

BASF Corporation

**Submission to
Docket No. 2004N-0454**

December 16, 2004

Introduction

BASF Corporation commends the Food and Drug Administration for taking the steps necessary to critically evaluate the implementation of the Dietary Supplement Health and Education Act of 1994 and appreciates the opportunity to comment on the October 20, 2004 Federal Register Notice entitled, "Premarket Notification for New Dietary Supplement Ingredients." In general, BASF believes it is appropriate for the FDA to undertake the effort to better determine what kinds of information are needed under FDCA sections 402(f)(1)(B) and 413(a)(2) in order to make more accurate and credible assessments of safety within the meanings of the "reasonable assurance" and the "reasonable expectation" standards. We believe the goal of this effort should be to create a process and requirements that more uniformly and reproducibly allow for a premarket safety analysis of new dietary ingredients under the so-called 75-day review and recommend that you consider establishing a federal advisory committee for this purpose.

As a transnational manufacturer and supplier of dietary supplement ingredients, BASF has had a long history of providing safe and beneficial supplemental nutrition to the marketplace. Informed consumers seek to supplement their daily diets with those dietary supplements that they believe will meet their own individual dietary needs. Responsible manufacturers strive to produce only products that are considered to be safe because a variety of pertinent information, including but limited to published, peer-reviewed studies, permits such a conclusion by an expert panel. Manufacturers can act responsibly by conducting a thorough review of the safety of those ingredients that they choose to market and so notify the FDA prior to selling these new dietary ingredients. The guidelines for undertaking these reviews and making these determinations are based upon a notion of sound scientific principles that should be common among those in the dietary supplement industry. This notion is arguably not consistently or equally applied by industry. BASF is supportive of a meaningful standard of safety for new dietary ingredients, which engages all members of the dietary supplement industry yet is not onerous or cost prohibitive to the extent that it would otherwise thwart the entry of new dietary ingredients.

A review of the 75-day notifications published by FDA demonstrates a wide disparity in the quality of submissions in terms of the comprehensiveness and quality of data submitted to demonstrate safety. Indeed, according to a recently published study (McGuffin and Young, 2004) very few of the nearly 150 new dietary ingredients submitted for review since the effective date of DSHEA were considered by the FDA to have an "adequate basis to determine that the ingredient is reasonably expected to be safe

under labeled or normal conditions of use.” Further, there appears to be uncertainty about the standard by which FDA determines the safety of new dietary ingredients for dietary supplements, even though a standard was established under DSHEA that was meant to be clearly separate from other standards of safety in the FFDCFA. Thus, even if, as the industry asserts, FDA has the appropriate regulatory authority over dietary supplements and ingredients, the overall regulatory framework for dietary supplements could be improved through specific guidance and clarity about the safety standard and required evidence. This clarification would go far in ensuring that manufacturers adequately demonstrate safety, that FDA has appropriate oversight of those safety determinations, and that consumers have confidence in the safety of products on the market.

The assessment of the safety of a food ingredient or a new dietary ingredient intended for dietary supplements should involve a critical evaluation by properly qualified and experienced experts of the available information on the particular substance and chemically related substances. The assessment is based upon adequate review of credible scientific data derived from appropriate studies that are designed to determine if there are adverse biological effects of the ingredient or supplement at use levels that have adequate margins of safety. The assessment is data-driven and the FDA is correct to pose for consideration the data specific kinds of questions that appear in the October 20, 2004 Federal Register Notice. An assessment of safety can be made in the absence of a less than complete complement of data by relying on the expertise of experienced professionals and we believe a clear objective of this evaluative exercise should be to create the correct and acceptable balance of data requirements that are appropriate for certain classes of new dietary ingredients.

Use of Expert Panels to Establish Reasonable Expectation of Safety

BASF agrees with several presenters at the November 15 CFSAN meeting who supported the use of some form of the Generally Regarded as Safe (GRAS) model. At BASF, we have used the self-determination GRAS process successfully for a number of dietary supplement ingredients. Other industries have successfully used GRAS procedures to examine the safety of products destined for the marketplace with a potential for widespread human exposure. Most notable among these is the Cosmetic Ingredient Review that was established nearly 30 years ago. There are other examples as well and they are briefly outlined in the paragraphs below.

Food safety experts assembled as a GRAS panel should be able to reliably evaluate available, published information on safety and conclude whether the available

information supports the safety of the new dietary ingredient for dietary supplement under specific conditions of use. In addition, the experts should also address the issue of general recognition of safety and conclude that there is general recognition (other experts in the respective fields would come to the same conclusion) or there is not.

These panels of recognized experts (national/international recognition, proper training and experience) would be identified as GRAS experts. Their credentials and reputations should be such that they are not challengeable. The individuals who comprise GRAS panels could be in the employ of the petitioner or be independently selected by a disinterested third party upon the request of the petitioner. The format for reviewing the data that is germane to making a determination of safety should remain flexible enough to accommodate the particular individual characteristics of the New Dietary Ingredient and to the expected dietary exposure parameters. Sufficient flexibility in the GRAS determination process should be retained in order to develop GRAS determination models that are most effective for evaluating a variety of classes of nutrients that may have characteristics in common.

The concept of “GRAS,” as found in the food additive definition (Section 201(s)), provides a touchstone for a discussion since this has worked effectively for decades and has broad support and credibility among the scientific and regulated industry communities. Following is a brief description and discussion on several of the active GRAS reviews.

The FEMA GRAS review effort is a successful industry supported model for affirming the safety of food ingredients. Its Expert Panel was established in 1960 and thus far has listed over 2000 materials on the FEMA GRAS list. The FDA support FEMA received at its initiation continues today. Then Deputy FDA Commissioner Winston Rankin said: “The manufacturers are entitled to reach their own conclusions based on the scientific evidence that a subject is, in fact, generally recognized as safe.” That perspective is still maintained on FDA’s current web site: “Under DSHEA, the dietary supplement manufacturer is responsible for ensuring that a dietary supplement is safe before it is marketed.”

In 1998-2000, the Research-Based Dietary Ingredient Association (RBDIA), an organization of companies representing food, food ingredients, medical food and dietary supplement industry segments, sought to establish standards for scientific research and appropriate use of such research for substantiating claims and safety. RBDIA worked closely with the Life Sciences Research Organization (LSRO) to establish a third party review mechanism. This effort did not reach closure and appears to be in a limbo status.

LSRO has been recognized as the invaluable third party reviewer with experience in assessing the safety of dietary ingredients. In March 1972, LSRO organized the Select Committee on GRAS Substances to assist FDA in evaluating scientific information. Ten years later, LSRO completed its task after preparing 144 reports on 486 food ingredients.

The Cosmetic Ingredient Review (CIR) was established in 1976 by the Cosmetic, Toiletry & Fragrances Association (CTFA) with support of the US Food and Drug Administration and the Consumer Federation of America. Although funded by CTFA, CIR and the reviews are independent from CTFA and the cosmetic industry. CIR reviews and assesses the safety of ingredients used in cosmetics and toiletry products in an unbiased and expert manner, and publishes the results in the open, peer-reviewed literature.

The CIR Procedures established an Expert Panel to set priorities and review and assess ingredient safety data. The CIR Expert Panel voting members include physicians and scientists who have been publicly nominated by consumer, scientific and medical groups, government agencies and industry. Three liaison members serve as non-voting members representing the U.S. Food & Drug Administration (FDA), Consumer Federation of America and Cosmetic, Toiletry & Fragrance Association (CTFA). By uniting industry, consumer and government, the Expert Panel creates a unique environment of discussions affecting public safety.

Working on the high priority ingredients, CIR staff conducts extensive literature searches, compiles data and prepares draft reports. If the open, scientific literature contains insufficient information, the Panel will call on industry or other interested parties to undertake specific studies or to provide previously unpublished data. After completion of a development process that includes multiple opportunities for public comment and open, public discussion of the report, a final report is issued. These final reports are available from CIR. Eventually, CIR final reports are published in the *International Journal of Toxicology*.

The Food Safety Council's (FSC) "A Proposed Food Safety Evaluation Process" was completed in 1982 and drew from the decision-tree approach developed and used by FEMA. The FSC report presented a framework for making comprehensive, systematic and scientifically sound decisions on food safety in an open and participatory manner. The report had a significant impact on changes in the regulatory process and in how the food industry identified and assessed risks from food substances. The report changed the way both FDA and the food industry applied science in their decision-making processes. The FSC report utilized expert committees with half the participation from industry and half non-industry including consumer advocates. The draft final report was submitted for extensive public peer review before publication.

Under a contract with the USFDA, the Food the Nutrition Board (FNB) of the National Academies of Sciences Institute of Medicine (IOM) initiated and completed in April 2004, a project entitled “Framework for Evaluating the Role of Dietary Supplements in Health.” The proposed framework includes a methodology to evaluate safety through a science-based process that can provide reasonable assessments, even when data about a substance’s safety in humans is scarce. Expert scientists using available, peer-reviewed literature conduct reviews, taking into consideration methods other expert bodies have used to categorize and review supplement safety and efficacy issues.

The use of any of these kinds of panels or variations thereof could be an efficient means of providing the finest and most critical evaluation of the safety of new dietary ingredients for dietary supplements. This could save considerable resources including time and costs for both industry as well as the Agency. GRAS determinations should be published in refereed journals as critical reviews. GRAS determinations and supporting information would be submitted to FDA as part of the 75-day review period for any new dietary supplement ingredient, even though GRAS affirmed ingredients are ready for market the moment the determination is final. In this way, more credibility is added and consumer confidence is improved as allowing the FDA to have an opportunity to review the GRAS determination as part of the 75-day review has the distinct advantage of having the FDA in the position to be the final decision maker on the entry of new dietary ingredients to the market.

Conclusion

BASF believes it is important for the FDA to provide more clarity and routineness in the new dietary ingredient review process. While there are numerous studies that could be required, we do not believe the FDA needs to create a “checklist” of data requirements for each 75-day review submission. BASF recommends that the FDA consider how the use of expert safety panels could optimize the process of new dietary ingredient safety reviews. BASF looks forward to working with all interested parties and the FDA to create an improved system that will maintain consumer confidence in the safety of this class of products.

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Reference

McGuffin, M and A. L.Young, *Premarket Notifications of New Dietary Ingredients—A Ten-Year Review*, Food and Drug Law Journal, 59(1): 2004

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