiving consumers that its products are natural, and selling products with ingredients not identified on its label, Hammer also misleads and deceives consumers with false claims about the safety and efficacy of the Garcinia Cambogia or hydroxycitric acid contained within its Appestat capsules.

25. On its website and elsewhere, Hammer claims: "Appestat is a stimulant-free appetite control supplement that safely suppresses appetite and increases carbohydrate metabolism, thereby helping to decrease body fat accumulation and weight gain without the use of potentially harmful stimulants. When you start off next season already at ideal weight, you'll be glad you invested a few dollars in Appestat." *See*, **Exhibit K**.

26. In a promotional video featured on its website and elsewhere, Hammer claims that "Appestat works with your body to help gently reduce your appetite" and "when you use Appestat, you've got a healthier, safer approach to weight loss."

27. On its website and elsewhere, Hammer claims:

> **HYDROXYCITRIC ACID (HCA)** may just be one of Nature's most remarkable weight loss nutrients. This active ingredient of the Garcinia Cambogia fruit safely inhibits an enzyme called citrate lyase, which is used in the conversion of carbohydrates into fat. It also gently suppresses appetite and reduces food intake. *See*, **Exhibit K**.

28. Contrary to Hammer's representation, hydroxycitric acid or Garcinia Cambogia does not work as a weight loss nutrient and has been proven to be unsafe.

29. In a Journal of the American Medical Association scholarly article entitled "Garcinia Cambogia (hydroxycitric acid) as a potential antiobesity agent: a randomized controlled trial," Steven Heymsfield, M.D and others evaluated the efficacy of Garcinia Cambogia for body weight and fat mass loss in overweight human subjects. They reported no significant differences in estimated percentage of body fat mass loss between treatment groups, and the fraction of subject weight loss as fat was not influenced by the treatment group. And, they concluded that Garcinia Cambogia failed to produce significant weight loss and fat mass loss beyond that observed with placebo. *See*, **Exhibit L**, Abstract for Garcinia Cambogia (hydroxycitric acid) as a potential antiobesity agent: a randomized controlled trial. Heymsfield SB, Allison DB, Vasselli JR, Pietrobelli A, Greenfield D, Nunez C., JAMA. 1998 Nov 11; 280 (18):1596-600.

30. In 2009, the journal of *Digestive Diseases and Sciences* published Drs. Sammy Saab's and Michael Sim's case report detailing the story of a 28-year old male who reported three weeks of fatigue, dyspnea on exertion, jaundice, and dark urine. The patient had ingested

the recommended dosage of Hydroxycut in order to lose weight. The report concluded, "[t]here is evidence that [] *Garcinia cambogia*...contained in Hydroxycut may be associated with severe and even fatal hepatotoxicity." *See*, **Exhibit M,** Michael Shim and Sammy Saab article: Severe Hepatotoxicity Due to Hydroxycut: A Case Report found in *Digestive Diseases and Sciences* (2009).

31. Defendant has made false claims about the efficacy and safety of its product despite the overwhelming evidence that Garcinia Cambogia or hydroxycitric acid does not work and is unsafe.

32. Hammer's conduct is unacceptable. Hammer misleads and deceives its consumers by labeling its products and falsely advertising to the public that its products are natural, when, in fact, they contain synthetic ingredients. Hammer misleads and deceives its consumers by omitting ingredients from its on-product labeling and advertising. And, Hammer misleads and deceives its consumers by falsely stating and advertising to the public that its products are safe and effective.

JURISDICTION AND VENUE

33. Jurisdiction is proper pursuant to 28 U.S.C. 1332(d)(2). Plaintiff is a citizen of the State of New York, and Defendant is a company organized and existing under the laws of Montana with its principal place of business in Montana. Upon information and belief, the amount in controversy is in excess of $5,000,000, exclusive of interests and costs.

34. This Court has personal jurisdiction over the Defendant because Defendant conducts and transacts business in the State of New York, contracts to supply goods within the State of New York, and supplies goods within the State of New York.

35. Venue is proper because Plaintiff and many Class Members reside in the Eastern

District of New York. Plaintiff purchased the Hammer products in this District. Hammer has, at all relevant times, been doing business in the Eastern District of New York, and throughout the state.

THE PARTIES

36. Plaintiff is a citizen of the State of New York in the County of Suffolk. During the class period, Plaintiff purchased Hammer products at retail stores and/or online in the Eastern District.

37. Plaintiff purchased the Hammer products because he saw the product labeling, product advertising, and read the packaging, which stated, *inter alia*, that they were made with natural ingredients and that they were safe and effective. After purchasing the Hammer products on or about 2012, he consumed them for several months.

38. Plaintiff was shocked and disappointed to learn of Hammer's deceptive marketing practices, specifically that the Hammer products not only contained synthetic ingredients, but they contained caffeine - an ingredient not identified on the label and which is a substance Plaintiff deliberately avoided in his daily dietary regimen. Moreover, Plaintiff was even more concerned to learn of the dangers and ineffectiveness of Appestat capsules.

39. The members of the proposed class ("Class Members") consist of men and women who live in New York and purchased the Hammer products.

40. Defendant Hammer is a corporation organized and existing under the laws of the State of Montana, with its principal place of business at 4952 Whitefish Stage Road in Whitefish, Montana, 59937. Hammer distributes various dietary supplements through retailers and online throughout the country, including New York State.

SUBSTANTIVE ALLEGATIONS

41. Hammer falsely advertises and misrepresents to its consumers, including Plaintiff and Class Members, that Hammer manufactures and sells its products with natural ingredients. This material misrepresentation induced Defendant's consumers, including Plaintiff and Class Members to purchase Defendant's products. Plaintiff and Class Members relied on Defendant's false and misleading misrepresentations.

42. Defendant's statements are false and its practices are deceptive and misleading because, *inter alia*, the Hammer products contain synthetic ingredients.

43. Defendant fails to include caffeine on its Appestat capsule labels and further fails to list this substance in its ingredients, which is a material misrepresentation. This material misrepresentation induced Defendant's consumers, including Plaintiff and Class Members to purchase Appestat capsules. Plaintiff and Class Members relied on Defendant's false and misleading misrepresentations.

44. Defendant's statements are false and its practices are deceptive and misleading because, *inter alia*, the Appestat capsules contain caffeine.

45. Hammer falsely advertises and misrepresents to its consumers, including Plaintiff and Class Members, that its Appestat capsules are safe and effective. This material misrepresentation induced Defendant's consumers, including Plaintiff and Class Members to purchase Appestat capsules. Plaintiff and Class Members relied on Defendant's false and misleading misrepresentations.

46. Defendant's statements are false and its practices are deceptive and misleading because, *inter alia*, the Appestat capsules are demonstrably not safe and effective.

CLASS ALLEGATIONS

47. Plaintiff brings this matter on behalf of himself and those similarly situated. As detailed at length in this complaint, Hammer orchestrated deceptive marketing and labeling practices. Hammer customers were uniformly impacted by and exposed to this misconduct. Accordingly, this Complaint is uniquely situated for class-wide resolution, including injunctive relief.

48. The class is defined as all consumers in the State of New York who purchased any of the below Hammer products at any time during the period within the applicable statute of limitations:

1. Appestat (a product which Hammer claims is made with natural ingredients, when, in fact, the product contains synthetic ingredients. Further, Appestat is unsafe and ineffective and contains caffeine, which is not identified in its advertising, labeling, or within its ingredient list.).
2. Perpetuem (a product which Hammer claims is made with natural ingredients, when, in fact, the product is manufactured with synthetic ingredients).

49. The Class is properly brought and should be maintained as a class action under Rule 23(a), satisfying the class action prerequisites of numerosity, commonality, typicality, and adequacy because:

50. Numerosity: Class Members are so numerous that joinder of all members is impracticable. Plaintiff believes that there are thousands of New York consumers who are Class Members described above who have been damaged by Hammer's deceptive and misleading practices.

51. Common Questions of Fact and Law: The questions of law and fact common to

the Class Members which predominate over any questions which may affect individual Class Members include, but are not limited to:

a) Whether Hammer is responsible for the conduct alleged herein which was uniformly directed at all consumers who purchased its products;

b) Whether Hammer's misconduct set forth in this complaint demonstrates whether Hammer has engaged in unfair, fraudulent, or unlawful business practices with respect to the advertising, marketing, and sale of its products.

c) Whether Hammer made false and/or misleading statements to the Class and the public concerning the content, safety, and efficacy of its products.

d) Whether Hammer's false and misleading statements concerning its products and its concealment of material facts regarding the content, safety, and efficacy of its products were likely to deceive the public.

e) Whether Plaintiff and the Class are entitled to injunctive relief; and

f) Whether Plaintiff and the Class are entitled to money damages under the same causes of action as the other Class Members.

52. Typicality: Plaintiff is a member of the Class. Plaintiff's claims are typical of the claims of each Class Member, in that, every member of the Class was susceptible to the same deceptive, misleading conduct and purchased the Hammer products. Plaintiff is entitled to relief under the same causes of action as the other Class Members.

53. Adequacy: Plaintiff is an adequate Class representative because his interests do not conflict with the interests of the Class Members he seeks to represent; his consumer fraud claims are common to all members of the Class and he has a strong interest in vindicating his

rights: he has retained counsel competent and experienced in complex class action litigation and they intend to vigorously prosecute this action. Plaintiff has no interests which conflict with those of the Class. The Class Members' interests will be fairly and adequately protected by Plaintiff and his counsel. Hammer has acted in a manner generally applicable to the Class, making relief appropriate with respect to Plaintiff and the Class Members. The prosecution of separate actions by individual Class Members would create a risk of inconsistent and varying adjudications.

54. The Class is properly brought and should be maintained as a class action under Rule 23(b) because a class action is superior. Pursuant to Rule 23(b)(3), common issues of law and fact predominate over any other questions affecting only individual members of the class. The Class issues fully predominate over any individual issue because no inquiry into individual conduct is necessary, just a narrow focus on Hammer's deceptive and misleading product marketing and labeling practices. In addition, this class is superior to other methods for fair and efficient adjudication of this controversy because, *inter alia*:

55. Superiority: A class action is superior to the other available methods for the fair and efficient adjudication of this controversy because:

a) The joinder of thousands of individual Class Members is impracticable, cumbersome, unduly burdensome, and a waste of judicial and/or litigation resources;

b) The individual claims of the Class Members may be relatively modest compared with the expense of litigating the claim, thereby making it impracticable, unduly burdensome, expensive, if not totally impossible, to justify individual actions;

c) When Defendant's liability has been adjudicated, all Class Members' claims can be determined by the Court and administered efficiently in a manner far less burdensome and expensive than if it were attempted through filing, discovery, and trial of all individual cases;

d) This class action will promote orderly, efficient, expeditious, and appropriate adjudication and administration of class claims;

e) Plaintiff knows of no difficulty to be encountered in the management of this action that would preclude its maintenance as a class action;

f) This class action will assure uniformity of decisions among Class Members; and

g) The Class is readily definable and prosecution of this action as a class action will eliminate the possibility of repetitious litigation.

INJUNCTIVE CLASS RELIEF

56. Rules 23(b)(1) and (2) contemplate a class action for purposes of seeking class-wide injunctive relief. Here, Hammer has engaged in conduct resulting in misleading consumers about ingredients in its products. Since Hammer's conduct has been uniformly directed at all consumers in New York, and the conduct continues presently, injunctive relief on a class-wide basis is a viable and suitable solution to remedy Hammer's continuing misconduct.

57. The injunctive class is properly brought and should be maintained as a class action under Rule 23(a), satisfying the class action prerequisites of numerosity, commonality, typicality, and adequacy because:

a) Numerosity: Individual joinder of the injunctive class members would be

wholly impracticable. Hammer products have been purchased by thousands of persons in New York.

b) Commonality: Questions of law and fact are common to members of the class. Hammer's misconduct was uniformly directed at all consumers. Thus, all members of the class have a common cause against Hammer to stop its misleading conduct through an injunction. Since the issues presented by this injunctive class deal exclusively with Hammer's misconduct, resolution of these questions would be necessarily common to the entire class. Moreover, there are common questions of law and fact inherent in the resolution of an injunctive class, including, *inter alia*:

i. Resolution of the issues presented in the 23(b)(3) class;

ii. Whether members of the class will continue to suffer harm by virtue of Hammer's deceptive product marketing and labeling; and

iii. Whether, on equitable grounds, Hammer should be prevented from continuing to omit material information from its labeling.

c) Typicality: Plaintiff's claims are typical of the claims of the injunctive class because his claims arise from the same course of conduct (i.e. Hammer's deceptive and misleading product marketing, labeling, and practices). Plaintiff is a typical class representative, because, like all member of the injunctive class, he purchased Hammer products which were sold unfairly, and deceptively to consumers within the State of New York.

d) Adequacy: Plaintiff will fairly and adequately represent and protect the interests of the injunctive class. His consumer protection claims are common to all members of the injunctive class and he has a strong interest in vindicating his rights. In addition, Plaintiff and the class are represented by counsel who is competent and experienced in both consumer protection and class action litigation.

58. The injunctive class is properly brought and should be maintained as a class action under Rule 23(b)(2) because Plaintiff seeks injunctive relief on behalf of the class members on grounds generally applicable to the entire injunctive class. Certification under Rule 23(b)(2) is appropriate because Hammer has acted or refused to act in a manner that applies generally to the injunctive class (i.e., Hammer has marketed its products using the same misleading and deceptive product labeling to all of the Class Members). Any final injunctive relief or declaratory relief would benefit the entire injunctive class as Hammer would be prevented from continuing its misleading and deceptive product marketing practices and would be required to honestly disclose to consumers the true ingredients in its products.

FIRST CAUSE OF ACTION
VIOLATION OF NEW YORK GBL §349
(On Behalf of Plaintiff and All Class Members)

59. Plaintiff repeats and realleges each and every allegation contained in all the foregoing paragraphs as if fully set forth herein.

60. New York General Business Law Section 349 ("GBL § 349") declares unlawful "[d]eceptive acts or practices in the conduct of any business, trade, or commerce or in the furnishing of any service in this state..."

61. GBL § 349(h) directs that "any person who has been injured by reason of any violation of [GBL § 349] may bring an action in his own name to enjoin such unlawful act or practice..."

62. The conduct of Defendant alleged herein constitutes recurring, "unlawful" deceptive acts and practices in violation of GBL § 349, and as such, Plaintiff and the Class Members seek monetary damages and the entry of preliminary and permanent injunctive relief against Hammer, enjoining it from inaccurately describing, labeling, marketing, and promoting its products.

63. There is no adequate remedy at law.

64. Defendant misleadingly, inaccurately and deceptively presents its products.

65. Defendant's improper consumer-oriented conduct - including labeling and advertising the products as "natural," omitting caffeine from the ingredients, and misrepresenting that its products are safe and effective - is misleading in a material way in that it, *inter alia*, induced Plaintiff and Class Members to purchase and pay a premium for Defendant's products and to consume and ingest the products.

66. Plaintiff and the Class Members have been injured inasmuch as they paid a premium for products that were – contrary to Defendant's representations – not natural, not safe and effective, and contained caffeine. Accordingly, Plaintiff and the Class Members received less than what they bargained and/or paid for.

67. Defendant's advertising and product labeling induced the Plaintiff and Class Members to buy Defendant's products

68. Defendant's deceptive and misleading practices constitute a deceptive act and

practice in the conduct of its business in violation of New York General Business Law § 349(a) and Plaintiff and the Class have been damaged thereby.

69. As a result of Defendant's recurring, "unlawful" deceptive acts and practices, Plaintiff and Class Members are entitled to monetary damages, injunctive relief, restitution and disgorgement of all monies obtained by means of Defendant's unlawful conduct, interest, and attorneys' fees and costs.

SECOND CAUSE OF ACTION
VIOLATION OF NEW YORK GBL §350
(On Behalf of Plaintiff and All Class Members)

70. Plaintiff repeats and realleges each and every allegation contained in all the foregoing paragraphs as if fully set forth herein.

71. N.Y. Gen. Bus. Law § 350, provides, in part, as follows:

> False advertising in the conduct of any business, trade or commerce or in the furnishing of any service in this state is hereby declared unlawful.

72. N.Y. Gen. Bus. Law § 350-a(1) provides , in part, as follows:

> The term 'false advertising' means advertising, including labeling, of a commodity, or of the kind, character, terms or conditions of any employment opportunity if such advertising is misleading in a material respect. In determining whether any advertising is misleading, there shall be taken into account (among other things) not only representations made by statement, word, design, device, sound or any combination thereof, but also the extent to which the advertising fails to reveal facts material in the light of such

> representations with respect to the commodity or employment to which the advertising relates under the conditions proscribed in said advertisement, or under such conditions as are customary or usual…

73. Defendant's labeling and advertisements contain untrue and materially, misleading statements concerning Defendant's products inasmuch as they misrepresent that the products contain natural ingredients, and they misrepresent that the Appestat capsules are safe and effective. Defendant's labeling and advertisements also misrepresent that the Appestat product does not contain caffeine.

74. Plaintiff and the Class Members have been injured inasmuch as they relied upon the labeling and advertising and paid a premium for products that were – contrary to Defendant's representations – not natural, not safe and effective, and contained caffeine. Accordingly, Plaintiff and the Class Members received less than what they bargained and/or paid for.

75. Defendant's advertising and product labeling induced the Plaintiff and Class Members to buy Defendant's products.

76. Defendant knew, or by exercising reasonable care should have known, that its statements and representations as described in this Complaint were untrue and/or misleading.

77. Defendant's conduct constitutes multiple, separate violations of N.Y. Gen. Bus. Law §350.

78. Defendant made the material misrepresentations described in this Complaint in Defendant's advertising and on its products' labels.

79. Defendant's material misrepresentations were substantially uniform in content,

presentation, and impact upon consumers at large. Moreover, all consumers purchasing the products were and continue to be exposed to Defendant's material misrepresentations.

80. As a result of Defendant's false or misleading labeling and advertising, Plaintiff and Class Members are entitled to monetary damages, injunctive relief, restitution and disgorgement of all monies obtained by means of Defendant's unlawful conduct, interest, and attorneys' fees and costs.

THIRD CLAIM FOR RELIEF
VIOLATION OF NEW YORK GBL LAW § 350-a(1) BY OMISSION
(On Behalf of Plaintiff and All Class Members)

81. Plaintiff repeats and realleges each and every allegation contained in the foregoing paragraphs as if fully set forth herein.

82. N.Y. Gen. Bus. Law § 350-a(1) expressly covers material omissions:

> In determining whether any advertising is misleading, there shall be taken into account (among other things) not only representations made by statement, word, design, device, sound or any combination thereof, but also the extent to which the advertising fails to reveal facts material in the light of such representations with respect to the commodity or employment to which the advertising relates under the conditions proscribed in said advertisement, or under such conditions as are customary or usual…

83. Defendant's product labeling and advertising contains misleading and/or unfair material omissions concerning Defendant's products, including:

a. Defendant's omission of caffeine within its listed ingredients.

b. Defendant's misrepresentations to the public regarding the safety and efficacy of its products, and the Defendant's omission of information about the unsafe and ineffective nature of the products.

c. Defendant's misrepresentation to the public that its products are manufactured and sold with natural ingredients, and Defendant's omission of information about the synthetic ingredients.

84. More specifically, Defendant's advertisements and labeling for its products omits:

a. That Defendant conducted no independent scientific tests to verify the truthfulness of Defendant's claims regarding its products;

b. That Defendant advertises and labels its products as containing natural ingredients, when, in fact, the products contain synthetic ingredients;

c. That Defendant's products contain the unlisted ingredient caffeine; and

d. That hydroxycitric acid is not effective for weight loss and that adverse health effects have been reported and demonstrated.

85. Plaintiff and the Class Members have been injured inasmuch as they relied upon the labels and advertising and paid a premium for products that – contrary to Defendant's labels and advertising – contained caffeine, were synthetic, and were not safe and effective.

86. Defendant knew, or in the exercise of reasonable care should have known, that the statements and representations made about Hammer products as described in this Complaint omitted material facts.

87. Defendant's conduct of omitting material facts in their advertising and labeling disseminated in New York constitutes multiple, separate violations of N.Y. Gen. Bus. Law § 350.

88. Defendant's material misrepresentations by way of omissions, as described in this Complaint, were substantially uniform in content, presentation, and impact upon consumers at large. Moreover, all consumers purchasing the products were and continue to be exposed to Defendant's material misrepresentations by way of omissions.

89. Defendant's advertising and product labeling induced the Plaintiff and Class Members to buy Hammer products.

90. Plaintiff and Class Members relied on Defendant's advertising, which was deceptive, false and contained material omissions.

91. As a result of Defendant's false or misleading advertising and labeling, the Plaintiff and Class Members are entitled to monetary damages, injunctive relief, restitution and disgorgement of all monies obtained by means of Defendant's unlawful conduct, interest, and attorneys' fees and costs.

FOURTH CLAIM FOR RELIEF
BREACH OF EXPRESS WARRANTY
(On Behalf of Plaintiff and All Class Members)

92. Plaintiff repeats and realleges each and every allegation contained in the foregoing paragraphs as if fully set forth herein.

93. Defendant provided the Plaintiff and Class Members an express warranty in the form of written and oral affirmations of fact promising and representing that its products were made with natural ingredients and were safe and effective.

94. The above affirmations of fact were not couched as "belief" or "opinion," and were not "generalized statements of quality not capable of proof or disproof."

95. These affirmations of fact became part of the basis for the bargain and were material to the transaction for the Plaintiff's and Class Members' transactions.

96. Plaintiff and Class Members reasonably relied upon the Defendant's affirmations of fact and justifiably acted in ignorance of the material facts omitted or concealed when they decided to buy Hammer products.

97. Defendant was given opportunities to cure its default but refused to do so.

98. Contrary to Hammer's affirmations of fact, Defendant breached the express warranty because the Hammer products contain synthetic ingredients and are unsafe and ineffective.

FIFTH CLAIM FOR RELIEF
BREACH OF IMPLIED WARRANTY OF MERCHANTABILITY
(On Behalf of Plaintiff and All Class Members)

99. Plaintiff repeats and realleges each and every allegation contained in the foregoing paragraphs as if fully set forth herein.

100. Defendant is in the business of manufacturing, producing, distributing, and selling dietary supplements.

101. Under the Uniform Commercial Code's implied warranty of merchantability, the Defendant warranted to the Plaintiff and the Class Members that the products contain natural ingredients, are safe and effective, and do not contain caffeine.

102. Defendant breached the implied warranty of merchantability in that Hammer's products' ingredients naturally deviate from the label and product description, and reasonable consumers expecting a product that conforms to its label would not accept the Hammer products if they knew that they were unsafe and ineffective and that the products actually contained caffeine and synthetic ingredients.

103. Defendant breached the implied warranty of merchantability. Hammer products

do not list caffeine as an ingredient, and the products contain synthetic ingredients. Furthermore, the product advertising falsely states that the products are safe and effective. Reasonable consumers expecting a product that conforms to its label would not accept the Hammer products if they knew that the products were unsafe and ineffective and actually contained caffeine and synthetic ingredients.

104. Defendant breached the implied warranty of merchantability in that the Hammer products do not conform to the promises or affirmations of fact made on the products' containers or labels or literature. Hammer products do not list caffeine as an ingredient on their labels, and the products contain synthetic ingredients. Furthermore, the products are unsafe and ineffective. Any reasonable consumer in the dietary supplement industry would not accept the Hammer products if they knew that the products actually contained caffeine and synthetic ingredients, and that the products were unsafe and ineffective.

105. Within a reasonable time after the Plaintiff discovered that the products contain caffeine and synthetic ingredients, Plaintiff notified the Defendant of such breach.

106. The inability of the Hammer products to meet the label description was wholly due to the Defendant's fault and without Plaintiff's fault or neglect, and was solely due to the Defendant's manufacture and distribution of the products to the public.

107. As a result of the foregoing, Plaintiff and the Class Members have been damaged in the amount paid for the Hammer products, together with interest thereon from the date of purchase.

SIXTH CLAIM FOR RELIEF
BREACH OF IMPLIED WARRANTY OF FITNESS FOR A PARTICULAR PURPOSE
(On Behalf of Plaintiff and All Class Members)

108. Plaintiff repeats and realleges each and every allegation contained in the

foregoing paragraphs as if fully set forth herein.

109. Plaintiff and other Class Members bought the Hammer products with the specific purpose of buying dietary supplements that were safe and effective and contained natural ingredients.

110. Defendant knew or had reason to know that the Plaintiff and the other Class Members were buying Hammer products with the specific purpose of buying dietary supplements that contained natural ingredients and that were safe and effective for weight loss.

111. Plaintiff and the other Class Members intending to ingest safe and effective products containing natural ingredients, relied on the Defendant to select the Hammer product to fit their specific intended use.

112. Defendant held itself out as having particular knowledge of the Hammer products' ingredients, safety, and efficacy.

113. Plaintiff and the other Class Members' reliance on Defendant to select Hammer products to fit the particular purpose was reasonable given Defendant's statements and representations in its advertising and labels concerning the products' ingredients, safety and efficacy.

114. Plaintiff and the other Class Members' reliance on Defendant to select its products to fit the particular purpose was reasonable given Defendant's particular knowledge of the products it manufactures and distributes.

115. As a result of the foregoing, Plaintiff and the Class Members have been damaged in the amount paid for the Hammer products, together with interest thereon from the date of purchase.

SEVENTH CLAIM FOR RELIEF
COMMON LAW UNJUST ENRICHMENT
(On Behalf of Plaintiff and All Class Members)

116. Plaintiff repeats and realleges each and every allegation contained in the foregoing paragraphs as if fully set forth herein.

117. Plaintiff, on behalf of himself and the consumers of New York, brings a common law claim for unjust enrichment.

118. Defendant's conduct violated New York General Business Law §§ 349, 350, and 350-a by manufacturing, advertising, marketing and selling its products while misrepresenting and omitting material facts.

119. Defendant's unlawful conduct as described in this Complaint allowed Defendant to knowingly realize substantial revenues from selling its products at the expense, and to the detriment or impoverishment, of the Plaintiff and Class Members, and to the Defendant's benefit and enrichment. Defendant has thereby violated fundamental principles of justice, equity, and good conscience.

120. Plaintiff and Class Members conferred significant financial benefits and paid substantial compensation to Defendant for products that were not as Defendant represented.

121. Under New York's common law principles of unjust enrichment, it is inequitable for Defendant to retain the benefits conferred by Plaintiff's and Class Members' overpayments.

122. Plaintiff and Class Members seek disgorgement of all profits resulting from such overpayments and establishment of a constructive trust from which Plaintiff and Class Members may seek restitution.

JURY DEMAND

Plaintiff demands a trial by jury on all issues.

WHEREFORE, Plaintiff, on behalf of himself and the Class, prays for judgment as follows:

(a) Declaring this action to be a proper class action and certifying Plaintiff as the representative of the Class under Rule 23 of the FRCP;

(b) Entering preliminary and permanent injunctive relief against Hammer, directing Hammer to correct its practices and to comply with New York law;

(c) Awarding monetary damages, including treble damages, pursuant to GBL § 349 and GBL § 350;

(d) Awarding Plaintiff and Class Members their costs and expenses incurred in this action, including reasonable allowance of fees for Plaintiff's attorneys and experts, and reimbursement of Plaintiff's expenses; and

(e) Granting such other and further relief as the Court may deem just and proper.

Dated: January 22, 2014

THE SULTZER LAW GROUP, P.C.

By: _____

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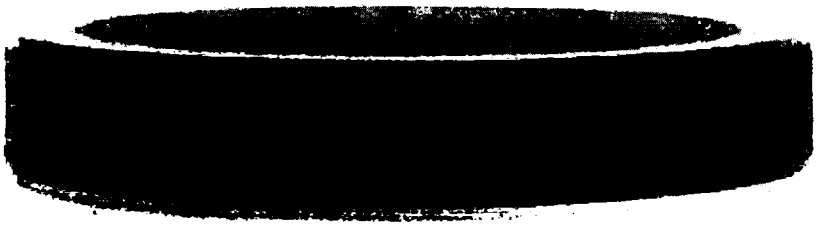
Counsel for Plaintiff and the Class

EXHIBIT "A"



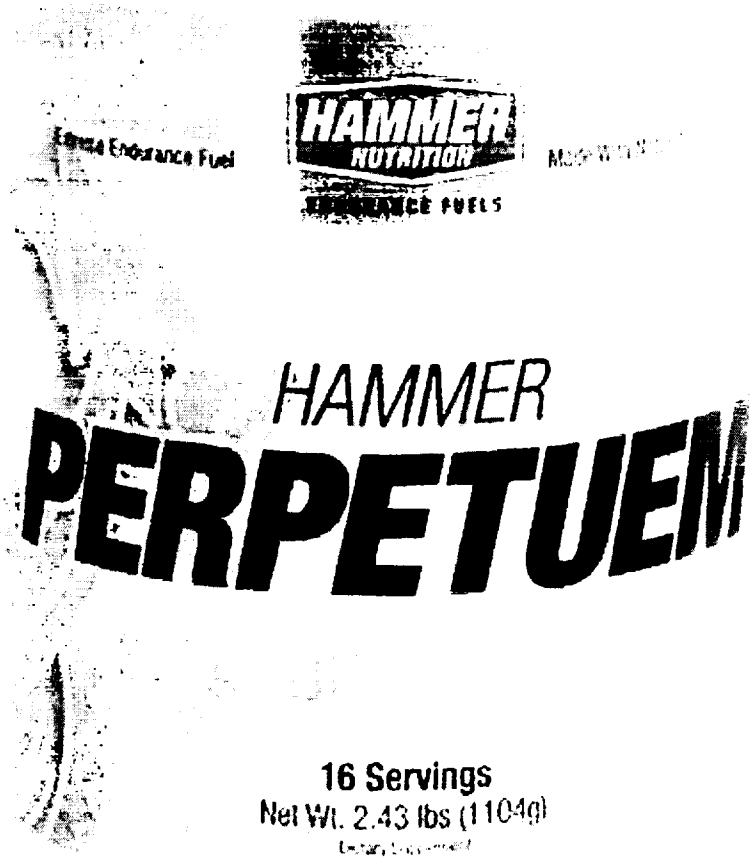

HAMMER
NUTRITION
HAMMER
PERPETUEM
16 Servings
Net Wt. 2.43 lbs (1104g)

EXHIBIT "B"


HAMMER
APPESTAT

EXHIBIT "C"

About FDA

What is the meaning of 'natural' on the label of food?

From a food science perspective, it is difficult to define a food product that is 'natural' because the food has probably been processed and is no longer the product of the earth. That said, FDA has not developed a definition for use of the term natural or its derivatives. However, the agency has not objected to the use of the term if the food does not contain added color, artificial flavors, or synthetic substances.

▸ Show all related FDA Basics Questions

How helpful was this information?

1 ○ **2** ○ **3** ○ **4** ○ **5** ○

Not Helpful ——————————→ **Very Helpful**

Please let us know why you chose the rating above so we can continue to improve these questions

Please limit your feedback to 1000 characters.

What other questions and answers would you like to see featured?

Please limit your feedback to 1000 characters.

To prevent the submission of spam, please enter the word FOOD in the box below.

Submit

If you would like to ask a specific question, please visit our "Contact Us[26]" page for more information about how to contact FDA.

Please note that any information you submit may become public or subject to release under the Freedom of Information Act (FOIA). For more information, read about our privacy policies[27] and the FOIA[28].

Page Last Updated: 04/04/2012
Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

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Silver Spring, MD 20993
Ph. 1-888-INFO-FDA (1-888-463-6332)
Email FDA

Links on this page:

1. /AboutFDA/Transparency/Basics/ucm194330.htm
2. /AboutFDA/Transparency/Basics/ucm214869.htm
3. /AboutFDA/Transparency/Basics/ucm210073.htm
4. /AboutFDA/Transparency/Basics/ucm204717.htm
5. /AboutFDA/Transparency/Basics/ucm214865.htm
6. /AboutFDA/Transparency/Basics/ucm214868.htm
7. /AboutFDA/Transparency/Basics/ucm224689.htm
8. /AboutFDA/Transparency/Basics/ucm214870.htm
9. /AboutFDA/Transparency/Basics/ucm214864.htm
10. /AboutFDA/Transparency/Basics/ucm214867.htm
11. /AboutFDA/Transparency/Basics/ucm214866.htm
12. /AboutFDA/Transparency/Basics/ucm230224.htm
13. /AboutFDA/Transparency/Basics/ucm221173.htm
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18. /AboutFDA/Transparency/Basics/ucm196389.htm
19. /AboutFDA/Transparency/Basics/ucm194327.htm
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23. /AboutFDA/Transparency/Basics/ucm194320.htm
24. /AboutFDA/Transparency/Basics/ucm194317.htm
25. /AboutFDA/Transparency/Basics/ucm194302.htm
26. /AboutFDA/ContactFDA/default.htm
27. /AboutFDA/AboutThisWebsite/WebsitePolicies/default.htm
28. /RegulatoryInformation/FOI/default.htm

EXHIBIT "D"

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

January 6, 2014

The Honorable Yvonne Gonzalez Rogers
United States District Court
Northern District of California
1301 Clay St., Suite 400S
Oakland, CA 94612-5212

The Honorable Jeffrey S. White
United States District Court
Northern District of California
450 Golden Gate Avenue, Box 36060
San Francisco, CA 94102-3489

The Honorable Kevin McNulty
United States District Court
District of New Jersey
Frank R. Lautenberg U.S. Post Office and Courthouse
2 Federal Square
Newark, NJ 07101-0999

Re: Referrals to the United States Food and Drug Administration in *Cox v. Gruma Corp.*, No. 4:12-cv-6502-YGR (N.D. Cal.), *Barnes v. Campbell Soup Co.*, No. 3:12-cv-05185-JSW (N.D. Cal.), and *In Re General Mills, Inc. Kix Cereal Litigation*, No. 2:12-cv-00249-KM-MCA (D.N.J.)

Dear Judges Gonzalez Rogers, White, and McNulty:

This letter responds to your Orders issued on July 11, July 25, and November 1, 2013, respectively, in the above-referenced cases, which referred the question of whether food products containing ingredients produced using bioengineered ingredients may be labeled "Natural" or "All Natural" or "100% Natural" to the Food and Drug Administration ("FDA" or "agency") for an administrative determination under 21 C.F.R. § 10.25(c). In those cases, the plaintiffs allege that the "Natural," "All Natural," and/or "100% Natural" labeling on the Defendants' products are misleading because the products contain corn grown from bioengineered, genetically modified seeds. The *Cox* and *Barnes* cases were stayed for six months with the potential for a further extension; the *Kix Cereal Litigation* was administratively terminated pending FDA's response to the referrals.

FDA has not promulgated a formal definition of the term "natural" with respect to foods. The agency has, however, stated that its policy regarding the use of the term "natural" on food labeling means that "nothing artificial or synthetic (including all color additives regardless of source) has been included in, or has been added to, a food that would not normally be expected to be in the food." *See* 58 Fed. Reg. 2302, 2407 (1993).

If FDA were inclined to revoke, amend, or add to this policy, we would likely embark on a public process, such as issuing a regulation or formal guidance, in order to determine whether to make such a change; we would not do so in the context of litigation between private parties. Issuance of a regulation or guidance document allows an agency to obtain data, information, and views from all stakeholders wishing to engage on an issue. Here, given the complexities of the current request, including the competing concerns among and between stakeholders (e.g., various consumer organizations, diverse industry segments), it would be prudent and consistent with FDA's commitment to the principles of openness and transparency to engage the public on this issue.

We note that defining the term "natural" on food labeling necessarily involves interests of Federal agencies other than FDA, including the United States Department of Agriculture ("USDA"), as well as competing views on the part of stakeholders. FDA has discussed the complexities of such a definition with USDA and both agencies have been considering the issue. Any definition of "natural" on food labeling has implications well beyond the narrow scope of genetically engineered food ingredients about which the Court's referral pertains. For example, if the agencies were to define the term, they would likely need to consider among other things: relevant science; consumer preferences, perceptions, and beliefs; the vast array of modern food production technologies in addition to genetic engineering (e.g., use of different types of fertilizer, growth promotion drugs, animal husbandry methods); the myriad food processing methods (e.g., nanotechnology, thermal technologies, pasteurization, irradiation); and any strictures flowing from the First Amendment. Thus, even if we were to embark on a public process to define "natural" in the context of food labeling, there is no assurance that we would revoke, amend, or add to the current policy, or develop any definition at all. [1]

At present, priority food public health and safety matters are largely occupying the limited resources that FDA has to address foods matters. These matters include developing food safety regulations that implement the FDA Food Safety Modernization Act of 2011, many of which have statutory and/or court-ordered deadlines; issuing nutrition labeling regulations, including regulations that implement the Patient Protection and Affordable Care Act of 2010; other actions with direct public health impact (such as addressing the legal status of partially hydrogenated oils); and numerous other matters, such as responding to outbreaks of food-borne illness and overseeing the safety of imported foods. Because, especially in the foods arena, FDA operates in a world of limited resources, we necessarily must prioritize which issues to address.

[1] FDA was notified by letter dated December 5, 2013, that the Grocery Manufacturers Association ("GMA") intends to file a citizen petition early in 2014 asking FDA to "issue a regulation authorizing foods containing ingredients derived from biotechnology to be labeled 'natural.'" For all of the reasons set forth previously, we believe that, if the agency were to decide to examine this policy question, the public would be better served if the agency used its administrative processes, rather than providing a response in the context of private litigation on the issue.

Based on the foregoing considerations, we respectfully decline to make a determination at this time regarding whether and under what circumstances food products containing ingredients produced using genetically engineered ingredients may or may not be labeled "natural."

Sincerely,

Leslie Kux
Assistant Commissioner for Policy

cc: The Honorable Madeline Cox Arleo
United States District Court for the District of New Jersey
Martin Luther King Building & U.S. Courthouse
50 Walnut Street Room 4015
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Rachel Jane Gallagher, Esq.
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Princeton, NJ 08540

EXHIBIT "E"

U.S. Food and Drug Administration

Protecting and Promoting *Your* Health

Food

Q&A on Dietary Supplements

***NOTE:** For information concerning DMAA (also known as 1,3-dimethylamylamine, methylhexanamine or geranium extract), see Q & A on DMAA in Dietary Supplements.*

General Questions:

- How do I, my health care provider, or any informed individual report a problem or illness caused by a dietary supplement to FDA?

What is a dietary supplement?

Congress defined the term "dietary supplement" in the Dietary Supplement Health and Education Act (DSHEA) of 1994. A dietary supplement is a product taken by mouth that contains a "dietary ingredient" intended to supplement the diet. The "dietary ingredients" in these products may include: vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandulars, and metabolites. Dietary supplements can also be extracts or concentrates, and may be found in many forms such as tablets, capsules, softgels, gelcaps, liquids, or powders. They can also be in other forms, such as a bar, but if they are, information on their label must not represent the product as a conventional food or a sole item of a meal or diet. Whatever their form may be, DSHEA places dietary supplements in a special category under the general umbrella of "foods," not drugs, and requires that every supplement be labeled a dietary supplement.

What is a "new dietary ingredient" in a dietary supplement?

The Dietary Supplement Health and Education Act (DSHEA) of 1994 defined both of the terms "dietary ingredient" and "new dietary ingredient" as components of dietary supplements. In order for an ingredient of a dietary supplement to be a "dietary ingredient," it must be one or any combination of the following substances:

- a vitamin,
- a mineral,
- an herb or other botanical,
- an amino acid,
- a dietary substance for use by man to supplement the diet by increasing the total dietary intake (e.g., enzymes or tissues from organs or glands), or
- a concentrate, metabolite, constituent or extract.

A "new dietary ingredient" is one that meets the above definition for a "dietary ingredient" and was not sold in the U.S. in a dietary supplement before October 15, 1994.

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Should I check with my doctor or healthcare provider before using a supplement?

See Tips For The Savvy Supplement User: Making Informed Decisions And Evaluating Information.

What is FDA's role in regulating dietary supplements versus the manufacturer's responsibility for marketing them?

In October 1994, the Dietary Supplement Health and Education Act (DSHEA) was signed into law by President Clinton. Before this time, dietary supplements were subject to the same regulatory requirements as were other foods. This new law, which amended the Federal Food, Drug, and Cosmetic Act, created a new regulatory framework for the safety and labeling of dietary supplements.Under DSHEA, a firm is responsible for determining that the dietary supplements it manufactures or distributes are safe and that any representations or claims made about them are substantiated by adequate evidence to show that they are not false or misleading. This means that dietary supplements do not need approval from FDA before they are marketed. Except in the case of a new dietary ingredient, where pre-market review for safety data and other information is required by law, a firm does not have to provide FDA with the evidence it relies on to substantiate safety or effectiveness before or after it markets its products.Also, manufacturers need to register themselves pursuant to the Bioterrorism Act with FDA before producing or selling supplements. In June, 2007, FDA published comprehensive regulations for Current Good Manufacturing Practices for those who manufacture, package or hold dietary supplement products. These regulations focus on practices that ensure the identity, purity, quality, strength and composition of dietary supplements.

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When must a manufacturer or distributor notify FDA about a dietary supplement it intends to market in the U.S.?

The Dietary Supplement Health and Education Act (DSHEA) requires that a manufacturer or distributor notify FDA if it intends to market a dietary supplement in the U.S. that contains a "new dietary ingredient." The manufacturer (and distributor) must demonstrate to FDA why the ingredient is reasonably expected to be safe for use in a dietary supplement, unless it has been recognized as a food substance and is present in the food supply.There is no authoritative list of dietary ingredients that were marketed before October 15, 1994. Therefore, manufacturers and distributors are responsible for determining if a dietary ingredient is "new", and if it is not, for documenting that the dietary supplements its sells, containing the dietary ingredient, were marketed before October 15, 1994. For more detailed information see new dietary ingredients.

What information must the manufacturer disclose on the label of a dietary supplement?

FDA regulations require that certain information appear on dietary supplement labels. Information that must be on a dietary supplement label includes: a descriptive name of the product stating that it is a "supplement;" the name and place of business of the manufacturer, packer, or distributor; a complete list of ingredients; and the net contents of the product.In addition, each dietary supplement (except for some small volume products or those produced by eligible small businesses) must have nutrition labeling in the form of a "Supplement Facts" panel. This label must identify each dietary ingredient contained in the product.

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Must all ingredients be declared on the label of a dietary supplement?

Yes, ingredients not listed on the "Supplement Facts" panel must be listed in the "other ingredient" statement beneath the panel. The types of ingredients listed there could include the source of dietary ingredients, if not identified in the "Supplement Facts" panel (e.g., rose hips as the source of vitamin C), other food ingredients (e.g., water and sugar), and technical additives or processing aids (e.g., gelatin, starch, colors, stabilizers, preservatives, and flavors). For more details, see: Federal Register Final Rule - 62 FR 49826 September 23, 1997.

Are dietary supplement serving sizes standardized or are there restrictions on the amount of a nutrient that can be in one serving?

Other than the manufacturer's responsibility to ensure safety, there are no rules that limit a serving size or the amount of a nutrient in any form of dietary supplements. This decision is made by the manufacturer and does not require FDA review or approval.

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Where can I get information about a specific dietary supplement?

Manufacturers and distributors do not need FDA approval to sell their dietary supplements. This means that FDA does not keep a list of manufacturers, distributors or the dietary supplement products they sell. If you want more detailed information than the label tells you about a specific product, you may contact the manufacturer of that brand directly. The name and address of the manufacturer or distributor can be found on the label of the dietary supplement.

What are some tips on searching the web for information on dietary supplements?

See Tips For The Savvy Supplement User; Making Informed Decisions And Evaluating Information.

Who has the responsibility for ensuring that a dietary supplement is safe?

By law (DSHEA), the manufacturer is responsible for ensuring that its dietary supplement products are safe before they are marketed. Unlike drug products that must be proven safe and effective for their intended use before marketing, there are no provisions in the law for FDA to "approve" dietary supplements for safety or effectiveness before they reach the consumer. Under DSHEA, once the product is marketed, FDA has the responsibility for showing that a dietary supplement is "unsafe," before it can take action to restrict the product's use or removal from the marketplace. However, manufacturers and distributors of dietary supplements must record, investigate and forward to FDA any reports they receive of serious adverse events associated with the use of their products that are reported to them directly. FDA is able to evaluate these reports and any other adverse event information reported directly to us by healthcare providers or consumers to identify early signals that a product may present safety risks to consumers. You can find more information on reporting adverse events associated with the use of dietary supplements at Dietary Supplements - Adverse Event Reporting.

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Do manufacturers or distributors of dietary supplements have to tell FDA or consumers what evidence they have about their product's safety or what evidence they have to back up the claims they are making for them?

No, except for rules described above that govern "new dietary ingredients," there is no provision under any law or regulation that FDA enforces that requires a firm to disclose to FDA or consumers the information they have about the safety or purported benefits of their dietary supplement products. Likewise, there is no prohibition against them making this information available either to FDA or to their customers. It is up to each firm to set its own policy on disclosure of such information. For more information, see claims that can be made for dietary supplements.

How can consumers inform themselves about safety and other issues related to dietary supplements?

It is important to be well informed about products before purchasing them. Because it is often difficult to know what information is reliable and what is questionable, consumers may first want to contact the manufacturer about the product they intend to purchase (see previous question "Where can I get information about a specific dietary supplement?"). In addition, to help consumers in their search to be better informed, FDA is providing the following sites: *Tips For The Savvy Supplement User;* Making Informed Decisions And Evaluating Information (includes information on how to evaluate research findings and health information on-line) and Claims That Can Be Made for Conventional Foods and Dietary Supplements, (provides information on what types of claims can be made for dietary supplements).

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What is FDA's oversight responsibility for dietary supplements?

Because dietary supplements are under the "umbrella" of foods, FDA's Center for Food Safety and Applied Nutrition (CFSAN) is responsible for the agency's oversight of these products. FDA's efforts to monitor the marketplace for potential *illegal* products (that is, products that may be unsafe or make false or misleading claims) include obtaining information from inspections of dietary supplement manufacturers and distributors, the Internet, consumer and trade complaints, occasional laboratory analyses of selected products, and adverse events associated with the use of supplements that are reported to the agency.

Does FDA routinely analyze the content of dietary supplements?

In that FDA has limited resources to analyze the composition of food products, including dietary supplements, it focuses these resources first on public health emergencies and products that may have caused injury or illness. Enforcement priorities then go to products thought to be unsafe or fraudulent or in violation of the law. The remaining funds are used for routine monitoring of products pulled from store shelves or collected during inspections of manufacturing firms. The agency does not analyze dietary supplements before they are sold to consumers. The manufacturer is responsible for ensuring that the "Supplement Facts" label and ingredient list are accurate, that the dietary ingredients are safe, and that the content matches the amount declared on the label. FDA does not have resources to analyze dietary supplements sent to the agency by consumers who want to know their content. Instead, consumers may contact the manufacturer or a commercial laboratory for an analysis of the content.

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Is it legal to market a dietary supplement product as a treatment or cure for a specific disease or condition?

No, a product sold as a dietary supplement and promoted on its label or in labeling* as a treatment, prevention or cure for a specific disease or condition would be considered an unapproved--and thus illegal--drug. To maintain the product's status as a dietary supplement, the label and labeling must be consistent with the provisions in the Dietary Supplement Health and Education Act (DSHEA) of 1994.*Labeling refers to the label as well as accompanying material that is used by a manufacturer to promote and market a specific product.

Who validates claims and what kinds of claims can be made on dietary supplement labels?

FDA receives many consumer inquiries about the validity of claims for dietary supplements, including product labels, advertisements, media, and printed materials. The responsibility for ensuring the validity of these claims rests with the manufacturer, FDA, and, in the case of advertising, with the Federal Trade Commission.By law, manufacturers may make three types of claims for their dietary supplement products: health claims, structure/function claims, and nutrient content claims. Some of these claims describe the link between a food substance and disease or a health-related condition; the intended benefits of using the product; or the amount of a nutrient or dietary substance in a product. Different requirements generally apply to each type of claim, and are described in more detail.

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Why do some supplements have wording (a disclaimer) that says: "This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease"?

This statement or "disclaimer" is required by law (DSHEA) when a manufacturer makes a structure/function claim on a dietary supplement label. In general, these claims describe the role of a nutrient or dietary ingredient intended to affect the structure or function of the body. The manufacturer is responsible for ensuring the accuracy and truthfulness of these

claims; they are not approved by FDA. For this reason, the law says that if a dietary supplement label includes such a claim, it must state in a "disclaimer" that FDA has not evaluated this claim. The disclaimer must also state that this product is not intended to "diagnose, treat, cure or prevent any disease," because only a drug can legally make such a claim.

How are advertisements for dietary supplements regulated?

The Federal Trade Commission (FTC) regulates advertising, including infomercials, for dietary supplements and most other products sold to consumers. FDA works closely with FTC in this area, but FTC's work is directed by different laws. For more information on FTC, go to the FTC web site. Advertising and promotional material received in the mail are also regulated under different laws and are subject to regulation by the U.S. Postal Inspection Service.

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How do I, my health care provider, or any informed individual report a problem or illness caused by a dietary supplement to FDA?

If you think you have suffered a serious harmful effect or illness from a dietary supplement, the first thing you should do is contact or see your healthcare provider immediately. Then, you or your health care provider can report this by submitting a report through the Safety Reporting Portal. If you do not have access to the internet, you may submit a report by calling FDA's MedWatch hotline at 1-800-FDA-1088.

FDA would like to know when a dietary supplement causes a problem even if you are unsure the product caused the problem or even if you do not visit a doctor or clinic. Anyone may report a serious adverse event or illness thought to be related to a dietary supplement directly to FDA by accessing the SRP mentioned above.

Consumers are also encouraged to report instances of product problems using the Safety Reporting Portal. Examples of product problems are foreign objects in the packaging or other apparent quality defects.

In addition to communicating with FDA on-line or by phone, you may use the postage-paid MedWatch form available from the FDA Web site.

NOTE: The identity of the reporter and/or patient is kept confidential. For a general complaint or concern about food products, including dietary supplements, you may contact the consumer complaint coordinator at the local FDA District Office nearest you. See the following Web address for the telephone number: Consumer Complaint Coordinators15.

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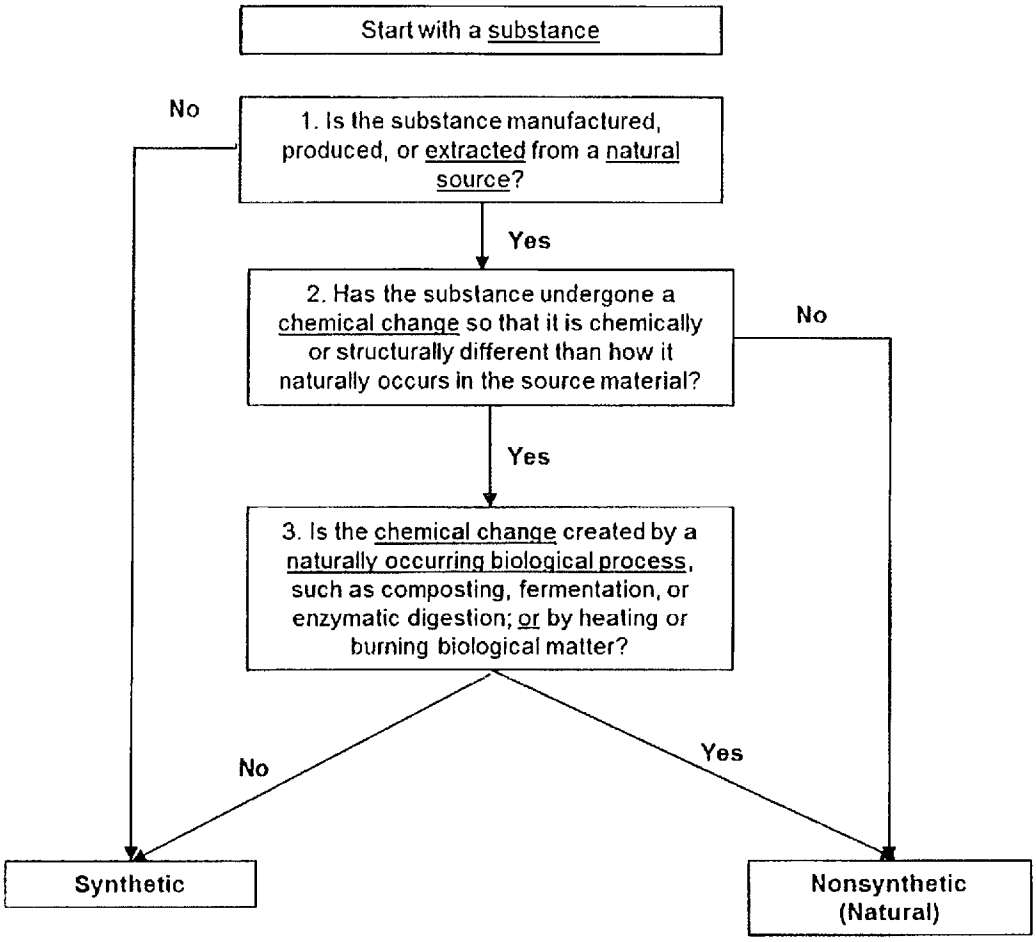
EXHIBIT "F"

Draft Guidance
Decision Tree for Classification of Materials as Synthetic or Nonsynthetic

Underlined terms defined on page 2



Definitions (bolded terms in 7 CFR 205.2)

Agricultural inputs. All substances or materials used in the production or handling of organic agricultural products.

Agricultural product. Any agricultural commodity or product, whether raw or processed, including any commodity or product derived from livestock, that is marketed in the United States for human or livestock consumption.

Allowed synthetic. A substance that is included on the National List of synthetic substances allowed for use in organic production or handling.

Chemical change. A process (i.e. chemical reaction) whereby a substance is transformed into one or more other distinct substances.

Extract. To separate, withdraw, or obtain one or more constituents of an organism, substance, or mixture by use of solvents (dissolution), acid-base extraction, or mechanical or physical methods.

Formulate. To combine different materials according to a recipe or formula.

Generic. The common and familiar non-proprietary name.

Manufacture. To make a substance from raw materials.

Natural source. Naturally occurring mineral or biological matter.

Naturally occurring biological process. A process that occurs due to the action of biological organisms or subcomponents of biological organisms, such as enzymes. Examples of naturally occurring biological processes include, but are not limited to, fermentation, composting, manure production, enzymatic processes, and anaerobic digestion.

Nonagricultural substance. A substance that is not a product of agriculture, such as a mineral or a bacterial culture, that is used as an ingredient in an agricultural product. For the purposes of this part, a nonagricultural ingredient also includes any substance, such as gums, citric acid, or pectin, that is extracted from, isolated from, or a fraction of an agricultural product so that the identity of the agricultural product is unrecognizable in the extract, isolate, or fraction.

Nonsynthetic (natural). A substance that is derived from mineral, plant, or animal matter and does not undergo a synthetic process as defined in section 6502(21) of the Act (7 U.S.C. 6502(21)). For the purposes of this part, nonsynthetic is used as a synonym for natural as the term is used in the Act.

Substance. A generic type of material, such as an element, molecular species, or chemical compound, that possesses a distinct identity (e.g. having a separate Chemical Abstracts Service

(CAS) number, Codex International Numbering System (INS) number, or FDA or other agency standard of identity).

Synthetic. A substance that is formulated or manufactured by a chemical process or by a process that chemically changes a substance extracted from naturally occurring plant, animal, or mineral sources, except that such term shall not apply to substances created by naturally occurring biological processes.

Table 1. Classification examples of inputs:

Substance	Classification	Explanation
Ash (burned wood)	Nonsynthetic	Substance is created by burning biological matter.
Calcium carbonate (limestone)	Nonsynthetic	Substance is produced from a natural source (mined mineral) and does not undergo chemical change.
Calcium oxide (quicklime)	Synthetic	Substance is produced from a natural source (mined mineral), but undergoes chemical change caused by heating the mineral.
Citric acid	Nonsynthetic	Substance is created from a naturally occurring biological process (microbial fermentation of carbohydrate substances).
Enzymes, without synthetic additional ingredients	Nonsynthetic	Substance is extracted from a natural source and is not formulated with synthetic ingredients
Gibberellic acid	Nonsynthetic	Substance is extracted from a natural source without further chemical change
Liquid fish products - pH adjusted with phosphoric acid	Synthetic	Substance is derived from a natural source, but is treated with synthetic acids for pH adjustment.
Molasses	Nonsynthetic	Substance is derived from a natural source and chemical change is due to heating or naturally occurring biological processes.
Newspaper	Synthetic	Substance is manufactured via a chemical process.
Raw manure	Nonsynthetic	Substance is from a natural source and used without further processing.
Rosemary oil	Nonsynthetic	Substance is extracted from a natural source.

EXHIBIT "G"

MAS

PRELIMINARY REPORT

HAMMER PRODUCTS

STUDY OF APPSTAT AND PERPETUEM NON-NATURAL INGREDIENTS

FOR: The Sultzer Law Group,

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MAS, LLC, Suwanee, GA

July 24, 2013

MAS

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MAS

INTRODUCTION

This report describes ingredients, natural and synthesized (non-natural), pertaining to certain nutritional supplements manufactured by Hammer Nutrition, LTD.

NATURAL VS SYNTHESIZED INGREDIENTS

"Natural" ingredients can be described as having ingredients that are from nature. Natural products do not contain any artificial colors, flavors or synthetic substances. In the biological world natural is anything "organic in nature", i.e., any substance that is produced by a plant, animal, bacteria or fungi. This encompasses the entire spectrum of biologically synthesized proteins, carbohydrates, enzymes, amino acids, genetic materials, and lipid (fats) and membrane components. Inorganic or "naturally occurring" ingredients would consist of mineral salts derived from naturally occurring geological sources such as calcium chloride, iron chloride, iron sulfate, calcium sulfate, calcium carbonate, potassium chloride, sodium chloride, etc. Many more examples of inorganic natural ingredients exist.

"Synthesized" ingredients or non-natural ingredients include any compound that is produced by man using synthesis chemical processes. A synthesis reaction to create a non-natural ingredient occurs through a combination of ingredients or chemicals in order to produce another type of chemical or compound. Though many compounds exist in nature without any prior synthesis by man, synthesized non-natural compounds can be manufactured and produced in large quantities by man directly from basic chemical building blocks using known industrial chemical processes during synthesis process manufacturing.

HAMMAR PRODUCTS INGREDIENTS ANALYSIS

I have assessed the components of certain Hammer nutritional supplement products to determine the compositional makeup according to the manufacturer's labeling for the presence or absence of synthesized vs "natural" ingredients. The following products were reviewed:

- Appestat capsules, described by the manufacturer to "Suppress appetite without stimulants..... helps increase fat metabolism.....can reduce potential for carbohydrate-to-fat conversion."
- Endurolytes Fizz Unflavored tablets, described by the manufacturer as a "superior, full-spectrum electrolyte support and effective cramp preventer."
- Hammer Bar Cashew Coconut, a food bar described to possess "natural all organic ingredients and a truly healthy energy bar."
- Hammer Gel Chocolate liquid formula described by the manufacturer that is a "rock solid energy drink" with "complex carbohydrates, natural ingredients, and real fruit."

- Perpetuem Orange powder, described by the manufacturer as "unique formula — complex carbohydrates, GMO-free soy protein, healthy fats, and key auxiliary nutrients such as sodium phosphate."
- Race Caps Supreme capsules, and "essential supplement" to "enhance energy, endurance and recovery...reduce muscle fatigue....increase work load capacity."

- Recoverite powder, a glutamine fortified recover drink to "minimize post exercise soreness... rebuild muscle tissue and restore glycogen it supplies carbohydrates and protein in an ideal 3:1 ratio for superior glycogen synthesis and muscle tissue rebuilding."

- Whey Vanilla powder described as a whey protein isolate "to maintain, repair, and grow lean muscle mass." Hammer Whey, is "ideal for supporting your immune system, and enhancing recovery between workouts and races."

REVIEW OF TWO HAMMER PRODUCTS FOR NON-NATURAL INGREDIENTS

After a review of the ingredients of all Hammer products named above, Appstat and Perpetuem were selected for a closer examination of the ingredients. I have determined that there are at least two or more components in each of the products that are not "natural" but are manufactured compounds. Additional compounds in the product may also not be "natural" based upon whether or not the compound was produced from one or more chemical components under process manufacturing conditions but certain ingredients in Appstat and Perpetuem as described below are known to be synthesized in large quantities using industrial chemical processes.

APPESTAT

Appestat is a dry capsule formulation described by the manufacturer to "Suppress appetite without stimulants..... helps increase fat metabolism...and....can reduce potential for carbohydrate-to-fat conversion." The regular recommended amount is 2 – 4 capsules per day for 3 weeks at a time. At least 3 of the ingredients in Appstat are not naturally occurring, they are: magnesium stearate, zinc monomethionine and chromium polynicotinate.

- Magnesium stearate is also called magnesium octadecanoate or magnesium salt. It is a white powder synthesized by the reaction of sodium stearate and magnesium sulfate. One of the ingredients for the manufacture of the sodium stearate component is either animal fat or vegetable fat. Magnesium stearate is used as a lubricant for pharmaceutical preparations and medical devices and as an anti-sticking agent. It is a man-made compound synthesized in large quantities by numerous chemical manufacturers for industrial uses and a variety of applications.

- Zinc monomethionine is the combination of the metal zinc with the amino acid methionine. Zinc monomethionine is produced by combining zinc oxide powder with DL-methionine powder in hydrochloric acid (25% w/w). Zinc monomethionine is precipitated out of solution with sodium hydroxide at neutral pH and the precipitated powder is dried and stored. Zinc

monomethionine is a man-made compound synthesized in large quantities by numerous chemical manufacturers for agricultural feed usage and for human and animal supplements as well as for other applications.

- Chromium polynicotinate is elemental chromium coupled to more than one molecule of niacin (also known as vitamin B3, nicotinate or nicotinic acid). Hammer products describes this compound as "ChromMate™ brand of trivalent niacin bound chromium polynicotinate." It is a dark grey powder produced by first combining nicotinate with sodium hydroxide to form an alkali metal salt of niacin. A green solution of chromium chloride hexahydrate is added to the nicotinate solution and the green solution turns purple indicating the reaction has occurred to form the precipitate chromium nicotinate. The solution is filtered and the precipitated chromium nicotinate is dried and stored for use. Alternatively, chromium nicotinate can be formed by adding nicotinate to sodium carbonate and adjusting the pH to 7.0, then chromium chloride is dissolved in ethanol or methanol and the sodium nicotinate solution is added. Precipitated purple chromium nicotinate is filtered out of solution, dried and stored. Chromium nicotinate is a man-made compound synthesized by numerous chemical manufacturers in large quantities for human and animal supplements and also for other uses.

In addition to the three compounds described above, caffeine was also detected by this laboratory in Appstat. Caffeine is not listed as an ingredient in Appstat.

PERPETUEM

Perpetuem powder is described by Hammer as a "unique formula - complex carbohydrates, GMO-free soy protein, healthy fats, and key auxiliary nutrients such as sodium phosphate." The regular recommended amount to consume is anywhere from 0.75 to 2.0 scoops of powder in 16-28 ounces (approximately 475-830 ml) of water per hour depending upon body weight during work-outs. At least 2 of the ingredients in Perpetuem are not naturally occurring, they are: chromium polynicotinate and choline bitartrate.

- Chromium polynicotinate is a man made compound. Its composition, manufacture and uses have been described under Appstat above.

- Choline bitartrate, also known as choline tartrate, is a white powder manufactured by reacting ethylene oxide with trimethylamine in water or in an acid if one of the salts is required. This process can be performed in a batch mode or in a continuous manufacturing process. The precipitated powder is dried and stored. Choline bitartrate is a man-made compound synthesized in large quantities by numerous chemical manufacturers for use as human and animal supplements.

This report is preliminary and additional work to determine the non-natural ingredients in the other Hammer products is anticipated.

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EXHIBIT "H"

Immunology 1990 70 379-384

Molecular basis for the immunosuppressive action of stearic acid on T cells

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SUMMARY

Studies were performed to determine the mechanism by which stearic acid (18:0) selectively inhibits T-dependent immune responses *in vitro*. Incubation of mitogen-activated B and T cells with 18:0 resulted in dissimilar patterns of incorporation of the saturated fatty acid into their membranes. High-performance liquid chromatography (HPLC) analyses of T cells showed an accumulation of desaturated 18:0-containing phosphatidylcholine (PC) that replaced normal cellular PC. Less significant quantities of the same PC species were seen to accumulate in B-cell membranes; rather, they increased their proportion of oleic acid (18:1)-containing PC. The different lipid compositions of the lymphocyte cell membranes after exposure to 18:0 were correlated with their plasma membrane potentials. In T cells, the accumulation of desaturated, 18:0-containing PC coincided with a rapid (within 8 hr) collapse of membrane integrity, as determined by flow cytometry. The collapse of membrane integrity was found to be time and dose dependent. No such depolarization was observed in B cells which, by virtue of their desaturating ability, were able to avoid incorporating large amounts of desaturated 18:0-containing phospholipids into their membranes. It is proposed that a lack of stearoyl-CoA desaturase in T cells precludes them from desaturating exogenously derived 18:0, thus leading to increased proportions of 18:0-containing desaturated PC in their cell membranes. The increased abundance of this PC species may enhance membrane rigidity to an extent that plasma membrane integrity is significantly impaired, leading to a loss of membrane potential and ultimately cell function and viability.

INTRODUCTION

Various saturated and unsaturated fatty acids have been reported to modulate the immunological role of lymphocytes both *in vitro* and *in vivo* (Erickson, 1986; Gurr, 1983; Meade & Mertin, 1978). Of particular interest is the finding that some fatty acids can selectively inhibit T-cell-mediated functions in the relative absence of effects on B cells. For example, stearic acid (18:0) has been shown to be a potent inhibitor of phytohaemagglutinin (PHA)-dependent T-lymphocyte proliferation while having little effect on lipopolysaccharide (LPS)-induced B-cell proliferation (Buttke, 1984). Further, 18:0 suppresses primary *in vitro* antibody responses to T-dependent but not T-independent antigens (Pourbohloul, Mallett & Buttke, 1985). T-helper cells are suggested to be the principle target of such immunosuppression, wherein interleukin-2 (IL-2) production is inhibited (Pourbohloul & Buttke, 1990). Lastly, 18:0 has been shown to be cytotoxic for T cells but not B cells (Buttke & Cuchens, 1984).

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Previous workers have proposed that saturated fatty acids may, via their incorporation into phospholipids, perturb the membrane structure, thus adversely affecting membrane-bound enzymes (Stubbs & Smith, 1984; Mahoney *et al.*, 1977; Tsang, Weyman & Smith, 1977). However, the differential effects of 18:0 on T and B cells suggest a fundamental difference between the two lymphocyte types in either lipid metabolism or membrane lipid composition. Indeed, further investigation has revealed that B cells can desaturate 18:0 to 18:1, whereas T cells can not (Buttke *et al.*, 1989). This finding suggests that B cells are better able to maintain a functional balance between saturated and unsaturated fatty acid levels in their membranes by virtue of their having higher levels of stearoyl-CoA desaturase, the enzyme responsible for converting 18:0 to 18:1 (Buttke *et al.*, 1989). Such results may signify an important difference in the regulation of lipid metabolism during B- and T-lymphocyte maturation, which may be related to their *in vivo* function.

The present studies attempted to define the biochemical basis for the selective cytotoxic effect of 18:0 on T cells. Since it has been shown previously that the inability of T cells to convert 18:0 to 18:1 coincides with an accumulation of desaturated

phospholipid species (Buttke *et al.*, 1989), it seemed possible that such changes in membrane lipid composition might lead to impaired membrane integrity (Kuypers *et al.*, 1984; Lange *et al.*, 1980). Indeed, the accumulation of desaturated 18:0-containing phospholipid species results in the loss of membrane potential in a significant proportion of T cells, implying perturbation of membrane integrity and loss of viability.

METHODS AND MATERIALS

Isolation and culture of lymphocytes

Male and female BALB/c mice, 8–12 weeks of age, were obtained from Charles River Breeding Laboratories (Raleigh NC). Spleen cell suspensions were depleted of erythrocytes and macrophages by NH_4Cl lysis and passage of cells through glass-wool columns, respectively (Buttke, Mallett & Cuchens, 1983). The lymphocyte-enriched suspension was further purified into immunoglobulin-positive (Ig^+) (B cells) and Ig^- cell populations by incubation on rabbit anti-mouse Ig (Accurate Chemical Co.)-coated Petri plates (Buttke *et al.*, 1983). The non-adherent Ig^- population was subsequently incubated in suspension with a monoclonal mouse alloantisera directed against the Thy-1·2 antigen, followed by a second round of selection on the rabbit anti-mouse Ig-coated Petri plates (Buttke *et al.*, 1983). The adherent populations recovered from the two rounds of positive selection were >95% viable, and considered to be highly enriched populations of B and T cells based on several criteria (Buttke *et al.*, 1983).

Lymphocytes were cultured in 96-well, round-bottomed, microtitre plates (Linbro, Flow Laboratories Inc., McLean, VA) at a concentration of $2{\cdot}5 \times 10^6$ cells per ml of culture medium. The culture medium consisted of RPMI-1640 containing 0·2% $NaHCO_3$, penicillin (50 U/ml), streptomycin (50 μg/ml) and 5% fetal bovine serum. T lymphocytes were stimulated with phytohaemagglutinin (PHA; Difco) at a concentration of 5 μg/ml and B lymphocytes with lipopolysaccharide (LPS; Difco) at 50 μg/ml. Cell cultures were incubated at 37° in a humidified atmosphere containing 6% CO_2 94% air.

Albumin-complexed fatty acids

Stearic acid (18:0), bovine serum albumin (BSA) and diatomaceous earth were obtained from Sigma Chemical Co. (St Louis, MO). The fatty acid was adsorbed onto diatomaceous earth and subsequently complexed to BSA to yield fatty acid: BSA ratios of ~3·5 (Buttke, 1984).

Phospholipid extraction and analysis

Aliquots of 5×10^7 B or T lymphocytes were collected by centrifugation at 250 *g* for 10 min, and the pellets were washed once with ice-cold culture medium. Lipids were extracted by the addition of 1 ml of methanol and 2 ml of chloroform (Folch, Lees & Sloan-Stanley, 1957). After 1 hr, 0·6 ml of 0·1 M KCl was added and the suspension was centrifuged at 200 *g* for 5 min to separate the aqueous and organic phases. The lower chloroform layer was recovered and the solvent evaporated under nitrogen in a 37° water bath. Recovered lipids were dissolved in 0·1 ml of 2:1 (v/v) chloroform-methanol prior to analysis.

Total lymphocyte phospholipids were separated by thin-layer chromatography (TLC) on silica gel 60 plates developed with chloroform-methanol-acetic acid-H_2O (75:45:12:5·5). TLC plates were predeveloped with acetone followed by heating at 110° for at least 1 hr to overcome adverse effects of humidity on phospholipid separation. Once spotted with sample, the TLC plates were incubated for a second time at 110° for 30 min. The plate was then transfered directly to a pre-equilibrated (approximately 1 hr) TLC chamber for development. Separated phospholipids were localized using I_2 vapour.

Phosphatidylcholine (PC) fractions were eluted from the silica gel with 10 ml of methanol, converted to diacylglycerides by phospholipase C digestion (Mavis, Bell & Vagelos, 1972), and dinitrobenzylated (Takamura *et al.*, 1986). The resultant diacylglycerobenzoates were separated into molecular species using a Beckman System Gold HPLC fitted with a $4{\cdot}6 \times 45$ mm precolumn and a Beckman $4{\cdot}6 \times 250$ mm analytical column, both packed with 5 μm C-18 Ultrasphere (Beckman). Elution with 1 ml/min acetonitrile:2-propanol (70:30 v/v for the first 5 min, followed by 75:25) allowed separation of 11 molecular species. Quantification of individual molecular species was carried out by monitoring UV absorption at 230 nm. Molecular species were identified by comparison of their retention times to those of known authentic standards, by gas-liquid chromatography of their acyl chains, and in some cases by conversion to diacylglyceroacetates and subsequent argentation TLC (Buttke *et al.*, 1989).

Flow cytometric measurements of relative membrane potential

Membrane potential measurements were made using the cationic potential-sensitive dye dihexyloxacarbocyanine iodide [$DiOC_6(3)$], obtained from Molecular Probes Inc. (Eugene, OR). A stock solution of $DiOC_6(3)$ was prepared in dimethyl sulphoxide and stored at −20°. Just prior to use, aliquots were thawed, diluted to 50 μM with phosphate-buffered saline (PBS) and added to 1×10^6 cells in 1 ml PBS. The final $DiOC_6(3)$ concentration attained (125 nm) is reported to be non-toxic for lymphocytes (Damjanovich *et al.*, 1987). After a 15-min incubation at room temperature, cells were analysed using a Becton-Dickinson FACS 440 flow cytometer. The laser was tuned to an excitation wavelength of 488 nm at an output of 400 mW. Emission of fluorescence was assayed within a band ranging from 515–545 nm as a measure of relative membrane potential (Shapiro, Natale & Kamentsky, 1979). Control and gramicidin-treated (20 μg/ml) lymphocyte populations were used to determine fluorescence values for fully polarized and totally depolarized cells, respectively. At each time-point, the number of cells in the polarized region for each culture condition was divided by the total number of cells analysed (~10^4) to derive the relative proportion of polarized cells. The ratio obtained at each time-point was multiplied by 100 to obtain the percentage of polarized cells in each sample.

RESULTS

PC molecular species of mitogen-activated B and T cells

It has been shown previously that incubation of mitogen-stimulated B and T cells in the presence of 50 μM 18:0 leads to substantial differences in the PC molecular species (Buttke *et al.*, 1989). The present studies were therefore performed to determine if such lipid changes could be correlated with decreased lymphocyte viability. In the initial phase of this study, purified B and T cells were analysed separately for their PC molecular species. To account for any anomalies of membrane composition which might have occurred as a result of culture, B and T

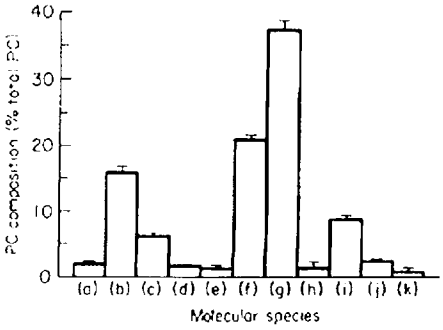

Figure 1. PC molecular species of mitogen-activated B and T lymphocytes. Purified B and T cells were stimulated with LPS or PHA, respectively. Cells were harvested and analysed for their PC molecular species by HPLC. Quantities of each molecular species are shown as a percentage of total PC. Data shown represent the mean (± SD) of three separate experiments. Molecular species: (a) 18:0–22:6 and 18:1–18:2; (b) 16:0–18:2; (c) 18:0–20:4; (d) 18:0–22:5; (e) 18:1–18:1; (f) 16:0–18:1 and 18:0–18:2; (g) 16:0–16:0; (h) 18:0–18:1; (i) 16:0–18:0; (j) 16:0–20:1; (k) 18:0–18:0.

cells were first stimulated for 6 hr with PHA or LPS, respectively, in the absence of 18:0.

Mitogen-activated B and T cells contained 11 separable PC molecular species, with the proportions of individual species being nearly identical within the two cell types. The results for each lymphocyte type were therefore combined and in Fig. 1 the level of each individual PC species is shown as the proportion of total PC. A comparison of the results shown in Fig. 1 with the data previously reported for mouse B and T cells (Buttke *et al.*, 1989) reveals a much higher level of dipalmitoyl (16:0–16:0) PC in the present study. Based on additional observations (T. M. Buttke and S. Van Cleave, unpublished data), the differing levels of 16:0–16:0 may have resulted from a change in murine diet. It is interesting to note that 16:0–16:0 PC has also been observed in human tonsil lymphocytes (Morimoto & Kanoh, 1980).

In addition to the desaturated molecular species, lymphocytes also contained several molecular species having the more expected composition of one saturated and one unsaturated fatty acid per PC molecule. PC species containing at least one molecule of 16:0 comprised the majority (~80%) of PC molecular species, the remainder containing primarily 18:0 as their saturated moiety.

Modulation of PC molecular species in response to 18:0 supplementation

Next the PC molecular species of mitogen-stimulated B and T cells that had been incubated for 6 hr in the presence of 60, 120 or 180 μM albumin-complexed 18:0 were examined. Selection of the lowest dose was based on previous studies showing that 50 μM 18:0 irreversibly inhibited T-cell proliferation by >90% in 10 hr while having much less effect on B-cell proliferation (Buttke & Cuchens, 1984). The higher doses of 120 and 180 μM 18:0 were used in an attempt to amplify 18:0-induced changes in membrane lipid composition. The major effects of 18:0 supplementation on B- and T-cell PC molecular species are shown in Fig. 2.

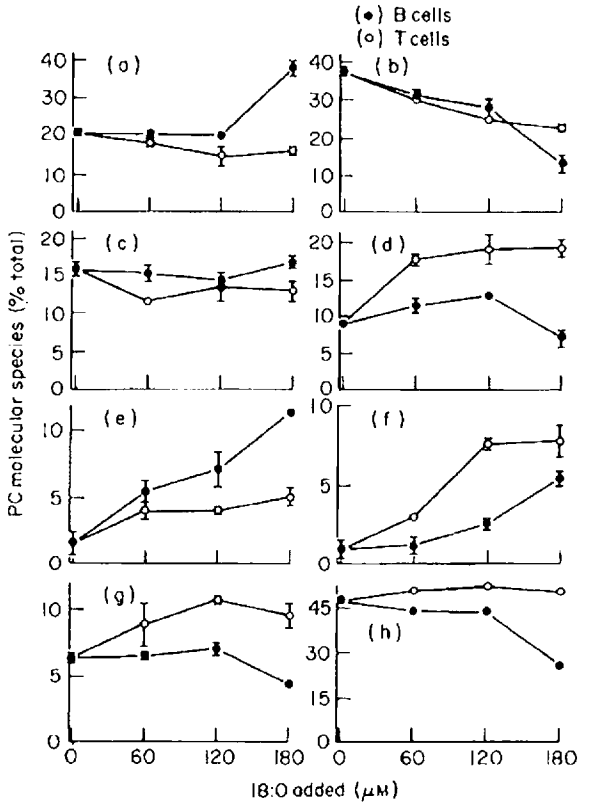

Figure 2. Effect of 18:0 addition on PC molecular species of B and T lymphocytes. Purified B and T lymphocytes were stimulated with PHA or LPS, respectively, in the absence or presence of 60 μM, 120 μM or 180 μM 18:0. After 6 hr the cells were harvested and analysed for their PC molecular species. Data are shown for the major molecular species of PC only and are represented as the mean (± SD) of three separate experiments. (a) 16:0–18:1 and 18:0–18:2; (b) 16:0–16:0; (c) 16:0–18:2; (d) 16:0–18:0; (e) 18:0–18:1; (f) 18:0–18:0; (g) 18:0–20:4; (h) total desaturates.

The addition of 18:0 was accompanied by changes in the levels of six of the seven major PC molecular species, with 16:0–18:2 being the singular exception (Fig. 2c). Because of their low levels (1–2%), it was not possible to reliably test for 18:0-induced changes in the four molecular species not shown in Fig. 2. In both B and T cells, levels of 16:0–16:0 PC declined with increasing doses of 18:0 added (Fig. 2b). However, whereas the proportion of 16:0–16:0 decreased from 40% to 25% in T cells exposed to 180 μM 18:0, a further reduction to 15% was observed in similarly treated B cells. The decline in 16:0–16:0 PC in T cells was largely accompanied by increased levels of 16:0–18:0 (Fig. 2d) and 18:0–18:0 (Fig. 2f), which resulted in the overall preservation of similar levels of total desaturated molecular species (Fig. 2h). By contrast, in B cells 16:0–16:0 was replaced by 18:0–18:1 (Fig. 2e) and 16:0–18:1 and 18:0–18:2 (Fig. 2a), resulting in a significant decline in total desaturated PC (Fig. 2h). Overall, with increasing doses of 18:0, T cells were found to substitute 18:0 for 16:0 with little change in the total amount of desaturated species. B cells, however, showed a paradoxical decrease in desaturated species as a consequence of 18:0 exposure.

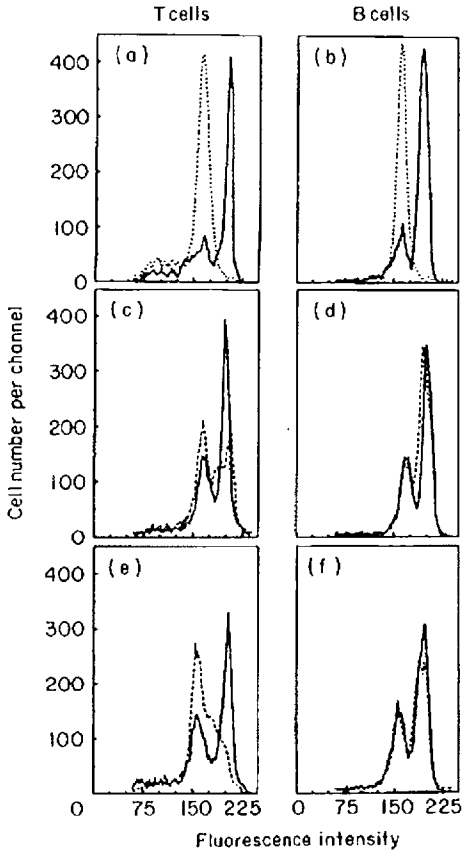

Figure 3. Relative membrane potential of B and T cells exposed to 18:0. Purified B and T cells were stimulated with PHA or LPS, respectively, and cultured in the absence (solid lines) or presence (dashed lines) of 180 μM 18:0. Aliquots were removed after 0 hr (a, b), 4 hr (c, d) and 8 hr (e, f), the cells stained with $DiOC_6(3)$, and analysed by flow cytometry. Gramidicin S was also used to determine the fluorescence intensity of totally depolarized cells (dotted lines, a, b).

Effect of 18:0 supplementation on lymphocyte membrane potential

Previous studies with erythrocytes have determined that cell haemolysis results after replacement of only 25% of native PC with 18:0–18:0 PC (Lange *et al.*, 1980; Kuypers *et al.*, 1984). An accumulation of the desaturated lipid species was thought to increase membrane rigidity and leakiness, and thus promote haemolysis. To test the effect of 18:0 exposure on the integrity of B- and T-cell membranes, experiments were undertaken to correlate 18:0 supplementation with changes in membrane potential, this being a marker for a functionally intact plasma membrane.

Upon incubation with the membrane potential-sensitive dye, $DiOC_6(3)$, both B and T lymphocytes displayed a level of fluorescence intensity expected for cells having an electronegative intracellular milieu (solid line, Fig. 3a,b). Gramicidin S, an antibiotic known to depolarize cells (Damjanovich *et al.*, 1987), was used to define cells in a totally depolarized state. At a concentration of 20 μg/ml, a maximum reduction in fluorescence intensity of both cell types was observed (dotted line, Fig. 3a,b).

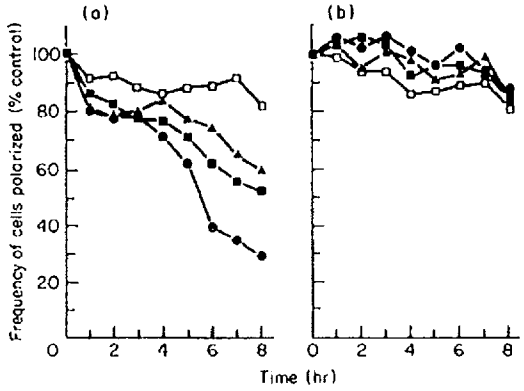

Figure 4. Disruption of T-cell membrane potential by 18:0 is time and dose dependent. Purified B (b) and T (a) cells were mitogen stimulated and cultured in the absence or presence of various doses of 18:0. Aliquots were removed at each hourly time-point and the cells were stained with $DiOC_6$ (3) prior to flow cytometric analysis. Fluorescence intensity values were assigned to depolarized and polarized cells based upon Gramicidin-treated and untreated cell populations. Data are expressed as the percentage of cells displaying fluorescence intensities comparable to control (polarized) cells; each data point is based upon the analysis of 10^4 cells. Symbols: (□) no 18:0; (▲) 60 μM 18:0; (■) 120 μM 18:0; and (●) 180 μM 18:0.

The proportion of viable lymphocytes has previously been reported to decrease with time even under optimal cell culture conditions (Buttke & Cuchens, 1984). This effect is also seen in the histograms shown in Fig. 3b–f at time-points of 0, 4 and 8 hr, respectively. Incubation of B and T cells with 180 μM 18:0 (dashed line, Fig. 3) resulted in a further time-dependent decrease in the proportion of polarized T cells to an extent comparable to that seen with Gramicidin S. By comparison, 18:0 had no significant effect on the proportion of polarized B cells.

A more detailed analysis of the effects of varying doses of 18:0 on T and B cell-membrane potential were subsequently carried out. Purified B and T cells were separately stimulated with LPS or PHA, respectively, in the absence or presence of 60 180 μM 18:0. Following incubation at 37°, aliquots were removed from each of the eight cultures at hourly intervals and the cells were stained with $DiOC_6(3)$ prior to analysis by flow cytometry. The proportion of polarized lymphocytes was subsequently determined as a function of both time and 18:0 dose (Fig. 4). The relative membrane potential of B cells was not altered by the addition of 18:0 to the culture medium, but T cells displayed a reduced membrane potential as early as 5–6 hr after exposure to 60 μM 18:0. Higher doses of 18:0 had more pronounced effects, reducing the number of polarized cells to $< 30\%$ at the 8 hr time-point. The results presented are in agreement with previous findings that the inhibitory effects of a similar dose (50 μM) of 18:0 on mitogen-induced DNA synthesis were manifest within 4–10 hr after exposure to 18:0 (Buttke & Cuchens, 1984).

It was attempted to discern a correlation between membrane lipid composition and membrane integrity by analysing data obtained from Fig. 2 as a function of data derived from Fig. 4. Although the level of total desaturated molecular species in B and T cells could not be correlated with the reduced membrane potential, an excellent correlation ($r = -0.85$) was observed

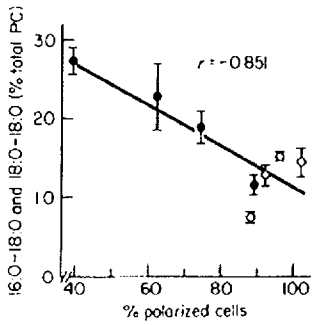

Figure 5. Correlation between membrane lipid composition and membrane integrity. The sum of 18:0–18:0 plus 16:0–18:0 PC molecular species in B (open circles) and T (solid circles) cells exposed to 0–180 μM 18:0 for 6 hr (derived from Fig. 2) was plotted as a function of the proportion of polarized cells at the 6 hr time-point (derived from Fig. 4). A best fit line was determined by linear regression analysis.

when the percentage of polarized cells was plotted versus the sum of 16:0–18:0 and 18:0–18:0 PC (Fig. 5). This suggests that the replacement of 16:0–16:0 with desaturates containing one or more 18:0 moiety per molecule are primarily responsible for 18:0-induced T-cell death.

DISCUSSION

The studies described in this report were designed to determine the mechanism by which 18:0 selectively kills murine T cells (Buttke & Cuchens, 1984). To this end, a model system for the study of saturated fatty acid uptake and subsequent metabolism by B and T lymphocytes has been developed. The system uses highly enriched populations of B and T lymphocytes (>95%) and albumin-complexed fatty acids. Both conditions were essential for defining the basis of 18:0 inhibition. Previous workers have used heterogenous leucocyte populations in which comparative studies of lipid metabolism between B and T lymphocytes were precluded. Further, in studies wherein the fatty acids were delivered as ethanolic solutions, large intracellular pools of non-esterified fatty acids were shown to accumulate (Klausner *et al.*, 1980). By contrast, other studies have shown that 18:0 provided as an albumin complex is efficiently taken up and esterified into cellular phospholipids, with <10% remaining unesterified (Yang, Cuchens & Buttke, 1986; Buttke *et al.*, 1989). Furthermore, using [^{14}C]18:0 it has been shown that the majority of exogenously supplied albumin-complexed 18:0 is incorporated into PC (Buttke *et al.*, 1989). Thus analyses of PC molecular species serves as a useful parameter for assessing the overall effects of 18:0 on B- and T-cell membranes.

As shown previously (Buttke *et al.*, 1989) and in this study, incubation of B and T cells with albumin-complexed 18:0 results in marked changes in the membrane lipid compositions of both cell types. Although both B and T cells take up similar quantities of 18:0 into PC (Buttke *et al.*, 1989), following 18:0 exposure the two cell types display substantial differences in their PC molecular species. The addition of 18:0 to B cells leads to an unexpected increase in unsaturated species at the expense of desaturates. Presumably, this shift in unsaturation is due to their ability to desaturate the exogenously supplied 18:0 using the stearoyl-CoA desaturase enzyme. Conversely, T cells, which are uniquely deficient in stearoyl-CoA desaturase (Buttke *et al.*, 1989) cannot similarly avoid the incorporation of 18:0 into their membrane phospholipids. As a result, the T cells are forced into increasing their levels of phospholipid species containing 18:0, in particular 16:0–18:0 and 18:0 18:0 PC. Importantly, the demonstrated changes were dose-dependent and occurred within 6 hr, a time sufficient to induce T-cell death (Buttke & Cuchens, 1984).

The ultimate effect of the observed changes in the membrane composition of 18:0-treated T cells may have been indicated previously. In studies with erythrocytes, Lange *et al.* (1980) and Kuypers *et al.* (1984) showed that stochiometric replacement of native erythrocyte PC with 18:0–18:0 was accompanied by increased osmotic fragility, resulting in haemolysis. Thus it was determined whether the previously observed accumulation of 18:0–18:0 PC in T cells (Buttke *et al.*, 1989) could also be associated with increased membrane leakiness. The ability of B and T cells to maintain a membrane potential was assayed as an indicator of plasma membrane integrity. It was found that 18:0 exposure led to a dose-dependent decline in the proportion of T cells capable of maintaining a membrane potential. A similar collapse of the plasma membrane permeability barrier was not observed in B cells. The concept that 18:0-induced depolarization is responsible for reduced T-cell viability is in agreement with the relatively rapid (4–10 hr) cytotoxic effect of the fatty acid. These studies do not prove a cause-and-effect relationship between membrane lipid changes and disruption of the membrane potential. Nevertheless, they do show a strong correlation ($r = -0.85$) between the proportion of polarized B and T cells and their levels of 16:0–18:0 plus 18:0–18:0 PC.

Data obtained in this study and elsewhere (Buttke & Cuchens, 1984; Buttke *et al.*, 1989) collectively suggest the following paradigm for the inhibition of T-dependent immune responses by 18:0: B cells incorporate 18:0, desaturate a portion of it to yield 18:1, and insert both fatty acids into phospholipids to maintain a functional level of membrane fluidity. T cells, however, due to their lack of stearoyl-CoA desaturase, cannot convert 18:0 to 18:1. Consequently, the T cells replace much of their 16:0 and olefinic moieties with 18:0, and accumulate significant amounts of both 16:0–18:0 and 18:0–18:0 PC. Replacement of 16:0–16:0, and perhaps other species, by 16:0–18:0 and 18:0–18:0 would be expected to decrease membrane fluidity and promote the formation of gel-like membrane domains. Such alterations in the physical properties of T-cell membranes may lead to a collapse of plasma membrane potential and, ultimately, cell death.

Lastly, the selective toxicity of 18:0 for T cells and its rapid mechanism of action may have clinical relevance in allograft or autoimmune situations. Immunosuppressive agents such as cyclosporin A are widely used for delaying the onset of allograft rejection (Borel *et al.*, 1976). The therapeutic value of cyclosporin derives from its marked selectivity toward T cells (Cohen *et al.*, 1984). Like 18:0, cyclosporin has also been shown to depolarize T cells (Damjanovich *et al.*, 1987), and both agents block IL-2 production (Kronke, Leonard & Depper, 1984; Pourbohloul & Buttke, 1990). Since cyclosporin has numerous potential side effects, including nephrotoxicity, hepatotoxicity and malignant lesions (Kahan *et al.*, 1986), alternative immunosuppressive agents are required. If the effects of 18:0 on T cells could be retained *in vivo*, the fatty acid could effectively and rapidly immunosuppress cell-mediated responses, but without the serious side-effects of cyclosporin.

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EXHIBIT "I"

Zinc Supplement Use and Risk of Prostate Cancer

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The high concentration of zinc in the prostate suggests that zinc may play a role in prostate health. We examined the association between supplemental zinc intake and prostate cancer risk among 46 974 U.S. men participating in the Health Professionals Follow-Up Study. During 14 years of follow-up from 1986 through 2000, 2901 new cases of prostate cancer were ascertained, of which 434 cases were diagnosed as advanced cancer. Supplemental zinc intake at doses of up to 100 mg/day was not associated with prostate cancer risk. However, compared with nonusers, men who consumed more than 100 mg/day of supplemental zinc had a relative risk of advanced prostate cancer of 2.29 (95% confidence interval = 1.06 to 4.95; P_{trend} = .003), and men who took supplemental zinc for 10 or more years had a relative risk of 2.37 (95% confidence interval = 1.42 to 3.95; P_{trend}<.001). Although we cannot rule out residual confounding by supplemental calcium intake or some unmeasured correlate of zinc supplement use, our findings, that chronic zinc oversupply may play a role in prostate carcinogenesis, warrant further investigation. [J Natl Cancer Inst 2003;95:1004–7]

Approximately 15% of the U.S. population uses dietary supplements that contain zinc *(1)*. Ten percent of men who take zinc supplements have an average daily zinc intake that is 2–3 times the recommended dietary allowance of 11 mg/day for men *(2)*. The reasons why individuals take supplemental zinc are not well documented.

The concentration of zinc in the prostate is higher than that in any other soft tissue in the body *(3)*. Zinc levels in prostate adenocarcinoma are markedly lower than those in the surrounding normal prostate tissues *(3)*. Several findings that link zinc with the suppression of prostate cancer cell growth *(4–6)* and inhibition of prostate tumor cell invasion *(7,8)* suggest that high intraprostatic zinc levels may protect against prostate carcinogenesis. However, results of other studies suggest that high intraprostatic zinc concentrations may adversely affect prostate cancer risk. For example, zinc enhances the activity of telomerase *(9)*, an enzyme thought to be responsible for unlimited proliferation of tumor cells and whose activity is increased in prostate cancer *(10)*. Zinc has also been found to antagonize the potential inhibitory effect of bisphosphonates on prostate tumor cell invasion *(11)*.

Whether dietary zinc intake affects intraprostatic zinc levels is unknown. However, ingestion of 150 mg/day or more of zinc has undesirable metabolic effects, such as immune dysfunction *(12)* and impaired antioxidant defense *(13)*, that are potentially related to prostate cancer. In animal studies, subtoxic zinc levels at doses of 200 parts per million of zinc in supply water may interfere with a cancer-protecting activity associated with selenium intake *(14)*. In humans, zinc intake is positively correlated with circulating levels of insulin-like growth factor-I *(15)* and testosterone *(16)*, growth factors that are directly related to prostate carcinogenesis. Thus, results of studies that have addressed the systemic effects of dietary zinc suggest that high zinc intakes may be positively associated with prostate cancer risk *(12–16)*. To address this issue, we examined the relationship between supplemental zinc intake and prostate cancer risk among participants in the Health Professionals Follow-Up Study. The Health Professionals Follow-Up Study was initiated in 1986, when 51 529 U.S. male health professionals aged 40 to 75 years responded to a mailed questionnaire concerning their medical history and disease risk factors. Since then, follow-up questionnaires have been mailed biennially to cohort members to update information on newly diagnosed illnesses. The Health Professionals Follow-Up Study was approved by the institutional review board on the use of human subjects in research of the Harvard School of Public Health.

Dietary intake was assessed in 1986 with the use of a 131-item semiquantitative food-frequency questionnaire that requested detailed information on the amount and duration of supplement use, including questions on the brand of multivitamin used and the use of vitamins A, C, and E, zinc, iron, and calcium. The Pearson correlation coefficient between zinc intake reported in this questionnaire and in two 1-week dietary records was 0.71 *(17)*, indicating reasonable validity of our questionnaire-based assessment of zinc intake. On each follow-up questionnaire, participants were asked to report whether they had been diagnosed with prostate cancer during the previous 2 years. We requested permission from men who reported a prostate cancer diagnosis (or from the next of kin for decedents) to obtain medical records and pathology reports, which were used to confirm the diagnosis and to determine the stage of the cases of prostate cancer. Multivariable relative risks (RRs) were computed using the Cox proportional hazards model *(18)*. The proportional hazards assumption was satisfied. All statistical tests were two-sided.

During 587 444 person-years of follow-up, we documented 2901 new cases of prostate cancer. Among the men in our study population, supplemental zinc provided 32% of total zinc intake and thus represented by far the major source of zinc. Other sources of zinc included beef and breakfast cereals, which provided 11% and 5%, respectively, of zinc intake. The median value of the highest

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category of supplemental zinc intake (reported by approximately 1% of the study population) was 143 mg/day, a dose that exceeds the current recommended dietary allowance by 13-fold. We examined supplemental zinc use in relation to various risk factors for prostate cancer (Table 1). Compared with nonusers, men who consumed supplemental zinc also consumed more multivitamins, supplemental calcium, supplemental vitamin E, lycopene, copper, iron, folate, and fish, but had lower intakes of red meat, and were slightly less likely to have had a history of prostate-specific antigen screening.

We next examined the association between supplemental zinc use and prostate cancer risk (Table 2). In age-adjusted and multivariable models, we observed no statistically significant associations between supplemental zinc intakes at doses less than or equal to 100 mg/day and the risk of prostate cancer. However, compared with nonusers of zinc supplements, men who consumed more than 100 mg/day of supplemental zinc had a multivariable RR of advanced prostate cancer of 2.29 (95% confidence interval [CI] = 1.06 to 4.95; P_{trend} = .003). By contrast, zinc obtained from food sources was not associated with prostate cancer risk (data not shown). We also examined the association between duration of supplemental zinc and the risk of prostate cancer (Table 2). Increasing duration of supplemental zinc use was unrelated to the risk of total or organ-confined prostate cancer. However, the multivariable RR of advanced prostate cancer for men who used supplemental zinc for 10 years or longer compared with nonusers was 2.37 (95% CI = 1.42 to 3.95; P_{trend}<.001).

Apart from chance, possible explanations for these findings are residual confounding by supplemental calcium intake or by some unmeasured correlate of zinc supplement use. We examined these possibilities in various subanalyses by restricting our study population to men who reported supplemental calcium intakes of less than 900 mg/day, by adjusting for intakes of copper, iron, and folate; by controlling for benign prostatic hyperplasia; and by excluding nonusers of zinc supplements. The results were essentially unchanged. Because zinc has long been associated with prostate health, the observed associations may also reflect the effects of self-medication of longstanding prostate symptoms with surplus amounts of supplemental zinc. In addition, increased zinc supplement use may have coincided with decreased medical surveillance, which could ultimately have resulted in late detection of prostate cancer and, thus, a greater probability of advanced prostate cancer in these men. However, accounting for history of prostate-specific antigen screening and excluding the early years of follow-up did not materially alter the results. In summary, we found that excessively high supplemental zinc intake was associated with an increased risk of advanced prostate cancer. Strong evidence to support a specific mechanism for this association is lacking at present. Nevertheless, our findings suggest that the role of chronic oversupply of zinc in prostate carcinogenesis requires further investigation.

Table 1. Selected characteristics of 46 974 participants in the Health Professionals Follow-Up Study in relation to level of supplemental zinc intake at baseline*

Characteristic	Level of supplemental zinc intake, mg/day†				
	Nonusers	1–24	25–74	75–100	≥101
Median supplemental zinc intake, mg/day‡	0	10	44	82	143
No. of participants	35 121	7479	3117	845	412
Age in 1986, y (mean ± SD)	54 ± 9.7	55 ± 9.8	56 ± 9.5	56 ± 9.1	56 ± 9.3
Body mass index in 1986, kg/m^2 (mean ± SD)	26 ± 3.4	25 ± 3.1	25 ± 3.1	25 ± 3.2	26 ± 3.7
Body mass index at age 21, kg/m^2 (mean ± SD)	23 ± 3.1	23 ± 3.1	23 ± 3.1	23 ± 3.2	23 ± 3.7
Family history of prostate cancer, %	12	12	11	11	12
History of type II diabetes, %	3	3	3	3	4
Routine screening for PSA by 2000, %	78	79	80	75	74
Smoked in the past 10 y, %	22	21	20	20	20
Vigorous physical activity (mean METs ± SD)	12 ± 26	14 ± 24	16 ± 31	16 ± 28	16 ± 28
Multivitamin use, %	26	96	84	83	87
Mean intakes (±SD)					
Supplemental calcium, mg/day	37 ± 150	168 ± 267	323 ± 376	584 ± 559	1021 ± 700
Supplemental vitamin E, mg/day	40 ± 128	144 ± 216	316 ± 269	326 ± 298	465 ± 315
Zinc from food sources, mg/day§	13.2 ± 4.1	13.3 ± 5.7	13.2 ± 7.0	13.3 ± 3.9	13.3 ± 2.9
Lycopene, μg/day§	10 312 ± 7411	10 374 ± 7832	10 759 ± 7541	11 052 ± 7545	10 982 ± 7816
α-Linolenic acid, g/day§	1.1 ± 0.36	1.1 ± 0.36	1.1 ± 0.35	1.1 ± 0.35	1.1 ± 0.35
Fructose, g/day§	49.0 ± 17.3	49.7 ± 17.9	50.0 ± 18.0	49.5 ± 18.1	49.6 ± 18.1
Total calcium, mg/day§	829 ± 348	984 ± 420	1169 ± 549	1445 ± 747	1919 ± 872
Copper, mg/day§	1.6 ± 0.4	2.9 ± 1.3	2.8 ± 1.8	2.5 ± 1.6	2.8 ± 1.6
Iron, mg/day§	15.7 ± 9.2	29.3 ± 15.6	35.3 ± 27.1	32.2 ± 25.8	44.7 ± 34.1
Folate, μg/day§	425 ± 218	583 ± 273	763 ± 413	793 ± 474	892 ± 485
Fish, servings/wk	2.3 ± 2.0	2.5 ± 2.1	2.8 ± 2.3	2.9 ± 2.3	2.9 ± 2.7
Red meat, servings/wk‖	6.9 ± 4.9	6.4 ± 4.8	5.5 ± 4.5	5.7 ± 4.7	5.8 ± 5.0

*All values (except age) are standardized to the age distribution of the study population. PSA = prostate-specific antigen; METs = metabolic equivalents per week.

†Specific information on the form of supplemental zinc was not available. However, for zinc supplements, the most common form is zinc gluconate.

‡Maximum value of highest category of supplemental zinc intake level is 270 mg/day.

§Nutrients are adjusted for total energy intake.

‖Red meat includes beef, pork, lamb, hamburgers, hot dogs, processed meat, and bacon. Servings of beef, pork, or lamb as a main dish were converted to servings as a mixed dish.

Table 2. Relative risk of prostate cancer in relation to level and duration of supplemental zinc intake at baseline among participants in the Health Professionals Follow-Up Study*

Variable	Nonusers	Users				P_{trend}
		Level of supplemental zinc intake, mg/day				
		1–24	*25–74*	*75–100*	*≥101*	
Total prostate cancer						
No. of cases/person-years	2127/440 052	469/93 031	215/38 843	54/10 515	36/5003	
Age-adjusted RR† (95% CI)	1.0 (referent)	0.90 (0.85 to 1.04)	0.99 (0.86 to 1.14)	0.90 (0.69 to 1.18)	1.24 (0.89 to 1.73)	.71
Multivariate RR‡ (95% CI)	1.0 (referent)	0.94 (0.83 to 1.07)	1.01 (0.86 to 1.19)	0.95 (0.71 to 1.26)	1.29 (0.88 to 1.89)	.34
Multivariate RR§ (95% CI)	1.0 (referent)	0.94 (0.83 to 1.07)	1.01 (0.86 to 1.19)	1.02 (0.76 to 1.37)	1.37 (0.91 to 2.01)	.17
Multivariate RR‖ (95% CI)		1.0 (referent)	1.08 (0.91 to 1.29)	1.05 (0.77 to 1.43)	1.43 (0.95 to 2.15)	.10
Organ-confined cancer						
No. of cases	1223	282	108	26	14	
Age-adjusted RR† (95% CI)	1.0 (referent)	0.99 (0.87 to 1.13)	0.87 (0.71 to 1.06)	0.76 (0.51 to 1.12)	0.83 (0.49 to 1.41)	.06
Multivariate RR‡ (95% CI)	1.0 (referent)	0.97 (0.82 to 1.15)	0.88 (0.71 to 1.10)	0.79 (0.52 to 1.19)	0.88 (0.49 to 1.58)	.19
Multivariate RR§ (95% CI)	1.0 (referent)	0.97 (0.82 to 1.15)	0.89 (0.72 to 1.12)	0.84 (0.55 to 1.27)	0.96 (0.53 to 1.72)	.35
Multivariate RR‖ (95% CI)		1.0 (referent)	0.95 (0.75 to 1.21)	0.92 (0.59 to 1.43)	1.10 (0.59 to 2.06)	.89
Advanced cancer						
No. of cases	317	56	40	11	10	
Age-adjusted RR† (95% CI)	1.0 (referent)	0.75 (0.56 to 0.99)	1.23 (0.88 to 1.71)	1.23 (0.68 to 2.25)	2.28 (1.22 to 4.28)	.008
Multivariate RR‡ (95% CI)	1.0 (referent)	0.81 (0.57 to 1.16)	1.45 (0.98 to 2.12)	1.39 (0.72 to 2.71)	2.29 (1.06 to 4.95)	.003
Multivariate RR§ (95% CI)	1.0 (referent)	0.81 (0.57 to 1.15)	1.36 (0.92 to 2.01)	1.68 (0.86 to 3.26)	2.39 (1.12 to 5.11)	.002
Multivariate RR‖ (95% CI)		1.0 (referent)	1.72 (1.11 to 2.69)	1.93 (0.92 to 4.03)	2.91 (1.23 to 6.90)	.002
		Duration of supplemental zinc use, y				
		1–4	*5–9*	*≥10*		
Total prostate cancer						
No. of cases/person-years	2127/440 052	606/118 870	92/16 870	76/11 653		
Age-adjusted RR† (95% CI)	1.0 (referent)	0.96 (0.87 to 1.05)	0.97 (0.78 to 1.19)	1.00 (0.79 to 1.25)		.67
Multivariate RR‡ (95% CI)	1.0 (referent)	0.97 (0.86 to 1.09)	0.95 (0.76 to 1.19)	1.02 (0.79 to 1.32)		.97
Multivariate RR§ (95% CI)	1.0 (referent)	0.97 (0.86 to 1.09)	0.96 (0.76 to 1.21)	1.09 (0.85 to 1.41)		.67
Multivariate RR¶ (95% CI)		1.0 (referent)	0.95 (0.75 to 1.21)	1.05 (0.81 to 1.35)		.93
Organ-confined cancer						
No. of cases	1223	349	49	32		
Age-adjusted RR† (95% CI)	1.0 (referent)	0.97 (0.86 to 1.09)	0.90 (0.68 to 1.20)	0.74 (0.52 to 1.05)		.05
Multivariate RR‡ (95% CI)	1.0 (referent)	0.96 (0.82 to 1.12)	0.86 (0.63 to 1.18)	0.75 (0.51 to 1.09)		.09
Multivariate RR§ (95% CI)	1.0 (referent)	0.96 (0.82 to 1.13)	0.88 (0.64 to 1.21)	0.79 (0.54 to 1.16)		.16
Multivariate RR¶ (95% CI)		1.0 (referent)	0.89 (0.64 to 1.24)	0.77 (0.53 to 1.14)		.89
Advanced cancer						
No. of cases	317	76	18	23		
Age-adjusted RR† (95% CI)	1.0 (referent)	0.80 (0.62 to 1.03)	1.26 (0.79 to 2.03)	2.01 (1.31 to 3.07)		.004
Multivariate RR‡ (95% CI)	1.0 (referent)	0.89 (0.65 to 1.23)	1.53 (0.90 to 2.61)	2.37 (1.42 to 3.95)		<.001
Multivariate RR§ (95% CI)	1.0 (referent)	0.88 (0.64 to 1.22)	1.47 (0.86 to 2.54)	2.56 (1.54 to 4.26)		<.001
Multivariate RR¶ (95% CI)		1.0 (referent)	1.44 (0.81 to 2.56)	2.55 (1.49 to 4.32)		<.001

*Total prostate cancer: we excluded stage T1a lesions (3% or less of the total) because stage T1a lesions are typically indolent and are especially prone to detection bias. Organ-confined cancers are those with no evidence of extraprostatic involvement at time of diagnosis; advanced cancers are those extending regionally to the seminal vesicle or other adjacent organs, pelvic lymph nodes, or distal organs (usually bone) at the time of diagnosis; or that were fatal by the end of follow-up. The sum of organ-confined prostate cancer cases and advanced prostate cancer cases does not equal the number of total prostate cancer cases because data on stage was not available for all cases and because we excluded stage T3a cancers in the organ-confined and the advanced categories because they are neither organ-confined nor are they usually advanced and hence do not fall into either group. RR = relative risk; CI = confidence interval.

†RR (95% CI) adjusted for current age.

‡RR (95% CI) adjusted for current age, time period (1986–1988, 1988–1990, 1990–1992, 1992–1994, 1994–1996, 1996–1998, 1998–2000), body mass index at age 21, height at baseline in 1986, pack-years of smoking in the previous decade, family history of prostate cancer, vigorous physical activity, regular aspirin use, intake of total energy, dietary calcium, supplemental calcium, fructose, supplemental vitamin E, tomato-based foods, fish, red meat, and α-linolenic acid.

§Excludes non-case subjects who had not had a prostate-specific antigen (PSA) test by 2000 (19.5% of person-years excluded). This analysis was conducted to examine the possibility that underlying differences in PSA screening behavior according to zinc supplement use affected the likelihood of prostate cancer detection, thereby biasing our results by creating spurious associations.

‖Excludes nonusers of zinc supplements; light users (1–24 mg/day) were the referent group. This analysis was performed to examine the possibility that supplement users differ from nonusers with respect to unmeasured, potentially confounding variables.

¶Excludes nonusers of zinc supplements; brief users (1–4 years) were the referent group. This analysis was performed to examine the possibility that supplement users differ from nonusers with respect to unmeasured, potentially confounding variables.

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NOTES

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EXHIBIT "J"

The New York Times

November 3, 2013

Herbal Supplements Are Often Not What They Seem

By ANAHAD O'CONNOR

Americans spend an estimated $5 billion a year on unproven herbal supplements that promise everything from fighting off colds to curbing hot flashes and boosting memory. But now there is a new reason for supplement buyers to beware: DNA tests show that many pills labeled as healing herbs are little more than powdered rice and weeds.

Using a test called DNA barcoding, a kind of genetic fingerprinting that has also been used to help uncover labeling fraud in the commercial seafood industry, Canadian researchers tested 44 bottles of popular supplements sold by 12 companies. They found that many were not what they claimed to be, and that pills labeled as popular herbs were often diluted — or replaced entirely — by cheap fillers like soybean, wheat and rice.

Consumer advocates and scientists say the research provides more evidence that the herbal supplement industry is riddled with questionable practices. Industry representatives argue that any problems are not widespread.

For the study, the researchers selected popular medicinal herbs, and then randomly bought different brands of those products from stores and outlets in Canada and the United States. To avoid singling out any company, they did not disclose any product names.

Among their findings were bottles of echinacea supplements, used by millions of Americans to prevent and treat colds, that contained ground up bitter weed, Parthenium hysterophorus, an invasive plant found in India and Australia that has been linked to rashes, nausea and flatulence.

Two bottles labeled as St. John's wort, which studies have shown may treat mild depression, contained none of the medicinal herb. Instead, the pills in one bottle were made of nothing but rice, and another bottle contained only Alexandrian senna, an Egyptian yellow shrub that is a powerful laxative. Gingko biloba supplements, promoted as memory enhancers, were mixed with fillers and black walnut, a potentially deadly hazard for people with nut allergies.

Of 44 herbal supplements tested, one-third showed outright substitution, meaning there was no trace of the plant advertised on the bottle — only another plant in its place.

Many were adulterated with ingredients not listed on the label, like rice, soybean and wheat, which are used as fillers.

In some cases, these fillers were the only plant detected in the bottle — a health concern for people with allergies or those seeking gluten-free products, said the study's lead author, Steven G. Newmaster, a biology professor and botanical director of the Biodiversity Institute of Ontario at the University of Guelph.

The findings, published in the journal BMC Medicine, follow a number of smaller studies conducted in recent years that have suggested a sizable percentage of herbal products are not what they purport to be. But because the latest findings are backed by DNA testing, they offer perhaps the most credible evidence to date of adulteration, contamination and mislabeling in the medicinal supplement industry, a rapidly growing area of alternative medicine that includes an estimated 29,000 herbal products and substances sold throughout North America.

"This suggests that the problems are widespread and that quality control for many companies, whether through ignorance, incompetence or dishonesty, is unacceptable," said David Schardt, a senior nutritionist at the Center for Science in the Public Interest, an advocacy group. "Given these results, it's hard to recommend any herbal supplements to consumers."

Representatives of the supplement industry said that while mislabeling of supplements was a legitimate concern, they did not believe it reached the extent suggested by the new research.

Stefan Gafner, the chief science officer at the American Botanical Council, a nonprofit group that promotes the use of herbal supplements, said the study was flawed, in part because the bar-coding technology it used could not always identify herbs that have been purified and highly processed.

"Over all, I would agree that quality control is an issue in the herbal industry," Dr. Gafner said. "But I think that what's represented here is overblown. I don't think it's as bad as it looks according to this study."

The Food and Drug Administration has used bar-coding technology to warn and in some cases prosecute sellers of seafood found to be "misbranded." The DNA technique has also

been used in studies of herbal teas, which showed that a significant percentage contain herbs and ingredients that are not listed on their labels.

But policing the supplement industry is a special challenge. The F.D.A. requires that companies test the products they sell to make sure that they are safe. But the system essentially operates on the honor code. Unlike prescription drugs, supplements are generally considered safe until proved otherwise.

Under a 1994 law, they can be sold and marketed with little regulatory oversight, and they are pulled from shelves generally only after complaints of serious injury. The F.D.A. audits a small number of companies, but even industry representatives say more oversight is needed.

"The regulations are very appropriate and rigorous," said Duffy MacKay of the Council for Responsible Nutrition, a supplement industry trade group. "But we need a strong regulator enforcing the full force of the law. F.D.A. resources are limited, and therefore enforcement has not historically been as rigorous as it could be."

Shelly Burgess, a spokeswoman for the F.D.A., said that companies were required to adhere to a set of good manufacturing practices designed to prevent adulteration, but that many were ignoring the rules.

"Unfortunately, we are seeing a very high percentage — approximately 70 percent — of firms' noncompliance," she said, "and we are very active in taking enforcement actions against such violations."

DNA bar coding was developed about a decade ago at the University of Guelph. Instead of sequencing entire genomes, scientists realized that they could examine genes from a standardized region of every genome to identify species of plants and animals. These short sequences can be quickly analyzed — much like the bar codes on the items at a supermarket — and compared with others in an electronic database. An electronic reference library at Guelph, called the International Barcode of Life Project, contains over 2.6 million bar code records for almost 200,000 species of plants and animals.

The testing technique is not foolproof. It can identify the substances in a supplement, but it cannot determine their potency. And because the technology relies on the detection of DNA, it may not be able to identify concentrated chemical extracts that do not contain genetic material, or products in which the material has been destroyed by heat and processing.

But Dr. Newmaster emphasized that only powders and pills were used in the new research, not extracts. In addition, the DNA testing nearly always detected some plant material in the samples — just not always the plant or herb named on the label.

Some of the adulteration problems may be inadvertent. Cross-contamination can occur in fields where different plants are grown side by side and picked at the same time, or in factories where the herbs are packaged. Dr. Gafner of the American Botanical Council said that rice, starch and other compounds were sometimes added during processing to keep powdered herbs from clumping, just as kernels of rice are added to salt shakers.

But that does not explain many of the DNA results. For instance, the study found that one product advertised as black cohosh — a North American plant and popular remedy for hot flashes and other menopause symptoms — actually contained a related Asian plant, Actaea asiatica, that can be toxic to humans.

Those findings mirror a similar study of black cohosh supplements conducted at Stony Brook University medical center last year. Dr. David A. Baker, a professor of obstetrics, gynecology and reproductive medicine, bought 36 black cohosh supplements from online and chain stores. Bar coding tests showed that a quarter of them were not black cohosh, but instead contained an ornamental plant from China.

Dr. Baker called the state of supplement regulation "the Wild West," and said most consumers had no idea how few safeguards were in place. "If you had a child who was sick and three out of 10 penicillin pills were fake, everybody would be up in arms," Dr. Baker said. "But it's O.K. to buy a supplement where three out of 10 pills are fake. I don't understand it. Why does this industry get away with that?"

EXHIBIT "K"

PRODUCT DETAIL

We've got lots of grizzlies here in northwest Montana, and in the off-season they set their activity level at "hibernate". We know you don't cut back your training that much, but you do cut back, and you stay awake all winter eating. Come next season, you look like you are ready to hibernate. If that's the case, then you need Appestat, the guaranteed way to restrict appetite during the off-season. Appestat is a stimulant-free appetite control supplement that safely suppresses appetite and increases carbohydrate metabolism, thereby helping to decrease body fat accumulation and weight gain without the use of potentially harmful stimulants. When you start off next season already at ideal weight, you'll be glad you invested a few dollars in Appestat.

What's in APPESTAT and What Do These Nutrients Do?

5-HYDROXYTRYPTOPHAN (5-HTP), is a plant-based precursor of serotonin. In addition to potentially enhancing the quality of sleep and growth hormone release, 5-HTP aids in reducing sugar cravings.

ZINC (we use the extremely bioavailable Monomethionine form) is an essential part of approximately 300 different bodily function including carbohydrate metabolism. Low zinc levels, common in high carbohydrate diets, can also reduce the athlete's ability to utilize oxygen and generate energy during exercise.

IODINE is needed for the synthesis of one of the thyroid hormones known as thyroxin that involved in regulating metabolic rate.

CHROMIUM POLYNICOTINATE helps insulin regulate blood sugar levels; supplementation tends to decrease blood sugar in people with high blood sugar levels and raises blood sugar in people with low blood sugar levels. It improves the uptake of cellular glucose for energy production and is believed to inhibit the synthesis of new fat from carbohydrates, which frees the mitochondria to burn already-stored fat. While there are many forms available to the consumer the polynicotinate form is superior, considered to be 300 times more biologically active (referring to absorption rates) than other forms of this trace mineral.

HYDROXYCITRIC ACID (HCA) may just be one of Nature's most remarkable weight loss nutrients. This active ingredient of the Garcinia Cambogia fruit safely inhibits an enzyme called citrate lyase, which is used in the conversion of carbohydrates into fat. It also gently suppresses appetite and reduces food intake.

RELATED PRODUCTS

ANTI-FATIGUE CAPS >
Reduce ammonia & reduce fatigue

EXHIBIT "L"

Garcinia cambogia (Hydroxycitric Acid) as a Potential Antiobesity Agent

A Randomized Controlled Trial

Steven B. Heymsfield, MD; David B. Allison, PhD; Joseph R. Vasselli, PhD; Angelo Pietrobelli, MD; Debra Greenfield, MS, RD; Christopher Nunez, MEd

Context.—Hydroxycitric acid, the active ingredient in the herbal compound *Garcinia cambogia*, competitively inhibits the extramitochondrial enzyme adenosine triphosphate–citrate (pro-3S)-lyase. As a citrate cleavage enzyme that may play an essential role in de novo lipogenesis inhibition, *G cambogia* is claimed to lower body weight and reduce fat mass in humans.

Objective.—To evaluate the efficacy of *G cambogia* for body weight and fat mass loss in overweight human subjects.

Design.—Twelve-week randomized, double-blind, placebo-controlled trial.

Setting.—Outpatient weight control research unit.

Participants.—Overweight men and women subjects (mean body mass index [weight in kilograms divided by the square of height in meters], approximately 32 kg/m^2).

Intervention.—Subjects were randomized to receive either active herbal compound (1500 mg of hydroxycitric acid per day) or placebo, and both groups were prescribed a high-fiber, low-energy diet. The treatment period was 12 weeks. Body weight was evaluated every other week and fat mass was measured at weeks 0 and 12.

Main Outcome Measures.—Body weight change and fat mass change.

Results.—A total of 135 subjects were randomized to either active hydroxycitric acid (n = 66) or placebo (n = 69); 42 (64%) in the active hydroxycitric acid group and 42 (61%) in the placebo group completed 12 weeks of treatment ($P = .74$). Patients in both groups lost a significant amount of weight during the 12-week treatment period ($P < .001$); however, between-group weight loss differences were not statistically significant (mean [SD], 3.2 [3.3] kg vs 4.1 [3.9] kg; $P = .14$). There were no significant differences in estimated percentage of body fat mass loss between treatment groups, and the fraction of subject weight loss as fat was not influenced by treatment group.

Conclusions.—*Garcinia cambogia* failed to produce significant weight loss and fat mass loss beyond that observed with placebo.

JAMA. 1998;280:1596-1600

EXCESSIVE ADIPOSITY and its concomitant health risks are among the most common conditions managed by health care practitioners. The limited long-term effectiveness of conventional weight management, including behavioral therapy,[1] is the impetus of major efforts aimed at developing alternative pharmacologic[2] and surgical weight reduction treatment strategies.[3] A rapidly growing therapeutic area, and one widely embraced by the general public, is the use of herbal weight loss products.

An herb-derived compound, hydroxycitric acid, is now incorporated into many commercial weight loss products. Obtained from extracts of related plants native to India, mainly *Garcinia cambogia* and *Garcinia indica*, hydroxycitric acid was first identified by Watson and Lowenstein[4b] in the late 1960s as a potent competitive inhibitor of the extramitochondrial enzyme adenosine triphosphate–citrate (*pro-3S*)-lyase. These investigators and others subsequently demonstrated both in vitro and in vivo that hydroxycitric acid in animals not only inhibited the actions of citrate cleavage enzyme and suppressed de novo fatty acid synthesis,[6] but also increased rates of hepatic glycogen synthesis,[7] suppressed food intake,[8] and decreased body weight gain.[9]

Although hydroxycitric acid appears to be a promising experimental weight control agent, studies in humans are limited and results have been contradictory[10-14] (also R. Ramos, J. Flores Saenz, F. Alarcon, unpublished data, 1996, and G. Kaats, D. Pullin, L. Parker, S. Keith, unpublished data, 1996). Supporting evidence of human hydroxycitric acid efficacy for weight control is based largely on studies with small sample sizes,[11,12] studies that failed to include a placebo-treated group,[10] and use of inaccurate measures of body lipid change.[12] Although hydroxycitric acid effectiveness remains unclear, at least 14 separate hydroxycitric acid–containing products are presently sold over-the-counter to consumers.[15] This investigation was designed to overcome limitations of earlier studies and examine the effectiveness of hydroxycitric acid for weight loss and fat mass reduction in a rigorous controlled trial.

METHODS

Protocol

We tested 2 primary hypotheses in a randomized, double-blind, placebo-controlled trial: (1) *G cambogia* produces a greater reduction in body weight than placebo, and (2) *G cambogia* produces a greater reduction in total body fat mass than placebo. Advertisements were placed in local newspapers, and over-

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weight subjects who responded and met entry criteria during a telephone screening interview were scheduled for a baseline visit. The evaluation included a physical examination, electrocardiogram, and screening blood studies. Subjects meeting entry criteria were seen within 2 weeks for randomization at treatment week 0. Subjects were assigned to placebo or active compound with equal probability through a random number generator.

The protocol with active herbal compound included *Garcinia cambogia* extract (50% hydroxycitric acid by chemical analysis), taken 3 times daily as two 500-mg caplets 30 minutes before meal ingestion. Total daily dose was *Garcinia cambogia* extract, 3000 mg, and hydroxycitric acid, 1500 mg. Placebo-treated subjects followed an identical protocol in which active compound was replaced with inert ingredients. Subjects taking active compound or placebo were provided a high-fiber, 5040-kJ/d diet plan, with 20%, 50%, and 30% of energy as fat, carbohydrate, and protein, respectively. The recommended daily food provision was divided into 3 meals with an evening snack. Subjects were asked to maintain a stable physical activity level and return for evaluation every 2 weeks for a total treatment interval of 12 weeks. Body weight was measured at each visit, and clinical information, including potential herb or weight loss adverse effects, was obtained. Biweekly pill counts and diaries were used to check patient medication compliance. Diet compliance was not quantitatively monitored during the study.

The study was approved by the institutional review board of St Luke's Roosevelt Hospital Center, New York, NY, and all subjects gave written consent prior to participation.

Subjects

Subjects were overweight but otherwise healthy adults aged 18 to 65 years who had a body mass index (BMI, defined as weight in kilograms divided by the square of height in meters) of more than 27 kg/m^2 and at most 38 kg/m^2. Subjects were excluded if they were pregnant, had any clinically significant medical condition, were taking prescription medications or appetite suppressants on a regular basis, had a history of alcohol or other drug abuse, were allergic to any of the study products, or had dieted with weight loss in the past 6 months.

Body Composition

Body weight and height were measured to the nearest 0.1 kg and 0.5 cm using a digital scale (Weight Tronix, New York, NY) and stadiometer (Holtain, Crosswell, Wales), respectively.

Table 1.- Baseline Subject Characteristics*

Group	No. of Patients	Age, y	Weight, kg	BMI, kg/m^2†	Total Body Fat Mass, %
Treatment					
Men	5	43.1 (7.8)	100.8 (11.0)	33.0 (3.7)	28.4 (2.6)
Women	61	38.7 (7.8)	82.9 (8.8)	31.1 (2.7)	41.9 (7.3)
Total	66	38.6 (7.7)	83.8 (10.1)	31.2 (2.8)	41.1 (7.8)
Placebo					
Men	14	40.5 (5.5)	101.7 (11.8)	32.3 (2.5)	36.6 (5.9)
Women	55	39.6 (7.6)	84.8 (10.9)	31.4 (3.2)	43.8 (4.2)
Total	69	39.4 (7.2)	88.2 (13.0)	31.9 (3.1)	42.0 (5.6)

*Data (except number of patients) are presented as group mean (SD).
†BMI indicates body mass index, defined as weight in kilograms divided by the square of height in meters.

Total body fat mass was measured at baseline and at the 12-week visit using several different procedures.

A pencil-beam dual-energy x-ray absorptiometry (DXA) scanner (Lunar DPX, Madison, Wis) was used to estimate total body fat mass. Subjects completed the slow-mode whole body scan and fat mass estimates were provided by Lunar, Version 3.6g, software.[16] The technical error of DXA percentage fat mass estimates in our laboratory is 3.1%.[17] The remaining body fat mass measurement methods used in our laboratory for this study included underwater weighing,[18] skinfold thicknesses,[19] and bioimpedance analysis.[20]

Statistical Analysis

Based on previous research,[1] we estimated that a study that included at least 30 completed subjects in each of 2 groups would have more than 80% power at the 2-tailed α level of .05 to detect any significant differences in body weight.

The 2 study hypotheses were tested in separate sets of statistical analyses. Statistical models were used in which the outcome variable, either loss of body weight or percentage of fat mass, was set as dependent variable and assigned treatment and other covariates were set as independent variables in an intent-to-treat analysis.[21] Within the intent-to-treat analysis, missing data due to measurement failure or subject dropout were imputed by carrying the last observation forward (LOCF).[22] The baseline value of the dependent variable (ie, initial body weight or percentage of fat mass) served as a potential independent variable in each analysis. Patient age and sex also served as additional independent variables. All analyses were conducted at the 2-tailed α level of .05.

For each of the 2 dependent variables, a set of secondary analyses were conducted, including (1) evaluation of completers only; (2) imputation of all missing data with a regression procedure rather than the LOCF; (3) imputation of missing data using the EM[23] algorithm rather than the LOCF; (4) use of weight loss slopes as outcomes[24] rather than the simple baseline to final measurement change when more than 2 time points for weight were available; (5) performance of a full repeated-measures analysis of variance using all time points; and (6) performance of a multivariate analysis of covariance using all time points simultaneously in the statistical model. In no case did any of these secondary sensitivity analyses lead to different conclusions than the primary LOCF intent-to-treat analysis. We therefore report only the results of the primary intent-to-treat analysis.

At baseline, DXA readings were unavailable for several subjects who had technically poor scans or who were evaluated during a brief period in which the DXA system was undergoing repair. However, each of these subjects had 1 or more measurements of fat mass taken with the other techniques mentioned herein and summarized in earlier articles.[16-20] Estimates of total body fat mass for these subjects by DXA were inferred using single imputation plus random error models based on multiple regression analysis of all other available measurements of fat mass for that subject, as described by Graham et al.[25] Similarly, several subjects completed the entire course of treatment and received some measurement of body fat mass after treatment but not by DXA. For these subjects, estimates of total body fat mass by DXA also were imputed using the same statistical methods and the other available measurements of body fat mass.

The purported fat-mobilizing properties of hydroxycitric acid were evaluated by computing the slope of change in fat mass vs change in body weight for the 2 treatment groups. Assuming approximately a zero intercept for this relation, the anticipated regression line slopes should approach 0.7 to 0.8, the generally acknowledged fraction of weight loss as fat mass in obesity trials.[26] Promotion of fat mass loss by active hydroxycitric acid would be associated with an increased fraction of weight loss as fat mass.

Group results are expressed as mean (SD) in text and tables. Data were analyzed using the statistical programs

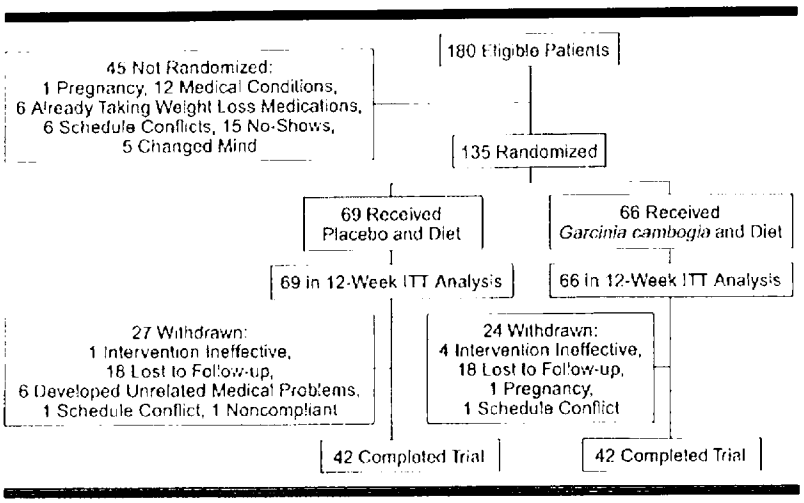

Figure 1.—Study CONSORT flow diagram. ITT indicates intent-to-treat.

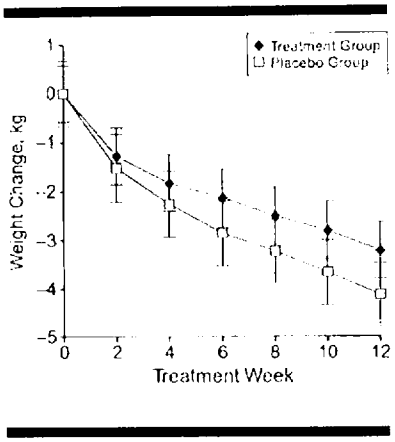

Figure 2.—Weight-change curves for 2 study groups. Results are plotted for group means (±95% confidence limits) for 69 subjects in the placebo group and 66 subjects in the treatment group. Data are from last-observation-carried-forward intent-to-treat analysis.

SPSSWIN, Version 7.5, and SPSSMVA, Version 7.5 (SPSS Inc, Chicago, Ill).

RESULTS

Baseline Characteristics

At baseline, 180 moderately overweight subjects were screened and, of those, 135 were randomized to placebo and active compound (Table 1 and Figure 1). There were 69 subjects (BMI, 31.9 [3.1] kg/m^2) in the placebo-treated group (14 men and 55 women) and 66 subjects (BMI, 31.3 [2.8] kg/m^2) in the *G cambogia*–treated group (5 men and 61 women).

Of the 69 placebo-treated subjects, 42 (61%) completed the 12-week protocol. The reasons for subject withdrawal (27 cases) are summarized in Figure 1. Of the 66 subjects randomized to active compound, 42 (64%) completed the 12 weeks of treatment. The reasons for subject withdrawal from this group (24 cases) are also summarized in Figure 1. There were no significant differences in age, body weight, or BMI between subjects who withdrew from the study and those who completed the 12-week protocol. There was also no significant difference between the 2 groups in the proportion of subjects who completed the entire course of treatment ($\chi^2 = 0.11$, $P = .74$). Among subjects completing the 12 weeks of treatment, medication compliance was 88.6% (10.9%) and 92.1% (10.0%) in the treatment and placebo groups, respectively ($P = .30$).

Weight Loss

Primary Analysis.—The weight loss curves for placebo and treatment groups are shown in Figure 2 for subjects in the intent-to-treat analysis with LOCF. The estimated mean (SD) [median (interquartile range)] weight loss for the placebo group was 4.1 (3.9) [3.9 (4.7)] kg and for the treatment group was 3.2 (3.3) [2.6 (4.1)] kg. The weight loss within each group was significantly different from baseline ($t_{134} = 11.795$, $P < .001$), although between-group weight loss differences were not statistically significant ($t_{134} = 1.474$, $P = .14$). Body weight change differences remained nonsignificant after controlling for patient starting weight, sex, and age. Assumptions of the applied parametric statistical analysis such as homogeneity of variance and normality of residuals were tested and no meaningful violations were detected. Given the lack of significant findings, questions of statistical power are important. Therefore, using the observed distributions of weight change and the within-group SD thereof, we estimated that the power of the current study to detect differences between the treatment and placebo groups in terms of weight change was 89% to detect a between-group difference in weight loss as small as 2 kg at the 2-tailed α level of .05.

Secondary Analyses.—In no case did any secondary analysis indicate any statistically significant effect for the active compound to produce more weight loss than placebo.

Fat Mass Loss

Primary Analysis.—Results for body fat mass analysis were imputed for 9 baseline and 4 post–weight loss subjects. With the LOCF intent-to-treat analysis, the estimated mean (SD) [median (interquartile range)] percentage of body fat mass loss for the placebo group was 2.16% (2.06%) [2.20% (2.7%)] and the estimated percentage of fat mass loss for the treatment group was 1.44% (2.15%) [1.60% (1.9%)]. This difference was tested using the Welch test because the variances were significantly heterogeneous by the Levene test (P for variance heterogeneity = .03). Using the Welch test, the placebo and treatment group mean differences were not statistically significant ($t_{127} = 1.7$, $P = .08$). This finding was consistent with that of the ordinary t test ($t_{132} = 1.78$, $P = .08$). Using analysis of covariance with age, sex, and pretest percentage of fat mass as covariates, the percentage of fat mass differences also was nonsignificant ($F_{1,129} = 1.67$, $P = .21$).

Secondary Analyses.—As for weight loss, all of the secondary analyses were consistent with the primary analysis. That is, in no case did analysis indicate any statistically significant effect for the active compound to produce a different percentage of body fat mass loss than the placebo.

Examination of the change in fat mass relative to change in body weight derived using least squares regression analysis for all subjects combined resulted in the relation, Δfat mass (kg) = 0.77 × Δbody weight (kg) 0.44, with $r = 0.89$ and $P < .001$. The association was not changed significantly ($P > .91$) by adding treatment group as a second independent variable, even after adjusting for 3 additional potential covariates: initial body weight, sex, and age.

Adverse Events

No patient was removed from the study protocol for a treatment-related adverse event, and the number of reported adverse events was not significantly different between the placebo and treatment groups (eg, headache, 12 vs 9, respectively; upper respiratory tract symptoms, 13 vs 16, respectively; and gastrointestinal tract symptoms, 6 vs 13, respectively).

Table 2.- Summary of Previous *Garcinia cambogia* Studies*

Author(s)	Publication Type	Study Design	Study Agent(s)	Sample	Duration, wk	Major Observations
Badmaev and Majeed[15]	Industrial	Single arm, open label	GCE, 500 mg, chromium picolinate, 100 µg, 3 times per day and healthy eating/exercise	77 obese adults, with 55 completing trial	8	5.5% weight loss in women, 4.9% in men†; combined, $P<.001$ vs baseline
Conte[11]	Peer-reviewed	Randomized, double-blind, placebo controlled	*Garcinia indica* extract 500 mg, nickel chromium, 100 µg, 3 times per day and low-fat substitution diet	54 obese subjects randomized, with 39 completing trial	8	Active, 11.14 lb, vs placebo, 4.2 lb††
Ramos et al (unpublished data)	Abstract	Randomized, double-blind, placebo controlled	GCE, 500 mg, 3 times per day, and low-fat 4200-6300 kJ/d diet	40 obese subjects randomized, with 35 completing trial	8	Active, 4.1 (1.8) kg, vs placebo, 1.3 (0.9) kg ($P<.05$)§
Kaats et al (unpublished data)	Abstract	Randomized, double-blind, placebo controlled	GCE, 1500 mg/d, chromium picolinate, 600 µg/d, L-carnitine, 1200 mg/d, and low-fat, high-fiber diet	200 subjects randomized, with 186 completing trial	4	Active, −2.84 lb, vs placebo, −1.4 lb fat mass loss ($P<.01$)†
Thom[12]	Abstract	Randomized, double-blind, placebo controlled	Hydroxycitric acid, 1320 mg/d, in 3 divided doses, and 5040-kJ/d low-fat diet	60 subjects randomized; number completing trial not reported	8	Active, 6.4 kg, vs placebo, 3.8 kg weight loss ($P<.001$), weight loss as fat, 87% in active vs 80% in placebo group††
Rothacker and Waitman[13]	Abstract	Randomized, double-blind, placebo controlled	GCE, 800 mg, natural caffeine, 50 mg, and chromium polynicotinate, 40 µg, 3 times per day, and 5040-kJ/d diet	50 obese subjects randomized, with 48 completing trial	6	Active, −4.0% (3.5%) vs placebo, −3.0% (3.1%) body fat mass ($P=.30$)
Girola et al[14]	Peer-reviewed	Randomized, double-blind, placebo controlled	GCE, 55 mg, chrome, 19 mg, and chitosan, 240 mg; randomized to 1 of 3 groups, active medication twice per day, placebo twice per day, or 1 placebo and 1 active medication per day, all groups treated with hypocaloric diet	150 obese subjects; number completing trial not reported	4	Active, twice per day, −12.5% (1.2%), active, once per day, −7.9% (0.9%); twice per day placebo, −4.3% (1.0%); "overweight reduction" ($P<.01$ for all 3 vs baseline)§

*GCE indicates *Garcinia cambogia* extract.
†No SDs reported.
‡No statistical analysis reported.
§Numbers in parentheses are SD.

COMMENT

In 1883 von Lippmann isolated hydroxycitric acid, a minor constituent of sugar beets.[27] More than half a century later, in 1941, Martius and Maué[28] discovered that the (+) isomer of a racemic hydroxycitric acid mixture is attacked by the enzyme isocitrate dehydrogenase. The (−) hydroxycitric acid isomer of hydroxycitric acid was first isolated by Lewis and Neelakantan in 1964,[29] and by 1969 Watson and colleagues[5] reported the powerful inhibition by (−) hydroxycitric acid of citrate cleavage enzyme. Evidently, the additional hydroxyl group's steric position, compared with citric acid, enhances its binding affinity and competitively inhibits catalytic action by the enzyme. Citrate, entering the cytoplasm from mitochondria, cannot be cleaved to release acetyl coenzyme A, the substrate for de novo fatty acid synthesis. Despite these century-old, well-grounded observations, there has been little effort to critically test the basic assumption underlying therapeutic use of hydroxycitric acid in overweight humans: that hydroxycitric acid inhibition of lipid synthesis will significantly reduce body fat mass beyond that observed with a placebo capsule.

The present study, carried out during a 12-week evaluation period and using accepted experimental design and in vivo analytic methods, failed to support the hypothesis that hydroxycitric acid as prescribed promotes either additional weight or fat mass loss beyond that observed with placebo. Specifically, body weight and fat mass change during the 12-week study period did not differ significantly between placebo and treatment groups. These results apply to both the primary and secondary statistical analyses. Additionally, there were no observed selective fat-mobilizing effects specifically attributable to the active agent, hydroxycitric acid.

Seven earlier *G cambogia* trials have appeared in peer-reviewed literature,[11,14] as abstracts,[12,13] and in industrial publications as an open-label study[15] and randomized controlled trials.[11-14] We chose to collectively review these studies even though *G cambogia* typically was used in combination with other ingredients for the claimed purpose of enhancing weight loss.

Of the 7 studies reviewed, 5 reported significant ($P<.05$) effects of *G cambogia* alone or in combination with other ingredients on body weight or fat mass loss in overweight humans (Table 2). These earlier studies all have limitations when specifically considering *G cambogia* as a weight loss agent, including lack of placebo control or double-blinding in 1 study,[15] coadministration of *G cambogia* in combination with other potentially active ingredients in 5 studies,[10,11,13,14] use of an inaccurate body composition method (near-infrared interactance)[12] in 1 study, and failure as of yet to publish study results in peer-reviewed literature in all but 2[13,14] of the 7 studies. However, our present investigation, carried out using accepted clinical trial design procedures and applying accurate body composition methods, failed to support a specific weight loss effect of *G cambogia* administered as recommended. The present 12-week study period also exceeded in duration all previous study treatment periods, which ranged from 4 to 8 weeks.

In our present investigation we failed to detect a weight loss or fat-mobilizing effect of active herb. The question therefore arises whether there exist conditions differing from those used in the present study that might support hydroxycitric acid efficacy. The 5040-kJ/d low-fat diet recommended in our current study was intended to mimic diets commonly prescribed as a component of weight control programs. The possibility exists that the lipid synthesis–inhibiting properties of hydroxycitric acid may be more evident in subjects relapsing following a failed diet attempt, particularly if high-carbohydrate foods are ingested.[30]

Another concern is related to the timing and dosage considerations of hy-

droxycitric acid. Sullivan and colleagues[11] showed that the effects of hydroxycitric acid in animals depend on time of administration in relation to a meal, with hydroxycitric acid maximally effective when administered 30 to 60 minutes prior to feeding. The approach used in our study and the others we reviewed suggested hydroxycitric acid ingestion about 30 minutes prior to meal intake, the lower end of the maximally effective range. A related concern is that hydroxycitric acid provided in divided doses also was found to be more effective than the same amount given as a single dose.[8] Although divided doses typically are used in weight loss protocols, human doses ranging between 750 and 1500 mg/d of hydroxycitric acid are at the extreme low end of the in vivo dose-response range established by Sullivan and colleagues.[32] Thus, in light of the many requirements for its effective use, it seems unlikely that the maximal effects of hydroxycitric acid will be realized in human weight loss studies unless treatment conditions are well defined and patient diet and medication compliance are tightly monitored.

Our study explored product safety only in the form of clinical evaluations and reported adverse events. No significant differences were observed between placebo and treatment groups in number of reported adverse events and no subjects were removed from the study for a treatment-related adverse event. Additional studies, potentially with larger subject groups, are needed to gather specific information on the long-term safety of *G cambogia*.

An important concern in all pharmacological trials, particularly those in which herbal products are evaluated, is the amount and bioavailability of the active agent. As standard procedure, we confirmed the presence and quantity of hydroxycitric acid in the supplied capsules using an independent testing laboratory. However, we did not measure hydroxycitric acid blood levels or evaluate tissue or cytosolic citrate-cleavage enzyme activity. Although the format of our experiment closely resembles current use of *G cambogia* as a weight loss product, our conclusions should not be interpreted as a failure to support the validity of the biochemical effects of hydroxycitric acid identified by earlier investigators.

In conclusion, our study evaluated the hypothesis that the active ingredient of *G cambogia*, hydroxycitric acid, has beneficial weight and fat mass loss effects. Our findings, obtained in a prospective, randomized, double-blind study, failed to detect either weight loss or fat-mobilizing effects of hydroxycitric acid beyond those of placebo. These observations, the first, to our knowledge, to appear in a peer-reviewed article using currently accepted experimental and statistical methods, do not support a role as currently prescribed for the widely used herb *G cambogia* as a facilitator of weight loss.

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EXHIBIT "M"

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CASE REPORT

Severe Hepatotoxicity Due to Hydroxycut: A Case Report

Michael Shim · Sammy Saab

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Case

A 28-year-old male was transferred to our institution with 3 weeks of fatigue, dyspnea on exertion, jaundice, and dark urine. In an effort to lose weight, he had been taking Hydroxycut, two tablets, two to three times per day (which is within the manufacturer's suggested dosing), from 3 months prior to admission up until the development of symptoms. Additionally, for soreness associated with his aerobic exercise program, he took an over-the-counter pain-reliever containing acetaminophen 250 mg, aspirin 250 mg, and caffeine 65 mg, four tablets per day for the 10 days leading up to the development of his symptoms. He was not a heavy drinker of ethanol, drinking 2–3 beers per week. Physical examination was unremarkable and without stigmata of chronic liver disease. Laboratory analysis revealed a serum aspartate aminotransferase of 1049 U/l (normal range 7–36 U/l), alanine aminotransferase of 2272 (normal 4–45 U/l), alkaline phosphatase of 152 U/l (normal 31–103 U/l), total bilirubin of 18.1 mg/dl (normal 0.2–1.1 mg/dl), conjugated bilirubin of 9.0 (normal 0.0–0.2 mg/dl), albumin level of 4 g/dl (normal 3.7–5.1 g/dl), prothrombin time of 12.8 s (normal 9.2–10.6 s), normal complete blood count, normal electrolyte panel, and normal estimated glomerular filtration rate. Aminotransferase levels and prothrombin time began to decline immediately after admission and bilirubin peaked on hospital day 2 at 22.4 mg/dl. Acetaminophen level was undetectable. Tests for viral hepatitis were negative. Ferritin was markedly elevated at 9519 ng/ml (normal 10–210 ng/ml). HFE genotyping was negative for H63D or C282Y mutations. Antinuclear antibody titer was 1:40 (normal, <1:40), smooth muscle antibody titer was 1:20 (normal, <1:20), liver kidney microsomal antibody was negative, and soluble liver antigen antibody was negative. Serum copper level was 96 mcg/dl (normal 70–140 mcg/dl) and ceruloplasmin was 31 mg/dl (normal 18–54 mg/dl). Twenty-four hour urine copper level was 290 mcg/dl (normal 3–50 mcg/dl). Slit-lamp examination for Kaiser-Fleischer rings was equivocal. Abdominal ultrasound with Doppler and computed tomography (CT) scan with intravenous contrast were both normal. The patient's liver function tests continued to improve and he was discharged on hospital day 9.

Discussion

Though the markedly elevated 24-h urine copper level and slit-lamp examination equivocal for Kaiser-Fleischer rings suggested the possibility of underlying Wilson disease, the normal serum copper and ceruloplasmin levels, lack of underlying cirrhosis, lack of supportive family history, lack of concomitant neurological or psychiatric disturbance, and lack of hemolysis all argued against this diagnosis. In the end, it was felt that the patient's elevated urinary copper

Recent reports have identified an association between hepatotoxicity and the weight loss supplement *Hydroxycut* (MuscleTech, Mississauga, Ontario, Canada). Here we report a case of severe hepatotoxicity associated with *Hydroxycut* and summarize the published data identifying an association between the herbal compounds in *Hydroxycut* and hepatotoxicity.

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level was due to his marked cholestasis and that his presentation was most consistent with hepatotoxicity associated with *Hydroxycut*.

This is the third reported case of hepatotoxicity associated with *Hydroxycut*. The first case demonstrated a predominantly hepatocellular injury pattern on liver function tests with peak alanine aminotransferase 3962 U/l that resolved after 4 weeks, while the other demonstrated a predominantly cholestatic pattern of injury (confirmed on liver biopsy) that resolved after 2 months [1]. In both cases, the patients were taking three tablets three times per day.

The manufacturer's list of active ingredients in *Hydroxycut* is shown in Table 1 [2]. Of the ingredients listed, extracts of *Garcinia cambogia*, *Gymnema sylvestre*, and green tea (*Camellia sinensis*) have been associated with cases of severe hepatotoxicity. In the one case associated with *Garcinia cambogia* and *Gymnema sylvestre*, the patient had taken a 7-day course of two dietary weight-loss supplements, one of which contained both *Garcinia cambogia* and *Gymnema sylvestre*, the week prior to becoming jaundiced [3]. This particular case progressed to fulminant hepatic failure and death. The authors speculated that a synergistic interaction between the weight-loss supplements and chronic use of a leukotriene antagonist inhibitor, a class of medicine that has been associated with severe hepatotoxicity, resulted in her fulminant and ultimately fatal presentation.

There have been at least 11 case reports associating green tea extract (*Camellia sinensis* extract) with severe hepatotoxicity [4–13]. In all cases, except two which required liver transplantation [9, 13], there was eventual recovery after cessation of the supplement containing the extract. In one case [4], there was some suggestion of causation, as the patient rechallenged herself with the same supplement and again presented with severe hepatotoxicity.

The mechanism of the potential toxicity of green tea extract is unclear. There has been speculation that the predominant polyphenol or catechin within this extract, epigallocatechin-2-gallate (EGCG), may be the causative agent [13]. An in vitro study suggested that high concentrations of EGCG were cytotoxic to rat liver cells [14]. However, this manuscript concluded that the oral bioavailability of EGCG in green tea extracts was probably too low to produce serum levels approaching the levels that were cytotoxic to the rat liver cells. Because of this, it has been further proposed that the hepatotoxicity associated with green tea extract may be an idiosyncratic and/or hypersensitivity-type reaction or that an undetected compound contaminating the extract may be the causative agent [4, 13, 14].

Finally, we cannot rule out an interaction between the compounds in *Hydroxycut* and the acetaminophen the patient was taking concomitantly. Although we found no studies directly investigating this possibility, one might speculate that one or more of the compounds in *Hydroxycut* could induce or stimulate the CYP2E1 cytochrome system, lead to more production of *N*-acetyl-*p*-benzo-quinone imine (NAPQI), and thus accentuate acetaminophen-induced hepatotoxicity, much like chronic ethanol consumption.

Caution should be exercised by consumers using the weight-loss supplement *Hydroxycut*. There is evidence that extracts of *Garcinia cambogia*, *Gymnema sylvestre*, and green tea (*Camellia sinensis*) contained in *Hydroxycut* may be associated with severe and even fatal hepatotoxicity.

Table 1 Listed ingredients in *Hydroxycut*

Garcinia cambogia extract
Gymnema sylvestre extract
Soy phospholipids
Rhodiola rosea extract
Withania somnifera extract
Green tea extract (as *Camellia sinensis*)
Caffeine anhydrous
White tea extract (as *Camellia sinensis*)
Oolong tea extract (as *Camellia sinensis*)
Other ingredients: hydroxypropyl cellulose, microcrystalline cellulose, polyvinlypyrrolidone, croscarmellose sodium, vegetable stearine, magnesium stearate, coating, silica, acesulfame-potassium, maltodextrin, propylene oxide

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JS 44 (Rev. 12/2012)

CIVIL COVER SHEET

CV-14-0459

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. (SEE INSTRUCTIONS ON NEXT PAGE OF THIS FORM.)

I. (a) PLAINTIFFS
PAUL HARABEDIAN, individually on behalf of himself and all others similarly situated.

(b) County of Residence of First Listed Plaintiff Suffolk County
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) Attorneys (Firm Name, Address, and Telephone Number)
The Sultzer Law Group, P.C.
85 Civic Center Plaza, Suite 104
Poughkeepsie, New York 12601

DEFENDANTS
HAMMER NUTRITION, LTD.

County of Residence of First Listed Defendant Flathead County (MT)
(IN U.S. PLAINTIFF CASES ONLY)

NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED.

Attorneys (If Known)

II. BASIS OF JURISDICTION (Place an "X" in One Box Only)

- ☐ 1 U.S. Government Plaintiff
- ☐ 3 Federal Question (U.S. Government Not a Party)
- ☐ 2 U.S. Government Defendant
- ☒ 4 Diversity (Indicate Citizenship of Parties in Item III)

III. CITIZENSHIP OF PRINCIPAL PARTIES (Place an "X" in One Box for Plaintiff and One Box for Defendant; For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	☒ 1	☐ 1	Incorporated or Principal Place of Business In This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☒ 2	Incorporated and Principal Place of Business In Another State	☐ 5	☒ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. NATURE OF SUIT (Place an "X" in One Box Only)

CONTRACT	TORTS		FORFEITURE/PENALTY	BANKRUPTCY	OTHER STATUTES
☐ 110 Insurance ☐ 120 Marine ☐ 130 Miller Act ☐ 140 Negotiable Instrument ☐ 150 Recovery of Overpayment & Enforcement of Judgment ☐ 151 Medicare Act ☐ 152 Recovery of Defaulted Student Loans (Excludes Veterans) ☐ 153 Recovery of Overpayment of Veteran's Benefits ☐ 160 Stockholders' Suits ☐ 190 Other Contract ☐ 195 Contract Product Liability ☐ 196 Franchise	**PERSONAL INJURY** ☐ 310 Airplane ☐ 315 Airplane Product Liability ☐ 320 Assault, Libel & Slander ☐ 330 Federal Employers' Liability ☐ 340 Marine ☐ 345 Marine Product Liability ☐ 350 Motor Vehicle ☐ 355 Motor Vehicle Product Liability ☐ 360 Other Personal Injury ☐ 362 Personal Injury - Medical Malpractice	**PERSONAL INJURY** ☐ 365 Personal Injury - Product Liability ☐ 367 Health Care/ Pharmaceutical Personal Injury Product Liability ☐ 368 Asbestos Personal Injury Product Liability **PERSONAL PROPERTY** ☐ 370 Other Fraud ☐ 371 Truth in Lending ☐ 380 Other Personal Property Damage ☐ 385 Property Damage Product Liability	☐ 625 Drug Related Seizure of Property 21 USC 881 ☐ 690 Other **LABOR** ☐ 710 Fair Labor Standards Act ☐ 720 Labor/Management Relations ☐ 740 Railway Labor Act ☐ 751 Family and Medical Leave Act ☐ 790 Other Labor Litigation ☐ 791 Employee Retirement Income Security Act	☐ 422 Appeal 28 USC 158 ☐ 423 Withdrawal 28 USC 157 **PROPERTY RIGHTS** ☐ 820 Copyrights ☐ 830 Patent ☐ 840 Trademark **SOCIAL SECURITY** ☐ 861 HIA (1395ff) ☐ 862 Black Lung (923) ☐ 863 DIWC/DIWW (405(g)) ☐ 864 SSID Title XVI ☐ 865 RSI (405(g))	☐ 375 False Claims Act ☐ 400 State Reapportionment ☐ 410 Antitrust ☐ 430 Banks and Banking ☐ 450 Commerce ☐ 460 Deportation ☐ 470 Racketeer Influenced and Corrupt Organizations ☐ 480 Consumer Credit ☐ 490 Cable/Sat TV ☐ 850 Securities/Commodities/ Exchange ☒ 890 Other Statutory Actions ☐ 891 Agricultural Acts ☐ 893 Environmental Matters ☐ 895 Freedom of Information Act ☐ 896 Arbitration ☐ 899 Administrative Procedure Act/Review or Appeal of Agency Decision ☐ 950 Constitutionality of State Statutes
REAL PROPERTY	**CIVIL RIGHTS**	**PRISONER PETITIONS**	**IMMIGRATION**	**FEDERAL TAX SUITS**	
☐ 210 Land Condemnation ☐ 220 Foreclosure ☐ 230 Rent Lease & Ejectment ☐ 240 Torts to Land ☐ 245 Tort Product Liability ☐ 290 All Other Real Property	☐ 440 Other Civil Rights ☐ 441 Voting ☐ 442 Employment ☐ 443 Housing/ Accommodations ☐ 445 Amer. w/Disabilities - Employment ☐ 446 Amer. w/Disabilities - Other ☐ 448 Education	**Habeas Corpus:** ☐ 463 Alien Detainee ☐ 510 Motions to Vacate Sentence ☐ 530 General ☐ 535 Death Penalty **Other:** ☐ 540 Mandamus & Other ☐ 550 Civil Rights ☐ 555 Prison Condition ☐ 560 Civil Detainee - Conditions of Confinement	☐ 462 Naturalization Application ☐ 465 Other Immigration Actions	☐ 870 Taxes (U.S. Plaintiff or Defendant) ☐ 871 IRS—Third Party 26 USC 7609	

FILED
IN CLERK'S OFFICE
U.S. DISTRICT COURT E.D.N.Y.
★ JAN 29 2014 ★
LONG ISLAND OFFICE

V. ORIGIN (Place an "X" in One Box Only)

☒ 1 Original Proceeding ☐ 2 Removed from State Court ☐ 3 Remanded from Appellate Court ☐ 4 Reinstated or Reopened ☐ 5 Transferred from Another District (specify) ☐ 6 Multidistrict Litigation

VI. CAUSE OF ACTION
Cite the U.S. Civil Statute under which you are filing (*Do not cite jurisdictional statutes unless diversity*):
28 U.S.C. 1332(d)(2)
Brief description of cause:
Violations of GBL 349 & 350, Breach of Warranties, and Unjust Enrichment

VII. REQUESTED IN COMPLAINT:
☒ CHECK IF THIS IS A CLASS ACTION UNDER RULE 23, F.R.Cv.P.
DEMAND $ 5,000,000.00
CHECK YES only if demanded in complaint:
JURY DEMAND: ☒ Yes ☐ No

VIII. RELATED CASE(S) IF ANY (See instructions)
JUDGE DOCKET NUMBER

DATE 01/20/2014
SIGNATURE OF ATTORNEY OF RECORD

FOR OFFICE USE ONLY
RECEIPT # AMOUNT $400.00 APPLYING IFP JUDGE MAG. JUDGE

EDNY REVISION 11-20-13

CERTIFICATION OF ARBITRATION ELIGIBILITY

Local Arbitration Rule 83.10 provides that with certain exceptions, actions seeking money damages only in an amount not in excess of $150,000, exclusive of interest and costs, are eligible for compulsory arbitration. The amount of damages is presumed to be below the threshold amount unless a certification to the contrary is filed.

I, Jason P. Sultzer, counsel for Plaintiff and Class Members, do hereby certify that the above captioned civil action is ineligible for compulsory arbitration for the following reason(s):

☒ monetary damages sought are in excess of $150,000, exclusive of interest and costs.

☒ the complaint seeks injunctive relief.

☐ the matter is otherwise ineligible for the following reason

DISCLOSURE STATEMENT - FEDERAL RULES CIVIL PROCEDURE 7.1

Identify any parent corporation and any publicly held corporation that owns 10% or more or its stocks:

RELATED CASE STATEMENT (Section VIII on the Front of this Form)

Please list all cases that are arguably related pursuant to Division of Business Rule 50.3.1 in Section VIII on the front of this form. Rule 50.3.1 (a) provides that "A civil case is "related" to another civil case for purposes of this guideline when, because of the similarity of facts and legal issues or because the cases arise from the same transactions or events, a substantial saving of judicial resources is likely to result from assigning both cases to the same judge and magistrate judge." Rule 50.3.1 (b) provides that " A civil case shall not be deemed "related" to another civil case merely because the civil case: (A) involves identical legal issues, or (B) involves the same parties." Rule 50.3.1 (c) further provides that "Presumptively, and subject to the power of a judge to determine otherwise pursuant to paragraph (d), civil cases shall not be deemed to be "related" unless both cases are still pending before the court."

NY-E DIVISION OF BUSINESS RULE 50.1(d)(2)

1.) Is the civil action being filed in the Eastern District removed from a New York State Court located in Nassau or Suffolk County: No

2.) If you answered "no" above:
a) Did the events or omissions giving rise to the claim or claims, or a substantial part thereof, occur in Nassau or Suffolk County? Yes

b) Did the events of omissions giving rise to the claim or claims, or a substantial part thereof, occur in the Eastern District? Yes

If your answer to question 2 (b) is "No," does the defendant (or a majority of the defendants, if there is more than one) reside in Nassau or Suffolk County, or, in an interpleader action, does the claimant (or a majority of the claimants, if there is more than one) reside in Nassau or Suffolk County?

(Note: A corporation shall be considered a resident of the County in which it has the most significant contacts).

BAR ADMISSION

I am currently admitted in the Eastern District of New York and currently a member in good standing of the bar of this court.

☒ Yes ☐ No

Are you currently the subject of any disciplinary action (s) in this or any other state or federal court?

☐ Yes (If yes, please explain) ☒ No

I certify the accuracy of all information provided above.

Signature: