HEALTH HAZARD EVALUATION BOARD

The Problem: Liver toxicity following consumption of dietary supplement, Hydroxycut

HHE No.:

Background. In 2002, the Center for Food Safety and Applied Nutrition's (CFSAN) adverse event monitoring system, CAERS, began receiving reports of liver-related illnesses in persons who reported consuming the dietary supplement Hydroxycut for periods ranging from as short as a week to months. Hydroxycut has been marketed by Iovate Health Sciences, Inc (381 North Service Rd. W., Oakville, ON L6M 0H4, Canada) and manufactured by Muscletech (Blassdell, NY, USA and Mississauga, Ontario, Canada) as a weight control, fat-burner, and energy enhancement dietary supplement. Hydroxycut products bear the Iovate or Musletech Brand names. The products contain a variety of individual ingredients as well as numerous proprietary blends such as "Hydroxagen Plus, Hydroxy Tea, HydroxyTea CF, Hydroxycut Proprietary Blend, Max! Liqui-Burn, Max! Weight-Loss Matrix, Hydroxycut Hardcore Proprietary Blend Proxyclene, Noreidrol Intensity focus Blend, Lasidrate Delivery Blend, or Yohimbacore." The products' labels declare minerals and herbs as well as extracts from *Garcinia cambogia*, *Guarana, gymnema sylvestre*, *Rhodiola rosea*, and *Camellia sinensis*. Prior to 2004, Hydroxycut, contained ephedra or Ma Huang as an ingredient; however, by the beginning of 2004, Hydroxycut was ephedra-free. Subsequent to the removal of ephedra, Hydroxycut had undergone numerous formulation changes. Since the earlier formulation of Hydroxycut contained ephedra, it was generally believed that the reports of liver injury associated with the use of the product were due either to ephedra or a combination of the ingredients found in the product. However, following the removal of ephedra from Hydroxycut, CFSAN continued to receive reports of liver injury associated with the use of Hydroxycut. The present Health Hazard Evaluation describes the product in question, summarizes reports in CAERS of liver-related adverse events associated with ingestion of the product, reviews reports of Hydroxycut-associated liver toxicity published in the peer-reviewed literature, and provides a synopsis of recent communications the Center has had with hepatologists regarding the product. In addition, the HHE presents findings from CAERS reports of severe adverse events involving organ systems other than the liver.

The Product. Hydroxycut is a Registered Trademark and is part of the name of many products, examples of which include Hydroxycut, Hydroxycut Hardcore, and Hydroxycut Caffeine Free. Iovate and Muscletech, a company owned by Iovate, both market Hydroxycut products. In addition to the label-declared ingredients listed above, the products contain variable amounts of caffeine. Consumption of Hydroxycut products in amounts recommended by the label would contribute to the ingestion of approximately 600 mg of caffeine per day. By comparison (and excluding Hydroxycut ingestion), the average American consumes approximately 168 mg of caffeine per day (coffee drinkers consume approximately 280 mg caffeine per day).

The following description of Hydroxycut is provided on a web site supported by the company (http://www.hydroxycut.com/products/hydroxycut/index.shtml - accessed March 19, 2009):

Plain and simple, Hydroxycut was created to help you reach your weight-loss goals. This medical doctor-formulated supplement contains ingredients that are of the highest quality and have been combined to make it one of the most effective weight-loss supplements available on the market today. Hydroxycut® is comprised of a blend of research-proven key ingredients that can help you lose up to 4.5 times the weight than diet and exercise alone. On top of that, this top selling weight-loss supplement increases your energy and helps control your appetite too. With Hydroxycut in your diet and exercise plan, you'll be well on your way to achieving your weight-loss goals in no time!*

An example of a Hydroxycut product and its Supplement Facts is provided below.

Supplement Facts

Serving Size 2 Rapid Release Caplets
Servings Per Container 15

Amount Per Serving	% Daily Value
Calcium (as hydroxycitrate)*** 156 mg	16%
Chromium (as polynicotinate)** 133 mcg	111%
Potassium (as hydroxycitrate)*** 218 mg	6%
Hydroxagen Plus® 1.32 g	
Garcinia cambogia extract (rind)***	†
Standardized for 60% hydroxycitric acid	
Gymnema sylvestre extract (leaf)	†
Standardized for 25% gymnemic acids	
Phosphatidylserine-enriched soy lecithin	†
Supplying 50% phosphatidylserine, 4% phosphatidylcholine, 2% phosphatidylethanolamine	
HydroxyTea® 473 mg	†
Green tea extract (as *Camellia sinensis*) (leaf)	†
Standardized for 90% polyphenols, 75% catechins, 45% epigallocatechin gallate - 117 mg EGCG	
Caffeine anhydrous	†
White tea extract (as *Camellia sinensis*) (leaf)	†
Standardized for 50% polyphenols, 35% catechins, 15% EGCG	
Oolong tea extract (as *Camellia sinensis*) (leaf)	†
Standardized for 50% polyphenols, 25% catechins, 15% EGCG	
Supplying 200 mg of caffeine	
Ginger extract (as *Zingiber officinale*) (root)	†
Standardized for 5% gingerols	
Raspberry ketone	†
Quercetin dihydrate (as *Fava d'anta*)	†

†Daily Value not established.

OTHER INGREDIENTS: MICROCRYSTALLINE CELLULOSE, HYDROXYPROPYL-CELLULOSE, COATING (POLYVINYL ALCOHOL, TITANIUM DIOXIDE, POLYETHYLENE GLYCOL, TALC), SODIUM CARBOXYMETHYLCELLULOSE, CROSPOVIDONE, STEARIC ACID, MAGNESIUM STEARATE, SILICA, ACESULFAME-POTASSIUM.

The directions for the product are stated as follows:

For men and women:

Take 2 caplets with a glass of water 3 times daily, approximately 30 to 60 minutes before meals (preferably before breakfast, lunch and dinner). To assess individual tolerance, refer to the chart. Do not exceed 6 caplets in a 24-hour period. Do not take within 5 hours of bedtime. For best results, use Hydroxycut for 8 weeks in conjunction with a calorie-reduced diet and a regular exercise program. Do not snack after dinner. Consume ten glasses of water per day. Read the entire label before use and follow directions.

Hydroxycut-associated liver toxicity reports in CAERS. To-date, 23 case reports of Hydroxycut-associated liver toxicity has been identified in CAERS for the period 2002 to the present. The number of reports, by event date, is listed below:

Year of event	Number of reports
2002	4
2003	3
2004	6
2005	0
2006	1
2007	6
2008	3
2009	0
Total	23

In cases for whom gender was known, 15 (65%) were female. Ages ranged from 20 years to 51 years (median = 29 years). Sixteen cases (70%) were hospitalized. The majority of cases reported no underlying risk factors for liver disease (e.g., no history of viral hepatitis, no HIV infection, no autoimmune diseases). While the reports vary in detail, several reports describe work-ups that ruled out infectious, autoimmune, and metabolic causes of liver disease. The severity of illness ranged from asymptomatic elevations in serum bilirubin to acute liver failure (one patient received a liver transplant in 2002, while a second patient was reportedly waiting for a liver transplant in 2004) to death. On March 24, 2009 CFSAN received information regarding the fatal case. The patient was a 20-year-old male who presented to an emergency room on January 19, 2007 in liver failure and hepatic encephalopathy. He was subsequently transferred to a liver transplant center where, in the operating room, he was found to have necrosis of both the large and small intestines. Given these findings, the procedure was aborted and the patient was returned to the intensive care unit. He died on February 12, 2007.

Reports of Hydroxycut-associated liver toxicity in the peer-reviewed literature. To our knowledge, there are four (1, 2, 3, 4) published reports in the peer-reviewed literature that describe liver disease that occurred in 6 persons following the consumption of Hydroxycut (Table 1). The two cases described by Stevens et al. (reference 1) were also reported to the CAERS database.

Table 1. Reports of Hydroxycut-associated liver toxicity in the peer-reviewed literature

Year	Age	Gender	Event
2005[1]			Both cases: Previously healthy; no recent foreign travel; no sick contacts; no risk factors for viral, alcoholic, autoimmune, or hereditary liver disease. No recent use of herbal (other than Hydroxycut) or prescription medications. Both underwent a similar serologic work-up, including viral studies (hepatitis A, B, and C viruses; Epstein-Barr virus [EBV]; cytomegalovirus

	27 30	Male Male	[CMV]; anti-nuclear and anti-smooth-muscle antibody levels, acetaminophen level, and toxicology screening, which was unremarkable. Both were admitted to the hospital after presenting to the emergency room. 8-day history of fatigue and jaundice. Had been taking Hydroxycut for 5 weeks (3 tablets 3 times/day). Labs: aspartate aminotransferase [AST] 1808 (normal 15-41); alanine aminotransferase [ALT] 3131 (normal 17-63); Bilirubin 7.8 (normal 0-1.5); alkaline phosphatase 171 (normal (38-126); prothrombin time [PT] 16 seconds (10-14 seconds). Four weeks later: AST 114; ALT 304. 10-day history jaundice, fever, vomiting, fatigue. For 5 days, between the 11th and 16th days before presentation, he had been taking 9 tablets of Hydroxycut per day. Labs: AST 59; ALT45; alkaline phosphatase 530; Bilirubin 7.8; PT 15 seconds. Abdominal CT, endoscopic retrograde cholangiogram negative. Liver biopsy: cholestasis, portal inflammation. Patient discharged after laboratory test results improved; 2 months later, both AST and ALT normal.
2007[2]	19	Male	Previously healthy U.S. Army soldier with no known risk factors for liver disease who, while serving in Iraq, developed acute hepatotoxicity after 4 months of ingesting Hydroxycut. Presented with nausea, vomiting, jaundice, and scleral icterus. Labs: AST 2964; ALT 1435; Bilirubin 11.7; alkaline phosphatase 153; PT 17.1 seconds. Bloodwork was negative for hepatitis A, B, C, E, as well as EBV, CMV, and HIV. Anti-nuclear antibody, anti-liver/kidney microsomal antibody, anti-smooth muscle antibody, serum acetaminophen, and urine drug screen were negative. Serum ceruloplasmin, iron studies, ferritin, and protein electrophoresis were all within normal limits. Doppler right upper quadrant ultrasound showed no gallstones and normal common bile duct caliber as well as normal portal and hepatic venous flow. The patient's jaundice resolved over the next month. His liver-associated enzymes normalized within 4 months.

2008[3]	40	Female	Presented with 3-day history of new-onset abdominal pain, nausea, vomiting, non-bloody diarrhea, anorexia and profound fatigue. One week prior to presentation, she began using Hydroxycut, 6 pills daily. She did not smoke or drink. Only other medication was levothyroxine for hypothryroidism. Admission labs: AST 1020; ALT 1150; Bilirubin 0.27, alkaline phosphatase 299; international normalized ration [INR] 0.96 (normal, 1.0). Diagnostic evaluation negative for hepatitis A, B,C; CMV; EBV; autoimmune liver disorders; alpha-1 anti-trypsin deficiency; and ehrlichiosis. Discharged on day 3 clinically well. As outpatient, AST 46; ALT 48. No further liver problems after 10 months of follow-up.
	33	Female	Prior history of pituitary adenoma, presented to ER with 1 month of new-onset jaundice, and 2-week history of nausea, abdominal pain, dark urine pruritis, and profound fatigue. During month prior to admission, took Hydroxycut for 2 weeks but discontinued supplement upon onset of symptoms. Only med= oral contraceptives; no alcohol or risk factors for viral hepatitis. Admission labs: AST 934, ALT 1570, Bilirubin 20.9; alkaline phosphatase 112; INR 1.08. Diagnostic evaluation negative for hepatitis A, B, C; CMV; Epstein-Barr virus, and herpes simplex virus infections. Autoimmune profile revealed low titer increase in anti-nuclear antibody and anti-smooth muscle antibody suggestive of immune-mediated drug-induced hepatitis. Jaundice eventually resolved and liver function normalized.
2009[4]	28	Male	Presented with 3-week history of fatigue, dyspnea on exertion, jaundice, and dark urine. Took Hydroxycut 2-3 tabs/d x 3 months prior to onset of symptoms. Also took an OTC pain-reliever containing acetaminophen 250 mg, aspirin 250 mg, and caffeine 65 mg (4 tabs/d x 10 d before onset of symptoms). History of consuming 2-3 beers/week. Labs: AST 1049; ALT 2272; alkaline phosphatase 152; Bilirubin 18.1; PT 12.8 seconds (normal 9.2-10.6 seconds); acetaminophen level undetectable. Patient's ALT and AST began to decline immediately after admission, and bilirubin peaked on hospital day #2. Viral hepatitis tests negative. Ferritin was elevated at 9519 ng/ml (normal 10-210 ng/ml). ANA, anti-smooth muscle antibody, liver kidney microsomal antibody and soluble liver antigen antibody were all negative. Despite normal serum copper, 24-hour urine copper level was elevated at 290 mcg/dl (normal 3-50 mcg/dl). Slit-lamp for Kaiser-Fleischer rings equivocal. Investigators attributed elevated urine copper to cholestasis, not to Wilson's disease, and stated: "his presentation was most consistent with hepatotoxicity with

			Hydroxycut."

The aforementioned cases are consistent with the diagnosis of idiosyncratic hepatotoxicity for a number of reasons: the temporal relationship between the consumption of Hydroxycut and the development of acute liver injury in persons who had no history of known liver disease; the exclusion of other causes of liver disease following extensive work-ups; and the resolution of liver injury upon discontinuation of Hydroxycut; the development of liver injury is not dose- dependent. Also apparent were two distinct patterns of liver injury: cholestatic and necrotic. It is not unusual for a single herbal preparation to produce more than 1 type of clinicopathologic liver injury (5).

Discussions with hepatologists. In discussions in March and April of 2009 with hepatologists Tse-Ling Fong, M.D. of the University of Southern California and William Lee, M.D. of the University of Texas Southwestern Medical Center, CFSAN has become aware of these physicians' case series of patients with severe liver disease associated with the use of Hydroxycut. Two cases from this series, representing additional cases to the ones reported to CFSAN, underwent liver transplantation following acute liver failure.

Serious non-hepatic adverse events identified in the CAERS database or the literature. When the CAERS database was queried for other serious adverse events associated with Hydroxycut, cases of seizures, rhabdomyolysis, and cardiovascular disorders were identified. For example, from 2004 to 2008, the CAERS database received 4 case reports describing consumers who experienced a seizure following ingestion of Hydroxycut. In one instance, a 26-year-old consumer increased her daily intake of Hydroxycut from 2 to 4 caplets on December 6, 2008. At 2 p.m. that day, following ingestion of the second serving of 2 caplets, the consumer felt tired and lay down. She was found by another person to be having a "seizure" (shaking and drooling).

The consumer was taken to the emergency room where a physician told her to discontinue using Hydroxycut.

The case report describing rhabdomyolysis involved a 23-year-old male who had been consuming Hydroxycut on and off over an eight-month period in 2002. On the day of hospital admission, he had taken 2 tablets for energy prior to working out. He reported feeling nausea, and then several hours later, he had severe shoulder pain and dark urine. He was diagnosed as having rhabdomyolysis on admission to the hospital. In addition to this CAERS report, the Board is aware of one case of Hydroxycut-associated rhabdomyolysis reported in the peer-reviewed literature. In this report, Dehoney and Wellen (6) described an 18-year-old male who experienced rhabdomyolysis after consuming Hydroxycut as per the product's instructions. During his overnight hospitalization, he received 6 liters of fluid before discharge.

The Board also identified 46 reports in CAERS of Hydroxycut-associated cardiovascular adverse events. These events ranged in severity from palpitations to a heart attack. Nineteen of these reports were received during or after 2004, a period when Hydroxycut's formulation was believed to be free of ephedra.

Conclusion:

Three lines of evidence derived from multiple disparate sources suggest it is very likely that exposure to Hydroxycut can cause idiosyncratic hepatotoxicity. First, many of the subjects described in the adverse event reports to CAERS, in the peer-reviewed literature, and in the case series described by hepatologists reported no history of liver disease or risk factors for liver disease (e.g., alcohol consumption, previous viral infection, hereditary factors, etc.) prior to experiencing liver injury following the ingestion of Hydroxycut. Second, in many subjects, thorough diagnostic evaluations performed in multiple settings ruled out a number of known causes of liver disease, including viral hepatitis, autoimmune diseases, and metabolic/inherited disorders. Third, prompt resolution of liver disease occurred in a number of patients following cessation of Hydroxycut ingestion. Further, while some adverse event reports involved users who had consumed more than the daily dosage recommended on the products' labeling, if these reports were excluded from consideration, the remaining evidence demonstrates liver-related adverse effects following exposure to Hydroxycut. In addition to Hydroxycut-associated liver-related adverse effects, the Board is aware of a number of CAERS reports that describe seizures, rhabdomyolysis, and cardiovascular signs and symptoms.

The Board does not know what ingredient(s) of Hydroxycut are responsible for producing liver toxicity. In addition, there is insufficient information to determine whether there is a dose-response effect between Hydroxycut ingestion and liver disease or whether its effects are cumulative over time. However, based on the totality of evidence presented above, the Board concludes that the ingestion of the dietary supplement, Hydroxycut, presents a severe potentially life-threatening hazard to some users. Although Hydroxycut–induced hepatotoxicity has been reversible in most patients that have come to the attention of CFSAN, in certain instances acute liver failure has resulted that has

required liver transplantation to ensure survival and death occurred in one instance prior to transplantation.

Members Present

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Robert Mozersky, D.O.

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References

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