

FEMA GRAS EVALUATION AND RE-EVALUATION OF FLAVOURING COMPLEX MIXTURES

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INTRODUCTION

Despite their incredible importance as food flavourings, there has not yet been significant effort placed on conducting scientifically-based safety evaluations of essential oils. This presentation reviews a safety re-evaluation programme for natural flavour complexes, including essential oils, currently being conducted by the Expert Panel of the Flavor and Extract Manufacturers Association (FEMA) and co-funded by IFEAT and the International Organization of the Flavor Industry (IOFI).

FEMA GRAS RE-EVALUATION OF NATURAL FLAVOUR COMPLEXES

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This project relies on an established paradigm for the safety evaluation of complex mixtures¹, a first of its kind approach that utilises sound science alongside the collection of analytical identification data, such that the safety of a complex mixture can be assessed by understanding the components of that mixture. But such an approach, while relying on expert judgment from a safety perspective, also requires that industry is willing to provide the necessary analytical data.

A WORD ABOUT TERMINOLOGY...

NFC = natural flavour complex
NCS = natural complex substance
NFC = NCS
For us, NFCs = NCSs = “naturals”

Essential Oils are NFCs
Essential Oils are NCSs
Essential Oils are “naturals”

The flavour industry usually uses the terms Natural Flavour Complex (NFC) and Natural Complex Substances (NCS).

NFC, for the purposes of this presentation, would be synonymous with NCS, and both of those terms would be synonymous with “naturals”. Essential oils are NFCs, they are NCSs, and therefore “naturals”.

THE FLAVOR AND EXTRACT MANUFACTURERS ASSOCIATION (FEMA) OF THE USA

The Flavor and Extract Manufacturers Association (FEMA) was established in 1909 in response to an increasingly challenging business climate, and a shared desire to ensure that there were strong standards in place for flavourings that were being used in food. Now well over 100 years old, FEMA continues to serve its more than 130 members, which includes companies that make flavours, those that use them, and other companies that have a strong interest in protecting and advancing the interests of the food flavouring industry in the United States. FEMA's primary mission is to assure flavour safety through the well-recognised FEMA Generally Recognised as Safe (GRAS) programme. In addition to this primary mission, FEMA also

FEMA

Flavor and Extract Manufacturers Association of the U.S.
FEMA was established in 1909 – over 100 years of service!
~130 members that include companies that make and use flavours.
Primary mission – Assure flavour safety through the FEMA GRAS programme.
Other work – Workplace safety, flavour and food labeling compliance, other regulatory matters.
Member of IOFI: The International Organization of the Flavor Industry

¹ Smith, 2004; Smith 2005

works with its members to support workplace safety, to educate and promote sound regulations regarding flavour and food labelling compliance, and to provide support and act as a voice to its members regarding other regulatory matters.

While FEMA is a US-based trade association, it operates in the international arena through its membership of the International Organization of the Flavor Industry (IOFI), which is an international trade association comprised of regional and national associations as well as company members. FEMA and IOFI work together, and in concert with other regional and national trade associations, to promote increasing harmonisation of food flavouring regulations around the world. Evidence of the success of this approach can be found in the fact that there are a number of countries that accept the FEMA GRAS list, either directly within their regulations, or by tacit reference.

THE REGULATION OF FLAVOURS IN THE USA

In 1938 the US Congress passed the Federal Food, Drug, and Cosmetic Act (FFDCA), which for the first time gave significant authority to the US Food and Drug Administration (FDA) to regulate the safety of substances added to food (www.FDA.gov). Twenty years later, in 1958, the FFDCA was amended by the Food Additives Amendment, which established a premarket approval process, controlled and conducted by the FDA, which was then required for all food ingredients unless they were considered to be “Generally Recognised as Safe” (GRAS). This amendment essentially established two classes of food ingredients: those that would go through the food additive petition process and those that could be, based on available data and scientific judgment by qualified experts, determined to be GRAS. Both substances are evaluated via a food additive petition process, and those that go through a GRAS determination, should meet the same high standards for safety. This point is often lost in criticisms of the GRAS process, but a stringent, thorough GRAS determination should ultimately (and only) result in a finding that the GRAS substance presents a “reasonable certainty of no harm”. In the absence of such a conclusion, the substance cannot be considered to be GRAS.

REGULATION OF FLAVOURS IN THE USA

Federal Food, Drug, and Cosmetic Act (FFDCA) of 1938:
U.S. Food and Drug Administration (FDA) regulates the safety of substances added to food. www.FDA.gov

Food Additives Amendments of 1958:
Established FDA premarket approval for all food ingredients unless ingredients are “generally recognised as safe” (GRAS).

GRAS

- GRAS based on the views of experts qualified by scientific training and experience to evaluate the safety of substances added to food
- Safety-based only: no risk/benefit
- Safety means “a reasonable certainty of no harm” as defined by FDA

As mentioned, GRAS relies on a careful evaluation by experts qualified by scientific training and expertise to evaluate the safety of substances added to food. This evaluation is purely safety-based; no risk/benefit considerations are made.

THE FEMA EXPERT PANEL

FEMA EXPERT PANEL

- Panel of Experts (6 – 8 members) in Toxicology, Organic Chemistry, Biochemistry, Metabolism and Pathology
 - Established in 1960
 - Scientifically independent but financially supported by industry
- Activities
 - Evaluate new flavouring materials for GRAS status
 - Natural flavour complexes (NFCs)
 - Chemically defined substances
 - Publishes the FEMA GRAS list (Food Technology; GRAS 327)
 - Review, remark upon relevant safety studies
 - **GRAS re-evaluations** – Panel continuously monitors usage and current information on FEMA GRAS flavouring materials

In response to the 1958 Food Additives Amendment, FEMA worked to develop the GRAS concept as it might apply to flavouring substances. This ultimately resulted, in 1960, in the formation of the FEMA Expert Panel, which has been conducting flavour safety evaluations since that time. The FEMA Expert Panel is typically comprised of 6 – 8 members with expertise in toxicology, organic chemistry, biochemistry, metabolism and pathology. While the work of the Panel is financially underwritten by the flavour

industry, the Panel remains fully scientifically independent and maintains very clear conflict of interest standards. The food and flavour industry has little to no direct contact with the Panel, to ensure this independence.

The Panel's principal function is to conduct safety evaluations (i.e. GRAS evaluations) for potential new flavourings. This includes GRAS evaluations for both chemically defined substances, as well as for natural flavouring complexes (NFCs). The outcomes of these GRAS evaluations are published in the form of FEMA GRAS lists, which are put into the journal *Food Technology* every 2-3 years. The first GRAS publication that listed the identity of FEMA GRAS substances was the so-called "GRAS 3" publication, in 1965. The Expert Panel published its GRAS 27 publication in August 2015.

In addition to new GRAS evaluations, the Panel also considers any newly available safety or exposure data for flavourings that are already considered to be FEMA GRAS. It is this function that has given rise to the FEMA GRAS re-evaluation of NFCs, including essential oils described in this presentation.

NFC GRAS AFFIRMATION PROJECT – STARTING POINT

There are >300 NFCs, including >200 essential oils, that are considered FEMA GRAS and that are currently used as food flavourings. Many of these NFCs were published in the very first GRAS list publication, the GRAS 3 publication from 1970, and since that time there has been very limited safety evaluation activity. Due to this, one might ask how we know that these NFCs are safe for use in human food. While the long history of use provides a helpful and comforting assurance of safety, conducting a scientifically-based safety evaluation provides a significant and important additional assurance.

NFC GRAS AFFIRMATION PROJECT – STARTING POINT

- There are >200 essential oils that are considered FEMA GRAS and that are currently used as food flavourings.
- Many NFCs published in very first GRAS list publication (GRAS 3, 1970)
- *How do we know that they are safe?*
 - Internationally, very limited safety evaluation activity since then
 - Recognised need for GRAS affirmations for NFCs
 - *Current data profiles on NFCs*
 - *Review current science*
 - *Review current usage*

IFEAT/IOFI FEMA GRAS RE-EVALUATION/AFFIRMATION PROJECT

IFEAT/IOFI GRAS RE-EVALUATION/AFFIRMATION PROJECT

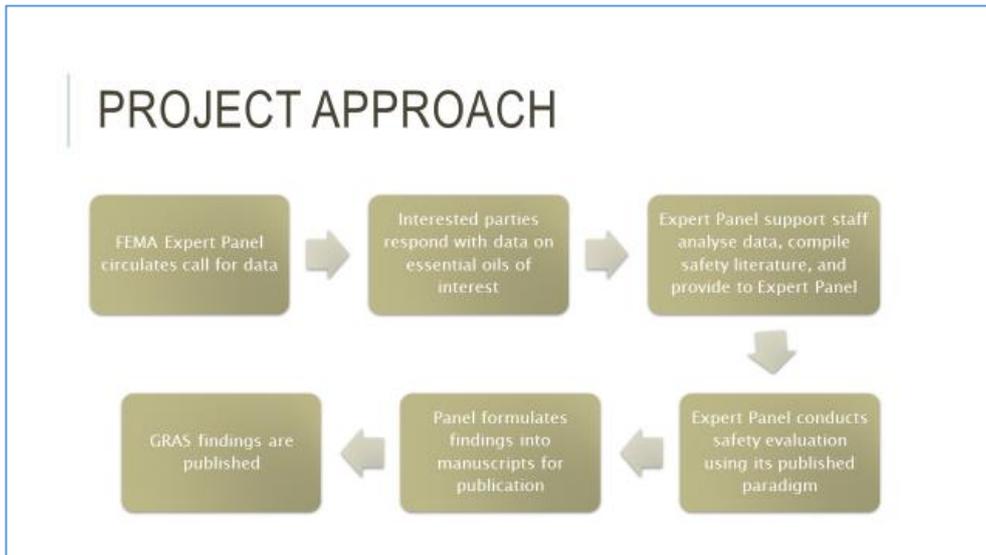
- FEXPAN multi-year project to conduct GRAS re-affirmations of ~250 Natural Complex Substances (NCS), including essential oils and related materials
- Initiated by FEMA Board, jointly funded by IOFI and the International Federation of Essential Oils and Aroma Trades (IFEAT)
- Program is executed by the Expert Panel but has oversight by IOFI Science Board & regular reporting to IFEAT (via technical advisor), FEMA, and IOFI
- Global NCS coordination group (IOFI/FEMA/EFEO/IFEAT/IFRA/RIFM)

Based on the above considerations, a programme of safety evaluation has been proposed by FEMA's Board of Governors, and is now jointly funded by IOFI and IFEAT. In this project, the FEMA Expert Panel is conducting a multi-year project to conduct GRAS re-affirmations of ~250 Natural Complex Substances (NCSs), including essential oils and related materials. Practically, this means that the Panel is reviewing the available identification data, exposure data, and safety data for each

NFC/essential oil for which data become available. While the programme is executed by the FEMA Expert Panel, who maintain scientific and functional independence, industry oversight is provided by the IOFI Science Board, a group of flavour and food industry toxicologists with expertise in flavour safety issues. Regular reporting is provided to IFEAT (via an appointed technical adviser), as well as to the FEMA and IOFI Boards. In addition, the flavour and fragrance industries, working with groups within the essential oils world, have developed a global NCS coordination group that receives information about the progress of this programme.

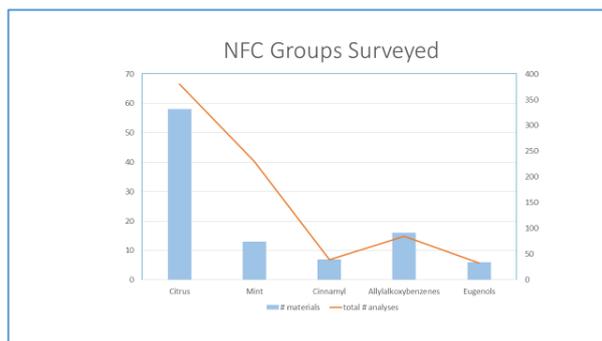
PROJECT APPROACH

The approach to the project by the Panel is straightforward. The Panel circulates a call for data on a periodic basis to interested parties. Each call for data requests analytical information (identity of constituents, physical property information, etc.) on a large number (~50) of NFCs. Those interested parties that have data available respond. The Expert Panel, supported by the FEMA and IOFI scientific staff, analyse the data provided and shape it into a form appropriate for FEMA GRAS re-evaluation. In addition, an exhaustive search of the published literature is conducted, and relevant unpublished references are identified and acquired. The Panel then utilises all of this data to make a GRAS determination, which it then publishes in the peer-reviewed literature. The detailed steps are described below.



Thus far, the response to the calls for data have been generally robust, and sufficient data have been collected for the majority of essential oils to conduct a safety evaluation. As the programme focuses on more arcane essential oils, with little to no use, it will be possible that insufficient data are collected. If no evidence of any global use can be found, these NFCs could be candidates to be removed from the FEMA GRAS list.

The Panel has requested data regarding the identity of the constituents, which is critical for the safety evaluation paradigm in use by them. However, much additional data has been requested and in many cases provided. Information regarding the method of production, including the natural source, physical property data, and the analytical methodology used in the collection of the constituent identity information is now available for many of these essential oils. While some of this data were available in disparate sources previously, this project will ultimately provide a significant compendium of information for essential oils.



FEMA EXPERT PANEL RE-EVALUATION – DATA COLLECTION

FEMA No.	0000	FEMA No.	Component Name	Analysis 1	Analysis 2
0001	Citrus Fruit Oil	0001	Limonene	05/01	08/02
0002	Essential Oil of Citrus	0002	alpha-pinene	05/01	08/02
0003	Essential Oil of Citrus	0003	beta-pinene	05/01	08/02
0004	Essential Oil of Citrus	0004	gamma-terpinene	05/01	08/02
0005	Essential Oil of Citrus	0005	linalyl acetate	05/01	08/02
0006	Essential Oil of Citrus	0006	linalool	05/01	08/02
0007	Essential Oil of Citrus	0007	geranyl acetate	05/01	08/02
0008	Essential Oil of Citrus	0008	geraniol	05/01	08/02
0009	Essential Oil of Citrus	0009	nerolidol	05/01	08/02
0010	Essential Oil of Citrus	0010	nerol	05/01	08/02
0011	Essential Oil of Citrus	0011	trans-nerolidol	05/01	08/02
0012	Essential Oil of Citrus	0012	trans-nerol	05/01	08/02
0013	Essential Oil of Citrus	0013	trans-nerolidol	05/01	08/02
0014	Essential Oil of Citrus	0014	trans-nerol	05/01	08/02
0015	Essential Oil of Citrus	0015	trans-nerolidol	05/01	08/02
0016	Essential Oil of Citrus	0016	trans-nerol	05/01	08/02
0017	Essential Oil of Citrus	0017	trans-nerolidol	05/01	08/02
0018	Essential Oil of Citrus	0018	trans-nerol	05/01	08/02
0019	Essential Oil of Citrus	0019	trans-nerolidol	05/01	08/02
0020	Essential Oil of Citrus	0020	trans-nerol	05/01	08/02

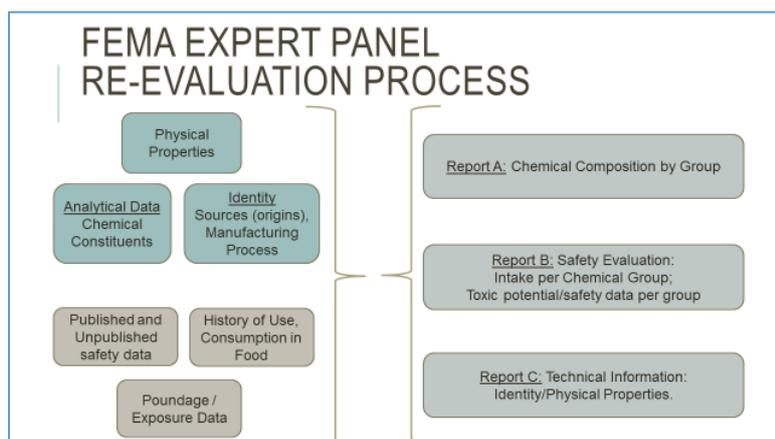
HOW THE FEMA EXPERT PANEL EVALUATES ESSENTIAL OILS (Smith, 2005)

As noted above, for this project the Panel begins with some initial assumption of safety based on a long history of use. However, the FEMA Expert Panel paradigm provides a scientifically-based approach to their safety evaluation. In essence, the Panel’s paradigm relies on two fundamental points: that all NFCs are in fact chemical mixtures and that any complex mixture can possibly be evaluated by evaluating the components that are used to compose that mixture.

HOW THE FEMA EXPERT PANEL EVALUATES ESSENTIAL OILS (SMITH, 2005)

- Panel notes that based on long history of use, many/most NFCs/essential oils can be assumed to be safe
- However, the FEMA Expert Panel paradigm provides a scientifically-based approach to their safety evaluation
- NFCs are chemical mixtures
- Fundamental approach: evaluate the components to conclude upon the safety of the whole

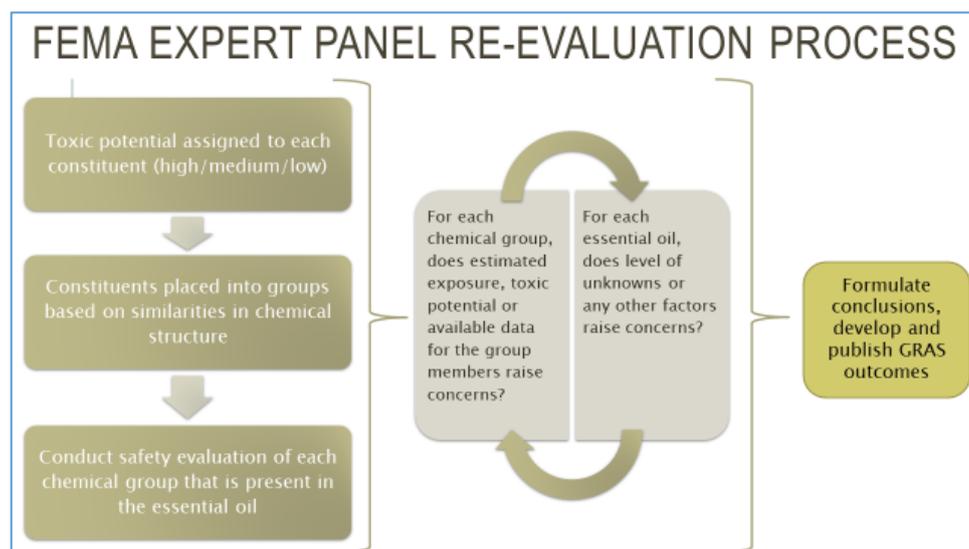
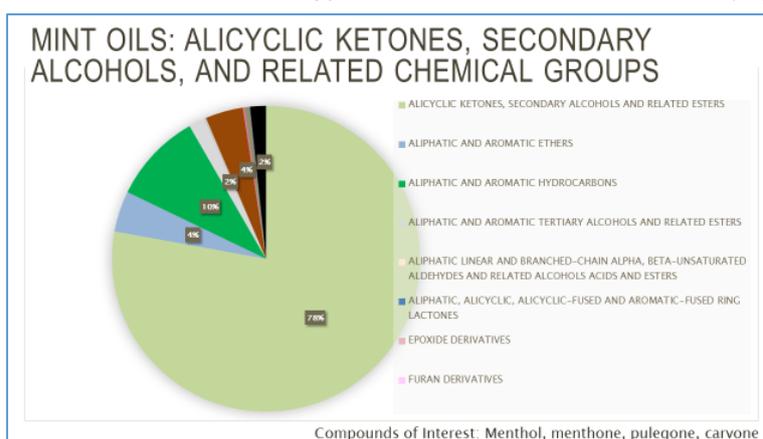
FEMA EXPERT PANEL RE-EVALUATION PROCESS



In the Panel's approach, much of the data that is supplied in response to the call for data—chemical constituent identification data, physical property data, and information related to the source and method of production—is combined with data that is available from other sources, such as the reported volumes of use (from flavour industry surveys), the levels at which the NFCs are used in flavours, and published and unpublished safety data. The data compilations are

used to produce reports for the Panel to evaluate. For each type of NFC within a call for data (e.g.

mint oils, citrus oils, etc.), a report on the chemical composition of the NFC is produced that has grouped the various constituents into chemical groups—groups of constituents related by chemical structure similarity and a likely shared behaviour in the human body. A second report focuses on the toxic potential of each chemical group that is identified within an NFC, as well as the available safety data and the available estimates of human exposure. Finally, a third report is presented that provides the technical information for each NFC, including the physical properties.



While all three reports are important and are reviewed by the Panel, it is the first two that provide the core information for the NFC re-evaluations. A consideration of the toxic potential for each constituent, and therefore an understanding of the toxic potential for each chemical group, is combined with the exposure estimates and the available toxicity data. This allows the Panel to ask a fundamental question: “For each chemical group, does estimated exposure, toxic potential or available data for the group members raise concerns?”

While analytical methodologies have very significantly increased our ability to almost fully describe essential oils and many other NFCs, there is still going to be a small percentage of unknowns (unidentified constituents) within the NFC. And this leads the Panel to ask a second fundamental question: “For each essential oil, does the level of unknowns or any other factors raise concerns?”

If the answers to both of these questions are no, then the Panel can typically make a determination that the FEMA GRAS status of the material can be affirmed. If the first question is answered by a “yes”, then it is likely that the Panel will ask for additional safety information, or possibly a refined exposure assessment. If the answer to the second question is “yes”, then it is likely that the Panel will request that the level of unknowns be reduced prior to drawing any conclusions about the GRAS status or request additional safety data to complete the evaluation.

In this way, the Panel has thus far conducted safety evaluations for more than 100 of the roughly 250 NFCs that are the scope of this programme. After two years, the programme is generally on schedule, with safety evaluations desired to be complete within 5 years (and publications to be in progress).

CURRENT STATUS/FUTURE PLANS

	Call for Data	Data Collection	Update Constituent Database	Data Analysis	FECPAN Safety Evaluation	Industry Expert Review	Manuscript Preparation - Draft 1	FECPAN Manuscript Review	Manuscript Revision	Manuscript submitted for publication
Citrus oils	February 2015								In progress	
Mint oils	December 2015					In planning	In progress			
Cinnamyls	December 2015									
Alkylbenzene containing oils	December 2015									
Eugenol-containing oils	December 2015									
"Uniques"	December 2015									
Tuberose										
Walnut Hull Extract										
Haw Bark Black Extract										
~50 NFCs	December 2016									
~50 NFCs	December 2017									
~50 NFCs	December 2018									

NFC GRAS RE-EVALUATION INTERNATIONAL IMPACT

IFEAT and IOFI provided support to this programme because it was concluded that conducting these safety evaluations would provide significant international impact, such as:

NFC GRAS RE-EVALUATION INTERNATIONAL IMPACT

Results of the GRAS evaluations could be used by global regulators in other formats (REACH/JECFA/EFSA...) in the coming years

Reinforce confidence in the safety of essential oils used as flavouring ingredients: essential oils are given a documented, scientific safety evaluation

Provide a format for addressing challenging constituents within natural complex mixtures

Provides a route for recognising and imparting FEMA GRAS status on NFCs that 'deserve' their own FEMA GRAS numbers

- The results of the GRAS evaluations could be used by global regulators in other formats (REACH/JECFA/EFSA...) in the coming years;
- This programme can reinforce confidence in the safety of essential oils used as flavouring ingredients: essential oils are given a documented, scientific safety evaluation;
- This programme, as it is the first of its kind for NFCs and essential oils, provides a format for addressing challenging constituents within natural complex mixtures;
- During the analyses that have been conducted thus far, it has been observed that some of the analytical data support a separation of NFCs that are currently “captured” under an existing FEMA GRAS number. The Panel has concluded that these materials should be granted new FEMA GRAS numbers, and be separately added to the FEMA GRAS list, if they are currently in use.

THANK YOU



Sean V. Taylor, PhD, is the Scientific Director of the International Organization of the Flavor Industry (IOFI), the Scientific Secretary to the Expert Panel of the Flavor and Extract Manufacturers Association (FEMA), and is a Managing Director of Verto Solutions, a trade association management and scientific consulting firm based in Washington, DC. He received a Bachelor's degree in Chemistry from Penn State University in 1992, a Master's degree from Cornell University in 1995, and a PhD in Chemistry from Cornell in 1998. From 1998-2002, he carried out postdoctoral research in protein engineering, directed evolution, and natural product biosynthetic pathways at the Swiss Federal Institute of Technology in Zürich, Switzerland. Dr. Taylor was an Assistant Professor in the Department of Chemistry at The Ohio State University from 2002 to 2005 before beginning his work with the flavour industry, initially as the Assistant Scientific Director for FEMA. In 2012 he was named the Scientific Director for FEMA, as well as the Scientific Secretary to the FEMA Expert Panel. In 2013, he assumed the role of Scientific Director for IOFO while continuing his role as Scientific Secretary to the FEMA Expert Panel. He serves as a senior scientific advisor to the International Association of Color Manufacturers, and provides scientific advice and consulting services to food ingredient and consumer products companies around the world.