Report of the Scientific Evaluation and Coordination Committee

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In the absence of Dr. Richard Hall and John Kirschman, I am pleased to present the report of the Scientific Evaluation and Coordination Committee. This is the third year I have served as the Consulting Director of Scientific Affairs for FEMA. It has been a very rewarding experience to work with the members of the Expert Panel, the SECC, the Board of Governors and individual members of FEMA.

This last year has been a very active one for the SECC. A number of significant new issues have risen and a number of important ongoing issues have required continued attention. This report will deal with a number of the topic areas.

MTS

The first topic is the Minimum Toxicity Screen (MTS). As you know, the LD_{50} has come under increasing scientific and social criticism as wasteful of animal life in comparison to the relevant data generated. While there are valid uses of the LD_{50} (determination of acute symptoms of overdose, approximate dosage range, comparison of acute toxicity for comparison and priority setting), the Expert Panel has decided to replace the classical LD_{50}. In its place, the MTS has been developed by Carrol Weil and myself to be employed in those cases where toxicity data is needed. Basically, the MTS consists of a 14-day dietary feeding study performed using five animals of each sex at a single dose level and a concurrent control preceded by a range-finding study.

FEXPAN

The second topic is the 25th Anniversary Celebration of the FEMA Expert Panel (FEXPAN). A splendid dinner commemorating this event was held April 2, 1985 at the Windows on the World Restaurant, World Trade Center in New York City, at which Dr. Bernard Oser was honored by being appointed as Chairman Emeritus of FEXPAN. As splendid as the affair actually was, it was but a token of the thanks that FEMA wants to express to Dr. Oser and the Expert Panel for their dedication and contributions to the industry for the last quarter century.

We note with pleasure that Dr. Lauren Woods, one of the original panel members, had served as Co-Chairman with Dr. Oser in 1984 and Mr. Carrol Weil will serve as Acting Chairman of FEXPAN for 1985.

While we regret the retirement of several panel members, we announce with pleasure the ap-

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pointment of Dr. Philip Portoghese as the newest member of FEXPAN. Dr. Portoghese, professor at the University of Minnesota, brings to the Panel expertise in biological receptor sites, organic chemistry, metabolic mechanisms and immune response.

α, β Unsaturated Ketones

The third topic is alpha, beta unsaturated ketones. Following a thorough review and study of a long-considered request by FEXPAN for more toxicity data on the alpha, beta unsaturated ketones, the SECC has nominated a number of compounds from which FEXPAN might select several for further testing. Fifteen out of forty FEMA GRAS alpha, beta unsaturated ketones are supported by studies of ninety days or longer. A literature search of the mutagenicity data base on these compounds has been completed. The additional data to be sought, at least as now foreseen, will concern metabolism and pharmacokinetics.

GRAS Applications

The committee has reaffirmed that it is the responsibility of companies making submissions to FEXPAN to perform complete literature reviews and have them included with their GRAS applications. Additional searches will not routinely be re-run by FEMA at the time of GRAS publication, but selected substances would be run as a quality control procedure. A new GRAS instruction sheet outlining the characteristics of the required literature search will be available in the near future.

FEMA Research Program

FEMA's Research Program at St. Mary's Hospital is on schedule. Publications are now appearing in press.

An example is the findings on estragole. The apparent primary carcinogenic metabolite of this substance is 1'-OH estragole. Toxicodynamics in humans and rats have shown both to be strongly dose related. Species differences are such that human exposures are 1/15,000,000 of those causing effects in rats. While this may make no difference under present practice with the Delaney Clause philosophy —that is, 1/15,000,000 is still not 0—it very much affects the risk extrapolation process.

Research on eugenol has shown that this route of metabolism (i.e., formation of 1-hydroxyeugenol) does not occur with eugenol. The work continues on eugenol and methyleugenol.

Similar comparative metabolism studies have begun on cinnamic and benzoic acids.

A manuscript for publication on disposition studies on cinnamyl anthranilate administered in the diet has been accepted for publication. A similar manuscript on the results of orallly administered benzyl acetate (BA) has been prepared. Current work on (BA) is designed to evaluate its disposition following dermal application.

GRAS 13

GRAS 13 was published in October 1984 and added eighty-nine new materials while three compounds were dropped from GRAS status. The related and important SLRs associated with this publication have been updated and are currently available through NTIS.

Process Flavors

The Board, FEXPAN, Hydrolyzed Vegetable Protein Committee, and the SECC are continuing a careful review of the issues involved in proper assurance of the safety in the use of process flavors.

Consumption Ratios

The concept of Consumption Ratios compares the natural occurrence of flavors in foods to that which is added to foods. The concept finally matured to the point that a paper "The Consumption Ratio of Flavoring Materials—A Mechanism for Priority Setting of Safety Evaluation" authored by Drs. Jan Stofberg and John C. Kirschman has been accepted for publication in *Food and Chemicals Toxicology*.

On the international scene, recent increased focus on safety review of flavors by the Council of Europe, Codex Alimentarius and the European Economic Community (EEC) warrants more intense liaison efforts from FEMA via the International Organization of the Flavor Industry (IOFI) and the Food & Drug Administration (FDA), as well as direct contacts (e.g. Joint Expert Committee on Food Additives) as appropriate. Committee assignments for such activities have been made. The SECC has directed me to begin attending some of these international meetings.

On the national scene, the final topic is the National Toxicology Program (NTP). Pursuant to the SECC's report at last year's annual meeting and lessons learned from our guest lecturer, Edith Efron, at the same meeting, NTP continues to warrant continuing attention from our industry.

Following a full year's effort, with much discussion and input from the SECC and other industry sectors, the Ad Hoc Panel (i.e., Doull Committee) submitted a final report to the NTP. NTP publicly reviewed this report with the Doull Committee on April 30, at which time there was little argument with any of the Panel's recommendations. According to the NTP, many of these suggestions have already been implemented.

Dr. Doull, Chairman, observed that his panel's report should be the first step only, and that NTP should have workshops to help with the scientific/regulatory interface which wasn't addressed in the report. Supported by comments from several of his panel members present at the meeting, Dr. Doull expressed concern about NTP's definition of the maximum tolerated dose (MTD). Dr. Doull felt it did not adequately incorporate his panel's discussion in reflecting the need for adding qualifiers. For example, in addition to no increased non-tumor related mortality, the MTD also *should not induce significant pathology other than irritation.* He also firmly stated that "NTP must look at the integrity of old studies and validate those on which regulatory decisions have been or will be based."

Dr. Pitot, a new member of the Board of Scientific Counselors, stated, "The bioassay is a qualitative test. We are in trouble if we use the MTD as a quantitative index for risk assessment." This is, of course, one of the major criticisms which FEMA has voiced for several years.

It appears that efforts now need to focus on the scientific/regulatory interface.

While the Doull Committee performed very well in its assignments, many of the issues prevailing at the time the panel was constituted in 1983 still have not been resolved. The charter, which was drawn up by NTP senior staff, specifically excluded the Panel from asking basic questions related to goals, purpose and function of the NTP and its bioassay program. These were and are the major concerns of FEMA. The important issues are not "what is the best number of animals employed in a study," but instead are "what is the purpose of each individual study and what was the basic data upon which the study was designed to meet that objective?"

It is one of our objectives to relegate the rote testing, check box type of toxicology to history.

The SECC thanks you for your attention and support.

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