

RESEARCH MONOGRAPH . COMPOUND PROFILE

1,3-DMAA

A branched-chain aliphatic amine originally developed by Eli Lilly as the inhaled nasal decongestant Forthane, subsequently repurposed as an ergogenic dietary supplement ingredient, and characterized pharmacologically as an indirect sympathomimetic acting principally through norepinephrine and dopamine release with substrate-like dopamine transporter regulation.

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ABSTRACT

1,3-Dimethylamylamine (1,3-DMAA; 4-methylhexan-2-amine; methylhexanamine) is a synthetic aliphatic sympathomimetic amine first introduced by Eli Lilly and Company in 1944 under the trade name Forthane as an inhaled nasal decongestant and voluntarily withdrawn from the market in 1983. The compound re-entered commercial circulation in 2006 when it was marketed as an ergogenic dietary supplement ingredient under the name Geranamine, following the regulatory removal of ephedrine alkaloids from the United States supplement market in 2004. The pharmacology of 1,3-DMAA is that of an indirect sympathomimetic: the compound acts as a norepinephrine and dopamine releasing agent, inhibits the norepinephrine transporter (NET) at low micromolar concentrations, and exhibits substrate-like regulation of the dopamine transporter (DAT) including competitive inhibition of dopamine uptake, binding at the S1 substrate site, induction of outward-facing-open to outward-facing-closed conformational transitions, and stimulation of DAT endocytosis through cocaine- and protein kinase A-sensitive mechanisms. These monoaminergic actions produce dose-dependent cardiovascular stimulation (vasoconstriction, elevation of systolic and diastolic blood pressure, tachycardia), central nervous system arousal, and thermogenic effects consistent with the broader sympathomimetic amine class that includes ephedrine, amphetamine, and phenylpropanolamine.

The sole formal human pharmacokinetic study (Schilling et al., 2013; n = 7 healthy men; single oral dose of 25 mg) reported a peak plasma concentration of approximately 70 ng/mL, time to peak of

3.57 hours, terminal elimination half-life of 8.45 hours, oral clearance of 20.02 L/hr, and volume of distribution of 236 L, indicating extensive tissue partitioning. Physiological monitoring in that study documented modest increases in heart rate and diastolic blood pressure that remained within normal clinical ranges at the 25 mg dose. However, case reports and postmarketing surveillance have associated substantially higher doses of 1,3-DMAA (often in combination with caffeine and other stimulants in multi-ingredient pre-workout and weight-loss supplements) with serious cardiovascular events including cerebral hemorrhage, myocardial infarction, cardiac arrest, hepatotoxicity, and death. The United States Food and Drug Administration has received at least 86 reports of illness and death associated with DMAA-containing supplements and has determined that 1,3-DMAA is not a dietary ingredient; its inclusion in products marketed as dietary supplements is unlawful under United States federal law. Preclinical abuse liability assessment (Dolan and Gatch, 2015) demonstrated that 1,3-DMAA fully substituted for cocaine and partially substituted for methamphetamine in drug discrimination assays, produced conditioned place preference in mice at intermediate doses, and generated dose-dependent locomotor depression, indicating psychostimulant-like abuse potential.

The compound is banned or restricted in the United States, Canada, Australia, New Zealand, the United Kingdom, Brazil, Sweden, Finland, and Switzerland, and is listed as a prohibited substance by the World Anti-Doping Agency. It is not approved as a medicine in any jurisdiction as of the date of this monograph. This monograph reviews the chemistry, synthesis, and structural classification of 1,3-DMAA; the historical development and regulatory trajectory; the molecular pharmacology at monoamine

transporters and adrenergic receptors; the limited human pharmacokinetic record; preclinical pharmacology including abuse liability; the clinical and adverse-event evidence base; sourcing and analytical verification considerations; reconstitution and handling; stack interaction and combination risks; the comprehensive adverse-event and safety signal; and a comparative assessment of five sympathomimetic amine stimulants against 1,3-DMAA on five competency standards (novelty, effect size, promising potential, side-effect profile, and overall validation).

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Methylhexanamine (recommended; not formally assigned by the World Health Organization as the compound is not a current therapeutic agent).

Common names and synonyms: 1,3-Dimethylamylamine (1,3-DMAA), dimethylamylamine (DMAA), methylhexanamine, methylhexamine, 4-methylhexan-2-amine, 2-amino-4-methylhexane, Forthane (Eli Lilly trade name, historical), Geranamine (Patrick Arnold trade name, 2006 onward) [1, 2].

Development codes: No formal pharmaceutical development code was assigned. The Eli Lilly internal designation was associated with the Forthane product line; published literature uses the Chemical Abstracts nomenclature or the abbreviated form DMAA.

Chemical Abstracts Service registry number: 105-41-9 (free base). The hydrochloride salt (methylhexanamine hydrochloride) does not carry a widely cited separate CAS number in the primary pharmacological literature but is the form most commonly supplied in supplement and research-grade preparations.

International Union of Pure and Applied Chemistry name: 4-Methylhexan-2-amine. The compound is a branched-chain primary aliphatic amine with the amino group at the 2-position and a methyl substituent at the 4-position of a hexane backbone [1].

1.2 Structural class and chemistry

1,3-DMAA is a simple aliphatic sympathomimetic amine. The structural class places it within the alkylamine stimulant family, a group of compounds that includes the amphetamines, the phenylpropanolamines, the ephedrines, and the cathinones, though 1,3-DMAA is distinguished from all of these by the absence of an aromatic ring system. The compound is an aliphatic (non-aromatic) amine; its

pharmacological activity derives entirely from the aliphatic chain bearing the primary amine, the alpha-carbon methyl substituent, and the 4-position methyl branch [2, 3].

Molecular formula: C₇H₁₇N (free base); C₇H₁₈ClN (hydrochloride salt).

Exact mass: 115.1361 g/mol (free base, monoisotopic).

Molecular weight: 115.22 g/mol (free base); 151.68 g/mol (hydrochloride salt).

Physical properties: Colorless to pale yellow liquid (free base) or white crystalline powder (hydrochloride salt). The free base is volatile and has a characteristic amine odor. The hydrochloride salt is freely soluble in water, soluble in methanol and ethanol, sparingly soluble in apolar organic solvents. Boiling point of the free base is approximately 131 to 133 degrees Celsius at standard atmospheric pressure [1, 2].

Stereochemistry: 1,3-DMAA contains one stereocenter at carbon 2 (the carbon bearing the amino group) and a second at carbon 4 (the branching methyl). Commercial and supplement-grade preparations are typically supplied as the racemic mixture; enantioselective synthesis and chiral separation are feasible but are not standard in the commercial supply chain. The contribution of individual stereoisomers to pharmacological activity has not been formally characterized in published literature [2].

Structural relationship to other sympathomimetics: The alpha-methyl substituent (methyl group on the carbon alpha to the amine) is a structural feature shared with amphetamine and methamphetamine. This substituent confers resistance to oxidative deamination by monoamine oxidase, prolonging the biological half-life relative to unsubstituted aliphatic amines. However, the absence of an aromatic ring distinguishes 1,3-DMAA from the phenethylamine class and reduces its affinity for monoamine receptors relative to the aromatic sympathomimetics [3, 4].

1.3 Synthesis

The published synthesis of 1,3-DMAA proceeds by oxime formation followed by catalytic hydrogenation. 4-Methylhexan-2-one (methyl isobutyl ketone analog with an additional methylene unit) is reacted with hydroxylamine (typically as the hydrochloride salt in the presence of a base such as sodium acetate or pyridine) to form 4-methylhexan-2-one oxime. The oxime is then reduced by catalytic hydro-

genation (palladium on carbon, platinum oxide, or Raney nickel catalyst under hydrogen atmosphere at moderate pressure) to yield 4-methylhexan-2-amine. The product is purified by distillation (free base) or by conversion to the hydrochloride salt with hydrogen chloride in diethyl ether or isopropanol, followed by recrystallization [1, 2].

Alternative reductive amination approaches (reaction of the ketone with ammonium formate or ammonium acetate under hydrogenation conditions, or with sodium cyanoborohydride in the presence of ammonium acetate) have been described in the general synthetic methodology literature and are applicable to the 4-methylhexan-2-one substrate. Industrial synthesis for supplement-grade material is straightforward and low-cost, reflecting the simplicity of the molecule [2].

The claim that 1,3-DMAA is a natural constituent of geranium (*Pelargonium graveolens*) oil has been investigated extensively. Multiple independent analytical studies, including gas chromatography-mass spectrometry analyses of authenticated geranium oil samples, have concluded that geranium oils do not contain 1,3-DMAA at detectable concentrations. The United States Food and Drug Administration has stated that the evidence does not support the claim of natural occurrence, and the compound in dietary supplement products is synthetic [5, 6].

2. Abstract

1,3-Dimethylamylamine (1,3-DMAA; methylhexanamine; 4-methylhexan-2-amine) is a synthetic aliphatic sympathomimetic amine that was developed by Eli Lilly and Company and marketed from 1944 to 1983 as the inhaled nasal decongestant Forthane [1, 2]. The compound was reintroduced to commercial markets in 2006 as an ergogenic and thermogenic dietary supplement ingredient, principally in pre-workout and weight-loss formulations, following the 2004 United States ban on ephedrine alkaloids in dietary supplements. The pharmacological mechanism is that of an indirect sympathomimetic: 1,3-DMAA acts as a norepinephrine and dopamine releasing agent, competitively inhibits the norepinephrine transporter (NET), and exhibits substrate-like regulation of the dopamine transporter (DAT) including binding at the primary substrate (S1) site, induction of conformational transitions from the outward-facing-open to outward-facing-closed state, and stimulation of transporter endocytosis [3, 7, 8].

The physiological consequences of these monoaminergic actions include vasoconstriction, elevation of blood pressure, tachycardia, central nervous system arousal, appetite suppression, and increased thermogenesis. The single formal human pharmacokinetic study (Schilling et al., 2013) in seven healthy men receiving a 25 mg oral dose reported a peak plasma concentration of approximately 70 ng/mL, time to peak of 3.57 hours, terminal half-life of 8.45 hours, oral clearance of 20.02 L/hr, and volume of distribution of 236 L [9]. Peak plasma concentrations at the 25 mg dose were reported to be approximately 15 to 30 times lower than concentrations estimated from case reports of serious adverse events, suggesting that reported injuries and deaths involved substantially higher doses.

Preclinical evaluation by Dolan and Gatch (2015) demonstrated that 1,3-DMAA fully substituted for cocaine in drug discrimination assays in Sprague-Dawley rats (ED₅₀ 3.30 mg/kg), partially substituted for methamphetamine (ED₅₀ 3.06 mg/kg), and produced conditioned place preference in Swiss-Webster mice at intermediate doses (3 and 10 mg/kg), establishing psychostimulant-like abuse liability [10]. Postmarketing adverse-event surveillance has associated 1,3-DMAA-containing supplement products with cerebral hemorrhage, myocardial infarction, cardiac arrest, hepatotoxicity, and at least five deaths [5, 11, 12]. The United States Food and Drug Administration determined in 2013 that 1,3-DMAA is not a lawful dietary in-

gredient, issued warning letters to manufacturers and distributors, and received at least 86 reports of illness and death [5]. The compound is banned or restricted in the United States, Canada, Australia, New Zealand, the United Kingdom, Brazil, Sweden, Finland, and Switzerland, and is listed as a prohibited substance by the World Anti-Doping Agency [2, 5, 13].

This monograph documents the chemistry, historical development, molecular pharmacology, limited pharmacokinetic record, preclinical abuse liability, clinical and adverse-event evidence, regulatory status, sourcing and analytical considerations, reconstitution and handling, combination and stack risks, and a comparative assessment of five sympathomimetic stimulant compounds against 1,3-DMAA.

3. Discovery and Development History

3.1 Origin and pharmaceutical development

1,3-DMAA was synthesized and developed by Eli Lilly and Company in the early 1940s as part of a medicinal chemistry program exploring aliphatic amines as nasal decongestants. The compound was introduced in April 1944 under the trade name Forthane as an inhaled nasal decongestant formulated for delivery via impregnated inhalation strips or solutions [1, 2]. The mechanism of the decongestant action was sympathomimetic vasoconstriction of nasal mucosal blood vessels, reducing edema and congestion. Forthane was one of several aliphatic amine decongestants marketed during the mid-twentieth century; others in the class included tuaminoheptane (Tuamine), propylhexedrine (Benzedrex), and cyclopentamine (Clopane).

The compound was marketed continuously as a nasal decongestant from 1944 through the early 1980s. Eli Lilly voluntarily withdrew Forthane from the market in 1983, coinciding with a general transition in the nasal decongestant market toward the imidazoline-class agents (oxymetazoline, xylometazoline) and the phenylethylamine-class oral decongestants (pseudoephedrine, phenylephrine) that offered improved safety profiles and more convenient administration routes [1, 2].

3.2 Reintroduction as a dietary supplement ingredient

In 2006, chemist Patrick Arnold reintroduced 1,3-DMAA to the consumer market as a dietary supplement ingredient under the trademarked name Geranamine. The reintroduction followed the 2004 United States Food and Drug Administration final rule banning ephedrine alkaloids from dietary supplements, which had been the dominant stimulant class in thermogenic and pre-workout supplement formulations [2, 5]. Arnold and subsequent supplement manufacturers marketed 1,3-DMAA as a natural constituent of *Pelargonium graveolens* (geranium) oil, a claim that was used to support its classification as a dietary ingredient under the Dietary Supplement Health and Education Act of 1994.

1,3-DMAA rapidly became one of the most widely used stimulant ingredients in the dietary supplement market, appearing in pre-workout formulations (notably OxyElite Pro, Jack3d, and Hemo Rage), weight-loss supplements, and energy prod-

ucts. The compound was typically combined with caffeine at doses of 100 to 300 mg and with other stimulant and thermogenic ingredients. Consumer doses of 1,3-DMAA in these products ranged from 25 mg to 75 mg per serving, though dose accuracy and label compliance were inconsistent across the supplement market [2, 5, 14].

3.3 Regulatory intervention and market removal

Beginning in 2012, the United States Food and Drug Administration issued a series of warning letters to manufacturers and distributors of 1,3-DMAA-containing dietary supplement products. The FDA's position, formalized in April 2013, was that 1,3-DMAA does not qualify as a dietary ingredient under the Dietary Supplement Health and Education Act, that manufacturers had failed to provide the required safety data (a New Dietary Ingredient notification with evidence of reasonable expectation of safety), and that the geranium-origin claim was not supported by the available analytical evidence [5, 6]. The FDA received at least 86 reports of illness and death associated with 1,3-DMAA-containing supplements, including reports of cerebral hemorrhage, myocardial infarction, cardiac arrest, and hepatic failure [5].

In parallel with the United States regulatory action, multiple international regulatory authorities banned or restricted 1,3-DMAA. Health Canada issued a stop-sale order in July 2011. The Australian Therapeutic Goods Administration classified 1,3-DMAA as a Schedule 10 (prohibited) substance. New Zealand, the United Kingdom, Brazil, Sweden, Finland, and Switzerland imposed bans or market restrictions between 2011 and 2013. The World Anti-Doping Agency added 1,3-DMAA to its prohibited list as a specified stimulant, and multiple athletes across Olympic, professional, and amateur sports received competition bans for positive tests [2, 13].

The United States military recalled all 1,3-DMAA-containing products from military exchange stores worldwide in 2010 following reports of adverse events among service members, including deaths during physical training [11, 12].

3.4 Current status

As of the date of this monograph, 1,3-DMAA is not approved as a medicine in any jurisdiction and cannot be lawfully sold as a dietary supplement ingredient in the United States. The compound continues to be identified in dietary supplement products in multiple international markets despite regulatory prohibitions, and is

detected in anti-doping controls in competitive athletics. It is available as a research-grade chemical from specialty chemical suppliers and is used in pharmacological research on sympathomimetic amine mechanisms [2, 5].

4. Mechanism of Action

1,3-DMAA is an indirect sympathomimetic amine. Its pharmacological actions are mediated through interactions with monoamine transporters and through consequent release of catecholamines (norepinephrine and dopamine) from presynaptic terminals. The compound does not act as a direct agonist at adrenergic or dopaminergic receptors at pharmacologically relevant concentrations; rather, it elevates synaptic catecholamine concentrations by promoting release and inhibiting reuptake [3, 7, 8].

4.1 Norepinephrine transporter inhibition and norepinephrine release

The norepinephrine transporter (NET; SLC6A2) is the principal molecular target of 1,3-DMAA. The compound inhibits NET-mediated norepinephrine reuptake at low micromolar concentrations in heterologous expression systems. The inhibition produces elevated synaptic norepinephrine concentrations in sympathetically innervated tissues, driving the vasoconstriction, blood pressure elevation, and cardiac stimulation that constitute the primary cardiovascular effects of the compound [3, 7].

In addition to reuptake inhibition, 1,3-DMAA functions as a norepinephrine releasing agent. The compound is transported into presynaptic terminals via the NET (functioning as a substrate) and promotes non-exocytotic release of stored norepinephrine through reverse transport. This dual mechanism (reuptake inhibition plus releasing activity) is shared with the amphetamines and with other indirect sympathomimetics such as ephedrine and pseudoephedrine, and produces a more sustained elevation of synaptic norepinephrine than reuptake inhibition alone [3, 7, 8].

4.2 Dopamine transporter regulation

The dopamine transporter (DAT; SLC6A3) interaction of 1,3-DMAA was characterized in detail by Small et al. (2023) in a study published in the Journal of Pharmacology and Experimental Therapeutics [8]. The principal findings were:

The compound competitively inhibits dopamine uptake via the DAT in a dose-dependent manner. Molecular docking and computational modeling demonstrated that 1,3-DMAA binds to the primary substrate (S1) binding site of the DAT, the same site occupied by dopamine and by substrate-type ligands such as amphetamine. Binding at this site induces a conformational transition from the outward-facing-open to the outward-facing-closed state of the transporter, a hallmark of substrate-type (as opposed to inhibitor-type) ligand interaction [8].

1,3-DMAA stimulated DAT endocytosis (internalization of the transporter from the plasma membrane) in a heterologous expression system. The endocytosis was sensitive to cocaine (blocked by cocaine co-application) and to protein kinase A inhibition, mirroring the regulatory mechanisms described for amphetamine-induced DAT internalization. This finding indicates that 1,3-DMAA shares substrate-like regulatory properties with amphetamine at the DAT, despite the structural difference of lacking an aromatic ring [8].

However, pharmacological distinctions from amphetamine were noted. The conformational dynamics and the relative potency at the DAT versus the NET differ between the two compounds. Earlier work by Simmler et al. (2013) reported that 1,3-DMAA blocked the NET but not the DAT in certain assay configurations, suggesting that the DAT interaction may be weaker or more context-dependent than the NET interaction [7]. The Small et al. (2023) findings resolved this apparent discrepancy by demonstrating that 1,3-DMAA does interact with the DAT but through a substrate-like mechanism that may not be detected by simple uptake inhibition assays conducted at low compound concentrations [8].

4.3 Trace amine-associated receptor 1 and other targets

Pharmacological profiling of 1,3-DMAA has identified interactions with trace amine-associated receptor 1 (TAAR1) and with adrenergic alpha-1A and alpha-2A receptors at submicromolar concentrations [7, 15]. The TAAR1 interaction is consistent with the structural class (aliphatic amines are endogenous and exogenous ligands for TAAR1) and may contribute to the central nervous system stimulant effects, as TAAR1 activation modulates dopaminergic neurotransmission in the mesolimbic pathway. The alpha-adrenergic receptor interactions at submicromolar concentrations are consistent with the direct vasoconstrictive activity that supplements the indirect sympathomimetic mechanism [7].

Additionally, interaction with the serotonin 5-hydroxytryptamine-1A (5-HT_{1A}) receptor has been reported at submicromolar concentrations in screening panels, though the functional significance of this interaction at physiologically achieved concentrations is uncertain [7].

4.4 Composite pharmacology

The composite mechanism of 1,3-DMAA at oral doses in the range of 25 to 75 mg (the supplement dose range) produces: (a) elevated synaptic norepinephrine through NET inhibition and norepinephrine release, driving peripheral vasoconstriction, blood pressure elevation, bronchodilation, and cardiac stimulation; (b) elevated synaptic dopamine through substrate-like DAT interaction and dopamine release, contributing to central nervous system arousal, euphoria, appetite suppression, and the psychostimulant subjective effects demonstrated in the conditioned place preference and drug discrimination paradigms; and (c) modest direct adrenergic receptor agonism that supplements the indirect sympathomimetic activity [3, 7, 8].

The alpha-carbon methyl substituent confers resistance to monoamine oxidase (MAO)-mediated oxidative deamination, prolonging the biological half-life relative to unsubstituted aliphatic amines and contributing to the 8.45-hour terminal elimination half-life observed in the Schilling et al. (2013) pharmacokinetic study [4, 9].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Oral absorption of 1,3-DMAA is rapid. In the Schilling et al. (2013) pharmacokinetic study in seven healthy men receiving a single 25 mg oral dose in a cellulose capsule, the lag time (t_{lag}) was 0.14 hours (approximately 8 minutes), and the time to peak plasma concentration (T_{max}) was 3.57 plus or minus 1.48 hours [9]. The extended T_{max} relative to the short lag time indicates that absorption occurs readily from the gastrointestinal tract but that peak systemic concentrations are delayed by distribution and first-pass considerations. Absolute oral bioavailability has not been determined in a formal crossover study comparing oral to intravenous administration.

5.2 Distribution

The volume of distribution (V_z/F) was 236 plus or minus 38 L in the Schilling et al. (2013) study, substantially exceeding total body water and indicating extensive tissue partitioning [9]. This large apparent volume of distribution is consistent with the lipophilicity of the free base form and with partitioning into adipose tissue, muscle, and other peripheral compartments. The compound is a small molecule (molecular weight 115.22 g/mol) with a primary amine that exists predominantly in the protonated (cationic) form at physiological pH; the unprotonated free base fraction is the species responsible for membrane permeation and tissue partitioning.

Plasma protein binding has not been formally characterized. Central nervous system penetration is inferred from the psychostimulant behavioral effects observed in preclinical studies and from the subjective central effects (arousal, euphoria, anxiogenesis) reported by human users, but has not been quantified by direct cerebrospinal fluid sampling or by positron emission tomography in humans [9, 10].

5.3 Metabolism

Formal metabolic studies of 1,3-DMAA in humans or animals have not been published. The structural features of the molecule (primary aliphatic amine, alpha-carbon methyl substituent) predict that the principal metabolic transformations are: (a) N-dealkylation and oxidative deamination by hepatic monoamine oxidase and cytochrome P450 enzymes, with the alpha-methyl group sterically retarding MAO-mediated deamination (analogous to the metabolic resistance conferred by the alpha-methyl substituent in amphetamine); (b) hydroxylation of the aliphatic chain by cytochrome P450 enzymes, producing hydroxylated metabolites subject to conjugation (glucuronidation, sulfation) and renal excretion; and (c) N-acetylation, the rate of which may be influenced by N-acetyltransferase 2 (NAT2) polymorphism [4, 9].

The absence of formal metabolite identification studies is a significant gap in the pharmacological characterization of 1,3-DMAA. The cytochrome P450 isoforms responsible for oxidative metabolism have not been identified, and the potential for pharmacokinetic drug-drug interactions through CYP inhibition or induction is uncharacterized [9].

5.4 Elimination

The terminal elimination half-life was 8.45 plus or minus 1.9 hours in the Schilling et al. (2013) study [9]. Oral clearance (CL/F) was 20.02 plus or minus 5 L/hr. The area under the plasma concentration-time curve (AUC_{0-infinity}) was 1204.55 plus or minus 262.89 hr*ng/mL after the 25 mg oral dose. The peak plasma concentration (C_{max}) was approximately 70 ng/mL, with individual values ranging from 60.23 to 108.1 ng/mL [9].

The elimination pathway has not been formally characterized. Renal excretion of unchanged 1,3-DMAA and of metabolites is presumed to be the principal elimination route, consistent with other low-molecular-weight aliphatic amines. Urinary pH dependence of renal clearance is expected (alkaline urine retards excretion of the protonated amine; acidic urine promotes it), though this has not been studied experimentally for 1,3-DMAA [9].

5.5 Routes of administration

Historical pharmaceutical route: Inhaled nasal administration via impregnated inhalation strips (Forthane, Eli Lilly, 1944 to 1983) [1, 2].

Supplement and recreational route: Oral administration as capsules, tablets, or powder, typically at doses of 25 to 75 mg, frequently in combination with caffeine (100 to 300 mg) and other stimulant ingredients. This was the predominant route during the 2006 to 2013 supplement-market era and remains the route used in remaining commercial products [2, 5, 14].

Research route: Oral and intraperitoneal administration in preclinical studies. The Dolan and Gatch (2015) abuse liability study used intraperitoneal injection at doses of 0.1 to 10 mg/kg in mice and rats [10]. Intravenous administration has been used in toxicological LD50 determination (reported LD50: 39 mg/kg in mice, 72.5 mg/kg in rats, intravenous) [2].

5.6 Special populations

No pharmacokinetic data exist for special populations (pediatric, geriatric, hepatic impairment, renal impairment, pregnancy, or lactation). The Schilling et al. (2013) study enrolled only healthy adult males aged 26 plus or minus 4.1 years, and pharmacokinetic parameters in females, in elderly subjects, or in individuals with hepatic or renal impairment are unknown [9]. Given the predicted hepatic metabolic elimination, hepatic impairment would be expected to prolong exposure, and renal impairment would be expected to reduce clearance of hydrophilic metabolites.

6. Preclinical Pharmacology

6.1 Cardiovascular pharmacology

The cardiovascular effects of 1,3-DMAA are consistent with indirect sympathomimetic activation. In preclinical rat models, 1,3-DMAA induced tachycardia and a pressor response via an indirect adrenergic mechanism related to stimulated norepinephrine release from sympathetic nerve terminals [3, 7]. The vasoconstriction is mediated by elevated synaptic norepinephrine acting on alpha-1 adrenergic receptors on vascular smooth muscle; the tachycardia reflects beta-1 adrenergic receptor activation on cardiac pacemaker and contractile cells [3].

In the Schilling et al. (2013) human study at 25 mg oral, heart rate increased from a baseline of 61.0 plus or minus 3.2 beats per minute to 69.1 plus or minus 2.9 beats per minute at 12 hours (effect size 1.9, large), though no individual pairwise time-point comparisons reached statistical significance. Systolic blood pressure showed no significant change (118 plus or minus 3 mm Hg at baseline; 115 plus or minus 3 mm Hg at 24 hours). Diastolic blood pressure showed a modest early increase (77 plus or minus 4.4 mm Hg at baseline; 82 plus or minus 3 mm Hg at 0.25 hours; effect size 0.5, moderate). All values remained within normal clinical ranges at this dose [9].

6.2 Abuse liability

Dolan and Gatch (2015) conducted a comprehensive preclinical abuse liability assessment of 1,3-DMAA in mice and rats, published in *Drug and Alcohol Dependence* [10]. The study comprised three paradigms:

Locomotor activity: In Swiss-Webster mice (n = 8 per dose group), 1,3-DMAA produced dose-dependent decreases in spontaneous locomotor activity at intraperitoneal doses of 0.1 to 10 mg/kg. Significant locomotor depression was observed at 3 and 10 mg/kg. The half-maximal inhibitory dose (ID₅₀) was 3.21 mg/kg (95% confidence interval: 0.33 to 31.12 mg/kg). Maximal depression occurred in the 0 to 30 minute post-administration period [10].

Drug discrimination: In Sprague-Dawley rats trained to discriminate cocaine from saline (n = 10), 1,3-DMAA fully substituted for cocaine, achieving 93 plus or minus 7 percent drug-appropriate responding at peak dose. The ED50 for cocaine substitution was 3.30 mg/kg (95% confidence interval: 0.61 to 17.83 mg/kg). In rats trained to discriminate methamphetamine from saline (n = 10), 1,3-DMAA partially substituted for methamphetamine at 77 plus or minus 16 percent drug-appropriate responding. The ED50 for methamphetamine substitution was 3.06 mg/kg (95% confidence interval: 0.01 to 840.8 mg/kg). Three of ten rats failed to respond at the 10 mg/kg dose [10].

Conditioned place preference: In Swiss-Webster mice (n = 16 per dose group), 1,3-DMAA produced an inverted-U-shaped dose-response curve for conditioned place preference. Significant place preference was observed at the 3 and 10 mg/kg doses. Peak preference at 10 mg/kg was 1127 plus or minus 67 seconds in the drug-paired compartment [10].

The authors concluded that 1,3-DMAA produces reward-like effects and subjective effects similar to those of abused psychostimulants, supporting the conclusion that the compound has potential for abuse [10].

6.3 Acute toxicity

The median lethal dose (LD50) has been determined by intravenous administration: 39 mg/kg in mice and 72.5 mg/kg in rats [2]. These values place 1,3-DMAA in the moderate acute toxicity range for a sympathomimetic amine. The cause of death at lethal doses is presumed to be cardiovascular collapse (cardiac arrhythmia, hypertensive crisis) consistent with catecholamine excess, though formal histopathological characterization of the mode of death has not been published.

Oral LD50 values have not been formally determined and published. The margin between the human supplement dose range (25 to 75 mg, or approximately 0.4 to 1.0 mg/kg in a 70 kg individual) and the intravenous LD50 in rodents (39 to 72.5 mg/kg) is substantial but is compressed by the route-of-administration difference and by the potential for higher consumer doses.

6.4 Genotoxicity and reproductive toxicity

No published genotoxicity (Ames test, micronucleus assay, chromosomal aberration) or reproductive toxicity studies of 1,3-DMAA were identified in the literature as of the date of this monograph. This absence of standard preclinical safety pharmacology data was cited by the United States Food and Drug Administration as part of the basis for its determination that the required safety data supporting the compound's use as a dietary ingredient were lacking [5, 6].

7. Clinical Evidence Base

7.1 Pharmacokinetic study

The sole formal human pharmacokinetic study of 1,3-DMAA was conducted by Schilling et al. (2013) and published in BMC Pharmacology and Toxicology [9]. Eight healthy men (age 26 plus or minus 4.1 years) were enrolled; one was excluded for abnormal baseline laboratory values, leaving seven evaluable subjects. Each received a single 25 mg oral dose of 1,3-DMAA in a cellulose capsule (verified content 23.9 plus or minus 1.9 mg by analytical assay). Plasma samples were collected over 24 hours and analyzed by high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) with a lower limit of quantitation of 1 to 2 ng/mL. The pharmacokinetic parameters are summarized in Section 5 of this monograph [9].

The study documented that peak plasma concentrations at the 25 mg dose were approximately 15 to 30 times lower than concentrations estimated from case reports of serious adverse events, leading the authors to conclude that the adverse events reported in association with 1,3-DMAA-containing supplements likely involved substantially higher effective doses than 25 mg, potentially in the range of 375 to 750 mg [9].

7.2 Cardiovascular effects in controlled settings

The Schilling et al. (2013) study is the only controlled human study of isolated 1,3-DMAA administration. As described in Section 6.1, cardiovascular parameters (heart rate, systolic and diastolic blood pressure) showed modest changes that remained within normal clinical ranges at the 25 mg dose [9].

Several studies have examined the cardiovascular effects of multi-ingredient supplement products containing 1,3-DMAA in combination with caffeine. These studies are difficult to interpret for the isolated pharmacology of 1,3-DMAA because of the confounding effects of caffeine and other co-administered stimulants. In general, supplement products containing 1,3-DMAA plus caffeine produced dose-dependent increases in systolic and diastolic blood pressure and heart rate that exceeded the effects of caffeine alone, consistent with an additive or synergistic sympathomimetic interaction [14, 16].

7.3 Absence of therapeutic efficacy trials

No randomized controlled trials of 1,3-DMAA for any therapeutic indication (nasal decongestant, weight loss, exercise performance enhancement, or any other) have been published. The historical Eli Lilly clinical experience with Forthane as a nasal decongestant predates the modern clinical trial framework and was not published in the peer-reviewed literature in a form that meets contemporary evidence standards [1, 2].

Exercise performance studies with 1,3-DMAA-containing supplement products have been conducted but are confounded by multi-ingredient formulations and do not isolate the contribution of 1,3-DMAA. No published study has demonstrated exercise performance enhancement attributable specifically to 1,3-DMAA at any dose [14].

7.4 Case reports of serious adverse events

Multiple case reports have associated 1,3-DMAA-containing supplement consumption with serious adverse events:

Cerebral hemorrhage: A 21-year-old New Zealand man experienced cerebral hemorrhage after ingesting an estimated 556 mg of 1,3-DMAA in 2010. This dose, approximately 7 to 8 mg/kg in a typical adult male, substantially exceeds the supplement-label dose range and approaches the intravenous LD50 range in rodents when adjusted for species and route [2, 11].

Cardiac events: Multiple case reports have described myocardial infarction and cardiac arrest in individuals consuming 1,3-DMAA-containing supplements, typically in the context of intense physical exertion and frequently in combination with caffeine. The United States Department of Defense Phase I investigation collected forty adverse medical event reports from military medical providers, including four deaths, three of which occurred during exercise and one from a presumed myocardial infarction [11, 12].

Deaths during exercise: At least five deaths have been associated with 1,3-DMAA-containing supplements. The death of Claire Squires during the 2012 London Marathon was attributed by the coroner to methylhexanamine as "probably an important factor" [2]. Military deaths during physical training prompted the 2010 recall of 1,3-DMAA-containing products from military exchange stores [11, 12].

Hepatotoxicity: Cases of liver failure were reported in association with the supplement product OxyElite Pro, which contained 1,3-DMAA among other ingredients. The relative contribution of 1,3-DMAA versus other ingredients (notably aege-line, which was added to reformulated versions of the product) to the hepatotoxicity signal has been debated [5, 17].

7.5 Adverse event surveillance

The United States Food and Drug Administration reported receiving at least 86 adverse event reports associated with 1,3-DMAA-containing dietary supplements, including reports of serious injury and death [5]. The Texas Poison Center Network received multiple exposure calls related to 1,3-DMAA-containing products, with reported effects including tachycardia, hypertension, nausea, and tremor [18]. A cross-sectional study of United States armed forces personnel reported that use of dietary supplements containing 1,3-DMAA was associated with self-reported tachycardia, tremors, dizziness, and numbness or tingling sensations [11].

7.6 Anti-doping violations

The World Anti-Doping Agency (WADA) lists 1,3-DMAA as a prohibited substance under the category of specified stimulants (Section S6.b of the Prohibited List). Multiple athletes have received competition bans for positive tests for 1,3-DMAA, including: athletes suspended at the 2014 Winter Olympics; Nesta Carter, whose positive retest from the 2008 Beijing Olympics resulted in the disqualification of the Jamaican 4x100 meter relay team and the loss of Usain Bolt's gold medal in that event; and athletes across baseball, boxing, cycling, motorsport, and weightlifting [2, 13].

8. Sourcing and Quality Verification

1,3-DMAA is not available as a pharmaceutical-grade preparation in any jurisdiction as of the date of this monograph. The compound is supplied by chemical and research-grade suppliers (Sigma-Aldrich/MilliporeSigma, Cayman Chemical, Toronto Research Chemicals, Cerilliant, others) at stated purities of greater than 95 to 99 percent by gas chromatography or high-performance liquid chromatography. Supply is in milligram to gram quantities, typically as the hydrochloride salt. The free base is a volatile liquid and is less commonly supplied [2].

Supplement-grade 1,3-DMAA, supplied as a bulk powder or as a pre-formulated product ingredient, has historically demonstrated variable purity and dose accuracy. Analytical surveys of 1,3-DMAA-containing dietary supplements conducted by the United States Food and Drug Administration and by independent analytical laboratories have documented substantial label-claim variability, with some products containing significantly more or less 1,3-DMAA than declared [5, 6].

Investigators should confirm compound identity and purity on every research-grade lot through:

- Gas chromatography-mass spectrometry (GC-MS) confirmation of molecular identity (molecular ion at m/z 115 for the free base)
- Gas chromatography or HPLC area-percent purity determination, ideally greater than 98 percent
- Nuclear magnetic resonance (^1H -NMR and ^{13}C -NMR) confirmation of structure and absence of positional isomers (notably 1,4-DMAA, which has different pharmacological properties)
- Chiral analysis (if enantiopure material is required for mechanistic studies; commercial material is typically racemic)
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis by gas chromatography if the material was purified by distillation or recrystallization from organic solvents

Third-party analytical verification is particularly important for 1,3-DMAA because of the history of label-claim inaccuracy in supplement-grade preparations and because of the existence of structurally related isomers (1,4-DMAA; 1,3-dimethylbuty-

lamine or DMBA) that may be present as synthetic impurities or as deliberate adulterants [5, 6].

9. Reconstitution and Handling

1,3-DMAA hydrochloride is a white crystalline powder that is freely soluble in water at room temperature. For research applications, the compound is typically supplied as the hydrochloride salt and is reconstituted as needed for in vitro or in vivo experimental use.

In vitro applications: Stock solutions are prepared at 10 to 100 mM in water, dimethyl sulfoxide (DMSO), or aqueous buffer. The compound is stable in aqueous solution at neutral pH and at refrigerated temperatures (2 to 8 degrees Celsius) for at least 30 days. For cell-based transporter assays, working concentrations in the low micromolar to high micromolar range are typical, depending on the specific assay and the target transporter [8].

In vivo applications: For preclinical administration in rodents, the compound is dissolved in sterile saline (0.9 percent sodium chloride) at the required concentration and administered by intraperitoneal injection or oral gavage. The Dolan and Gatch (2015) study administered 1,3-DMAA at 0.1 to 10 mg/kg by intraperitoneal injection in volumes of 1 mL/kg [10].

Storage: The hydrochloride salt should be stored at room temperature (15 to 25 degrees Celsius) in a sealed container protected from moisture. The free base is volatile and should be stored sealed under inert atmosphere (nitrogen or argon) at 2 to 8 degrees Celsius. Aqueous stock solutions should be used within 30 days of preparation when stored at 2 to 8 degrees Celsius, or within 7 days at room temperature. Aliquoting of stock solutions for single use is recommended to minimize repeated freeze-thaw exposure, though the compound demonstrates acceptable stability through at least three freeze-thaw cycles in aqueous solution.

Safety handling: 1,3-DMAA is a sympathomimetic amine with physiological activity at milligram doses by the oral route. Laboratory personnel should avoid inhalation of the free base (volatile liquid with an amine odor) and should handle the compound with appropriate personal protective equipment (gloves, safety glasses, fume hood for weighing and dissolution of the free base). The compound is not classified as acutely dangerous at typical laboratory handling quantities but should be treated as a pharmacologically active substance with a low threshold for systemic effects.

10. Stack Interactions and Combinations

1,3-DMAA interacts with several drug and supplement classes through its sympathomimetic mechanism and through predicted pharmacokinetic interactions. Investigators and consumers using 1,3-DMAA, especially in combination products, should consider the following:

Caffeine: The most common co-administered substance in supplement formulations. Caffeine is an adenosine receptor antagonist and phosphodiesterase inhibitor that produces additive sympathomimetic stimulation through a complementary mechanism. The combination of 1,3-DMAA and caffeine produces greater cardiovascular stimulation (blood pressure elevation, tachycardia) than either compound alone. The majority of serious adverse event reports associated with 1,3-DMAA involved co-administration with caffeine at doses of 100 to 300 mg [5, 14, 16].

Other sympathomimetic amines: Concurrent administration with ephedrine, pseudoephedrine, synephrine, phenylephrine, phenylpropanolamine, or amphetamine produces additive or potentially synergistic sympathomimetic stimulation. The combination substantially increases the risk of hypertensive crisis, cardiac arrhythmia, and stroke. Concurrent use with prescription sympathomimetics (amphetamine, methylphenidate, lisdexamfetamine) is particularly hazardous [3, 7].

Monoamine oxidase inhibitors (MAOIs): Concurrent administration with MAO inhibitors (phenelzine, tranylcypromine, selegiline, isocarboxazid, moclobemide) is potentially life-threatening. MAO inhibition prevents the metabolic degradation of released norepinephrine and dopamine, producing a hypertensive crisis when combined with an indirect sympathomimetic agent. This interaction class is the most dangerous pharmacological interaction for 1,3-DMAA [3].

Serotonergic agents: The reported interaction of 1,3-DMAA with the 5-HT_{1A} receptor and the potential for serotonin release at high doses create a theoretical risk of serotonin syndrome when combined with serotonin reuptake inhibitors (SSRIs, SNRIs), serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, or other serotonergic agents, though no clinical cases of serotonin syndrome specifically attributed to 1,3-DMAA have been published [7].

Beta-adrenergic blockers: Concurrent beta-blocker use may produce unopposed alpha-adrenergic stimulation (vasoconstriction without the protective reflex tachycardia that limits blood pressure elevation), increasing the risk of hypertensive crisis. This interaction pattern is analogous to the well-characterized cocaine-beta-blocker interaction [3].

QT-prolonging agents: The sympathomimetic-induced tachycardia and the potential for catecholamine-driven cardiac arrhythmia create additive risk when combined with QT-prolonging medications (fluoroquinolones, macrolide antibiotics, antipsychotics, methadone, certain antihistamines).

Alcohol: Concurrent alcohol consumption may mask the sedative effects of alcohol through the stimulant action of 1,3-DMAA, potentially increasing the risk of alcohol toxicity through delayed recognition of intoxication.

11. Adverse Events and Safety Signal

11.1 Common adverse events

Based on the limited controlled data (Schilling et al., 2013, n = 7) and on consumer and military surveillance reports, the commonly reported adverse events associated with 1,3-DMAA at supplement doses (25 to 75 mg) include:

- Elevated blood pressure (dose-dependent; the principal acute cardiovascular effect) [9, 11]
- Tachycardia (dose-dependent) [9, 11]
- Headache [5, 11]
- Nervousness and anxiety [5, 11]
- Tremor [11, 18]
- Sweating and diaphoresis [5]
- Insomnia (reflecting the 8.45-hour half-life and the central stimulant mechanism) [5, 9]
- Nausea [18]
- Numbness and tingling sensations (paresthesia) [11]

These effects are consistent with the sympathomimetic mechanism and are dose-dependent. At the 25 mg controlled dose in healthy men, cardiovascular parameters remained within normal clinical ranges [9].

11.2 Serious adverse events

Serious adverse events reported in association with 1,3-DMAA use include:

- **Cerebral hemorrhage:** The most dramatic single-dose adverse event, reported in a 21-year-old who ingested an estimated 556 mg [2, 11]
- **Myocardial infarction:** Multiple case reports, typically during intense physical exertion and in combination with caffeine [5, 11, 12]
- **Cardiac arrest and sudden death:** At least five deaths associated with 1,3-DMAA-containing supplements, including military personnel during physical

training and a marathon runner [2, 11, 12]

- **Hepatotoxicity and liver failure:** Reported in association with OxyElite Pro and other 1,3-DMAA-containing supplements, though confounded by other product ingredients [5, 17]
- **Rhabdomyolysis:** Reported in association with intense exercise and 1,3-DMAA supplement use [11]

11.3 Dose-response and risk factors

The serious adverse event reports are concentrated in individuals who consumed doses substantially exceeding the label-recommended range (typically 25 to 75 mg), who engaged in intense physical exertion concurrent with 1,3-DMAA use, who co-administered caffeine and other stimulants, or who had unrecognized predisposing cardiovascular conditions. The Schilling et al. (2013) observation that peak plasma concentrations at 25 mg were 15 to 30 times lower than estimated case-report concentrations supports a dose-dependent risk model in which the serious adverse events are attributable to supratherapeutic dosing [9].

Risk factors for serious adverse events include: pre-existing cardiovascular disease (hypertension, coronary artery disease, cardiomyopathy, arrhythmia); co-administration with caffeine or other sympathomimetics; intense physical exertion (which independently elevates catecholamine levels); dehydration and electrolyte imbalance; and environmental heat exposure.

11.4 Regulatory safety determination

The United States Food and Drug Administration's determination that 1,3-DMAA cannot be lawfully marketed as a dietary supplement ingredient was based on: the absence of a history of use as a food or dietary supplement ingredient before the Dietary Supplement Health and Education Act of 1994; the absence of a New Dietary Ingredient notification with evidence of reasonable expectation of safety; the absence of evidence supporting the claim of natural occurrence in geranium; and the accumulation of adverse event reports, including serious injury and death [5, 6]. The FDA has stated that it "does not have any information to demonstrate that consuming DMAA is safe" [5].

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five sympathomimetic amine stimulants against 1,3-DMAA, evaluated on five competency standards: novelty, effect size, promising potential (current regulatory and research trajectory), side-effect profile, and overall validation. The five comparators were selected as the principal indirect sympathomimetic amines that have been used or studied as ergogenic, thermogenic, or decongestant agents, with priority on compounds that share the supplement-market or regulatory context of 1,3-DMAA.

12.1 Ephedrine

Mechanism: Mixed indirect and direct sympathomimetic amine. Promotes norepinephrine release from sympathetic nerve terminals (indirect mechanism); acts as a direct agonist at alpha-adrenergic and beta-adrenergic receptors (direct mechanism). Also inhibits norepinephrine reuptake. The dual indirect-plus-direct mechanism produces more sustained cardiovascular and thermogenic stimulation than a purely indirect agent [19, 20].

Historical context: Ephedrine is derived from the *Ephedra sinica* plant and has been used in traditional Chinese medicine for millennia. Synthetic ephedrine was introduced as a pharmaceutical decongestant and bronchodilator in the 1920s. In the 1990s and early 2000s, ephedrine was the dominant stimulant ingredient in dietary supplement weight-loss and energy formulations in the United States. The FDA banned ephedrine alkaloids in dietary supplements effective April 2004 following reports of serious cardiovascular adverse events, including myocardial infarction, stroke, and death [20, 21].

Novelty: Low. The mechanism is the longest-studied and most thoroughly characterized of the indirect sympathomimetic class.

Effect size: Ephedrine, particularly in the ephedrine-caffeine combination, has the strongest evidence base for thermogenic and weight-loss efficacy of any sympathomimetic amine studied in controlled clinical trials. Meta-analyses of random-

ized trials have demonstrated a modest but statistically significant weight-loss effect (approximately 0.9 kg per month greater than placebo) [21].

Promising potential: None as a dietary supplement ingredient (banned). Remains available as a pharmaceutical product for bronchospasm and nasal congestion in some jurisdictions.

Side-effect profile: Dose-dependent cardiovascular stimulation (hypertension, tachycardia, palpitations), insomnia, tremor, headache. Serious adverse events include myocardial infarction, stroke, cardiac arrest, and death, which were the basis for the FDA ban. Risk is amplified by co-administration with caffeine [20, 21].

Overall validation: High for pharmacological mechanism; moderate for thermogenic efficacy. The ephedrine ban is the regulatory precedent that directly created the market conditions for 1,3-DMAA.

Comparison to 1,3-DMAA: Ephedrine has a substantially larger evidence base for both efficacy and toxicity. The pharmacological mechanisms overlap (indirect sympathomimetic, norepinephrine releasing) but ephedrine additionally has direct adrenergic agonist activity. Both compounds were banned from the dietary supplement market for similar safety reasons. 1,3-DMAA has far less clinical evidence for efficacy at any endpoint.

12.2 Synephrine (p-Synephrine)

Mechanism: Direct and indirect sympathomimetic amine. p-Synephrine (the naturally occurring isomer in *Citrus aurantium*, bitter orange) acts predominantly at beta-3 adrenergic receptors with modest activity at alpha-1 adrenergic receptors. It lacks the beta-1 and beta-2 adrenergic stimulation that characterizes ephedrine, producing less pronounced cardiovascular effects at equimolar doses [22, 23].

Historical context: Following the ephedrine ban, *Citrus aurantium* extract (standardized for p-synephrine content) became the most common replacement stimulant ingredient in thermogenic and weight-loss supplement formulations. p-Synephrine has remained in the dietary supplement market without FDA enforcement action as of the date of this monograph.

Novelty: Low. The beta-3 adrenergic receptor selectivity is a modest pharmacological distinction from ephedrine and 1,3-DMAA.

Effect size: Small. Controlled studies of p-synephrine as a thermogenic agent have demonstrated modest increases in resting metabolic rate (approximately 65 kcal/day) and in fat oxidation. Weight-loss efficacy in randomized trials has been marginal and inconsistent [22, 23].

Promising potential: Moderate. The compound remains legally available in the dietary supplement market and has a more favorable cardiovascular safety profile than ephedrine or 1,3-DMAA.

Side-effect profile: The cardiovascular effect profile of p-synephrine at supplement doses (10 to 50 mg) is modest, with minimal or no significant increase in heart rate or blood pressure in most controlled studies. The more favorable cardiovascular profile relative to ephedrine and 1,3-DMAA is attributed to the beta-3 selectivity [22, 23].

Overall validation: Low to moderate. The evidence base is moderate in size but limited in effect magnitude. The compound is legally marketed but has not produced compelling efficacy data.

Comparison to 1,3-DMAA: p-Synephrine has a substantially more favorable safety profile than 1,3-DMAA and remains legally marketed. However, it has weaker sympathomimetic potency and smaller effect sizes for thermogenic and stimulant endpoints. The regulatory trajectory is stable (p-synephrine) versus terminated (1,3-DMAA).

12.3 DMHA (2-Aminoisoheptane; 1,5-DMHA; Octodrine)

Mechanism: Indirect sympathomimetic amine structurally related to 1,3-DMAA. DMHA (2-amino-6-methylheptane or 2-amino-5-methylheptane, depending on isomeric form) promotes norepinephrine release and inhibits norepinephrine reuptake through a mechanism analogous to 1,3-DMAA. The compound was introduced to the supplement market as a direct replacement for 1,3-DMAA following the DMAA ban [24].

Historical context: Like 1,3-DMAA, DMHA (octodrine) was historically used as a nasal decongestant. It entered the dietary supplement market around 2016 as a "next-generation" stimulant following 1,3-DMAA restrictions. The FDA has issued warning letters regarding DMHA-containing products, though enforcement has been less comprehensive than for 1,3-DMAA [24].

Novelty: Very low. The mechanism is essentially identical to 1,3-DMAA with minor structural modification.

Effect size: No controlled human studies of DMHA for any endpoint have been published. The effect size is presumed to be comparable to 1,3-DMAA on the basis of structural similarity, but this has not been established experimentally.

Promising potential: Low. The compound faces the same regulatory and safety challenges as 1,3-DMAA. No formal pharmacokinetic, efficacy, or safety studies have been published.

Side-effect profile: Uncharacterized in controlled studies. Presumed to be similar to 1,3-DMAA on the basis of shared mechanism. No formal adverse event surveillance data are available.

Overall validation: Very low. The compound has essentially no published pharmacological characterization and represents a regulatory arbitrage product rather than a scientifically validated compound.

Comparison to 1,3-DMAA: DMHA is pharmacologically and structurally similar to 1,3-DMAA but has substantially less published characterization. 1,3-DMAA, despite its limited evidence base, has more pharmacological, pharmacokinetic, and preclinical data than DMHA.

12.4 BMPEA (beta-Methylphenylethylamine)

Mechanism: Indirect sympathomimetic amine of the phenethylamine class. BMPEA (beta-methylphenylethylamine; 1-amino-2-phenylpropane) is a positional isomer of amphetamine that promotes catecholamine release and inhibits monoamine reuptake. The compound was identified as an undeclared ingredient in dietary supplements marketed as containing *Acacia rigidula* extract [25].

Historical context: BMPEA was identified in dietary supplements by Cohen et al. (2015) and by FDA laboratory analyses of *Acacia rigidula*-containing products. The compound is structurally an amphetamine isomer and is pharmacologically active as a sympathomimetic amine. The FDA determined that BMPEA is not a natural constituent of *Acacia rigidula* in amounts sufficient to contribute to supplement activity and that it is an undeclared active pharmaceutical ingredient in adulterated products [25].

Novelty: Low. The mechanism is that of a conventional phenethylamine sympathomimetic.

Effect size: No controlled human efficacy or pharmacology studies have been published.

Promising potential: None. The compound is considered an adulterant rather than a legitimate ingredient.

Side-effect profile: Uncharacterized in controlled studies. The sympathomimetic mechanism predicts cardiovascular stimulation and associated risks.

Overall validation: Very low. The compound is pharmacologically uncharacterized in formal studies and is classified as an adulterant.

Comparison to 1,3-DMAA: Both compounds represent sympathomimetic amines that entered the supplement market without adequate safety or efficacy characterization. 1,3-DMAA has substantially more published pharmacological data. BMPEA, as an amphetamine isomer, may have different abuse liability and potency characteristics, but these have not been formally studied.

12.5 Caffeine

Mechanism: Adenosine A1 and A2A receptor antagonist; phosphodiesterase inhibitor at supratherapeutic concentrations. Caffeine is not an indirect sympathomimetic amine and acts through a fundamentally different mechanism from 1,3-DMAA, but it is included in this comparator panel because it is the most commonly co-administered substance with 1,3-DMAA and is the benchmark stimulant in the dietary supplement and ergogenic markets [26].

Historical context: Caffeine is the most widely consumed psychoactive substance globally. It has been extensively studied for ergogenic, thermogenic, cognitive, and alertness-promoting effects over decades, with thousands of published clinical trials and meta-analyses.

Novelty: Low. The pharmacology is the most thoroughly characterized of any dietary stimulant.

Effect size: Moderate to large for acute ergogenic effects (approximately 3 to 5 percent improvement in endurance exercise performance). Small for thermogenic effects (approximately 100 kcal/day increase in energy expenditure at 200 to 400 mg

doses). Moderate for cognitive alertness and attention [26].

Promising potential: High. Caffeine remains the most widely available and least regulated stimulant in global commerce.

Side-effect profile: Well characterized. Dose-dependent anxiety, insomnia, tachycardia, gastrointestinal disturbance, diuresis, tremor. Serious adverse events (cardiac arrhythmia, seizure, death) are rare and are associated with massive overdose (typically greater than 5 to 10 grams) or with concentrated caffeine powder. The therapeutic index is substantially wider than for 1,3-DMAA or ephedrine [26].

Overall validation: Very high. Caffeine has the largest evidence base of any dietary stimulant for ergogenic, thermogenic, and cognitive endpoints.

Comparison to 1,3-DMAA: Caffeine operates through a distinct (adenosinergic rather than sympathomimetic) mechanism, has a vastly larger safety and efficacy evidence base, and has a substantially wider therapeutic index. The compounds are pharmacologically complementary (different mechanisms converging on arousal and sympathetic activation), which is the basis for their frequent co-formulation. 1,3-DMAA does not replicate the efficacy evidence base of caffeine at any studied endpoint.

12.6 Comparator summary

The five comparator compounds occupy distinct positions in the sympathomimetic stimulant space. **Ephedrine** is the closest pharmacological analog with the most robust efficacy and safety evidence base, banned from dietary supplements for the same safety reasons that led to the 1,3-DMAA ban; it is the direct regulatory antecedent. **p-Synephrine** is the most commercially viable legal alternative with a more favorable cardiovascular safety profile but substantially weaker stimulant potency. **DMHA** is a structural analog of 1,3-DMAA with essentially no independent pharmacological characterization, representing a regulatory successor rather than a scientifically distinct compound. **BMPEA** is an amphetamine isomer adulterant with no legitimate evidence base. **Caffeine** is the benchmark dietary stimulant with the largest safety and efficacy evidence base, operating through a distinct mechanism but frequently co-administered with 1,3-DMAA.

1,3-DMAA occupies an intermediate position in this landscape: more potent as a sympathomimetic than p-synephrine, less well characterized than ephedrine, better studied than DMHA or BMPEA, and operating through a distinct mechanism

from caffeine. The compound's regulatory trajectory (banned in most major markets, determined by the FDA to be an unlawful dietary ingredient) reflects the combination of meaningful sympathomimetic potency with an insufficient safety evidence base. The absence of any controlled therapeutic efficacy trial, the absence of formal metabolic studies, and the accumulation of serious adverse event reports distinguish 1,3-DMAA from ephedrine (which at least had controlled weight-loss trials) and from caffeine (which has extensive controlled evidence across multiple endpoints).

Investigators considering 1,3-DMAA for pharmacological research should recognize that the compound's principal scientific value lies in its role as a structurally simple aliphatic sympathomimetic amine probe for monoamine transporter pharmacology (particularly the substrate-like DAT regulation characterized by Small et al., 2023), rather than as a candidate for clinical translation. The regulatory, safety, and evidentiary profile does not support clinical development for any therapeutic indication.

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