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Review

Pharmacokinetic and Toxicological Aspects of 1,3-Dimethylamylamine with Clinical and Forensic Relevance

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Abstract: 1,3-dimethylamylamine (1,3-DMAA) is a simple straight-chain aliphatic sympathomimetic amine, which was used as a nasal decongestant between 1948 and 1983. It reappeared in both dietary supplements as a substitute for ephedrine, and in party pills as an alternative to 3,4-methylenedioxymethamphetamine and/or 1-benzylpiperazine, after these substances were banned. Following its introduction to the market, it became one of the most widely used stimulants, and several case reports started to raise concerns about the safety and adverse effects of 1,3-DMAA. As a result, many countries banned or restricted the sale of 1,3-DMAA. Nevertheless, despite the efforts of regulating agencies, it has been reported that 1,3-DMAA is still found in dietary supplements and has been identified in doping controls. Therefore, the objective of this work is to review both the clinical and forensic aspects of 1,3-DMAA.

Keywords: 1,3-dimethylamylamine; 1,3-DMAA; dietary supplements; methylhexaneamine; intoxications

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1. Introduction

1,3-DMAA was patented in 1944 by the pharmaceutical company Eli Lilly® (Indianapolis, IN, USA) and sold for the first time in 1948 [1–3]. Potential side effects were described as headache, nervousness, mental stimulation, and tremors, upon nasal administration [3]. 1,3-DMAA was later removed from the market in 1983 [3]. In 2005, 1,3-DMAA was reintroduced into the market to be used for different reasons, such as a dietary supplement for weight loss in obesity [4], as an athletic muscle performance enhancer [5], as a party pill [6,7] and as an appetite inhibitor [8]. This is even more important since up to a third of adolescent males in the United States use dietary and fitness supplements, with peer pressure playing an important role [9]. Influencers, social media, as well as other forms of media routinely portray individuals with extreme physiques and may further incentivize adolescents to take the products in search of better results. Members of the military are also an important population when it comes to dietary and fitness supplements, both because of their inherent necessity to maintain a good physical condition [10], as well as due to the fact that they are heavily targeted by advertisers [11]. Athletes also represent a group of special interest, with about 89% of college athletes reporting using pre-workout nutritional supplements [12]. In a study [13] carried out after the ban of 1,3-DMAA in Mainz, Germany, it was found that from among those using pre-workout boosters, 20.5% of them procured products specifically containing 1,3-DMAA or similar substances. 1,3-DMAA could also be found in the form of party pills, with reported dosages of between 50 and 300 mg of 1,3-DMAA per pill, which are higher than the ones recommended in dietary and fitness supplements (see below) [7]. The use of the pills occurred mostly in Ireland and New

Zealand, where their recreational use was motivated by the search for legal alternatives to 3,4-methylenedioxymethamphetamine and/or 1-benzylpiperazine [6,7].

Following the publishing of case reports of severe adverse effects associated with the consumption of 1,3-DMAA, this substance ended up being banned or had its sale restricted in countries such as Canada in 2011 and New Zealand, United States, Australia, Brazil, Finland, Hong Kong, Ireland, Sweden and the United Kingdom in 2012 and 2013 [14], as well as in the European Union [13] to name a few. It was also placed on the World Anti-Doping Agency (WADA) prohibited list in 2009 with the enforcement beginning in 2010 [14] due to its similarities with other banned substances and potential for harm [15]. Nevertheless, the enforcement of the ban of 1,3-DMAA is complex due to the fact that the agencies in charge of regulating dietary supplements have little power to do so, as this market is highly unregulated [14]. Moreover, sellers attempt to get around the ban of 1,3-DMAA by either not listing the substance, or by using other designations such as those reported in Table 1.

Table 1. Different designations for 1,3-DMAA. Data compiled from [16–18].

Methylhexaneamine	2-amino-4-methylhexane	Floradrene
1,3-dimethylpentylamine	2-hexanamine	Forthan
Dimethylamylamine	4-methyl-2-hexanamine	Forthane
Dimethylpentylamine	4-methyl-2-hexylamine	Fouramin
Geranium flower extract	4-methylhexan-2-amine	Geranamine
Geranium oil	2-aminoisoheptane	Geranium extract
Geranium stems and leaves	Metexaminum	Methexaminum

This use of different terms is not only made to fool authorities but also the consumers, making it so that even those who are careful and check the label for banned substances, such as 1,3-DMAA, are not able to identify them [4,14,18]. This is not exclusive to 1,3-DMAA, as it has been evidenced for other substances; for example, caffeine can also appear under other names such as 1,3,7-trimethylxanthine, to mislead consumers [4,12].

Despite being banned in several countries, 1,3-DMAA is still found in supplements, as evidenced in the United States in the period from 2017 to 2021 [19]. A study carried out in Norway about doping in athletes found a case of the use of 1,3-DMAA as recently as 2020 [16]. In a study in Brazil, in 108 supplements seized by the Brazilian Federal Police, 1,3-DMAA was found to be present in 20% of them [20], and in Italy, 1,3-DMAA was reported to be present in 1 of 12 supplements tested in 2015 [21]. A study in the United States showed that there was a significant number of weight loss supplements that contained either banned or discouraged substances by the FDA, including 1,3-DMAA [4]. They were shown to also be accessible in Northern Ireland [22]. In 2014, a study analyzed supplements sold in webstores targeting the Dutch market, and found that six products contained 1,3-DMAA [23]. Finally, according to wastewater-based epidemiology (WBE), 1,3-DMAA was identifiable in Athens (Greece) in 2017 [24], and in Bristol and London (United Kingdom) in 2014 [25]. At a satellite laboratory facility that carried out the doping testing at the XXII Winter Olympic and XI Paralympic games in Sochi in 2014, four cases of doping were positive for 1,3-DMAA [26]. Given that the use of 1,3-DMAA is still a reality, this work aims to fully review the clinical and forensic aspects of 1,3-DMAA, focusing on the chemistry of the molecule, pharmacokinetic, pharmacodynamic and abuse potential.

2. Methodology

For the purpose of this review, a search for articles was performed using PubMed, Scopus and Web of Science, in which there was no limiting period or exclusion based on language. The following terms were used: 1,3-dimethylpentylamine, 4-methylhexan-2-amine, methylhexaneamine, 2-amino-4-methylhexane, 1,3-dimethylamylamine, 4-Methyl-2-hexylamine, methylhexanamine, 4-methyl-2-hexanamine, geranamine and 1,3-DMAA. The retrieval of articles was carried out by an analysis of their abstracts, and afterwards,

in a second phase, a read of the full article, should they have not been excluded in the first phase. In both phases, the inclusion criteria took into account the legal, laboratorial, clinical, ethical, pharmacokinetic, pharmacodynamic, forensic and safety aspects related to 1,3-DMAA. Furthermore, additional articles, which were deemed pertinent to this review, were included upon review of the references of the previously included articles.

3. Chemical Structure of 1,3-DMAA

1,3-dimethylamylamine (1,3-DMAA, Figure 1) is a simple straight chain aliphatic sympathomimetic amine, with two chiral centers, which in turn result in four possible stereoisomers, with two pairs of enantiomers and two diastereomers [27,28]. 1,3-DMAA has two methyl groups, one at C1 and the other at C3 carbon positions, which results, if racemic, in a double chromatographic peak in mass spectrometry, each peak for each diastereomer [27].

Figure 1. 1,3-Dimethylamylamine chemical structure. Chiral centers are denoted with asterisks (*).

4. Natural or Synthetic Origin of 1,3-DMAA

Manufacturers have implied that 1,3-DMAA can be found naturally in the plants from the Geraniaceae plant family, which includes both pelargonium and geranium [29]. The claim that 1,3-DMAA was found naturally was first published in 1996, in which geranium oil extracted from *Pelargonium graveolens* was evidenced to contain >0.7% of 1,3-DMAA through gas chromatography and mass spectrometry analysis [30]. However, due to the lack of transparency in their methodology, as was well as the absence of the description of the appropriate confirmatory test [30], this result has been brought into question, with several authors demonstrating by different analytical techniques (namely, chromatographic ones) that 1,3-DMAA does not have a natural origin due to its inexistence in several geranium (pelargonium and geranium) plant samples and/or essential oils [29–37]. However there were also studies that found the presence of 1,3-DMAA in plant samples and essential oils [38,39], but, upon reviewing this subject, Pawar and colleagues [1] pointed out that the integrity and the chain of custody of the geranium plant samples and essential oils was not satisfactory in these studies, and that despite the use of valid methods, these were not independently verified, which takes away from the ability to establish the presence of 1,3-DMAA in said natural sources [1]. It also should be noted that the studies that found 1,3-DMAA in natural sources received funding from USPLabs® (Dallas, TX, USA) [38,39], a supplement company that at the time sold products containing 1,3-DMAA.

Furthermore, it has been pointed out that the indication of the presence of 1,3-DMAA may be a result of mistranslation as the original text reports the presence of 2-hexanamide,4-methyl and 2-hexanamide,5-methyl, but the translation has these described as 4-methyl-2-hexanamine (1,3-DMAA) and 5-methyl-2-hexanamine [34,36]. The question of whether 1,3-DMAA is found in dietary supplements of natural origin pertains to the fact that in terms of regulations, substances that have a natural origin are not held to the same scrutiny as those that are synthetic [2]. Indeed, in spite of being first described as synthetic aliphatic amine, due to the later claim of being found naturally in a plant species, 1,3-DMAA was allowed to be released to the market by vendors without human testing [2].

From another perspective, even if 1,3-DMAA does occur naturally, the level at which it would occur in plants would be too low to explain the high levels found in dietary supplements, indicating that the 1,3-DMAA in dietary supplements would be synthetic [34,37]. Moreover, even if one was to agree that 1,3-DMAA can be found naturally, this does not automatically mean that the 1,3-DMAA present in dietary supplements comes from a natural source and not from spiking. This is why attention was given to the stereoisomeric composition of 1,3-DMAA [28]. As mentioned above, 1,3-DMAA is a chiral compound with two stereogenic centers that form a mixture of four stereoisomers (two pairs of

enantiomers) [27,28]. As such, natural plant-derived 1,3-DMAA would be expected to be enantiomerically enriched due to its asymmetric enzymatic process, while synthetic 1,3-DMAA would present racemic pairs of enantiomers, as well as a diastereomeric ratio characteristic in accordance with the synthetic process [28]. Studies investigating this question found that the diastereomeric and enantiomeric ratios of 1,3-DMAA evidenced in dietary supplements were the ones expected for synthetic 1,3-DMAA, which indicates that 1,3-DMAA found in dietary supplements is likely to be synthetic, and as such, it does not have a natural origin [27,28,34]. Comparison with the diastereomeric and enantiomeric ratios of 1,3-DMAA in geranium oils was not possible due to the absence of 1,3-DMAA in these [34]. In the studies in which 1,3-DMAA was identified in geranium plant samples and essentials oils, it was reported that their racemic profile of 1,3-DMAA was not the one expected for a natural source, but the one expected for a synthetic source, with racemic pairs [38] and the same diastereomeric ratio as the synthetic standard [39]. The authors proposed that this was an exception to the notion that, through the enzymatic process, compounds present in plants would have one chiral configuration, pointing to other reported examples [38]. As such, given that the racemic profile and diastereomeric ratio of 1,3-DMAA was the same across natural sources, synthetic sources and dietary supplements, it was suggested that the one present on the latter could have been sourced naturally [39]. However, no explanation for this was given other than that it was an exception to the rule, and so Pawar and colleagues [1] pointed out the necessity of further investigation, namely, the biosynthetic pathway of 1,3-DMAA in geranium plants so that it could be established if the said process could lead or not to a chirality similar between natural and synthetic 1,3-DMAA [1].

5. Pharmacokinetics

Data regarding the pharmacokinetics of 1,3-DMAA is very scarce with only a few articles that alluded to the subject being identified during the process of this review. We point out the study of Schilling and colleagues with only eight human subjects (all young healthy men) [40]. As suggested by other authors, this represents a very small sample, and as such, does not rule out interindividual differences in terms of pharmacokinetics [41]. Moreover, it was claimed that the study received funding from a company that at the time sold dietary supplements containing 1,3-DMAA [40]. Despite these shortcomings, the article is still pertinent given the scarcity of information regarding the pharmacokinetics of 1,3-DMAA.

5.1. Absorption and Distribution

The preferred route of administration is ingestion, with it consisting mostly of dissolving the powder containing 1,3-DMAA in a liquid and then ingesting it [42]. Nasal insufflation has also been reported to be used but is less preferred as users report a sensation of burning in the nasal cavities [42]. Another route is smoking, but users report that it produces less potent effects and that it can incinerate vapors in mid-air, making it less popular [42]. Intravenous administration has also been reported [43]. A scientific opinion [44], which analyzed data about the pharmacokinetics of 1,3-DMMA, evidenced an adequate but slow absorption when taken orally [44]. The 25 mg dose of 1,3-DMAA led to an oral volume of distribution of 235.95 $\pm$ 37.82 L [40].

5.2. Metabolism and Interactions

It was reported that 1,3-DMAA is hardly metabolized, with most of the 1,3-DMAA being recovered upon excretion in its original form [44]. 1,3-DMAA has also been characterized as a strong inhibitor of CYP2D6 but not of CYP3A4 [45]. CYP2D6 is known to be responsible for the metabolism of about 25% of all drugs (e.g., antidepressants, antipsychotics, β-adrenoceptor antagonists, antiarrhythmics or analgesics), and as such, its inhibition would lead to their accumulation in an individual's system, and to harmful clinical and forensic consequences [45].

5.3. Excretion

In a study reviewing DARTS-MS methods, a volunteer ingested a dietary supplement containing 1,3-DMAA (Ripped Juice EX2®), and its levels were accessed in multiple samples of urine with a peak observed within 2 h of the ingestion, as well as a relative abundance of ≥1% of 1,3-DMAA in the urine at different times of collection and analysis, over a period of 48 h after ingestion [46]. In another study, two human subjects consumed a dietary supplement known to contain 40 mg of 1,3-DMAA, with it being excreted in urine unchanged for 80 to 105 h post-intake [47]. Despite the excretion of 1,3-DMAA being prolonged in time, the concentration in urine peaked at 4 h post-intake with 18 µg/mL (18,000 ng/mL), with levels at 50 h post-intake being between 500 and 2000 ng/mL, meaning that higher concentrations mean a more likely recent consumption, although these levels are specific for the 40 mg dose [47]. For a single dose of 25 mg of 1,3-DMAA, oral clearance was classified as 20.02 ± 5 L/h, and terminal half-life was determined to be 8.45 ± 1.88 [40]. An opinion article [44] pointed out that 1,3-DMAA excretion is very slow and this, coupled with the low metabolism, poses a problem as the daily intake of 1,3-DMAA may lead to a buildup and consequently lead to stronger pharmacological effects [44]. 1,3-DMAA was still detectable in a urine sample collected 29 h post-ingestion [36].

6. Pharmacodynamics

When 1,3-DMAA was first introduced to the market, animal tests showed that its vasopressor effects were 3.5 times stronger and more prolonged than those of epinephrine, and that it had a systemic toxicity higher than ephedrine and lower than amphetamines [3]. With 1,3-DMAA being viewed as a lookalike of other stimulants also gives it potential effects such as raising the metabolic rate and the risk of metabolic hyperthermia [48].

1,3-DMAA is an indirect agonist of noradrenaline (NA) due to its capability to inhibit NAT, the reuptake transporter of this neurotransmitter [49–51]. 1,3-DMAA was also shown to have no effect over the dopamine transporter (DAT), serotonin transporter (SERT) [49,50] and trace amine-associated receptor 1 (TARR1) [49]. In a study carried out in rats, it was identified that 1,3-DMAA caused a rise in heart rate, a vasopressor response, elevated blood pressure and small tonic contractions in rats' vas deferens [52]. The effects of 1,3-DMAA were reduced upon sympathectomy, which is in accordance with the belief that 1,3-DMAA's effects are those of an indirect agonist of adrenoceptors [52].

7. Effects of 1,3-DMAA

Self-reported symptoms associated with the consumption of 1,3-DMAA products included tachycardia, dizziness, tremors, palpitations, chest pain, headache and numbness/tingling [53]. Lieberman and colleagues [53] suggested that at least some of these symptoms may increase the popularity of 1,3-DMAA as the development of perceptible physiological changes may lead users to believe that supplements containing 1,3-DMAA are more effective than most other dietary supplements that do not produce any discernible physiological change. Others consumers have self-reported feeling cold, fatigued and lightheaded, with facial and nasal paresthesia ("tingly") [54].

In a scientific opinion [44], the authors estimated the pharmacological effects of 1,3-DMAA and dose threshold necessary for their onset by comparing 1,3-DMAA to other sympathomimetic amines. Regarding cardiac effects, such as tachycardia, a dose of 50 mg propylhexedrine was estimated to be the equivalent to 50–75 mg of 1,3-DMAA [44]. Effects upon blood pressure were estimated by comparing 1,3-DMAA with ephedrine and propylhexedrine, both raising blood pressure, with an oral dose of 25–60 mg of ephedrine or 97 mg (free base) of propylhexedrine being estimated to be the equivalent to about 100 mg of 1,3-DMAA [44]. Finally, taking a look at the effects on the respiratory tract, 1,3-DMAA was compared to ephedrine, which can alleviate nasal congestion and act as a bronchodilator, with it being estimated that an oral dose of 15–60 mg ephedrine was the equivalent to 4–15 mg 1,3-DMAA [44].

7.1. Consumption with Caffeine

Given that in most supplements containing 1,3-DMAA, caffeine is also present, it is important to understand the effects of taking the two in combination. Indeed, the consumption of 1,3-DMAA in combination with other stimulants found in dietary supplements may end up acting synergically and lead to an increase in the risk of adverse effects [4], due to them generating a stronger stimulant effect as well as the lowering of the dosage necessary to cross the threshold for such events, with the critical dosage for toxicity in the combinations being unknown [3]. Individually, consumption of caffeine in amounts higher than 500 mg are viewed as having a higher potential to lead to adverse effects [12], while the consumption of a dose of 1,3-DMAA higher than 100-200 mg is expected to also lead to severe adverse effects [44]. The self-reported effects when ingesting a combination of 1,3-DMAA and caffeine were lack of appetite, feeling very "awake" or lightheaded, labored breathing, feeling that ears had "stopped up", "buzzed", chest tightness and clearing up of the nose [54]. In another study, participants self-reported a heightened sense of focus and energy, being talkative, a perception of improvements in workouts, sleeplessness, shakiness, anxiety, chills, sweating, nausea, tingling, headaches, feeling jittery and fatigue [55].

7.1.1. Human Testing with 1,3-DMAA and Caffeine Alone or in Combination

A study was performed in humans (five men and five women) to investigate the effects of 1,3-DMAA (50–75 mg) with caffeine (250 mg), alone or in combination, with each participant taking a single dose of each scheme over 5 different days [54]. Overall, this study found that heart rate, and plasma norepinephrine and epinephrine did not present a significant change with any of the schemes [54]. The schemes with 1,3-DMAA showed an increase in both blood pressure and rate pressure product (RPP), with the scheme that led to the highest percentage change in these parameters being the combination of 250 mg caffeine and 75 mg of 1,3-DMAA at 60 min [54]. Furthermore, the increase in the evaluated parameters, especially in the case of systolic blood pressure, when comparing the 50 mg scheme to the 75 mg scheme of 1,3-DMAA, seems to indicate that the effects of 1,3-DMAA are dose-dependent [54]. It was also concluded that gender did not lead to different outcomes [54].

Another study was carried out in humans (both men and women) in which 1,3-DMAA (1 mg/kg) and caffeine (4 mg/kg) were administered alone or in combination (plus 30 g of carbohydrate), and after an hour, this was followed by a 10 km run [56]. Overall, there was no improvement in exercise with some subjects self-reporting a feeling of euphoria that they considered a hinderance [56]. A rise in glycerol and free fatty acids (FFA) was noted post-exercise, with the consumption of 1,3-DMAA having the greatest increase in these parameters, which the authors attributed to the effects of 1,3-DMAA as a NET inhibitor, as NE has been described as influencing lipolysis through its effects on hormone sensitive lipase [56]. A condition effect was noted for trolox equivalent antioxidant capacity (TEAC) with the placebo showing higher antioxidant capacity than caffeine alone or in combination with 1,3-DMAA [56]. Systolic blood pressure for caffeine and 1,3-DMAA alone was statistically significantly higher than the placebo and the combination of the two [56].

A study was carried out in healthy men to understand the effects of 1,3-DMAA (50 mg) with caffeine (250 mg), alone or in combination for 12 weeks, with none of the evaluated outcomes having a significant change [57]. However, despite not being statistically significant: an increase in heart rate, and subsequently for rate pressure product, was identified in the 1,3-DMAA condition; an increase in resting respiratory rate was discovered for the combination of 1,3-DMAA and caffeine; a decrease in C-reactive protein was identified for both 1,3-DMAA alone or in combination with caffeine; and an increase in advanced oxidation protein product was evidenced in 1,3-DMAA and caffeine when taken alone [57]. The authors of the study also admitted that one of the major limitations of this study was the recruitment of only healthy young men (n = 50), making it unable to extrapolate its results to the general population, as well as it being a small sample size [57].

7.1.2. Human Testing with Dietary Supplements Containing 1,3-DMAA and Caffeine

Another study (25 young men) investigated the effects of ingesting dietary supplements containing 1,3-DMAA and caffeine (Jack3d) over a period of 10 weeks, 30 min before exercising, with an average of 4 day per week of exercising [58]. Overall, it was found that there was no significant change in blood pressure (increase systolic blood pressure = 6 mmHg; decrease in diastolic blood pressure = 4 mmHg) or heart rate (decrease of 3 bpm); however, there was a significant effect with the decrease in low-density lipoprotein cholesterol (7 mg/dL) [58]. An increase in creatinine was also noted; however, the authors pointed out that this substance was present in the dietary supplement [58]. The researchers set the criteria for the amount of dietary supplement by the participants as being between 1 and 3 servings, with on average there being a consumption of 2.4 ± 0.3 servings [58].

Another study was conducted with healthy men and women, to evaluate the effects of acute consumption of two capsules of OxyELITE Pro®, which contained 1,3-DMAA and caffeine, among other substances, with analysis being performed up to 2 h after ingestion [59]. The results showed an increase in plasma glycerol, free fatty acid and metabolic rate; however, as the authors pointed out, this could be attributed, in part, to 1,3-DMAA but also to caffeine and other substances present in the supplement [59]. An increase in blood pressure, namely, systolic blood pressure ($p = 0.0001$), heart rate ($p = 0.02$) and rate pressure product ($p = 0.002$), was also evidenced, and is in accordance with that expected for stimulants such as 1,3-DMAA and caffeine [59].

Yet another study was carried out, this time comparing two dietary supplements containing 1,3-DMAA (e.g., OxyELITE Pro® and Jack3d®, from USPlabs, Dallas, TX, USA), with the duration of 2 weeks and intake of two servings occurring every day, in young men and women [55]. Appetite was significantly lower with OxyELITE Pro® but not Jack3d®, while fasting glucose was significantly higher with Jack3d® but not with OxyELITE Pro® [55]. No other significant effects were identified, such as heart rate, blood pressure, rate pressure product, complete blood count and lipid panel, when comparing day 1 to day 15 for both supplements [55]. When evaluating the immediate effects upon intake of supplements, it was identified there was an increase in systolic blood pressure and a decrease in diastolic blood pressure and rate pressure product, although the only change that was statistically significant was that of systolic blood pressure with OxyELITE Pro® [55].

The effects of OxyELITE Pro® were also evaluated in trained young men and women, with the dietary supplement being consumed daily for a total of 8 weeks, beginning with one capsule during the first 3 days, and if that was tolerated, then taking two capsules, if tolerated, with not return to one capsule [60]. In the group taking the supplements, 11 took two daily capsules and 5 took one daily capsule, reporting sleeplessness and jitteriness as the causes to revert to a single daily capsule [60]. The results showed that when comparing pre- to post-intervention, the group taking the supplement had a significant decrease in body weight, BMI, waist circumference, waist/hip ratio, total body fat percentage, fat mass, fat free mass, skin fold thickness and appetite, and a significant increase in heart rate and total cholesterol [60]. Both the placebo and supplement showed that, when comparing pre- and post-intervention, both had a significant increase in HDL-C and malondialdehyde, and a significant decrease in LDL-C/HDL-C ratio and total cholesterol/HDL-C ratio [60]. No significant alterations were noted in the liver enzymes, and an interaction effect was noted for monocytes, with levels higher after the intervention for the supplement condition [60].

Another study, carried out by a different team of researchers, investigated whether the consumption of a supplement containing 1,3-DMAA and caffeine (Jack3d®) could improve neurocognitive measures in such a way as to mislead doctors performing concussion management using tools such as Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT), with results showing a faster reaction time and higher score for the cognitive efficiency index, with improved memory and visual processing speed [61]. As such, the authors recommended that doctors performing the management of concussions should question the use of dietary supplements as well as the consumption of stimulants, as

the effects of these may lead to premature return-to-participation in athletes [61]. However, the authors noted that the study was carried out in healthy participants, and as such, there is no guarantees that the same effects would be observed in patients with concussions, and despite there being significant differences, there is no guarantees that these would end up swaying doctors to the wrong decision [61].

8. Critical Look at Human Studies Funded by the Industry

A considerable portion of the experimental studies that investigated the effects of 1,3-DMAA in humans were in fact carried out by a particular group of researchers, with the majority of these studies being funded wholly or in part by a company that sold dietary supplements that contained 1,3-DMAA [15], and such is the case for the studies just referenced. Overall these studies have been criticized for the lack of transparency in the recruitment strategy [15], as well as the small size of the sample [15,41,62] with no power calculation [15]., Furthermore, the samples consisted mostly of healthy trained young men and sometimes women [15] when dietary supplements are used by the population in general, and as such, it is not possible to extrapolate the results of these studies into the general population [57,58]. The fact that the individuals were trained could also influence the results of the outcomes evaluated. The duration [62] and the frequency of administration was also not optimal to understand the eventual build-up effect given the slow rate of metabolism and excretion of 1,3-DMAA [44], which would be important given that dietary supplements are taken chronically. Another shortcoming was the fact that in the studies in which dietary supplements were ingested, the quantities of 1,3-DMAA, caffeine and other substances present in each serving were not reported [41,62].

Unfortunately, the evidence of the effects of 1,3-DMAA alone or in combination with caffeine were not consistent in these studies, with different studies reporting different outcomes, and not allowing a concrete conclusion to be reached. This could be due to the different study design and interventions, as well as due to the small samples used, which do not allow interindividual differences in terms of pharmacokinetics to be ruled out [41], as well as the opting for young, trained, healthy subjects.

8.1. In Vitro Testing

In vitro studies evidenced the absence of genotoxic or mutagenic effects of 1,3-DMAA either alone or in combination with caffeine [63]. On the other hand, 1,3-DMAA, especially in high doses, both alone and in combination with caffeine, caused a decrease in cell viability, and an increase in LDH level, mitotic index and oxidative stress [63]. Vascular irritant effects were also noted for 1,3-DMAA both alone or in combination, with the authors pointing out that these were dose-dependent and exacerbated by the combination, which translated into potential negative effects upon the vascular system [63]. In another study, human rhabdomyosarcoma cells were used to investigate the effects of dietary supplements (one of them OxyELITE Pro®), with different doses being administered (high dose 90 µg/mL; low dose 45 µg/mL) for over a period of 24 h [64]. It found that OxyELITE Pro® in both dosages was capable of inducing peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1α, which in turn resulted in a rise in mitochondrial biosynthesis and consequently increased mitochondrial content [64]. The authors do refer to the fact that they had evidenced this effect previously on caffeine, and as such, given that this substance is present in the supplement in question, it may be the cause for these changes [64]. In matters related to metabolism, OxyELITE Pro® administration in a high dosage led to a significant increase in glycolytic, oxidative, basal and total metabolism, with caffeine also already having been evidenced as increasing the metabolic rate [64]. The authors also admit that one of the limitations of the study was the use of cancerous cells, whose metabolism differs from that of noncancerous-cells [64].

8.2. Animal Studies

Another study was carried out in rats, with the administration of OxyELITE Pro® in the equivalent doses to 1, 3 or 6 capsules in humans, over a period of 4 weeks (the dose equivalent to 1 capsule was only consumed acutely) [65]. In this study, it was found that acute OxyELITE Pro® caused an improvement in the exercise test, but after 4 weeks of consumption, a negative effect on exercise capacity was evidenced, while at 4 weeks an antioxidant effect and a decrease in expression of PGC-1α mRNA was also noted [65]. No effects were identified in the inhibition of appetite, weight loss, liver injury markers or skeletal muscle total mitochondria amount [65].

Yet another study was carried out in rats, with a single administration of OxyELITE® Pro, with two different formulations being used, one containing 1,3-DMAA and the other not, in such a way that the following schemes were used: the human equivalent of three capsules without 1,3-DMAA, the human equivalent of three capsules with 1,3-DMAA (the maximum dose recommend by the manufacturer) and the human equivalent of six capsules with 1,3-DMAA [66]. The purpose of this study was to evaluate the alterations in systolic blood pressure, diastolic blood pressure, mean arterial pressure, heart rate and rate pressure product. In the case of the dosage equivalent to six capsules with 1,3-DMAA, it was evidenced that all parameters evaluated were significantly elevated, for a considerable amount of time, when comparing pre- and post-ingestion results: SBP, HR and RPP from 5 min until 90 min post-ingestion, and DBP and MAP from 5 min until 60 min post-ingestion [66]. This scheme also presented statistically significant increases when compared to a placebo in DBP and MAP at 30 and 60 min, as well as for rate pressure product at 60 and 90 min [66]. When it came to the dosage equivalent to three capsules with 1,3-DMAA, it was evidenced that several parameters were significantly elevated, although for a shorter amount of time overall, when comparing pre- and post-ingestion results: systolic blood pressure, diastolic blood pressure and mean arterial pressure for the 5 min post-ingestion, heart rate from 30 min until 90 min post-ingestion and rate pressure product from 5 min until 90 min post-ingestion [66]. Given that the effects were weaker and less prolonged in time with the administration of the dosage equivalent to three capsules when compared to the six capsules, it suggests that the effects were dose-dependent [66]. When it came to the scheme of three capsules without 1,3-DMAA, no statistically significant changes were evidenced in any of the parameters evaluated, which could point to the fact that despite the supplement containing multiple substances, the effects observed were due in part to 1,3-DMAA and/or its potential synergistic effects (caffeine concentration was equal in the capsules with and without 1,3-DMAA) [66].

9. Adverse Effects

As previously said, in a study in rats, 1,3-DMAA caused a rise in heart rate and a vasopressor response, elevating blood pressure, and that these effects were indirect as evidenced by the reduction in the effects upon sympathectomy [52] and this elevation of blood pressure could lead to cardiovascular events [67]. Individuals who practice intensive exercise may be at greater risk of harmful effects through the cardiovascular system [15]. There is the risk that 1,3-DMAA could lead to exertional heat stroke, with this potentially being achieved by several mechanism as referenced by O'Connor [48]: "Increasing cardiovascular strain from vasopressor effects; impairing thermoregulation by adversely affecting skin vasodilation to facilitate conduction; increasing catecholamine secretion, lipolysis, and metabolic rate; and diminishing the athlete's sense of fatigue as a central nervous stimulant to perpetuate a continued "pushing," when they should be cutting back" [48].

With 1,3-DMAA being viewed as a lookalike of other stimulants [48], it is possible, that given that amphetamines in combination with creatinine have been described as increasing the risk of dehydration and heatstroke (shift of the water from the extracellular space to muscle cells), the same relationship may occur between 1,3-DMAA and creatinine [3].

This is relevant as certain dietary supplements that contained 1,3-DMAA also contained creatinine such as Jack3d® [55].

9.1. Consumption of 1,3-DMAA Party Pills

In association with the consumption of party pills containing 1,3-DMAA, there have been reported cases of brain hemorrhages in New Zealand [7]. The characteristics of these brain hemorrhages were in accordance with what is expected in a hemorrhage due to amphetamines (mostly intracerebral or both intracerebral and subarachnoid, and preferably restricted to the frontal lobe and sometimes in the basal ganglia) [7]. The patients reported taking the party pills and developing symptoms after 30–60 min, such as vomiting, dizziness, agitation, severe headaches, focal neurological deficits and denied head trauma [7]. During their stay at the hospital, computerized tomography scans were performed, and the cerebral hemorrhages confirmed, and DMAA levels were accessed with the following levels being detected: Patient 1—1.09 mg/L—100 min after ingestion; Patient 2—0.76 mg/L—17 h after ingestion; Patient 3—2.31 mg/L—2 h after ingestion [7]. It is notable that some patients reported the taking of other substance such as alcohol and these party pills often contain other substances such as caffeine that provide an additive effect to 1,3-DMAA [7]. It was theorized by Gee and colleagues that these events happened due to a spike in blood pressure, although in patient 2, doubt arose if the hemorrhage was due to vasculitis or vasospasm, with a conclusion not being reached due to the necessity of histology to differentiate between them [7].

Some of these authors had already published another case report of cerebral hemorrhage in a 21-year-old patient who had consumed two tablets of 1,3-DMAA (278 mg per capsule) and another of caffeine (150 mg) [6]. Thirty minutes after consumption there was an onset of a severe headache, confusion, urinary incontinence and vomiting, and later, drowsiness, slurred speech and focal neurological deficits [6]. Following the lack of improvement in his condition, he was brought to the hospital with the realization of a CT revealing a large hemorrhage at the left basal ganglia, which conditioned a 5 mm midline shift [6]. Other neurological deficits were evidenced, and a cerebral angiogram excluded other potential causes of cerebral hemorrhage, leading to the proposal of 1,3-DMAA as being the probable cause [6].

9.2. Consumption of Dietary Supplements Containing 1,3-DMAA

The general practice by the supplement industry to produce products containing multiple substances makes it difficult to attribute specific effects caused by the supplement to one of them [68], and as such, the case reports that were referenced regarding the use of supplements containing 1,3-DMAA only give us an idea of the potential effects of 1,3-DMAA, with additional studies being necessary to confirm these effects [69]. However, it is still important to discuss them here as 1,3-DMAA is mostly consumed as a constituent of these products. Dietary supplements containing 1,3-DMAA are reported to contain, in general, somewhere between 25 and 65 mg of this substance [44], although there have been cases that evidenced levels as high as 285 ± 51 mg per serving [34]. The presence of other substances also allows us to theorize about the interaction between such substances and 1,3-DMAA.

9.2.1. Cardiac Arrest

A case was reported of a 21-year-old male, without relevant past history, who went into cardiac arrest while training at the gym, with a story of the consumption of a supplement containing 1,3-DMAA for the first time [70]. In a complementary diagnostic test, the electrocardiogram showed diffuse ST-segment elevation without QT prolongation, the computerized tomography and magnetic resonance showed evidence of hypoxic–ischemic injury of caudate and lentiform nuclei and the cardiac MR showed no structural or perfusion deficits, with a Left Ventricular Ejection Fraction (LVEF) at 35% on the second day, rising to 65% by the fourth day [70]. Urinalysis was positive for amphetamines, and upon further

testing by gas chromatography/mass spectrometry (GC/MS), this was found to be a false positive, something that can occur with 1,3-DMAA, with other substances known to cross-react with the amphetamines' immunoassay being excluded [27,70]. The patient denied consumption of other substances, with urinalysis also being negative [70]. The patient recovered after 4 months and denied any lasting deficits [70]. The plasma levels of 1,3-DMAA were not reported.

Another case was reported of a female who went into cardiorespiratory arrest during the running of a marathon, with no prior relevant medical history, and family reporting the consumption of two scoops of Jack3d®, known to contain 1,3-DMAA, dissolved in a bottle of water [43]. The runner ended up passing away with postmortem evaluation detecting 1,3-DMAA in a whole blood sample, with the level being lower than those reported in other cases [43]. Upon examination of the heart, no morphological or histologic abnormalities were noted, and no evidence was found of coronary artery spasm, myocarditis, myocardial fibrosis, familial "channelopathies", exercise-related hyponatremia, hyperthermia and conduction system and myocardium abnormalities [43]. The conclusion was that the cause of death was acute cardiac failure (presence of markedly edematous lungs, with validation by histology), caused by the overt physical exertion of running 25 miles of the marathon in combination with the consumption of the supplement containing 1,3-DMAA [43].

Another series of case reports referenced the deaths of military members [3]. One of these was of a 22-year-old male, without any prior relevant medical history, who had been taking a supplement containing 1,3-DMAA for 4 weeks, within the recommended dose, that began with leg cramps during training, and then went into cardiac arrest [3]. Upon examination, the patient had hyperthermia (40.8 °C), renal insufficiency, anion gap metabolic acidosis and elevated cardiac and muscle enzymes [3]. Despite the best efforts of the medical team, the patient passed away after 4 h, and the autopsy pointed to shock and heat stroke, although the environmental conditions alone did not explain such a condition [3]. The plasma level of 1,3-DMAA was 0.22 mg/L and caffeine was 2.9 mg/L [3]. The other case was of a 31-year-old female, with a history of mild obesity and sickle cell trait, who, during training, began to feel dyspnea and leg cramps and afterwards went into cardiac arrest [3]. Upon examination, the patient was in shock, was hypotensive, tachycardic, and hyperthermic, and had renal insufficiency, anion gap metabolic acidosis and liver dysfunction, with her later developing rhabdomyolysis, pancreatitis, disseminated intravascular coagulopathy and pulmonary edema, and needing a liver transplant [3]. As with the previous case, the environmental conditions alone did not explain such a condition [3]. Upon investigation, two supplements containing 1,3-DMAA were found in the patient's car, and on the fourth day of the hospital stay, the plasma level of 1,3-DMAA was 0.04 mg/L and caffeine was 1.9 mg/L [3]. The patient ultimately passed away from refractory sepsis [3].

9.2.2. Cerebral Hemorrhage

A 26-year-old, with no prior relevant medical history, presented with a severe headache after taking three scoops of Jack3d® (the maximum dose recommended for a period of 24 h), a dietary supplement containing 1,3-DMAA as well as caffeine, that he had started taking 3 weeks before, followed by his habitual weight-lifting exercise [10]. Computerized tomography revealed a right midbrain–thalamic hemorrhage, and together with the neurological deficits present, the patient was diagnosed with Dejerine–Roussy syndrome (i.e., condition developed after a thalamic stroke) [10]. There was also a small patent foramen ovale and an elevation of hepatic transaminases [10]. The plasma level of 1,3-DMAA was not reported. Another case of cerebral hemorrhage was reported in which a 37-year-old man, following the consumption of a dietary supplement containing 1,3-DMAA for 3 days, presented with acute dysarthria, left hemiparesis and gait impairment, with the onset of these symptoms occurring after sexual intercourse [71]. Computerized tomography evidenced an acute hemorrhage in the right lentiform nucleus and internal capsule, and blood pressure was 192/132 mmHg [71].

9.2.3. Non-ST-Elevation Myocardial Infarction (NSTEMI)

Another case was reported of a 22-year-old who, despite having no relevant past medical history, presented with an NSTEMI [68]. The patient admitted to taking two dietary supplements, one containing 1,3-DMAA (Jack3d®) and another containing citrus aurantium (Phenorex), for 3 weeks [68]. Citrus aurantium is also known to have sympathomimetic properties, and as such, it together with 1,3-DMAA may have acted synergistically, and through vasoconstriction and/or plaque rupture and subsequent thrombosis, led to the adverse cardiac event [68].

9.2.4. Other Adverse Effects

A case report of an adolescent who had hypertension for over 3 years (162/90 mmHg in the last evaluation) admitted to consuming supplements containing both caffeine and 1,3-DMAA, as well as ingesting one to two caffeinated drinks a day [67]. One month after stopping the intake of supplements his blood pressure had lowered to the 120 s/70 s mmHg range [67].

A case was reported of a 20-year-old, with no prior relevant medical history, who presented with unilateral mydriasis of her right pupil, which was consequently directly and consensually nonresponsive to light, and showed no changes upon testing with pilocarpine. [72]. The patient admitted to rubbing her eye after handling Jack3d®, a supplement containing 1,3-DMAA, and was ultimately diagnosed with pharmacological anisocoria, after excluding other causes such as trauma [72]. Given sympathomimetics characteristics of the 1,3-DMAA, it is plausible that it could have potentially caused the pharmacologic dilation evidenced in this case [72].

Another case report was that of a 32-year-old sailor serving in the Navy Special Operations Forces (SOF) who developed atrial fibrillation with a rapid ventricular response during training, with it being reported that he had taken a supplement containing 1,3-DMAA earlier [73]. During his treatment and with the intent of heart rate control, it was necessary for the administration of an intravenous calcium channel blocker and β-blockers [73].

A case report also associated a dietary supplement containing 1,3-DMAA with necrotizing myopathy in a young woman who had been consuming the supplement for a period of one month before the onset of her clinical condition [74].

9.2.5. Potential for Causality

Overall, dietary supplements containing 1,3-DMAA have been linked to cardiac arrest and hypoxic–ischemic injury [70], acute cardiac failure due to extreme physical exertion [43], cerebral hemorrhage [10,71], hypertension [67], NSTEMI [68], exertional heat stroke [3], mydriasis [72], atrial fibrillation with rapid ventricular response [73] and necrotizing myopathy [74]. This does not mean that 1,3-DMAA was the cause of these situations, as case reports are not meant to establish causation but to allow for the development of a hypothesis, which can then be tested, functioning as a guide for research [69]. Another benefit of case reports is to flag for the potential harm of dietary supplements containing 1,3-DMAA [62]. Unfortunately, most of them did not report the plasma levels of 1,3-DMAA, which would be important to theorize about the potential for causation, as well as understanding the cut-off levels of 1,3-DMAA necessary for such severe adverse effects. In fact, as pointed out by Reedy and colleagues [75] from the Armed Forces Medical Examiner System (AFMES), in the case report by Eliason et al. [3], the levels detected (0.22 mg/L; 0.04 mg/L) were much lower than doses reported in other cases such as the ones of the cerebral hemorrhage reported by Gee et al. [7] (1.09 mg/L; 0.76 mg/L; 2.31 mg/L). A possible explanation is that the combination of 1,3-DMAA and caffeine, which when taken together may have the potential for synergic effects, might explain why, despite the lower plasma levels of 1,3-DMAA, the adverse events still end up manifesting [3].

9.3. Can 1,3-DMAA Cause Hepatotoxicity?

The fact that 1,3-DMAA is a sympathomimetic amine leads it to be grouped together with other sympathomimetic amines and it assumed to have the same potential adverse effects, such as hepatotoxicity [76]. There are case reports that link 1,3-DMAA to hepatotoxicity, with one example being a series of cases of seven members of the US military who developed hepatoxicity after taking OxyELITE Pro® [11]. Patients reported symptoms such as jaundice, pruritus, fatigue, exercise intolerance, steatorrhea, lethargy, abdominal pain/discomfort, headache and vomiting [11]. The duration of the consumption of the supplements varied between 1 week prior to the episode and 3 years [11]. Patients also referred to taking different daily doses, as well as taking other supplements simultaneously, including others containing 1,3-DMAA [11]. Markers of liver damage were altered, such as transaminases, INR and bilirubin [11]. Further exams were performed to exclude other causes for hepatotoxicity, with pathologies investigated varying between patients [11]. Two of the cases were so severe that a liver transplant was necessary [11]. Plasma levels of 1,3-DMAA were not reported. Some of the patients reported suspending the supplement after symptoms began; however, in some of these cases, symptoms did not alleviate [11]. Some patients had been taking 1,3-DMAA-containing supplements for years, with Case 3 taking several dietary supplements containing 1,3-DMAA for over 3 years, and only now developing this condition, which brings into question if these supplements were the cause of the hepatotoxicity, as drug-induced liver disease bases itself in a temporal relationship with the consumption of the substance and the onset of the condition [11].

One aspect that complicates the debate around whether or not 1,3-DMAA causes hepatotoxicity is the fact that OxyELITE Pro® altered its formula and substituted 1,3-DMAA for aegeline after the first one was banned (starting in May 2013), and when comparing the two, it shows that 2 in 13 confirmed known exposures to 1,3-DMAA resulted in liver disease, while 9 in 10 confirmed known exposures to aegeline resulted in liver disease, indicating that the new formula was probably more likely to result in hepatotoxicity [5], with a cluster of cases of hepatotoxicity in Hawaii following the consumption of OxyELITE Pro® starting in May 2013 when the change in the formula took place [5]. However, this does not exclude the possibility that the formula with 1,3-DMAA may also cause hepatotoxicity, as both formulas could lead to hepatotoxicity [5].

In a study that evaluated the different known pathways by which sympathomimetic amines are known to cause hepatotoxicity, such as: the "production of reactive metabolites, hyperthermia, increased neurotransmitter efflux, oxidation of biogenic amines, mitochondrial impairment and apoptosis", no evidence was found that 1,3-DMAA could cause hepatotoxicity by those same pathways [76].

As such, it is unlikely that 1,3-DMAA is the direct cause of hepatotoxicity, with other possible explanations being the coincidence with the taking of another substance or supplement that caused the hepatotoxicity as well as the presence of an undisclosed substance or contamination of the supplement. Another possible explanation could be the interaction of 1,3-DMAA with other substances, for example, through its inhibition of CYP 2D6, which could lead to the alteration of the pharmacokinetics of the said substances, which could cause hepatotoxicity [1,45].

10. Acute Intoxication and Treatment

A study investigated reports to poison centers in Texas (2000–2011), finding a total of 54 cases related to acute intoxication with products containing 1,3-DMAA (between 2010 and 2011), with the majority being due to OxyElite Pro® [77]. Symptoms were mostly cardiovascular, gastrointestinal or neurological with the most frequent being tachycardia, nausea, vomiting, agitation, irritability, tremor, abdominal pain, chest pain, dizziness, headache, hypertension, elevated creatine phosphokinase and numbness, with the majority of cases being reported as not serious [77]. Treatment varied with the methods used being dilution, food/snack, activated charcoal, benzodiazepines, intravenous fluids, cathartic, antiemetics and oxygen [77]. The majority of cases reported happened to children under

five who had inadvertently ingested the dietary supplement [77]. The explanation given by the authors was that, given the perception by the general population that dietary supplements are mostly harmless and safe, parents do not have the same reservations about these products as they have with medications [77].

Another report, this time based on New South Wales Poisons Information Centers (NSWPIC) data, told of 50 calls to this center related to 1,3-DMAA (between 2009 and 2012), reporting adverse effects with 16 due to recreational use and 33 for "therapeutic" use (1 case without information) [78]. The median age was 20 years, with 5 children being less than 3 years old. Multiple symptoms were reported with the most common being nausea, vomiting, palpitations, tachycardia, headache, anxiety, agitation, chest pain, sweating, dizziness, tremor, shakiness, hypertension, flushing, insomnia and CNS depression [78]. The case of a 2-year-old who ended up needing hospitalization and who was administered benzodiazepines for the control of their agitation and tachycardia was also reported [78].

If a patient presents with a severe headache and there is suspicion that there was the consumption of 1,3-DMAA, they should be evaluated with a cranial CT scan [7]. A possible scheme for treatment was described by Gee and colleagues [7]: the hypertension and agitation of the patient should be controlled with benzodiazepines as the primary line of treatment; a second line of treatment would be with calcium channel blockers or a titrated glyceryl trinitrate infusion; and nonselective β-blockers should not be administered in these cases due to the risk of unopposed α-agonism and its resulting vasospasm and paradoxical hypertension.

11. Potential for Abuse

As 1,3-DMAA has been reported as being consumed for recreational purposes, an important question is the potential that this substance has for being abused. A study carried out in mice, which sought to evaluate if 1,3-DMAA was liable for abuse, found that the substance could lead to locomotor depression, the substitution of a discriminative stimulus (fully substituting the discriminative stimulus effects of cocaine, and partial substitution for methamphetamine (77%)), conditioned place preference and rewarding effects similar to those of other abused psychostimulants [79]. As such, they reached the conclusion that 1,3-DMAA had the potential to be liable for abuse [79]. A study [42] was carried out with the purpose of understanding the knowledge that consumers possessed about 1,3-DMAA, as well as their experience when consuming it. Users said the main reasons for experimenting with 1,3-DMAA was their curiosity, the low price and the availability on the internet, where most acquired the substance, with some reporting the existence of impurities in some types of sources [42]. Forums contained information about the optimal dose for recreational use, 50 mg, and advertised the higher risk of adverse effects with doses higher than 100 mg [42]. Recreational use was reportedly not pleasurable, without any euphoria or mood lift, with users instead reporting a sensation of adrenaline rush, which led to agitation, irritation and anger that receded slowly, with dissociation, hallucination and synesthesia also being reported [42]. Users also described experiencing late negative effects that manifested after the initial aforementioned effects started to wane, such as nausea, vomiting, headaches, leg pain, paranoia, depression, panic attacks, loss of consciousness, enuresis, diaphoresis, fatigue, vertigo, atrial fibrillation, hypothermic reactions and intention to self-harm, with the effects being exacerbated upon redosing [42]. Positives effects were recognized in terms of sexual performance, and as a support for withdrawal from opiates and methamphetamines, and its combination with caffeine was described as a "pick me up" [42].

The locomotor depression evidenced in mice [79] is different from the reported energy boost reported in humans [42], and as such, these differences in responses to 1,3-DMAA in terms of locomotor activity may also mean that other effects of the substance upon mice, such as those that evidenced 1,3-DMAA's potential for abuse, might not be produced in humans. Given the few self-reported positive effects and the extensive negative effects,

which are exacerbated upon redosing, 1,3-DMAA is viewed as having low recreational value [42], which in turn lowers its potential for abuse.

12. Forensic Aspects and Doping

Athletes may unintentionally consume 1,3-DMAA due to the fact that its presence might not be disclosed in the label of the supplement, or due to it being given a different name from the one specified in the WADA Prohibited List [14]. Indeed, in 2017, 1,3-DMAA was found to have caused the most failed drug tests in athletes when compared to other stimulants [14].

Detection of the presence of 1,3-DMAA in supplements can be achieved through different methods, such as high-performance liquid chromatography with a UV detector (HPLC-UV) and liquid chromatography with mass spectrometry (LC–MS) [80], direct analysis in real-time tandem mass spectrometry (DART-MS/MS) [20], a combination of direct analysis in real time with a high-resolution quadrupole time-of-flight mass spectrometer (DART-QToF-MS) [33], ^{63}Ni ionization ion mobility spectrometry (IMS) and electrospray ionization–high-performance ion mobility spectrometry–mass spectrometry (ESI-HPIMS–MS) [81], ^{1}H nuclear magnetic resonance (NMR) spectroscopy [82,83], ultra-performance liquid chromatography–tandem mass spectrometry (UPLC–MS/MS) [29], derivatization with trifluoroacetic anhydride (TFAA) followed by gas chromatography–high-resolution time-of-flight mass spectrometry (GC-high-resolution-TOFMS) with soft ionization [84], among others. These techniques have been applied for different matrices, such as blood [3,7], dried blood spots [85], whole blood sample (postmortem) [43], urine [8,86] and exhaled breath [87].

It is important to be aware that 1,3-DMAA has also been found to be a major cause of amphetamine false positives by immunoassays [14,27]. In fact it was responsible for about 92.3% of false positive cases (the presence of 1,3-DMAA confirmed through LC–MS–MS analysis), with the remaining cases being caused by other substances known to cross-react with amphetamine immunoassays (phentermine, bupropion and its metabolites, pseudoephedrine), in a study conducted by the USA's Department of Defense [27]. Moreover, this is not a matter solely present in the military, as a case report identified this in the case of a healthy volunteer for a mental health study, whose urine tested positive for amphetamines, and who had taken a supplement containing 1,3-DMAA [88], and another instance in the case report previously mentioned [70]. As such, a certain degree of suspicion should be kept after a positive result for amphetamines, especially if there is a history of the consumption of dietary supplements and the patient belongs to one of the groups that are more likely to take these [88].

13. Conclusions and Future Perspectives

Despite its size and wide populational reach, the supplement industry is not held to high standards or regulations when it comes to the manufacturing and marketing of its products [9]. Physicians should remain alert for patients taking dietary or fitness supplements, as these may contain 1,3-DMAA or other substances without proper disclosure [14]. In particular, 1,3-DMAA is a strong inhibitor of CYP2D6 and therefore could have important interactions with antidepressants, antipsychotics, β-adrenoceptor antagonists, antiarrhythmics or analgesics [45]. It would be advised that individuals with hypertension avoid products containing 1,3-DMAA given the higher risk for adverse effects [54,59,66]. Dietary supplements should also be kept out of reach from children to prevent episodes of acute intoxications [77]. As it was the main purpose of this review to ascertain the clinical and forensic characteristics of 1,3-DMAA, the following Figure 2 seeks to consolidate the information gathered.

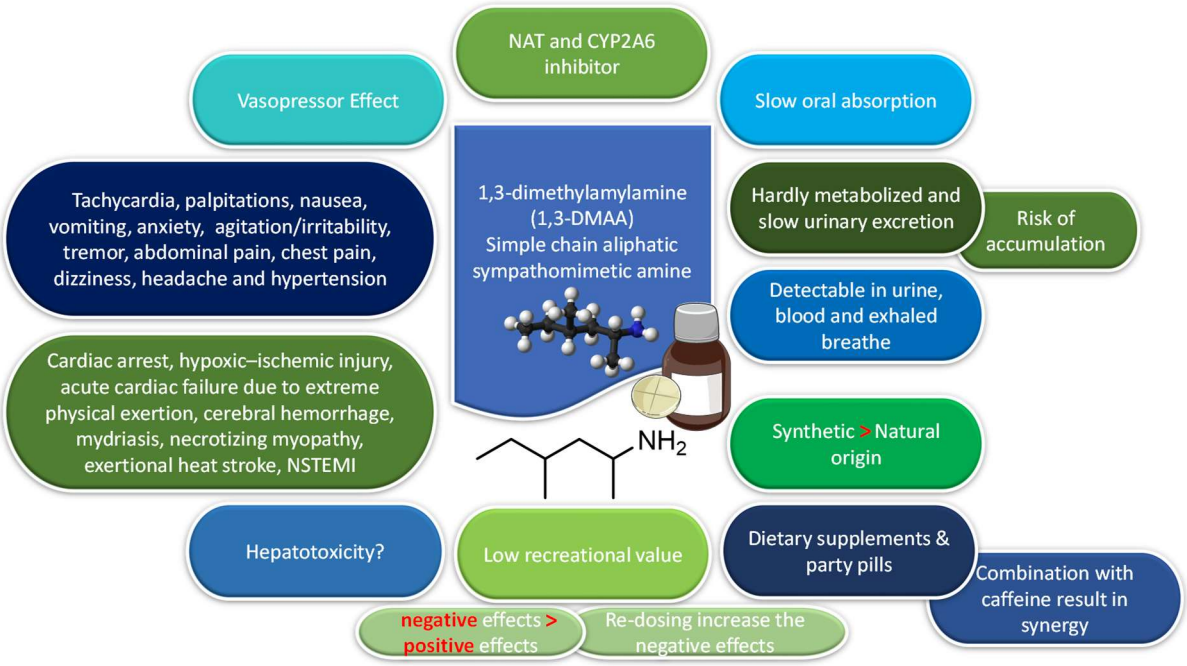

Figure 2. Main pharmacological, clinical and forensic aspects of 1,3-DMAA.

Even though it is important to inform and educate the population about the dangers of 1,3-DMAA, and how to avoid its unwitting consumption, the most important step is to up the regulation of the dietary supplement industry [9], as the current self-regulation measures for the production of nutritional supplements are not effective [23]. The current system in many countries puts a great burden upon the regulatory agency, and given the size of the industry, as well as the quantity of novel substances entering the market, proper oversight is not feasible [89]. Some solutions have been presented, such as the one advanced by Palmer [89] who suggested that all substances contained in supplements should be pre-approved regarding their efficacy and safety [89]. In this way, instead of the regulatory agency having to prove that a certain substance is dangerous to have it removed from the market, the seller has to be the one to demonstrate the safety and efficacy of the product before releasing it, passing the burden of proof to the latter [89]. In fact, in the USA, the FDA was able to ban 1,3-DMAA not because it proved its lack of safety, but because it successfully argued that 1,3-DMAA found in the supplements was synthetic and that it had not been registered as a new dietary ingredient (NDI) as was required by law [89]. In the case of the European Union (EU), its legislation is tighter than that of the USA, stipulating that active compounds require licensing as medicine [44]. However, this definition is more relaxed for food supplements, only applying to those that are pharmacologically effective [44]. In the case of 1,3-DMAA, it was estimated that products containing doses >4 mg of 1,3-DMAA are pharmacologically active and so should be required to be licensed as medicine [44]. Another action proposed by Cancio and colleagues [90] is the promotion of the sale of supplements with an independent third party certification, in regards to both purity and quality [90], as it was reported that only 12.1% of products had received third party certification, with 28.5% being only self-certified and 59.4% not certified [90]. Despite this, in the USA, it was found that 84% of consumers trust in these products' safety, effectiveness and quality [89].

On top of that, after the regulating agencies ban a certain dangerous substance, mainstream sellers switch to others, and in the case of 1,3-DMAA, some of the substances that came after were 1,3-dimethylbutylamine DMBA [22] and octodrine/2-amino-6-methylheptane (DMHA) [14]. As such, this turns into game of whack-a-mole. 1,3-DMAA itself came into the market to act as a substitute for ephedrine, which was banned in 2004 as a dietary supplement [2,89], and as party pills as a substitute for 3,4-methylenedioxymethamphetamine

and/or 1- benzylpiperazine, after these were also banned [7,91]. Unfortunately, the use of 1,3-DMAA has not been completely abandoned, with dietary supplements containing 1,3-DMAA still being available for purchase in webstores and other places, making 1,3-DMAA a relevant problem still.

Finally, further studies are needed to clarify the pharmacokinetics of 1,3-DMAA as the available information is scarce and the methods and conditions in which they were obtained are far from ideal. Moreover, most of the human testing was financed by the supplements industry and did not reach a consensus on the effects of 1,3-DMAA. They also had several problems in their methodology that bring in to question the validity and potential for generalization to the rest of the population, and as such, further study of the effects of 1,3-DMAA in humans is needed. When it comes to the interactions of 1,3-DMAA with other substances, most of the studies center around its combined intake with caffeine, while the potential with other substances remains mostly unexplored. It is especially important that these interactions are investigated as the dietary supplements that contain 1,3-DMAA tend to contain many other substances that could have the potential to increase the severity and likelihood of adverse effects.

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