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# NEW APPROACH FOR REPLACING MACROINGREDIENTS AND RISK ASSESSMENT

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***Abstract***

*The issues that arise in the evaluation of the safety and regulatory acceptability of dietary fat substitutes are not unlike those of other novel macroingredients. The principal factors to be considered include specification for identity and purity of the material, safety assessment, potential impact on nutritional status, and regulatory matters related to fortification policy, labeling and compliance. Thus, in the course of developing guidelines for the evaluation of macroingredients, by drawing on current examples, certain clear patterns emerge as to the priority issues to be addressed. This paper discusses the general concepts that are applicable to the safety evaluation of macroingredients, and highlights some special issues that are necessary to consider with reference to fat substitutes.*

## INTRODUCTION

The principles that emerge in the evaluation of a non-caloric fat substitute like olestra, serve as a template for the safety evaluation of other fat substitutes. Olestra is the common and usual name proposed for the mixture of hexa-, hepta- and octa-esters that are formed by the reaction of sucrose with long-chain fatty acids derived from edible fats and oils. A typical preparation will consist predominantly of octa-esters, which provides the optimum characteristics desired. In practice, olestra would never be sold neat, that is, it will always be sold as a blend in combination with existing fats and oils, where it may constitute from 35 to 75% of the mixture.

The particular uses of interest include home use for cooking and in salad oils, institutional uses for deep frying of food, for example in the fast-food industry, and industrial uses as a medium for preparing fried, packaged foods. Olestra has the advantage that it provides the technological qualities of traditional sources of lipid, that is, it may be used as a medium for food preparation, it contributes certain textural and organoleptic properties to foods, but it does not contribute calories to the diet. The fundamental properties of the material that give it these characteristics lie in the design of the molecule, which on the one hand possesses the physical properties of traditional edible lipid sources, while on the other is physiologically and toxicologically inert under usual conditions of exposure. The principal feature that accounts for this inertness, in the case of olestra, is its lack of absorption. This tends to limit the importance of detailed toxicological evaluation in the classical sense. It does not mean, however, that there are no potential safety concerns, but that the physical characteristics of the material coupled with its lack of absorption provide guidance to the toxicologist and regulatory scientist concerned with its safety evaluation. The potential safety concerns focus largely on the possible effects of olestra on the gut and the possible effects it may have on nutrient utilization.

## MATERIALS AND METHODS

### ABSORBTION-RELATED ISSUES

To meet the criteria of a non-caloric fat substitute a dietary lipid replacement must demonstrate chemical stability in each technological application, and in the gastro-intestinal tract. This requires the establishment of a very strict and narrow chemical specification on the product so that it does not contain metabolizable fragments or reactive groups that may be

subject to chemical hydrolysis during food preparation or to lipolysis or microbiological degradation in the gastro-intestinal tract even after repeated, long-term exposure. So, like other macroingredients, non-caloric fat substitutes need to possess a well defined product specification that provides assurance of both chemical stability and its presumed metabolic fate, and ensures that it is free of potentially toxic impurities.

Given these characteristics one can now speculate on the specific issue that might surround the safety evaluation of such products. The first relates to the nature of toxicological evaluation. As with other materials that are not absorbed, the principal initial focus of the toxicological investigation must be on the gastro-intestinal tract. Factors to be considered include potential adverse effects of unabsorbed fat substitutes on the gastro-intestinal epithelium and regional lymphatic tissues, and effects on microbial populations and on the metabolism and pharmacokinetics of bile acids. Other anticipated consequences at the level of the gastro-intestinal tract would include the impact of lipid-like fat substitutes on the absorption of fat-soluble vitamins, and the digestion and utilization of macronutrients, and the impact on the uptake of lipid soluble drugs, particularly those used to control serious medical conditions. A knowledge of these potential effects is critical in the design of appropriate and relevant tests to evaluate possible systemic toxicity.

In considering the design of toxicological test on fat substitutes it must be borne in mind that these substances, like other macroingredients, are not food additives in the traditional sense. Food additives constitute only a minor fraction to the diet, usually in the ppm range. Macroingredients, like fat substitutes, may constitute a significant portion of diet, and are designed to replace traditional sources of nutrients. For this reason, the usual approach applied to the safety evaluation of food additives has only limited

application in the case of macroingredients. Past experience has demonstrated that toxicity testing of macroingredients in animal studies may present a number of problems not encountered in classical toxicity studies with xenobiotics. When large amounts of dietary components, including both nutritive and non-nutritive substances, are incorporated into the diet of animals at levels of several percent, it is not uncommon to find spurious responses in feeding trials. These responses may at first glance to be considered to be of toxicological significance but on further inspection are usually the result of dietary nutrient imbalance or physiological perturbation induced by the test material when fed are excessive exposure levels. An example of this phenomenon is the induction of an enlarged colon in animals fed high levels of osmotically active substances such as xylitol, sorbitol, polydextrose and certain modified starches. It is important to separate these physiological responses and their toxicological sequelae from genuine toxicological effects.

As a result of these problems studies in animals cannot usually be used to establish an acceptable daily intake for macroingredients in the traditional sense employed for food additives, since it is not possible to include sufficient of the test material into the diet of animals to achieve the usual 100-fold safety factor approach. This is particularly true for food material that may be used at several percent in human diet. To an extent these problems limit the usefulness of animal studies in assessing the safety of major food ingredients. On the other hand, animal studies may serve a valuable purpose to ensure the macroingredient's material possesses no unexpected toxicity are usual exposure levels for long periods of time. It must be recognized that if animal studies are employed in the safety factor approach to establishing acceptable human exposure will have limited validity. Often, a safety factor of only 2-19 may exist between the feeding

levels in animals (the no-observed-adverse-effect level) and the anticipated human exposure level. It should perhaps be recognized when extrapolating the results of such studies to humans that macroingredients like olestra are, per se, non-toxic and that large safety factors are not necessary. The support for this concept comes from the recognition that any common foodstuff when fed at several times the usual exposure might be expected to induce adverse physiological and possibly toxic effects.

A fundamental issue that often arises in a discussion of guidelines for the safety evaluation of macroingredients relates to the extent of toxicity testing that may be required. In theory, only limited studies seem necessary, provided one has a full understanding of the biochemical and physiological effects of the test substances. In practice, however, regulatory agencies have increasingly emphasized the need for the full range of toxicity test for food constituents that may be consumed in large amounts. In analyzing the rationale for this position one finds that two factors have influenced the development of government guidelines on this matter. The first has been our collective failure, in the past, to conduct a sufficiently detailed analysis of the potential of macroingredients to produce apparent toxic effects that arise secondarily to nutritional imbalance, etc. I am convinced that if we do a careful analysis of the potential then it should be possible to limit the extent of testing required. The second factor relates to the general sense of comfort regulatory agencies find in being able to say that a material has been thoroughly tested in all the classical toxicological tests. Taking this approach does not leave them open to criticism. This, I believe, more than anything, drives the regulatory process. If we are ever to overcome the hurdle of having to conduct detailed and duplicative toxicological tests on every new macroingredient, then we must improve our ability to predict potential toxicological effects based on the chemical and physiological

properties of the substance in question. Another approach that requires consideration is the increased use of a hierarchical series of tests in human subjects. My strategy would be to concentrate on well designed short-term studied in a range of animal species to investigate absorption and special effects, and complement this with appropriate clinical investigations. In the short-term and long-term studies, particular attention should be paid to the lymphatics draining the gastro-intestinal tract. A long-term study may be considered to assess the potential effects of exposure.

## RESULTS AND DISCUSSION

### THE ROLE OF CLINICAL STUDIES

There are several issues relating to the safety assessment of fat substitutes that are best resolved through the use of human studies. The principal issues that arise are:

a. Whether non-caloric fat substitutes reduce total energy intake from the diet when consumed chronically under typical use conditions or whether there is compensation for reduced energy intake by consumption of other sources of dietary fat and/or carbohydrate. Ideally one would like to see and overall reduction in the intake of calories from fat, and compensation, if it does occur, by way of increased carbohydrate intake. This sort of question is amenable to clinical investigation.

b. Whether consumption of a fat substitute-containing diet will lead to reduced micro-nutrient or essential fatty acid status when consumed over the long term. This question is also amenable to clinical investigation.

c. Whether consumption of a fat substitute will adversely affect individuals with compromised gastro-intestinal

tracts. This may be clinically evaluated in special subpopulations if supported by sufficient animal data and results of clinical studies in a normal population.

## ISSUES RELATED TO NUTRIENT SUPPLEMENTATION

I shall now turn to a regulatory issue that needs to be addressed in the more generic context. Macroingredients, particularly those that are non-caloric or severely reduced in calories, may replace significant quantities of traditional dietary ingredients. Regulatory agencies have been concerned that widespread use of non-caloric macroingredients may lead to nutritional imbalance in certain individuals who make extensive use of these products. Collectively, industry has a responsibility to ensure that recommended daily allowances for essential macroingredients will be met even when non-caloric macroingredients are consumed in significant amounts. Traditional food ingredients may also contribute significant quantities of important micronutrients o the diet. The question that arises is whether it is appropriate to fortify non-caloric replacement foods with the equivalent levels of micronutrients that are present in traditional foods. Regulatory agencies in many countries have attempted to prohibit or limit the addition of vitamins and minerals to what may be called trivial dietary components since they are concerned that people would believe those to be nutritionally balanced foods. The important point, however, before macroingredients use becomes widespread, is the extent to which appropriate fortification should be permitted in order to maintain optimal nutrient status. Fortification of macroingredients may be essential to ensure that nutritional status is unaffected, and therefore appropriate guidelines must be developed.

## LABELING AND COMPLIANCE ISSUES

With increased consumer awareness of the nutritional quality of foods, coupled with efforts in most developed countries to introduce some form of nutrition labeling, the question of labeling and advertising in respect to macroingredients becomes significant. While claims for caloric reduction or other positive nutritional attributes of new specialty products are desirable, it is becoming increasingly evident that such claims must be considered in the context of the total diet. Individuals who are interested in reducing calories from fat, for example, must be informed about the amount of fat in typical servings of traditional counterpart foods so that they may make informed decisions regarding the appropriate dietary role of non-caloric fat replacements. For this reason it is important to strive for comparative nutritional claims that assist in putting new products in their proper context in relation not only to traditional foods but also to recommended dietary goals.

Macroingredients are by nature complex mixture that may not be easily detected and measured by analytical techniques. This raises issues regarding compliance policy and how governments can assure consumers that they are not subject to fraudulent practices. Increased use of advanced processing techniques and production methods in many undeveloped exporting countries raises the question of methodology to detect macroingredients that may not be in compliance with national guidelines and regulation. When developing new macroingredients it is therefore important to give thought to procedures for ensuring that regulations governing the identity and uses of the product will not be violated.

**CONCLUSIONS**

Fat substitutes, like other macroingredients, may be expected to comprise a substantial portion of the diet. The safety evaluation of this class

of substances needs to be viewed in the context of proposed uses if a material taking into consideration the product's chemical and physical properties together with a knowledge of its potential to induce subtle changes in nutritional status at expected levels of exposure. It is becoming increasingly evident that macroingredients, when fed at high dietary levels in animals, may induce alterations in normal physiology leading to spurious toxicological effects of no consequence to humans at typical exposure levels. The appropriate role of animal studies in the safety evaluation of macronutrients needs to be addressed taking into consideration the fact that studies in humans may serve a more valuable purpose in assessing the physiological consequences of macroingredient consumption. In addition to these safety considerations there is a need to valuate nutritional supplementation policies as they apply to macroingredients. The question of appropriate labeling and compliance policy must also be addressed.

**CONCLUSIONS**


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