DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: October 3, 2016

From: [redacted]
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Office of Food Additive Safety (OFAS)
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To: [redacted]
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Subject: Regulatory status and review of available information pertaining to 1,3-dimethylamylamine (DMAA): lack of general recognition of safety for its use in conventional foods.

GRAS Provision in Defining a Food Additive

As defined in section 201(s) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) [21 U.S.C. § 321(s)], the term "food additive" refers to any substance the intended use of which results in its becoming a component of any food, unless the substance is the subject of a prior sanction or is generally recognized as safe (GRAS) among qualified experts under the conditions of its intended use. Furthermore, under section 201(s) of the FD&C Act, a substance is exempt from the definition of a food additive and thus, from premarket approval requirements, if its safety is generally recognized by qualified experts.

As there is no food additive regulation establishing safe conditions of use for DMAA as an ingredient in foods, this memorandum will consider the applicability of the GRAS criteria for the use of DMAA as an ingredient in foods.

GRAS Criteria

A conclusion that a particular use of a substance is GRAS under the conditions of its intended use requires both general recognition and evidence of safety.

General recognition of safety requires common knowledge, throughout the expert scientific community knowledgeable about the safety of substances added to food, that there is reasonable certainty that the substance is not harmful under the conditions of its intended use. General recognition of safety through scientific procedures must be based upon the application of generally available and accepted scientific data, information, or methods, which ordinarily are published, as well as the application of scientific principles, and may be corroborated by the application of unpublished scientific data, information, or methods. The usual mechanism to establish that scientific information is generally available is to show that the information is published in a peer-reviewed scientific journal. Mechanisms to establish the basis for concluding that there is common knowledge throughout the expert scientific community about the safety of a substance are more varied. Most often, publication in a peer-reviewed scientific journal of data on a test substance has been used to establish common knowledge throughout the expert scientific community in addition to general availability. These criteria are discussed in the GRAS final rule, which will take effect on October 17, 2016 (81 Federal Register (FR) 54960; August 17, 2016). This rule was previously proposed in 1997 (62 FR 18938; April 17, 1997; Substances Generally Recognized as Safe (GRAS); the GRAS proposal). In this memorandum, reference is made to the current citations in FDA's regulations in Title 21 of the Code of Federal Regulations (21 CFR). However, these citations will be amended as of the effective date of the GRAS final rule, i.e., October 17, 2016.

A demonstration of safety under GRAS criteria requires that information about the substance establish that the intended use of the substance is safe. FDA has defined "safe" (21 CFR 170.3(i)) as a reasonable certainty in the minds of competent scientists that the substance is not harmful under its intended conditions of use. FDA's regulations in 21 CFR Part 170 describe the eligibility criteria for classification of a substance added to food as GRAS. Under 21 CFR 170.30(a)-(c), general recognition of safety must be based on the views of qualified food safety experts. The basis of such views may be either through: (1) scientific procedures; or, (2) in the case of a substance used in food prior to January 1, 1958, experience based on common use in food.

FDA's regulations in 21 CFR Part 170 define "common use in food" and establish eligibility criteria for classification as GRAS through experience based on common use in food. Under 21 CFR 170.3(f), common use in food means "a substantial history of consumption of a substance for food use by a significant number of consumers."

Similarly, FDA's regulations in 21 CFR Part 170 define "scientific procedures" and establish eligibility criteria for classification as GRAS through scientific procedures. Under 21 CFR 170.3(h), scientific procedures "include those human, animal, analytical, and other scientific studies, whether published or unpublished, appropriate to establish the safety of a substance." Under 21 CFR 170.30(b), general recognition of safety based upon scientific procedures "shall require the same quantity and quality of scientific evidence as is required to obtain approval of a food additive regulation for the ingredient." Section 170.30(b) further states that general recognition of safety through scientific procedures is ordinarily based upon published studies, which may be corroborated by unpublished studies and other data and information.

Regulatory Status of DMAA

In the case of DMAA, FDA is unaware of its use in food prior to 1958, thus it does not meet the "common use in food" criteria. Thus, its eligibility for classification as GRAS needs to be on the basis of "scientific procedures." That is to say, adequate technical evidence of safety must exist and this technical evidence would have to be generally known and accepted by qualified food safety experts to demonstrate the safety of the intended use. FDA notes that regulatory agencies in Australia, Canada, and New Zealand have banned the sale of DMAA, a consideration inconsistent with general recognition.

PubMed Literature Searches. A search of the published scientific literature was conducted several times between April, 2013 and June, 2015. PubMed was searched using the search terms dimethylamylamine, 1,3- dimethylamylamine and methylhexaneamine. Although PubMed goes back to about 1951, the searches showed that most of the information on DMAA in the scientific literature has been published within the last five years. The PubMed searches yielded articles on case reports that point to observations of adverse effects (such as cardiac arrest) after the consumption of DMAA containing products (Armstrong, 2012; Archer et al., 2015; Eliason et al., 2012; Foley et al., 2014; Gee et al., 2012; Karnatovskaia et al., 2015; McDermott, 2012; Smith et al., 2014; Young et al., 2012). Human studies investigating products containing DMAA were retrieved in the search (Bloomer et al., 2011a; Bloomer et al., 2013; Powers, 2015; Schilling et al., 2013; Whitehead et al., 2012; Farney et al., 2012). Additional human studies not retrieved in searches or on products containing DMAA were brought to our attention (Bloomer et al., 2011b; Jacobs, 2012; McCarthy et al., 2012a,b). Miscellaneous information was also found in the PubMed searches including a poison control center report (Forrester, 2013) and two studies on the analyses of human urine and blood samples. One of these two studies reported an analytical method to determine prohibited drugs in dried blood spots (Thomas et al., 2012); the other was an analysis of urine to identify variation in the use of novel psychoactive substances in London (Archer et al., 2014). There were three regulatory articles identified in the searches: one related to third-party certification of dietary supplements (Cancio et al., 2012); a second related to the availability of DMAA dietary supplements despite FDA action (Gregory, 2013); and, the third addressed policy reform (Carpenter, 2012). Other articles addressed dietary supplement use by warfighters (O'Connor, 2012) and research on botanical ingredients used in dietary supplements (Pawar et al., 2013). From references cited in the articles from the PubMed search, a case of toxicity from DMAA party pill was found (Gee et al., 2010). In addition, a Google Scholar search identified a publication by Venhuis and de Kaste (2012) expressing a scientific opinion on the regulatory status of DMAA in the European Union.

The scientific material in the public domain contains little information relevant to a food safety assessment. The available data are insufficient to address safety for use in foods that will be consumed by the general public. The available data assess DMAA's effects primarily in young, athletic consumers who are interested in dietary supplement use for performance enhancement. Typically, the number of subjects in these studies is small thereby further limiting their value. No traditional toxicology studies conducted in laboratory animals that are relevant to a safety assessment for the use of DMAA as an ingredient in food were found in the searches conducted.

Safety Data

Data in the publicly available scientific literature raises concerns about the safety of DMAA. The structure of DMAA is similar to methamphetamine (Gee et al., 2012), which alone is cause for concern. Studies in humans by Marsh et al., (1951) and Bloomer et al. (2011a) report increases in blood pressure following oral administration of DMAA. The pressor effect was also observed in dogs given DMAA intravenously (Swanson and Chen, 1948). Writing about products containing DMAA, Farney et al. (2012) stated that "…it appears that such products should be avoided by individuals who are hypertensive (resting blood pressure $\geq$ 140/90 mm Hg) or those who are pre-hypertensive (resting blood pressure $\geq$ 120/80 mmHg)." These authors recommended that the general population should not use DMAA-containing products. The article by McCarthy et al.(2012a) cautions about use of the DMAA containing product OxyELITE Pro by stating "…it may be wise for hypertensive individuals to avoid use of this supplement as any increase in these variables maybe undesirable." In addition, DMAA has been associated with cardiac arrest in a report on the deaths of two solders (Eliason et al., 2012). Further, hemorrhagic stroke was reported by Young et al. (2012).

Subjects in the human studies cited above were young, in good health, and typically exercise-trained. As noted, some of the articles state that individuals that are pre-hypertensive or hypertensive should avoid or use caution before using products containing DMAA (McCarthy et al., 2012a,b; Farney et al., 2012). A case study reported by Gee et al. (2010) was on a 21 year old man who took two tablets each containing 278 mg of 99.9% pure DMAA (stated as the recommended dose by the authors) along with a capsule containing 150 milligrams (mg) of caffeine, after consuming one can of beer. At approximately 30 minutes later, the first adverse effect (severe headache) was observed. It was determined that the man suffered a cerebral hemorrhage. The publication by Venhuis and de Kaste (2012) reviewed the literature on DMAA and similar amines for their effective oral dosage for medicinal uses in Europe. These authors caution that use greater than 4 milligrams of DMAA should be subject to regulation as a drug. This review references two studies, one by Marsh et al. (1951) and the other by Swanson and Chen (1948), which address adverse effects of DMAA on blood pressure. These two studies are described in more detail below. The available human data raise safety concerns and there is no compelling evidence that DMAA is safe for consumption by the general population.

Additional Data and Information Evaluated

Recently, FDA was asked to evaluate additional information. A letter to the Editor authored by Rodricks et al. (2013) disputes the case report published by Gee et al. in 2012 based on a study Rodricks et al. themselves conducted in eight adult males given 25 mg of DMAA. This study, which was funded by USPlabs (USPlabs at one time made products containing DMAA), was reported within their letter to the Editor. Rodricks et al. (2013) reported "… no meaningful effect on body temperature, pulse rate, or blood pressure." FDA notes that the limited information presented in the letter is not sufficient to discount the report by Gee et al. (2012). Gee et al. (2012) reported on adverse events in three patients after consuming DMAA. Patient 1 consumed two tablets containing 66 mg DMAA and 84 mg caffeine after consuming alcohol. Patient 2, while in a bar, mixed one quarter of a packet of a powdered substance that was labeled as containing 50 mg DMAA into a drink (it is unclear if the drink contained alcohol or not). Patient 3, while in a bar, was given water with a powder dissolved in it. Two hours later Patient 3's blood was drawn and his DMAA level was 2.31 mg/liter. Gee et al. (2012) reported that cerebral hemorrhage occurred in the three patients who consumed DMAA. This is a serious adverse health effect.

A second letter to the Editor/Opinion authored by Rodricks and Lumpkin (2013) disputed a short article by Cohen (2012). Cohen points out the similarities between DMAA and amphetamines and discusses DMAA as the possible cause of several adverse effects such as hemorrhagic stroke, seizures and stress-induced cardiomyopathy reported in case studies. Rodricks and Lumpkin (2013) state that none of the adverse observation reported in the case studies were observed in the clinical studies. Cohen (2013) replied to Rodricks and Lumpkin by noting the inadequacies of the clinical trials that have been conducted. FDA also considers the design of the clinical studies to be lacking; however, we note that the clinical studies still raise safety concerns.

FDA reviewed an article by Jackson (1974) on activity and lethality in mice given beta-phenylethylamine and cholinergic compounds contained in dietary supplement products. However, this study is not relevant to this review because DMAA itself was not administered.

A report entitled "Safety evaluation of 1,3-dimethylamylamine (DMAA) in dietary supplement products" by Rodricks JV, Turnbull D, and Lumpkin M. (May, 2012) was brought to our attention but it was not provided to FDA. FDA cannot locate the report and therefore we presume that it is unpublished. The Department of Defense (DOD) cited this report in their report on DMAA (Lammie, 2013). The DOD report indicates that the Rodricks et al. report is a review of available studies and notes that the review does not assess the quality of the studies it summarizes. For this reason, and because a review does not contain primary data, the report by Rodricks et al. (2012) will not be useful to establish safety.

Two studies on the maximum tolerated dose (MTD) of 1,3-dimethylpentylamine (a synonym for DMAA) conducted in rabbits and rats (Deshmukh et al., 2012a,b) were brought to FDA's attention. However, according to Clintox Bioservices (the laboratory that performed the studies) these studies are unpublished and not available to the public, or FDA. Therefore, these studies are irrelevant for making a GRAS conclusion related to the use of DMAA in foods.

In two human clinical studies, subjects were given a dietary supplement product named Fastin-RR (RR for rapid release). From the study reports, it is unclear if DMAA is contained in Fastin-RR. The first study by Jacobs (2013) was conducted in 11 volunteers (6 men and 5 women, 28.5 $\pm$ 5 years of age) and described in a brief article. The body mass index was reported to be between 25 and 35; no other clinical information, such as blood pressure and pulse rate, was reported. The author concluded, "These findings indicate that resting energy expenditure is significantly enhanced with Fastin-RR." This short article lacks any information that could be used to determine the safety of DMAA in foods. The second article, also by Jacobs (2014), describes an 8 week weight loss program in 20 volunteers. The age and weight of the volunteers are not reported. The author reports that Fastin-RR did not significantly change resting blood pressure or heart rate. However, there is no data provided to substantiate this statement. The author did report that Fastin-RR reduced the volunteers' body weight (-8.0 $\pm$ 6.5 lbs) and body fat (-6.3.0 + 7.3 lbs). This short article also lacks information that could be used to determine the safety of DMAA in foods. Furthermore, the identity of the test article, with respect to presence of DMAA is unknown.

Conclusions

There is no food additive regulation in effect that provides for the safe use of 1,3-dimethylamylamine (DMAA). In light of published scientific data and information, DMAA does not meet the criteria for GRAS. There are inadequate safety data and general recognition of safety cannot be established. Indeed, the available data indicate that the use of DMAA in food is a cause for concern. As such, the use of DMAA in food constitutes use of an unapproved food additive, rendering the product unsafe within the meaning of Section 409 of the FD&C Act, and hence adulterated within the meaning of Section 402(a)(2)(C) of the FD&C Act.

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