



Memorandum

Date August 24, 2021

From [REDACTED] (HFS-255)
Toxicology Reviewer
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Subject Updated review of available information pertaining to 1,3-dimethylamylamine: lack of general recognition of safety for its use in foods.

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Keywords: 1,3-dimethylamylamine (1,3-DMAA); 1,3-dimethylpentylamine; 4-methylhexan-2-amine; methylhexaneamine; geranamine; forthane; CAS# 105-41-9

This is an addendum to the October 3, 2016 memorandum that discussed the regulatory status and review of available information pertaining to 1,3-dimethylamylamine (1,3-DMAA) use in food. FDA previously concluded that based on the current status of data and information, 1,3-DMAA did not meet the experience based on common use in food (prior to 1958) criterion or the technical evidence of safety and the general recognition of safety necessary for it to be GRAS for use in food. Furthermore, the available information suggested that 1,3-DMAA use in food would raise serious safety concerns. Additionally, an addendum dated October 3, 2016 summarized the details of a review of additional information on 1,3-DMAA from an updated literature search conducted on September 6, 2016 and supplementary unpublished materials provided by the U.S. Department of Justice (Lammie, 2013), which identified no new information to support the safe use of 1,3-DMAA in food.

The Division of Food Ingredients’ (DFI) toxicology review team was asked to conduct an updated literature review to evaluate if any new scientific information has become available which would amend our previous conclusion regarding the GRAS status of 1,3-DMAA use in food. This addendum summarizes the findings of an updated search of publicly available information since the previous search was completed on September 6, 2016.

Overview of 1,3-DMAA

1,3-DMAA is an indirect sympathomimetic amine vasoconstrictor, likely exerting its physiological effects by influencing the release or reuptake of norepinephrine (Alsufyani & Docherty, 2019). 1,3-DMAA is a stimulatory molecule chemically similar to ephedrine. 1,3-DMAA is reported to have the CAS #:105-41-9 and is marketed under various trade names: methylhexanamine and geranamine, among others.

Literature Search Parameters and Results

A search of the scientific literature published since September 6, 2016 was conducted in two databases– PubMed¹ and Web of Science Core Collection². A search of the published scientific literature was conducted between June 3, 2021, and August 24, 2021. The results from PubMed and Web of Science Core Collection database using the search terms “1,3-dimethylamylamine”, “1,3-dimethylpentylamine”, “methylhexylamine”, and “geranamine”, and a publication date after September 6, 2016 are summarized in Table 1.

Table 1: Summary of literature search terms and results.

Search Terms	Database	Search Results (Number)
1,3-dimethylamylamine	PubMed	11
	Web of Science (Core Collection)	19
1,3-dimethylpentylamine	PubMed	2
	Web of Science (Core Collection)	2
methylhexylamine	PubMed	0
	Web of Science (Core Collection)	0
geranamine	PubMed	2
	Web of Science (Core Collection)	1

Based on these search criteria, several new publications related to 1,3-DMAA were identified, however, none were considered relevant to support the safe use of 1,3-DMAA as an ingredient in food. The available literature consisted of numerous publications reporting on the detection and quantification of 1,3-DMAA levels in dietary supplements (Cohen et al., 2018; Cohen et al.; dos Santos et al., 2018; dos Santos et al., 2019; Duiven et al., 2021; Eichner et al., 2016;

¹ Pubmed, <https://pubmed.ncbi.nlm.nih.gov/>, accessed between June 3, 2021 and August 24, 2021.

² Web of Science, <http://www.webofknowledge.com/>, accessed between June 3, 2021 and August 24, 2021.

Pellegrini et al., 2017; Zaremba et al., 2019; Zovico et al., 2016).

No studies conducted in laboratory animals supporting the safe use of 1,3-DMAA as an ingredient in food were identified in our updated review. A publication by Alsufyani and Docherty (2019) reported that 1,3-DMAA induced tachycardia and pressor response in rats via an indirect adrenergic action related to stimulated norepinephrine release (Alsufyani & Docherty, 2019). Another study reported the effects of the dietary supplement formulation OxyElite Pro™ produced by USPLabs on physical performance, metabolic parameters, liver injury markers and oxidative stress markers and mitochondrial biogenesis in skeletal muscle in male Wistar rats (Zovico et al., 2016). However, this study was not considered relevant to the updated review because the design was insufficient to address toxicity/safety and 1,3-DMAA was not the sole substance administered in this study. OxyElite Pro™ is described as a proprietary mixture which contains 1,3-DMAA as one of the ingredients.

No clinical studies supporting the safe use of 1,3-DMAA as an ingredient in food were identified in our updated review. A cross-sectional study of U.S. armed forces personnel reported that use of dietary supplements containing 1,3-DMAA was associated with multiple self-reported adverse events, including tachycardia, tremors, dizziness, and numbness/tingling sensations (Lieberman et al., 2018). FDA notes that such reports of adverse events associated with 1,3-DMAA use are cause for safety concerns and are inconsistent with general recognition of safety of use as a food ingredient.

Conclusion

Based on the updated literature search, no new information was identified that would amend our conclusion that there is no basis to conclude the use of 1,3-DMAA in food is GRAS.

The 1,3-DMAA memorandum dated October 3, 2016, contains excerpts which describes the lack of general recognition of safety for the use of 1,3-DMAA in “conventional foods”. DFI notes and further expands that the available data are insufficient to support the safety of 1,3-DMAA for use in “foods generally”. Additionally, 1,3-DMAA may be marketed as specific ionic salts which incorporate different counterions. 1,3-DMAA salts are anticipated to disassociate into its 1,3-DMAA (active) and counterion components when consumed. Therefore, in the absence of sufficient scientific evidence to demonstrate otherwise, all safety concerns identified in our reviews related to use or presence of 1,3-DMAA in foods are pertinent to all salt forms of 1,3-DMAA. Accordingly, our previous conclusion regarding the GRAS status of 1,3-DMAA use in food dated October 3, 2016, is applicable to all salt forms of 1,3-DMAA.



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