Unlike with most food additives, the safety evaluation of macronutrients poses a challenge to risk assessors because of their inherent nutritional value and relatively large dietary exposure. A safety assessment model of macronutrients based solely on traditional toxicological studies faces limitations, whereas nutritional studies of macronutrients are often designed to provide information to support dietary recommendations for optimal health. Although both nutritional and toxicological research shares a common goal of improving public health, the manner in which the studies are used differ because of limitations in their design and conduct. Many nutritional studies enjoy the benefit of using human subjects that can reflect real-world exposure scenarios, but consequently these studies are beset with unknown confounding variables that make drawing causative conclusions difficult. Toxicological studies must be conducted with laboratory animals, but they are concomitantly more easily controlled, permitting better causation determinations. What is needed to improve the safety determination of macronutrients is a hybrid model that encompasses both types of studies integrated toward a shared problem definition. Contingent on the creation of this hybrid model is the development of a common set of definitions and terms that will permit scientists from both disciplines to collaborate in designing and conducting a research agenda to satisfy a particular defined problem in assessing the safety of a specific macronutrient.

In creating a hybrid model of macronutrient safety assessment, it would be useful to develop a framework of core research studies that fulfills the data needs of the risk assessor. Modern toxicological approaches are increasingly focusing on understanding toxicity pathways and the effect of perturbations by the test agent on cellular homeostasis. Other mechanistic studies essential for understanding biological responses to macronutrients should include ADME (absorption, distribution, metabolism, excretion) studies, which, given the nature of inherently low toxic potency of macronutrients, can often be conducted with human subjects. Use of this type of data can lead to the development of PBNK (physiologically based, nutrico-kinetic) models that offer the ability to predict human responses to the macronutrient across doses and to consider human phenotypic variation.

Complementing this suite of traditional pathophysiological and mechanistic toxicological studies should be well-designed, clinical intervention studies of the macronutrient capable of demonstrating dose-responsive, causal effects. As well as identifying effects in humans under realistic exposure scenarios, these studies can be invaluable in producing hypotheses for further follow-up in well-controlled laboratory animal studies. In addition, human studies of macronutrients can permit improved understanding of gastrointestinal effects and dietary interactions, including alterations in nutritional status, which are a challenge to conduct with laboratory animals.

In developing this new paradigm of integrating toxicological animal studies and mechanistic research along with clinical nutritional trials for the evaluation of the safety of macronutrients, it is important to have a weight-of-evidence scheme as part of
the framework. This scheme would be useful to the risk assessor in apportioning the relative degree to which certain types of evidence should be considered in evaluating the risk. Included in the hybrid model, and appropriately weighted by the scheme, should be consideration of the health benefits of the macronutrient. This effort necessitates performing research studies that capture the hermetic responses of the macronutrient, thus enabling the risk assessor to consider the risks and benefits of the macronutrient.

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Suggested Citation


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