

***Dietary Supplement Use in Children:  
Who, What, Why, and Where Do We Go From Here?***

**Tentative Date: February 12-13, 2001**

**Place: Natcher Auditorium, NIH Campus, Bethesda, MD.**

**Background/Purpose:**

The use of dietary supplements has increased dramatically as our knowledge about the role of nutrients and other bioactive components of food in health has increased. Although much of the information about the diet and health connection that has driven this trend is related to the reduction of chronic disease risk in adults, belief in the prophylactic use of these substances has been extended to consumers throughout the life cycle.

A recent conference supported by the ODS, in conjunction with the USDA, FDA, and CDC, and the corporate community focused on the research needed to expand our knowledge about the bioavailability of nutrients and other bioactive components of dietary supplements. One of the clearest findings emerging from these discussions is that the use of dietary supplements in children (preschool through adolescents) is increasing. However, little is known about the interaction between the use of these supplements and developmental physiology and behavior in children. Such knowledge is critical when evaluating either the justification or safety of this trend.

As part of the planning process for a large conference/workshop to develop a research agenda focused on dietary supplement use in children, a planning workshop was held involving 15-20 scientists who serve as a Scientific Steering Committee (SSC). The SSC discussed currently available data/research in both U.S. and international populations and developed an agenda for the larger conference/workshop.

Conceptually, the conference workshop will be designed to develop a research agenda to address specific issues relevant to the use of dietary supplements in children. The coverage would include the following developmental stages:

- prenatal environment (including maternal status and use of supplements beyond standard prenatal vitamins),
- infancy and early childhood (birth-through preschool, including issues pertaining to the use of DS during lactation),
- school age-pre-pubescence, and adolescence;

***Goals and Planning Strategies***

The Office of Prevention Research and International Programs (OPRIP) of the National Institute of Child Health and Human Development (NICHD) has taken the lead responsibility in the initiation and planning of this effort. The goal of this project will be

to identify key gaps in our knowledge about factors influencing the use, justification, and safety of dietary supplements in children and to establish a realistic research agenda to address these gaps. The products of this effort will be published proceedings and a well-defined research agenda that can be used for future program planning.

To accomplish these goals the multi-step process has been defined and initiated.

### **The Planning Process**

#### **Step 1:**

An initial proposal for this concept was submitted to the Office of Dietary Supplements (ODS) by the OPRIP/NICHD. The ODS approved the proposal and provided support for the initial stages of the planning and organization of this effort.

#### **Step2:**

An initial planning session held on April 3, 2000 was attended by representatives of several institutes and centers (IC's) within the NIH. Attendees included representatives from NICHD, ODS, NCI, NCCAM, NHLBI, NIDDK/NRCC, and NIDA. Several other IC's have agreed to participate in the planning process including NIDCR and NIMH. Subsequent to this meeting, several other agencies, including USDA/ARS, CDC, and FDA, have been contacted and asked for comment and suggestions about this project.

The participants at the initial planning meeting agreed that the goal should be an inclusive conference/workshop similar in size and scope to the recently held conference entitled "Bioavailability of Nutrients and Other Bioactive Components of Dietary Supplements." Using that meeting as the model, the next step in the planning process was the organization of a Scientific Steering Committee (SSC). The SSC members were selected from a list of candidates provided by the core group of supporters listed above.

#### **Step 3:**

A planning meeting of the Scientific Steering Committee (SSC) was held on June 23, 2000. Meeting attendees included:

##### **SSC:**

Lindsay Allen (UC-Davis), Dennis Bier (Baylor College of Medicine, USDA/HNRC), Kathy Kemper (Harvard Univ.), Nancy Krebs (Univ. Colorado), Gail Mahady (Univ. Illinois-Chicago), Chris Sempos (SUNY-Buffalo)

##### **NIH Staff:**

Gray Handley, Dan Raiten (NICHD), Nancy Ernst (NHLBI), Marguerite Evans (NCAMM), George Giacoia (NICHD), Gilman Grave (NICHD), Lynn Haverkos (NICHD), Jag Khalsa (NIDA), Mary Frances Picciano (ODS), Pam Starke-Reed (NRCC/NIDDK), Christine Swanson (ODS), Ben Vitiello (NIMH)

## **Management and Organizational issues.**

**Question:** Source of Conference Support?

**Resolution:** It was agreed that the planning of the agenda, identification of speakers and other substantive matters be the sole responsibility of the SSC/NIH planning committee. The SSC strongly endorsed the development of a broad-based consortium of support including other relevant federal agencies and the corporate community and emphasized the need to have a full representation of the views of all stakeholder communities in the conference as presenters and members of the working group sessions.

**Question:** What are the appropriate communities to be represented by speakers in the opening session?

**Resolution:** It was concluded that in the opening session following the Keynote speakers, representatives from the following constituent communities should provide overviews. These presentations should focus on the respective constituent group's needs and role in the context of data use and generation, i.e., research priorities.

- FDA or someone familiar with the regulatory process:: Suggestions: Elizabeth Yetley (FDA), Scott Bass, Esq.
- FTC: Suggested speaker: Michelle Rusk
- Dietary supplement industry: CRN. Alternatively, Dr. Bier suggested an academic who is familiar with industry databases and research perspectives might be possibility for this slot.
- Consumer community; Suggested speaker: someone from Consumer Union; Sylvia Rowe, IFIC

**Question:** Is the conference/workshop organization as currently envisioned the best approach?

The current construction is a two-day conference with the first day consisting primarily of plenary sessions and the second consisting of working groups designed to address specific question around the central themes of the meeting, i.e, evidence basis for indications of use and safety.

In addition to the extended discussion about the conceptual coverage of the conference (see below) there was some discussion about how best to get a product, i.e., a usable research agenda.

**Resolution:** As the workshop session are the driving force for obtaining input, it was decided that the best approach would be to have a committee structure for each workshop group, n=3 with a Chair. The committee members would each be responsible for presenting **brief** “straw man” papers to stimulate discussion.

Following these presentations and subsequent group discussions, each committee would be responsible for generating a summary report with specific research recommendations. The committee chairs would then be asked to participate in a follow-up session with workshop organizers and members of the SSC/NIH consultation to make a final report containing the results and recommendations derived over the full breadth of the conference.

### **Conceptual issues**

**Question:** What is the scope of the conference. What are dietary supplements?

The discussion revolved around the universe of materials currently available for consumption by children. It was suggested that the place to start would be the DSHEA definition, but because of the ambiguity of that definition a presentation be included as part of the opening session to make clear to the conference attendees what will be covered. Essentially, the universe will include nutrients, botanicals and bioactive substances that might be derived from foods either animal or botanical.

“The Dietary Supplement Health and Education Act defines dietary supplements as a: product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin, mineral, amino acid, herb or other botanical; OR a dietary substance for use to supplement the diet by increasing the total dietary intake; OR a concentrate, metabolite, constituent, extract, or combination of any ingredient described above; AND intended for ingestion in the form of a capsule, powder, softgel, or gelcap, and not represented as a conventional food or as a sole item of a meal or the diet.” (DSHEA, Public Law 103-417, October 25, 1994).

The definition includes the substance and consideration of the vehicle. To the extent that the later issue was covered by the previous ODS conference on Bioavailability, the focus of this conference will be on the presumed indication of use and safety of the dietary supplement irrespective of origin.

**Resolution:** Publicity announcing the conference, e.g., pamphlets, fliers, etc. will include the DSHEA definition. The opening session of the conference will include a presentation by Paul Coates (Director, ODS) describing our understanding of the universe of dietary supplements to be covered during the conference.

**Question:** Rather than efficacy discussions focused on type of dietary supplement, shouldn't the question be evidence based support for a given indication for use and if there such an evidence base is the supplement at the suggested dose safe for children?

The identification of the components needed to address this question is the core of what the conference will be designed to accomplish. There was considerable discussion about

whether to separate approaches to this question by category of dietary supplement, i.e., essential nutrients versus herbal versus others, and/or by clinical category. The latter seems a bit arbitrary. Aside from idiosyncratic methodological issues, it is not immediately clear what would distinguish the generic approach that would establish justification irrespective of hypothetical rationale from one clinical entity, e.g., a developmental disability, to another, e.g., early intervention with antioxidants to prevent cancer. Conceivably, there could be a “one size fits all” model into which specific data could be plugged that would get the answer.. The organizing committee agreed that it would be useful to get the insights of the various stakeholder communities on this issue

**Resolution:** The focus needs to be on the process to determine indications for use. The agenda as currently written (see below) contains slots for four (4) generic areas of justification. It might be helpful, particularly for identification of research agendas and priorities of individual IC s, within these areas, to include discussions of specific clinical categories. For example, it was suggested that the section on prophylaxis against childhood diseases should be expanded to prophylaxis and treatment and could include in addition to infectious diseases, childhood disorders such as ADHD or other developmental disabilities.

Clearly, the question around the indications of use for things such as “performance enhancers” that seem to be on the rise particularly in adolescents will have to be included perhaps under the talk on “optimization of growth and development.”

In the case of both justification and safety, the critical need will be the identification and utilization of acceptable biomarkers of outcome. This issue will need to be a major focal point both of plenary talks and within workshop groups.

With regard to safety, it was agreed that unless there is an evidence-based indication for use, a given dietary supplement should not be used by children. However, realistically it was recognized that many supplements are being touted and used in the absence of such indications. Consequently, safety must be discussed irrespective of the indication.

**Question:** Should there be a separation between Herbals and Dietary Essentials?

There was also some concern that because of the many divergent issues separating essential nutrients from other types dietary supplements that these distinctions be made clear.

**Resolution:** Clearly, distinctions should be made throughout the conference wherever appropriate to highlight the difference issues pertaining to justification and safety of use of these classes of dietary supplements.

Perhaps in the opening session, separate talks could be given to cover these distinctions. One suggestion might be to have a talk by Dr. Garza or someone representing the DRI process on the nutrient side and Dr. Mahady on pharmacognosy side as a lead in to discussions about indications.

The conference organizers will continue to refine our definition of this universe and pass it on to the NIH/SSC consultative group for concurrence.

**Question:** Should there be a separate coverage of domestic versus international issues?

This is a complex question as there are numerous issues related to indications, e.g., amelioration of dietary insufficiency as opposed to medicinal use as part of traditional medicine and use to “enhance optimal health” or as a presumptive prophylaxis against chronic diseases of adulthood. In addition, there is internationally in the context of developed versus resource-poor countries. In this latter case it was felt that particularly in the case of many of the commonly used botanicals, there is a wealth of research experience, e.g., the work on St. Johns wort in Germany.

In the context of the undeveloped or resource-poor world, the key issues from a research perspective are ethical and design issues in the conduct of studies to examine the role of essential nutrients in disease prevalence or natural history of disease. In addition, the history of use of traditional medicines might provide useful context for many of the supplements that are not being marketed in the US.

**Resolution:** The group agreed that there should be an inclusion of international issues wherever appropriate throughout the conference (at the discretion of individual speakers). In addition, there will be a separate workshop session devoted entirely to international issues with a particular emphasis on ethic and design issues in resource-poor settings.

**Step 4:**

After review of the agenda and solicitation of additional input from members of the initial planning committee regarding potential speakers and participants, efforts will begin to create a consortium of support for this effort. Using the Bioavailability workshop model, sources of support will be sought from NIH IC's, other Federal agencies, and members of the corporate community.

## Tentative Agenda

Convocation and Welcome

Keynote Speakers:

### **Plenary Session I: Overview of Dietary Supplements**

- I. Conference Purview: suggested speaker, Paul Coates, Director, ODS
- II. Dietary Essentials: overview of the process of identifying dietary essentials; and safe levels of intake. Suggested speaker: Cuthberto Garza, FNB/Cornell Univ.
- III. Herbals/botanical supplements: Indications and safety. Suggested speaker Gail Mahady or Kathy Kemper.
- IV. Other bioactive components of dietary supplements: indications and safety

### **Plenary Session II: Data Needs of Constituent Communities**

- I. Consumers
- II. Manufacturers
- III. Regulatory: FDA and FTC
- IV. Research: suggested speaker; Christine Swanson, ODS

### **Plenary Session III: Justification for use**

Focus: Evidence based justifications for use of dietary supplements by developmental stage. Talks would include availability of data to support justification for use in children based on one of the following categories.

- I. “Optimization” of growth and development, including use of “performance enhancing” supplements.
- II. Amelioration of dietary inadequacies: Nationally and Internationally
- III. Prophylaxis and treatment against childhood diseases, e.g., herbals as prophylaxis against infectious diseases or the “orthomolecular approach” for the treatment of developmental disabilities
- IV. Antecedents of adult disease: e.g., antioxidants as a prophylaxis against cancer and/or CVD. When are interventions appropriate

### **Plenary Session IV: Safety**

Focus: identification of essential components of safety evaluation of dietary supplements to be used by children including development of safe upper limits.

- I. Developmental pharmacology
- II. Age-dependent factors influencing bioavailability
- III. Toxicology including process for determining safe upper limits for use in children
- IV. “History of use”

### **Plenary Session V: Issues related to the determination of patterns of use**

Focus: identification of processes planned and in place to provide data about who uses dietary supplements, which ones and possible justification based on national survey data. This session will also include an appreciation of behavioral/cognitive factors influencing decision by caregivers and children about whether to use dietary supplements.

- I. Current usage patterns: who, what, why, how much?
- II. National nutrition monitoring system: NHANES, CSFII etc: suggested speaker, Ronette Briefel
- III. Industry-based data: suggested speaker, Dr Jim Tillotson
- IV. National and International survey data regarding dietary adequacy
- V. Obstacles for collecting relevant data;  
Suggested speaker: Dale Obermyer.

### **Plenary Session VI: Factors influencing the Decision to Use Dietary Supplements**

Focus: discussions of those factors that influence one's exposure to and decision to use dietary supplements.

- I. Attitudes and beliefs of caregivers
- II. Cognitive development of attitudes and beliefs in children
- III. Socio/cultural issues; sources of information, e.g., community/cultural beliefs, medical, media etc.

### **Plenary Session VII: Research Issues**

- I. Appropriate design for clinical trials involving children, Domestically? Internationally?
- II. Ethical issues in the conduct of clinical trials involving children, e.g. informed consent, issues related to conduct of trials in resource-poor settings, equity in standards of care.
- III. Methodology: particular reference to the identification of molecular targets and biomarkers for assessing efficacy

### **Working Group Sessions**

The working group sessions are intended to be interactive opportunities for cross fertilization of ideas from members of each of the stakeholder communities. Each session will have a chair and a committee of three each of who will present provocative "straw-man papers" designed to stimulate discussion around assigned topics. The workshop attendees will have an opportunity to deliberate and develop a focused research agenda designed to address their assigned topic. The workshop committee members will compile a summary of these deliberations to be presented by the respective chairs at a follow-up session of the workshop organizing/SSC committee to be held following the

conference. The final summary document will provide the basis of a targeted research agenda to be used for program planning purposes. The suggested topical areas for the working group sessions include:

1. What are the essential components of a process to provide science-based justification for dietary supplement use in children?
2. What are the essential components of the safety analysis relative to dietary supplement use in children? What is the best process for ensuring safety of dietary supplements for children? Toxicology? Risk analysis? Safe upper limits. NAS/DRI model? What do we need to know about the physiological differences, e.g., developmental pharmacology, to ensure safe use of dietary supplements in children?
3. Methodologies: experimental design issues
  - A. Epidemiology
  - B. Biomarkers/outcomes for interventions and descriptive studies
4. How can we get input from and to consumers about dietary supplement use in children?
5. International research issues
  - A. To be able to determine the effects of environment versus genetics on outcomes, how can we insure comparability of data across settings?
  - B. What are the ethical and scientific issues that need to be considered in the conduct of clinical trials in children in general and in resource-poor settings?