

# Achieving GRAS for Flax

**Kelley Fitzpatrick, M.Sc.**  
**Director of Health and Nutrition**  
**FLAX CANADA 2015**

**[kellelyf@shaw.ca](mailto:kellelyf@shaw.ca)**



# GRAS

## Generally Recognized as Safe

- Applies to any substance that is generally recognized, among qualified experts, as having been adequately shown to be safe under the conditions of its intended use.
- A GRAS substance is distinguished from a food additive on the basis of the *common* knowledge about the safety of the substance for its intended use.
- Administered by the **Office of Food Additive Safety**, U.S. Food and Drug Administration (FDA)

# What is GRAS?

**GRAS applies to a **use**, not to a substance alone:**

- **A fully characterized substance**
- **Used at minimum needed levels**
- **In specific categories of foods**
- **To produce specific technical effects.**

# What GRAS is not?

- **A loophole**
- **A shortcut**
- **A lower standard of safety assurance**

# GRAS is a higher standard of safety assurance

- Safety **standard** is the same as that for food additives, “reasonable certainty of no harm”
- **Evidence of safety** (“technical element”) is the same as is required to support approval of a food additive petition
  - *breadth and quantity of information*
  - *quality of information*
- Primary information must be:
  - *Generally available*
  - *Generally accepted*

## *Generally available...*

The usual mechanism to establish that scientific information is generally available is to show that the information is published in a peer-reviewed scientific journal (FDA 1997).

# *Generally accepted...*

- Mechanisms to establish the basis for concluding that there is expert consensus about the safety of a substance are more varied (FDA 1997):
  - Publication of data and information in secondary scientific literature (i.e. scientific review articles, textbooks, and compendia);
  - documentation of the opinion of an “expert panel” specifically convened for this purpose; or
  - the opinion or recommendation of an authoritative body such as the National Academy of Science.

# GRAS Determination: Two Routes

- **Experience based on common use in food prior to Jan. 1, 1958**  
(“Historical use”)
- **Scientific procedures**  
(Comprehensive review of the totality of the literature)

# **GRAS Determinations Based on Scientific Procedures --Monograph Elements--**

- **Description of the substance**
- **Proposed use of the substance**
- **Methods for detecting and quantitating the substance in foods**
- **Safety and toxicology of the substance**
  - **N.B. Requirement to include any unfavorable information, including safety studies, adverse-reaction reports, consumer complaints, etc.**

# GRAS Dossier Elements

## --Description of the Substance--

- **Common or usual name**
- **Chemical name**
- **CAS registry number**
- **Empirical formula**
- **Structural formula**
- **Source information such as genus and species**
- **Product description**
- **Final product specifications for food-grade material**
  - identity specifications
  - purity specifications
  - acceptance specifications and quality assurance

# GRAS Dossier Elements

## --Description of the Substance--

- Chemical and physical properties
- Quantitative compositions
  - Impurities/contaminants (including heavy metals)
  - Degradation products
  - Analytical methodologies
- Manufacturing process
  - Manufacturer
  - Raw materials
  - Processing method
  - In-process quality controls
- Quality controls for addition of component to foods
- Stability data
  - Expiration date
  - Organoleptic degradation

# GRAS Dossier Elements

## --Proposed Use of the Substance--

- **History of food use of substance or related substances**
  - U.S.
  - International
- **Proposed use of substance**
  - Foods in which substance will be used
  - Proposed maximum use levels
  - Any self-limiting levels of use
- **Functionality (technical effect)**
  - Efficacy
  - Minimum required level (GMP)
- **Consumer information**
  - Use directions
  - Proposed labeling

# GRAS Dossier Elements

## -Safety & Toxicology of the Substance-

- **Animal and human studies**
- **Maximum allowable daily intake (ADI)**
- **Safety of any impurities, contaminants, degradation products**
- **Exposure analysis: Estimated daily intake (EDIs)**

# Biologically Active Ingredients vs. Traditional Food Additives

- Not consumed because of:
  - Processing function
  - Technical effect on food
- Are consumed because of:
  - Biological activity in the body
  - Anticipated positive effect on health

# Biologically Active Ingredients vs. Traditional Food Additives

## “Traditional” relevant disciplines

- Chemistry
- Toxicology (“Redbook”)

## “Bioactive ingredients” relevant disciplines

- Chemistry
- Biochemistry
- Toxicology
- Medicine
- Nutrition
- Immunology
- Biostatistics
- Psychology
- ????????

# **“Standard” Approach to GRAS for Proposed Uses of Biologically Active Substances**

- **There is no “standard” approach like “Redbook”**
- **Approach is completely driven by**
  - **Characterization of the functional substance**
  - **Anticipated exposures**
  - **Target (and incidental) populations**

# Biologically Active Ingredients

- **Safety determination may include**
  - History of use in human populations
  - Substantial equivalence to similar substances
  - *In-vitro* studies and pharmacokinetic modeling to predict *in-vivo* kinetics
  - Preclinical toxicology studies
  - Clinical evidence of safety

# Animal Toxicology Studies

- **Animal studies are used to evaluate toxicity**
- **Animal models must be chosen appropriately to extrapolate to humans**
- **Includes consideration of**
  - **Bioavailability**
  - **Nutritional requirements/limitations**
  - **Metabolic activity**
  - **Developmental stage**

# **Safety of Bioactive Substances**

## **--Endpoints of Animal Studies--**

- **Potential repeat dose toxicity (target organ evaluation)**
- **Carcinogenicity (mutagenicity screen)**
- **Developmental toxicity**
- **Reproductive toxicity**
- **Neurotoxicity**

# Safety of Bioactive Substances

## --Human Clinical Trials--

- **Clinical studies used for:**
  - **Safety verification**
  - **Pharmacokinetic endpoints**
  - **Physiologic endpoints**
  - **Biological effects**
  - **Identifying risk factors presented by genetic differences**
- **Clinical study populations:**
  - **General population**
  - **Special populations**

# Why did FLAX CANADA 2015 bother ?

- **GRAS Self Determination**
  - Industry lack of resources to compile the literature (210 references reviewed) and submit a dossier
- **Funding made possible through Agriculture and Agri-Food Canada's Agricultural Policy Framework (APF) Science and Innovation Program**



Agriculture and  
Agri-Food Canada

Agriculture et  
Agroalimentaire Canada

# Why did FLAX CANADA 2015 bother ?

- **GRAS Self Determination**
  - Mass Market Food Company's require assurance of 'safety'
  - New International Markets (Japan, Korea)
  - "Unwritten" requirement for Health Claim approval (SSA or Qualified)

# Specimen FDA Response

*“Based on the information provided and other information available to FDA, the agency has no questions at this time regarding the conclusion that [substance] is GRAS under the proposed conditions of use.*

*The agency has not, however, made its own determination regarding the GRAS status of the subject use of [substance].”*

# The Flax Monograph

- Taxonomy
- Proximate analysis
- Production, processing and manufacturing
- Kinetic, metabolism
- Safety, Developmental and Reproductive Animal studies



# Intervention Studies in Humans

**Most human studies had benefit rather than safety endpoints:**

- **Glycemic response (4 studies)**
- **Blood lipids (14 studies)**
- **Laxation (3 studies)**
- **Hormonal effects (18 studies)**
- **Cancer progression (3 studies)**
- **Bone metabolism (4 studies)**
- **Immune function (3 studies)**
- **Blood chemistry (6 studies)**
- **Vascular stress response (1 study)**
- **Kidney function (3 studies)**
- **Cyanide accumulation (3 studies)**

**No intolerance or adverse effects in any study.**

# GRAS Determination

## January 13, 2009

*The totality of the research demonstrates that oral toxicity has not been seen at any tested dose and consistent adverse hormonal effects are not observed at doses of flaxseed as high as 3750 mg/kg bw/day (5% dietary concentration). It is also notable that human studies in which flaxseed was fed at high doses have generally found an absence of estrogenic effects...*

***Since the EDI of flaxseed from its intended use as a food ingredient is 16 g/day, only a tiny fraction of the amount that has been shown to be without harm or hormonal effects in a large number of animal toxicity studies and human studies, it may be concluded that there is a reasonable certainty of no harm from the intended addition of flaxseed to food at a maximum level of 12% in the finished food.***

### **Expert Panel**

**Joseph F. Borzelleca, Ph.D.**

**Walter H. Glinsmann, M.D.**

**Robert J. Nicolosi, Ph.D.**

**John A. Thomas, Ph.D.**