

## RESEARCH MONOGRAPH . COMPOUND PROFILE

# 1,4-DMAA

*A branched-chain aliphatic amine structurally related to methylhexanamine (1,3-DMAA), identified in geranium plant material and in dietary supplements, with presumed sympathomimetic and catecholamine-releasing activity but no approved pharmaceutical application and a minimal primary pharmacological literature.*

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## ABSTRACT

1,4-Dimethylamylamine (1,4-DMAA), systematically named 5-methylhexan-2-amine, is a branched-chain aliphatic amine of the alkylamine stimulant class. It is a positional isomer of the better-characterized 1,3-dimethylamylamine (1,3-DMAA, methylhexanamine), differing in the placement of the methyl branch along the carbon backbone: in 1,3-DMAA the branch is at carbon 4 (producing 4-methylhexan-2-amine), whereas in 1,4-DMAA the branch is at carbon 5 (producing 5-methylhexan-2-amine). The compound has never been developed or marketed as a pharmaceutical agent, in contrast to 1,3-DMAA, which was introduced by Eli Lilly as an inhaled nasal decongestant (Forthane) in 1948 and voluntarily withdrawn in 1983. 1,4-DMAA came to regulatory and scientific attention through its identification in dietary supplements marketed for pre-workout stimulation and weight loss, where it was detected at doses of 21 to 94 mg per serving alongside other undeclared stimulants including 1,3-DMAA, octodrine, and 1,3-dimethylbutylamine, as reported by Cohen et al. (2018) in *Clinical Toxicology*. The compound has also been detected at trace concentrations (13 to 162 ng/g) in *Pelargonium graveolens* (geranium) plant material from the Changzhou region of China, as documented by Fleming et al. (2012), though these concentrations are insufficient to account for the milligram-scale quantities found in commercial supplement formulations. The pharmacology of 1,4-DMAA has not been independently characterized in published receptor-binding, transporter-interaction, or in vivo behavioral studies. Its mechanism of action is inferred by structural analogy to 1,3-DMAA and to the broader class of aliphatic alkylamine

sympathomimetics. 1,3-DMAA has been characterized as an indirect sympathomimetic agent that competitively inhibits dopamine uptake at the human dopamine transporter (DAT) with an IC<sub>50</sub> of approximately 29.4 micromolar (roughly 60-fold less potent than amphetamine) and that induces DAT endocytosis through cocaine- and protein kinase A-sensitive mechanisms, as reported by Bhatt et al. (2023). By structural analogy, 1,4-DMAA is presumed to function as a catecholamine releasing agent with sympathomimetic properties, producing vasoconstriction, elevated blood pressure, increased heart rate, and central nervous system stimulation, though the potency and selectivity of these effects relative to 1,3-DMAA remain unquantified. No human pharmacokinetic data specific to 1,4-DMAA have been published. The pharmacokinetic profile of 1,3-DMAA, characterized by Bloomer et al. (2013) in seven healthy men receiving a single 25 mg oral dose, provides the closest available analog: peak plasma concentration of approximately 70 ng/mL at 3.6 hours, terminal elimination half-life of 8.5 hours, oral clearance of 20 L/hr, and volume of distribution of 236 L. Whether these parameters translate to the 1,4-isomer is unknown. The safety of 1,4-DMAA in humans is unknown. The compound has not been studied in controlled clinical trials at any dose. Cardiovascular adverse events (hypertension, tachycardia, and theoretical risk of hemorrhagic stroke and sudden cardiac death) are inferred from the pharmacology of structurally related sympathomimetic amines and from case reports associated with 1,3-DMAA-containing products. The United States Food and Drug Administration considers 1,4-DMAA to be an illegal ingredient in dietary supplements and has stated that products containing it should not be consumed. The World Anti-Doping Agency includes 1,4-dimethylamylamine on the Prohibited List under category S6

(stimulants, prohibited in competition). This monograph reviews the chemistry, structural classification, inferred mechanism of action, pharmacokinetic analogy data, detection in plant material and supplements, regulatory status, adverse-event signal, sourcing and handling considerations, and a comparative assessment of five structurally or functionally related alkylamine stimulants against 1,4-DMAA on five competency standards: novelty, effect size, side-effect profile, regulatory status, and overall validation.

# 1. Compound Identification

## 1.1 Names, synonyms, and registry identifiers

**Systematic (IUPAC) name:** 5-methylhexan-2-amine.

**Common names:** 1,4-dimethylamylamine; 1,4-DMAA; 1,4-dimethylpentylamine; 2-amino-5-methylhexane.

**Chemical Abstracts Service registry number:** 28292-43-5 (free base).

**PubChem CID:** 34204.

**ChemSpider ID:** 31520.

**Development codes:** None. The compound has never entered pharmaceutical development and carries no development-stage designators.

**Marketed names:** None. The compound has never been marketed as a pharmaceutical product in any jurisdiction. It has appeared as an undeclared or incompletely declared ingredient in dietary supplements, sometimes listed under the names "2-aminoisoheptane" or as a component of plant extracts (Aconitum kusnezoffii extract) [1].

## 1.2 Structural class and chemistry

1,4-DMAA is a branched-chain primary aliphatic amine belonging to the alkylamine class of sympathomimetic stimulants. It is structurally defined by a seven-carbon backbone with an amine group at the 2-position and a methyl branch at the 5-position. The compound lacks the phenyl ring system present in amphetamine, methamphetamine, and the phenethylamine class of sympathomimetics, and it lacks the aromatic hydroxyl substituents that permit direct adrenergic receptor agonism. This structural absence restricts its pharmacological activity to indirect sympathomimetic mechanisms (catecholamine release and/or reuptake inhibition) rather than direct receptor activation [2, 3].

**Molecular formula:** C<sub>7</sub>H<sub>17</sub>N.

**Molecular weight:** 115.22 g/mol.

**Exact mass:** 115.1361 g/mol (monoisotopic).

**Physical properties:** Colorless to pale yellow liquid at room temperature (free base). The free base is volatile with an amine odor. Soluble in water, methanol, ethanol, and dilute mineral acids. The hydrochloride salt form is a white crystalline solid with higher melting point and improved stability for storage and analytical work.

**Stereochemistry:** The compound contains one stereocenter at carbon 2 (the amine-bearing carbon), producing R and S enantiomers. Commercial and supplement-derived material is typically racemic. No enantioselective pharmacological studies have been published for 1,4-DMAA. In the related compound 1,3-DMAA, which contains two stereocenters, diastereomeric ratios have been used to distinguish synthetic from plant-derived material [4].

**Partition coefficient:** The predicted XLogP3 value is approximately 1.5 to 1.9 (comparable to 1,3-DMAA at 1.9), consistent with moderate lipophilicity and the capacity for blood-brain barrier penetration characteristic of the alkylamine stimulant class.

## 1.3 Structural relationship to 1,3-DMAA and other alkylamines

1,4-DMAA is a positional isomer of 1,3-DMAA (4-methylhexan-2-amine, CAS 105-41-9, methylhexanamine). The sole structural difference is the position of the methyl branch on the hexane backbone: at carbon 4 in 1,3-DMAA and at carbon 5 in 1,4-DMAA. This positional change alters the steric environment around the amine nitrogen, potentially affecting receptor and transporter binding affinity, metabolic stability, and pharmacokinetic behavior, though these differences have not been experimentally quantified [5].

Other structurally related aliphatic alkylamine stimulants include octodrine (2-amino-6-methylheptane, also designated 2-aminoisoheptane or DMHA), 1,3-dimethylbutylamine (1,3-DMBA, 4-amino-2-methylpentane), tuaminoheptane (2-aminoheptane), and propylhexedrine (N, $\alpha$ -dimethylcyclohexaneethylamine). These compounds share the aliphatic amine scaffold and the indirect sympathomimetic mechanism but differ in chain length, branching pattern, and (in the case of propylhexedrine) the presence of a cyclohexane ring [1, 6].

## 1.4 Synthesis

No peer-reviewed synthesis of 1,4-DMAA has been published. The compound is readily accessible through standard organic chemistry routes for aliphatic amines. The most direct approach is reductive amination of 5-methylhexan-2-one (methyl isobutyl ketone) with ammonia or ammonium acetate in the presence of a reducing agent (sodium cyanoborohydride or sodium triacetoxyborohydride) or by catalytic hydrogenation over palladium or platinum catalyst. Alternative routes include the Gabriel synthesis (N-alkylation of potassium phthalimide with the corresponding alkyl halide followed by hydrazinolysis) and direct nucleophilic substitution of 2-chloro-5-methylhexane with ammonia under pressure. The hydrochloride salt is prepared by treatment of the free base with hydrogen chloride in anhydrous diethyl ether or dioxane. Purification is by distillation (free base) or recrystallization (hydrochloride salt). Industrial-scale synthesis for supplement-grade material has not been publicly documented but is presumed to follow reductive amination or catalytic hydrogenation routes optimized for cost rather than enantiomeric purity.

## 2. Abstract

1,4-Dimethylamylamine (1,4-DMAA; 5-methylhexan-2-amine; CAS 28292-43-5) is a branched-chain aliphatic amine belonging to the alkylamine class of sympathomimetic stimulants. It is a positional isomer of 1,3-dimethylamylamine (1,3-DMAA, methylhexanamine), the well-characterized indirect sympathomimetic that was originally developed by Eli Lilly as the inhaled nasal decongestant Forthane (1948), voluntarily withdrawn from the market in 1983, and subsequently reintroduced into the dietary supplement market in 2006 by Patrick Arnold as "Geranamine" following the United States ban on ephedrine alkaloids [7, 8].

Unlike its 1,3-isomer, 1,4-DMAA has never been developed, registered, or marketed as a pharmaceutical agent in any jurisdiction. The compound entered the scientific and regulatory literature through two independent routes: its detection at trace concentrations in *Pelargonium graveolens* (geranium) plant material by Fleming et al. (2012) using high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) [4]; and its identification as an undeclared stimulant ingredient in dietary supplements marketed for pre-workout energy and weight loss by Cohen et al. (2018) [1]. The Cohen et al. study, published in *Clinical Toxicology*, detected 1,4-DMAA at doses of 21 to 94 mg per serving in commercial products, alongside 1,3-DMAA, octodrine, and 1,3-dimethylbutylamine, none of which were accurately declared on the product labels.

The pharmacology of 1,4-DMAA is uncharacterized in primary experimental literature. No receptor-binding, transporter-interaction, electrophysiological, or behavioral pharmacology studies specific to the compound have been published as of the date of this monograph. Its mechanism of action is inferred entirely by structural analogy to 1,3-DMAA and to the broader alkylamine sympathomimetic class. 1,3-DMAA has been characterized as a norepinephrine and dopamine releasing agent (NDRA) that competitively inhibits dopamine uptake at the human dopamine transporter (IC<sub>50</sub> approximately 29.4 micromolar) and that induces transporter endocytosis through substrate-like mechanisms analogous to amphetamine, though at approximately 60-fold lower potency [3]. By structural analogy, 1,4-DMAA is presumed to produce indirect sympathomimetic effects through catecholamine re-

lease from presynaptic terminals and/or monoamine transporter inhibition, resulting in peripheral vasoconstriction, elevated blood pressure, increased heart rate, bronchodilation, and central nervous system stimulation.

No human pharmacokinetic data have been published for 1,4-DMAA. The pharmacokinetic profile of 1,3-DMAA (single 25 mg oral dose in seven healthy men: C<sub>max</sub> approximately 70 ng/mL, T<sub>max</sub> 3.6 hours, t<sub>1/2</sub> 8.5 hours, V<sub>d</sub> 236 L, oral clearance 20 L/hr) serves as the closest available pharmacokinetic analog [9]. Whether these parameters are representative of 1,4-DMAA kinetics is unknown; the positional isomerism may affect metabolic handling, particularly with respect to hepatic deamination and hydroxylation pathways.

No controlled clinical trials of 1,4-DMAA have been conducted. Safety in humans is unknown. The cardiovascular risk profile is inferred from the sympathomimetic mechanism and from adverse-event reports associated with 1,3-DMAA-containing products, which have included hypertension, tachycardia, hemorrhagic stroke, and sudden cardiac death [10, 11]. The United States Food and Drug Administration considers 1,4-DMAA to be an illegal ingredient in dietary supplements. The World Anti-Doping Agency (WADA) includes 1,4-dimethylamylamine on the Prohibited List under category S6 (stimulants, prohibited in competition) [12]. Multiple national regulatory authorities, including those of Australia, Canada, the United Kingdom, New Zealand, and several European Union member states, have taken enforcement actions against dietary supplements containing DMAA isomers.

This monograph documents the chemistry and structural classification of 1,4-DMAA; the inferred mechanism of action based on structural analogy to 1,3-DMAA and the alkylamine sympathomimetic class; the available pharmacokinetic analog data; the detection of the compound in plant material and dietary supplements; the regulatory and anti-doping status; the adverse-event signal; sourcing and quality verification considerations; reconstitution and handling; stack-interaction implications; and a comparative assessment of five structurally or functionally related alkylamine stimulants against 1,4-DMAA.

## 3. Discovery and Development History

### 3.1 Origin and early chemistry

1,4-DMAA (5-methylhexan-2-amine) is a simple branched-chain aliphatic amine that has been catalogued in chemical registries since at least the mid-twentieth century (CAS 28292-43-5). The compound did not originate from a pharmaceutical development program and was not the subject of deliberate structure-activity relationship exploration in the manner of the phenethylamine and amphetamine classes. Its first appearance in the biomedical and regulatory literature came through analytical chemistry investigations of the DMAA family of compounds in the 2010s, following the emergence of 1,3-DMAA as a controversial dietary supplement ingredient.

### 3.2 Reemergence of the DMAA class in dietary supplements

The regulatory and scientific context for 1,4-DMAA is inseparable from the history of its 1,3-isomer. 1,3-DMAA (methylhexanamine) was originally synthesized and developed by Eli Lilly and Company as the inhaled nasal decongestant Forthane, receiving pharmaceutical market authorization in 1948 on the basis of its sympathomimetic vasoconstrictive properties in the nasal mucosa [7]. The compound was voluntarily withdrawn from the market in 1983, for reasons that have not been publicly documented but are generally attributed to the availability of superior alternatives (oxymetazoline, xylometazoline) and to limited commercial demand.

In 2006, Patrick Arnold, a chemist associated with the Bay Area Laboratory Cooperative (BALCO) steroid scandal, reintroduced 1,3-DMAA into the United States dietary supplement market under the trade name "Geranamine," claiming that the compound was a natural constituent of geranium oil and therefore qualified as a dietary ingredient under the Dietary Supplement Health and Education Act (DSHEA) of 1994 [8]. The compound was incorporated into pre-workout and weight-loss supplements, most notably OxyElite Pro and Jack3d (USPlabs), which achieved substantial commercial success. These products were marketed for their stimulant, thermogenic, and appetite-suppressant properties.

### 3.3 Detection of 1,4-DMAA in plant material

The claim that DMAA compounds are naturally present in geranium plants was a central element of the regulatory defense offered by supplement manufacturers. Fleming et al. (2012) at the University of Memphis developed a sensitive HPLC-MS/MS method for the detection of both 1,3-DMAA and 1,4-DMAA in *Pelargonium graveolens* plant material collected from three Chinese regions (Changzhou, Kunming, and Guiyang) [4]. The study detected 1,3-DMAA at concentrations of 68 to 496 ng/g and 1,4-DMAA at 13 to 162 ng/g in Changzhou samples, with concentrations below the method detection limit in samples from the other two regions. The study was funded by USPlabs, the manufacturer of OxyElite Pro and Jack3d, a conflict of interest that was noted in subsequent regulatory and scientific commentary.

The concentrations detected in plant material (nanograms per gram) are orders of magnitude below the milligram-per-serving quantities found in commercial supplements (21 to 94 mg per serving for 1,4-DMAA; 24 to 35 mg per serving for 1,3-DMAA), rendering natural plant extraction an implausible source for the supplement-grade material [1]. Multiple independent analytical studies, including those by Lisi et al. (2011) and ElSohly et al. (2012), failed to detect DMAA in geranium oil or geranium plant material using validated methods, further questioning the natural-occurrence claim [13, 14].

### 3.4 Identification of 1,4-DMAA in supplements

Cohen et al. (2018) published a systematic analysis in *Clinical Toxicology* identifying four experimental stimulants in dietary supplements sold in the United States: octodrine (2-amino-6-methylheptane), 1,4-DMAA, 1,3-DMAA, and 1,3-dimethylbutylamine [1]. The study purchased products from mainstream retail outlets and analyzed them by gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-mass spectrometry (LC-MS). 1,4-DMAA was detected at quantities of 21 plus or minus 11 mg to 94 plus or minus 48 mg per serving in products that either did not declare the ingredient or listed it under alternative nomenclature. The authors characterized 1,4-DMAA as a "previously unidentified 1,3-DMAA analog" in the context of dietary supplement surveillance and noted that its safety in humans was unknown.

## 3.5 Regulatory actions

The United States Food and Drug Administration initiated enforcement actions against DMAA-containing supplements beginning in April 2012, issuing warning letters to manufacturers stating that DMAA is not a lawful dietary ingredient and that products containing it are adulterated under the Federal Food, Drug, and Cosmetic Act [10]. In 2013, the FDA administratively detained OxyElite Pro and Jack3d products after USPlabs refused voluntary compliance; USPlabs subsequently destroyed the detained inventory (estimated retail value exceeding 8 million dollars) and agreed to cease manufacturing with DMAA. The FDA also seized DMAA-containing products from Hi-Tech Pharmaceuticals; subsequent litigation between Hi-Tech and the FDA over the legal status of DMAA under DSHEA has been protracted and, as of the date of this monograph, remains partially unresolved [15].

The FDA has stated that it received 86 reports of illnesses and deaths associated with supplements containing DMAA, though attribution of causation in individual cases is complicated by the multi-ingredient nature of the products and by concurrent stimulant exposure (notably caffeine). The agency's position applies to both 1,3-DMAA and 1,4-DMAA isomers: both are considered illegal in dietary supplements.

The World Anti-Doping Agency added methylhexanamine (DMAA) to the Prohibited List under category S6 (stimulants, prohibited in competition) in 2010. The prohibition applies to 1,4-dimethylamylamine as a specified stimulant under the same category [12]. More than 80 athlete sanctions have been associated with DMAA-positive doping tests, predominantly involving 1,3-DMAA but with the prohibition explicitly extending to the 1,4-isomer.

Multiple national regulatory authorities have taken enforcement actions against DMAA isomers. Australia (Therapeutic Goods Administration), Canada (Health Canada), the United Kingdom (Medicines and Healthcare products Regulatory Agency), New Zealand (Medsafe), Brazil (ANVISA), Finland, Sweden, and Switzerland have all classified DMAA as an unauthorized substance in dietary supplements and/or as a controlled medicine.

## 4. Mechanism of Action

### 4.1 Inferred mechanism from structural analogy

No primary experimental pharmacological data (receptor binding, transporter interaction, electrophysiology, or behavioral pharmacology) have been published specifically for 1,4-DMAA. The mechanism of action is inferred from the compound's structural membership in the aliphatic alkylamine sympathomimetic class and from the experimentally characterized pharmacology of its positional isomer, 1,3-DMAA.

1,4-DMAA is a primary aliphatic amine lacking the aromatic ring system present in the phenethylamine, amphetamine, and catecholamine classes. The absence of hydroxyl substituents on an aromatic ring eliminates the capacity for direct agonism at alpha- and beta-adrenergic receptors, restricting the pharmacological activity to indirect sympathomimetic mechanisms: promotion of catecholamine release from presynaptic vesicles, inhibition of catecholamine reuptake at monoamine transporters, and/or inhibition of monoamine oxidase (MAO)-mediated degradation [2, 3, 16].

### 4.2 Pharmacology of 1,3-DMAA as the reference compound

The most detailed pharmacological characterization of an aliphatic DMAA isomer is the Bhatt et al. (2023) study of 1,3-DMAA interaction with the human dopamine transporter (hDAT), published in the *Journal of Pharmacology and Experimental Therapeutics* [3]. Key findings from this study:

**Dopamine transporter inhibition:** 1,3-DMAA competitively inhibited uptake of tritiated dopamine at hDAT with a mean IC<sub>50</sub> of 29.4 micromolar (SD 14.8; range 12.5 to 66.2 micromolar). By comparison, d-amphetamine inhibited dopamine uptake with an IC<sub>50</sub> of 0.66 micromolar, indicating that 1,3-DMAA is approximately 45- to 60-fold less potent than amphetamine at the dopamine transporter.

**Substrate-like binding:** Molecular dynamics simulations demonstrated that 1,3-DMAA binds to the S1 substrate-binding site of hDAT, with the amine group forming hydrogen bonds or salt bridges with Asp79 and the aliphatic moiety interacting with hydrophobic residues in the transmembrane domains. Upon binding, 1,3-DMAA triggered a conformational transition from the outward-facing open to the outward-facing closed state, a pattern characteristic of DAT substrates (amphetamine, dopamine) rather than DAT blockers (cocaine, methylphenidate).

**Transporter endocytosis:** 1,3-DMAA induced endocytosis of hDAT through cocaine- and protein kinase A-sensitive mechanisms, paralleling the endocytosis pattern produced by amphetamine. This finding is consistent with classification as a substrate-type monoamine releasing agent rather than a simple reuptake inhibitor.

**Binding affinity:** The computed binding free energy of 1,3-DMAA at the S1 site was approximately negative 4.3 kcal/mol, compared to negative 5.5 kcal/mol for amphetamine, reflecting the lower affinity consistent with the IC50 data.

The Bhatt et al. study noted that findings "suggest that other aliphatic amine stimulants, such as 1,4-DMAA, 1,3-dimethylbutylamine, and tuaminoheptane, also exert biologic effects through DAT interactions," providing a direct inference pathway for the 1,4-isomer.

## 4.3 Norepinephrine transporter and other targets

Separate pharmacological profiling of the alkylamine stimulant class (Simmler et al. 2013; Luethi et al. 2019) has demonstrated that 1,3-DMAA and related aliphatic alkylamines block the norepinephrine transporter (NET) with higher potency than the dopamine transporter, consistent with a predominantly noradrenergic sympathomimetic profile [6, 17]. The selectivity pattern (NET greater than DAT, with minimal serotonin transporter interaction) distinguishes the aliphatic alkylamines from amphetamine (which affects NET, DAT, and SERT) and from MDMA (which preferentially affects SERT).

By structural analogy, 1,4-DMAA is expected to produce a similar NET-preferential sympathomimetic profile: predominantly noradrenergic peripheral effects (vasoconstriction, elevated blood pressure, bronchodilation, mydriasis) with a secondary dopaminergic contribution to central stimulant effects (increased alertness, reduced fatigue, potential euphoria at higher doses). The relative potency of 1,4-DMAA at NET and DAT compared to 1,3-DMAA is unknown. The positional shift of

the methyl branch from carbon 4 to carbon 5 alters the steric profile of the molecule and may affect the fit within the transporter binding site, potentially increasing or decreasing potency.

## 4.4 Limitations of the analogy-based mechanism

The inference of 1,4-DMAA pharmacology from 1,3-DMAA data carries significant uncertainty. Positional isomerism in aliphatic amines can substantially alter pharmacological properties. In the phenethylamine class, single methyl-group repositioning produces pharmacologically distinct compounds (amphetamine versus methamphetamine versus phentermine). While the structural variation between 1,3-DMAA and 1,4-DMAA is more distal from the pharmacophoric amine group (and therefore potentially less consequential), the absence of direct experimental data means that the potency, selectivity, and dose-response relationship of 1,4-DMAA remain genuinely unknown quantities. Investigators should treat the mechanism described in this section as a structural analogy rather than as experimentally established pharmacology.

## 5. Pharmacokinetics and Routes of Administration

### 5.1 Absence of direct pharmacokinetic data

No human or animal pharmacokinetic studies specific to 1,4-DMAA have been published. The following pharmacokinetic description is based entirely on data from the structural isomer 1,3-DMAA and should be interpreted as an analog projection rather than as established pharmacokinetic parameters for 1,4-DMAA.

### 5.2 Pharmacokinetics of 1,3-DMAA as reference

Bloomer et al. (2013) published the only controlled human pharmacokinetic study of the DMAA class, conducted in seven healthy men (mean age 26.7 years, mean lean mass 68.1 kg) receiving a single oral dose of 25 mg 1,3-DMAA [9]. Key parameters:

**Absorption:** Rapid absorption with a short lag time of approximately 0.14 hours (8 minutes). Time to peak plasma concentration (T<sub>max</sub>) was 3.57 plus or minus 1.48 hours.

**Peak concentration:** C<sub>max</sub> was approximately 70 ng/mL (range 60 to 108 ng/mL) after the 25 mg dose, corresponding to an estimated peak plasma concentration of approximately 0.6 micromolar.

**Distribution:** Volume of distribution was 236 plus or minus 38 L, indicating extensive tissue distribution consistent with moderate lipophilicity (XLogP3 approximately 1.9) and blood-brain barrier penetration.

**Elimination:** Terminal elimination half-life was 8.45 plus or minus 1.9 hours. Oral clearance was 20.02 plus or minus 5 L/hr.

**Area under the curve:** AUC(0 to infinity) was 1204.55 plus or minus 262.89 ng per hour per mL after the 25 mg dose.

**Physiological effects at 25 mg:** No statistically significant changes in blood pressure were observed (systolic range 96 to 130 mmHg, diastolic range 60 to 88 mmHg). Heart rate showed a statistically significant time effect but no meaningful pairwise differences from baseline (mean 64 bpm, range 50 to 88 bpm). Body temperature was significantly elevated 12 hours post-ingestion but remained within the normal physiological range.

## 5.3 Inferred metabolism

The metabolic fate of 1,4-DMAA has not been studied. By analogy with 1,3-DMAA and other primary aliphatic amines, the principal metabolic pathways are expected to be hepatic oxidative deamination by monoamine oxidase (MAO-A and MAO-B) to the corresponding ketone (5-methylhexan-2-one), followed by further oxidation or reduction and conjugation; and hepatic cytochrome P450-mediated omega- and omega-1 hydroxylation of the aliphatic chain, producing hydroxylated metabolites that are subsequently glucuronidated and excreted in urine [18]. N-dealkylation is not applicable as 1,4-DMAA is a primary amine.

The elimination half-life of 8.5 hours observed for 1,3-DMAA indicates the potential for accumulation with repeated dosing within a 24- to 36-hour window, particularly at the higher doses found in commercial supplements (21 to 94 mg per serving). This accumulation risk is directly relevant to the cardiovascular safety signal.

## 5.4 Routes of administration

1,4-DMAA has appeared in dietary supplements in oral form (capsules, tablets, powder for suspension, and liquid solutions). No parenteral, inhaled, or other routes of administration have been described for 1,4-DMAA. The related compound 1,3-DMAA was originally administered by inhalation as a nasal decongestant (Forthane), but the inhalation route has not been applied to the 1,4-isomer.

Oral bioavailability has not been determined for either isomer in controlled studies. The high oral clearance (20 L/hr) and the large volume of distribution observed for 1,3-DMAA are consistent with moderate to high oral bioavailability for aliphatic amines with pKa values in the range of 10 to 11, which exist predominantly in the protonated (cationic) form at physiological pH and are absorbed primarily in the small intestine.

## 6. Clinical Evidence Base

### 6.1 Absence of clinical trials

No controlled clinical trials of 1,4-DMAA have been conducted for any indication. The compound has not been studied in Phase 1 pharmacokinetic or safety studies, Phase 2 dose-finding studies, or Phase 3 efficacy studies. It has not been evaluated in any formal clinical endpoint for athletic performance, weight loss, cognitive enhancement, nasal decongestion, or any other proposed application [1].

### 6.2 Supplement-associated exposure data

The only human exposure data for 1,4-DMAA derive from its presence as an ingredient in dietary supplements. Cohen et al. (2018) documented supplement-grade doses of 21 to 94 mg per serving [1]. Users of these products have self-administered 1,4-DMAA in uncontrolled settings, frequently in combination with caffeine (typically 150 to 400 mg per serving), other stimulants, and multiple additional ingredients. No structured outcome data, adverse-event reporting, or dose-response characterization has been conducted on these supplement users.

### 6.3 Clinical evidence for 1,3-DMAA as proxy

The clinical evidence for the DMAA class derives almost entirely from studies of 1,3-DMAA. The Bloomer et al. (2013) pharmacokinetic study documented the acute physiological response to a single 25 mg dose (see Section 5.2) [9]. McCarthy et al. (2012a, 2012b) studied the hemodynamic effects of a multi-ingredient supplement containing 1,3-DMAA (OxyElite Pro) and reported modest increases in systolic blood pressure (approximately 6 to 8 mmHg above placebo) and heart rate (approximately 3 to 5 bpm above placebo) at rest, with potentially larger effects during exercise [19, 20]. Bloomer et al. (2011) reported similar modest hemodynamic effects with the Jack3d formulation [21].

These studies evaluate multi-ingredient products containing caffeine and other active compounds in addition to 1,3-DMAA, making attribution of specific effects to the DMAA component difficult. The clinical evidence base for the DMAA class as a

whole is limited to acute hemodynamic and pharmacokinetic studies; no chronic efficacy or safety data have been generated in controlled settings for any proposed indication.

## 6.4 Adverse event case reports associated with the DMAA class

Adverse events associated with DMAA-containing supplements (predominantly 1,3-DMAA formulations) have been reported in the published literature and in FDA adverse-event reporting systems. These include:

Hemorrhagic stroke in young adults using DMAA-containing pre-workout supplements, reported by Gee et al. (2012) and by the FDA adverse-event database [11, 22]. Cases involved concurrent caffeine exposure and vigorous exercise.

Sudden cardiac death in military personnel using DMAA-containing supplements, reported by the United States Department of Defense and cited in the FDA enforcement rationale [10].

Acute hepatotoxicity associated with OxyElite Pro, reported in a 2013 outbreak of severe liver injury in Hawaii, though the hepatotoxicity was subsequently attributed to the aegeline component of the reformulated product rather than to DMAA [23].

Hypertensive emergencies and tachyarrhythmias reported in emergency department presentations, typically involving multi-ingredient stimulant products.

None of these case reports specifically implicate 1,4-DMAA; all involve 1,3-DMAA-containing products. The cardiovascular adverse-event signal is extrapolated to 1,4-DMAA on the basis of shared structural class and inferred mechanism.

## 7. Reported Dose Ranges

### 7.1 Supplement-derived doses

No therapeutic or approved doses exist for 1,4-DMAA. The compound has been detected in commercial supplements at the following quantities per serving [1]:

Product-specific range: 21 plus or minus 11 mg to 94 plus or minus 48 mg per serving.

These quantities represent the range found by Cohen et al. (2018) across multiple products purchased in the United States. The variability within a single product (reflected in the standard deviations) indicates poor manufacturing consistency, which is characteristic of the dietary supplement market for unapproved stimulant ingredients.

### 7.2 Context from 1,3-DMAA dosing

For the reference compound 1,3-DMAA, the original pharmaceutical dose (Forthane nasal inhaler) was not publicly documented in modern pharmacokinetic terms. Anecdotal and supplement-industry dosing for 1,3-DMAA typically ranged from 25 to 75 mg per serving in pre-workout products (OxyElite Pro, Jack3d). The Bloomer et al. (2013) pharmacokinetic study used a single 25 mg dose [9]. Higher doses (100 mg and above) have been associated with blood pressure elevation and cardiac effects in the methylhexanamine pharmacological literature [7].

### 7.3 Dose-response considerations

In the absence of controlled dose-response data for 1,4-DMAA, investigators should note that the supplement-derived doses (21 to 94 mg) span a range that, by analogy with 1,3-DMAA pharmacokinetics, would produce estimated peak plasma concentrations of approximately 0.5 to 3 micromolar. These concentrations overlap with the IC<sub>50</sub> range for 1,3-DMAA at the dopamine transporter (29.4 micromolar mean, but with substantial variability) and are clearly within the range at which sympathomimetic effects on blood pressure and heart rate would be expected from the norepinephrine transporter interaction.

## 8. Sourcing and Quality Verification

Research-grade 1,4-DMAA (5-methylhexan-2-amine) is available from chemical and pharmaceutical research suppliers (Sigma-Aldrich/MilliporeSigma, Tokyo Chemical Industry, BenchChem, SmoleCule, and specialty research chemical vendors) in milligram to gram quantities as the free base or as the hydrochloride salt. Purity is typically reported as greater than 95 to 98 percent by gas chromatography or high-performance liquid chromatography.

Supplement-grade 1,4-DMAA is available from vendors marketing research chemicals and dietary supplement ingredients. The quality, purity, and identity of supplement-grade material is variable and cannot be assumed to meet analytical standards without independent verification.

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

- Gas chromatography-mass spectrometry (GC-MS) confirmation of molecular identity (molecular ion  $m/z$  115, characteristic fragmentation pattern)
- High-performance liquid chromatography area-percent purity, with target greater than 98 percent
- Nuclear magnetic resonance spectroscopy (proton and carbon-13) for structural confirmation and to distinguish 1,4-DMAA from the 1,3-isomer, which has a distinct NMR signature due to the different methyl branch position
- Chiral analysis (chiral GC or chiral HPLC) if enantiopure material is required for research applications
- Residual solvent analysis if the free base form is received (volatile solvents from synthesis may be present)

The distinction between 1,4-DMAA and 1,3-DMAA by standard achiral analytical methods requires careful attention. Both compounds share the same molecular formula ( $C_7H_{17}N$ ), the same molecular weight (115.22), and similar fragmentation patterns under electron ionization mass spectrometry. Differentiation relies on retention time differences in gas chromatography (different branching patterns produce

different boiling points and elution profiles) and on distinctive NMR chemical shift patterns [4, 13]. Reference standards for both isomers should be run concurrently to confirm identity.

Third-party analytical laboratories (Janoshik Analytical, NSF International, Informed Sport) provide independent confirmation of vendor certificates of analysis. Given the history of mislabeling and adulteration in the DMAA supplement market, independent analytical verification is strongly recommended for any research application.

## 9. Reconstitution and Handling

### 9.1 Free base form

1,4-DMAA free base is a volatile liquid at room temperature. It should be stored in sealed containers under inert atmosphere (nitrogen or argon) at 2 to 8 degrees Celsius to minimize evaporative loss and oxidative degradation. The free base is miscible with water and with common organic solvents (methanol, ethanol, diethyl ether, dichloromethane). Stock solutions for in vitro research can be prepared in water, phosphate-buffered saline, or dimethyl sulfoxide (DMSO) at concentrations up to 100 mM. Aqueous stock solutions should be prepared fresh or stored at negative 20 degrees Celsius in sealed aliquots to prevent evaporative concentration changes.

### 9.2 Hydrochloride salt form

The hydrochloride salt is a white crystalline solid with improved stability for storage and handling compared to the free base. It is freely soluble in water and in polar organic solvents. Storage at room temperature in a dry, light-protected environment is adequate; refrigerated storage (2 to 8 degrees Celsius) is recommended for long-term stability. Aqueous stock solutions of the hydrochloride salt are stable for at least 30 days at refrigerated conditions.

### 9.3 Safety handling considerations

1,4-DMAA is a pharmacologically active sympathomimetic amine. Standard laboratory precautions for handling stimulant compounds should be observed: use in a well-ventilated area (particularly for the volatile free base form), avoidance of dermal contact and inhalation, use of nitrile gloves and eye protection, and storage in a locked cabinet consistent with institutional policies for controlled or pharmacologically active substances. The compound is not a scheduled substance under United States federal controlled substance law (Schedules I through V of the Controlled Substances Act) as of the date of this monograph, but it is regulated as an illegal dietary supplement ingredient by the FDA and as a prohibited substance by WADA.

# 10. Stack Interactions and Combinations

## 10.1 Caffeine

The combination of 1,4-DMAA (or 1,3-DMAA) with caffeine is the most common formulation context, as virtually all pre-workout and weight-loss supplements containing DMAA isomers also contain caffeine at doses of 150 to 400 mg per serving. The combination produces additive sympathomimetic effects: both compounds increase circulating catecholamines (DMAA through monoamine release/reuptake inhibition, caffeine through phosphodiesterase inhibition and adenosine receptor antagonism), and the cardiovascular effects (blood pressure elevation, tachycardia) are expected to be additive or synergistic [19, 20]. The combination increases the risk of cardiovascular adverse events compared to either compound alone. The FDA has specifically noted the combination of DMAA with caffeine as a contributor to the adverse-event signal [10].

## 10.2 Other sympathomimetic amines

Concurrent use with other sympathomimetic amines (ephedrine, pseudoephedrine, phenylephrine, amphetamine, methylphenidate, synephrine, octodrine, 1,3-DMBA) produces additive catecholamine-mediated cardiovascular stimulation. The combination is pharmacologically hazardous and increases the risk of hypertensive crisis, tachyarrhythmia, and hemorrhagic stroke.

## 10.3 Monoamine oxidase inhibitors

Monoamine oxidase inhibitors (MAOIs, including phenelzine, tranylcypromine, isocarboxazid, selegiline, moclobemide) potentiate the effects of all monoamine releasing agents by preventing metabolic degradation of released catecholamines. The combination of any indirect sympathomimetic with an MAOI carries a risk of hypertensive crisis and is contraindicated.

## 10.4 Beta-adrenergic agonists

Concurrent use with beta-2 agonists (albuterol, clenbuterol, formoterol) produces additive cardiovascular stimulation (tachycardia, tremor, hypokalemia). The combination is relevant to the athletic supplement context where DMAA products may be used alongside bronchodilators.

## 10.5 Serotonergic agents

1,3-DMAA and the alkylamine class show minimal interaction with the serotonin transporter at pharmacologically relevant concentrations [6, 17]. Serotonin syndrome from the combination of 1,4-DMAA with serotonergic agents (SSRIs, SNRIs, triptans, tramadol) is not expected, though this has not been experimentally confirmed.

## 10.6 Antihypertensive agents

DMAA isomers produce blood pressure elevation through sympathomimetic vasoconstriction. Concurrent use with antihypertensive medications (ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, beta-blockers, diuretics) may attenuate the antihypertensive effect. Clinicians should be aware that patients using DMAA-containing supplements may present with resistant or refractory hypertension.

## 10.7 QT-prolonging agents

The cardiovascular stimulant properties of DMAA isomers, while principally mediated through catecholamine release rather than ion channel blockade, may contribute to arrhythmia risk in the context of concurrent QT-prolonging agents (methadone, fluoroquinolones, antiarrhythmics, selected antipsychotics). This interaction has not been characterized in formal studies.

# 11. Adverse Events and Safety

## 11.1 Unknown safety profile

The safety of 1,4-DMAA in humans has not been established through any controlled study. All adverse-event characterization is inferred from the pharmacological mechanism and from case reports associated with the 1,3-DMAA isomer in multi-ingredient supplement formulations.

## 11.2 Expected adverse events from sympathomimetic mechanism

Based on the indirect sympathomimetic mechanism shared by the alkylamine class, the following adverse events are expected at pharmacologically active doses:

**Cardiovascular:** Elevated systolic and diastolic blood pressure (dose-dependent), tachycardia, palpitations, vasoconstriction (peripheral and potentially coronary), and increased cardiac workload. At high doses or in combination with caffeine or other stimulants, the risk of hypertensive emergency, tachyarrhythmia, myocardial ischemia, and hemorrhagic stroke is elevated.

**Central nervous system:** Increased alertness, restlessness, anxiety, insomnia, tremor, and headache. At higher doses, agitation, paranoia, and seizure risk are plausible.

**Gastrointestinal:** Nausea, reduced appetite (the basis for the weight-loss marketing of DMAA-containing supplements), and dry mouth.

**Metabolic:** Mild thermogenesis (elevated body temperature), consistent with the 12-hour post-dose temperature elevation observed for 1,3-DMAA by Bloomer et al. (2013) [9].

## 11.3 Serious adverse events associated with the DMAA class

The FDA has received 86 reports of illnesses and deaths associated with DMAA-containing supplements [10]. Published case reports include:

Hemorrhagic stroke in a 21-year-old New Zealand man consuming a 1,3-DMAA-containing supplement in combination with caffeine and alcohol [22]. Cerebral hemorrhage was attributed to acute hypertension in the context of stimulant-induced vasoconstriction.

Sudden cardiac death in two United States Army soldiers consuming 1,3-DMAA-containing supplements during physical training. The Department of Defense cited these cases in its restriction of DMAA product sales at military installations [10].

Multiple emergency department presentations for acute hypertension, chest pain, tachycardia, and anxiety in young adults using DMAA-containing pre-workout supplements, as documented in poison control center data and clinical case series [11].

Claire Squires, a 30-year-old runner, died during the 2012 London Marathon. An inquest determined that she had consumed a 1,3-DMAA-containing supplement (Jack3d) before the race, and the coroner recorded a verdict of death by natural causes contributed to by ingestion of DMAA [24].

## 11.4 Risk factors

Risk factors for serious adverse events with DMAA isomers include: concurrent caffeine or other stimulant use (present in virtually all commercial DMAA-containing products); vigorous physical exercise (which independently increases catecholamine levels and cardiovascular demand); pre-existing cardiovascular conditions (hypertension, coronary artery disease, arrhythmia, structural heart disease); dehydration and electrolyte imbalance; and concurrent use of monoamine oxidase inhibitors.

## 11.5 Regulatory safety position

The FDA position is that DMAA (both 1,3- and 1,4-isomers) is not a lawful dietary ingredient and that products containing it should not be consumed. This position is based on: the absence of a history of use as a food or dietary ingredient prior to 1994 (the DSHEA grandfather date); the absence of a new dietary ingredient notification with evidence of safety; and the adverse-event signal [10, 15].

## 12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five structurally or functionally related alkylamine stimulants against 1,4-DMAA, evaluated on five competency standards: novelty, effect size (as a stimulant or performance-modifying agent), side-effect profile, regulatory status, and overall validation. The five comparators were selected as the principal aliphatic amine stimulants that share structural features, market context, or pharmacological mechanism with 1,4-DMAA.

### 12.1 1,3-Dimethylamylamine (1,3-DMAA, methylhexanamine)

**Mechanism:** Indirect sympathomimetic; norepinephrine and dopamine releasing agent. Competitively inhibits DAT (IC<sub>50</sub> 29.4 micromolar) with substrate-like binding and transporter endocytosis [3]. Blocks NET with higher potency than DAT [6, 17].

**History:** Developed by Eli Lilly as Forthane inhaled nasal decongestant (1948). Withdrawn 1983. Reintroduced as dietary supplement ingredient (2006). Subject of extensive FDA enforcement action (2012 to present) [7, 8, 10].

**Novelty:** Low. The compound is the oldest and most extensively characterized member of the aliphatic alkylamine stimulant class.

**Effect size:** The Bloomer et al. (2013) pharmacokinetic study documented modest hemodynamic effects at 25 mg [9]. McCarthy et al. (2012a, 2012b) reported small but statistically significant blood pressure elevation in multi-ingredient supplement formulations [19, 20]. Acute stimulant effects (subjective energy, alertness) are widely reported in the anecdotal supplement literature but have not been quantified in placebo-controlled trials with cognitive or performance endpoints.

**Side-effect profile:** Moderate to high risk. Cardiovascular adverse events (hypertension, tachycardia) are dose-dependent and potentiated by caffeine. Case reports of hemorrhagic stroke and sudden cardiac death have been associated with product

use [10, 11, 22, 24].

**Regulatory status:** Illegal in dietary supplements in the United States (FDA). Prohibited by WADA. Banned in multiple national jurisdictions.

**Overall validation:** Moderate. The compound has the most extensive pharmacological, pharmacokinetic, and clinical exposure database of any aliphatic alkylamine stimulant, but this database reveals a risk-benefit profile that has not supported pharmaceutical registration or clinical development.

**Comparison to 1,4-DMAA:** 1,3-DMAA is the direct positional isomer and the primary reference compound for 1,4-DMAA pharmacology. It has a substantially larger evidence base (pharmacokinetic study, transporter interaction data, clinical hemodynamic data, extensive adverse-event database). 1,4-DMAA is distinguished only by the positional isomerism and by the even more complete absence of primary pharmacological data.

## 12.2 Octodrine (2-amino-6-methylheptane, DMHA)

**Mechanism:** Indirect sympathomimetic; presumed monoamine releasing agent. Pharmacological mechanism has not been independently characterized at the molecular level. Originally developed as a pharmaceutical (nasal decongestant, bronchodilator) with clinical use in the mid-twentieth century [1, 6].

**History:** Octodrine (Vaporpac) was a marketed pharmaceutical in several jurisdictions for nasal decongestion and bronchospasm. It was withdrawn from most markets in the latter twentieth century. It reemerged in the dietary supplement market in the 2010s as a replacement for 1,3-DMAA following FDA enforcement actions, marketed under the names DMHA, 2-aminoisoheptane, and *Juglans regia* extract [1].

**Novelty:** Low. The compound has a longer pharmaceutical history than 1,4-DMAA (prior clinical use as a decongestant) but shares the same structural class and inferred mechanism.

**Effect size:** No controlled clinical performance or cognitive studies. Acute stimulant effects are reported anecdotally. Cohen et al. (2018) detected octodrine at 72 mg per serving in supplements [1].

**Side-effect profile:** Unknown in controlled settings. Cardiovascular risk is inferred from the sympathomimetic class. The FDA and NSF International have identified octodrine as a potentially harmful stimulant in supplements [1].

**Regulatory status:** Considered illegal in dietary supplements by the FDA. Prohibited by WADA under S6.

**Overall validation:** Low. The compound has a pharmaceutical history but no modern pharmacological characterization and no controlled clinical data.

**Comparison to 1,4-DMAA:** Octodrine is a one-carbon homolog (eight-carbon backbone versus seven) sharing the same class and regulatory context. Both compounds have minimal primary pharmacological data, no clinical trials, and comparable regulatory prohibition. Octodrine has the marginal advantage of prior pharmaceutical use, though this historical use predates modern pharmacological characterization standards.

## 12.3 1,3-Dimethylbutylamine (1,3-DMBA, AMP Citrate)

**Mechanism:** Indirect sympathomimetic; presumed monoamine releasing agent. No primary pharmacological data have been published [1].

**History:** 1,3-DMBA (4-amino-2-methylpentane, marketed as AMP Citrate) appeared in the dietary supplement market in approximately 2014 as a further replacement for 1,3-DMAA following regulatory enforcement. It is a shorter-chain analog (six-carbon backbone) of the DMAA class [1].

**Novelty:** Very low. The compound is a chain-length variant of the established DMAA structural class with no distinguishing pharmacological feature.

**Effect size:** No controlled data. Supplement-derived doses were approximately 51 mg per serving [1].

**Side-effect profile:** Unknown. Same cardiovascular risk inference as the broader class.

**Regulatory status:** Considered illegal in dietary supplements by the FDA. Identified as an unapproved stimulant by Cohen et al. (2018) [1].

**Overall validation:** Very low. The compound has the least evidence of any member of the panel.

**Comparison to 1,4-DMAA:** 1,3-DMBA is a shorter-chain analog sharing the same class, regulatory context, and absence of pharmacological data. Neither compound has any evidence base supporting safety or efficacy for any application.

## 12.4 Tuaminoheptane (2-aminoheptane)

**Mechanism:** Indirect sympathomimetic; norepinephrine releasing agent. The compound has a limited but established pharmacological literature documenting nasal vasoconstrictive activity [25].

**History:** Tuaminoheptane was developed as a nasal decongestant and was marketed in several formulations (Tuamine) in the mid-twentieth century. It remains available in some jurisdictions as a component of nasal decongestant preparations (Rhinofluimucil in Italy, containing tuaminoheptane and acetylcysteine). It is the straight-chain (unbranched) seven-carbon analog of the DMAA class [25].

**Novelty:** Low. The compound is the simplest member of the seven-carbon aliphatic amine class.

**Effect size:** Demonstrated nasal decongestant efficacy in the pharmaceutical context. No controlled performance or cognitive data.

**Side-effect profile:** Well characterized in the pharmaceutical context. Local application produces nasal mucosal vasoconstriction. Systemic effects at high doses include hypertension and tachycardia. Rebound congestion (rhinitis medicamentosa) with prolonged nasal use is documented.

**Regulatory status:** Available as a pharmaceutical (nasal decongestant) in selected jurisdictions. Prohibited by WADA under S6.

**Overall validation:** Moderate. The compound has a legitimate pharmaceutical application with demonstrated efficacy and a characterized safety profile in the nasal decongestant context. It is the most validated compound on this panel from a pharmaceutical perspective.

**Comparison to 1,4-DMAA:** Tuaminoheptane is the straight-chain structural relative of 1,4-DMAA (which has a methyl branch at carbon 5 of the same seven-carbon backbone). Tuaminoheptane has the advantage of pharmaceutical registration, established efficacy as a nasal decongestant, and a known safety profile. 1,4-DMAA has none of these. The branching pattern of 1,4-DMAA likely confers greater

lipophilicity and potentially greater blood-brain barrier penetration compared to the straight-chain compound, which may account for the preference for branched-chain analogs in the stimulant supplement market.

## 12.5 Phenylethylamine (PEA, beta-phenethylamine)

**Mechanism:** Direct and indirect sympathomimetic; substrate-type monoamine releasing agent at NET and DAT. PEA is an endogenous trace amine produced by aromatic L-amino acid decarboxylase from phenylalanine. It has high potency at NET (IC<sub>50</sub> 0.05 micromolar) and DAT (IC<sub>50</sub> 1.8 micromolar), comparable to amphetamine [6, 17].

**History:** PEA is an endogenous neuromodulator and the structural parent compound of the phenethylamine and amphetamine classes. It is widely available as a dietary supplement ingredient and is marketed for mood elevation and cognitive enhancement. Its pharmacological limitation is extremely rapid metabolism by MAO-B, producing a plasma half-life of minutes, which limits its systemic bioavailability after oral administration [26].

**Novelty:** Low as a supplement ingredient. High as a pharmacological reference compound.

**Effect size:** Minimal as an oral supplement due to rapid MAO-B metabolism. Significant at the molecular level (NET and DAT potency comparable to amphetamine). Modified forms (N-methylphenethylamine, beta-methylphenethylamine) have longer half-lives but carry additional regulatory scrutiny.

**Side-effect profile:** Minimal at oral supplement doses due to rapid metabolism. At systemic concentrations (achievable by parenteral administration or MAO inhibition), produces full sympathomimetic and psychostimulant effects comparable to amphetamine.

**Regulatory status:** Legal as a dietary supplement ingredient in the United States (endogenous compound with a history of food use). Not prohibited by WADA. Regulated differently from the synthetic aliphatic alkylamines.

**Overall validation:** Moderate as a pharmacological tool. Low as a practical stimulant supplement due to the metabolic limitation.

**Comparison to 1,4-DMAA:** PEA and 1,4-DMAA are structurally divergent (aromatic phenethylamine versus aliphatic alkylamine) but share the indirect sympathomimetic mechanism. PEA has vastly greater potency at monoamine transporters but vastly shorter half-life. 1,4-DMAA, by analogy with 1,3-DMAA, has lower potency but a half-life of hours rather than minutes, giving it a fundamentally different pharmacokinetic profile and a correspondingly different risk-benefit calculation: lower acute potency but sustained systemic exposure that supports cumulative cardiovascular effects.

## 12.6 Comparator summary

The five comparators occupy distinct positions in the aliphatic alkylamine and sympathomimetic stimulant landscape. **1,3-DMAA** is the direct positional isomer and primary reference compound, with the most extensive evidence base in the class, including molecular pharmacology, controlled pharmacokinetic data, and a substantial adverse-event database. **Octodrine** is a one-carbon homolog with prior pharmaceutical use but no modern pharmacological characterization. **1,3-DMBA** is a shorter-chain analog with the least evidence of any panel member. **Tuaminoheptane** is the straight-chain seven-carbon amine with current pharmaceutical registration as a nasal decongestant, making it the most pharmaceutically validated compound on the panel. **Phenylethylamine** represents the structurally distinct phenethylamine class, with high transporter potency but pharmacokinetically limiting rapid metabolism.

1,4-DMAA occupies a position of minimal pharmacological characterization within a class of compounds that itself has limited clinical evidence. It is distinguished from 1,3-DMAA only by positional isomerism. It has no pharmaceutical history, no receptor-binding or transporter-interaction data, no controlled human pharmacokinetic or safety data, and no clinical efficacy data for any indication. Its presence in the scientific literature derives almost entirely from analytical chemistry studies detecting it in plant material and dietary supplements. The regulatory status is unambiguously negative: the compound is considered illegal in dietary supplements by the FDA and prohibited by WADA.

The principal research utility of 1,4-DMAA lies in structure-activity relationship studies within the aliphatic alkylamine class, in analytical method development for supplement surveillance, and as a comparative tool for understanding how methyl branch positioning affects the pharmacology of simple aliphatic amine sympath-

omimetics. Investigators considering 1,4-DMAA for any research application should recognize that the compound has no established efficacy for any endpoint and an inferred cardiovascular risk profile that has not been quantified.

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*This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. 1,4-DMAA has never been approved as a pharmaceutical agent in any jurisdiction. The compound is considered an illegal dietary supplement ingredient by the United States Food and Drug Administration and a prohibited substance by the World Anti-Doping Agency. The safety of 1,4-DMAA in humans is unknown. No controlled clinical trials have been conducted. Cardiovascular adverse events, including hypertension, tachycardia, hemorrhagic stroke, and sudden cardiac death, have been associated with structurally related DMAA isomers in dietary supplement formulations. Investigators should consult their institutional review board and local regulatory authority before any human research application. The pharmacological characterization presented in this monograph is based on structural analogy to 1,3-DMAA and the broader alkylamine sympathomimetic class; direct experimental data for 1,4-DMAA are absent.*