FLAVOR AND EXTRACT MANUFACTURERS ASSOCIATION OF THE UNITED STATES
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Dr. Ruth Lunn
Director, Office of the RoC, DNTP
National Institute of Environmental Health Sciences
P.O. Box 12233
Research Triangle, NC 27709

Dear Dr. Lunn:

On behalf of the Flavor and Extract Manufacturers Association (FEMA), please find below additional information relevant to the nomination of alkenylbenzenes (selected dietary: estragole, myristicin, isosafrole) to the Report on Carcinogens.

Estragole was determined to be GRAS (Generally Recognized as Safe) by the FEMA Expert Panel in 1965 and is listed in the U.S. Code of Federal Regulations permitting use as a flavoring ingredient in food in the United States (21 CFR 172.515). In 2001, the FEMA Expert Panel re-evaluated the safety of methyl eugenol, a structurally related allyl alkoxybenzene, as a flavoring ingredient and concluded that:

> *...present exposure to methyl eugenol . . . resulting from consumption of food, mainly spices and added as such, does not pose a significant cancer risk. Nevertheless, further studies are needed to define both the nature and implications of the dose-response curve in rats at low levels of exposure to methyl eugenol . . ." (Smith et al., 2001).*

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) recently evaluated a group of allyl alkoxybenzenes, including methyl eugenol, present in foods and essential oils and used as flavouring agents (JECFA, 2009a). Their conclusions are summarized below:

> *The Committee concluded that the data reviewed on the six alkoxy-substituted allylbenzenes provide evidence of toxicity and carcinogenicity to rodents given high doses for several of these substances. A mechanistic understanding of these effects and their implications for human risk have yet to be fully explored and will have a significant impact on the assessment of health risks from alkoxy-substituted allylbenzenes at the*

concentrations at which they occur in food. Further research is needed to assess the potential risk to human health from low-level dietary exposure to alkoxy-substituted allylbenzenes present in foods and essential oils and used as flavouring agents.

Below we have summarized ongoing research to address the JECFA's and the FEMA Expert Panel's recommendations for further research. This research includes biochemical studies investigating the metabolic activation and detoxication of the reactive metabolites of methyl eugenol and its close structural relative, estragole, and the possible matrix effects in methyl eugenol and related alkoxy-substituted allylbenzene-containing naturals (e.g. basil oil) (see Biochemical Studies below). Research has also been undertaken to investigate the relationship of dose to the initiating effects for carcinogenesis (see Short-term Studies below). Although both of these research programs are not yet completed, the preliminary results are relevant to the Report on Carcinogens consideration of estragole, myristicin and isosafrole. Both programs are expected to be completed by the end of 2012.

Also presented is a short summary of a recent publication applying the margin of exposure (MoE) approach to methyl eugenol.

IOFI and FEMA would be pleased to continue to discuss this ongoing research program with the National Toxicology Program. Please contact us for further information and explanation as needed.

Sincerely,

[Redacted]

Timothy B. Adams
FEMA Senior Scientist
[Redacted]

Sean V. Taylor
FEMA Scientific Director