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POSITION STATEMENT ON METHYL EUGENOL AND ESTRAGOLE: SAFETY WITH RESPECT TO USE AS FRAGRANCE INGREDIENTS (ADDED AS SUCH AND AS COMPONENTS OF NATURAL OILS)

INTRODUCTION

The Methyl Eugenol/Estragole Working Group of Scientific Experts (see attached list for composition) evaluated the current toxicological, metabolic, pharmacokinetic and exposure data for methyl eugenol (ME) and estragole (E) at a two-day Workshop sponsored by The Research Institute for Fragrance Materials and The Flavor and Extract Manufacturer's Association held in Washington, DC, May 1-2, 2000. The evaluation addressed questions raised by the issuance of the National Toxicology Program (NTP) Draft report of a chronic bioassay of ME in rats and mice. In particular the review raised major questions regarding the adequacy of the NTP study to address the safety assessment of ME, particularly at the low levels of exposure associated with its use as a fragrance ingredient. A summary of the outcome of this workshop has been previously circulated (see attached).

Since the safety review undertaken at the workshop focused on the exposure to ME when it was used as a component of essential oils and did not include exposure from its deliberate addition as such, that evaluation is regarded as being incomplete.

A second meeting of a sub-group of the original Working Party (referred to hereinafter) as the "Steering Group" was convened in New York on December 7-8, 2000 for the purposes of (1) to further discuss and determine exposure to ME from its use as such and as an ingredient of essential oils and (2) to identify and map out a sequence of further toxicology and metabolic/pharmacokinetic studies that were judged to be needed to assess definitively the safety of ME to humans at very low levels of exposure. The Steering Group also reviewed in detail a publication from the National Institutes of Environmental Health dealing with human biomonitoring studies, which have established the presence and levels of ME in the general U.S. population (Barr *et al.*, 2000, Environmental Health Perspectives, 108(4), 323-328).

EXPOSURE TO ME FROM FRAGRANCED PRODUCTS

The data for ME and E added as such (see Tables 1 and 2, respectively) are for average levels (using values greater than 1 ppm) and are for the 50 and 97.5 percentile use of fragrance compounds in fine fragrances. The data for ME and E in essential oils were similarly derived from typical essential oils containing ME and E in fine fragrances. Tables 1 and 2 also give the estimated total skin exposure from the use of multiple cosmetic products containing ME and E (added as such, from essential oils and total fragrance use).

TABLE 1: SUMMARY OF METHYL EUGENOL EXPOSURE IN FRAGRANCED PRODUCTS

Methyl Eugenol	Methyl Eugenol In Fragrance Compounds		Total Methyl Eugenol Human Dermal Exposure[3]	
	50th %ile	97.5%ile	50th %ile	97.5%ile
Added As Such[1]	0.061%	0.43%	1.55 μg/kg/day	11.21 μg/kg/day
From Essential Oils[2]	0.003%	0.05%	0.07 μg/kg/day	1.3 μg/kg/day
TOTAL			1.62 μg/kg/day	12.51 μg/kg/day

1 Reported by IFRA, August 30, 1999 (data from 2 members; 24/72 formulae contained ME directly added to fragrance compounds)

2 Reported by IFRA, October 19, 1999 (data from 6 members; typical essential oils containing ME in fine fragrances that were sold at more than 50 kg in 1998)

3 Calculated by exposure table detailed in Ford *et al*., 2000, Regulatory Toxicology and Pharmacology, 31, 166-181.

TABLE 2: SUMMARY OF ESTRAGOLE EXPOSURE IN FRAGRANCED PRODUCTS

Estragole	Estragole In Fragrance Compounds		Total Estragole Human Dermal Exposure[3]	
	50th %ile	97.5%ile	50th %ile	97.5%ile
Added As Such[1]	0.04%	0.8%	1.1 μg/kg/day	20.4 μg/kg/day
From Essential Oils[2]	0.02%	0.3%	0.5 μg/kg/day	7.6 μg/kg/day
TOTAL			1.6 μg/kg/day	28.0 μg/kg/day

1 Reported by IFRA, March 9, 1999 (data from 4 members; 739/2570 formulae contained E directly added to fragrance compounds)

2 Reported by IFRA, April 2, 2000 (data from 8 typical essential oils containing E in fine fragrances)

3 Calculated by exposure table detailed in Ford *et al*., 2000, Regulatory Toxicology and Pharmacology, 31, 166-181.

SAFETY ASSESSMENT OF ME IN FRAGRANCED PRODUCTS

For the purpose of the safety assessment of ME in fragranced products, the total human dermal exposure has been assumed to be 12.5 microgram/kg body weight/day. This is an extremely conservative assumption since it is derived from the 97.5 percentile use and it assumes 100% bioavailability through percutaneous absorption, which remains highly unlikely.

The currently available metabolic, biochemical and toxicological data found for ME in laboratory species provide clear evidence of non-linearity in the dose-response relationships for ME and E with respect to metabolic activation and mechanisms associated with the carcinogenic effects. Consideration of this data indicates, that in all probability, a No-Observed-Effect-Level (NOEL) for ME in the rat exists in the dose-range of 1-10 mg/kg body weight/kg. If the combined exposure to ME from its use in fragrance products (added as such and from essential oils) is taken as the conservative estimate of 12.5 microgram/kg body weight/day, then the margin of safety can be calculated to be in the range of 80-800, according to the NOEL. In the case of estragole there is metabolic evidence that the NOEL is likely to be significantly higher, perhaps in the region of 10-100 mg/kg. Thus, for a similar exposure, the margin of safety would be on the order of 360-3600.

CONCLUSION

Based on the available data, the ME Steering Group concluded, consistent with the conclusion from the May Meeting of the Working Group, that neither ME or E is likely to present a human cancer risk at current levels of exposure arising from their addition to fragranced products (added as such or from essential oils). However, in making this judgment, the ME Working Group also concluded that it is essential to undertake additional studies to characterize the lower-end of the dose-response curves for metabolic and toxicity endpoints. In addition, sub-chronic and chronic studies should be undertaken in order to characterize the NOEL at low levels of exposure and where damage to the glandular stomach does not occur as a confounding factor. This future work will allow a more reliable risk assessment to be based on proper hazard identification data.

The May Meeting of the Working Group agreed that NTP bioassays are hazard identifications, not safety assessments. The WG noted that NTP bioassays may provide relevant data for safety assessment, if they are appropriately designed and conducted. It was concluded that the data from this NTP bioassay were not adequate for assessing the safety of methyl eugenol at the very low levels of exposure consistent with its use as a flavoring substance or fragrance ingredient.

Approved by the RIFM EXPERT PANEL
May 7, 2001
Helmut A. Greim, Chairperson
David R. Bickers
Peter Calow
Jon M. Hanifin
Adrianne E. Rogers
Jean H. Saurat
I. Glenn Sipes
Robert L. Smith
Hachiro Tagami

International Workshop on p-Alkoxyallylbenzene Derivatives – Methyl Eugenol and Estragole

Ritz Carlton Hotel
Tyson's Corner, Virginia
May 1 and 2, 2000

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), District of Columbia
	Dr. Anne Marie Api*	The Research Institute for Fragrance Materials (RIFM), Hackensack, New Jersey
	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*	Astra-Zeneca Corporation London, United Kingdom
	Dr. Jim Knaak*	State University of New York at Buffalo Buffalo, New York
	Dr. Scott Masden*∞	National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina
	Dr. Glenn Sipes*	University of Arizona Tucson, Arizona
	Dr. Ladd Smith	The Research Institute for Fragrance Materials (RIFM), Hackensack, New Jersey

* Presenters
∞ NTP representatives were in attendance, but were not involved in any way in the preparation of the report.

Methyl Eugenol Steering Committee

December 7-8, 2000
RIFM Offices

Chairman of the Steering Committee	Dr. Robert Smith	Imperial College School of Medicine London, United Kingdom
	Dr. Tim Adams	Flavor and Extract Manufacturers' Association (FEMA), District of Columbia
	Dr. Anne Marie Api	The Research Institute for Fragrance Materials (RIFM), Hackensack, New Jersey
	Dr. John Caldwell	Imperial College School of Medicine London, United Kingdom
	Dr. Lawrence J. Marnett*	Vanderbilt University Nashville, Tennessee
	Dr. Adrianne Rogers	Boston University School of Medicine Boston, Massachusetts
	Dr. Glenn Sipes	University of Arizona Tucson, Arizona

* Not present at the December 2000 Steering Committee Meeting