



Stephen Tallon, Ph.D.
Callaghan Innovation
69 Gracefield Road
Lower Hutt 5040
NEW ZEALAND

Re: GRAS Notice No. GRN 000741

Dear Dr. Tallon:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000741. We received Callaghan Innovation (Callaghan)'s notice on November 2, 2017, and filed it on December 1, 2017. We received an amendment to the notice on February 22, 2018 pertaining to some study results in the notice.

The subject of the notice is dimethyl ether for use as an extraction solvent at levels ranging from 5 to 6 volumes per unit volume of food extracted (% v/v). The notice informs us of Callaghan's view that this use of dimethyl ether is GRAS through scientific procedures.

Callaghan provides information about the identity of dimethyl ether. Callaghan describes dimethyl ether as a gas at standard temperature and pressure. Dimethyl ether has a chemical formula of C_2H_6O and is designated by the CAS Registry Number 115-10-6.

Callaghan describes the manufacturing process of dimethyl ether. Dimethyl ether is produced by catalytic dehydration of methanol using a standard catalyst under high temperature and pressure conditions. No other reactants or processing aids are used in the manufacturing process. Following the production of dimethyl ether, the catalyst, unreacted methanol, and by-product water are removed from the system. Gaseous dimethyl ether is collected by condensation.

Callaghan provides food grade specifications for dimethyl ether. These include dimethyl ether content ($\geq 99.99\%$), as well as limits on residual methanol, water, and C1–C4 hydrocarbons. Callaghan provides results of five non-consecutive batch analyses to demonstrate that dimethyl ether can be manufactured to meet specifications. Callaghan states that dimethyl ether is stable at temperatures up to 80° C.

Callaghan estimates dietary exposure to dimethyl ether to be 0.03 mg/kg body weight (bw)/day (d) for a 60-kg individual based on the assumption that the extracted food ingredients (either lipid or defatted products) are consumed in the amount of 1 kg/d and

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dimethyl ether is present at the detection limit (2 mg/kg). Callaghan states that dietary exposure to dimethyl ether will be negligible due to rapid evaporation of any residual dimethyl ether present in food following processing. To support this statement, Callaghan provides results of analyses of five different extracted food ingredients to demonstrate that the residual levels of dimethyl ether were below the detection limit.

Callaghan relies on published findings and information to assess the safety of dimethyl ether. Callaghan discusses the characteristics of the absorption, distribution, metabolism, and excretion of inhaled dimethyl ether. Callaghan notes that following inhalation in rats, dimethyl ether is absorbed and distributed but it does not undergo metabolism prior to its elimination in expired air. Callaghan states that no oral toxicity studies for dimethyl ether were identified in the literature, and thus, discusses two published toxicity studies in which dimethyl ether was administered to rats via inhalation. Given the nature of dimethyl ether processing in the body, Callaghan assumes that internal systemic doses of dimethyl ether that result following inhalation and oral intake would be comparable, following the general principle of route-to-route extrapolation used by the European Food Safety Authority (EFSA).^{1,2} In the first inhalation study, rats were exposed to dimethyl ether for 13 weeks at dose levels of 0, 2,000, 10,000, or 20,000 ppm (equivalent to the internal doses, respectively, of 0, 728, 3,645 or 7,289 mg/kg bw/d in males and 0, 748, 3748, or 7,495 mg/kg bw/d in females). In the second inhalation study, rats were exposed to dimethyl ether for 30 weeks at dose levels of 0, 197, 1,964, or 18,830 ppm (equivalent to the internal doses, respectively, of 0, 63, 631, 6048 mg/kg bw/d in males and 0, 70, 701, 6,720 mg/kg bw/d in females). Callaghan considers the results of the dimethyl ether toxicity studies along with the dietary exposure estimate of 0.03 mg/kg bw/d and concludes that there are no safety concerns for dimethyl ether for its intended use. In addition, Callaghan discusses corroborative unpublished findings and information.

Based on the information presented in the notice, Callaghan concludes that dimethyl ether is GRAS for its intended uses in foods.

Section 301(II) of the FD&C Act

Section 301(II) of the FD&C Act prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under section 505 of the FD&C Act, a biological product licensed under section 351 of the Public Health Service Act, or a drug or a biological product for which substantial clinical investigations have been instituted and their existence made public, unless one of the exemptions in section 301(II)(1)-(4) applies. In our evaluation of Callaghan's notice concluding that dimethyl ether is GRAS under its intended conditions of use, we did not consider whether section 301(II) or any of its exemptions apply to foods containing dimethyl

¹ Safety in use of dimethyl ether as an extraction solvent. Scientific Opinion of the Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). EFSA Journal 2009; 7(3):984, 13 pp.

² Scientific Opinion on the safety of use of dimethyl ether as an extraction solvent under the intended conditions of use and the proposed maximum residual limits. EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). EFSA Journal 2015;13(7):4174, 13 pp.

ether. Accordingly, our response should not be construed to be a statement that foods containing dimethyl ether, if introduced or delivered for introduction into interstate commerce, would not violate section 301(l).

Conclusions

Based on the information that Callaghan provided, as well as other information available to FDA, we have no questions at this time regarding Callaghan's conclusion that dimethyl ether is GRAS under its intended conditions of use. This letter is not an affirmation that dimethyl ether is GRAS under 21 CFR 170.35. Unless noted above, our review did not address other provisions of the FD&C Act. Food ingredient manufacturers and food producers are responsible for ensuring that marketed products are safe and compliant with all applicable legal and regulatory requirements.

In accordance with 21 CFR 170.275(b)(2), the text of this letter responding to GRN 000741 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

**Michael A.
Adams -S**

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