HHS Public Access

Author manuscript

Drug Test Anal. Author manuscript; available in PMC 2017 March 01.

Published in final edited form as:

Drug Test Anal. 2016 March ; 8(3-4): 319–327. doi:10.1002/dta.1894.

Hepatotoxicity associated with the dietary supplement OxyELITE Pro™ — Hawaii, 2013

David I. Johnston[a,*], **Arthur Chang**[b], **Melissa Viray**[a], **Kevin Chatham-Stephens**[b], **Hua He**[a], **Ethel Taylor**[b], **Linda L. Wong**[c], **Joshua Schier**[b], **Colleen Martin**[b], **Daniel Fabricant**[d], **Monique Salter**[e], **Lauren Lewis**[b], and **Sarah Y. Park**[a]

[a]Disease Outbreak Control Division, Hawaii Department of Health, Honolulu, HI, USA

[b]Health Studies Branch, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, GA, USA

[c]The Queen's Medical Center, Honolulu, HI, USA

[d]Natural Products Association, Washington, DC, USA

[e]Office of Foods and Veterinary Medicine/Coordinated Outbreak Response and Evaluation Network, U.S. Food & Drug Administration

Abstract

Dietary supplements are increasingly marketed to and consumed by the American public for a variety of purported health benefits. On 9 September 2013, the Hawaii Department of Health (HDOH) was notified of a cluster of acute hepatitis and fulminant hepatic failure among individuals with exposure to the dietary supplement OxyELITE Pro™ (OEP). HDOH conducted an outbreak investigation in collaboration with federal partners. Physicians were asked to report cases, defined as individuals with acute onset hepatitis of unknown etiology on or after 1 April 2013, a history of weight-loss/muscle-building dietary supplement use during the 60 days before illness onset, and residence in Hawaii during the period of exposure. Reported cases' medical records were reviewed, questionnaires were administered, and a product investigation, including chemical analyses and trace back, was conducted. Of 76 reports, 44 (58%) met case definition; of these, 36 (82%) reported OEP exposure during the two months before illness. No other common supplements or exposures were observed. Within the OEP-exposed subset, two patients required liver transplantation, and a third patient died. Excessive product dosing was not reported. No unique lot numbers were identified; there were multiple mainland distribution points, and lot numbers common to cases in Hawaii were also identified in continental states. Product analysis found consumed products were consistent with labeled ingredients; the mechanism of hepatotoxicity was not identified. We report one of the largest statewide outbreaks of dietary

[*]Correspondence to: David I. Johnston, MPH, 1250 Punchbowl Street, Honolulu, HI 96813, USA. david.johnston@doh.hawaii.gov.

Disclaimer

The findings and conclusions in this manuscript are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry.

Conflicts of interest

DF is now employed by the Natural Products Association, a nonprofit organization that represents the interests of members of the natural products industry, including manufacturers and retailers of foods, dietary supplements, and health/beauty aids. At the time of the investigation he was an employee of the Center for Food Safety and Applied Nutrition, US Food & Drug Administration.

supplement-associated hepatotoxicity. The implicated product was OEP. The increasing popularity of dietary supplements raises the potential for additional clusters of dietary supplement-related adverse events.

Keywords

toxic hepatitis; dietary supplements

Introduction

More than half of adults in the United States use dietary supplements, most commonly to ‘improve’ or ‘maintain’ overall health.[1] Weight-loss supplements are especially popular.[2,3] Although dietary supplements often appear in a capsule or tablet similar to prescription medicine, they are regulated as food and not subjected to the same premarket requirements for safety or efficacy; thus, post-market surveillance and epidemiology are the only means of identifying problems in the marketplace and protect consumers.

Over 1100 agents, including drugs and herbs, are recognized to cause liver injury.[4] However, attributing causality is often challenging given the limited clinical laboratory tests to identify specific hepatotoxins.[5] Hepatotoxicity has been previously reported as a serious adverse reaction to dietary supplement consumption; a study of 20 cases of fulminant hepatic failure seen by a liver transplantation service found half of the cases were active or recent users of dietary supplements with known potentially hepatotoxic supplements or herbs, with 7 cases having no other etiology identified.[6] A review of the United Network for Organ Sharing liver transplant database from 1990 to 2002 demonstrated an ‘herbal’ etiology in 5% of 270 people who received transplantation for drug-induced hepatotoxicity.[7]

On 9 September 2013, clinicians at Hawaii’s single liver transplant centre notified the Hawaii Department of Health (HDOH) of seven previously healthy adults who had presented with acute and/or fulminant hepatitis of unknown etiology since May 2013. A case series describing the clinical course of their cases has been published previously.[8] The clinicians reported all cases had used the dietary supplement OxyELITE Pro™ (OEP), containing per product labelling ‘proprietary blends of plant-derived extracts’ (Table 1), for weight-loss or muscle-building before illness onset. Given the potential association with a commercial product and the patients’ serious conditions, HDOH, with the Centers for Disease Control and Prevention (CDC) and Food and Drug Administration (FDA), initiated a public health investigation.

We report here the findings and conclusions of that epidemiologic investigation and the public health actions taken in response. This report contributes to the published literature on dietary supplement-associated hepatitis, and provides the findings from the epidemiological investigation and more in-depth examination of the events in Hawaii, initially uncovered by the cases depicted in the case series by Roytman *et al.*[8] Additionally, this report serves as a final update and offers resolution to the brief description of preliminary findings that was published early in our investigation.[9]

Methods

Case definition

A case was defined as an individual with acute onset hepatitis of unknown etiology on or after 1 April 2013, who had a history of weight-loss/muscle-building dietary supplement use during the 60 days before illness onset, and had lived in Hawaii during the period of exposure. The date – 1 April – was selected to detect cases that may have had onset before the earliest onset of the first seven reported cases. Acute onset hepatitis of unknown etiology was defined as both an alanine aminotransferase (ALT) level four times the normal upper limit and a total bilirubin (TBili) level twice the normal upper limit without other explicative diagnosis. A probable case required a medical evaluation that excluded alternative explicative etiologies, specifically: hepatic imaging not consistent with an alternative etiology; no evidence of acute hepatitis A or acute or chronic hepatitis B and C infection; no pre-existing chronic liver disease; no recent hypotensive shock or septic episodes; and no history of alcoholism. Further work-up for less common causes of acute fulminant hepatitis (e.g. autoimmune markers, hepatitis E serologies) was performed at the discretion of the diagnosing physician. A patient meeting probable criteria but without complete documentation of a negative work-up for infectious or other explicative etiologies for hepatitis including at least a negative viral hepatitis testing and hepatic imaging not consistent with alternative, explicative etiologies was considered a suspect case.

Epidemiologic investigation

Case finding—On 25 September 2013, HDOH emailed and faxed a statewide medical advisory requesting clinicians report anyone presenting in the last six months with hepatitis, jaundice, or hyperbilirubinemia concomitant with weight-loss/muscle-building dietary supplement use. A six-month period was chosen to promote ease of recall by the providers while ensuring adequate detection of earlier-onset cases. Additionally, a 26 September 2013 press release[10] alerted the public regarding the investigation, potential symptoms, and advised using dietary supplements only under a physician's supervision. HDOH requested all medical records for all those meeting at least suspect case criteria.[11] Case collection for the purposes of the initial investigation was closed as of 1 November 2013 although HDOH continued to collect reports of acute hepatitis in individuals with OEP exposure after this date.

Data collection—A standardized questionnaire administered by phone or in person elicited patient demographics; comorbidities; clinical symptoms and course; and exposures of interest including alcohol use, prescription and over-the-counter medications including Tylenol® (acetaminophen), home remedies, and any dietary supplements. As initial cases had reported OEP (USPLabs, LLC, Dallas, TX, USA) exposure, we queried this specifically as well as any other supplements consumed during the two months before illness. Dosage, exposure dates, purchase dates, purchase location, and shopper loyalty programme information were obtained when possible. When precise dates could not be recalled, we imputed a date (e.g. 1 May for 'beginning of May', 15 May for 'middle', and 28 May for 'end'). To ensure this did not affect our results, data were analyzed with and without the estimated dates.

We used a standardized medical chart abstraction form to collect clinical course and laboratory, radiological, and pathology findings. A Council for International Organizations of Medical Sciences (CIOMS) score for hepatocellular injury as described by Teschke *et al.*[12,13] was assigned for cases reporting OEP consumption to estimate potential causality. The CIOMS scale is a suspected herb-induced hepatotoxicity causality assessment method that incorporates timing of supplement exposure to illness onset, evaluation for alternative diagnoses, and exposures to other potential hepatotoxins; it estimates causality as 'highly probable', 'probable', 'possible', 'unlikely', and 'excluded'.[12–15]

Product investigation

HDOH environmental inspectors queried Hawaii dietary supplement retailers on OEP sale and distribution information. The number of units of all weight-loss dietary supplements sold in Hawaii from January–September 2013 was requested from retail chains to estimate OEP market share in Hawaii.[16]

HDOH collaborated with the FDA to collect any remaining product from cases. Lot numbers and detailed product and container pictures were obtained. Product was forwarded to the FDA's Forensic Chemistry Center (FCC) in Cincinnati, OH, for testing. For all submitted samples, liquid chromatography-mass spectrometric (LC-MS) detection was used as a general screen to identify a variety of drugs, poisons, and other active constituents. Liquid chromatography with ultraviolet detection was used to confirm and quantify the amounts of the labeled ingredients aegeline and higenamine (norcoclaurine HCL) reported by the manufacturer.

On a representative sub-sample of products from Hawaii cases, a more comprehensive set of analyses were performed, including liquid chromatography-high resolution mass spectrometry (LC-HR/MS) and gas chromatography–mass spectrometric (GC-MS) detection targeted screens for compounds previously identified in investigations as potential hepatotoxins,[13,17] such as pyrrolizidine alkaloids, N-nitrosofenfluramine, catechins, usnic acid, phenethylamines, and aristolochic acid. Inductively coupled plasma mass spectrometry (ICP-MS) was used to screen for the presence of toxic elements or potentially harmful levels of other elements.

Data analysis

All data were entered into a Microsoft Excel database (Microsoft, Redmond, CA, USA), and ArcGIS (ESRI, Redlands, CA, USA) was used to map cases statewide. Data were analyzed using SAS 9.3 (SAS Institute Inc., Cary, NC, USA), and descriptive case statistics were generated. Comparisons were performed between cases who took OEP, either alone or with other supplements, and those who only took other supplements. Differences between those hospitalized versus not hospitalized and those who stopped taking OEP at or before onset of illness versus those who continued taking it were also compared. Differences in proportions were compared using Chi-squared test or Fisher's exact test, and comparisons between pairs of group medians were examined using Wilcoxon rank-sum test. A Bonferroni correction and bootstrap methodologies were applied to account for multiple comparisons.

Results and discussion

Epidemiologic investigation

Summary of all cases—As of 1 November 2013, we received 76 reports of acute hepatitis of unknown etiology (Figure 1). The epidemiological curve of the 44 reports meeting case criteria by illness onset is shown in Figure 2, and demographics for these 44 cases are presented in Table 2. Patients were distributed across all Hawaii counties with no geographic clustering.

Thirty-six (82%) cases reported taking OEP (Table 3). Only one other supplement for weight loss or muscle gain was common to multiple cases. Three cases reported using that other supplement; two of those also reported OEP exposure. In 16 (57%) of 28 cases with records dated before the first medical advisory, physicians documented suspicion of supplement-related hepatotoxicity, with OEP specifically noted in 8 (29%). All cases reported taking the manufacturer-recommended daily dose, 1–3 (median 2) capsules or scoops. After Bonferroni correction, no significant differences were found in demographics (listed in Table 2), symptoms, other exposures, laboratory values and symptom duration (both listed in Table 4), and length of hospital stay among OEP-exposed (alone or with other supplements) cases and other supplement-exposed cases. Similarly, there were no differences in demographics, symptoms, and laboratory values between those hospitalized versus not hospitalized and those who stopped taking OEP at or before illness onset versus those who continued.

All 36 OEP-exposed cases reported having dark urine, and almost all (92%) reported yellowing of the eyes or skin, loss of appetite, and fatigue (Table 4). Radiological imaging did not reveal biliary obstruction or alternative diagnoses. Of 12 cases who underwent liver biopsy, findings for 8 demonstrated inflammation and necrosis consistent with drug or toxic injury. Causality assessment using the CIOMS scale showed that 94% of cases were in the ‘possible’ and ‘probable’ range (Table 3).

Additional outbreak cases—After case collection for the initial investigation ended on 1 November 2013, we continued to collect reports of acute hepatitis in individuals with OEP exposure. An additional 8 OEP-exposed cases were identified; only one occurred outside the onset range of the original 36 cases (9 November 2013). Demographic, clinical, and exposure data for these cases were compared to and found not significantly different from the initial 36 cases.

Illustrative cases

Case 1—A 28-year-old female without co-morbidities presented on 6 June 2013 to her physician with anorexia and nausea, one week of fatigue and yellowing skin, and two weeks of ‘yellowing in both eyes’. Laboratory work-up yielded ALT 1420 IU/L, aspartate aminotransferase (AST) 1390 IU/L, alkaline phosphatase (ALP) 166 IU/L, and TBili 6.9 mg/dL. Viral hepatitis serologies were negative. She later reported that she had been taking OEP before onset and continued after this visit for another month and then stopped, with improvement in symptoms. She restarted OEP in September and was seen in a local emergency department on 17 September for lightheadedness, subjective fevers, nausea,

emesis, and abdominal pain. Her ALT was 150, AST 200, ALP 100, and TBili 1.1. She stopped OEP again after hearing media reports in late September and presented to her physician on 9 October with similar symptoms as previously. She was subsequently admitted 10 October with ALT 1494, AST 1446, ALP 197, and TBili 3.3. An ultrasound demonstrated heterogeneous liver parenchyma consistent with hepatitis. She was treated supportively and was clinically improving when discharged on 17 October 2013. Her CIOMS score was determined to be 8, suggesting a 'probable' supplement or drug-related liver injury.[13]

Case 2—A 42-year-old female without co-morbidities presented on 18 September 2013 with four days of intractable nausea, emesis, and diarrhoea to her physician, who administered intravenous fluids. On 22 September, she presented to a local emergency department with altered mental status and history of taking OEP with ~2 pounds per day weight loss, which continued despite stopping OEP on 7 September. Laboratory values on 22 September demonstrated ALT 835, AST 537, ALP 139, and TBili 23.9. She was transferred to the state's transplant centre on 23 September with evidence of coagulopathy (prothrombin time 35.7, INR 4) and developed hepatic encephalopathy on 24 September. Her work-up was negative for alternative etiologies. Her encephalopathy worsened, and she was intubated and transferred to the intensive care unit on 26 September. An emergent liver transplantation work-up revealed ductal carcinoma *in situ* of the breast, precluding liver transplantation. Despite aggressive care, she developed cerebral oedema and died on 4 October 2013. This case's CIOMS score was ultimately determined to be 7, also suggesting a 'probable' supplement or drug-related injury.[13]

Product investigation

Review of product distribution from January to September 2013 in Hawaii demonstrated two types of OEP available for purchase: a 1,3-dimethylamylamine (DMAA)-containing OEP (the 'original' OEP formula) and multiple DMAA-free OEP formulations (comprising several different formulas). USPLabs began producing DMAA-free OEP formulations in lieu of DMAA-containing OEP starting in late 2012 after the FDA issued a warning letter[18] on 24 April 2012 advising USPLabs that it had failed the legal requirement to inform the FDA of the basis for concluding that dietary supplements containing a new dietary ingredient (i.e., DMAA) would reasonably be expected to be safe. While the DMAA-free formulas became available in late 2012, the original formula was still available and being purchased through July 2013. Case onset dates appeared to correlate with the increasing popularity of DMAA-free OEP formulations. From January to September 2013, in Hawaii, an average of 6912 units per month of weight-loss supplements, 43% of which were OEP, was sold.

Table 3 demonstrates the OEP product types purchased by cases; the overwhelming majority (83%) used at least one DMAA-free formulation. Of the cases that used the DMAA-free formulation, the majority reported using the Super Thermo capsules; only four (11%) reported using Super Thermo Powder, half of whom also reported using Super Thermo capsules. Product was purchased from multiple retailers; six cases purchased product online. Product was collected from 13 cases (10 on Oahu, 3 on Hawaii Island). No common lot

number was identified. Investigation-associated lot numbers were identified among products in other states, and retailers reported ordering product as needed, with product shipped directly from multiple continental distribution points.

A total of 18 product samples patients from Hawaii were submitted to the FDA's FCC. All underwent initial screening with five undergoing more extensive testing; LC-HR/MS, GC-MS, and ICP-MS screening detected none of the targeted hepatotoxins, drugs, poisons, or toxic elements. Substances identified in the samples were consistent with ingredients and levels indicated in the product formulations provided by the manufacturer.

Outbreak response in Hawaii

HDOH issued an embargo on all OEP products sold in the state on 8 October 2013, and alerted the public via a press release;[19] concurrently, a medical advisory requested clinicians advise patients to discontinue OEP use immediately and seek medical care for compatible symptoms. HDOH promoted public education on supplement safety with an online 'frequently asked questions' resource.[20] A 18 November 2013 press release[21] alerted the public that HDOH was notifying retailers to voluntarily destroy the embargoed OEP or surrender it to HDOH for collection and destruction. This action followed a voluntary OEP recall by USPLabs.[22]

Eighty-two percent of our cases reported OxyELITE Pro™ consumption; no other common supplement or exposure was identified. Our cases' clinical presentations could arguably be consistent with other hepatitis etiologies; however, our case definition excluded cases with known etiologies. One case re-challenged herself with OEP and developed hepatitis that resolved after discontinuation. Excessive daily dosing of OEP or other medications like Tylenol® (acetaminophen) and NSAIDs was not reported. Finally, even before the outbreak was identified, case clinicians documented dietary supplement, specifically OEP, hepatotoxicity.

Interpretation

As in previously reported cases of hepatotoxicity associated with dietary supplements, a causal link between exposure and hepatotoxicity was difficult to assess.[12] However, we estimated the majority of cases to be 'possible' or 'probable' using the CIOMS-based scale, a preferred causality assessment method validated previously and used in multiple reports.[12] Despite limitations, CIOMS-based assessment has reasonable sensitivity (86%), specificity (89%), and positive predictive value (93%).[13] In herb-associated hepatotoxicity cases judged 'possible' or higher, liver histology findings were similar;[13] others have reported the majority of herb/dietary-associated hepatotoxicity cases have a 'possible' CIOMS rating.[15]

Other reports of dietary supplements associated with hepatotoxicity have been reported in recent years.[23–27] Case presentations and findings, including variability in duration of product use before illness onset and course severity, among these reports appear similar to each other and to our cases. As elsewhere,[27] almost a third of our cases demonstrated positive autoimmune markers; however, the significance is unclear. The clinical course and outcome of our cases appeared to be independent of age, dose, or exposure duration as

observed with other hepatotoxic supplements.[23,24] Others have noted that outcome appears related only to the degree of liver dysfunction and not to any particular demographic factor or aspect of supplement consumption.[4]

The FDA has warned the manufacturer that the DMAA-free formulations contain aegeline, a plant-derived compound used in Ayurvedic medicine, that is considered 'a new dietary ingredient' (i.e., not marketed in the United States before 15 October 1994) and therefore requires federal notification and evidence that products containing it are 'reasonably expected to be safe, under the conditions of use described in the labeling'.[28] Whether aegeline, or another ingredient(s), is the etiologic hepatotoxic agent is not yet known and may remain unanswered, as with other supplement investigations. An unrecognized race-dependent pharmacogenetic factor (e.g. genetic polymorphisms involving drug metabolism) is possible; some have reported an excess of Asian/Pacific Islanders among supplement-associated hepatotoxicity cases,[6,29] while others have reported excess cases among other minority groups[7,27] or a general overrepresentation by minorities.[4] However, race-dependent factors are unlikely to be readily determined here, given the majority of cases reported mixed racial/ethnic origin as commonly observed among Hawaii's population. After controlling for differences in data collection methods between our investigation and federal census data, the racial background of our cases did not vary greatly from US Census data for Hawaii.

The investigation of this single outbreak in Hawaii had important implications for multiple sectors of healthcare and public health. Our epidemiologic investigation focused on determining the most likely cause of illness in Hawaii's cases with the ultimate purpose of protecting the health of Hawaii's residents through implementation of specific health or control measures; the clinical case series published by Roytman *et al.* focused on the presentation and subsequent clinical course of patients with hepatitis within their clinic who reported OEP use.[8] Additionally, after being alerted of the cases in Hawaii, the CDC investigated reports meeting similar case criteria in multiple other states. The cases identified from these reports and the cases from Hawaii were included in a separate national investigation; findings of that investigation will be published in a forthcoming article in *Drug Testing and Analysis*. Furthermore, the impact of national adverse event reporting through FDA MedWatch, the only official mechanism for reporting and tracking drug and dietary supplement adverse events,[30] and the FDA investigation of and response to this outbreak from the federal regulatory perspective were examined; those data are in publication.[31] Possible cases in other countries have also been reported.[32,33]

Our investigation is limited by a dearth of studies or surveillance data to provide baseline incidence of supplement- or even drug-associated idiosyncratic hepatitis, although it does provide a starting point to develop such data. With over 85 000 dietary supplement products on the market, background rates of events associated with a given product or ingredients are largely unknown.[34] While lack of understanding of the pathogenesis and likely disease risk factors as well as a relatively small sample size for comparisons further hindered the ability to identify the specific etiology of OEP hepatotoxicity and associated risk factors, our findings add further depth to the existing literature on dietary supplement-related hepatotoxicity. Although widespread media exposure could have contributed reporting bias

and limited identification of cases related to other dietary supplements, our case-finding did identify cases of idiopathic hepatitis without OEP exposure; yet, no other commonality emerged. Lastly, for unknown reasons, many OEP consumers appear to have remained unaffected; asymptomatic presentation with abnormal liver function tests is possible and has been reported previously.[15,25] Ultimately, the large number of severe hepatitis cases with OEP exposure and no other clear etiology, occurring in a matter of months, suggests a likely association that requires further examination.

Drug-induced liver injury has an estimated prevalence of 1/10 000–1/100 000; studies have shown approximately 10–16% of those are thought to be caused by herbal or other dietary supplements.[4,35] Yet, the true incidence is unknown, partly because of underreporting.[36] Systematic identification of these events, however, is problematic. Currently, federal law does not require review and approval of herbal products for safety and effectiveness before marketing,[2,37] although the 2006 amendment to the federal Food, Drug, and Cosmetic Act[38] required industry to report all serious dietary-supplement-related adverse events to the FDA. Adverse events associated with pharmaceuticals or dietary supplements are not reportable to state or local health departments and would likely be unrecognized except as part of a substantial outbreak. Additionally, identifying adverse events related to supplements is challenging clinically when many patients tend not to report supplement use,[3,39] given that supplements are not marketed or sold as medications. Soliciting supplement history would greatly augment clinical care. The situation is further confounded by the fact that initial hepatitis symptoms (i.e., loss of appetite, abdominal discomfort) could be misinterpreted by patients as weight-loss supplement effectiveness. The case with self-rechallenge is an example of the product's popularity and possible denial of association with health problems as observed with other weight-loss supplements.[26]

We still do not understand the mechanism of action for many dietary supplements, their pharmacologically active components, or their potential interactions with other agents including regular medications. Given the popularity of these products, their likelihood to be used to self-manage conditions, and the potential for serious adverse events, an improved understanding of the safety and efficacy of these products could positively impact public health.

Conclusion

HDOH identified a total of 44 individuals with acute onset hepatitis of unknown etiology on or after 1 April 2013 with a history of weight-loss/muscle-building dietary supplement use during the 60 days before illness onset and residence in Hawaii during the exposure period, all with symptom onset dates ranging from April through October, 2013 (Figure 2). Of those cases, 36 (82%) reported exposure to the dietary supplement OEP; no other significant common exposures were identified. Two of the OEP-exposed cases required liver transplants and one OEP-exposed case died. As a result of the findings of the statewide investigation, an embargo was issued against all OEP products sold in Hawaii; then, following a national recall of the OEP products, HDOH notified retailers to voluntarily destroy their supply or surrender it to HDOH for destruction.

We still do not understand the mechanism of action for many dietary supplements, their pharmacologically active components, or their potential interactions with other agents including regular medications. Given the popularity of these products, their likelihood to be used to self-manage conditions, and the potential for serious adverse events, an improved understanding of the safety and efficacy of these products could positively impact public health.

Acknowledgements

The authors thank the clinicians and staff of the Liver Center at The Queen's Medical Center, Honolulu, HI, especially Marina Roytman, MD; Peter Poerzgen, PhD; Timothy Kuo, MD; Peter Bryant-Greenwood, MD, MBA; and Naoky Tsai, MD. The authors also thank Kara Levri, MD; CDC/Office of Surveillance, Epidemiology, and Laboratory Services/Epidemic Intelligence Service (Oregon); Rebecca Noe, MPH; Johnni Daniel; and Judith Qualters, PhD, MPH at CDC/National Center for Environmental Health/Health Studies Branch; Stephen Ostroff, MD; Karl Klontz, MD, MPH; Jennifer A. Thomas; (USPHS) CDR Quyen T. Tien, RPh; FDA/Center for Food Safety and Applied Nutrition; Nicole Yuen, FDA/Office of Regulatory Affairs/Pacific Region/San Francisco District; Roberta Hammond, PhD; Pamela LeBlanc, MPH; FDA/Office of Foods and Veterinary Medicine/Coordinated Outbreak Response and Evaluation Network; Samuel Gratz, PhD; Douglas T. Heitkemper, PhD; R.D. Satzger, PhD; FDA/Forensic Chemistry Center; William A Correll Jr; FDA/Center for Food Safety and Applied Nutrition/Office of Compliance; Heidi DeBeck, MPH; Elisa L. Elliot, PhD; Sharon Seelman, MS, MBA (ORISE); FDA/Office of Foods and Veterinary Medicine/Coordinated Outbreak Response and Evaluation Network; Caitlin Monahan, FDA/Office of Foods and Veterinary Medicine/Coordinated Outbreak Response and Evaluation Network/Post Response Team; Rebecca Dreisch, MS, FDA/Office of Regulatory Affairs; Reynaldo R. Rodriguez, Jr, FDA/Office of Regulatory Affairs/Dallas District; Bonnie Young, MPH and Matthew Turnure, MPH, Council of State and Territorial Epidemiologists Applied Epidemiology Fellows assigned to HDOH; Jennifer Roden, BA, MPH intern in HDOH/Disease Outbreak Control Division/Public Health Preparedness Branch; the Hawaii Medical Reserves Corps volunteers, and all of the patients involved as well as their clinicians for their assistance on this investigation. LLW is on the Speaker's Bureau for Bayer Healthcare, which produces a medication for the treatment of liver cancer DIJ, MV, HH, and SYP had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. HH (HDOH) conducted and is responsible for the data analysis.

References

1. Bailey RL, Gahche JJ, Miller PE, Thomas PR, Dwyer JT. Why US adults use dietary supplements. JAMA Intern. Med. 2013; 173:355. [PubMed: 23381623]
2. Navarro VJ. Herbal and dietary supplement hepatotoxicity. Semin. Liver Dis. 2009; 29:373. [PubMed: 19826971]
3. Blanck HM, Serdula MK, Gillespie C, Galuska DA, Sharpe PA, Conway JM, Khan LK, Ainsworth BE. Use of nonprescription dietary supplements for weight loss is common among Americans. J Am. Diet. Assoc. 2007; 107:441. [PubMed: 17324663]
4. Reuben A, Koch DG, Lee WM. Drug-induced acute liver failure: results of a US multicenter, prospective study. Hepatology. 2010; 52:2065. [PubMed: 20949552]
5. Stickel F, Patsenker E, Schuppan D. Herbal hepatotoxicity. J Hepatol. 2005; 43:901. [PubMed: 16171893]
6. Estes JD, Stolpman D, Olyaei A, Corless CL, Ham JM, Schwartz JM, Orloff SL. High prevalence of potentially hepatotoxic herbal supplement use in patients with fulminant hepatic failure. Arch. Surg. 2003; 138:852. [PubMed: 12912743]
7. Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug induced liver injury in the United States. Liver Transpl. 2004; 10:1018. [PubMed: 15390328]
8. Roytman MM, Porzgen P, Lee CL, Huddleston L, Kuo TT, Bryant-Greenwood P, Wong LL, Tsai N. Outbreak of severe hepatitis linked to weight-loss supplement OxyELITE Pro. Am. J. Gastroenterol. 2014; 109:1296. [PubMed: 25091255]

9. Notes from the field: acute hepatitis and liver failure following the use of a dietary supplement intended for weight loss or muscle building--May–October 2013. MMWR Morb. Mortal. Wkly. Rep. 2013; 62:817.
10. Hawaii Department of Health. [13 December 2013] Department of Health Investigates Hepatitis, Liver Failure in Persons Taking Diet Supplements. Available at: http://health.hawaii.gov/news/files/2013/05/13-055-Department-of-Health-Investigates-Hepatitis-Liver-Failure-in-Persons-Taking-Diet-Suppliments.pdf
11. [1 February 2015] Haw. Rev. Stat. § 321-29(b) Available at: http://www.capitol.hawaii.gov/hrscurrent/Vol06_Ch0321-0344/HRS0321/HRS_0321-0029.htm
12. Teschke R, Frenzel C, Schulze J, Eickhoff A. Herbal hepatotoxicity: challenges and pitfalls of causality assessment methods. World J. Gastroenterol. 2013; 19:2864. [PubMed: 23704820]
13. Teschke R, Schwarzenboeck A, Eickhoff A, Frenzel C, Wolff A, Schulze J. Clinical and causality assessment in herbal hepatotoxicity. Expert Opin. Drug Saf. 2013; 12:339. [PubMed: 23458441]
14. Teschke R, Wolff A, Frenzel C, Schulze J, Eickhoff A. Herbal hepatotoxicity: a tabular compilation of reported cases. Liver Int. 2012; 32:1543. [PubMed: 22928722]
15. Bunchorntavakul C, Reddy KR. Review article: herbal and dietary supplement hepatotoxicity. Aliment. Pharmacol. Ther. 2013; 37:3. [PubMed: 23121117]
16. [1 February 2015] Haw. Rev. Stat. § 328-25(a)(3) Available at: http://www.capitol.hawaii.gov/hrscurrent/Vol06_Ch0321-0344/HRS0328/HRS_0328-0025.htm
17. Kanda T, Yokosuka O, Tada M, Kurihara T, Yoshida S, Suzuki Y, Nagao K, Saisho H. N-nitroso-fenfluramine hepatotoxicity resembling chronic hepatitis. J Gastroenterol. Hepatol. 2003; 18:999. [PubMed: 12859734]
18. Food and Drug Administration. [16 January 2013] USP Labs, LLC 4/24/12, Warning Letter. Available at: http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2012/ucm302167.htm
19. Hawaii Department of Health. [13 December 2013] Department of Health Requests Voluntary Removal of OxyElite Pro Supplement from Sale. Available at: http://health.hawaii.gov/news/files/2013/05/13-056-DOH-Requests-Voluntary-Removal-of-OxyElite-Pro-From-Sale1.pdf
20. Hawaii Department of Health. [19 December 2013] Dietary Supplements: Be an Informed Consumer. Available at: http://health.hawaii.gov/docd/files/2013/04/Dietary-Supplements-Factsheet.pdf
21. Hawaii Department of Health. [13 December 2013] Voluntary Destruction of Embargoed OxyElite Pro Products. Available at: http://health.hawaii.gov/news/files/2013/05/13-066-Vountary-Destruction-of-Embargoed-OxyELITE-Pro-Products.pdf
22. Food and Drug Administration. [13 December 2013] FDA News Release: USPlabs LLC recalls OxyElite Pro dietary supplements; products linked to liver illnesses. Available at: http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm374395.htm
23. Adachi M, Saito H, Kobayashi H, Horie Y, Kato S, Yoshioka M, Ishii H. Hepatic injury in 12 patients taking the herbal weight loss AIDS Chaso or Onshido. Ann. Intern. Med. 2003; 139:488. [PubMed: 13679326]
24. Kawata K, Takehira Y, Kobayashi Y, Kitagawa M, Yamada M, Hanajima K, Murohisa G, Kawamura M, Iwaoka Y, Wada T, Morita S, Iwaizumi M, Makino S. Three cases of liver injury caused by Sennomotokounou, a Chinese dietary supplement for weight loss. Intern. Med. 2003; 42:1188. [PubMed: 14714956]
25. Elinav E, Pinsker G, Safadi R, Pappo O, Bromberg M, Anis E, Keinan-Boker L, Broide E, Ackerman Z, Kaluski DN, Lev B, Shouval D. Association between consumption of Herbalife nutritional supplements and acute hepatotoxicity. J Hepatol. 2007; 47:514. [PubMed: 17692424]
26. Schoepfer AM, Engel A, Fattinger K, Marbet UA, Criblez D, Reichen J, Zimmermann A, Oneta CM. Herbal does not mean innocuous: ten cases of severe hepatotoxicity associated with dietary supplements from Herbalife products. J Hepatol. 2007; 47:521. [PubMed: 17692989]
27. Fong TL, Klontz KC, Canas-Coto A, Casper SJ, Durazo FA, Davern TJ 2nd, Hayashi P, Lee WM, Seeff LB. Hepatotoxicity due to hydroxycut: a case series. Am. J. Gastroenterol. 2010; 105:1561. [PubMed: 20104221]

28. Food and Drug Administration. [11 November 2013] Warning Letter: USP Labs 10/11/13. Available at: http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm371203.htm
29. Favreau JT, Ryu ML, Braunstein G, Orshansky G, Park SS, Coody GL, Love LA, Fong TL. Severe hepatotoxicity associated with the dietary supplement LipoKinetix. Ann. Intern. Med. 2002; 136:590. [PubMed: 11955027]
30. Food and Drug Administration. [17 November 2013] Reporting Serious Problems to FDA. Available at: http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm
31. Klontz KC, DeBeck HJ, LeBlanc P, Mogen KM, Wolpert BJ, Sabo JL, Salter M, Seelman SL, Elliot EL, Lance SE, Steigman DS, Gensheimer K. The Role of Adverse Event Reporting in a U.S. Food and Drug Administration Response to a Multi-State Outbreak of Liver Disease Associated with a Dietary Supplement. Public Health Rep. in press.
32. Queensland Health--Queensland Government. [13 December 2013] Sport and dietary supplement warning. Available at: http://www.health.qld.gov.au/news/stories/131122-sports-dietary.asp
33. New Zealand Ministry for Primary Industries. [13 December 2013] Director-General Statement under the Food Act 1981. Available at: http://www.mpi.govt.nz/portals/0/Documents/food/dg-statement-oxyelite.pdf
34. Muth, MK.; Ball, MJ.; Coglaiti, MC.; Karns, SA. Model to estimate costs of using labeling as a risk reduction strategy for consumer products regulated by the Food and Drug Administration: Prepared for U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition. RTI International, Research Triangle Park, NC; 2011.
35. Navarro VJ, Barnhart H, Bonkovsky HL, Davern T, Fontana RJ, Grant L, Reddy KR, Seeff LB, Serrano J, Sherker AH, Stolz A, Talwalkar J, Vega M, Vuppalanchi R. Liver injury from herbals and dietary supplements in the U.S. Drug-Induced Liver Injury Network. Hepatology. 2014; 60:1399. [PubMed: 25043597]
36. Lewis JD, Strom BL. Balancing safety of dietary supplements with the free market. Ann. Intern. Med. 2002; 136:616. [PubMed: 11955030]
37. Food and Drug Administration. [11 November 2013] Dietary Supplements. Available at: http://www.fda.gov/food/dietarysupplements/
38. Food and Drug Administration. [11 November 2013] Dietary Supplement and Nonprescription Drug Consumer Protection Act. Available at: http://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdcact/significantamendmentstothefdcact/ucm148035.htm
39. Kennedy J. Herb and supplement use in the US adult population. Clin. Ther. 2005; 27:1847. [PubMed: 16368456]

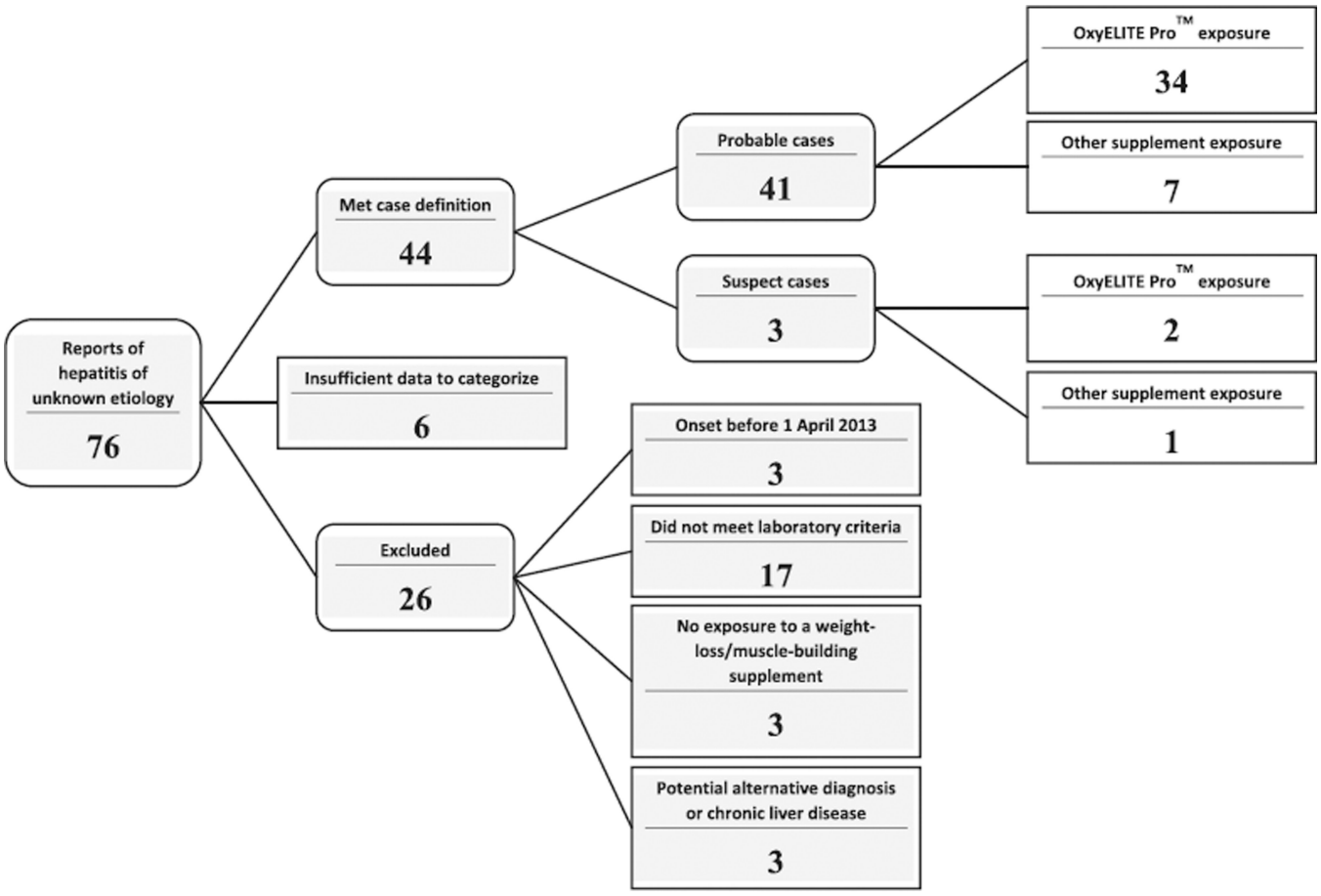

Figure 1.
Hepatitis case investigation determination flow-chart, Hawaii, 2013.

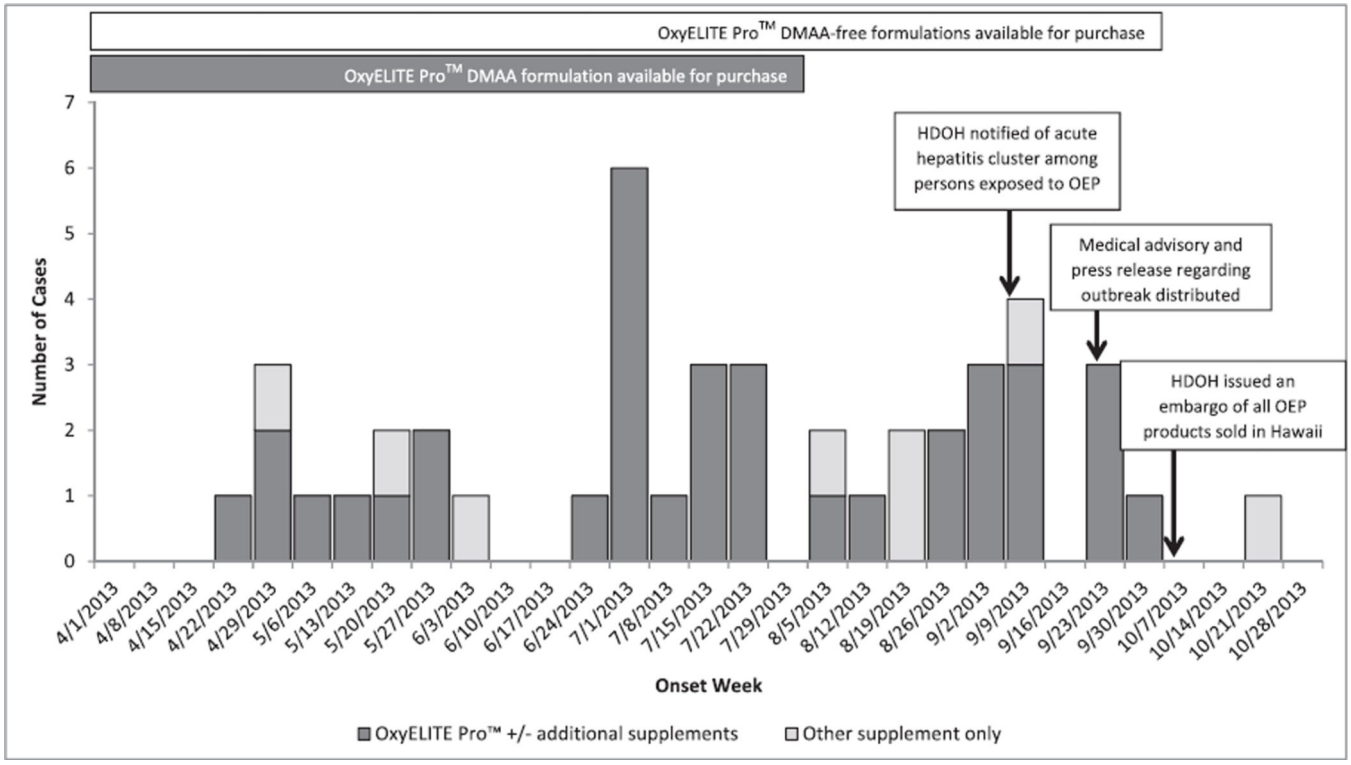

Figure 2.

Onset of hepatitis of unknown etiology by supplement taken, Hawaii, April–October 2013 (N=44).

Table 1

OxyELITE Pro™ product ingredients

DMAA-Containing Product (Available for purchase through July 2013)	
OxyELITE Pro® – Super Thermogenic™ *	
Serving Size 1 Capsule	Amount per serving
Proprietary Blend	119.5 mg
Bauhinia Purpurea L.(Leaf and Pod) Extract,	
Bacopa (Leaf)(Bacopa Monnieri) Extract,	
1,3-Dimethylamylamine HCl, Cirsium Oligophyllum	
(Plant) Extract, Yohimbe (Pausinystalia Johimbe) Bark Extract	
Caffeine	100 mg
DMAA-Free Products (Available for purchase late 2012–October 2013)	
OxyELITE Pro® – Super Thermo™ (New Formula) *	
Serving Size 1 Capsule	Amount per serving
Proprietary Blend	140 mg
Bauhinia Purpurea L.(Leaf and Pod) Extract, Aegeline, Norcoclaurine HCl,	
Hemerocallis Fulva (Flower) Heat Concentrated Extract, Yohimbe (Pausinystalia Johimbe)	
(Bark) Extract (AlphaShred™)	
Caffeine	135 mg
OxyELITE Pro™ – Super Thermo Powder *	
Serving Size 1–2 Scoops	Amount per scoop
OEP Thermo-Powder Blend	1058.5 mg
ExerciseStim Matrix	
Choline Bitartrate, Caffeine Anhydrous (125 mg), Aegeline,	
Norcoclaurine HCl, Yohimbe (Pausinystalia Johimbe)(Bark) Extract (AlphaShred™)	
OTCN2 Carnitine Transport System	
L-Carnitine-Tartrate,(Z)-N-(2-hydroxyethyl)octadec-9-enamide,	
Eriobotrya Japonica (Leaf) Extract (Standardized for Ursane-Type Triterpenoids)	

*Ingredient lists obtained from product labels.

Table 2

Demographics of cases meeting investigation criteria for dietary supplement associated hepatotoxicity, Hawaii, 2013 (N=44)

		n	%
Female gender		25	57
Age (years)	Median 33, Range 16–66		
BMI	Median 28.5, Range 20–42		
Normal (<25)		11	25
Overweight (25–29.9)		17	39
Moderately Obese (30–34.9)		6	14
Severely Obese (>35)		2	4
Unknown/Refused		8	18
Comorbidities (as listed in the medical chart)[a]			
No comorbidities		22	50
1–2 comorbidities		18	41
3–5 comorbidities		4	9
Race			
White		1	2
Asian		10	23
Pacific Islander		1	2
Black/African American		0	
American Indian/Alaska Native		0	
Two or more races[b]		25	57
Unknown		7	16
Duration of residence in Hawaii (years)	Median 30.5, Range 2–60		
Case Status			
Probable		41	93
Suspect		3	7

[a]Comorbidities seen in ≥2 cases: obesity, hypertension, chronic headache/migraine, asthma, obstructive sleep apnea, hyperlipidemia, hypothyroid.

[b]Comprising typically Asian, Pacific Islander, and/or Caucasian, as commonly observed among Hawaii's population. Note that in 2012, of the 18,986 births to 2 parents, 65% were reported to claim 2 races (unpublished data per HDOH Office of Health Status Monitoring).

Table 3

Exposures of cases investigated for dietary supplement associated hepatotoxicity, Hawaii, 2013

	n	%
All Cases (N=44):		
Dietary supplement exposure in the two months before illness		
Any OxyELITE Pro™	36	82
OxyELITE Pro™ only	14	32
OxyELITE Pro™ and another dietary supplement	22	50
Other supplements only[a]	7	16
Unknown supplement	1	2
Other exposures		
Tylenol® (general use)	13	30
NSAIDs (per medical chart or reported in the 3 weeks prior to onset)	18	41
Alcohol use (in the two months before onset)	22	50
More than 4 beverages in a sitting	7	16
Cigarette/cigar smoking (ever)	12	27
Current smoker	5	11
Cases with any OxyELITE Pro™ use (N=36)		
CIOMS scores (median score 5)		
0 (excluded)	0	0
1–2(unlikely)	2	6
3–5 (possible)	24	66
6–8 (probable)	10	28
>8 (highly probable)	0	0
OxyELITE Pro™ formulation exposure in the two months before illness		
DMAA-free formulations[b] only	27	75
DMAA formulation[c] AND DMAA-free formulations	3	8
DMAA formulation only	1	3
Unknown formulation	5	14
Latency (Days from initial exposure[d] to onset)		
Using estimated dates (n=31) Median 62, Range 7–732		
Using precise dates (n=9) Median 89, Range 12–422		

[a]'Other supplements' include: multivitamins, protein shakes/powders, 'Neem', calcium carbonate, 'Deca', 'Versa-1', and 'True-Slim', as reported by cases.

[b]OxyELITE Pro NF, OxyELITE Pro Purple Top, OxyELITE Pro Powder, or OxyELITE Pro Advanced Formula.

[c]OxyELITE Pro Original Formula.

[d]Initial exposure could be earlier than 60 days before illness onset; the last exposure had to have been within 60 days of illness onset to meet case definition.

Table 4

Clinical presentation of cases using OxyELITE Pro™, Hawaii, 2013 (N=36)

				n	%
Hospitalization				14	39
Days hospitalized		Median 15, Range 1–44			
Intensive Care Unit (ICU)				4	11
Days in ICU		Median 11, Range 4–18			
Required Liver Transplantation				2	6
Expired				1	3
Time (days) from onset to first medical evaluation					
Using estimated dates (n=36)		Median 16, Range 5–440			
Using only precise dates (n=20)		Median 11.5, Range 0–36			
Duration of symptoms in days					
Using estimated dates (n=14)		Median 33, Range 1–128			
Using only precise dates (n=9)		Median 28, Range 14–128			
Presenting Symptoms					
Dark urine				36	100
Anorexia				33	92
Fatigue				33	92
Jaundice/scleral icterus				33	92
Light stool				27	75
Abdominal pain				25	69
Nausea				24	67
Body aches				16	44
Emesis				15	42
Diarrhea				13	36
Fever				10	28
Fever reported at presentation on medical chart[a]				2	6
Peak Laboratory Values[b]	*Median*	*Range*	*Units*		
Alanine aminotransferase (ALT)	1740	428–3285	IU/L		
Aspartate aminotransferase (AST)	1134	128–2184	IU/L		

				n	%
Alkaline phosphatase (AP)	141	72–277	IU/L		
Total bilirubin	9.4	2.6–41.6	mg/dL		
INR	1.1	0.9–11.0			
White blood cell (WBC)	7.0	3.9–15.2	$\times 10^3$/uL		
Creatinine (Cr)	0.8	0.4–1.5	mg/dL		
Autoimmune markers					
Any autoimmune marker				12	33
ANA				8	22
Anti-liver-kidney-microsome antibody				0	0
Anti-smooth muscle antibody OR F-actin antibody				8	22
Anti-mitochondrial antibody				1	3

[a]Only one case with documented temperature >100.3F on initial evaluation.

[b]No eosinophilia seen on admission in cases.