Overview of regulation of dietary supplements in the USA and issues of adulteration with phenethylamines (PEAs)

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The multi-billion dollar dietary supplement industry in the USA and worldwide has grown very rapidly over the past 15 years with annual sales now in the multi-billions of dollars. The results of a recent survey of total retail sales of herbal and botanical dietary supplements alone (excluding herbal teas, herbs sold in natural cosmetic products, or herbs sold as Food and Drug Administration (FDA) approved ingredients in nonprescription medications) in the USA showed that sales reached more than 6 billion dollars. The industry is benefiting from a larger health-conscious consumer base with growing interests in wellness and also from aging populations around the world. Information from the FDA’s website states that there are more than 85,000 different dietary supplements on the market. According to data from the 2007–2010 nationally representative National Health and Nutrition Examination Survey (NHANES), about half (49%) of adults in the USA use dietary supplements. Many are motivated by broad desires to improve or maintain health.

A large and growing literature has shown that ingredients in dietary supplements may sometimes cause unexpected side effects or severe intoxications. These risks include, among others, exposure to chemical contaminants (e.g. plant toxins), pesticides, mycotoxins, or heavy metals, or interaction of natural components in a botanical product with prescription drugs. Other serious risks may result from the intentional adulteration of botanical supplements or herbal remedies with synthetic compounds in order to develop an immediate pharmacologic action or to intensify a claimed biological effect. Adulterants may include approved prescription drugs, their analogues, patented drugs not undergoing clinical trials, or pharmaceuticals withdrawn because of their serious side effects. The FDA’s Center for Drug Evaluation and Research (CDER) has reported that more than 700 products marketed as dietary supplements have been found to be adulterated with pharmaceuticals or their analogues, including new stimulants, novel anabolic steroids, unapproved anti-depressants, banned weight-loss medications, and untested sildenafil analogues. Vaclavik et al. and others have noted that the products most frequently adulterated with pharmaceuticals are usually advertised for management of various chronic illnesses (e.g. diabetes mellitus, hypertension, arthritis) or for conditions such as obesity/overweight or erectile dysfunction (see Vaclavik et al. for references). Products targeting amateur or professional athletes are another group that is frequently adulterated.

In this review, we provide an overview of how dietary supplements are regulated in the USA and the significance of New Dietary Ingredient (NDI) notifications with respect to charges of adulteration. We then review the presence, either as naturally occurring constituents or as added synthetic chemicals, of biologically active phenethylamines (PEAs) in dietary supplements and of PEA drugs (e.g. clenbuterol, fenfluramine, sibutramine, ephedra) and synthetic (e.g. β-methylphenethylamines, methylsynephrine, α-ethyl-phenethylamine) biologically active phenethylamines (PEAs) in dietary supplements and of PEA drugs (e.g. clenbuterol, fenfluramine, sibutramine, lorcaserin) in weight-loss products. Regulatory actions against manufacturers of products labelled as dietary supplements that contain the aliphatic amines 1,3-dimethylamine and 1,3-dimethylbutylamine, and PEAs such as β-methylphenethylamine, aegeline, and Dendrobium illustrate the FDA’s use of its authority under the FD&C Act to promote dietary supplement safety.
dietary supplements from the market and identify FDA resources available to consumers regarding the use of dietary supplements.

Regulation of dietary supplements in the USA

General

In the USA, dietary supplements are regulated by the US FDA under the Federal Food, Drug and Cosmetic Act (FD&C Act). The Dietary Supplement Health and Education Act of 1994 (DSHEA) amended the FD&C Act to provide a new regulatory framework for dietary supplements but applicable food and drug provisions are also used for dietary supplements, as needed.[5] DSHEA defined dietary supplements, described a procedure for addressing safety issues, regulated labelling and health claims on dietary supplements, and provided for the establishment of Current Good Manufacturing Practices (CGMP). DSHEA also established a new government body, the Office of Dietary Supplements (ODS), within the National Institutes of Health (NIH). This new office was charged with coordinating research on dietary supplements, developing a database of dietary supplements research, and serving as the principal advisor to the Secretary of the DHHS, the Director of the Centers for Disease Control (CDC), and the Commissioner of the FDA on issues relating to dietary supplements, including dietary intake regulations, safety, claims, and scientific issues arising in connection with labelling and composition.[7]

Under US food law, dietary supplements are deemed to be food under section 201(ff) of the FD&C Act (21 U.S.C. § 321 (ff)). Under DSHEA, a dietary supplement is defined as a product (other than tobacco) that is intended to supplement the diet that contains one or more of the following dietary ingredients: a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite, constituent, extract or combination of any of the ingredients listed above. The forms in which a dietary supplement can be provided include capsules, powders, softgels, gelcaps, tablets, liquids, or other forms. Dietary supplements must be labelled as such and cannot be represented for use as a conventional food or as a sole item of a meal or the diet.

DSHEA also describes the conditions under which dietary supplements are adulterated. It applies the existing food standards for adulteration to dietary supplements but requires that such a determination be based on conditions of use recommended or suggested on the product label, or, in the absence of such recommendations or suggestions, on ordinary conditions of use. DSHEA also establishes in section 402(g)(1) of the FD&C Act that dietary supplements are adulterated if they are produced under conditions that do not meet current good manufacturing practices. These will be discussed later in the review.

Statements of nutritional support

Dietary supplement labels may carry a variety of statements of nutritional support without obtaining pre-market approval from the FDA. Specifically, DSHEA described several types of ‘statements of nutritional support’, commonly known as structure/function claims. Such claims, according to section 403(i)(6) of the FD&C Act, include claims related to a classic nutrient deficiency disease, claims describing the role of a nutrient or dietary ingredient in affecting the structure or function in humans, claims that characterize a documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or function, and claims that describe general well-being from consumption of a nutrient or dietary ingredient. The 6 January 2000, final rule defines the types of statements that can be made concerning the effect of a dietary supplement on the structure or function of the body.[8] DSHEA requires that manufacturers must have substantiation of such label statements and must notify the FDA within 30 days after marketing a product with a statement of nutritional support that such a statement is being made. The label must also carry the disclaimer ‘This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.’ DSHEA did not change the requirements for health claims on dietary supplement labels and such claims still require significant scientific agreement regarding the proposed claim and are still subject to pre-market approval by the FDA. More information on this topic can be found in Guidance for Industry: Substantiation for dietary supplement claims made under section 403(r)(6) of the Federal Food, Drug and Cosmetic Act[9] published by the FDA.

Good manufacturing practices (GMPs, CGMPs)

DSHEA, among other things, amends the FD&C Act by the addition of section 402 (g). Section 402 (g) provides in part that the Secretary, DHHS may, by regulation, prescribe good manufacturing practices for dietary supplements. Section 402 (g) also stipulates that such regulations be modelled after CGMP regulations for food and not impose standards for which there are no current and generally available analytical methods. On 25 June 2007, the FDA published its final rule establishing CGMPs in manufacturing, packaging, labelling, or holding operations for dietary supplements.[10] This final rule established new part 111 in Title 21 in the Code of Federal Regulations (21 CFR part 111). The rule requires that persons who manufacture, package, label, or hold a dietary supplement establish and follow CGMPs to ensure that the dietary supplement is packaged and labelled as specified in the master manufacturing record. Current law renders a dietary supplement product adulterated if the supplement is prepared, packaged, or held under conditions that do not meet CGMPs. The general food CGMPs in part 110 (21 CFR 110) largely address practices designed to ensure that food is manufactured, processed, packed, and handled under sanitary conditions and that the food is safe, clean, and wholesome. The general food CGMPs do not address the unique characteristics of certain specific types of food products and over the years, the FDA has implemented separate and more specific CGMPs for these types of foods (e.g. infant formula, thermally processed low-acid canned food). Dietary supplements were another type of food for which specific CGMPs were needed. In its final rule, the FDA noted that unlike most foods, the majority of dietary supplements are packaged into tablets, gelcaps, and capsules and may contain bioactive ingredients that must be present in controlled amounts. For these and other reasons, processing controls for dietary supplements need to differ from those in place for conventional foods. Dietary supplement manufacturers are expected to comply with both the food and dietary supplement CGMPs. New rules implementing the Food Safety Modernization Act (FSMA), address hazard analysis and preventive controls and foreign supplier verification, among other topics. These new rules will impact dietary supplements and dietary supplement ingredients but a review of the potential effects is beyond the scope of this review.

Facilities registration

The Public Health Security and Bioterrorism Preparedness and Response Act of 2002[11] directed the FDA to take steps to protect
the public from a threatened or actual attack on the US food supply. To carry out certain provisions of the Bioterrorism Act, the FDA established regulations requiring that food facilities register with the FDA and that the FDA be given advance notice on shipment of imported foods. These regulations became effective on 12 December 2003. Thus, as dietary supplements are a category of foods, there is a requirement for the registration of dietary supplement facilities.[14]

Adverse event reports (AERs)

DSHEA did not address the issue of reporting of adverse events that might be experienced by consumers of dietary supplements. However, Congress enacted the Dietary Supplement and Nonprescription Drug Consumer Protection Act on 22 December 2006.[13] It amended the FD&C Act with respect to serious adverse event reporting for dietary supplements and nonprescription drugs. Specifically, it requires dietary supplement manufacturers, packers, and distributors to comply with adverse event reporting and recordkeeping. The law requires that all serious adverse events, such as death, a life-threatening experience, inpatient hospitalization, a persistent or significant disability or incapacity, a congenital anomaly, or a birth defect, be reported to the FDA by the responsible person within 15 business days of its receipt.

MedWatch is the FDA's agency wide safety information and adverse event reporting programme. Individuals may also call or e-mail health problems directly to the Center for Food Safety and Applied Nutrition (CFSAN), which collects and stores AERs related to foods and dietary supplements. Dietary supplement firms are required to include contact information on the product label for the receipt of adverse events. The firm is expected to evaluate the problem and, if it is determined to be serious in accordance with the Dietary Supplement and Nonprescription Drug Consumer Protection Act,[14] then the firm is required to submit it, and a copy of the product label, to the FDA. The firm can also submit the information electronically via the FDA's Safety Reporting Portal (SRP). Since the Dietary Supplement and Nonprescription Drug Consumer Protection Act has come into effect, the number of serious AERs submitted by firms has increased significantly, as expected. The FDA has published guidance on how and what information to submit regarding serious adverse event reports for a dietary supplement via the FDA's SRP (formerly referred to as MedWatchPlus).

Mandatory recall authority

The FSMA[15] was signed into law on 4 January 2011, amending the FD&C Act. The FSMA strengthens food safety measures and provides the FDA with additional enforcement tools to better protect public health. Among these new enforcement tools is the authority for mandatory food recalls. In general, the procedures under this new authority operate as follows: If the Secretary of the DHHS determines that there is a reasonable probability that an article of food (other than infant formula) is adulterated or misbranded under sections 402 or 403, respectively, of the FD&C Act, and that the use of or exposure to the article will cause serious adverse health consequences or death to humans or animals, the Secretary can provide the responsible party with an opportunity to cease distribution and recall the product. If the responsible party refuses to or does not voluntarily cease distribution of the product, the Secretary may order the responsible party to immediately cease distribution and to notify all parties to which the product has been distributed, transported, or sold, to immediately cease distribution. The Secretary must provide the responsible party an opportunity for an informal hearing to be held not later than two days after the issuance of the order to explain why the product should not be recalled. If, after providing the opportunity for an informal hearing, the Secretary determines that removal of the product from commerce is necessary, the Secretary can amend the order to require a recall and to specify a timetable by which the recall shall occur. The FDA has used this new recall authority twice, in one case to remove the dietary supplements OxyElite Pro® and VERSA-1® from the market. The details of this action are provided in the section on Aegeline and in the FDA's 2014 Annual Report to Congress on the Use of Mandatory Recall Authority.[16] The FDA issued its Draft Guidance for Industry on Mandatory Food Recalls on 7 May 2015.[17]

New dietary ingredients (NDIs) and NDI notifications

DSHEA defines an NDI as a dietary ingredient that was not marketed in the USA before 15 October 1994. Under most conditions, the manufacturer of an NDI must provide the FDA with information, based on a history of use or other evidence of safety that supports the conclusion that the dietary supplement containing the NDI will reasonably be expected to be safe. Such information must be provided at least 75 days before the NDI is introduced into interstate commerce. A product is deemed to be adulterated if the required NDI notification is not submitted or if there is inadequate information to provide reasonable assurance that the NDI does not present a significant or unreasonable risk of illness or injury. In making a determination that the product is adulterated, the burden of proof rests with the FDA. DSHEA does not give the FDA the authority to approve the 75-day notifications for NDIs. Rather, the agency generally responds with one of four responses: an acknowledgement without comment or objection; acknowledgement with comment that the notification does not provide adequate information on identity, history of use and/or other evidence of safety; acknowledgement of an incomplete notification (does not meet the requirements listed in 21 CFR 190.6); or a letter stating that the ingredient that is the subject of the notification is not a dietary ingredient.[18]

The section of DSHEA which defines NDIs and describes the requirement for a pre-market notification is among its most complex. In order to assist industry in complying with DSHEA, the FDA, in September 1996, proposed a procedure by which manufacturers could submit information on which they relied to determine that an NDI was reasonably expected to be safe.[19] This proposed rule was finalized on 23 September 1997 and became effective one month later on 23 October 1997 (62 FR 49886).[20] The Code of Federal Regulations was updated to include 21 CFR § 190.6 which specifies the information that the manufacturer or distributor must include in its premarket NDI notification.

Section 113(b) of FSMA requires the FDA to publish, within 180 days of the date of enactment (4 January 2011), guidance that clarifies when a dietary supplement ingredient is an NDI, when the manufacturer or distributor of an NDI or of a dietary supplement containing an NDI should submit an NDI notification to the FDA, the evidence needed to document the safety of the NDI, and appropriate methods for establishing the identity of the NDI. In July 2011, in response to the FSMA requirement, the FDA published its Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues.[19] The draft guidance spells out the NDI notification procedures and timeframes for the process. The manufacturer or distributor of an NDI or a dietary supplement containing an NDI must notify the FDA at least 75 days before the...
dietary supplement containing the NDI is marketed in the USA. The ‘date of filing’ is the date when the FDA receives a complete notification (i.e., a notification that contains all of the information required by 21 CFR 190.6).

Among the many issues addressed in the Draft Guidance was the question of whether a synthetic copy of a constituent or extract of an herb or other botanical was a dietary ingredient. The FDA responded to this question by stating that a synthetic copy of a botanical was never part of the botanical and thus could not be a constituent of the botanical that qualifies as a dietary ingredient under section 201(ff)(1)(F) of the FD&C Act (21 U.S.C. 321(ff)(1)(F)). (See Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because They Present an Unreasonable Risk.[25]). Similarly, a synthetic version of a botanical extract is not an ‘extract’ of a botanical under section 201(ff)(1)(F) because it was not actually extracted from the botanical. In June 2012, a manufacturer recalled from nation-wide distribution more than 60,000 bottles of four dietary supplement products that contained synthetic equivalents of spermine and/or spermidine.[26] The reason for recall stated that ‘The products contain synthetic equivalents of spermine and/or spermidine, which are constituents or extracts of an herb or other botanical, and that a synthetic copy of a constituent or extract of an herb or other botanical is not a dietary ingredient.’

DMAA and DMBA

Two situations have been reported recently in which dietary supplements have been found to contain aliphatic amine stimulants. The cases of DMAA and DMBA are summarized below:

DMAA/Geranium

A number of dietary supplements were found to contain the aliphatic amine DMAA (1,3-DMAA, methylhexaneamine, 2-amino-4-methylhexane, 1,3-dimethylamylamine) (Fig. 1), some with claims that it is a constituent of the botanical rose geranium Pelargonium graveolens (Family: Geraniaceae). Products containing DMAA were sold under such names as ‘oil of geranium’ or ‘geranium extract’. DMAA is a bioactive compound and was used in weight-loss products and performance-enhancing products. The issue of the natural occurrence of DMAA is contentious.[25,26] Pawar et al. provided a detailed critique of studies supporting the presence or absence of DMAA in rose geranium.[24]

DMAA was the active ingredient in Forthane, an over-the-counter (OTC) drug introduced and then withdrawn by Eli Lilly.[27] In New Zealand and Europe, DMAA was reported to be used as a ‘party pill’. In New Zealand, three cases of cerebral haemorrhage were reported following recreational use of DMAA.[28] Recently, cases of cardiac arrest[29] and cardiac failure[30] have also been reported following ingestion of DMAA-containing supplements. Concern regarding DMAA became more serious when, between 2011 and 2012, four US soldiers died during physical exercise.[27] It is reported that they suffered cardiac arrest and heat strokes.[27] All individuals were found to have consumed dietary supplements that contained DMAA as one of the ingredients. As a precautionary move, in December 2011 the Army and Air Force Exchange System withdrew all DMAA-containing products from the Exchange and concession shelves. A Safety Review Panel that consisted of representatives from three Services, Health Affairs, and the Army Public Health Command was assembled to evaluate the safety of the DMAA-containing products.[27] In June 2013, the Department of Defense (DOD) safety review panel published the findings of its two-year investigation.[27] The Panel concluded that DMAA posed an elevated health risk for tens of thousands of military users. However, the panel did not conclusively establish that DMAA-containing substances were causally associated with the adverse medical events.

On 24 April 2012, the FDA sent warning letters to 11 companies[32] that declared 1,3-dimethylamylamine on their product labels. The FDA notified the companies that their products were considered to be adulterated because there was no information demonstrating that DMAA was lawfully marketed as a dietary ingredient in the USA prior to 15 October 1994, or had been present in the food supply in a form in which the food had not been chemically altered. In the absence of such information, DMAA is subject to the 75-day notification requirement for an NDI. In addition, because the DMAA used in products may have been produced synthetically, it would not be a dietary ingredient as defined under the law. The companies were asked to immediately cease distribution of their products and to respond to the warning letters within 15 days of receipt. Companies were warned that failure to immediately cease distribution of the products could result in enforcement action by the FDA (e.g., seizure of violative products, injunction against the manufacturers and distributors). Subsequent Warning Letters from the FDA posted in 2013 and 2014 declared DMAA as an unsafe food additive, as opposed to an NDI because the totality of the scientific evidence did not demonstrate the presence of DMAA in P. graveolens.[33–35]

Following these letters, most companies removed products containing DMAA from distribution. As of 11 April 2013, the FDA had received more than 80 reports of illnesses and deaths associated with the use of DMAA. The FDA issued a public warning to consumers on the dangers of DMAA.[36] In a follow-up letter to one company (18 April 2013 to USPlabs, LLC), the FDA challenged the company’s assertion that DMAA was a constituent of P. graveolens and stated that the totality of the evidence available on this subject did not credibly support such a claim.[37] The FDA maintained its position that the products containing DMAA were adulterated. As a result of follow-up legal action by the FDA, USPlabs voluntarily destroyed its DMAA-containing products and agreed to stop manufacturing dietary supplements containing DMAA. The FDA’s actions were carried out under the administrative detention authority provided by the FSMA.

DMBA/Pouchong Tea

The aliphatic amine DMBA (1,3-dimethylbutylamine; 2-amino-4-methylpentane; 4-methyl-2-pentamine) (Fig. 1) is an analogue of DMAA. DMBA has been found in a number of dietary supplements labelled as sport supplements, weight loss supplements, and supplements that claim to enhance brain function (e.g., by enhancing memory, clear thinking, focus, alertness).[38] Cohen et al. analyzed dietary supplements available for sale by US distributors that listed ingredients that might refer to DMBA (e.g., see names above and AMP citrate, 4-AMP, 4-amino-2-methylpentane citrate, 1,3-dimethylbutylamine citrate). DMBA was detected in 12 of 14 dietary supplements tested. Labels on two of the supplements implied that DMBA was extracted from Pouchong tea. Cohen et al. reviewed the literature on this subject and were unable to find any scientific evidence supporting such a claim.

Figure 1. Chemical structures of aliphatic amines in dietary supplements.
evidence that DMBA had ever been extracted from a plant. Based on the results of animal studies, Cohen et al. concluded that DMBA, which has never been studied in humans, should be considered an active pharmaceutical ingredient that requires rigorous testing and evaluation prior to marketing. In another recent study, the analysis of 25 authentic and commercial samples of *Camellia sinensis* tea leaves did not show the presence of DMBA.

On 28 April 2015, the FDA sent warning letters to 14 companies selling dietary supplements whose labels identified DMBA as a dietary ingredient. The FDA notified the companies that their products were considered to be adulterated because there was no information demonstrating that DMBA was lawfully marketed as a dietary ingredient in the USA prior to 15 October 1994, or had been present in the food supply in a form in which the food has not been chemically altered. In the absence of such information, DMBA is subject to the 75-day notification requirement for an NDI. Because the DMBA used in products may have been produced synthetically, it would not be a dietary ingredient as defined under the law. The companies were asked to respond to the letters within 15 days of receipt and were warned that failure to immediately cease distribution of the products could result in enforcement action by the FDA (e.g. seizure of violative products, injunction against the manufacturers and distributors).

### Phenethylamines in dietary supplements

**Phenethylamines as biologically active molecules**

PEAs are a diverse class of bioactive natural and synthetic compounds that includes stimulants, hormones, hallucinogens, neurotransmitters, anti-depressants, anorectics, and bronchodilators.[41] PEA (β-phenethylamine) itself is a biogenic amine that is formed naturally by decarboxylation of amino acids.[42] Higher amounts of PEA are reported in fermented food articles such as cheese, wine, chocolate, and salami. PEA and related compounds are also abundant in plants, algae, and fungi. Many plants belonging to Cactaceae, Leguminosae, Gnetaceae, and Rutaceae families are known to contain PEA and related compounds.[42] Many PEAs have stimulant properties but they are rapidly metabolized in the body by monoamine oxidases (MAO). Metylation of nitrogen and the α-carbon atom in the ethyl chain increases the effect of the compound partly due to the increased lipophilicity and reduced MAO deactivation.[43]

PEA derivatives are found in many common foods and some, such as tyramine, may exert mild stimulating effects in mammals. PEAs may be modified at the phenyl ring, side chain, and/or amino group. The simple structure of these compounds makes them relatively easy to synthesize and dozens if not hundreds of derivatives have been synthesized. Slight structural modifications may lead to dramatic changes in potency (e.g. amphetamine) and toxicity (e.g. nitrosofenfluramine).[44]

Applications of PEA derivatives vary from therapeutic to recreational uses. These compounds affect the serotoninergic, dopaminergic, and noradrenergic systems. As therapeutic agents, they act as appetite suppressants, vasoconstrictors, bronchodilators, and calcium channel blockers.[45] When used for recreational purposes, they may provide so-called legal highs or be promoted as ‘party drugs’. It is often difficult to determine the intended uses of a new PEA derivative based solely on structural considerations.

PEA derivatives including amphetamines are among the most widely abused drugs. Abuse of prescription drugs such as methylphenidate (Ritalin, Concerta), dextroamphetamine (Dexedrine), and dextroamphetamine-amphetamine (Adderall) in college students is a growing problem.[46] Metylenedioxy derivatives of amphetamine and methamphetamine represent one of the largest groups of so-called designer drugs. Designer drugs are compounds in which a structural modification has been made that results in retention of a pharmacological property of the original drug while avoiding its classification or detection as an illegal drug. Amphetamine derivatives such as 3,4-methylenedioxy-methamphetamine (MDMA) and 3,4-methylenedioxy-amphetamine (MDA) synthesized in the early 1990s as appetite suppressants were later used for recreational purposes.[47] Another group of designer drugs of abuse are the cathinones which are chemically β-keto substituted amphetamines. Cathinone is a naturally occurring compound in the plant *Catha edulis* (khat or qat) from East Africa and the Arabian Peninsula. Numerous synthetic cathinone derivatives have become popular as legal highs and ‘bath salts’.[48] Further discussion on these drugs of abuse is beyond the scope of this review.

The World Anti-Doping Agency (WADA) has banned ‘phenethylamine and its derivatives’ for athletes participating in competitive sports because of the stimulative effects of these compounds.[49] The addition of PEA itself to the WADA Prohibited List in January 2015[50] necessitates the development of a test method for urine that could discriminate between illicit intakes and metabolic elimination of endogenously produced PEA. Although consideration of this topic is beyond the scope of this review, the interested reader is referred to the recent work of Sigmund et al.[51] in evaluating the use of analyte abundance ratios as a means of potentially identifying the use of PEA by athletes.

### Naturally occurring phenethylamines in dietary supplements

Though PEAs are widely distributed in the plant kingdom, only a few botanicals containing them are used in dietary supplements. Forty-four (44) plant families are reported to contain some form of PEA.[41] Smith (1977) also showed that the family Cactaceae includes the greatest number of species containing PEAs. Some of these species, such as Peyote, contain mescaline, a controlled substance in the USA. Other species such as *Ephedra, Hordeum, Accacia*,[52] *Desmodium*,[53] *Sida*, *Prunus*, and *Citrus* are reported to contain PEAs.

Phenethylamine, tyramine, and their methyl derivatives

We do not know the total number of dietary supplements that may list PEA, tyramine, and their methyl derivatives (Fig. 2) on their labels. PEA appears to be a very popular ingredient in weight-loss and pre-workout supplements. The NIH Dietary Supplement Label Database (DSLD) lists only 70 products whose labels state the presence of PEA, tyramine, or their methyl derivatives.[44] PEA is often referred as phenethylamine or beta-phenethylamine (β-phenethylamine) on product labels. The DSLD also shows that some of these products contain up to 400 mg PEA/serve, though most of the product labels do not provide information about PEA content.

Many such products claim that extracts of *A. rigidula* or *Dendrobium* are the source of PEA. Despite the popularity of PEA as an ingredient in dietary supplements, few investigators have analyzed this ingredient in specific supplements, probably because quantitative information on this compound may not be included on product labels. Pawar et al. measured PEA in dietary supplements labelled as containing *A. rigidula* and reported that maximum potential intakes of 200 to 800 mg PEA/day could be obtained from some of the supplements that they analyzed.[55] Additional information on PEA content of dietary supplements is found in the *Acca rigidula* section below.
Tyramine and N-methyltyramine appear on the labels of more than 50 products. Hordenine (N-dimethyltyramine) is a constituent of bitter orange, Hordeum vulgare (barley), and some cacti species. Hordenine is increasingly advertised as a ‘nootropic’ to improve cognitive function and increase energy, and is commonly ‘stacked’ with PEA for purposes of cognitive enhancement. We were unable to find any human studies supporting these claims. The DSLD lists more than 60 products containing hordenine or its salt among their ingredients. N-methyltyramine is widely used as a stimulant in pre-workout supplements and in fat-loss supplements. It is also claimed to be a ‘focus enhancer’. Stohs and Harman reviewed mechanistic studies of N-methyltyramine and concluded that this compound will have an effect opposite to that for which it is widely advertised and that it should not be used in conjunction with exercise-weight-loss programs. These authors note that there are no published studies in humans or animals involving the oral administration of N-methyltyramine that demonstrate the effects of p-synephrine, the compound whose effects N-methyltyramine are assumed to mimic.

**Ephedra and ephedrine**

Ephedra is a Traditional Chinese Medicine and is the herbal (botanical) source of ephedrine alkaloids. These alkaloids are sympathomimetic and mimic the effects of epinephrine in the human body. Palamar has provided a historical review of the complicated history of use of ephedrine in the USA from the 1920s until the present time. Throughout the 1990s and early 2000s, ephedra was aggressively marketed in the USA and Europe for its weight-loss and performance-enhancing activity. However, numerous cases of adverse events resulting from the consumption of dietary supplements containing ephedrine alkaloids led the FDA to rule that such supplements were adulterated under section 402(f)(1)(A) of the FD&C Act. These adverse events included primarily cardiovascular effects (e.g. hypertension, palpitations, tachycardia or both, arrhythmia, myocardial infarction, cardiac arrest, or sudden death) and central nervous system effects (e.g. stroke, transient ischemic attack, seizure). Other adverse events that may have been related to the use of supplements containing ephedrine alkaloids included rhodobomolysis, premature delivery, and spontaneous abortion.

The FDA concluded that dietary supplements containing ephedrine alkaloids presented an unreasonable risk of illness or injury to the consumer. The FDA published its final rule on 11 February 2004, Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because They Present an Unreasonable Risk. A Utah federal judge in 2005 restricted the FDA’s action to ban the sale of ephedra dietary supplements, stating that the FDA had failed to prove by a preponderance of the evidence that ephedrine alkaloid dietary supplements pose an unreasonable risk of illness or injury at 10 milligrams (mg) or less per day. The judge ruled that the FDA would have to prove that the products are unsafe ‘when used as recommended and suggested in the labelling’. He ruled that 10 mg ephedrine alkaloids is not a dangerous amount and therefore, the FDA cannot ban the sale of dietary supplements containing 10 mg or less of ephedrine alkaloids. He also ruled that the FDA does not have the authority to compare benefits and risks as part of its evaluation of unreasonable risk. Within a year, however, this decision was overturned when, in 2006, the US Court of Appeals for the Tenth Circuit ruled in favor of the FDA and determined that Congress intended to incorporate a risk-benefit analysis into DSHEA and that the FDA had met the legal burden by doing extensive research on the issue. The court ruled that there is no dosage level of ephedrine alkaloid-containing dietary supplement acceptable for the market. The FDA’s rule to ban ephedrine alkaloids was thus final.

In its final rule regarding dietary supplements containing ephedrine alkaloids, the FDA noted it did not affect the use of Ephedra preparations in traditional Asian medicine. Rather, the final rule applied only to products regulated as dietary supplements. Dietary supplements containing sources of ephedrine alkaloids such as Sida cordifolia L. or Pinella ternata (Thunb.) Makino were deemed to be adulterated, as were dietary supplements containing ephedrine alkaloids from various species of Ephedra.

The natural occurrence of ephedrine in *S. cordifolia* (Family: Malvaceae) was first reported in 1930. Prakash reported that *S. acuta*, *S. humilis*, *S. rhombifolia* and *S. spinosa* all contained J-PEA, ephedrine and β-ephedrine. Khatoon *et al.* also reported finding ephedrine in *S. acuta*, *S. cordata*, *S. cordifolia* and *S. rhombifolia*. Another recent publication reported a high performance liquid chromatography with photo-diode array detector (HPLC-PDA) method for the estimation of ephedrine and cryptolepine in different *Sida* species. In this publication, contrary to the report of Khatoon *et al.*, Chatterjee *et al.* reported the presence of only trace amounts of ephedrine and stated that the content of ephedrine is dependent on the habitat and the origin of the plant. Jadhav *et al.* reported the isolation of ecysysteroids from the whole plant of *S. rhombifolia* and also reported that they did not find ephedrine by their HPLC analysis.

*S. cordifolia* is used in Brazilian folk medicine and is also an important drug in the Ayurvedic system of medicine. Marchei *et al.* analyzed 18 dietary supplements labelled as containing Mahuang...
(Ephedra Sinica) or Sida cordifolia or Ephedra extract that were being sold in esoteric and nature stores in Italy.[66] Among these, five S. cordifolia- containing dietary supplements contained ephedrine and pseudoephedrine, with concentrations of ephedrine ranging from 6.8 to 9.7 μg/mg. In the same study,[66] Ephedra products were found to contain 4.2 to 78.6 μg/mg ephedrine.

Pinellia ternata (Family: Araceae) is a Traditional Chinese Medicine. Preparations containing Pinellia tuber are available for sale by online vendors. The presence of ephedrine in the tuber of P. ternata was reported by Osioh et al.[67] and L-ephedrine was isolated at a level of 0.002% (0.02 μg/mg). In another report,[68] ephedrine was detected at a level of 0.0002% (0.002 μg/mg) in addition to lower amounts of d-pseudoephedrine, dl-norephedrine and dl-pseudonorephedrine in commercially available Pinellia tubers in Japan. To the best of our knowledge, there have been no reports of the analysis of ephedrine alkaloids in P. ternata dietary supplements sold in the USA.

Zell-Kanter et al. analyzed the effect of the FDA's ban on ephedrine alkaloid products from 2001 to 2013 and showed that the cases of the analysis of ephedrine alkaloids in Citrus aurantium from 2001 to 2013 and showed that the cases of the analysis of ephedrines in the USA that resulted in reducing potential toxicity events. Analysis of ephedrine alkaloids in Citrus aurantium (Citrus family: Rutaceae, bitter orange).[71,72] Synephrine and octopamine are reported to be weak a- and β- adrenergic agonists.[71,72] Synephrine is abundant in the unripe peel of bitter orange and was first reported as a natural constituent in plants when it was isolated from a few Citrus varieties in 1964.[73]

Most of the extracts are standardized for their synephrine content (6–8%). However, commercial extracts containing 95% synephrine are also available.[74] Several investigations had earlier debated the issue about the natural form of synephrine. There is now a consensus that para- substituted forms are the only forms that occur naturally in bitter orange.[75,76] However, studies have detected the presence of both para and meta synephrine in bitter orange supplements.[70] m-Synephrine is more biologically active than p-synephrine and exhibits stronger a- and β- adrenoceptor activity in animal studies.[71,72] m-Synephrine is also commonly known as phenylephrine and is a prescription decongestant.

Animal studies have reported adverse cardiovascular effects from C. aurantium extract.[77] A recent 28-day study showed that synephrine, either as the bitter orange extract or as pure synephrine, increased heart rate and blood pressure in rats.[78] While 95% synephrine exhibited little effect on heart rate and blood pressure, bitter orange extract itself provided more significant effects, possibly due to other components in the botanical preparations. The increase in heart rate and blood pressure were more pronounced when caffeine was added.[78,79]

Based on the potential of synephrine to cause cardiovascular toxicity, Health Canada[80] adopted a limit of 30 mg/day as a maximum allowable dose for total synephrine and octopamine, which is chemically and pharmacologically related to synephrine. Health Canada guidelines also require that risk information be provided on products providing > 3 mg synephrine + octopamine in a total daily dose. The following ‘duration-of-use’ statement is also required: 'Consult a health practitioner for use beyond 8 weeks.' Caffeine or caffeine sources are not permitted in synephrine-containing products without submission of sufficient clinical evidence of safety in humans. In the USA, the National Center for Complementary and Integrative Health (NCCIH) has cautioned the public saying that bitter orange contains chemicals that may accelerate the heart rate and raise blood pressure and may not be safe to use as a dietary supplement.[81] In 2015, WADA listed octopamine as a prohibited compound and placed synephrine in its 2015 Monitoring programme.[82] Compounds in this monitoring programme are not prohibited. However, WADA continues to monitor them in order to detect patterns of their misuse in sport.

Acacia rigidula

In addition to C. aurantium, many pre-workout and weight-loss products are labelled as being formulated with Acacia rigidula (Family: Fabaceae).[83] We could not find any record of a traditional or medicinal use for this species. Investigations into incidences of toxicity in grazing sheep and goats led to the discovery of the presence of PEAs in the leaves of several Acacia species.[83] Similarly, several Acacia species in Australia and New Zealand were also reported to contain PEAs.[83] Camp and Norvell identified N-methyl-PEA and N-methyltyramine in the leaves of A. rigidula material collected from Texas.[84] Chemical analysis of A. rigidula leaf using a gas chromatography-mass spectrometry (GC-MS) method conducted in 1998 identified 44 amines and alkaloids.[85] The investigation reported mainly PEA, N-methylphenethylamine, tyramine, pipocelamidine, N-methyltyramine, N,N-di methyltryptamine, hordenine, N,N-di methylphenethylamine and N,N-dimethyl-α- methylphenethylamine. Clement et al. also reported the presence of several amphetamine derivatives in the enriched methanol extract.[85] A more recent investigation with liquid chromatography-mass spectrometry (LC-MS) analysis on different parts of A. rigidula collected from four counties in Texas reported only the presence of tyramine, tryptamine, and PEA and a minor amount of their methyl derivatives.[86] Amphetamine and its derivatives were not detected in any of the plant samples analyzed.[86]

The investigation of Pawar et al. demonstrated that the amine profiles of the leaves of authenticated plant material and supplements differ significantly.[55] While the leaves contained about 19–33 μg/g amine and tyramine as the predominant one, 20 of 21 supplements contained 1190–171 620 μg/g amines with PEA as the main amine in most of the products. The occurrence of β-methylphenethylamine (β-MePEA) in these supplements will be discussed in the section β-Methylphenethylamine (β-MePEA) and derivatives below.

In a letter to interested parties dated 24 October 2013, the United Kingdom's Food Standards Agency stated that it was not aware of any evidence for a history of consumption of ingredients obtained from A. rigidula anywhere in the EU before May 1997, and for this reason, considered it to be a novel food which cannot be sold legally until it has been formally authorized. The Agency requested information from businesses that might demonstrate a significant history of consumption for A. rigidula in the EU before 15 May
1997. In March 2014, on reviewing the information received, the Food Standard Agency concluded that it had not received any information that provided evidence of a history of significant consumption of A. rigidula prior to 15 May 1997. Therefore, the agency maintained its position that A. rigidula is a novel food and falls within the scope of the EU legislation (EC) 258/97 on novel food. Companies wishing to market a novel food in the EU are required to obtain EU authorization under Regulation (EC) 258/97. On 15 March 2016, the FDA sent warning letters to several manufacturers of products containing A. rigidula saying that A. rigidula is an NDI. According to the FDA, the products are adulterated as there is no information demonstrating that A. rigidula was lawfully marketed as a dietary ingredient in the USA before 15 October 1994, nor is there information demonstrating that this ingredient has been present in the food supply as an article used for human food in a form in which the food has not been chemically altered. In the absence of such information and as the required NDI notification was not submitted by the company the products were adulterated. More information is available on the FDA’s dietary supplements webpage on A. rigidula.

Aegeline

Aegeline (N-[2-hydroxy-2-(4-methoxyphenyl)ethyl]-3-phenyl-2-propanamide) (Fig. 2) is an alkaloid from the leaves of the bael tree (Aegle marmelos, Family: Rutaceae), a native of India. It is said to have a long history in the food supply, and bael fruit, leaves, and extracts are used around the world in food, tea, and as natural remedies. The alkaloid aegeline was found in the dietary supplements OxyElite Pro™ and VERSA-1™, advertised for muscle building and weight loss. In 2013 the FDA, the CDC, the US DoD Armed Forces Health Surveillance Center, and state and local health officials investigated an outbreak of acute non-viral hepatitis which began in Hawaii. These cases were reported between April 2013 and October 2013 and a significant number of the affected individuals had reported exposure to an OxyElite Pro™-branded dietary supplement product.

On 11 October 2013, the FDA issued a warning letter to the manufacturer informing the company that the dietary supplements OxyElite Pro™ and VERSA-1™ were adulterated and that failure to immediately cease distribution could result in enforcement action. The warning letter stated that the products were deemed to be adulterated because they contained aegeline, an NDI for which the required 75-day NDI notification had not been submitted. The company failed to provide the FDA with information that would assist in a safety evaluation of the compound was carried out in 1945. Pawar et al. confirmed the findings and conclusions of their epidemiologic investigation of the outbreak. While the implicated product was OxyELITE Pro™, these authors commented that whether aegeline or another ingredient was the etiologic hepatotoxic agent was not known and that this question may remain unanswered.

Synthetic phenethylamines in dietary supplements

β-Methylphenethyamine (β-MePEA) and derivatives

Pawar et al. first demonstrated the presence of β-MePEA (Fig. 3) in dietary supplements during their studies on authenticated A. rigidula. Their analysis of dietary supplements labelled as containing A. rigidula found β-MePEA in 9 of 21 supplements tested. β-MePEA had not been detected in any of the authenticated plant materials analyzed. Pawar et al. calculated maximum daily intakes of β-MePEA if the supplements were consumed at levels recommended on their labels and estimated potential intakes of 1.6 to 145.6 mg/day from the 9 supplements that contained this compound. The recent investigation of Cohen et al. confirmed the findings of Pawar et al. and showed that more than half (52.4%) of the A. rigidula-labelled supplements they analyzed contained β-MePEA. Cohen et al. also estimated maximum daily intakes of β-MePEA if the supplements were consumed according to label recommendations and reported potential intakes of 2.9 to 93.7 mg/day. These findings are in good agreement with those of Pawar et al.

To date, no study has reported the presence of β-MePEA in any plant. β-MePEA was first synthesized in 1915. The earliest biological evaluation of the compound was carried out in 1945. Its toxicity, pressor and bronchodilatory effects were evaluated in rats, dogs, and isolated rabbit lung, respectively. The work of Graham et al. focused primarily on evaluating the pharmacological effects of structural changes in a group of phenyl propylamines and phenyl isopropylamines on the test animals and does not provide specific information that would assist in a safety evaluation of β-MePEA. Mosnaim et al. recently demonstrated that β-MePEA readily crosses

![Figure 3. Chemical structures of synthetic PEAs.](https://example.com/figure3.png)
the blood-brain barrier of rats treated with the MAO inhibitor prargline.\textsuperscript{[96]} At high doses, β-MePEA has been shown to exhibit small but consistent antinociceptive effect in rats treated with prargline.\textsuperscript{[97]} Earlier it has been shown that PEA analogs (including β-MePEA) are metabolized by MAO while amphetamine is not.\textsuperscript{[98]} The safety of β-MePEA has not been studied in humans.

β-MePEA is listed as an S6 stimulant and is banned by WADA for use by athletes.\textsuperscript{[100]} There have been reports of several cases of violations by athletes in various sporting events.\textsuperscript{[99,100]} Cholbinski et al. reported the development and application of a simple and rapid analytical procedure for urine samples that enables discrimination between β-MePEA and amphetamine, its positional isomer.\textsuperscript{[101]} Four urine samples found positive for β-MePEA were used to evaluate the impact of glucuronide and sulfate deconjugation on method performance.\textsuperscript{[101]} This work is expected to be of significance in the area of forensic analysis of anti-doping samples because it provides a validated procedure for discriminating between amphetamine and β-MePEA.

Recently, an N-dimethyl derivative of β-MePEA was found in urine samples of four athletes, (two of whom had failed urine drug tests in 2013, the others in 2014) and in the nutritional supplement NOXPUMP Pre-Training Formula, a powdered mix, which was la-

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of amphetamine. The high levels of synephrine and theophylline cast doubt on their purported natural origin. In addition, none of the major constituents of A. rigidula were identified.\textsuperscript{[116]}

The choice of methods for analyzing samples for their methylexynephine content, reported as oxilofrine, has varied according to prevailing techniques and instruments available. Thin layer chromatography (TLC), gas chromatography, and liquid chromatography with electrochemical detection have been used in the past. Currently, the most commonly used method is separation of methylexynephine from other analytes by ultra high pressure liquid chromatography followed by identification with mass spectrometry (UHPLC-MS).\textsuperscript{[118,119]} The UHPLC-MS techniques are designed to provide simultaneous anti-doping screening of blood and urine samples for multiple prohibited drugs, including oxilofrine. UHPLC-MS methods, specifically sample preparation, can be adjusted for detecting oxilofrine in dietary supplements.\textsuperscript{[116]} A diffusion-ordered spectroscopy (DOSY) \textit{H} nuclear magnetic resonance (NMR) analysis was also used to identify methylexynephine in a product labelled as containing it.\textsuperscript{[120]}

\textbf{N-Isopropyloctopamine}

Isopropyloctopamine (4-[1-hydroxyphenyl-2-(isopropylamino)ethyl]phenol) (synonyms: Deterenol, Deterenolium, Betaphrine \textsuperscript{®}) (Fig. 3) is another PEA that has been listed on the labels of pre-workout dietary supplements.\textsuperscript{[54]} An NDJ notification for Betaphrine was filed with the FDA in September 2004.\textsuperscript{[121]} Information with the notification included the proposed use of a caution statement that persons with hypotension or those with a history of low blood pressure should not consume Betaphrine. After reviewing the notification, the FDA concluded that Betaphrine was not a dietary ingredient. Rather, it appeared to be a chemically synthesized substance. The FDA noted further that while Betaphrine may be synthesized using one or more precursors that are themselves dietary ingredients, the substance such as Betaphrine that is chemically synthesized using such substances as starting materials is not itself a substance defined as a dietary ingredient in 21 U.S.C. 321(f)(1).\textsuperscript{[122]}

Little research on the effects of isopropyloctopamine has been reported. Pilkington \textit{et al.} administered isopropyloctopamine (identified as d-M.1.39) intravenously to six normal individuals.\textsuperscript{[123]} The main effect observed was an increase in free fatty acids in plasma and an increase in pulse rate. No side effects on arterial blood pressure were recorded. An in vitro study using human adipocytes found that isopropyloctopamine stimulated lipolysis. It was therefore suggested that isopropyloctopamine might be used in vivo to bring about triglyceride breakdown.\textsuperscript{[124]} Because there is no information on the response of specific organs to isopropyloctopamine, it is premature to state that there are no side effects in humans. Isopropyloctopamine has also been evaluated in vitro and appeared to act as a highly \textit{β}-selective, direct-acting adrenergic agonist in guinea pig trachea and rabbit aortic strips.\textsuperscript{[125]} LD\textsubscript{50},values of 370 mg/kg (intraperitoneal administration) and 144 ± 10 mg/kg (intravenous administration) have been reported in mice.\textsuperscript{[126]} This study also demonstrated that isopropyloctopamine was a depressor compound and caused marked cardiac stimulation.\textsuperscript{[126]}

Deterenol was recently detected in dietary supplements that caused adverse events in consumers in the Netherlands.\textsuperscript{[118]}

Because the supplements contained synephrine, Deterenol (isopropyloctopamine), oxilofrine (methylexynephine, see above), yohimbine, caffeine, and theophylline, among others, it was not possible to identify a specific ingredient as the cause of the adverse events.

\textbf{α-Ethyl-phenethylamines (\textit{α}-Ethyl-PEAs)}

A bulk crystalline powder suspected of being amphetamine crystals was found in an unclaimed article shipped from Vietnam to Korea and was seized by Korean narcotics agents as an item of suspicious trade.\textsuperscript{[45]} Forensic identification revealed the powder to be \textit{α}-ethyl-\textit{α}-ethylphenethylamine (\textit{N}-ethyl-\textit{α}-ethyl-PEA, NADEP, \textit{N}, \textit{α}-DEPEA, and also \textit{N}-\textit{α}-diethylphenethylamine) (Fig. 3). NMR experiments were used to elucidate the structure. Based on its structure, it was considered to be a PEA-based designer drug for use in a manner similar to that of amphetamines. Shortly after the seizure of the bulk powder and its identification as NADEP, Lee \textit{et al.} identified NADEP in pre-workout supplements branded as CRAZE™ and sold via the Internet.\textsuperscript{[127]}

The product CRAZE™ (Driven Sports, Inc. Franklin Square, NY, USA) was labelled as containing a proprietary blend named Dendrobrex™ (Dendrobium Extract) (stem) which was said to contain alkaloids such as dendrobine, dendroxine, dendramine, \textit{β}-PEA, \textit{N},\textit{N}dimethyl-\textit{β}-PEA, and \textit{N},\textit{N-diethyl-β}-PEA (Fig. 3). The PEAs were claimed to be natural constituents of an orchid Dendrobium (Family: Orchidaceae). However, contrary to statements on product labels, the occurrence of PEA-type compounds has not been reported in the scientific literature. Dendrobium species are only reported to contain dendrobin-type alkaloids.\textsuperscript{[128]} In a contemporary study, Cohen \textit{et al.}\textsuperscript{[129]} analyzed three samples of CRAZE™. The samples were purchased from an online supplement retailer, a mainstream retailer of supplements and a European online supplement retailer. All samples were from separate lots. All were found to contain NADEP. The quantities found (\textless;20 mg/serving) suggested that the NADEP was not a minor contaminant resulting from the manufacturing process nor a previously undiscovered trace component of Dendrobium.\textsuperscript{[129]}

In investigating the possibility that NADEP was being added as an unlabeled ingredient to dietary supplements, specifically those marketed for performance enhancement, ElSohly and Gul analyzed samples of CRAZE™ (powder) and DETONATE™ (capsules), two specific products with performance-enhancing claims.\textsuperscript{[130]} NADEP (ETH in their terminology) was quantitated in 4 of 5 samples of CRAZE™ powder analyzed and in both of the DETONATE™ samples analyzed. Levels ranged from 4.3 to 8.5 mg/g for the CRAZE™ powders and were 18.4 and 23.4 mg/capsule for the DETONATE™ capsules. Since some of the products they examined were labelled as containing Dendrobium extract as well as other PEAs, ElSohly and Gul updated their method to include PEA and \textit{N},\textit{N-diethylphenethylamine (NDP)}. All samples (n = 19) were found to be negative for NDP.\textsuperscript{[130]} ElSohly and Gul also quantified the amount of PEA in 19 dietary supplements. Eight of these samples were found to contain PEA, including 5 samples of CRAZE™ and 2 samples of DETONATE™. Concentrations of PEA in the 5 lots of CRAZE™ varied from 1.4 to 16.4 mg/g. Concentrations of PEA in the two samples of DETONATE™ were 24 and 25 mg/capsule.\textsuperscript{[130]}

Wahlstrom \textit{et al.} published additional studies on the dietary supplement CrazE™.\textsuperscript{[131]} In their study, which was supported by the manufacturer of CRAZE™, they reported the discovery of a new compound, namely \textit{N}, \textit{β}-diethyl-PEA in addition to \textit{N},\textit{N-diethyl-PEA} and a small amount of NADEP (60–230 ng/g). Wahlstrom \textit{et al.} suggested that the products seemed to vary between lots in the degree of homogeneity and content of the analytes.\textsuperscript{[131]} The report of Wahlstrom \textit{et al.} created an uncertainty regarding which isomeric compound ElSohly and Gul had detected, as both the compounds (i.e., \textit{N}, \textit{β}-diethyl-PEA and \textit{N},\textit{α}-diethyl-PEA) have identical mass and can produce identical mass fragmentation patterns.
Therefore, to corroborate their earlier finding of the presence of NADEP in the CRAZE™ and DETONATE™ products, ElSoHy and Gul published results of a second analysis of their products. In their most recent study, they reanalyzed samples using standards for both the α and β isomers of diethyl-PEA. N,β-diethyl-PEA was not detected in any of their samples. They also reported the absence of three PEs in Dendrobium nobile stem samples.

Uralets et al. analyzed urine samples from a large pool of routinely tested samples submitted to the Redwood Toxicology Laboratory (Santa Rosa, CA, USA). The samples were obtained from various clients, mostly drug rehabilitation programs, throughout the USA. During a three-month period from May to July 2013, 42 urine samples from all geographical areas of the USA were found to contain NADEP (EAPB in their terminology) and a second compound identified as 2-amino-1-phenylbutane (APB). The authors analyzed a sample of the dietary supplement CRAZE™ as well as the urine of a known user of CRAZE™. EAPB and caffeine were found in the sample of the supplement. APB was not found in the supplement. Both EAPB and APB were found in the urine of the known user of CRAZE™, which suggested to Uralets et al. that APB may be a metabolite of EAPB. Uralets et al. also noted that the finding of the designer drug in many urine samples from across the country suggested the existence of a supply source throughout the USA.

On April 2014, the FDA sent a warning letter to the manufacturer of the dietary supplement CRAZE™. The FDA informed the company that the products claiming to contain Dendrobex™ (Dendrobium Extract) were concentrated for alkaloid content including Dendrobine, Dendroxine, Dendramine, β-phenethylamine, N,N-dimethyl-β-phenethylamine, and N,N-diethyl-β-phenethylamine, were subject to the NDI requirement in section 413(a)(2) of the FD&C Act and with 21 CFR 190.6. Because the company had not submitted the required NDI notification, the products were deemed to be adulterated under sections 402(f)(1)(B) and 413(a) of the FD&C Act. The NDI notification would have been expected to provide a history of use or other evidence of safety establishing that Dendrobex™, when used under the conditions recommended or suggested in the labelling would reasonably be expected to be safe. Lacking such information, the FDA deemed the supplements to be adulterated. The company was informed that further distribution of all products containing Dendrobex™ may result in enforcement action by the agency without further notice.

The FDA provided two additional comments in its warning letter. The FDA reviewed the literature on the composition of Dendrobium and stated that while several studies established the presence of some alkaloids in Dendrobium species, none revealed the presence of β-PEA, N,N-dimethyl-β-PEA or N,N-diethyl-β-PEA. The company was asked to explain how the PEs are present in their product. The FDA also noted that recent studies indicated that the CRAZE™ product may contain NADEP, an ingredient not listed on the product labels. The FDA noted that dietary supplements containing this ingredient are also subject to the NDI notification requirements and that products that contain NADEP for which the required notification has not been submitted would be adulterated under sections 402(f)(1)(B) and 413(a) of the FD&C Act.

**PEA drugs in weight-loss supplements** (clenbuterol, fenfluramine, dexfenfluramine, sibutramine and derivatives, lorcaserin)

More than one-third of adults and approximately 17% of children and adolescents aged 2–19 years in the USA are obese. Treatment of obesity has emerged as a significant unmet medical need and is often a target for pharmacologic intervention. Successful weight loss and weight maintenance often require significant lifestyle and behavioural changes (e.g. reduced calorie consumption, increased physical activity), which are often not easy to manage.

Pillitteri et al. reported the results of a nationwide survey that looked at use of dietary supplements for weight loss and report that among adults who made a serious attempt at weight loss (n = 1444 in their survey of a total of 3500 adults), 34% reported using a dietary supplement at some time for weight loss. Many users and non-users of dietary supplements had misperceptions about such products: many believed that they were evaluated for safety and efficacy by the FDA and that such supplements were safer than OTC or prescription medicines. Sales of weight-loss supplements were estimated to total >$1.6 billion in 2005. Use of such supplements is often promoted as requiring less effort than traditional behavioural or lifestyle changes and such supplements are heavily promoted with claims of effectiveness. Use of bodybuilding, energy, and weight-loss supplements has also been associated with deployment and physical activity among US military personnel. In the survey of 106 698 military personnel, about 47% reported using at least one bodybuilding, energy, and weight-loss supplement. Among the participants, 17.3% reported use of bodybuilding supplements (22.8% of men, 5.3% of women), 30.0% reported use of energy supplements (40.5% of men, 35.5% of women), and 19.4% reported use of weight-loss supplements (15.9% of men, 26.9% of women). These data indicate that men were more likely to use body-building and energy supplements while women used weight-loss supplements.

It is nearly impossible to achieve rapid short-term effects with dietary supplement use alone and some products have been adulterated with compounds such as sibutramine, sennosides, and ephedrine to improve the efficacy of weight loss. Dietary supplements sold for weight-loss purposes are among the most adulterated supplements. In the following section, we provide a short review of findings regarding four PEs in weight-loss products. Among the four PEs considered, all are or were approved prescription drugs for specific uses.

**Clenbuterol**

Clenbuterol is a halogenated PEA (Fig. 4) and is widely recognized as a sympathomimetic and anabolic agent. It was investigated in the 1970s by Boehringer Ingelheim as a bronchodilator with preferential action on β2-adrenergic receptors in bronchial smooth muscle. Although available as a racemic mixture, most of its activity is due to the ileove form. The FDA has only approved clenbuterol for veterinary use in the USA and it is indicated for management of airway obstruction in horses. Its use is prohibited in the USA in food-producing animals.

The anabolic effects of clenbuterol on skeletal muscles are well-documented. The anabolic effects are a primary reason for the illegal use of clenbuterol in animal feeds and, more recently, in some dietary supplements. Clenbuterol is used by bodybuilders and athletes for its ability to increase lean muscle mass and reduce body fat. Parr et al. provided the first confirmation of the presence of clenbuterol in a dietary supplement. Clenbuterol was identified as an adulterant in a dietary supplement product ‘Anabolic Burner’, advertised as a slimming product combined with muscle-building ana-bolic effects. The product was purchased in Germany in 2007 and clenbuterol was identified according to the WADA recommended method. Although clenbuterol is currently not controlled under the Controlled Substances Act (CSA), it is listed by WADA and the International Olympic Committee as a performance-enhancing drug. Therefore, athletes are banned from its use.
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An unusual situation regarding clenbuterol was reported recently. In 2010, a team of athletes returned to Germany from competition in China and regular doping control samples were taken within the next two days. All urine samples were found to contain low amounts of clenbuterol – a finding which drew attention to a well-known problem, i.e., the possibility of an unintended clenbuterol intake with or from food. A sensitive and specific isotope dilution liquid chromatography–tandem mass spectrometry (LC-MS/MS) assay was developed using liquid/liquid extraction for clean-up with limits of detection and quantification of 1 and 3 pg/mL, respectively. Clenbuterol was detectable in 79% of the analyzed urine samples suggesting that it may be due to consumption of contaminated meat. This occurred despite an official clenbuterol prohibition in China for livestock. Prior to the withdrawal of fenfluramine and dexfenfluramine from the US market in 1997, practitioners were prescribing fenfluramine or dexfenfluramine in combination with phentermine (referred to as ‘fen-phen’ or ‘dexphen-phen’, respectively), often for extended periods of time as part of weight-loss programmes. These combinations represented ‘off-label’ uses of the prescription medications and no studies were submitted to the FDA to demonstrate effectiveness or safety of the drugs in combination for extended periods of time. In September 1997, following reports from the Mayo Clinic and others of the development of heart valve disease in patients after taking fen-phen, the FDA asked the manufacturers of fenfluramine and dexfenfluramine to voluntarily withdraw both the drugs from the market.

The adulteration of Traditional Chinese Medicine with fenfluramine was reported as early as 1999. Ku et al. reported that fenfluramine was detected in two capsule products from mainland China using capillary electrophoresis and GC-MS. The two products contained 2.9 and 4.1 mg fenfluramine/capsule. Since the report of Ku et al. numerous reports of findings of fenfluramine in Chinese medicines can be found in the literature. For example, a case of a comatose patient whose condition was due to consumption of fenfluramine/dextrofenfluramine was reported in Chicago, IL in 2005. The patient showed signs of acute poisoning as a result of fenfluramine use. In another case, Lau et al. reported a fatal incident of hepatic failure possibly due to consumption of a Chinese medicine adulterated with nitrosofenfluramine. In addition to these cases, between 2001 and 2002, over 800 incidences of liver damage were reported in Japan in patients using herbal anti-obesity products. Investigation revealed the presence of the S isomer of N-nitroso-fenfluramine. This N-nitroso derivative may have been added to enhance the activity or to evade the detection of fenfluramine in the products.

Sibutramine and derivatives

Sibutramine was introduced into the US market in November 1997 as Meridia®, a prescription drug approved for the treatment of obesity. It is also classified as a Schedule IV substance (low abuse potential) by the United States Drug Enforcement Administration (DEA). Sibutramine acts as a monoamine (serotonin-norepinephrine) reuptake inhibitor. Sibutramine was not recommended for use in patients with a history of coronary artery disease, cardiac arrhythmias, congestive heart failure, or stroke. In 2010, the FDA asked the maker of Meridia® (Abbott) to withdraw the drug from the market as it may pose ‘unnecessary cardiovascular risks to patients’.

This request followed reports from the Sibutramine Cardiovascular

Figure 4. Chemical structures of PEA drugs identified in tainted weight-loss dietary supplements.
Outcomes Trial (SCOUT) conducted in Europe which found a 16% increase in risk of major adverse cardiovascular events such as heart attack, stroke, resuscitation after cardiac arrest, and cardiovascular death in patients taking sibutramine.\[157,158\]

Sibutramine is an appetite suppressant that is a frequent adulterant in weight loss and slimming products sold worldwide.\[159–161\] Its low therapeutic dose and its ease of synthesis make it a convenient and economical adulterant. A number of methods have been reported for the detection and quantification of sibutramine. Many LC-MS methods for detection of sibutramine are available and GC-MS methods have also been successfully applied.\[155\] Considering the higher frequency of sibutramine adulteration and the need for extensive analyses, easier and faster techniques that do not need extensive sample preparation are gaining attention. Methods using ion mobility mass spectrometry,\[162\] TLC image analysis,\[163\] attenuated total reflectance-infrared spectroscopy, micro-near infrared systems, and direct analysis in real time-mass spectrometry (DART-MS)\[164\] have been reported.

In addition to sibutramine itself, several other derivatives such as desmethylsibutramine, di-desmethylsibutramine, and desisobutylbenzylsibutramine have been detected in products marketed as dietary supplements. The FDA website on tainted products reveals that since 2007, sibutramine and its derivatives have been involved in 228 of 629 (36%) of findings of tainted products. The FDA website also reveals that sibutramine is most frequently co-adulterated with phenolphthalein. A routine ion mobility spectrometry based screening of products revealed the presence of a new analogue of sibutramine.\[169\] The analogue was identified as 11-desisobutyl-11-benzylsibutramine by mass spectrometry and detailed NMR experiments.

The results of a survey published in 2014 on food and dietary supplement samples collected and analyzed in South Korea between 2009 and 2012 also showed the prevalence of sibutramine derivatives in these products. A total of 188 samples were analyzed for a total of 29 weight loss compounds.\[165\] Among the 62 samples that tested positive, 25 contained sibutramine, desmethylsibutramine, and didesmethylsibutramine as well as other weight loss compounds. Ephedrine/pseudoephedrine and the laxatives bisacodyl and sennosides A and B were also found.\[165\]

A series of 17 cases of documented poisonings in Germany from 2005 to 2008 revealed that sibutramine-containing products were involved in all of the cases.\[161\] The analysis of the remaining product showed that each capsule contained nearly twice the maximum daily dose of sibutramine licensed for use as a drug in Germany. A possible association of psychosis and consumption of herbal medicines adulterated with sibutramine was reported in a case from Hong Kong.\[166\] Sibutramine was detected and quantified by GC-MS in five slimming food samples collected in China.\[159\]

The FDA has addressed the risk posed by sibutramine-adulterated products. The case of Pai You Guo provides an example of such activities. Pai You Guo, a Chinese product that was marketed for weight loss, was found to be contaminated with sibutramine and phenolphthalein.\[167\] The FDA issued a safety alert to consumers, an import alert to customs officials to prevent importation of this supplement, and a recall of the product by its American distributor.\[168\]

**Lorcaserin**

Lorcaserin is not a typical PEA but is a cyclized form of halogenated PEA (Fig. 4). Lorcaserin is the newest member of the anti-obesity drug family\[169\] and is sold under the brand name Belviq in the USA. Lorcaserin is a selective 5-HT2C receptor agonist in the hypothalamus that was approved by the FDA in 2012. It is primarily indicated as an adjunct in chronic weight control along with reduced-calorie diets and increased physical activity. Because of its greater selectivity for the 5-HT2C receptor over the 5-HT2B receptor subtype, the risks of cardiovascular side effects, including heart valve disease, are thought to be low.\[169\] Lorcaserin is classified as a Schedule IV drug by the DEA because it is a central nervous system hallucinogen and euphoric compound. Based on the available evidence, the FDA stated that there is substantial evidence for potential abuse due to use of lorcaserin.\[170\]

As with other popular weight loss drugs, lorcaserin has already been found as an adulterant in products marketed as dietary supplements. In 2013, a Chinese product purchased in France claiming to be a natural slimming diet pill was analyzed by HR-MS/MS. The analysis indicated the presence of ions matching those of lorcaserin.\[170\]

MS and NMR experiments confirmed the presence of lorcaserin. Further, using quantitative NMR (qNMR), the content of lorcaserin in this product was calculated to be 6.6 mg/capsule. The recommended dose of Belviq is 10 mg administered orally twice daily. By March 2015, the FDA had reported three incidences of products marketed as dietary supplements adulterated with lorcaserin.\[171\]

**Naturally occurring constituents or added synthetic chemicals?**

The cases of DMBA and *Dendrobium* illustrate the consequences of marketing dietary supplements containing an NDI which lacked the required 75-day notification. Manufacturers of supplements containing these compounds had not provided the FDA with the notification providing the basis on which they concluded that a dietary supplement containing the NDI would reasonably be expected to be safe. In its warning letter related to dendrobium, the FDA questioned the manufacturer’s label claim that specific phenethylamine compounds were naturally present in the *Dendrobium* extract. The warning letter described the FDA’s examination of the peer reviewed and credible scientific literature and stated the agency’s findings that specific phenethylamines had never been reported in *Dendrobium*. The FDA’s warning letter for β-MePEA stated: ‘We are aware of no evidence to support an assertion that BMPEA is, in fact, a constituent of this botanical.’

Often, the concentrations at which a claimed ‘natural’ component is found in a dietary supplement preclude its being of natural origin. The case of DMBA illustrates this. Labels of several dietary supplements found to contain DMBA implied that the compound was extracted from Pouchong tea.\[158\] Cohen et al. estimated that even if DMBA were found in Pouchong tea as a degradant at levels of 0.012 ppm (0.012 μg/g), a manufacturer would require at least 1000 kg (2,205 pounds) of the tea to extract 12 mg of DMBA. In contrast, the dietary supplements whose labels implied a natural origin for DMBA contained 86–110 mg DMBA per serving.\[158\] Similarly, the quantities and patterns of PEA, tyramine, and tryptamine compounds found in authenticated plant materials when compared to the pattern in dietary supplements labelled as containing *A. rigidula*, strongly suggest that the plant material present in the dietary supplements could not have provided the amine levels that were measured.\[155\]

Development of a coherent picture of a compound’s origin is difficult when attempts are made to compare analytical results obtained with current methodologies, standards, and authenticated plant materials with results obtained decades ago with poorly described methods which included few or no standards and...
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inadequately authenticated or traceable plant materials. Parper
and Khan[172] recently raised the additional concern that once a
‘natural’ plant source of an ingredient has been ‘established’ by
publication in a journal, suppliers of herbal supplements may mis-
use that finding to advertise that a product containing the perti-
nent plant material will also contain the phytochemical ingredient
and beneficial effects of the ingredient, if any, will be bestowed
upon the supplement.

When the FDA addressed these issues with respect to Dendrobium
supplements, the Agency noted that while several alkaloids had
been reported in Dendrobium, the various PEAs specifically men-
tioned on product labels were not among them. This called into
question the information relied on by the manufacture to assert that
Dendrobium contained PEAs. In the case of β-MePEA, the Agency
reviewed the available literature and noted that there was no
evidence to support the manufacturer’s assertion that β-MePEA origi-
nated from Acacia plant material. While the charges against these
supplements were adulteration based on failure to file an NDI notifi-
cation (DMBA, Dendrobium) and misbranding based on listing the in-
gredient as a dietary ingredient (β-MePEA), the Agency’s literature
reviews and comments in the warning letters or follow-up corre-
spondence show that the issue of naturally occurring constituents
versus added synthetic chemicals is a continuing one.

Conclusions

With international products widely available over the Internet,
the problem of adulteration has become a global issue. Findings
of adulteration have been reported from many countries.
[127,139,161,165] The investigation of dietary supplements
adulterated with biologically active compounds, including prescrip-
tion drugs, is increasingly important because of the rapid growth of
the dietary supplement market[173] and the globalization of market-
places via the Internet. Adulterated or misbranded dietary supple-
ments pose risks to consumers’ health which may be particularly
serious when unlabelled ingredients or bioactive compounds not
generally recognized as such by consumers are present at pharma-
cologically effective levels. Recent studies have shown the presence
of potentially unsafe ingredients such as NADEP in several types of
dietary supplements.[90,129]

In this review, we show that a wide range of bioactive PEAs are
found in a variety of dietary supplements. In some cases such as
Ephedra, Citrus aurantium, Acacia, and aegeline, PEAs are naturally
occurring, while in other cases, PEAs such as β-MePEA,
methylnorephrine, N-isopropylcathine, and ethyl-PEA appear
as added synthetic chemicals. PEAs such as fenfluramine, dexfen-
fluramine, sibutramine, and lorcaserin, which are the active mole-
cules in prescription drugs used for weight control, have also been
found in products marketed as dietary supplements.

In the USA, dietary supplements are regulated under the FD&C
Act. Publication of CGMPs for manufacture, packaging, labelling,
and holding of dietary supplements[10] and draft guidance for in-
dustry on NDI notifications[21] fleshed out important sections of
DSHEA and the FSMA (2011) recently provided the FDA with man-
datory recall authority. Under the FD&C Act, if a dietary supplement
contains an NDI, the manufacturer must provide the FDA with infor-
mation based on a history of use or other evidence of safety, which
is the basis on which the manufacturer has concluded the dietary
supplement containing the NDI can reasonably be expected to be
safe. Such information must be provided to the FDA at least 75 days
before the new ingredient is introduced into interstate commerce.

A dietary supplement containing an NDI may be found to be adul-
tered if there is inadequate information to provide reasonable as-
surance that the new ingredient does not present a significant or
unreasonable risk of illness or injury. The FDA bears the burden of
proof in making such a determination.

The charges brought against dietary supplements containing
DMBA, aegeline, and Dendrobium illustrate the FDA’s use of its au-
thority to deem that these products are adulterated based on their
manufacturers’ failure to submit the required 75-day notifications.
NDI notifications are not optional. The NDI provision of DSHEA pro-
gives a critical safety provision, requiring that there must be ade-
quate evidence about the safety of NDIs added to dietary
supplements. The FDA has addressed the issue of whether a com-
ponent in a botanical dietary supplement is of natural origin or is
an added synthetic chemical in several recent actions and this issue
will likely recur and continue to be challenging.

The potential presence in dietary supplements of hidden active
ingredients that could be harmful has been recognized for a num-
ber of years. Consumers may unknowingly take products laced with
varying quantities of approved prescription drug ingredients, con-
trolled substances, or untested or unstudied pharmacologically ac-
tive ingredients. The FDA cannot test all products on the market
that may contain potentially harmful ingredients. Similarly, enforce-
ment actions and consumer advisories for tainted products only
cover a small fraction of the suspected tainted OTC products on
the market.

However, as part of the FDA’s targeted effort to reduce adultera-
tion in weight loss, body building, and sexual health products, the
agency periodically publishes Public Notifications. These Public Noti-
fications advise consumers not to purchase or use a specific product
in which FDA laboratory analysis has confirmed the presence of an
approved or unapproved drug. The FDA has published hundreds
of such notifications in the last several years. The Public Notifications
are available at the FDA’s Medication Health Fraud webpage.[174]

In December 2010, the FDA established an RSS feed[175] on its
website to alert consumers more rapidly when it finds that a prod-
uct marketed as a dietary supplement is tainted. The FDA has also
created a secure method for consumers to let the Agency know
when they find a problem with a dietary supplement. This new
reporting method is an all-electronic version of paper MedWatch
forms that has been tailored for dietary supplements. Consumers
who experience an adverse health-related event that they suspect
may be related to a dietary supplement or who find defects in the
quality or safety of a dietary supplement can submit a report
through the SRP.[176]

Using these tools, consumers may sign up for e-mail alerts on
tainted products sold as dietary supplements and report an adverse
event via SRP. The Agency also provides a mechanism for industry
to alert the Agency about potentially tainted products and about
the firms that make them. The FDA’s Dietary Supplements
website[177] provides links to many topics of interest including
safety alerts and advisories and guidance documents. Consumers
may be interested in visiting these websites to learn more about
dietary supplements, how they are regulated, and possible risks
that may be associated with their use.

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