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Review

Safety evaluation of substituted thiophenes used as flavoring ingredients

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ABSTRACT

This publication is the second in a series by the Expert Panel of the Flavor and Extract Manufacturers Association summarizing the conclusions of its third systematic re-evaluation of the safety of flavorings previously considered to be generally recognized as safe (GRAS) under conditions of intended use. Re-evaluation of GRAS status for flavorings is based on updated considerations of exposure, structural analogy, metabolism, pharmacokinetics and toxicology and includes a comprehensive review of the scientific information on the flavorings and structurally related substances. Of the 12 substituted thiophenes reviewed here, 11 were reaffirmed as GRAS based on their rapid absorption, metabolism and excretion in humans and animals; the low estimated dietary exposure from flavor use; the wide margins of safety between the conservative estimates of intake and the no-observed-adverse effect levels; and the lack of significant genotoxic and mutagenic potential. For one of the substituted thiophenes, 3-acetyl-2,5-dimethylthiophene, it was concluded that more detailed exposure information, comparative metabolism studies and comprehensive toxicity data, including an in-depth evaluation of the mechanism of action for any adverse effects observed, are required for continuation of its FEMA GRAS™ status. In the absence of these data, the compound was removed from the FEMA GRAS list.

Contents

Abbreviations: bw, body weight; CYP, cytochrome P450; DNA, deoxyribonucleic acid; DT, decision tree; F, female; FEMA, the Flavor and Extract Manufacturers Association; GLP, good laboratory practice; GRAS, generally recognized as safe; GRASa, GRAS affirmed; GRASr, GRAS reaffirmed; GSH, glutathione; *i.p.*, intraperitoneal; LD_{50}, median lethal dose; JECFA, Joint FAO/WHO Expert Committee on Food Additives; M, male; MNBN cells, micronucleated binucleate cells; MS, mass spectrometry; MSDI, maximized survey-derived intake; MTD, maximum tolerated dose; NA, data not available; NAS, National Academy of Science; NMR, nuclear magnetic resonance; NOAEL, no-observed-adverse effect level; NOEL, no-observed-effect level; NTP, National Toxicology Program; PADI, possible average daily intake; ppm, parts per million; S-9, metabolic activation system; TTC, threshold of toxicological concern.

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1. Introduction

Following the adoption of the 1958 Food Additive Amendment to the Food, Drug and Cosmetic Act (FDCA), the Flavor and Extract Manufacturers Association (FEMA) established the "generally recognized as safe" (GRAS) Program to evaluate the safety of food flavor ingredients based on scientific data. The safety of flavor ingredients is determined by the FEMA Expert Panel, a body of independent scientists in fields of biochemistry, toxicology and medicine who serve as reviewers of scientific data related to the safety of flavor ingredients (Smith et al., 2005a). The GRAS status of flavor ingredients is re-affirmed periodically as part of ongoing FEMA GRAS re-evaluations, a key component of the FEMA GRAS Program. Re-evaluations are prioritized when there is a significant increase in exposure, or a substantial body of new scientific data that has become available since the previous evaluation.

This paper is the second publication (following Marnett et al., 2014) from the third cycle of re-evaluations of the GRAS status of flavoring substances. It represents the Expert Panel's re-evaluation of the GRAS status of flavoring substances that belong to the group of substituted thiophenes, five-member aromatic heterocycles with sulfur as the only heteroatom in the ring. The current re-evaluation was initiated by the availability of new toxicity data, particularly genotoxicity data for a number of substances in the group, and new data on the metabolism of other representative substituted thiophenes.

2. Chemical identity

This group of twelve flavoring agents (Table 1) includes thiophene derivatives, which are five-membered heterocycles containing only sulfur as the ring heteroatom. The substances in this group are all ring-substituted with one or more of the following substituents or functional groups: aliphatic (3), thioether (1), disulfide (1), alkyl thiol (2), alkyl alcohol (1) and alkyl ketone (4) moieties (Table 1).

The structural class of the 12 thiophenes presented here was determined based on the Decision Tree (DT) criteria (Cramer et al., 1978), with 7 substances assigned to structural class II (FEMA Nos 3209, 4137, 4142, 4387, 4642, 4643, 4645) and 4 substances to class III (FEMA Nos 3062, 3323, 4184, 4646). The compound 3-acetyl-2,5-dimethylthiophene (previously FEMA No 3527) was assigned to structural class II.

3. Status as flavoring substances

Of the group of 12 substituted thiophene substances, four members, 2-thienyl mercaptan, 5-methyl-2-thiophenecarboxaldehyde, 2-thienyldisulfide and 3-acetyl-2,5-dimethylthiophene were originally assigned their FEMA GRAS status as part of the GRAS 3, 4, 5 and 11 publications, respectively (Hall and Oser, 1965, 1970; Oser and Hall, 1972; Oser and Ford, 1978). Subsequently, these substances were re-evaluated by the Expert Panel in 2001 and reaffirmed as GRAS under conditions of use as flavoring ingredients. The remaining eight members of this