INDEPENDENT GRAS & SAFETY ASSESSMENT PROGRAMS

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SUCCESSFUL PROGRAMS

- Flavor and Extract Manufacturers Association - FEMA GRAS – Flavors
- Cosmetic Ingredient Review - CIR – Cosmetic Ingredients
- International Pharmaceutical Excipients Council (IPEC) – New Excipient Safety Evaluation Procedure – Pharmaceutical Excipients
- Self Affirmed GRAS – Expert Toxicologist Panel performs safety assessment of a food additive on behalf of a sponsor
  - Currently there are some questions being raised about this process by some consumer groups, however, this process has been very useful and has been handled credibly by industry. IFAC is working on a guideline for Best Practices.

FEMA's approach to GRAS

General recognition

- Must be general and not known to applicant only
- Must be published in open literature

Among experts

- GRAS reviewers must be true experts (training & experience)
- Independence is crucial

Safety through scientific procedures

- Sound, recognized scientific principles for evaluation

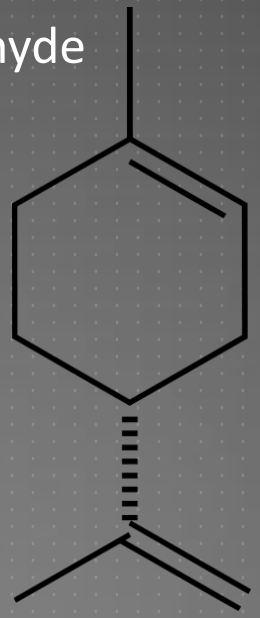
GRAS status only applies under its conditions of intended use

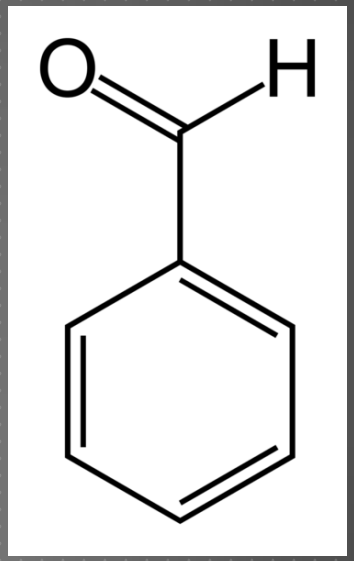
- GRAS for use as a flavoring substance, not for other purposes

ABOUT FLAVORS

Single chemically defined flavoring substances

- Individual substances – limonene, benzaldehyde
- May be natural or synthetic in origin
- Most have simple structures
- More than 2,400 are FEMA GRAS





Natural flavor complexes

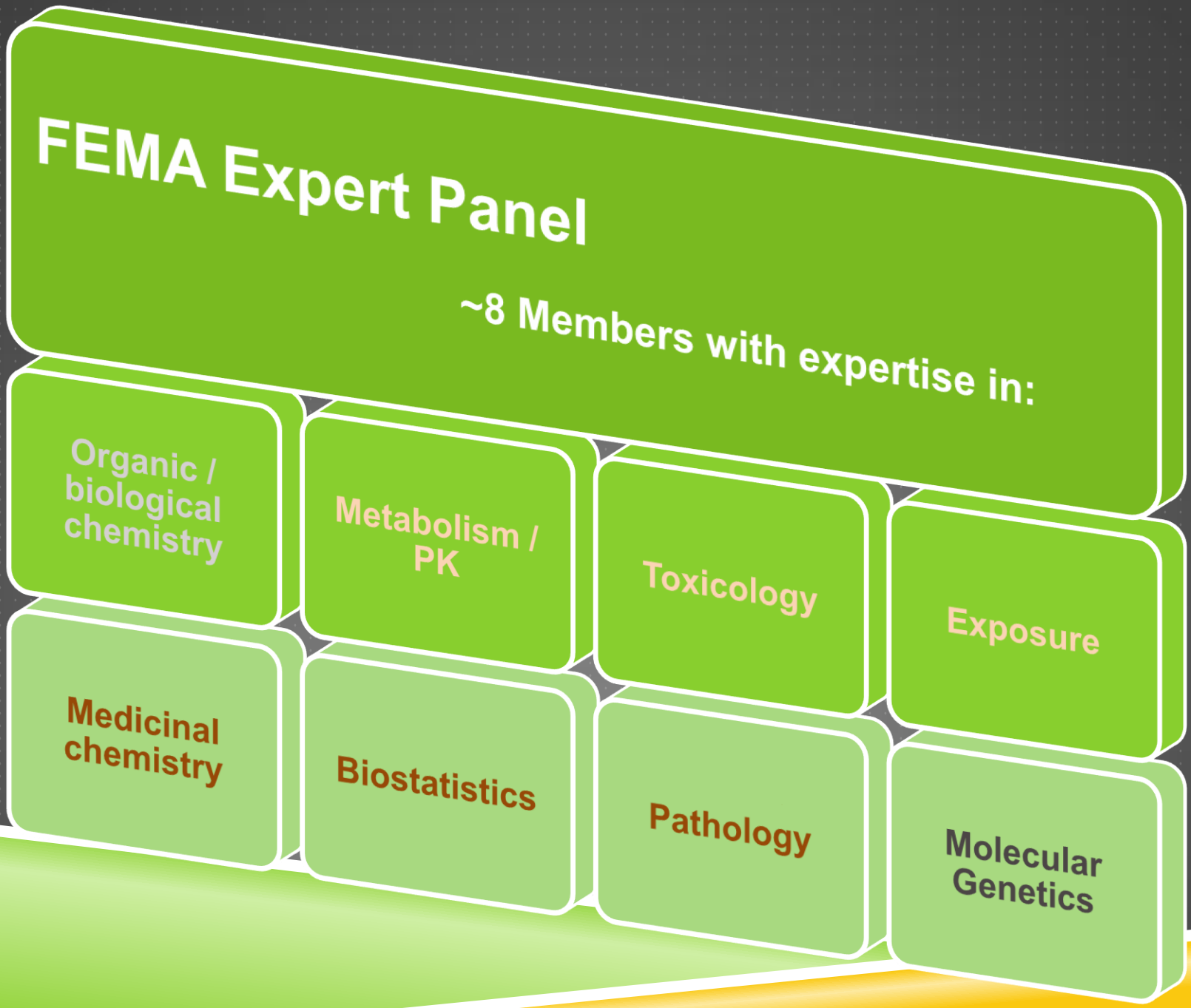
- Essential oils, extracts
- Orange oil, vanilla extract
- More than 300 are FEMA GRAS

FLAVORS: WELL-SUITED FOR GRAS

Compounded flavors

- Composed of flavoring substances and/or natural flavor complexes *plus* adjuvants to make the flavor functional in food/beverage (e.g., emulsifiers, preservatives)
- Uses many, many flavoring substances to create endless combinations
- Individual flavoring substances are commonly used in very low ppm levels (i.e., very low exposure)

FEMA GRAS applies only to single chemically defined flavoring substances, natural flavor complexes, and adjuvants, not to compounded flavors


FEMA Expert Panel
~8 Members with expertise in:
Organic / biological chemistry
Metabolism / PK
Toxicology
Exposure
Medicinal chemistry
Biostatistics
Pathology
Molecular Genetics

THE FEMA GRAS PROGRAM

Expert Panel is financially supported by FEMA and GRAS fees, but has full scientific independence

- Applicants for GRAS status are not allowed contact with the Panel
- Interaction between Panel and applicant occurs through FEMA staff
- The Panel is free to accept, reject, or defer action on GRAS applications
- Panel membership is not controlled by industry; FEMA Expert Panel chooses its members

THE FEMA GRAS PROCESS

GRAS assessment of single chemically defined flavoring substances

- Well-defined criteria for GRAS assessment – Smith et al., 2004
- Chemical identity – specifications
- Exposure – amount consumed (volume of use, use levels)
- Safety data – toxicology, metabolism, pharmacokinetics for substance plus structural analogs

Natural flavor complexes

- Well-defined criteria for GRAS assessment – Smith et al., 2004, 2005
- Constituent-based approach ('sum of parts' evaluation)
- Characterization
- Exposure (volume of use, use levels)
- Safety data on constituents

THE FEMA GRAS PROCESS

Panel evaluates data, concludes on:

- **FEMA GRAS** status under conditions of intended use as a flavor ingredient
- **HOLD** status, with a request for additional information to be supplied by applicant (e.g., toxicity study, additional specification information)
- **DENY** status, in that the Panel concludes the ingredient can not be considered generally recognized as safe for use as a flavoring ingredient

THE FEMA GRAS PROCESS

If GRAS status is granted by the Expert Panel:

- Successful applicant is notified
- Flavoring substance will be included in the next FEMA GRAS publication in *Food Technology*
- All information supporting GRAS status provided to FDA

Publication and data-sharing with FDA are key to address "general recognition" requirement

FEMA GRAS POST-MARKET MONITORING

FEMA GRAS evaluations are pre-market, but post-market vigilance is crucial

- Post-market monitoring of flavor usage via 5-year volume of use surveys
- Periodic re-evaluations of FEMA GRAS substances
  - Chemical Group evaluations
  - Publication in Food Chem. Toxicol., other formats as useful
- Evaluation of relevant new data on FEMA GRAS materials as it becomes available
  - NTP studies, published literature studies, etc.

The Cosmetic Ingredient Review

www.cir-safety.org

CTFA
Cosmetic, Toiletry, and Fragrance Association

The Cosmetic Ingredient Review

- Founded in 1976
- Written procedures similar to those regulating the U.S. Food and Drug Administration's Over the Counter Drug Review
- Financial Support

CTFA
Cosmetic, Toiletry, and Fragrance Association

Mission

- To thoroughly evaluate all available information on the safety of ingredients used in cosmetics in an open and unbiased, scientific manner,
- To determine if there is a reasonable certainty, in the judgment of competent scientists, that the ingredient is safe under its conditions of use,
- To publish the results of the evaluations and determinations in the open scientific literature.

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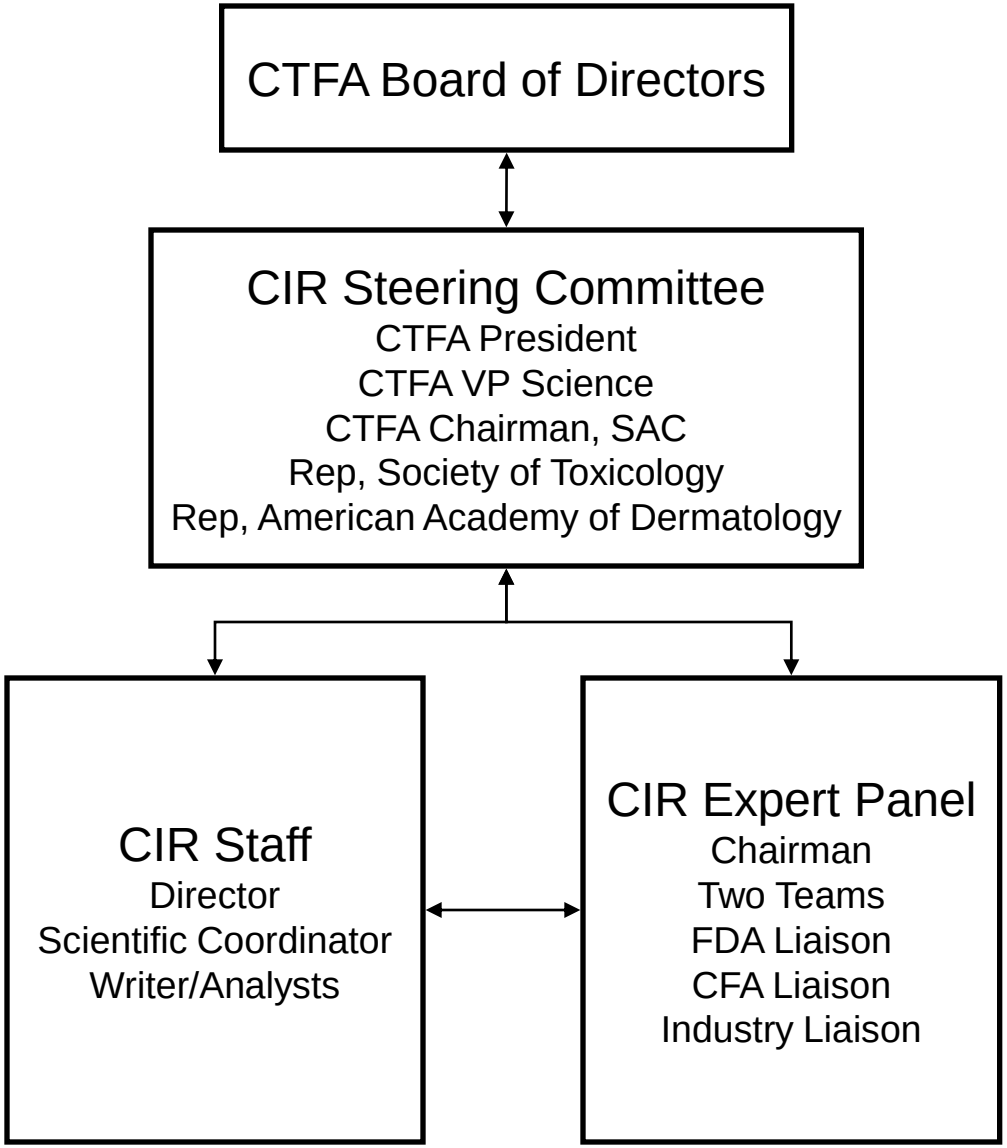

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Criteria for Assessing Safety

- Chemical structure and chemical/physical properties
- Method of manufacture and impurities
- Product use and concentration
- Oral, ocular, inhalation, and dermal toxicity, acute and chronic
- Allergenicity and Photosensitivity
- Absorption, distribution, metabolism and excretion
- Genotoxicity
- Teratogenicity/reproductive toxicity
- Carcinogenicity

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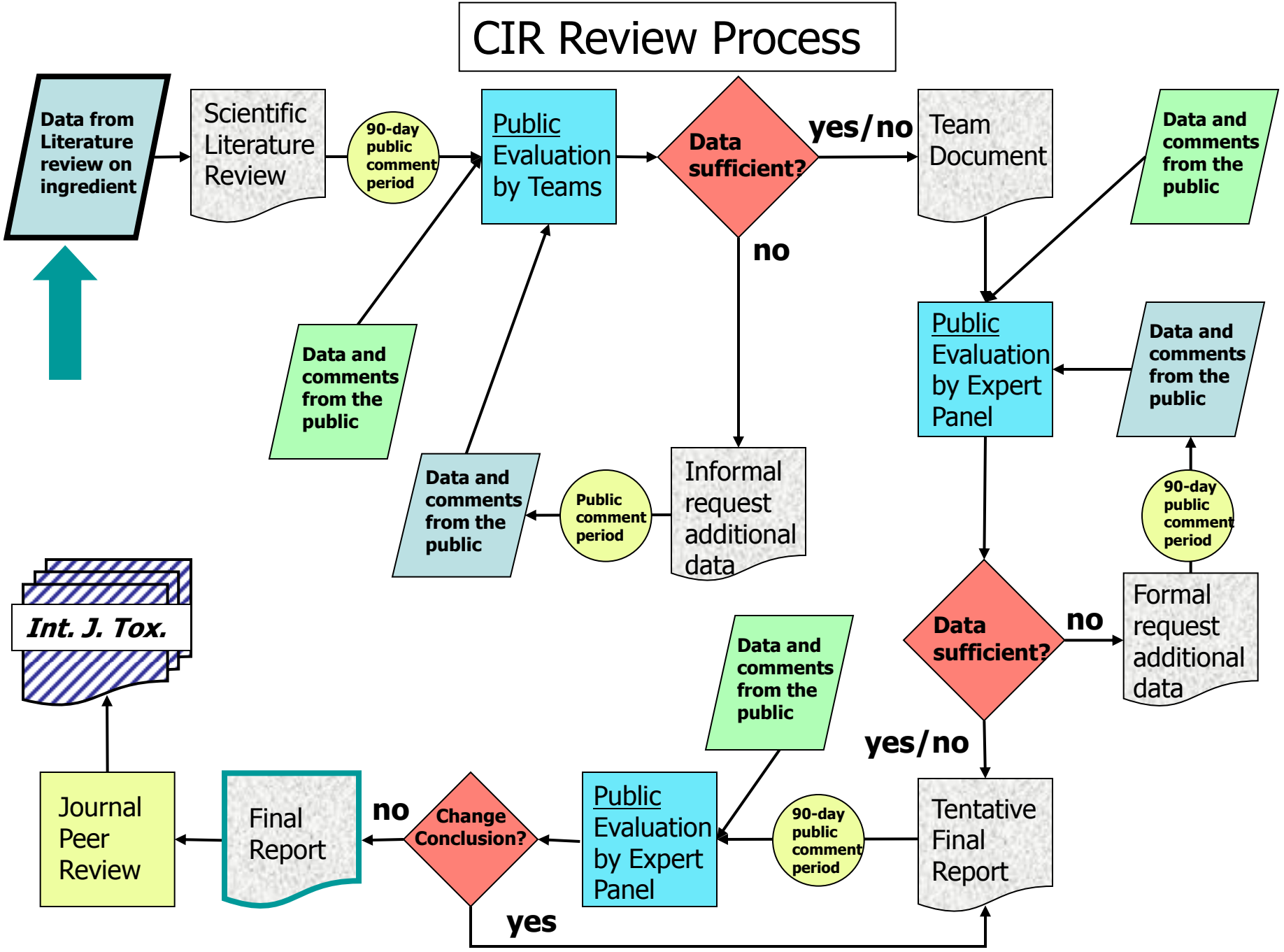
CIR Review Process
Data from Literature review on ingredient
Scientific Literature Review
90-day public comment period
Public Evaluation by Teams
Data sufficient?
yes/no
Team Document
Data and comments from the public
no
Public Evaluation by Expert Panel
Data and comments from the public
Data and comments from the public
Public comment period
Informal request additional data
90-day public comment period
Formal request additional data
Data sufficient?
no
yes/no
Data and comments from the public
Int. J. Tox.
Journal Peer Review
Final Report
no
Change Conclusion?
Public Evaluation by Expert Panel
90-day public comment period
Tentative Final Report
yes

Summary

- Experts must have appropriate scientific training and expertise to properly assess the safety of the type of material being reviewed
- Independence of Experts is absolutely critical
- Structured Process to standardize the reviews is needed
- Oversight committees provide additional credibility to demonstrate the strength of the conclusions
- Funding is done by industry but is coordinated through the trade associations (FEMA and CTFA)