Safety Assessment for Feed Ingredients

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AAFCO Mid-Year Meeting

Fort Worth, TX

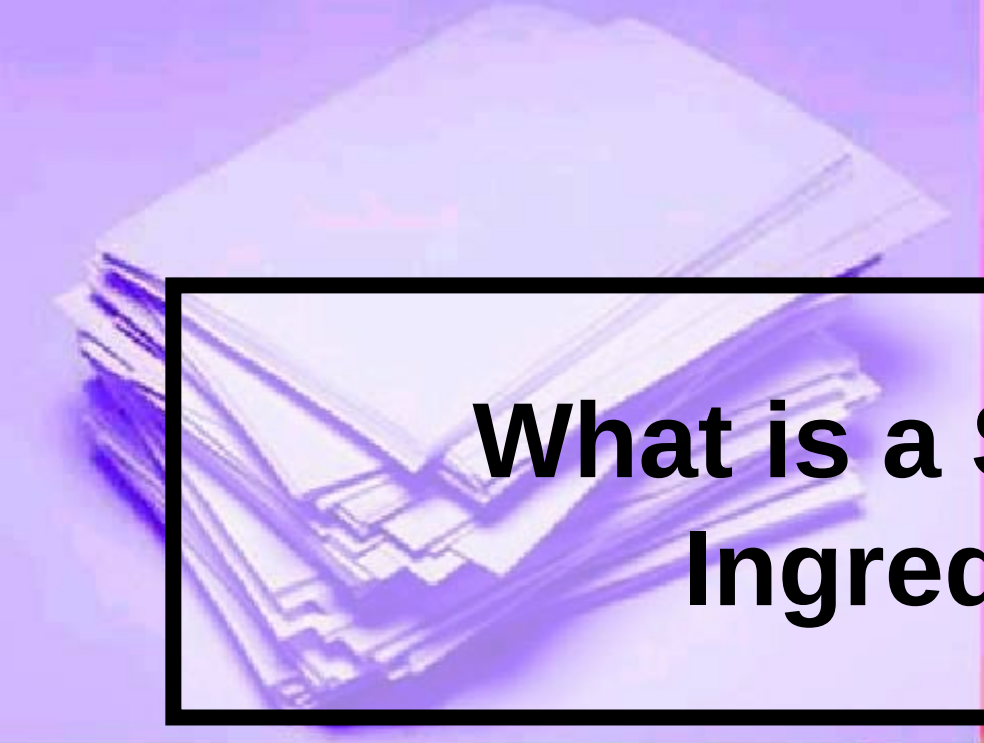
January 17, 2004

Safety Assessment for Feed Ingredients

Topics

- What is a safe feed ingredient?
- How do you establish the safety of an AAFCO Feed Ingredient?
- Where to go for assistance!

What is a Safe Feed Ingredient?



What is a Safe Feed Ingredient?

Definition of safe

- Is based on the legislative history of the FD&C Act and has been codified in the CFR
- Requires proof that there is a reasonable certainty that no harm will result from the proposed use
- Does not--and cannot--require proof beyond any possible doubt that no harm will result under any conceivable circumstance
- It is a high, but not absolute, standard
- The burden of meeting the standard belongs to the sponsor

What is a Safe Feed Ingredient?

In general, animal feed ingredients are safe if they:

- **Are FDA approved food additives for use in animal feed**
- **Are FDA affirmed GRAS substances for use in animal feed**
- **Have a published feed ingredient definition in AAFCO's Official Publication**

What is a Safe Feed Ingredient?

Food additives and GRAS substances approved by FDA are usually safe feed ingredients, except…

- **Different uses may not be safe (e.g. may lead to higher exposures)**
- **Different species may not be safe (e.g. some species may be more sensitive to adverse effects of the ingredient than others)**
- **Approval for use in human food may not be a sufficient basis for deciding that an ingredient is safe for animals**

What is a Safe Feed Ingredient?

Feed ingredients currently listed in AAFCO's Official Publication are usually safe, except…

- **Different uses may not be safe (e.g. may lead to higher exposures)**
- **Different species may not be safe (e.g. some species may be more sensitive to adverse effects of the ingredient than others)**
- **New evidence may bring into question their safety**

What is a Safe Feed Ingredient?

FDA has agreed to permit the marketing of unapproved food additives in animal feed as long as

- **There are no safety issues and**
- **The additive is defined in AAFCO's Official Publication**

If the safety criterion is not met, FDA may require the sponsor to submit a food additive petition for approval of the ingredient

What is a Safe Feed Ingredient?

"No safety issues" never means

- **No data are available**
- **No adverse results were observed in inadequate toxicity studies**
- **"Everyone knows" the ingredient is safe**
- **Other countries have approved the product**

What is a Safe Feed Ingredient?

"No safety issues" never means

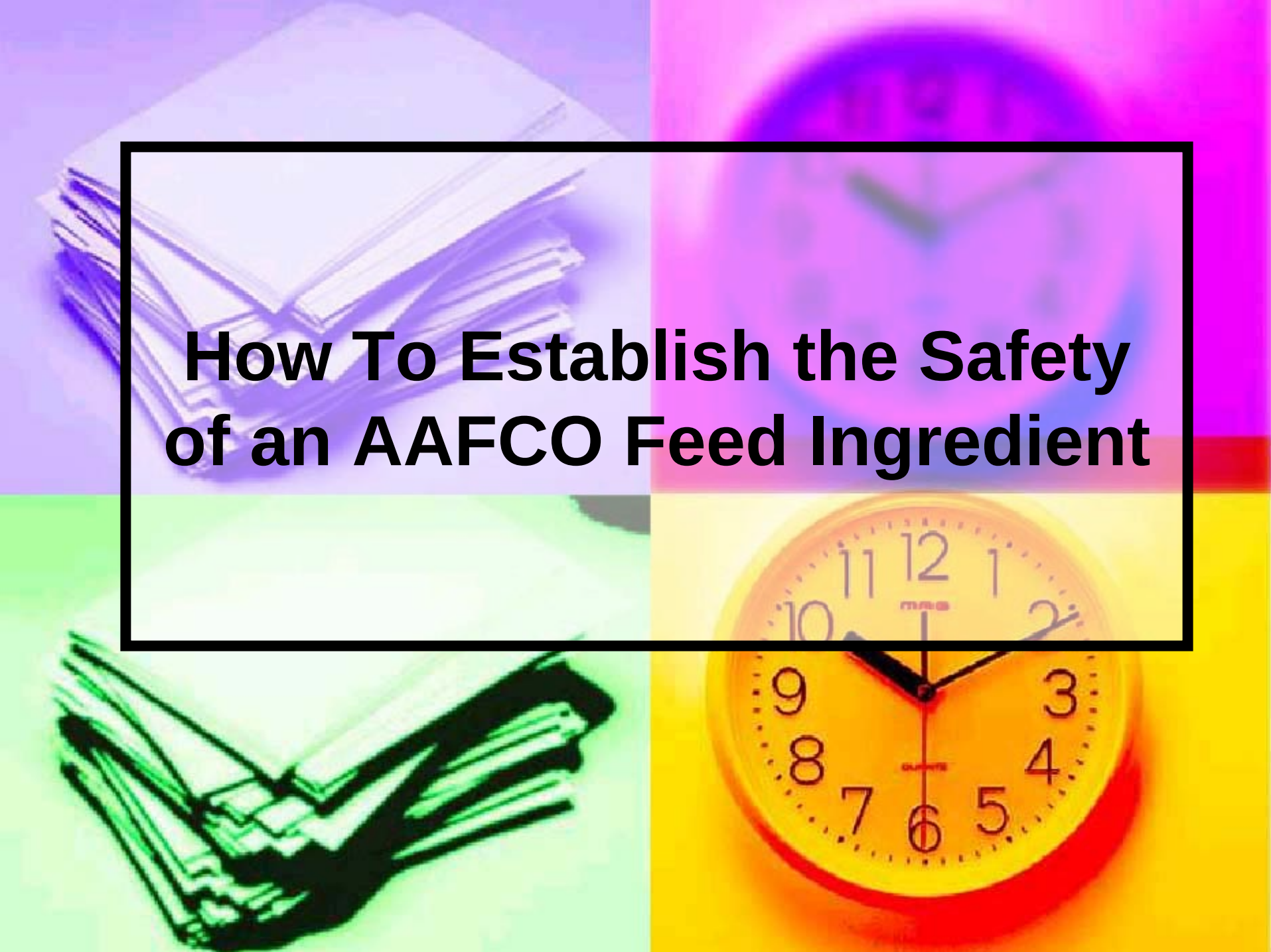
- The product has been in use for a while and no one has reported any problems
- Since the product is a(n) _____ no one would expect any adverse effects (*fill in the blank with: natural constituent of foods/feeds; protein; lipid; carbohydrate; amino acid, etc)*

What is a Safe Feed Ingredient?

"No safety issues" usually means:

- The appropriate toxicity (safety) studies have been conducted, based on
  - Known or expected toxicity of the substance
  - Duration of exposure
  - Expected daily consumption (exposure)
- Adverse effects identified in the toxicity studies are not expected to occur under conditions of use

How To Establish the Safety of an AAFCO Feed Ingredient



How to Establish the Safety of an AAFCO Feed Ingredient

Special factors that affect the safety assessment of most feed ingredients:

- They are not very toxic compared to industrial chemicals *(exceptions: some antioxidants, indirect additives and secondary direct additives)*
- The toxicities are usually subtle and chronic, not acute and obvious
- Because of these factors, studies need to be designed to identify safety issues that may be associated with the consumption of a feed ingredient (*nutrition or tolerance studies may not provide adequate information*)

How to Establish the Safety of an AAFCO Feed Ingredient

Safety can be established through:

- **History of prior safe use (e.g., GRAS)**
- **Published data and information in peer-reviewed journals**
- **Safety studies conducted by the sponsor or a third party**
- **A combination of the above**

How to Establish the Safety of an AAFCO Feed Ingredient

- How many and what type of studies are needed to establish safety?
  - **In general, ingredients with greater known toxicity, fed at higher levels and for longer durations will require more and longer safety studies**
  - **Recommended protocols for safety studies are available from a number of sources**
  - **A sponsor should consult with CVM before conducting safety studies; this could save a lot of time, money and effort**

How to Establish the Safety of an AAFCO Feed Ingredient

The safety section of a submission should include:

- **Legible reports of all toxicity studies on the ingredient; (*translations should be provided for all non-English language reports)***
- **A description of how studies in the published scientific literature were identified (e.g., databases searched and search parameters used)**
- **A safety narrative**

How to Establish the Safety of an AAFCO Feed Ingredient

The safety narrative should:

- **Identify studies that are pivotal to a safety decision, and explain why**
- **Provide a detailed report of the conduct and results of each pivotal study**
- **Summarize the results of non-pivotal studies**
- **Identify and discuss studies that do not support a safety decision, and explain why they are not relevant**

How to Establish the Safety of an AAFCO Feed Ingredient

The safety narrative should:

- **Explain how the results of the pivotal studies demonstrate that the ingredient is safe for the specified use (*safety assessment or risk assessment*)**
- **Explain why data and information available on the ingredient are sufficient to establish safety (*with reference to expected consumption, duration of consumption, and toxicity of the ingredient*)**

How to Establish the Safety of an AAFCO Feed Ingredient

Points to consider when interpreting the results of toxicity/safety studies:

- **Data interpretations** should be
  - **scientifically sound**
  - **clearly explained**
  - **supported by peer-reviewed**
  - **references**

How to Establish the Safety of an AAFCO Feed Ingredient

Safety Assessment for traditional feed ingredients (< 5% in feed):

- **Identify the highest No Observed (Adverse) Effect Level (NOAEL or NOEL) from each pivotal safety study**
- **Divide the NOAEL/NOEL by appropriate safety factor to account for uncertainty**
- **The resulting value is the Acceptable Daily Intake (ADI) of the ingredient (*the maximum amount that can be safely consumed*)**

How to Establish the Safety of an AAFCO Feed Ingredient

- **Safety Assessment for traditional feed ingredients (< 5% in feed):**
  - **In general, if the ADI is greater than the expected daily consumption, the ingredient is considered to be safe for the specified use**
- **If data suggests that an ingredient or one of its components may cause cancer, the FDA is likely to request that a food additive petition be submitted for the ingredient**

How to Establish the Safety of an AAFCO Feed Ingredient

Safety assessment of ingredients present in the feed at 5% or more:

- **Traditional paradigms for assessing safety may not be useful because it's impossible to dose test animals at high enough levels so that meaningful ADIs can be derived**
- **Often need to rely on "customized" testing for each macro-ingredient: metabolism studies, GI fate studies**
- **Usually need to assess safety on a case-by-case basis; written guidance is not available**

Where To Go For Assistance!

Where To Go For Assistance

- **Consult with CVM**
  - **To determine what toxicology information is needed to support safety**
  - **For partial or complete protocol review (e.g. is the test substance appropriate?)**
  - **To discuss appropriate ways of dealing with significant deviations from protocol or from expected results**

Where to Go For Assistance

- **Initial FDA contact for ingredient safety issues:**

Karen Ekelman, Ph.D.
HFV-222
7500 Standish Place, Rockville, MD 20855
Phone (301) 482-0256;
FAX (301) 482-1484
kekelman@cvm.fda.gov

- **There is no written guidance for determining the safety of feed ingredients**
- **However, some guidance for conducting safety studies for animal drugs and food additives for human use can be helpful**

Where to Go For Assistance

- **Useful animal drug guidance can be found at http://www.fda.gov/cvm-/default.html or is available upon request:**
  - **Target Animal Safety Guidelines for New Animal Drugs**
  - **Protocol Development Guideline for Clinical Effectiveness and Target Animal Safety Trials**
  - **The Use of Published Literature in Support of New Animal Drug Approval**
  - **Content and Format of Effectiveness and Target Animal Safety Technical Sections and Final Study Reports For Submission to the Division of Therapeutic Drugs for Non-Food Animals**

Where to Go For Assistance

- **CFSAN/FDA guidance for safety assessment of food additives is available at http://www.cfsan.fda.gov/list.html or upon request**
  - **Preparation of Food Contact Notifications for Food Contact Substances: Toxicology Recommendations**
  - **Toxicological Principles for the Safety Assessment of Food Ingredients (Redbook)**
  - **Toxicological Testing of Food Additives**