National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

FRONT OFFICE FOOD AND PRODUCT SAFETY

Fact sheet DMAA, DMBA and DMHA in supplements

Risk assessment requested by:	Netherlands Food and Consumer Product Safety Authority
Risk assessment performed by:	RIVM
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Subject
At the Dutch market, several dietary supplements are sold that concentrate on weight loss, increasing performance and/or stimulating the libido. In many cases, these supplements contain pharmacologically active substances like DMAA, DMBA and DMHA to meet their target effect. Pharmacologically active substances in this type of supplements may pose a human health risk since it is often not known which substances are present in the supplement or in what quantity.
For enforcement purposes, a risk assessment is needed on possible health risks for Dutch consumers.

Question
Prepare a fact sheet for 1,3-dimethylamylamine (DMAA), 1,3-dimethylbutylamine (DMBA) and 1,3-dimethylhexylamine (DMHA, octodrine). The factsheet shall contain the following elements:

- If possible, a health-based guidance value
- Known synonyms of the substance
- Toxicology
- If present, known interactions with other substances
- When no information is available for risk assessment, what other substances can be used for read-across

Conclusions

- Health based guidance values: Based on the reported toxicology data, it is not possible to derive health-based guidance values for DMAA, DMBA and DMHA.
- Common names are listed in table 1.
- Pharmacology: The aliphatic amines DMAA, DMBA and DMHA are sympathomimetics and thus affect the sympathetic nervous system. Pharmacology data on sympathomimetics indicate pharmacological effects may result from oral doses of 4 mg daily.
- Toxicology: Given 1) the severe adverse effects reported after the use of DMAA-containing supplements; 2) the potential for misuse or abuse; 3) that these supplements are used by population groups that may have a higher risk on adverse effects (sportsmen and -women, obese persons) and 4) that the actual DMAA con-

tent may be higher than reported on the product information leaflets, the use of DMAA-containing supplements may result in severe health effects. It is noted that there is no information on toxicity of DMAA after long-term exposure or on developmental or reproductive toxicology and carcinogenesis. Further, in many countries DMAA-containing supplements are prohibited.

- Interactions: Cardiovascular effects of the aliphatic amines could cause hypertensive crises when consumed together with monoamine oxidase inhibitors, like caffeine. In general, an increase of the stimulating effects of DMAA, DMBA and DMHA is to be expected when these compounds are combined with other sympathomimetics and adrenergic components.

- Read across: For DMBA and DMHA no controlled safety and efficacy studies in humans are available in the public literature. However, these substances show structural similarity to and have a similar mode of action as DMAA. In addition, data on historical use of DMHA as a medicine to treat hypotension indicate that the potency of DMHA is within an order of magnitude of the potency of DMAA. Therefore, until new data are available, the conclusions reached for DMAA (see above) are used in a read-across approach to conclude that use of DMBA- and /or DMHA-containing dietary supplements may also result in severe health effects.

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1 Introduction

DMAA, DMBA and DMHA are pharmacologically active substances that are being used in dietary supplements that are taken to lose weight and increase performance.
In 2009, RIVM was asked to assess the pharmacological properties of DMAA (then referred to as geranamine) and isomers. Based on scientific literature and the fact that geranamine has been used as a medicine in the past, the conclusion was that geranamine in dietary supplements should be seen as a pharmaceutical ingredient (1). In 2010, RIVM was requested to derive a limit for oral exposure above which geranamine is assumed to be pharmacologically active. RIVM concluded that pharmacological effects at the lungs (bronchodilation) and the nasal mucous membrane could occur after an oral dose of 4-15 mg per day. Pharmacological effects on the heart are expected to occur after a dose of 50-75 mg, and on blood pressure after 100 mg. It was further noted that due to the long half-life accumulation of the substance with as a result an increased risk on or more pronounced pharmacological effects may occur when several doses are taken within 24-36 hours (2). In addition, in 2012 RIVM made an overview of studies in humans looking at the effects of the DMAA-containing supplements Jack3d™, OxyELITE Pro™ and DMAA (3).
In 2012, NVWA wrote an advisory report about the risk assessment of DMAA in dietary supplements, partly based on the RIVM advisory reports. The main conclusions were that dietary supplements containing DMAA should be seen as preparations containing active substances. Pharmacological and toxicological effects in humans may occur at single doses of 4 mg and higher, with severe adverse effects occurring from daily doses of 30 mg (4). Based on this report, the Dutch Health Care Inspectorate decided on 30 July 2012 that DMAA should be classified as a pharmaceutically active ingredient (4). The current fact sheet compiles the information known about DMAA and gives an update of the literature since 2012. Also, information about the structurally-related substances DMBA and DMHA will be presented, which have not been assessed before by RIVM.

2 Literature search strategy

Search strategies were developed to search the following databases: Medline and Embase (both via Embase.com), the Hazardous Substances Data Bank (HSDB) and Toxline. On the Embase.com data bank the substance name (including synonyms) was searched as keyword, to which subsequently the subheading(s) Adverse drug reaction and/or Drug toxicity and/or Pharmacokinetics and/or Pharmacology and/or Drug Safety were added. When this led to too many hits, the search was combined with the name of the substance in the title and/or by assigning ‘major’ to the keyword. When the substance could not be searched for as a keyword, all text fields were searched for the substance name. In addition, CAS numbers were used to find literature. To check whether all relevant references were found with this strategy, an additional search was conducted with the substance name as (major) keyword and/or the substance name in the title/abstract. The HSDB data bank was searched using the substance name and Toxline by CAS number.
In addition, the NVWA has provided a background document with information and references were added that were available from former projects on these substances.
In total, for DMAA, DMBA and DMHA, about 200 references were available.

3 Chemical structure and common names

1,3-dimethylamylamine (DMAA), 1,3-dimethylbutylamine (DMBA) and 1,5-dimethylhexylamine (DMHA) are all three aliphatic amines (Figure 1). The synthesis of DMAA, DMBA and DMHA is relatively easy and the synthesized products are widely used. All three aliphatic amines described in this fact sheet have been marketed as natural products, but scientific proof for these claims is not available.

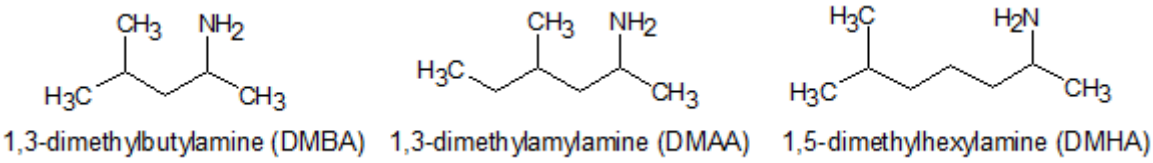

Figure 1. Chemical structures of 1,3-dimethylbutylamine (DMBA), 1,3-dimethylamylamine (DMAA), and 1,5-dimethylhexylamine (DMHA).

Many different trivial names have been reported. An overview of these trivial names can be found in Table 1.

Table 1. The different trivial names of DMAA, DMBA and DMHA.

DMAA	DMBA	DMHA
2-amino-4-methylhexane	AMP	2-amino-6-methylheptane
1,3-dimethylpentylamine	4-AMP	1,5-dimethylhexylamine
1,3-dimethylamylamine	AMP Citrate	6-methyl-2-heptanamine
1,3-dimethylpentylamine	4-AMP Citrate	6-methyl-2-heptylamine
Floradrene	Amperall	Octodrine
Forthan	2-amino-4-methylpentane	
Forthane	2-amino-4-methylpentane citrate	
Geranamine	4-amino-2pentanamine	
Geranium extract	4-amino methylpentane citrate	
Methylhexaneamine	4-amino-2-methylpentane citrate	
4-methyl-2-hexaneamine	1,3-dimethylbutylamine	
4-methyl-2-hexylamine	4-methyl-2-pentanamine	
	Pentergy	
	Nor-DMAA	

Aliphatic amines are known to cause vasoconstriction and affect cardiovascular activity, and are considered pressor amines because of these effects (1, 5). In the 1920's aliphatic amines gained interest when ephedrine, an extract from the Chinese herb *Ephedra spp* that shows pharmacological activity after oral consumption, was introduced (6). In 1944, Eli Lilly & Co patented the medical application of aliphatic amines as vasoconstrictors (7). DMAA is specifically described in the patent as a nasal decongestant. Several other aliphatic amines are available medicines for the treatment of for example migraine and for bronchodilation (8). The use of ephedra in dietary supplements is not allowed since 2004 because of its adverse effects.

4 DMAA

DMAA is the most studied of the three compounds described in this factsheet, and it was concluded previously by RIVM that DMAA should be considered pharmacologically active when a dose of 4 mg or more is consumed orally (9). DMAA is pharmacologically active after oral administration, although the exact oral availability is unknown as the effect of aliphatic amines is strongly dependent on the co-consumption of other stimulants.

DMAA is often marketed as a natural extract of geranium oil, but it is under debate if DMAA indeed is a component of natural geranium oil. One paper, published in the journal of *Guizhou Institute of Technology* in 1996, reported that DMAA was extracted from the geranium (*Pelargonium graveolens*) (10). Since then multiple other groups have tried to repeat this experiment, but no other groups succeeded to detect DMAA in geranium oil

(11-13). Regulation by the Food and Drug Administration (FDA) was avoided because of the claim that DMAA is a naturally occurring component of the geranium plant.

4.1 Pharmacology

DMAA is a sympathomimetic and thus affects the sympathetic nervous system. The only once-registered medicine containing DMAA was used for inhalation. Eli Lilly & Co patented synthetic DMAA as a nasal decongestant under the brand name Forthane with a dose of 0.6 mg/ml. Inhaled doses of 0.6 mg or more are considered pharmacotherapeutically effective according to the patent (7). The use of DMAA as a decongestant stopped around 1970 for unknown reasons and nowadays DMAA is used as a dietary supplement (3, 9, 12). It is known that DMAA does not only affect bronchodilation but also cardiovascular activity and blood pressure. Different side effects of DMAA are reported such as headaches, concentration problems and mental stimulation (14). The stimulating effects of DMAA were described as side effects of the medicine, but nowadays these side effects are regularly a primary reason for people to consume DMAA-containing products (15, 16).

More information about the pharmacological effects of DMAA could be retrieved from a few animal studies that were performed halfway the last century (17-21). These studies reported effects on the heart, blood pressure and on bronchodilation.

4.2 Kinetics[1]

The pharmacokinetic profile of DMAA was determined in a study where eight healthy male volunteers were given a single oral dose of 25 mg DMAA in a capsule after an 8-hour overnight fast. The mean maximum plasma concentration was 76.5 ng/mL and was reached after 3.6 hours. Plasma half-life was 8.4 hours. There were no significant effects on heart rate, body temperature or blood pressure. The authors note that compared to plasma values reported to be associated with adverse effects, the DMAA plasma concentration in this study is about 15-30 times lower (external dose unknown). However, it is difficult to make this comparison due to possible interactions, differences in bioavailability or variability in exposure in the case reports (22). Rodricks et al. compared the blood levels found by Schilling et al. (single serving of 25 mg) with those reported by Gee et al. (recreational ingestion; case reports) and noticed that the blood levels reported in the case reports of 1090, 760 and 2310 µg/L (at 100 minutes, 17 hours and 2 hours post-ingestion, respectively) are between a factor 19 and 37 times higher than the levels found in the pharmacokinetic study of 56, 35 and 62 µg/L at the same time points, respectively (16, 22, 23).

Perrenoud et al. describe the excretion of DMAA in urine after a single oral dose of 40 mg. The absorption of DMAA was relatively slow (4-12 hours). In total, 32 mg was recovered unchanged in urine with the maximum concentration reached after 4 hours with a DMAA level of 18 µg/mL. This leads to the conclusion that DMAA is hardly metabolised after oral administration in humans. DMAA was still detected at a level of 350 ng/mL after 4 days. Together with the relatively slow absorption, a half-life of 24 hours could lead to high concentrations of DMAA in the body (9, 24).

DMAA was found to be an inhibitor of CYP2D6 *in vitro* with human recombinant enzymes with an IC_{50} value of 6.5 ± 0.6 µM. Inhibition of CYP3A4 was <15% at a concentration of 100 µM. It was further mentioned that according to clinical data the maximum plasma concentration of DMAA and other stimulants is around 1 µM at a single dose of 25 mg (approx. 114 ng/ml) (25).

[1] For a more detailed description of the studies, see Appendix I

4.3 Effect level

As in 2010, the available information on DMAA is not sufficient for the derivation of an effect level. Hence, quantitative effect information on DMAA is retrieved by extrapolation of data from structurally similar compounds such as ephedrine and amphetamine. Studies on laboratory animals with DMAA show similar vasoconstrictor activity and effects as those of ephedrine and amphetamine analogues (1). Propylhexedrine, another amphetamine analogue (6), has therapeutic effects on bradycardia after inhalation (0.5 mg/800 ml air) and oral administration (50 mg) (26). A similar therapeutic effect is expected for 50-75 mg DMAA. The measured effect on blood pressure is larger, but this is compensated by the slow oral absorption of DMAA (24, 27).

The influence of DMAA on blood pressure is 4.5 times lower than that of ephedrine when administered orally. However, after intravenous administration, the effect on blood pressure of DMAA is 4 times higher than that of ephedrine. DMAA and ephedrine have a similar intrinsic effect, but differences in oral absorption lead to differences in peak plasma concentrations. An orally administered dose of 25-60 mg ephedrine leads to elevated blood pressure. As the oral absorption of DMAA is lower, a dose of about 100-250 mg is expected to cause similar elevation in the blood pressure (28, 29). After oral administration of 97 mg of propylhexedrine an elevation of 17-23 mmHg of the blood pressure was reported. Even though the intrinsic effect of DMAA on the blood pressure is larger, the slow oral absorption compensates for this and a dose of 100 mg of DMAA is expected to cause a comparable elevation in blood pressure.

The intrinsic effect of DMAA on nasal congestion is 19 times stronger than that of ephedrine (30). Ephedrine was administered orally to treat nasal congestion and as bronchodilator. An administered dose of 15-60 mg ephedrine was needed for effects. To achieve a comparable effect with DMAA, an expected oral dose of 4-15 mg DMAA is needed, when taking into account the higher intrinsic effect and the slow oral absorption.

4.4 Toxicology[2]

The safety of DMAA in supplements is not proven and is a subject of debate. The first papers that described the potential side effects and toxicity during *in vivo* studies were already published in the nineteen fifties and nineteen sixties (14, 31-33). Recently, trials in humans were performed and several case reports were published (see below).

Animal studies

Acute toxicity

The intraperitoneal LD_{50} of DMAA, injected in its hydrochloride form, in mice was determined to be 185 mg/kg bw (14).

No information is available on other acute effects.

Long term toxicity

No animal studies investigating the long term toxicity of DMAA were found.

Genotoxicity

No animal studies investigating the genotoxicity of DMAA were found.

Carcinogenicity

No animal studies investigating the carcinogenicity of DMAA were found.

Reproductive toxicity

[2] For a more detailed description of the studies, see Appendix I

No animal studies investigating the effects of DMAA on fertility and development were found.

Studies in humans
In the nineteen fifties, Marsh et al. described that an oral dose of 3 mg/kg DMAA (given as hydrochloride) or other amine hydrochlorides in young adult men led to moderate elevation of the cardiac rhythm and blood pressure (no further details provided). Typical side effects were a dry mouth and goosebumps, but also more severe effects such as confusion and concentration issues were reported (14).

In a series of trials in humans, recently conducted, the (acute) effects of oral DMAA intake were investigated in healthy young men and/or women.
In one trial, they were administered 250 mg caffeine, 50 mg DMAA, 75 mg DMAA, 250 mg caffeine + 50 mg DMAA, or 250 mg caffeine + 75 mg DMAA after a 10-hour overnight fasting period. Systolic blood pressure was significantly increased in the 75 mg DMAA (≤+10%) and caffeine + 75 mg DMAA (≤+17%) group compared to the caffeine group, and in the caffeine + 75 mg DMAA group (≤+14%) compared to the 50 mg DMAA group (34). Unfortunately, no negative control group was included.

In another trial, a single dose of placebo, 4 mg/kg bw caffeine, 1 mg/kg bw DMAA or a combination before a 10 km run were given. A significant increase was observed in heart rate in the caffeine + DMAA group (112±5 bpm[3]) compared to the DMAA group (100±5 bpm) but not compared to the placebo group, in systolic blood pressure in the caffeine group (141±4 mmHg) and DMAA group (147±4 mmHg) when compared to placebo (126±3 mmHg) or to the caffeine + DMAA group (126±3 mmHg), and in diastolic blood pressure in the DMAA group (66±3 mmHg) compared to the caffeine + DMAA group (61±2 mmHg) but not compared to the placebo group (35).

In a follow-up study, men were subject to daily supplementation with placebo, 250 mg/day caffeine, 50 mg/day DMAA, or a combination of both for 12 weeks. There were no statistically significant changes in any of the parameters investigated. Heart rate increased with 5 beats per minute from baseline to 12 week measurement in the DMAA group and respiratory rate increased in the caffeine + DMAA group, which may have been an additive effect as a smaller increase was observed in the caffeine and DMAA alone groups (36).

Seven healthy men ingested two servings of the DMAA- and caffeine-containing supplement Jack3d™ and four healthy men and two healthy women two capsules of the DMAA- and caffeine-containing supplement OxyELITE Pro™ once a day for two weeks. No effects were observed for heart rate, blood pressure, rate pressure product, blood count, lipid panel or metabolic panel for both supplements following two weeks of ingestion except for an increase in fasting blood glucose levels after ingestion of Jack3d™ ($P=0.02$). Following acute ingestion of OxyELITE Pro™, heart rate was lower directly after ingestion compared to prior to ingestion ($P=0.008$), systolic blood pressure was higher 60-120 minute post-ingestion than prior ($P<0.05$), rate pressure product was lower post-intervention than prior ($P=0.004$). For Jack3d™, no acute effects were noted (37).

Twelve healthy and active men and women ingested two capsules of OxyELITE Pro™ or placebo on two separate days. Plasma glycerol levels were significantly higher in the treatment group compared to placebo ($P=0.001$), and higher for women compared to men ($P=0.0007$). Free fatty acids and kilocalorie expenditure were also higher in the

[3] Results presented for 5 minutes post-exercise

treatment group compared to control (P<0.0001 and P=0.005, respectively). Statistically significant increases were observed in heart rate (70±5 bpm vs 59±2 bpm), systolic blood pressure (118±3 mmHg vs 102±3 mmHg) and rate pressure product (8298±637 vs 6083±298) post-ingestion of OxyELITE Pro™ compared to placebo. In addition, a time effect was observed for systolic blood pressure with higher levels 90 and 120 min post-ingestion (118±3 mmHg) than at baseline (103±2 mmHg) (38).

To further investigate whether the increase in circulating free fatty acids and glycerol and increase in metabolic rate is related, exercise-trained subjects (16 per group, some of them overweight to obese) were assigned to ingest OxyELITE Pro™ or placebo once daily for eight weeks. Dependent on the occurrence of adverse effects, subjects were allowed to take one or two capsules per day after taking one capsule for the first three days. Significant decreases in body weight, BMI, waist circumference, waist:hip ratio, total body fat percentage, fat mass, fat free mass and skinfold thickness (P<0.05) and a significant increase in resting heart rate (P<0.01) were found in the treatment group when comparing post-intervention data with pre-intervention data. For malondialdehyde, a marker of oxidative stress, significantly lower values were found for the treated group compared to control (P<0.0001) (39).

Twenty-five healthy men were randomly given a placebo or Jack3d™ at a dose of 1-3 servings on each workout day, 30 minutes prior to exercise, for 10 weeks. There were no significant differences between the control and the intervention group in blood pressure, however systolic blood pressure increased approximately 6 mmHg in the intervention group (40).

Case reports
Several case reports have been published showing severe adverse effects such as brain haemorrhage, neurological effects, necrotizing myopathy, cardiac arrest, acute liver injury (in some cases liver transplantation needed) and death after using DMAA-containing supplements whether or not in combination with (heavy) exercise and/or other supplements (16, 41-60). Although precise doses were not known, use of the supplements according to the recommendations from the manufacturer was frequently mentioned. Blood analysis in some patients with severe effects revealed the presence of DMAA in combination with the presence of other compounds such as caffeine (16, 41, 44). DMAA content of the supplements was determined in two publications and varied from 50 mg to 278 mg per capsule/tablet (16, 45). In the cases where a causality assessment was performed, the relationship between the supplement use and outcome ranged from possible to probable/highly likely.

Recently, Dunn reviewed human studies for the health effects of DMAA and concluded that the evidence base describing the adverse effects of DMAA is small as only 16 studies (of the 842) met the inclusion criteria. These studies included publications described above (16, 22, 34-40, 44-46, 50, 56, 59). He noted that although serious adverse effects were reported, their prevalence and causal relationship with DMAA are still unclear (61).

4.5 Status in other countries

In the United States, the FDA has been working on the removal of DMAA-containing supplements of the market as the FDA 'does not have any information to demonstrate that consuming DMAA is safe'. Consumers are advised not to take any products that contain DMAA. They have received 86 reports of adverse events, including psychiatric disorders, heart problems, nervous system disorders and death, where DMAA-containing products were involved (62). In December 2011, DMAA-containing products were withdrawn from military exchanges as four soldiers who died after physical exercise were shown to have DMAA in their blood. In 2013, a safety review was conducted by the Department of De-

fence. They concluded that an elevated health risk was associated with the use of DMAA-containing products, and that for some individuals the health consequences may be severe based on the reported deaths, hepatic failure, myocardial infarction, heat stroke and rhabdomyolysis, seizure and stroke. Further they conclude that 'although direct causality cannot be concluded, the seriousness of the observed adverse medical events and deaths where Service members had used DMAA-containing products led Safety Review Panel members to assess DMAA-associated health risks as low to moderate' (63).
The World Anti-Doping Agency (WADA) lists DMAA specifically as forbidden stimulant, but it is also noted that all aliphatic pressor amines are on the list of forbidden compounds (64). In Canada, DMAA is not authorized for use as a medicine. In addition, Health Canada took measures to remove dietary supplements containing DMAA from the market (65, 66). In Ireland DMAA is considered a forbidden medicine and the import and trade are not allowed (67). Also in many other European countries, DMAA-containing dietary supplements are banned from the market as for example in the UK, Finland and Sweden (68-70). In Australia, the Therapeutic Goods Administration (TGA) banned DMAA as of 8 August 2012 reasoning that DMAA is not beneficial to health but a toxic substance, severe health risks may occur, its long-term safety has not been assessed, and that a high risk of abuse, misuse and illicit use is present (71).

5 DMBA

Shortly after the FDA banned DMAA from dietary supplements, the analogue DMBA, also called nor-DMAA, was discovered in different supplements (72). In contrary to DMAA and DMHA, DMBA was never a registered medicine and no extensive studies are performed with this substance.

Two Chinese groups reported that DMBA could be found as a natural product. One group detected small amounts of DMBA as a degradation product of Pouchong tea, and the other group discovered DMBA in essential oil from the oleoresin of the Plains coreopsis (*Coreopsis tinctoria*) (73, 74). Both groups did not use reference standards to prove their findings and other groups could not confirm their findings with similar experiments, so there is no strong scientific evidence for the natural occurrence of DMBA (75).

5.1 Pharmacology

In two animal studies from the 1940's the effects of DMBA on pithed cats and dogs was tested. It was discovered that DMBA has pressor effects but is less potent than DMAA (19, 76). In literature Cohen et al. state that DMBA should be considered a pharmaceutically active compound (72).

5.2 Kinetics

DMBA was found to be an inhibitor of CYP2D6 *in vitro* using human recombinant enzymes. However, DMAA was at least 15 times more potent than DMBA (IC_{50} value of >100 µM). Inhibition of CYP3A4 was <15% at a concentration of 100 µM (25).

5.3 Effect level

No minimal effect level could be derived for DMBA due to limited data.

5.4 Toxicology

Animal studies

Acute toxicity

No animal studies investigating the acute toxicity of DMBA were found.

Long term toxicity
No animal studies investigating the long term toxicity of DMBA were found.

Genotoxicity
No animal studies investigating the genotoxicity of DMBA were found.

Carcinogenicity
No animal studies investigating the carcinogenicity of DMBA were found.

Reproductive toxicity
No animal studies investigating the effects of DMBA on fertility and development were found.

Studies in humans
No studies in humans with DMBA were found.

Case reports
Three cases of adverse effects were reported after using the supplement 'Unstoppable', containing DMBA as confirmed by analysis but not reported on the label. Reported symptoms were similar between the cases and included the feeling of rushing, difficulty sitting still, a sense of motion and increased focus. The relationship of these effects and the use of DMBA was not scientifically proven though (72).

5.5 Status in other countries
In 2015 the FDA undertook actions to remove DMBA from dietary supplements as well, as there is no history of use or evidence of safety (77).
The WADA considers DMBA as a prohibited substance because of its similarity with tuamine (78). Also in Germany, DMBA is not authorized to be used in supplements (79). In Australia, DMBA has been included in Schedule 10 which is a list of substances of such danger to health as to warrant prohibition of sale, supply and use, starting from 1 October 2017, based amongst others on the structural similarities with DMAA, the significant health risk, the fact that the WADA considers DMBA as a health risk, and the high potential for misuse and abuse (80). A risk assessment conducted by the Swedish authorities concluded that DMBA in dietary supplements poses a severe health risk to humans, due to its similarities with DMAA, and a warning was issued not to use these supplements (69).

6 DMHA
Another analogue of DMAA that recently was discovered in dietary supplements is DMHA, or octodrine (81).
Different studies suggest the natural occurrence of DMHA in Forsythia suspension, Acotinum kusnezoffii, Microcystis aeruginosa (an algae), Datura stramonium (jimson weed), Kigelia africana (sausage tree), Biomphytum veldkampii (a small palm), Psetta mexima (turbot fish) and in an unidentified species of sea shrimp (81). None of these studies though led to conclusive confirmations whether or not DMHA is a natural occurring product.

6.1 Pharmacology
DMHA was the active pharmaceutical ingredient in Eskay's oralator, and was produced by the Smith, Kline & French Laboratories in the 1940's (82). The oralator provided an aerosolized treatment for bronchitis, pharyngitis and other conditions (83). A second aerosolized DMHA product was approved by the FDA, but this product never reached the market for unknown reasons (84).

In Europe, but not in the Netherlands, DMHA was sold between the 1960's and mid 2000's as an active ingredient in three registered multi-ingredient tablets. All three tablets were for oral consumption and were sold under the trade names Ambredin, Ordinal Retard and Ordinal Forte. Different doses of DMHA were used in these tablets: Ambredin contained 8.2 mg, Ordinal Retard contained 16.5 mg and Ordinal Forte contained 33 mg (85-87). Octodrine was used for the treatment of hypotension (88). Nowadays doses of up to 72 mg DMHA per serving are detected in dietary supplements (81).

The effects of DMHA intake have been investigated in multiple preliminary studies on both humans and animals in the last century. Multiple animal studies have been published that investigated the effects of DMHA via intraperitoneal injection or inhalation in mice, rats, guinea pigs, rabbits, cats and dogs. The studies in mice and rats showed stimulation of the central nervous system (89-91). Larger animals showed an increase in blood pressure and cardiac output after DMHA administration (81, 89-92).

6.2 Kinetics

Maximum serum concentrations of radiolabeled DMHA were reached two hours after consumption (93).

6.3 Effect level

No minimal effect level could be derived for DMHA.

6.4 Toxicology[4]

Animal studies

Acute toxicity

The acute toxicity of DMHA was studies in mice, rats, rabbits, and guinea pigs after intraperitoneal injection (89). An overview of the reported effects is given in Table 3.

Table 3. Overview of reported effects in mice, rats, rabbits, and guinea pigs after intraperitoneal injection with DMHA (adapted from (89).

Animal	Dose (mg/kg bw)	Effects	Number of animals affected/Number of animals
Mice	40	signs of restlessness	20/20
	50	depression followed by excitement	25/25
	65	tremors and convulsions	25/25
		mortality	13/25
	75	convulsions	20/20
		mortality	19/20
Rats	30	tremors	4/10
		increased activity	10/10
	40	convulsions	8/10
		tremors, salivation and increased activity	10/10
		mortality	4/10
	50	convulsions and mortality within 20 minutes	10/10
	60	convulsions and mortality within	10/10

[4] For a more detailed description of the studies, see Appendix I

Animal	Dose (mg/kg bw)	Effects	Number of animals affected/Number of animals
		10 minutes	
Rabbits	50	tremors	2/6
	60	convulsions, tremors and mortality	3/6
	75	convulsions and mortality	4/6
	100	tremors	1/6
		convulsion and mortality within 8 minutes	6/6
Guinea pigs	25	slight tremors	6/6
	35	convulsions	2/6
		excitement	6/6
		mortality	2/6
	50	convulsions and mortality within 1 hour	6/6
	75	convulsions and mortality within 30 minutes	6/6
	100	tremors, convulsions and mortality within 15 minutes	6/6

Based on the mortality, LD_{50} values of 59, 41.5, 44 and 39 mg/kg bw were estimated for mice, rats, rabbits and guinea pigs, respectively.

In a preliminary experiment, the intraperitoneal LD_{50} of DMHA, injected in its hydrochloride form, in mice was determined to be 90 mg/kg bw (92).

In cats receiving intraperitoneal injections with 2.0, 3.0, 5.0, 7.5, 10.0 or 15.0 mg/kg DMHA hydrochloride several effects were noted such as dilated pupils, vomiting and hyperpnoea at lower doses and convulsions and tremors at higher doses (89).

The subacute toxicity of DMHA was tested in rats, rabbits and guinea pigs (89).
Ten rats were administered DMHA via intraperitoneal injection at 20 mg/kg bw for 30 days. The average weight gain was 38 grams.
Nine rats received daily doses of 100 mg/kg bw DMHA orally for 30 days. All rats showed signs of depression followed by piloerection and restlessness, and had an average weight gain of 38 grams. Six other rats received oral doses of 75 mg/kg bw DMHA for 30 days. The rats had an average weight gain of 49 grams, and signs of a slight depression were noted. Histopathology of heart, lungs, liver, kidneys, spleen, intestine, stomach, brain and cord did not show adverse effects.
Guinea pigs (six per group) received a dose of 20 or 25 mg/kg bw DMHA via intraperitoneal injection daily for 30 days. Animals from both groups gained weight (~80 grams) during the experimentation period. All animals of the 25 mg/kg bw dose group showed slight tremors during the first dosing days, and restlessness the rest of the dosing period. Histopathology of heart, lungs, liver, kidneys, spleen, intestine, stomach, brain and cord did not show adverse effects.
Rabbits (n=8) received daily doses of 20 mg/kg bw DMHA via intraperitoneal injection for 30 days. No effects were reported. Histopathology of heart, lungs, liver, kidneys, spleen, intestine, stomach, brain and cord did not show adverse effects.

To investigate whether DMHA would produce irritation to the respiratory tract, 12 rats inhaled DMHA plus flavouring agents continuously for 6 hours daily for 30 days (0.4 to 0.55 mg/L air; 6L air per minute), and 20 rabbits inhaled fixed doses of 5 to 10 mg DMHA daily for 10 days. After the experiment, the animals were sacrificed and (sections

of) the trachea, lungs, brain and cord, kidney, spleen, intestine and stomach were removed. No histopathological effects were found.

Long term toxicity
No animal studies investigating the long term toxicity of DMHA were found.

Genotoxicity
No animal studies investigating the genotoxicity of DMHA were found.

Carcinogenicity
No animal studies investigating the carcinogenicity of DMHA were found.

Reproductive toxicity
No animal studies investigating the effects of DMHA on fertility and development were found.

Studies in humans
Studies on humans have been published reporting the effects of DMHA after inhalation and after oral administration. Inhalation of an unidentified dose of DMHA led to an increase of lung volume in two studies (94, 95). Oral administration of DMHA as a single pharmaceutical agent at doses of 4 mg/kg DMHA hydrochloride was found to increase the diastolic blood pressure by 8-12 mmHg and to increase the systolic blood pressure by 20-25 mmHg for 2-3 hours after intake in four humans. Reported effects included pain in the stomach, dry mouth, pronounced pilomotor effects, urination, warm skin and sweating, decrease in finger plethysmograph volume, and involuntary sighing. No marked effects were found at 1 and 2 mg/kg (92). A multi-ingredient product, that included DMHA, was investigated as a treatment for low blood pressure in 20 patients (81).

Case reports
No case reports were found with respect to DMHA.

6.5 Status in other countries
In Australia, DMHA has been included in Schedule 10 which is a list of substances of such danger to health as to warrant prohibition of sale, supply and use starting from 1 October 2017 based amongst others on the structural similarities with DMAA, the significant health risk, and the high potential for misuse and abuse (80).

7 Interactions
The cardiovascular effects of the aliphatic amines could cause hypertensive crises when consumed together with products that inhibit monoamine oxidase (MAO). Caffeine is a known weak MAO-inhibitor, and consumption of caffeine together with an aliphatic amine can accelerate the development of the stimulating side effects of the aliphatic amine at low doses (96). This knowledge leads to conscious consumption of different DMAA-containing party drugs such as “Crack” and “Dynapep” together with caffeine for the stimulating effects (7). In general, an increase of the stimulating effects of DMAA, DMBA and DMHA are to be expected when combined with other sympathomimetics and adrenergic components. It is noted that in many cases sports supplements contain several of such stimulants (97).

8 Vulnerable groups
The pharmacological effects of DMAA, DMBA and DMHA on blood pressure and heart rate make that people sensitive to these effects, i.e. due to an already elevated blood pressure or heart rate, are at an increased risk on adverse effects. This includes individuals suffering from cardiovascular disease, individuals with obesity and athletes when extreme

efforts are done. In contradiction however, these people are also the target groups of dietary supplements with DMAA, DMBA or DMHA.

9 Risk assessment

Since the RIVM advisory reports of 2010, 2011 and 2012 and the NVWA advisory report of 2012, no new information became available about the pharmacology of DMAA. With respect to the toxicology of DMAA, several case reports and a few human trials were published. The human trials where DMAA in doses of about 1 mg/kg was given as a compound whether or not together with caffeine (about 4 mg/kg) and whether or not before exercising showed a significant increase in systolic blood pressure in one study (at 75 mg DMAA but not at 50 mg DMAA), which could be clinically relevant especially in the high risk groups that are also the target population, while in another no effect was noted. In addition, the combination of caffeine and DMAA did not lead to a synergistic effect. In the other human trials, DMAA-containing supplements were given at doses of one to three capsules/scoops per day for different durations varying from two days to 10 weeks in one study. Again the results are not unambiguous with in some cases a significant increase in systolic blood pressure and heart rate but in other cases not. Possibly this difference is due to the supplement itself as effects were seen with OxyELITE Pro™ but not with Jack3d™. Further, effects were noted on some metabolic and lipid panel biomarkers such as malondialdehyde, plasma glycerol levels and free fatty acids. On the other hand, the case reports show severe adverse effects including brain haemorrhage, neurological effects, necrotizing myopathy, cardiac arrest, acute liver injury and death after the use of DMAA-containing dietary supplements. Precise doses were not known other than that in a number of cases the subjects reported to have taken the supplement following recommendations on the leaflet. In one case, an identical capsule to the one taken was analysed and 278 mg DMAA was found.

In total, the toxicity data for DMAA now consists of human data from trials and case reports and one acute toxicity study in mice. The data obtained in the human studies have several limitations as only a small number of participants was included, a control group was not always present, and they were conducted under strict experimental conditions with respect to age (young), health status (healthy and normal weight, only in one study also obese subjects), environmental conditions, and exercise. The latter makes it difficult to extrapolate to individuals not meeting those criteria, which are in fact the target population of these supplements, i.e. overweight or obese individuals, athletes etc. In the case reports information with respect to dose is lacking as precise use information is not always known, in addition to the fact that the DMAA content reported on the leaflet does not always correspond to the real dose in the capsule. In addition, DMAA is very often taken in combination with other (stimulating) substances which makes it difficult to estimate the precise effects of DMAA and to assess its safety.

Hence, based on the currently available information no health-based guidance value (HBGV) can be derived for DMAA. Oral doses of 4-15 mg DMAA exert pharmacological effects at the lungs (bronchodilation) and nasal mucous membrane, 50-75 mg on the heart and 100 mg on blood pressure, as was concluded in an earlier RIVM advisory report (1). At which dose the effects become toxicologically relevant cannot be estimated. However, given

- the severe adverse effects reported after the use of DMAA-containing supplements in case studies,
- similarity to ephedra,
- the potential for misuse or abuse,
- that supplements with DMAA are used by population groups that may have a higher risk on adverse effects (sportsmen, obese persons), that the actual DMAA content may be higher than reported on the leaflet,

the use of DMAA-containing supplements may result in severe health effects. In addition, no information is available on a potential to cause fertility or developmental effects or on

long-term toxicity or carcinogenicity. Further, in many countries DMAA-containing supplements are prohibited.

For DMBA, the pharmacological and toxicological information is very limited. DMBA has similar pressor effects as DMAA but is less potent. Three case reports describing adverse effects after using a supplement that contained DMBA have been reported. Based on this information, several countries have taken measures to remove DMBA from the market. Due to the limited information present, no HBGV can be derived for DMBA.

DMHA has been used in the past as an active ingredient in human medicines in oral doses of 8.2 to 33 mg to treat hypotension. In dietary supplements, doses up to 72 mg have been found. The available toxicological information is limited and consists of a few (sub)acute toxicity studies in several animal species showing severe adverse effects at high doses of several tens of mg/kg bw. The drawback of this data is however that none of this information was obtained after oral administration. One human study is available with single oral doses of 1 to 4 mg/kg where only the highest dose led to an increase in blood pressure. Data after long-term exposure, reproductive toxicity and carcinogenesis is however missing. Due to the lack of toxicological information to determine safe use especially after long-term use, no HBGV for DMHA could be derived.

Read across between DMAA and DMBA or DMHA
A generally applicable theoretical approach to justify read across has been, amongst others, written down by ECHA (98-100). Read across may be applied for a chemical for which data is lacking when it can be considered to be similar to another chemical for which data exists. In the case of DMBA and DMHA it can be seen that there is a structural similarity with DMAA. All three are branched aliphatic saturated short-chain amines with the amino-group located at the second carbon atom. There is a constant change across the category, i.e. an increase in chain-length (C4-C6). In addition, all three amines have similar biological properties, i.e. a sympathomimetic effect and consequential to this, both DMAA and DMHA have been used as medicines to treat hypotension at dose levels that are in the same order of magnitude (72, 81). Hence, it is proposed to extrapolate the conclusions for DMAA to DMBA and DMHA until new data is available.

10 Conclusions

Based on the reported toxicology data, it is not possible to derive health-based guidance values for DMAA, DMBA and DMHA. Pharmacology data on DMAA indicate that sympathomimetic effects may result from oral doses of 4 mg daily. Given 1) the severe adverse effects reported in case studies after the use of DMAA-containing supplements; 2) the potential for misuse or abuse; 3) that this supplements are used by population groups that may have a higher risk on adverse effects (sportsmen and -women, obese persons); and 4) that the actual DMAA content may be higher than reported on the leaflet, the use of DMAA-containing supplements may result in severe health effects. It is noted that there is no information on toxicity of DMAA after long-term exposure or on developmental or reproductive toxicology and carcinogenesis. Further, in many countries DMAA-containing supplements are prohibited.
For DMBA and DMHA no controlled safety and efficacy studies in man are available in the public literature. However, these substances show structural similarity to and have a similar mode of action as DMAA. In addition, data on historical use of DMHA as a medicine to treat hypotension indicate that the potency of DMHA is within an order of magnitude of the potency of DMAA. Therefore, until new data are available, the conclusions reached for DMAA (see above) are used in a read-across approach to conclude that use of DMBA- and /or DMHA-containing dietary supplements may also result in severe health effects.

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Appendix I Overview kinetic and toxicology studies

Kinetics

DMAA

To determine the pharmacokinetic profile of a single dose of DMAA, a study with eight healthy male volunteers was done, who were given a single oral dose of 25 mg DMAA in a capsule after an 8-hour overnight fast. Subjects were asked not to take any DMAA-containing supplement 72 hours prior to the experiment or conduct physical activity 36 hours prior. Heart rate, blood pressure and cutaneous temperature were measured prior to ingestion as well as afterwards and blood samples were collected over the next 24 hours. Due to extreme high blood levels of DMAA, including the baseline level, that kept on rising over the 24-hour period, one subject was excluded from analysis. It remained unknown what the reason for this was as the subject denied taking DMAA-containing supplements in the 72 hours prior to the experiment.
Heart rate was slightly higher at 12-hours post-ingestion (69.1 ± 2.9 BPM) compared to baseline (61.0 ± 3.2 BPM). Cutaneous temperature was significantly increased 12-hours post-dose compared to 2-hours and 3-hours post-dose but still in the normal range. No changes were observed for blood pressure. The mean maximum plasma concentration was 76.5 ng/mL and was reached after 3.6 hours. Mean $AUC_{0-\infty}$-value was 1204 ng*hr/mL. Oral plasma clearance was 20 L/hr and terminal half-life 8.4 hours. The authors note that compared to plasma values reported to be associated with adverse effects, the DMAA plasma concentration in this study is about 15-30 times lower. However, it is difficult to make this comparison due to possible interactions, differences in bioavailability or variability in exposure in the case reports (22).
Rodricks et al. looked further into comparing the kinetic data with blood levels obtained from case reports. They noticed that the blood levels reported in Gee et al. of 1090, 760 and 2310 µg/L (at 100 minutes, 17 hours and 2 hours post-ingestion, respectively) are between a factor 19 and 37 times higher than the levels found in the study of Schilling et al. of 56, 35 and 62 µg/L at the same time points, respectively (16, 22, 23).

The urine of two healthy male volunteers was investigated for the presence of DMAA after self-administration of a single dose of 40 mg DMAA. In one subject unchanged DMAA was found up to 105 hours post-dose whereas for the other nothing was detected after 80 hours. The maximum concentration in urine was reached after 4 hours with a DMAA level of 18 µg/mL. In total, 32 mg was recovered unchanged in urine. This leads to the conclusion that DMAA is hardly metabolised after oral administration in humans. DMAA could be detected at a level of 350 ng/mL up to 4 days (9, 24).

Toxicology

DMAA

Studies in humans
Five young adult males (22-32 years, 61-82 kg) were given 3 mg/kg DMAA HCl or other amine hydrochlorides orally with 200 mL water, four hours after a light morning meal. Systolic and diastolic blood pressure and pulse rate were measured every 15 minutes for three hours while the subjects were sitting quietly. Experienced clinical signs included a rise in blood pressure, an increase in systolic-diastolic difference, a decrease in pulse rate, dry mouth, itchy or tingling skin, confusion and concentration issues. In one of the five males, DMAA was the most potent in elevating blood pressure, while in the other four it was 4-methyl-2-hexyl methylamine (14).

In a double-blind, randomized, crossover design to assess the effects of oral DMAA intake on heart rate and blood pressure, ten young healthy men and women were administered 250 mg caffeine, 50 mg DMAA, 75 mg DMAA, 250 mg caffeine +50 mg DMAA, or 250 mg caffeine + 75 mg DMAA after a 10-hour overnight fasting period. Heart rate, systolic and diastolic blood pressure, and rate pressure product were measured before the ingestion and every 30 minutes up to 2 hours afterwards. In addition, plasma norepinephrine and epinephrine were measured before and 1 and 2 hours post-administration. No effect was observed on heart rate or on the catecholamines. A significant effect was however found for an increase in systolic blood pressure in the 75 mg DMAA (≤+10%) and caffeine + 75 mg DMAA (≤+17%) group compared to the caffeine group, and in the caffeine + 75 mg DMAA group (≤+14%) compared to the 50 mg DMAA group. In addition, a significant increase in rate pressure product was observed in the caffeine + 75 mg DMAA group compared to the caffeine group. For the diastolic blood pressure, a significant increase (≤+20%) was observed over time compared to baseline in all groups (34).

To investigate the effect on exercise performance and blood markers of lipolysis and oxidative stress, 12 exercise-trained men and women were given a single dose of placebo (vehicle, 30 g carbohydrate), 4 mg/kg bw caffeine, 1 mg/kg bw DMAA or a combination before a 10 km run in a double-blind cross-over trial. The subjects fasted overnight (10 hours) and did not exercise 24 hours prior to the test. Heart rate, systolic and diastolic blood pressure, and rate pressure product were measured at baseline (twice) and 5 and 30 minutes after the exercise. Blood samples collected at baseline, immediately after the run and 15 and 30 minutes afterwards were analysed for glycerol, free fatty acids, malondialdehyde, nitrate/nitrite, and trolox equivalent antioxidant capacity (TEAC). After receiving the combination of caffeine and DMAA, many subjects reported feelings of euphoria. No effects were noted on run time, perceived exertion, mood/vigour and heart rate during the race in any of the treatment groups. Glycerol levels were significantly higher in the DMAA group compared to the caffeine + DMAA group at 30 minutes post-exercise. TEAC was significantly lower in the caffeine and caffeine + DMAA groups than in placebo, and in the caffeine group compared to the DMAA group. No significant differences between treatment groups were found for free fatty acids, malondialdehyde and nitrate/nitrite levels, although there was a non-significant increase in free fatty acids in the DMAA group compared to the other groups. Blood levels for glycerol and free fatty acids were highest 5 minutes post-exercise and declined thereafter. With respect to the haemodynamic parameters, a significant increase was observed in heart rate in the caffeine + DMAA group (112±5 bpm[5]) compared to the DMAA group (100±5 bpm), in systolic blood pressure in the caffeine group (141±4 mmHg) and DMAA group (147±4 mmHg) when compared to placebo (126±3 mmHg) or to the caffeine + DMAA group (126±3 mmHg), and in diastolic blood pressure in the DMAA group (66±3 mmHg) compared to the caffeine + DMAA group (61±2 mmHg) (35).

In a follow-up study to assess the safety profile of caffeine and DMAA, 50 young and healthy men were subject to a daily supplementation with placebo (n=11), caffeine at 250 mg/day (n=14), DMAA at 50 mg/day (n=13), or a combination of both (n=12) for 12 weeks. Before the experiment and after 6 and 12 weeks body mass/composition, resting respiratory rate, blood pressure, electrocardiogram, urinalysis, complete blood count, metabolic panel, lipid panel and oxidative stress, inflammatory, and cardiac biomarkers were measured. There were no statistically significant changes in any of these parameters. Non-significant changes included an increase in heart rate of 5 beats per minute from baseline to 12 week measurement in the DMAA group, and an increase in respirato-

[5] Results presented for 5 minutes post-exercise

ry rate in the caffeine + DMAA group, which may have been an additive effect as a smaller increase was observed in the caffeine and DMAA alone groups (36).

To assess the haemodynamic and haematologic profile of two supplements containing DMAA and caffeine, seven healthy men ingested two scoops of Jack3d™ and four healthy men and two healthy women two capsules of OxyELITE Pro™ once a day for two weeks. Resting heart rate, systolic and diastolic blood pressure were measured on Days 1 and 15 prior to ingestion of the daily dose and every 30 minutes for two hours post-ingestion. In addition, fasting blood samples were drawn at Day 1 and 15 and analysed for complete blood count, and metabolic and lipid panel. Appetite was scored significantly lower post-intervention (4.3±0.6) than pre-intervention (6.3±0.5) for OxyELITE Pro™ but not for Jack3 consumption. This was probably due to other ingredients in OxyELITE Pro™ than DMAA and caffeine. No effects were observed for heart rate, blood pressure, rate pressure product, blood count, lipid panel or metabolic panel for both supplements following two weeks of ingestion except for an increase in fasting blood glucose levels after ingestion of Jack3d™ ($P=0.02$). Following acute ingestion of OxyELITE Pro™, heart rate was lower directly after ingestion compared to prior to ingestion ($P=0.008$), systolic blood pressure was higher 60-120 minute post-ingestion than prior ($P<0.05$), rate pressure product was lower post-intervention than prior ($P=0.004$). For Jack3d™, no acute effects were noted (37).

Twelve healthy and active subjects (six men and six women) ingested two capsules of OxyELITE Pro™ or placebo on two separate days in a double-blind cross-over design to study the acute effects. Blood samples were collected prior to ingestion and at one and two hours post-ingestion, and analysed for plasma glycerol and free fatty acids and AUC calculation. In addition, breath samples were taken prior to and every half hour for two hours after ingestion for metabolic rate measurement. Heart rate and blood pressure were measured at all time points. Plasma glycerol levels were significantly higher in the treatment group compared to placebo ($P=0.001$), and higher for women compared to men ($P=0.0007$). Free fatty acids and kilocalorie expenditure were also higher in the treatment group compared to control ($P<0.0001$ and $P=0.005$, respectively). Statistically significant increases were observed in heart rate (70±5 bpm vs 59±2 bpm), systolic blood pressure (118±3 mmHg vs 102±3 mmHg) and rate pressure product (8298±637 vs 6083±298) post-ingestion of OxyELITE Pro™ compared to placebo. In addition, a time effect was observed for systolic blood pressure with higher levels 90 and 120 min post-ingestion (118±3 mmHg) than at baseline (103±2 mmHg) (38).

To further investigate whether the increase in circulating free fatty acids and glycerol and increase in metabolic rate is related, exercise-trained subjects (16 per group) were randomly in a double blind manner assigned to ingest OxyELITE Pro™ or placebo once daily for eight weeks. Dependent on the occurrence of adverse effects, subjects were allowed to take one or two capsules per day after taking one capsule for the first three days. Body weight, body composition, resting heart rate, blood pressure, skinfold thickness and appetite were recorded pre- and post-intervention. Blood samples were collected for a complete blood count, lipid and metabolic panel determination pre- and post-intervention. Of the subjects in the treatment group, five took one capsule per day because of feelings of jitters and sleeplessness and eleven two capsules without noted adverse effects. No effects were observed for any anthropometric or haemodynamic variable. However, significant decreases in body weight, BMI, waist circumference, waist:hip ratio, total body fat percentage, fat mass, fat free mass and skinfold thickness ($P<0.05$) and a significant increase in resting heart rate ($P<0.01$) were found in the treatment group when comparing post-intervention data with pre-intervention data. For malondialdehyde, significantly lower values were found for the treated group compared to control ($P<0.0001$) and within the treated group when comparing pre-intervention with post-

intervention data (P=0.02). In addition, in the treated group, significant increases were observed in total cholesterol and HDL-C (P<0.05), and significant decreases in LDL-C:HDL-C and total cholesterol:HDL-C ratios (P<0.05) when comparing pre-intervention data with post-intervention data. However, significant increases in HDL-C and malondialdehyde and decreases in LDL-C:HDL-C and total cholesterol:HDL-C ratios were also noted for the placebo group (39).

Twenty-five healthy men were randomly given a placebo (n=13) or a supplement (Jack3d™) containing among others DMAA and caffeine (n=12) at a dose of 1-3 servings on each workout day, 30 minutes prior to exercise, for 10 weeks. Before and after ingestion, resting blood pressure and heart rate were measured and blood samples were collected for complete blood count, and metabolic and lipid panel. There were no significant differences between the control and the intervention group in blood pressure, however systolic blood pressure increased approximately 6 mmHg in the intervention group. Heart rate was statistically significantly reduced post-intervention compared to pre-intervention but no differences were noted between treatment groups. Creatinine and alkaline phosphatase levels were significantly higher and lower, respectively, post-intervention compared to pre-intervention. No effects of treatment on blood count or metabolic or lipid panel were found (40).

Case reports

A 30-year-old female with no medical history collapsed during running a marathon with a cardiorespiratory arrest and died in hospital. She had put 2 scoops of the energy powder called Jack3d™, which contains DMAA, in her water bottle that she used during the marathon. Post-mortem examination revealed that both lungs were markedly heavy and congested with copious intra-alveolar haemorrhage. Blood analysis showed the presence of DMAA in her blood estimated to be 75 ng/mL. Other components found in her blood were caffeine (<1 µg/mL), ethanol (<10 mg/L), diazepam (0.21 µg/ml) and pseudoephedrine (0.43 µg/mL). The cause of death was determined to be acute heart failure in combination with extreme physical exertion (41).

Gee et al. described a case of a 21-year-old man who ingested the recommended dose of two legal party pills identified as 99.9%-pure DMAA together with a capsule identified as 150 mg caffeine, after consuming one can of beer. Within half an hour, he developed a severe headache and became confused, incontinent and vomited for 2-3 hours. The next day he was taken to hospital with a slurred speech, disorientation, a right facial droop and right-sided weakness. A CT of the brain revealed a large haemorrhage in the left basal ganglia. There was no evidence of an aneurism, arteriovenous malformation of cerebral vasculitis. After 20 days, he was discharged with severe impairment to memory and abstract reasoning and mild impairments of speech and right hand coordination. Analysis of identical pills showed the presence of 278 mg DMAA per capsule, with no caffeine, amphetamine, 1-benzylpiperazine or other stimulants present (45).

Another three cases of cerebral haemorrhage after recreational use of DMAA have been reported by Gee et al. A 23-year-old woman had taken 2 tablets of party pills known as Pure X-S after ingested already a quantity of alcohol. She was hospitalized with a severe frontal headache with dizziness, vomiting and involuntary twitching of arms and legs. A CT scan of the brain showed a subarachnoid haemorrhage, and a cerebral angiogram could not show evidence of an aneurysm or an arteriovenous malformation. After three days, she was discharged with follow-up. Blood analysis revealed a DMAA plasma concentration of 1.09 mg/L (100 minutes post-ingestion). No other drugs were identified. Analysis of the tablet showed the presence of DMAA (66 mg), caffeine (84 mg) and phenethylamine with palmitic and stearic acid. A 36-year-old man purchased legal party drugs with a listed composition of 50 mg DMAA HCl, and ingested one quarter of the

packet with a drink. Within an hour he developed a severe headache, weakness in his right hand and an unstable walk. After a night sleep, he woke with a left facial droop and left-sided weakness. A CT scan showed a right-sided intraparenchymal haemorrhage, and angiography vasculitis. After 2 weeks in hospital, he was discharged with follow-up. Blood analysis revealed a plasma level of 0.76 mg/L DMAA 17 hours post-ingestion. In urine, DMAA, ethanol, nicotine and paracetamol were found. A 41-year-old man had ingested water in which a white powder was dissolved and developed a severe headache and vomited. CT showed a haemorrhage in the left basal ganglia. Blood analysis conducted 2 hours post-ingestion showed the presence of DMAA at 2.31 mg/L. No other drugs were found, only a trace amount of cannabis in urine. He was discharged after 2 days with no headache or detectable neurologic deficit (16).

Eliason et al. reported two case reports of soldiers who were taking commercially available dietary supplements containing amongst others DMAA. It concerned one young healthy male in excellent physical condition who collapsed during physical training session and died because of a hyperthermic cardiac arrest after a few hours. Toxicological analysis revealed a DMAA level of 0.22 mg/L and caffeine level of 2.9 mg/L. He was using one supplement according to the recommendations on the product label for about 4 weeks. The other case was of a female with a history of mild obesity and sickle cell trait whom recently started using supplements to achieve weight loss. During a physical fitness test she collapsed of cardiac arrest where after she was hospitalized with multiple organ failure and died after 5 weeks due to sepsis. Toxicological screening of her blood showed the presence of 0.04 mg/L DMAA and 1.9 mg/L caffeine (4 days post-ingestion). In her car, two different supplements were found which both contained DMAA. Further details about her supplement use were unknown. Both subjects had taken the same supplement containing, amongst others, DMAA, β-alanine, arginine α-ketoglutarate, caffeine, creatine monohydrate and Schizandrol A (44).

A 21-year-old male, who had taken a supplement containing DMAA for the first time, had a cardiac arrest while exercising. He did not use caffeine or illicit drugs. He was hospitalized and received an ICD (46).

After using a dietary supplement containing DMAA prior to physical exercise, a 32-year-old Navy Special Operations Forces Sailor developed atrial fibrillation with rapid ventricular response (42) (abstract only).

Durgam et al. described the case of a young healthy woman who was using DMAA-containing dietary pills for a month when she started to experience rapidly progressing muscle weakness, impaired ambulation and generalized muscle atrophy. She was diagnosed with necrotizing myopathy without inflammatory findings (43) (abstract only). In 2014, the same authors report two case reports concerning two different DMAA-containing supplements. A 37-year-old man had been taking Jack3d™ for five days when he developed left-sided weakness. He was diagnosed with right-sided cerebral haemorrhage without any vascular anomalies or aneurysms. A 34-year-old woman[6] was diagnosed with necrotizing myopathy without inflammatory findings after presenting with rapidly progressive muscle weakness and impaired ambulation. She had been using Oxy-ELITE Pro for a few months (47) (abstract only).

Smith et al. reported the case of a 22-year-old healthy man who presented himself with angina chest pain that had started during coaching basketball. Three weeks before

[6] It is not clear if this may be the same case as described by Durgam et al. (2013) due to similarities in the case description.

presentation, he started using Jack3d™ and Phenorex™, containing DMAA, caffeine and Citrus aurantium, daily before physical exercise. He did not smoke, use alcohol or illicit drugs. He was diagnosed with a non-ST-elevation acute myocardial infarction and developed a thrombus. Six days after admission, he was discharged and fully recovered (59).

A 37-year-old man presented himself at the hospital with acute onset dysarthria, left hemiparesis and gait impairment. Since two days ago he had started to take two scoops of a supplement containing DMAA and caffeine before exercise. On the night before presentation at the hospital he drank two glasses of wine. CT revealed an acute haemorrhage in the right lentiform nucleus and internal capsule. Cerebral angiogram was normal (49) (abstract only).

Foley et al. reported seven cases involving DMAA-containing supplement use leading to acute liver injury. A 45-year-old female sailor presented to the hospital with 1 week of jaundice, fatigue, exercise intolerance and steatorrhea. She was using OxyELITE Pro™ for two years, and had stopped two weeks earlier because of increasing fatigue. She finally needed a liver transplant because of encephalopathy and coagulopathy. A 28-year-old male had been using OxyELITE Pro™ for about eight weeks when he developed fatigue, lethargy and jaundice. After stopping the supplement use, his symptoms continued and he was hospitalised for a liver transplant. A 19-year-old healthy male was suffering from persistent headache, abdominal pain and vomiting. He was using several sport supplements containing DMAA concomitantly, including OxyELITE Pro™, C4 Extreme, Jack3d and a proprietary sport enhancement blend, for three years. He recovered rapidly with supportive care. A 28-year-old healthy female had been taking OxyELITE Pro™ and C4 Extreme for a month when she developed nausea and abdominal pain. She was diagnosed with drug-induced liver injury and recovered with supportive care. A 23-year-old healthy male had recently begun taking OxyELITE Pro™ and RoxyLean supplements, when he was admitted to the hospital with abdominal discomfort and jaundice. He recovered with supportive care. A 23-year-old male Marine presented with complaints of jaundice and pruritus. He started using OxyELITE Pro™ about one week earlier. The diagnosis was acute hepatic dysfunction due to drug-induced liver injury secondary to supplement use. With supportive care he recovered. The last case is of a 24-year-old female who presented with persistent nausea and vomiting along with jaundice and pruritus. She was using OxyELITE Pro™ twice daily for a year. She was diagnosed with drug-induced liver injury due to supplement use. She recovered with supportive care (50).

A 17-year-old male was investigated because of hypertension. He reported no tobacco, alcohol or illicit drug use, and consumed one to two caffeinated beverages per day. He had been using dietary supplements as part of a training program with ingredients including ashwagandha, β-phenylethylamine, caffeine-based substances, creatine and DMAA. Because the man did not want to stop taking the supplements, medication was prescribed which was stopped after a few weeks due to compliance issues and systolic blood pressure being returned to normal levels (57).

A 20-year-old marine presented to the Emergency Department with an enlarged pupil without any other symptoms. She had been taking an increased amount of energy drinks including a supplement powder mix. During handling the mix she had rubbed her eye. Examination showed an assymetric, nonreactive pupil both directly and consensually. The pupil was unresponsive to pilocarpine challenges. She was diagnosed with potentially pharmacological dilation secondary to contact with the powder. (56).

Eight cases were reported of previously healthy but overweight individuals who presented themselves with acute drug-induced liver injury after using the new formula of OxyELITE Pro™ (containing aegeline[7] instead of DMAA according to the leaflet) following the recommendations of the manufacturer. The duration of the new formula use ranged from 2 to 6 weeks. Six of eight individuals had previously used the old formula (containing DMAA) for 3-24 months. Two of the patients used concomitantly another dietary supplement. Symptoms included myalgia, nausea, vomiting, abdominal pain, jaundice, fatigue, anorexia, rash, and confusion. Two patients needed a liver transplant, one died, four recovered and one was still recovering and on the transplant list. Causality assessment showed one case as highly probable and the other seven as probable (58).

Young et al. described the case of a 26-year-old active duty male who was presented to the hospital with a headache, left hemidysesthesia, weakness and lack of coordination. The man had taken three scoops, which is the maximum recommended use in 24 hours, of Jack3d followed by exercising. He was using the supplement for about three weeks. Eight weeks before admission he started the use of a hormone supplement which he discontinued after five weeks due to behavioural problems. In addition, he was using tobacco (four pack years) but quit a week prior. He had a right midbrain-thalamic haemorrhage, and was diagnosed with Dejerine-Roussy Syndrome, a lacunar thalamic stroke variant. There was also a small patent foramen ovale found in his heart but it was not expected that this resulted in the stroke (60).

In a retrospective study, data from the Texas Poisoning Center Network (6 poison centers covering a population of about 25 million) was gathered to describe the demographic and clinical characteristics and outcomes of exposure to DMAA-containing supplements in the period 2010-2011 (no cases were found between 2000 and 2010). Fifty-six cases were identified in which all exposures occurred via ingestion, 38 were unintentional (e.g. accidental ingestion by a child), eight were intentional (e.g. suspected attempted suicide), nine were adverse reactions to the product, and one for an unknown reason. Of the patients, 51.8% was male and 48.2% was female with a mean age of 11. The number of capsules taken varied between 1-4 for children ≤5 years, 1-3 for 6-19 years, and 1-30 for ≥20 years. In 47 cases (83.9%), no other substances were involved than DMAA-containing product. With respect to outcome, 45 (80.4%) of the total ingestions and 39 (83.0%) of the ingestions concerning DMAA-containing products only were known or expected to result in no or minor effect, not followed, and non-toxic or minimal effects expected. There were no deaths or major effects recorded, effects included cardiovascular, gastrointestinal or neurological effects such as tachycardia (28.6% of all cases), nausea (16.1% of all cases) and vomiting (12.5% of all cases) (51).

Johnston et al. reported a cluster of acute hepatitis and fulminant hepatic failure among individuals using OxyELITE Pro™. Thirty-six cases reported taking the supplement during two months before illness according to the recommended daily dose of 1-3 capsules or scoops. They did not use other common supplements. Causality assessment showed that in 94% of the cases the relation between supplement use and outcome was possible to probable (54).

A case of a 27-year-old male was reported who misused a DMAA-containing preparation called ‘Hydroxy Elite’. It was reported that, over time, he showed a marked change in behaviour, including irritability, increased impulsivity and risk-taking, decreased sleep and aggression, which resulted in a serious suicide attempt. After cessation of use, the symp-

[7] DMAA in OxyELITE Pro™ is in 2013 replaced by the manufacturer by aegeline

toms gradually resolved. An association with DMAA misuse was made (48) (abstract only).

Dunn reviewed human studies for the health effects of DMAA. The author concludes that the evidence base describing the adverse effects of DMAA is small as only 16 studies (of the 842) met the inclusion criteria. These studies included (16, 22, 34-40, 44-46, 50, 56, 59). It was noted that although serious adverse effects were reported, their prevalence and causal relationship with DMAA are still unclear (61).

Heidemann et al. described a case series of seven patients (one male, six females) with liver injury attributed to OxyELITE Pro™ (53). Six of the seven patients had symptoms of hepatitis and acute hepatocellular injury. Six were hospitalized of which three developed acute liver failure and two underwent liver transplantation. Of the patients that did not underwent transplantation, four recovered completely whereas one had mild residual elevations in alanine aminotransferase levels. They had used OxyELITE Pro™ according to the recommendations from the manufacturer for five to 102 weeks (median duration: 18 weeks). Three patients had been using other formulations of OxyELITE Pro™ without adverse effects prior to 2013. Causality assessment showed that a causal relationship between OxyELITE Pro™ use and liver injury was definite in one case, highly likely in three, probable in two, and possible in one.

Reports of consumers who ingested OxyELITE Pro™ alone or in combination with other dietary supplements and suffered from liver disease submitted to the FDA between February 2012 and February 2014 were investigated, and samples of OxyELITE Pro™ were analysed. In this period, 114 reports were received describing cases between January 2011 and January 2014 in which OxyELITE Pro™ was mentioned as the sole dietary supplement used in 85 cases (75%) and was used in combination with other supplements in the other 29 cases. In 55 cases (48%) liver disease was diagnosed without the presence of a viral cause, gallbladder disease, autoimmune disease or other known cause. Of these, 60% (n=33) was hospitalized and three needed a liver transplantation. In three cases, the consumers died from multi-organ failure (see (44)), atherosclerotic cardiovascular disease in combination with ingestion of multiple dietary supplements in addition to OxyELITE Pro™, and a brain aneurism after taking 13 capsules of OxyELITE Pro™ during a period of 27 days. Ingredients of OxyELITE Pro™ were listed in 22 reports showing the presence of DMAA in 12 cases, aegeline in 9 cases, and in one case initially DMAA followed by aegeline later on. Analysis of 18 samples (a.o. obtained from 13 cases) revealed the presence of combinations of aegeline (range: 33.2 mg/capsule – 112.0 mg/capsule), higenamine (range: 15.5 mg/capsule – 41.6 mg/capsule), caffeine and yohimbine (range: 1.6 mg/capsule – 3.2 mg/capsule), or a combination of DMAA, caffeine and yohimbine. Causality assessment performed by the FDA showed that a causal relationship between OxyELITE Pro™ and liver injury is likely based on the fact that the liver injury reversed after cessation of the product, in 55 cases other causes of liver injury were excluded, liver biopsies indicated drug-induced liver injury, and that the reported cases abruptly diminished after removal of the supplement from the market (55).

In a review where literature was searched for publications describing the possible hepatotoxicity of dietary supplements, 71 cases were found of subjects whom suffered from acute hepatitis or acute liver failure and where an association was found with using dietary supplements containing amongst others DMAA (52).

DMHA

Studies in humans

Four young adult males (25-32 years, 66-82 kg) were orally administered 1, 2 or 4 mg/kg DMHA HCl or other 6-methyl-2-heptylamine hydrochlorides with 200 mL water at three-day intervals two and a half hours after a light morning meal. No marked effects were noted after taking 1 or 2 mg/kg. At a dose of 4 mg/kg, the systolic blood pressure rose with 20-25 mmHg and the diastolic with 8-12 mmHg from around one hour post-ingestion till three to four hours post-ingestion. Pain in the stomach was reported after ingestion, together with dry mouth, pronounced pilomotor effects, urination, warm skin and sweating, decrease in finger plethysmograph volume, and involuntary sighing. Effects disappeared within three to four hours (92).