Chapter VII

Emerging Issues in Safety Assessment of Food Additives and Color Additives Used in Food

A. Introduction

This section discusses approaches to testing that may be useful in assessing the safety of macro-additives (see **Chapter VI B**), bioengineered additives (see **Chapter VII C**), additives that are enzymes (see **Chapter VII D**), and microbially-derived additives (see **Chapter VI E**). This section also discusses the use of alternatives to whole (vertebrate) animal testing in safety evaluation (see **Chapter VII F**) and FDA's recognition of the potential for direct food additives and color additives used in food to cause both heritable and somatic genetic toxicity (see **Chapter VII G**).

Because the Agency's approaches to determining the safety of these additives will continue to evolve for some time, it is not yet appropriate to provide separate guidelines for acquiring toxicology information on the types of additives in this document. In general, the Agency recommends that petitioners follow guidelines for toxicity tests presented in other sections of this publication. In addition, this section suggests some important issues to consider when planning a program of toxicity testing designed to demonstrate the safety of unique additives. As always, we strongly recommend that petitioners discuss planned testing programs and protocols for toxicity tests with Center scientists before tests begin.

B. Macro-Additives

Macro-additives are a class of food additives that are intended to be replacements for conventional macro-nutrients such as fats, proteins, and carbohydrates and are intended for use at relatively high levels in food. Macro-additives may be nutritive or non-nutritive; they may be reasonably pure, well characterized chemicals or they may be complex mixtures whose complete characterization is not feasible; they may be well absorbed from the gastrointestinal tract or poorly absorbed; they may be manufactured from unusual or novel food sources or obtained by chemical synthesis.

The common characteristic of macro-additives is that they will be consumed in large quantities compared to conventional food additives and, as a consequence, they will present testing problems that require "customized" approaches. For example, it may not be feasible to calculate safety factors in the conventional way, that is, as a fraction of the highest oral dose that has no adverse effects in animals. Other means of providing margins of safety for macro-additives will have to be used; these may include information derived from metabolic, pharmacokinetic, and human clinical studies.

1. Nutritional Concerns in Animal Toxicological Tests

Because of the expected high level of human consumption of these additives, animal test doses that are orders of magnitude greater than the Expected Daily Intake (EDI) for humans will often not be feasible. Attempts to achieve very high doses in the animal studies might result in nutritional imbalances or caloric deprivation that could confound interpretation of the toxicity studies. In order to test the highest dose feasible and yet avoid nutritional problems, it may be necessary for toxicity testing to be preceded by nutritional studies to determine adequate test diets and appropriate control diets for animals in toxicity studies.

If appropriate dietary controls include nutrient enhancement, care should be taken to avoid over-enriching the diet or changing nutrient ratios that would mask toxicological endpoints under consideration. For example, mineral oil as a test material would be mostly unabsorbed in the intestine where it would solubilize fat-soluble vitamins, leading to deficiencies of these nutrients. This effect may be eliminated by appropriate fortification of the diet with vitamins A, D, E, and K. Quantities of nutrients to be used for fortifying the diet should be determined experimentally, in relation to the amount of mineral oil (test substance) used. Under-fortification could fail to protect against nutrient deficiencies and over-fortification could lead to altered toxicological responses to xenobiotics and "background" pathology rates. Sufficiently great over-fortifications could produce hypervitaminosis.

Control and test diets should be of the same caloric density and nutritionally (micronutrients) equal to test diets. Selection of appropriate control diets may present particular problems when testing non-caloric food substitutes or food substitutes that interfere with absorption of nutrients. Due to nutrient variations in chow diets from batch to batch, it is preferable to use a semi-purified diet base in these studies.

Additional information can be found in **Chapter IV B 5**, Diets for Toxicity Studies and in **Chapter IV B 1**, General Guidelines for Toxicity Studies.

2. Absorption, Metabolism, Distribution, and Elimination Studies

Studies designed to follow the metabolic path and fate of macro-additives take on particular importance in providing assurance of safety if the conventionally calculated safety factor cannot be used. Greater understanding of the disposition and pharmacokinetics of the additive should help to diminish uncertainties regarding safety. Questions of the following types should be answered through appropriate studies:

- Does the product or its metabolites alter or interfere with absorption, metabolism, or excretion of normal nutrients or metabolic intermediates?

- Does the product or its metabolites alter the action of commonly used drugs?

- Is the product absorbed, metabolized, distributed, stored or excreted differently in man than in test animals?

- Does the product or its metabolites accumulate in tissues, and what are the toxicological consequences if there is accumulation?

- If the product is poorly absorbed, does the high concentration in the gut affect gut morphology, physiology, or biochemistry? Are any changes in the gut morphology or biochemistry associated with the development of neoplasms of the gut?

- Does the product alter the composition or nature of the gut flora? If it does, what are the toxicological consequences of the changes?

3. Impurities and By-products

Because of the anticipated high human consumption levels of macro-additives, there is a concomitant high potential intake of impurities and by-products. Therefore, every effort should be made to identify and quantify the chemical constituents of the product. If any of these raise particular concerns, toxicity testing of the impurity or by-product itself may be recommended. Limits for impurities such as heavy metals, natural toxins, and anti-nutrition factors may need to be specified for the marketed product.

4. Clinical Studies

When animals studies have been completed or when there is reasonable assurance of safety of the macro-additive from animal studies, clinical studies with human subjects may be useful for increasing confidence in the safety of the product for human consumption. For example, humans may suffer subtle adverse effects not detected in animal studies due to differences in physiology or metabolism between animals and humans; human subpopulations (the old, young, and chronically ill) may each react differently to the food substitute. In addition, human studies may help compensate for the fact that conventional methods of calculating the Acceptable Daily Intake (ADI) may not be applicable to the results of standard toxicity studies on macro-additives.