December 1, 2000

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Dear Dr. Wolfe:

On behalf of the the Flavor and Extract Manufacturers' Association (FEMA) and the FEMA Expert Panel, I request time to make an oral presentation concerning methyl eugenol, a nomination for listing in the 10th Report on Carcinogens. The written comments attached included the conclusions of the Workshop on Methyl Eugenol and Estragole convened by the Research Institute for Fragrance Materials (RIFM) and FEMA in May of 2000. The proceedings ofthe Workshop are scheduled for publication in the Journal of Food and Chemical Toxicology in mid 2001. A list of workshop participants and attendees are also attached. My oral presentation is scheduled to last between five and ten minutes.

Thank you for the opportunity to present this information on methyl eugenol.If you have any questions, please feel free to contact me at any time (202-331-2325)

Sincerely,
Dr. Timothy B. Adams, Scientific Secretary
The Flavor and Extract Manufacturers' Association
1620 I Street N.W.
Washington, D.C. 20006

The Safety Assessment of *Methyl Eugenol and Estragole* Used in Fragrance and Flavors

The Methyl eugenol(ME)/Estragole (E) Working Group (WG) of scientific experts evaluated the current toxicologic, metabolic, and exposure data on ME and E in a two-day workshop sponsored by the Flavor and Extract Manufacturers Association and the Research Institute for Fragrance Materials. The evaluation addressed questions raised by the National Toxicology Program (NTP) Draft Report concerning the safety of ME when it is used as a food flavoring substance and as a fragrance ingredient. Data on the structurally related alkoxyallylbenzene including E were considered relevant and also evaluated.

The WG agreed that NTP bioassays are hazard identification studies, not safety assessments. The WG noted that NTP bioassays may provide relevant data for safety assessment, if they are appropriately designed and conducted.

The WG concluded that the ME bioassay was compromised by inappropriately high dose levels, administered by gavage, that caused significant hepatic dysfunction, gastric damage, and malnutrition in both mice and rats. The presence of *Heliobacter hepaticus* in the livers of mice was also thought to have compromised the interpretation of the findings. The hepatic tumors occurred in severely damaged livers while neuroendocrine tumors were likely to have resulted from endocrine responses to chronic gastric damage. It was concluded that the data from this NTP bioassay were not adequate for assessing the safety of ME used as a flavoring substance or fragrance ingredient.

The combined exposure to ME from its presence in food, its use as an added flavor, and as a fragrance is estimated to be <10 _g/kg body weight/day and the combined exposure to E is approximately <10 _g/kg body weight/day.

Biomonitoring data from the U.S. population and experimental data from consumers of food containing ME confirm systemic exposure at very low levels.

Thus far, toxicity studies for ME and E have been performed at dose levels that were decidedly toxic and many orders of magnitude above those to which humans are exposed. The currently available data on metabolism, enzyme pharmacokinetics, protein and DNA adduct formation, and genotoxicity provide clear evidence of non-linearity in the dose-response relationship for ME and E. These data indicate that a no-effect level for ME, probably exists in the dose range of 1 - 10 mg/kg body weight/day. This level is approximately 1000 times the total exposure to ME from intake of food and from its use in fragrance products. For E, the no-effect level is likely to be significantly higher. Additional studies are needed to characterize the lower end of the dose-response curves for metabolic and toxicity endpoints. Further *in vivo* chronic studies should be performed 1) at doses that do not damage the glandular stomach and 2) using an mode of administration (*i.e.,* the diet) more relevant to human experience.

Based on the available data, the Working Group concluded that neither ME nor E are likely to present a human cancer risk at current levels of exposure arising from their addition to fragrance products and their occurrence in food added as such as flavoring substances, as constituents of added essential oils and primarily as naturally occurring components of traditional foods.

International Workshop on p-Alkoxyallylbenzene Derivatives- Methyleugenol and Estragole

Washington, D.C.
1, 2 May 2000

The Flavor and Extract Manufacturers' Association (FEMA) and Research Institute for Fragrance Materials (RIFM) jointly sponsored an international workshop to evaluate current state of the science on p-alkoxyallylbenzene derivatives. The group of substances included estragole, methyleugenol, and safrole. The objective of the workshop was to bring together government and academic scientists who have been actively involved in research related to the safe use of p-alkoxyallylbenzene derivatives as components of food, food flavorings and fragrance substances. Invitees from a broad range of disciplines presented their research results during the first day of the workshop. During the morning of the second day, panel meetings were convened in three major areas:

1. Assessment of Exposures
2. Toxicology/Pathology
3. Metabolism/Pharmacokinetics/Detoxication/Intoxication Mechanisms

Panels were composed of invited participants in their area of interest and a panel moderator. The purpose of each panel was to discuss the relevance of their research results to "terms of reference" which specifically address safe use of these substances as flavor and fragrance materials. A plenary of workshop members was held the afternoon of the second day to finalize responses to the terms of reference and discuss publication of the meeting proceedings.

Invited participants were requested to prepare a concise 1-2 page abstract of their presentation. Panel moderators were requested to prepare a summary of the results of the panel discussion including the current state of scientific knowledge concerning this group of substances. The content of workshop abstracts will be incorporated into the proceedings of the workshop planned for publication during early 2001.

List of Invited Participants and Attendees

Chairman of the Workshop

Dr. Robert Smith	Imperial College School of Medicine London, United Kingdom

Panel Moderators

Metabolism/Pharmacokinetics/ Detoxication/Intoxication Mechanisms	Dr. Philip Portoghese	University of Minnesota Minneapolis, Minnesota
Toxicology/Pathology	Dr. Adrianne Rogers	Boston University School of Medicine Boston, Massachusetts
Assessment of Exposures	Dr. Ron Walker	University of Surrey Surrey, United Kingdom

Researchers

Dr. Kamal Abdo	National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina
Dr. Tim Adams	Flavor and Extract Manufacturers' Association (FEMA) Washington, District of Columbia
Dr. John Bucher	National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina
Dr. John Caldwell	Imperial College School of Medicine London, United Kingdom
Dr. Mike Cunningham	National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina
Dr. Jay Goodman	Michigan State University East Lansing, Michigan
Dr. Thomas Guenthner	University of Illinois Chicago, Illinois
Dr. Gerry Kenna	Imperial College School of Medicine London, United Kingdom
Dr. George Lucier	National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina
Dr. Scott Masten	National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina
Dr. Glenn Sipes	University of Arizona Tucson, Arizona
Dr. Ladd Smith	Research Institute for Fragrance Materials (RIFM) Hackensack, New Jersey