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Review

The JFFMA assessment of flavoring substances structurally related to menthol and uniquely used in Japan

Yoshiharu Mirokuji [a], Hajime Abe [b], Hiroyuki Okamura [a], Kenji Saito [a], Fumiko Sekiya [a], Shim-mo Hayashi [a], Shinpei Maruyama [a], Atsushi Ono [c], Madoka Nakajima [d], Masakuni Degawa [e], Shogo Ozawa [g], Makoto Shibutani [b,*], Tamio Maitani [f]

[a] Japan Flavor and Fragrance Materials Association, Sankei Nihonbashi Bldg. 6F, 4-7-1 Nihonbashi-Honcho, Chuo-ku, Tokyo 103-0023, Japan
[b] Laboratory of Veterinary Pathology, Tokyo University of Agriculture and Technology, 3-5-8 Saiwai-cho, Fuchu-shi, Tokyo 183-8509, Japan
[c] Division of Risk Assessment, National Institute of Health Sciences, Tokyo 158-8501, Japan
[d] Planning Department, Public Interest Incorporated Foundation, BioSafety Research Center, 582-2 Shioshinden, Iwata-shi, Shizuoka 437-1213, Japan
[e] Department of Molecular Toxicology, School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Suruga-ku, Shizuoka 422-8526, Japan
[f] School of Food and Nutritional Sciences, University of Shizuoka, 52-1 Yada, Suruga-ku, Shizuoka 422-8526, Japan
[g] Department of Pharmacodynamics and Molecular Genetics, School of Pharmacy, Iwate Medical University, 2-1-1 Nishitokuta, Yahaba-cho, Shiwa-gun, Iwate 028-3694, Japan

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ABSTRACT

Using the procedure devised by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), we performed safety evaluations on four flavoring substances structurally related to menthol (L-menthyl 2-methylbutyrate, DL-menthyl octanoate, DL-menthyl palmitate, and DL-menthyl stearate) uniquely used in Japan. While no genotoxicity study data were available in the literature, all four substances had no chemical structural alerts predictive of genotoxicity. Moreover, they all four are esters consisting of menthol and simple carboxylic acids that were assumed to be immediately hydrolyzed after ingestion and metabolized into innocuous substances for excretion. As menthol and carboxylic acids have no known genotoxicity, it was judged that the JECFA procedure could be applied to these four substances. According to Cramer's classification, these substances were categorized as class I based on their chemical structures. The estimated daily intakes for all four substances were within the range of 1.54–4.71 μg/person/day and 60–1250 μg/person/day, using the methods of Maximized Survey-Derived Intake and Single Portion Exposure Technique, respectively, based on the annual usage data of 2001, 2005, and 2010 in Japan. As the daily intakes of these substances were below the threshold of concern applied to class I substances viz., 1800 μg/person/day, it was concluded that all four substances raise no safety concerns when used for flavoring foods under the currently estimated intake levels.

Contents

Abbreviations: ADI, acceptable daily intake; EFSA, European Food Safety Authority; FEMA, Flavor and Extract Manufacturers Association; MSDI, Maximized Survey-Derived Intake; NOEL, no observed effect level; JECFA, Joint FAO/WHO Expert Committee on Food Additives; JFFMA, Japan Flavor and Fragrance Materials Association; JASREC, The JFFMA Safety Re-evaluation Committee; SAR, Structure Activity Relationship analyses; SPET, Single Portion Exposure Technique; WHO, World Health Organization.

* Corresponding author. Tel./fax: +81 42 367 5771.
E-mail address: mshibuta@cc.tuat.ac.jp (M. Shibutani).

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1. Introduction

1.1. Flavoring substances in Japan

There is a wide variety of flavoring substances that have no nutritional properties but are used to improve the taste and aroma of food. This wide variety enables the food industry to satisfy its requirement to mimic the flavor of foods. According to the annual usage survey by the Japan Flavor and Fragrance Materials Association (JFFMA), approximately 3230 flavoring substances have been used in Japan (Someya, 2012). Among these, 128 substances are currently approved as designated additives by the Ministry of Health, Labour and Welfare, Japan. The remaining 3102 substances have been classified into 18 chemical structure groups and approved for use in Japan under the Food Sanitation Act without any safety evaluation.

1.2. Safety evaluation procedures

In 1996, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) adopted a novel safety evaluation procedure for flavoring substances (WHO, 1996). According to this procedure, the safety evaluation of many flavoring substances can be efficiently conducted using the safety data for substances that have similar chemical structures or metabolic pathways, even if the substances under investigation have no safety data. Further evaluation methods similar to the JECFA procedure are used in the United States and the European Union. In addition, the results of safety evaluations by JECFA, Flavor and Extract Manufacturers Association (FEMA) and the European Food Safety Authority (EFSA) are now widely accepted in more than 70 countries (Someya, 2012; Konishi et al., in press). Since 2003, the Food Safety Commission of Japan has performed safety evaluations of 50 selected flavoring substances and their results are consistent with the group evaluation by the JECFA procedure (Someya, 2012).

From this viewpoint, regarding the approximately 3230 flavoring substances used in Japan, approximately 2400 flavoring substances have been judged safe under limited conditions of use for flavoring by JECFA, FEMA, EFSA, and the Food Safety Commission of Japan. However, this leaves 800 flavoring substances not yet subjected to safety evaluation by any governmental or international organization. For this reason, in 2009, JFFMA established a Safety Re-evaluation Committee (JASREC) comprised of expert scientists in the fields of toxicology and food chemistry as well as representative members of JFFMA. Since then, the JASREC has begun to evaluate substances uniquely used in Japan using the JECFA evaluation procedure as shown in Supplementary Fig. 1 with the order of priority determined by annual volume of production.

In this paper, we evaluate the safety of four flavoring substances structurally related to menthol, which have been uniquely used in Japan: L-menthyl 2-methylbutyrate, DL-menthyl octanoate, DL-menthyl palmitate, and DL-menthyl stearate, according to the JECFA evaluation procedure. These substances are all carboxylic acid esters of menthol having a menthol-like cool fresh flavor, and are used for manufacturing sweet foods such as chewing gum and candy.

2. Collecting information for evaluation procedure

2.1. Estimated daily intake of flavoring substances by MSDI and SPET methods

CAS No., chemical structure and molecular weight for these four flavoring substances, L-menthyl 2-methylbutyrate, DL-menthyl octanoate, DL-menthyl palmitate, and DL-menthyl stearate, are listed in Table 1. These substances have not been reported to occur naturally, and thus, all four substances are expected to be ingested only from foods containing them as flavoring agents (JFFMA, 2003, 2006, 2011). According to the annual usage data in 2001, 2005, and 2010 in Japan, the total annual estimated volumes of L-menthyl 2-methylbutyrate, DL-menthyl octanoate, DL-menthyl palmitate, and DL-menthyl stearate, are 0.11–10.34, 4.86–17.89, 0.10–5.98, and 3.10–5.83 kg, respectively (JFFMA, 2003, 2006, 2011). Based on these data, the daily intake of each substance was calculated using the methods of the Maximized Survey-Derived Intake (MSDI; Young et al., 2006) and Single Portion Exposure Technique (SPET; WHO, 2008).

MSDI method was developed based on disappearance data from periodic surveys of ingredient manufacturers using the volume of ingredients produced during the survey year (Young et al., 2006). Because the usage volume differs every year, the maximal usage volume of each substance was selected among annual usage data obtained to avoid underestimation of the intakes. The resultant daily intakes per person of the four flavoring substances were estimated to be in the range of 1.54–4.71 μg (Table 2).

By means of the SPET method (WHO, 2008), the estimated daily intakes of L-menthyl 2-methylbutyrate, DL-menthyl octanoate, DL-menthyl palmitate, and DL-menthyl stearate, were calculated to be 1250, 60, 60, and 250 μg, respectively, based on the average use levels for flavoring substance with standard portion sizes of flavoring foods (Table 2).

Because the estimated daily intakes by SPET method were higher than those by MSDI method, it was decided to conduct a safety evaluation using the calculation values of the SPET method.

2.2. Prediction of genotoxic potential by chemical structure and in silico models

We evaluated the genotoxic potential of each menthol-related substance by analyzing the biological potential of its chemical structure. While the JECFA decision tree approaches do not cover