



RESEARCH REINFORCES NEED FOR DIETARY SUPPLEMENT GMPS, PRODUCT TESTING AND CERTIFICATION

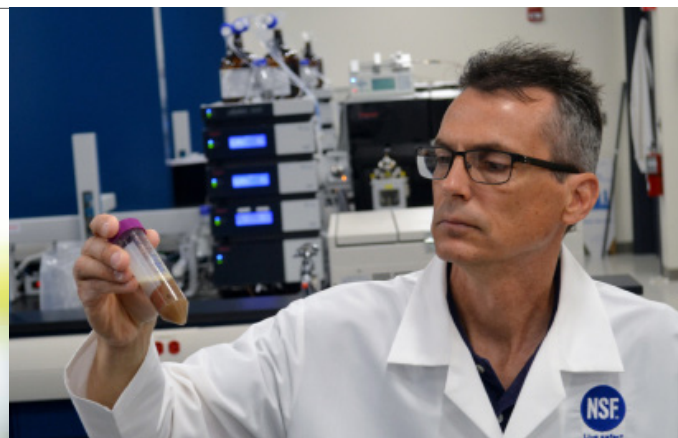
Hidden Stimulants Associated with 2-aminoisoheptane and Aconitum Kusnezoffii

Recent research conducted by scientists from NSF International, Harvard Medical School, the United States Department of Defense and the National Institute for Public Health and the Environment in the Netherlands (RIVM), identified four unapproved, DMAA-like stimulants in common over-the-counter weight-loss and pre-workout supplements. The peer-reviewed research was published in the journal *Clinical Toxicology* in November 2017.

These potentially harmful compounds were not listed as ingredients on any of the product labels, but the researchers believe they may have been disguised as 2-aminoisoheptane or extract of Aconitum kusnezoffii.

The unapproved compounds may be pharmacologically similar to ephedrine, a stimulant banned by the U.S. Food and Drug Administration (FDA) in 2004 due to serious side effects, including death. These hidden stimulants may cause adverse cardiac events, hemorrhagic strokes or sudden death, especially if combined with caffeine or taken prior to a rigorous workout. Exposure to extreme heat or dehydration may also increase the health risks associated with the compounds.

Based on the findings, the researchers encourage consumers to avoid using products labeled as containing 2-aminoisoheptane or Aconitum kusnezoffii.



OVER A DECADE OF HIDDEN AND POTENTIALLY HARMFUL STIMULANTS

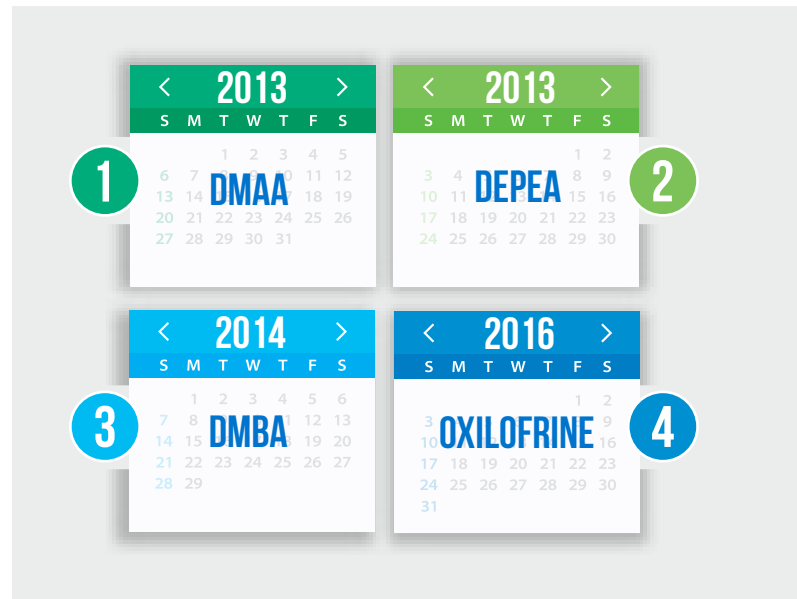
Since 2004, when ephedrine was deemed dangerous and banned by the FDA, manufacturers of some weight-loss and pre-workout products have been searching for replacement ingredients that will provide a stimulant kick to their products. Researchers at NSF International and other institutions have been following developments in this market segment closely – searching for hidden stimulants and testing ingredients in sports supplements to evaluate their quality and safety. Over the years, researchers have identified many potentially harmful substances sometimes used in supplements. Here's a brief timeline of the research:

2004 | In an *International Journal of Sports Medicine* article, the International Olympic Committee found that 15 percent of 634 supplements across 13 countries contained steroids prohibited in sport, none of which were declared on the product labels.

2013 | In an article published in the *Journal of the American Medical Association*, researchers found that dietary supplements account for half of all Class I drug recalls in the United States. The research was conducted over a nine-year period (2004-2012), and showed that 51 percent of FDA recalls involved dietary supplements containing unapproved ingredients or drugs.

| In an article published in *Drug Testing and Analysis*, researchers found evidence of an emerging and potentially harmful adulterant called N,alpha-diethylphenylethylamine (N,-DEPEA) in two dietary supplement products. The substance has a chemical structure similar to methamphetamine and was not disclosed on at least one of the product labels. While the addictive and pharmacological properties of this substance are unknown, it has been linked to failed drug tests.

| In another article published in *Drug Testing and Analysis*, researchers at NSF International and the U.S. Army Research Institute of Environmental Medicine



(USARIEM) determined that 1,3-Dimethylamylamine (DMAA) is not “natural” in origin and should not be used as an ingredient in dietary supplements. Products containing DMAA have been linked to health problems and at least five deaths. As a result of this research, the FDA issued warnings to manufacturers and urged the public to avoid products containing DMAA.

2014 | In a study published in *Drug Testing and Analysis*, researchers from NSF International, Harvard Medical School and RIVM found an unapproved synthetic stimulant in 12 over-the-counter dietary supplements. The synthetic stimulant, 1, 3-Dimethylbutylamine (DMBA), has a chemical structure similar to DMAA.

2016 | A research team consisting of scientists from NSF International, Harvard Medical School, the National Center for Natural Products Research (NCNPR) at the University of Mississippi and RIVM published their findings in *Drug Testing and Analysis*. Their research revealed the use of an unapproved pharmaceutical stimulant, oxilofrine, in 14 over-the-counter dietary supplement products. According to the FDA, oxilofrine is an illegal dietary ingredient. It has been studied in animals and humans and has been found to cause heart effects similar to ephedrine.



LATEST STUDY FINDS EXPERIMENTAL STIMULANTS IN PRODUCTS LABELED 2-AMINOISOHEPTANE OR ACONITUM KUSNEZOFFII

The most recent study, which was published in *Clinical Toxicology*, focused on a new ingredient used in weight loss and pre-workout supplements: 2-aminoisoheptane. Researchers at NSF International and Harvard Medical School learned of this popular new ingredient by following bodybuilding and workout blogs. Unfamiliar with any legal dietary ingredient known as “2-aminoisoheptane,” they began to wonder what was really in those products.

In order to study this ingredient, the researchers purchased six products that listed 2-aminoisoheptane, DMBA, 2-amino-6methylheptane or Aconitum kusnezoffii as ingredients. In a targeted analysis, the researchers used ultra-high performance chromatography (UHPLC) and tandem mass spectrometry to detect and measure compounds. This technology allowed them to eliminate the compounds that corresponded to the known labeled ingredients. From there, the scientists worked on identifying the remaining ingredients by characterizing their features using a targeted method and reference standard to confirm the presence and quantity of each ingredient.



The results of this research showed that DMBA was in one product, DMAA was in two products and 1,4-DMAA (related to DMBA and DMAA) was in three products. Besides being potentially harmful, these ingredients were not disclosed on the product labels. Of the six products tested, only one contained all the labeled ingredients. Moreover, all of the products tested came from high-risk categories of supplements.

High-Risk Categories of Supplements



MUSCLE BUILDING



PRE-WORKOUT



WEIGHT LOSS



SEXUAL PERFORMANCE

Products Tested

PRODUCT	MANUFACTURER	UNAPPROVED COMPOUNDS
Game Day	MAN Sports	Octodrine
Infrared	Gold Star	1,3-DMAA* ILLEGAL
2-aminoisoheptane	Chaos and Pain	1,4-DMAA
Simply Skinny Pollen	Bee Fit with Trish	1,3-DMAA* ILLEGAL 1,4-DMAA
Cannibal Ferox AMPED	Chaos and Pain	1,3-DMBA* ILLEGAL
Triple XG	Gold Star	1,4-DMAA

*Previously found to be unlawful dietary ingredient by the U.S. FDA



THE IMPORTANCE OF DIETARY SUPPLEMENT CERTIFICATION

For manufacturers, certifications are important to gain consumer confidence and demonstrate compliance with regulatory requirements. For products that are sold in the U.S., manufacturers must register with the FDA. This means they are on the FDA's radar for inspections and may receive warning letters or other regulatory actions if they don't meet the FDA's Good Manufacturing Practice (GMP) requirements. Obtaining certification for a supplement product not only ensures the manufacturer's facility is meeting FDA GMP requirements, it helps to ensure that products do not contain ingredients or contaminants that could be harmful to human health.

LEVELS OF GMP FACILITY REGISTRATION AND PRODUCT CERTIFICATION

There are three levels of independent, third-party facility registration and product certification:

GMP Facility Registration

Good Manufacturing Practice (GMP) registration for a manufacturing facility is the first step toward product certification. Dietary supplement manufacturing facilities must pass bi-annual audits to earn this registration, which verifies continued compliance

with GMPs required by the FDA. Only after all corrective actions, if any, have been addressed by the manufacturer can the facility become GMP registered.

Product Certification

In addition to passing the bi-annual GMP audits to obtain certification to the only American National Standard for dietary supplements - (NSF/ANSI 173) - supplement products must be tested at accredited third-party laboratories, like those of NSF International. This testing and certification process includes a label claim review, toxicology review and contaminant review. The product is then subject to periodic auditing and testing in order to verify continual compliance to the NSF/ANSI 173 standard.

Sport Supplement Certification

In addition to the testing and auditing required for certification to NSF/ANSI 173, supplement products for athletes can be tested for athletic banned substances through certification programs such as NSF's Certified for Sport®. Products certified to this program are tested for over 270 athletic banned substances on prohibited substances lists provided by the World Anti-Doping Agency (WADA), the NFL and the MLB.

About the Author

John Travis | Senior Research Scientist, Dietary Supplements | NSF International

John Travis has more than 20 years of experience as an analytical chemist specializing in the analysis of dietary supplements. As Senior Research Scientist at NSF International, Travis analyzes hundreds of dietary supplement products each year for various contaminants, emerging drugs and harmful compounds. Utilizing techniques ranging from gas chromatography to high-performance liquid chromatography to mass spectrometry, John has developed and validated analytical methods for numerous marker compounds and trace contaminants. He is an active member of the Association of Analytical Communities (AOAC), participating on expert review panels for carotene and lutein, and is a member of the AOAC stakeholder panel for dietary supplements. Travis is also a subject matter expert on athletic banned substances and was instrumental in the development of the screening methods used for the NSF International's Certified for Sport® program, which now screens products for more than 270 banned substances on the World Anti-Doping Agency, National Football League, Major League Baseball and National Collegiate Athletic Association lists.

Travis is currently involved with the analysis of pharmaceutical agents and illicit drugs, stimulants and other prohibited substances as both adulterants and contaminants in dietary supplements and functional foods, co-authoring scientific papers on ingredients of concern including stimulant drugs DMAA, DEPEA and DMBA found in dietary supplements.

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789 N. Dixboro Road, Ann Arbor, MI 48105 USA | www.nsf.org