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PHOTOCOPY
PRESERVATION

CONFECTION RESPONSIBLE
NUTRITION

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PHOTOCOPY
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Dietary Supplements

Tiered - New Issues

Paul Carter Dietary Supplement
 Fed. Adv. Group
 Revised Int. Progress Report
 (Speak) Here

- Cartelini
- Heathcote
- ☐ P. E. Annette Dickinson
- ☐ Christine Lewis
- ☐ Laren Israelson
- ☐ Scott Bass
- Tony Young Esq

~~Chantilly Report~~
 had Groundwork for CAAM
 - ~~David~~
 - ~~1991~~ - Here is what has
 - ~~Robert Lurie~~ Purvis Lurie
 - ~~NCCAV~~ ~~DSHEA~~ ~~Devices~~
 - ~~Cost of~~ ~~Use~~ ~~Self Care Movement~~
 - ~~Cost~~ ~~of~~ ~~Blame~~ ~~of~~ ~~Medicine~~ ~~Federal~~ ~~Trade~~ ~~Act~~
 - ~~names + references~~
 - ~~Introductory~~

- Jay Betty
- AHP Good Assoc
- Consumer Health Food Assoc

EPA
 FTC
 Michelle Rusk
 Anne Mann

⇒ ~~CAAM~~
 • Furs, Low Dog, Linnar, Bresler
 - Chapell

- Everything Through Me
- December Outline - Review + Review
- Wellness Approval - Extension of Burroughs - Wellness & Self Care as 2 components of health as acknowledge importance & science
- Recommendation - Short
- Summary of Content

tell them what you told them

Introduction to Issue
Issue Background
Rec in Body
Summary

1 tell them what you are going to tell them
2 tell them what you want to say
3 tell them what you told them

- Introduction to Report - to ask for comment
(Case Navigators)

Groft, Stephen (NCCAM)

From: Cathy Fomous [cfomous@crnusa.org]
Sent: Wednesday, October 17, 2001 11:41 AM
To: Groft, Stephen (NCCAM)
Cc: Fisher, Ken (NCCAM)
Subject: DSHEA experts

Dr. Groft,

During the last day of discussion at the October WHCCAMP meeting, you suggested that the Commissioners meet with the lawyers who were involved in the creation of DSHEA--Scott Bass and Loren Israelsen. While the Council for Responsible Nutrition (CRN) thinks this is a good idea, we would like the Commissioners to include Annette Dickinson in the discussion. Dr. Dickinson was also critically involved in the passage of DSHEA, was a member of the White House Commission on Dietary Supplement Labels, and participated in an Oct. 6, 2000 WHCCAMP panel. As CRN represents 110 dietary supplement manufacturers and suppliers, Dr. Dickinson could provide a national industry perspective. Dr. Dickinson could also provide valuable comment on the adverse event reporting system. CRN was invited to respond to the OIG report and found many flaws in the report and resulting recommendations. Dr. Dickinson can be reached at 202-872-1488 or through her assistant (Ms. Hogen-Heath) at 202 263-1024. Thank you for considering this request.

CRN will be submitting comments to the WHCCAMP draft recommendations at the end of this week.

Sincerely,
Cathy Fomous, Ph.D.
VP, Research Evaluation
Council for Responsible Nutrition
Washington D.C.
202 263-1018



Council for Responsible Nutrition

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October 19, 2001

White House Commission on
Complementary and Alternative Medicine Policy
6707 Democracy Boulevard, Room 880
Mail Stop 5467
Bethesda, MD 20892

To the Commissioners:

The Council for Responsible Nutrition (CRN) thanks the Commission for the opportunity to submit comments to the draft recommendations. CRN is a trade association representing more than 100 companies in the dietary supplement industry.

CRN staff was present for each Commission meeting held in the Washington, D.C., area and participated in a panel (Oct. 6, 2000) that discussed coordinated research. The submitted comments are offered in the spirit of the Commission's guiding principles and discussions. In finalizing its report and recommendations, CRN asks that the Commission uphold the findings and intent of the Dietary Supplement Health and Education Act (DSHEA).

Recommendation 1: *The Commission recommends that a) a public-private partnership be formed to develop voluntary standards that will promote accuracy, fairness, comprehensiveness, and timeliness of information on CAM internet sites, as well as disclosure of any conflicts of interest; and b) an ongoing process be developed to review participating websites to determine compliance with these standards. Sites reviewed and found in compliance with the criteria could publicize this achievement and display a logo identified with this level of merit.*

This recommendation should be deleted. While noble in intent, it is resource-intensive and difficult to enforce. Instead, efforts and resources would be better spent on an education campaign, as noted in the following comment. If recommendation 1 is pursued, Commissioners should note the activities of Hi-Ethics, Inc. and the E-Health Seal program as reported in the Jan. 1 issue of *The Tan Sheet*. Hi-Ethics is a coalition of 18 internet health sites and content providers and seeks development of a seal to certify health websites.

Recommendation 2: *The Commission recommends that a) a public education campaign be conducted that teaches people how to evaluate CAM information on the internet; and b) partnerships be formed with schools that use computers to develop students' skills at evaluating internet information on health care.*

Part (a) should be amended to read "a public education campaign, *using experts in the field*, be conducted that teaches people how to evaluate CAM information on the internet." This recommendation should be amended further to include a partnership with public libraries (i.e., incorporate recommendation 6) and computer software and web browser companies.

Recommendation 3: *The Commission recommends that the privacy of individuals using CAM internet sites be protected by a) encouraging CAM sites to disclose if users are tracked and how that information is utilized (including whether that information is sold to third parties), and b) assessing if current legislation or regulations are adequate to assure the protection of privacy of CAM health information seekers on the internet, and if not, amending or developing new legislation.*

Because this recommendation is applicable beyond CAM, the language should be broadened as discussed during the October meeting. All websites that require registration should disclose how the information is to be used. As part of the education campaign (recommendation 2), consumers should be warned to avoid websites that do not disclose this information.

Recommendation 4: *The Commission recommends that an interagency task force of federal agencies be formed to a) identify gaps in CAM information (e.g., information on training and licensure requirements of practitioners, access and reimbursement, wellness, self-care, clinical applications) and develop strategies to reduce the gaps; and b) improve internet linkages of CAM information between federal and nonfederal agencies and organizations and promote the use of Firstgov.gov for people seeking information on the internet.*

The preface of the recommendation should be amended to read “The Commission recommends that an interagency task force of federal agencies, *in partnership with industry representatives and CAM practitioners*, be formed to . . .” Depending on the issue, industry representatives might be from insurance companies, health maintenance organizations or healthcare product manufacturers. In part (b) of the recommendation, the use of any single website should not be promoted. In this case, firstgov.gov is not particularly useful.

Recommendation 5: *The Commission recommends that a centralized source of CAM information be established in DHHS for the public, including the media, with a toll-free telephone number that would provide information or refer the caller to the appropriate agency and person.*

The National Center for Complementary and Alternative Medicine (NCCAM) is the logical site for centralized CAM information, and making reliable scientific information readily available to the public is one of the goals in the Center’s strategic plan. NCCAM’s staff and resources should be enhanced to meet this goal. The centralized site should also link to other available resources such as the Natural Medicines Comprehensive Database. In addition, as government websites are often slow to generate and update information due to bureaucratic review, alternative sites should be considered, such as the Division for Research and Education in Complementary and Alternative Medical Therapies at Harvard University.

Recommendation 6: *The Commission recommends that, in partnership with the National Library of Medicine and the American Library Association, training materials be developed to assist librarians in guiding people to find CAM information on the internet.*

This recommendation should be incorporated as part of recommendation 2.

Recommendation 7: *The Commission recommends that a) CAM information materials be developed at a reading level that the general public can understand and utilize, and b) CAM information be developed that is targeted to different population groups.*

This recommendation should be incorporated as part of recommendation 5.

Recommendation 9: *The Commission recommends that additional support be provided to FTC to a) identify false and deceptive CAM-related health claims on the internet and to take appropriate actions to minimize the occurrence of these claims; b) monitor the Spanish media and other English and non-English advertising outlets, especially radio and television that target vulnerable populations; and c) increase consumer education in identifying deceptive and unsubstantiated claims in all forms of marketing and advertising.*

Recognize the achievements of the Federal Trade Commission (FTC), such as their success with Operation Cure.All. The recommendation might be reworded to specify that additional support be provided to FTC for Operation Cure.All activities.

Recommendation 10: *The Commission recommends that national and local leaders of communities of special populations be brought together to identify strategies to protect their constituency from being targeted for products or services that are unnecessary, harmful, exorbitantly priced, or otherwise detrimental.*

As written, the recommendation is a recipe for “Big Brother.” “Special populations” should be defined, and the term “unnecessary” (products or services) should be deleted as it invites broad interpretation and abuse.

Recommendation 11: *The Commission recommends that health professionals be required to clearly post information that explains their level and scope of training so that consumers understand and can make informed choices.*

Recommendation 12: *The Commission recommends that states and local governments make information on state guidelines, requirements, licensure, and certification of CAM providers readily available to the public.*

The order of these recommendations should be reversed.

Recommendation 13: *The Commission recommends that the AER system be strengthened by a) encouraging voluntary registration of dietary manufacturers so that the FDA can identify and contact them if an adverse event is reported; b) requiring dietary supplement manufacturers to report serious adverse events to the FDA (similar to requirements for OTC drugs); c) mandating registration of manufacturers and developing a database of manufacturers and product ingredients; d) simplifying the system to facilitate increased usage and easier reporting; and e) increasing outreach activities to health professionals (including poison control centers and emergency room physicians) and consumers regarding the importance of reporting adverse events, and provide information on how to use the system.*

The elements of this recommendation are based on the Report on Adverse Event Reporting for Dietary Supplements from the Health and Human Services Office of the Inspector General (OIG), which CRN found quite flawed. The Commissioners are encouraged to read the attached comments to the OIG report, which CRN was invited to provide. It should be noted that this recommendation contains inaccurate language. Part (b) implies that there is a mandatory requirement to report adverse events for over-the-counter (OTC) drugs, and this is not true. The recommendation targets dietary supplements when other healthcare products (e.g., cosmetics, homeopathic products, medical foods, OTC monographed drugs) do not carry a mandatory requirement for adverse event reporting. There

is no basis for imposing adverse event reporting uniquely on dietary supplement products, and therefore, part (b) should be deleted. If part (b) remains, the term “serious” should be well defined in the recommendation, and the language should be broadened to include all healthcare products. Regarding part (c), mandatory registration is not necessary as the information is available to the Food and Drug Administration (FDA) through other means (e.g., notification of structure/function claims and facility inspection records). The Commissioners are reminded that dietary supplements are classified as a subcategory of food and should be regulated as such.

Recommendation 14: *The Commission recommends that the availability of consumer information of dietary supplements be increased through a) improved labeling, package inserts, and information at point-of-sale; b) inclusion of information on possible interactions with prescriptions or OTC drugs, foods, or other health products; and c) inclusion of information on possible risks to vulnerable populations such as children, the elderly, pregnant or nursing women, and those with certain health conditions or compromised immune systems.*

As mentioned in the discussion during the October meeting, the term “possible interactions” (part b) should be changed to “known interactions.” Also, the recommendation should include a statement that known interactions will be determined by appropriate scientific authorities, in consultation with industry experts. Additionally, as noted by Dr. Low Dog, the recommendation does not address information on benefit. The recommendation should state that structure/function claims should be permitted to provide information more meaningful to the consumer (in the spirit of DSHEA).

Recommendation 15: *The Commission recommends that claims of standardization be limited to products with industry-approved standards.*

This recommendation should be deleted, as there are no industry-approved standards. There is no general agreement on the meaning of standardization, and any recommendation at this time could promote artificial manipulation of (botanical) products to meet standards.

Recommendation 16: *The Commission recommends that the FDA's good manufacturing practices (GMPs) be implemented to help assure the purity of dietary supplements.*

The recommendation should be amended as follows: The Commission recommends that the FDA's good manufacturing practices for dietary supplements be *published, finalized and* implemented to *ensure consistent product quality.*

Recommendation 17: *The Commission recommends that a) the DHHS, USDA, Environmental Protection Agency (EPA), U.S. Customs Service, and other appropriate federal departments and agencies work with manufacturers and importers to monitor the quality of imported and domestic dietary supplements and identify and prevent contaminated or adulterated products from entering the U.S. marketplace; and b) DHHS, USDA, EPA and others work with the World Health Organization and other appropriate international organizations to establish guidelines to help assure the purity of herbal ingredients and, where possible, set international standards for consistency.*

This recommendation should be deleted as much of this work is already being done.

Recommendation 18: *The Commission recommends that there be an adequate staff of professionals within the FDA and NIH Office of Dietary Supplements (ODS) with expertise in dietary supplements, especially areas other than vitamins and minerals (e.g., plant, animal, synthetic and microbial products). This could include hiring people with these specific skills and/or providing training to current staff and may require increased staffing levels and/or funding.*

Consider deleting this recommendation and incorporating it as part of recommendations 9 and 20. If left as a separate recommendation, the first sentence should be amended to read "...adequate staff within the FDA to fully implement DSHEA by 2005 and the Office of Dietary Supplements ..." The last sentence should not be deleted as suggested by Dr. Jonas, and the wording should be amended to read "This *must* include hiring people with these specific skills ..." Also, during the discussion Dr. Groft stated that FDA has an advisory board for dietary supplements. This is not quite accurate; the FDA Food Advisory Committee (FAC) has a subcommittee for dietary supplements. CRN has recommended on several occasions that FDA establish a separate advisory committee for dietary supplements.

Recommendation 19: *The Commission recommends strengthening and building on the emerging dialogue between conventional medicine and CAM by developing ways to enhance communication, cooperation, and collaboration among conventional and CAM researchers, clinicians, and practitioners; research centers, programs, and institutions; professional leadership organizations; federal and state research and health agencies; and the public, private and nonprofit sectors.*

Recommendation 20: *The Commission recommends including trained and licensed CAM professionals on research, journal, and regulatory advisory and review committees in both the public and private sectors, and adapt as appropriate, any regulations that might impede such representation.*

These are good recommendations; however, for optimal coordination of CAM research, industry researchers should be included.

Recommendation 21d: *Support research on why people use CAM, how they determine its effectiveness, and what they find satisfying about CAM in comparison to conventional medicine, and parallel this research with the public impact on the emerging integrated healthcare system.*

The role of the NIH Office of Dietary Supplements (ODS) should be recognized. Under goal 4 of the ODS strategic plan, one objective is to "develop new and validate existing epidemiological/survey methods for assessing dietary supplement usage." The recommendation should be amended so that ODS receives the necessary resources to carry out this goal.

Recommendation 21g: *Continue to support career development awards to enable investigators focusing on CAM to develop into independent investigators and mid-career awards to provide support for the time required to mentor new CAM investigators.*

This recommendation should be deleted as NCCAM already carries out this activity.

Recommendation 21i: *Solicit a study of FDA methods for reviewing and approving CAM products, devices, and practices, using a step-wise approach for increasing data with increasing risk.*

The intent of this recommendation is unclear, as FDA does not "approve" most CAM products or practices. The only items, related to CAM, that FDA approves are medical devices and drugs.

Recommendation 21j: *Use mechanisms such as the NIH Small Business Innovative Research program and the Small Business Technology Transfer Research program to offer the private sector opportunities for research support.*

The recommendation, as written, is already performed. The recommendation might be rewritten to advise that NIH hold workshops, targeting the private sector, to explain all appropriate granting mechanisms. ODS has expressed an interest in sponsoring such a workshop.

Recommendation 21l: *Request a study from the Institute of Medicine on the prioritization process for CAM research including how to maintain rigor while obtaining input from a variety of stakeholders.*

This recommendation should be deleted because it is unnecessary; NCCAM has such a process. CRN emphasizes that should this recommendation remain, a prioritization process must be flexible to respond to shifting consumer interest and market demands.

Recommendation 22: *The Commission recognizes that it is essential that all biomedical research meet the highest standards of quality and recommends that the standards of research quality for CAM be the same as for conventional biomedical research—neither lower nor higher.*

This recommendation should be incorporated as part of recommendation 21.

Recommendation 22 a: *Develop programs to bring together a variety of disciplines to find innovative research approaches for solving difficult questions in focused CAM areas (example: NCI/SPORE program).*

Recommendation 22b: *Encourage public, private, or foundation supported multidisciplinary conferences and workshops to increase opportunities for CAM and conventional practitioners, clinicians, and researchers to exchange ideas and to discuss methodological approaches to studying CAM questions.*

These recommendations should be combined.

Recommendation 22c: *Request recommendations from the National Science Foundation on how to study in a credible manner, the high-risk, emerging scientific ideas associated with CAM research.*

This recommendation should be deleted unless “high-risk” is well defined.

Recommendation 23: *The Commission recommends ensuring public participation in shaping and prioritizing the CAM research agenda. Include public input on advisory committees, institutional review board (IRBs), and institutional research teams, methods to disseminate research results, and the shaping of regulatory and health services activities.*

This recommendation should be deleted; it is already in effect as evidenced by public participation in the NIH Director’s Council of Public Representatives (COBR), various Institute and Center advisory councils, and the FDA advisory committees.

Recommendation 24: *The Commission recommends that CAM research results be submitted to the most rigorous peer-reviewed journals. Include both CAM and conventional medical expertise on journal review boards when reviewing CAM manuscripts.*

This recommendation should be deleted. The first sentence is somewhat insulting, and the second sentence is reflected in recommendation 20.

Recommendation 25: *The Commission recommends that public and private resources be provided to support systematic reviews of CAM research literature.*

This recommendation should be deleted, as demand will drive the production of systematic reviews.

Recommendation 25b: *Produce and maintain up-to-date summaries of current evidence on safety and efficacy of CAM practices and products similar to the U.S. Preventive Task Force.*

This recommendation could be deleted, as it is similar to recommendation 5.

Recommendation 25c: *Develop nontechnical, understandable summaries of all systematic reviews of the literature; include them in NLM's Medline Plus database, accessible directly and through public libraries and other publicly available information services.*

This recommendation should be incorporated as part of recommendations 5 and/or 7.

Recommendation 30: *The Commission recommends that collaboration between CAM and conventional healthcare institutions should be encouraged and funded.*

This recommendation should be deleted as it is captured in other recommendations.

Recommendation 33: *The Commission recommends that a basic curriculum that surveys the CAM modalities and ensures basic skills in collaborating with or supervising CAM professionals should be developed for conventional healthcare professionals in professional schools, postgraduate training programs, and continuing education programs to increase knowledge and understanding of CAM in order to enhance and protect the public's health.*

Recommendation 34: *The Commission recommends that curricula in CAM fundamentals and principles should be developed at conventional healthcare professional schools in conjunction with CAM experts and CAM institutions.*

These recommendations should be combined.

Recommendation 46: *The Commission recommends that the Secretary of Health and Human Services authorize and fund detailed and expanded epidemiologic surveys of CAM patterns of use, with special attention to ethnic populations. This information is essential to inform public policy and to protect particularly vulnerable populations.*

This recommendation should be incorporated as part of recommendation 21d.

Recommendation 55: *The Commission recommends that purchasers, insurers, managed care organizations, and other health plan sponsors consider coverage of CAM interventions shown to be safe and cost-effective.*

This recommendation should be incorporated as part of recommendation 52.

Recommendation 61: *The Commission recommends that DHHS sponsor or co-sponsor with external partners, an easily accessible, continuously updated website that provides information on CAM practices and products proven to be safe, clinically efficacious, and cost effective. The Commission believes that information should be provided for both consumer and professional use. The Commission encourages an outreach effort be made to inform purchasers, such as employers and community health centers, of the availability of this website.*

This recommendation should be incorporated as part of recommendation 5.

Recommendation 66: *The Commission recommends that in partnership with the business community and school boards, incentives be developed for schools to limit the sale and advertising of high fat snacks, soft drinks, and other products that do not contribute to a healthy lifestyle.*

As discussed during the October meeting, the language of this recommendation should be changed to deliver a positive message, such as "...incentives should be developed to *promote the sale and advertising of products that contribute to a healthy lifestyle.*"

Recommendation 68: *The Commission recommends that questions on specific CAM usage be included in the national surveys that are the sources of the Healthy People 2010 data (e.g., NHIS, NHANES, MEPS, etc.).*

This recommendation should be incorporated as part of recommendation 21d.

Recommendation 69: *The Commission recommends that a) CAM be included in all federal worksite wellness and health promotion programs, and b) federal health coverage plans offer a CAM wellness option.*

Recommendation 70: *The Commission recommends that a) DHHS, in consultation with the business community, develop incentives for employers to include CAM in worksite wellness programs and health coverage; and b) DHHS form partnerships with private organizations such as the Wellness Councils of America to encourage inclusion of CAM services in their worksite wellness programs.*

These recommendations should be combined.

Recommendation 76: *The Commission recommends that DHHS, in consultation with the American Association of Health Plans, National Committee for Quality Assurance, representatives of major health plans, Center for Medicare and Medicaid Services, Department of Defense, and others, including CAM professionals and consumers, identify strategies to incorporate CAM wellness, prevention, and self-care in health plans.*

This recommendation should be incorporated as part of recommendation 52.

Recommendation 78: *The Commission recommends that the President, Secretary of the Department of Health and Human Services, or Congress should create an Office at the highest possible and most appropriate level with sufficient staff and budget to perform functions that include, but are not limited to, coordination of federal CAM activities; federal CAM policy liaison with conventional health care and CAM professionals, organizations, institutions, and commercial ventures; planning and convening conferences, workshops, and necessary advisory groups; centralized federal media point of contact; and facilitation of implementation of the WHCCAMP recommendations.*

The role of the centralized office should be limited to implementing the Commission recommendations. The language used to create the office should include a sunset clause, which will serve as an incentive to execute the recommendations in a timely manner.

CRN hopes that the Commission will carefully consider these comments and would be pleased to provide any further information necessary to support the important work of the Commission.

Sincerely,

A handwritten signature in black ink, appearing to read "John B. Cordaro". The signature is written in a cursive style with a horizontal line underneath the name.

John B. Cordaro
President and Chief Executive Officer



Council for Responsible Nutrition

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April 6, 2001

Michael F. Mangano, Acting Inspector General
HHS Office of Inspector General
Room 5246 Cohen Building
330 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Mr. Mangano,

The Council for Responsible Nutrition (CRN) appreciates the opportunity to provide comments on the draft report of the IG on adverse event reporting for dietary supplements. This opportunity seems especially critical to us, in that we see a number of serious problems and even errors of fact in the report as it now stands.

CRN is a trade association representing about 110 manufacturers of dietary supplement products. Our members are committed to providing consumers with safe and beneficial dietary supplements manufactured to high quality standards. We recognize the importance of an adverse event reporting system that provides regulators and the industry with signals alerting them to the existence of potential problems with any consumer product. This is especially important with regard to products that are ingested, including conventional foods, dietary supplements, and pharmaceutical products. We have worked with the Food and Drug Administration on issues relating to the safety of dietary supplements for many years, and have made recommendations to the agency and to Congressional committees regarding improvements needed in the adverse event reporting system. We recognize several of our suggestions in some of the recommendations that are already covered in the IG's report. CRN worked with the appropriations committees in the last Congress to build support for the additional funds FDA needs to improve its handling of adverse event reports, with some success.

While CRN recognizes the need for an effective adverse event reporting system, we also strongly believe the approach to collecting and evaluating such reports relating to dietary supplements should be viewed in the context of other food-related systems. We are extremely troubled by the view repeatedly expressed in the IG's report that the appropriate comparison is to prescription drug reporting systems. This is entirely inappropriate. The correct comparison is to the systems currently in place for other self-selected consumable products, including foods such as medical foods and infant formula, as well as OTC drugs.

We are equally concerned about the negative view of dietary supplements that we believe pervades the IG's report. The popularity of dietary supplements and the belief that they are generally safe are viewed as risk factors, rather than as evidence that the vast majority of products are indeed both beneficial and benign. We believe in this respect the IG's report represents a failure to fairly evaluate the product category.

Because dietary supplements are not subject to a requirement for premarket approval based on proprietary research submitted by the manufacturer, the IG's report concludes that there is little scientific basis for the purported benefits of these products. This is an entirely false assumption. In fact it is the abundance of publicly available scientific research that drives both the manufacturers' and the consumers' interest in dietary supplements, and this needs to be fully acknowledged in the report.

The report paints a negative picture of the dietary supplement industry, implying that many companies are fly-by-night operations that FDA has difficulty locating. In fact, the vast majority of dietary supplements are manufactured by large corporations that are well known to the agency since they are regularly inspected. *Nutrition Business Journal* estimates that the largest 65 manufacturers in the business account for about 75% of the products on the market. The products these companies make are properly labeled, as required by regulations, but unfortunately labels are not routinely submitted by individuals reporting an adverse event. The report indicates that FDA lacks a product label in 77% of the adverse event reports in the database, but fails to make the point that the lack of a label may largely explain the agency's difficulty in tracking products.

These general concerns will be reflected in many of our specific comments, keyed to specific page numbers in the IG's report. The specific comments are attached.

CRN and its member companies are very hopeful that our comments will be taken seriously and will result in significant changes in the overall tone and content of the IG's draft report on adverse event reporting for dietary supplements. We believe extensive changes are essential, before the report is made public, and we would welcome the opportunity to review the next draft before a decision is made to release it. The faults in the present draft are so severe that we believe releasing it in its current form would be a major disservice to the dietary supplement industry and could impede rather than advance productive discussion of the important issue of improving the adverse event reporting system for dietary supplement products. We are prepared to work with the IG's office in any way possible to provide the information necessary to support vitally needed improvements in the current draft.

Sincerely,
Annette Dickinson, Ph.D.
Vice President, Scientific and Regulatory Affairs.

**INSPECTOR-GENERAL'S REPORT ON ADVERSE EVENT REPORTING
FOR DIETARY SUPPLEMENTS
COMMENTS SUBMITTED BY
THE COUNCIL FOR RESPONSIBLE NUTRITION
APRIL 6, 2001**

EXECUTIVE SUMMARY

Page 1, end of "background" paragraph

This paragraph notes, "unlike prescription drugs, FDA does not require supplements to undergo premarket approval for safety and efficacy. Instead it relies mostly on its adverse event reporting system to identify safety problems." This statement is the first of many instances in which the prescription drug reporting system is taken as the appropriate comparison category for dietary supplements. CRN believes this comparison is inappropriate. At the least, the IG should add an additional statement such as: "FDA also relies on adverse event reporting to identify and quantify potential safety problems in food products including medical foods and infant formula. FDA also has periodically imposed specific reporting requirements to ensure adequate monitoring of some food ingredients. This was the case in the past with sulfites and aspartame, and is currently being required for products containing olestra."

Page 2, paragraph on "limited product information"

The final sentence of this paragraph states: "Product samples are especially helpful because dietary supplement ingredients are not standardized." This is a curious statement. Product samples are always helpful, even with foods or standardized pharmaceutical products, because adverse events can be due to errors in formulation or accidental contamination. The value of product samples accompanying any adverse event report has nothing to do with whether ingredients are "standardized."

Page 2, paragraph on "limited manufacturer information"

This paragraph states that FDA receives 90 percent of adverse event reports about prescription drugs from their manufacturers. It should also acknowledge that the reason for this is that prescription drug manufacturers are subject to a mandatory reporting requirement. There is no mandatory reporting requirement for adverse events associated with OTC drugs or with foods, including medical foods and infant formula. This should also be acknowledged.

Page 3, paragraph on "limited clinical information"

This paragraph says there is little clinical research on the safety and efficacy of supplements, because premarket clearance is not required. This is a false statement. In fact, there is an abundance of clinical research on the safety and efficacy of supplements, ranging from vitamins and minerals to omega-3 fatty acids to botanical ingredients. Indeed, it is the existence of this rich and ever-expanding scientific research base that drives marketers to provide ingredients such as these in the form of dietary supplements. It is this abundant and publicly available database that provides the foundation of both the consumer and the commercial interest in the product category.

Page 3, paragraph on “limited information on consumer use”

This paragraph suggests that it is essential that FDA have a mechanism for tracking the number of consumers using a particular supplement, in order to determine the incidence and seriousness of adverse events. In fact, it is not always necessary to know the denominator of consumer usage in order to justify action based on safety concerns. One example cited in the IG’s report is the plaitain warning and product recall, based initially on a single adverse event report due to a misidentified ingredient, namely a variety of digitalis instead of the intended ingredient plantain.

Page 3, heading asserting that FDA “rarely takes safety actions” based on adverse event reports

This heading is not supported by the text, which in fact says that FDA took 31 actions between January 1994 and June 2000. This number of actions cannot be characterized as “rare” events. The fact is that most dietary supplements have a broad range of safe intakes and the number of products presenting a significant safety concern is small. This in itself explains to a large extent why numerous actions are not required or taken by FDA.

RECOMMENDATIONS

Page 4, recommendation 1

The IG’s first recommendation is that manufacturers of dietary supplements should be required to report adverse events to FDA. The paragraph notes that such reporting is currently mandatory for pharmaceutical products marketed under a new drug application. Again, the IG’s report proceeds on the assumption that the appropriate comparison is between dietary supplements and prescription drugs. This is not the case. It should be acknowledged that mandatory reporting is currently not required for OTC monographed drugs or for conventional foods, including medical foods and infant formula. As the report stands, it is made to appear that only dietary supplements are free of the requirement for mandatory reporting, and this is not correct.

It is CRN’s belief that a potential requirement to report serious adverse events is an issue that bears further discussion. CRN would be opposed, however, to a general requirement to report all events, including minor effects. In order to facilitate further discussion, further definition of serious adverse events—and even of adverse events *per se*—will be needed. For example, adverse events need to be distinguished from simple product complaints, such as complaints about taste or color, even recognizing that changes in organoleptic qualities of a product may sometimes be an indicator of a potential safety issue. Also, serious events need to be distinguished from minor events. CRN and other industry trade associations are currently reviewing proposals from third-party organizations that could provide services relating to collecting and evaluating serious adverse event reports.

The third part of the first recommendation is that an FDA phone number should appear on all dietary supplements labels. It should be noted that there is no such requirement for any other consumer product category, including OTC drugs and prescription drugs. It is CRN’s belief that there is no basis for imposing any such requirement uniquely on dietary supplement products. Many dietary supplement manufacturers currently provide an 800 number to facilitate consumer inquiries, including reports of adverse events. CRN believes providing an 800 number is a commendable company policy, which should be encouraged.

Pages 4 and 5, recommendation 2

It is suggested that dietary supplement manufacturers be required to register with FDA, and that individual products should also be registered. This is a suggestion that bears further discussion, provided the topic is simple registration and not the precursor of a cumbersome registration or licensing system such as exists in some countries.

It should also be noted that FDA currently has a vast amount of information available on dietary supplement manufacturers and products, since the agency has in the past several years received thousands of notifications from hundreds of companies regarding structure/function statements used in labeling, as required by DSHEA. These notifications have been compiled in a database made available commercially by AAC Consulting, and that database provides a valuable source for cross-referencing many products and manufacturers.

The IG's report also suggests that FDA should notify manufacturers upon receipt of an adverse event report, to alert the company and to obtain more product information. CRN has suggested this, in comments submitted to FDA on program priorities and in testimony presented in Congressional hearings. We believe it deserves serious consideration. The company would then be in a position to provide important information on the actual formulation of the product as well as substantive data relating to any potential safety concerns.

It is suggested that FDA develop an improved computer database for tracking and analyzing adverse events. CRN has also suggested this in the past, and we worked with appropriations committees in the last Congress for additional FDA appropriations for this purpose, with some success.

Page 5, recommendation 3

The IG's report suggests that FDA issue guidance on the type of safety information needed in a 75-day notice. Several industry members have supported the need for additional guidance in this area, and CRN believes guidance could be helpful, provided the guidance does not result in creating a burden equivalent to the current food additive approval system.

The report suggests that a set of monographs be developed on the safety and benefits of dietary supplements. CRN believes this is a good idea, in concept, provided a drug standard of proof is not applied and providing the monograph is not taken as the equivalent of a preapproval system such as the one that exists for OTC monographed drugs.

In the Nutrition Labeling and Education Act, it was recognized that health claims for foods do not need to be based on a drug-like level of proof. For example, foods are not typically subject to the type of controlled trials that are undertaken for drugs. However, epidemiological data regarding healthful dietary patterns in large populations can provide the basis for scientifically sound public recommendations as well as health claims relating to the importance of certain nutrients or types of foods. In other cases, there may be substantial clinical data regarding the effects of some specific nutrients or food components, as in the case of the role of calcium in reducing the risk of osteoporosis. The food model rather than the drug model should be utilized in evaluating dietary supplements, if and when monographs are developed.

It is noteworthy that FDA has already contracted with IOM (Institute of Medicine) for the development of monograph concepts relating to the safety of dietary supplements, and the Research-Based Dietary Ingredient Association has likewise contracted with LSRO (Life Sciences Research Office) for a set of monographs on the safety and benefits of certain ingredients used both in dietary supplements and in functional foods. Thus, the value of third-party reviews of dietary supplement safety and benefits is a concept, which is being recognized both by industry and by the agency.

The IG report suggests that FDA collaborate with NIH in setting a research agenda including dietary supplement safety issues. This is an excellent idea and is already to some extent ongoing.

The report suggests that the industry and USP should standardize dietary supplement ingredients, particularly botanicals. It is unclear in this context what the IG envisions by the term “standardization.” Dietary supplements are formulated to meet the health needs and preferences of a wide variety of people. Even in the vitamin area, ingredients and formulations are not “standardized,” and there is a demand for products ranging from multivitamins to single nutrients, and from low potencies (only a fraction of the RDI) to high levels of some nutrients (vitamin E at 400 IU, vitamin C at 1000 mg). In the botanical arena, there could be a legitimate purpose served by products providing different levels of intake or different combinations of ingredients. CRN does not believe there is a need to “standardize” all ingredients and products. However, it may well be desirable to define certain terms used in product labeling to improve consumer understanding of products that are “standardized” to contain a certain percent of an active ingredient, for example.

The IG’s report recommends that FDA expedite the development of GMPs. It should be noted that the industry fully supports GMPs, has worked diligently to provide FDA with a model for dietary supplement GMPs, and is anxious to see appropriate GMPs finalized. Also, most of the industry associations have already committed that their members are observing the GMPs set forth in the initial FDA publication in 1997, and some associations are sponsoring audit programs to verify this. CRN fully supports GMPs, and has taken an active role in creating and promoting the version currently under discussion. However, the IG’s report may overestimate what can be accomplished merely by GMPs. The law already requires that products provide 100% of label claim, for example, and companies that flaunt that requirement are not likely to be brought into line merely because an additional regulation is in place supporting the requirement. The GMPs, in and of themselves, will not in fact be able to provide assurance of the precise contents of each batch manufactured. As is the case now with all other legal and regulatory requirements, any assurance provided will be the result of a combination of factors, including the companies’ commitment to following GMPs and FDA’s commitment to enforcing them.

Page 5, recommendation 4

The recommendation that FDA put more useful information on its website about adverse events may have value, provided it is made very clear what the limitations of adverse event reports are, particularly with regard to demonstrating any real association between a product and an event. It would be useful to consider limiting any publicly available adverse event information to some type of summary form, categorized by product types or generic ingredients. It should be noted that, in the food area, FDA has not published reports that identify adverse events by company or even product name, but rather has grouped events related to ingredients of potential concern (aspartame, sulfites, olestra). Similarly, reports prepared by the Poison Control Centers are

summarized in broad categories and do not identify specific products or companies. This could provide a useful pattern for dietary supplement reports as well.

INTRODUCTION

Page 8, second line

This line says that reported events range in severity “from nausea and cardiac arrest to death.” This is awkward phrasing. A suggested edit might incorporate two minor and two major effects, such as: “Reported events range in severity from nausea or dizziness to cardiac effects or death.”

Page 8, section on DSHEA

This is a good basic summary of DSHEA.

Page 8, section on “Our Inquiry”

The first sentence says “FDA’s adverse event reporting system for dietary supplements is a particularly important safety valve for consumers due to the lack of other complementary oversight systems.” This statement implies that dietary supplements are unique among FDA-regulated products in the lack of complementary oversight systems. This is not the case. Dietary supplements are a category of foods, and are no more lacking in oversight than are other foods, including conventional foods, functional foods, infant formula, and medical foods. It is entirely appropriate that the oversight systems should be the same for all these food categories. This paragraph of the IG’s report also falsely suggests that dietary supplements are not subject to manufacturer inspections. This is not the case. Dietary supplements are subject to manufacturer inspections, and the inspections that are conducted are often extensive, requiring several days to complete. These inspections are based on the same GMPs that apply to conventional foods, until such time as new dietary supplement GMPs are adopted. This paragraph also suggests that the increased popularity of dietary supplements, by itself, is a risk factor for adverse events. This is not a logical statement. Foods, after all, are used by one and all, and their popularity or universal usage does not itself confer risk.

IMPORTANCE OF THE SYSTEM

Page 11, last paragraph

The IG’s report says FDA has received only 38 new dietary ingredient notifications covering 32 ingredients. AAC Consulting has a commercially available database showing more than 100 new ingredient notifications, to date.

Page 12, chart on regulatory mechanisms

The box summarizing regulatory requirements should show that dietary supplements are subject to food GMPs until new dietary supplement GMPs are developed. Likewise infant formula is subject to food GMPs until new ones are developed.

Page 12, first paragraph under “popularity of dietary supplements”

This paragraph emphasizes: “Today, dietary supplements are widely available in grocery stores, retail pharmacies, health food stores, and on the Internet.” Except for the internet aspect, this is not a new phenomenon, as the paragraph implies. Dietary supplements have been “widely available” in grocery stores, retail pharmacies, and health food stores for at least 60 years, if not longer.

Pages 13-14, warning labels on dietary supplements

The report notes that some dietary supplements bear warning statements about potential contraindications, even though FDA does not specifically require such warnings. The extensive efforts of industry associations to encourage appropriate warnings are dismissed with the statement, “Some industry groups have established standard warnings for certain products, but manufacturers’ use of these standard warnings is voluntary.” It would be more appropriate for the report to fully acknowledge the extent of the industry’s efforts, especially with regard to controversial products such as ephedra.

Although FDA has not yet finalized a regulation relating to ephedra, the industry has largely complied with trade association recommendations to include a very extensive warning statement on products containing ephedra. The warning is modeled on the OTC drug warning label for ephedrine-containing products. Some states have also passed laws requiring extensive warning statements for ephedra-containing products. Some associations have recommended warning statements for other products, and some have recommended dosage limits for ingredients that may present safety concerns. The associations, which have been pro-active in this regard, include the Council for Responsible Nutrition, the American Herbal Products Association, the Consumer Healthcare Products Association, the National Nutritional Foods Association, and the Utah Natural Products Alliance. These efforts deserve more attention and more credit than they are given in the present draft IG report.

This may also be an appropriate place to include some comment regarding the importance of consumer compliance with label directions. All dietary supplements recommend a specific level or range of use for the product, and many of the reported adverse event reports involve misuse or abuse of the product by the consumer.

Page 15, first paragraph

An FDA-commissioned paper by A. Walker is cited to the effect that adverse event reports capture only about 1 percent of actual adverse reactions. Is this paper available? CRN would appreciate the opportunity to review it.

Page 15, comparison to other adverse event reporting systems

The IG’s report suggests that the large number of reports received by the Poison Control Centers provides a more realistic view of true consumer experience than the much smaller number received by FDA. It should be noted, however, that all calls received by the Poison Control Centers are considered “reports,” even if they involve no adverse event and possibly no ingestion at all. For example, if a mother finds her toddler on the floor with an open bottle of tablets and calls the Poison Control Center for advice that is considered a report, even though the child

may have no symptoms and may not in fact have even swallowed any of the tablets. It is also notable, and should be mentioned in this report, that the vast majority of reports received for dietary supplements by Poison Control Centers involve accidental exposures in young children rather than deliberate consumption by any age group, and result in no symptoms or minor symptoms.

The report currently gives the incorrect impression that the thousands of reports received by the Poison Control Centers represent significant adverse events not captured by the FDA system, and this is not necessarily the case. If the State of Texas has received large numbers of reports, this is in part due to active solicitation of reports relating to ephedra-containing dietary supplements. CRN is aware that the state forwarded some of these reports to FDA, but is not aware of the reasons why all reports apparently were not forwarded. Perhaps only significant reports were forwarded.

Page 16, top of page

The first paragraph on this page says that manufacturers do not share adverse event information with FDA. The implication is that ONLY dietary supplements are exempt from mandatory reporting of adverse events. In fact, this is true of conventional foods as well as OTC drugs. Only prescription drugs or NDA drugs are required to report adverse events to FDA. The report should clarify these facts.

Page 16, paragraph on “presumed safety”

This paragraph states: “The presumed safety of dietary supplements may cloud the consumers’ ability to link an adverse event with a supplement product.” Is the implication that an attack should be mounted on “presumed safety”? The fact is that the vast majority of dietary supplements are safe when used as directed in labeling, or when used in the manner that is common among most consumers.

Page 16, paragraph on “self-care products”

This paragraph asserts, “another factor that may contribute to under-reporting of supplement adverse events is that they are self-care products.” It should be acknowledged that many other products, including OTC drugs, are also self-care products. People also utilize conventional foods specifically for health purposes. It is a well established and valid assumption that people can and should take substantial responsibility for their own health care. This is a critical and positive aspect of overall health care in the U.S. By definition, “self-care” occurs mostly without the guidance of the physician. The IG’s report inappropriately casts aspersions on the whole concept of self-care. This is in contrast to the findings of Congress at the time of the enactment of DSHEA, which recognized that better nutrition and supplementation can contribute to consumer health and can even help control escalating health care costs. DSHEA emphasized that “consumers should be empowered to make choices about preventive health care programs based on data from scientific studies of health benefits related to particular dietary supplements.”

Page 19, first paragraph

The IG’s report indicates that FDA may need to test products to determine the actual ingredients and levels of each ingredient in the product. It would be appropriate to recognize

at this point that there are in some cases a variety of methodologies available for analyzing some ingredients, and that there is a need for validated methods as well as good laboratory practices in order to ensure that appropriate results are obtained. Some of the publicity about variable levels of some ingredients has been based on inappropriate methods of analysis. The industry is currently supporting several efforts to establish validated analytical methods, including the INA/MVP program (Institute for Nutraceutical Advancement/Methods Validation Program), a new initiative being undertaken by AOAC, the ongoing efforts of the USP, and a new certification program recently launched by NSF.

Page 19, second paragraph

The IG's report implies that the new dietary supplement GMPs will permit access to records not currently available for food products generally. It should be noted, however, that DSHEA does not include any specific change to the current law regarding access to records for foods generally, including dietary supplements.

Page 19, paragraph on "limited manufacturer information"

The IG's report says nonreporting of adverse events by dietary supplement manufacturers "contrasts starkly" with the number of reports from pharmaceutical and device manufacturers, as if this were the correct comparison. In fact, the correct comparison is to reporting for OTC drugs and for foods, since these categories—like dietary supplements—are also self-care products and have no statutory requirement to report. It is hardly surprising that FDA receives numerous reports from those industries required by law to provide such reports.

Pages 19-20, characterization of the industry

The report paints a negative picture of the dietary supplement industry, implying that many companies are fly-by-night operations that FDA has difficulty locating. In fact, the vast majority of dietary supplements are manufactured by large corporations that are well known to the agency since they are regularly inspected. *Nutrition Business Journal* estimates that the largest 65 manufacturers in the business account for about 75% of the products on the market. The products these companies make are properly labeled, as required by regulations, but unfortunately product labels are not routinely submitted to FDA by individuals reporting an adverse event. The report indicates that FDA lacks a product label in 77% of the adverse event reports in the database, but fails to make the point that the lack of a label may largely explain the agency's difficulty in identifying manufacturers and tracking products.

The IG's report incorrectly states that products sold through multi-level organizations may be especially difficult to track. CRN's membership includes many of the major multi-level marketers, and they indicate that their products bear the name and location of the company headquarters, not of a local distributor.

This is not to say that in all cases the company named on the label of a product will be the actual manufacturer of the product. Labeling regulations for all foods, including dietary supplements, require that the label show the name and address of the manufacturer, packer or distributor. This can become an issue when any company manufactures a food, drug, or dietary supplement, which is marketed through another company. For example, major chains such as Safeway, CVS and Walmart typically sell their own store brands of many products, including dietary

supplements, and these products are almost always manufactured by another firm. The chain may prefer that its name appear on the label as the distributor of the products, so that consumer complaints or inquiries will come to the chain rather than going to the actual manufacturer. In such cases, however, it is unlikely that FDA would face a major difficulty in obtaining the name of the actual manufacturer from the chain distributing the product.

Page 21, number of new ingredient notifications

The report says only 38 new ingredient notifications have been received, but AAC Consulting has a commercially available database indicating that more than 100 have been filed.

Page 21, section on consumer use

Once again, it is taken as a given that the correct comparison is between dietary supplements and prescription drugs. Dietary supplements are widely distributed and intended for self-selection, as are conventional foods and OTC drugs. The denominators of usage for dietary supplements, conventional foods, and OTC drugs are generally unknown, but large. Prescription drug practices are not the appropriate comparison.

Page 22, number of actions taken by FDA

CRN suggests that 31 safety actions from January 1994 to June 2000 is not a small number and does not support the IG's assertion that FDA "rarely" takes such actions. Also, the fact that FDA took only 31 actions during a period when more than 100 million people were taking dietary supplements is not necessarily low, let alone "strikingly low." During that period, it is likely that around 60 million of those people were specifically taking a multivitamin, and it is not at all surprising that not a single FDA action was taken against a multivitamin. In fact, it would be striking if any actions were taken against the multivitamin category, given the longstanding record of safe use of such products by a large fraction of the population.

The IG's report repeatedly presumes that the dietary supplement category is inherently risky and that the very prevalence of consumer use is a risk factor. This presumption is not justified, and the final report must be revised to more fairly reflect the actual safety profile of the most commonly used dietary supplement products. Over the decades, hundreds of millions of consumers have used dietary supplements on a regular basis. Many of those consumers are longterm satisfied users who have never experienced an adverse event associated with the dietary supplements that are an integral part of their efforts to construct a healthy lifestyle.

Pages 25-30: Recommendations

See CRN comments on the summary IG recommendations, in pages 2-5 of these comments.

APPENDIX A, FDA experience with ephedra-containing products

Page 31, ephedra discussion

The approved dosage of synthetic ephedrine for use in OTC drugs as a bronchodilator is incorrectly stated as "up to 25 mg a day." The correct statement would be that ephedrine is approved for use in

OTC drugs as a bronchodilator at levels up to 25 mg per dose, with a maximum daily intake of up to 150 mg.

Pages 34-35, IG's commentary on criticisms of FDA's proposed rule on ephedra

These two pages cite some criticisms that have been raised regarding FDA's proposed rule on ephedra-containing products, and provide commentary from the IG's office. Curiously, in most cases the IG's commentary appears to CRN to be unrelated to the substance of the criticism cited. Examples are mentioned below.

Page 34, comment on meeting label claim

The IG's "commentary" in this section is unrelated to the criticism about FDA's selection of the 8 mg maximum dose. The criticism cited is that FDA's proposed limit of 8 mg is based in large part on the agency's analysis of the adverse event reports. The IG's commentary is related to the possibility that products may not always meet label claim, and therefore FDA needs product samples to permit analysis of the product actually used by consumers. These two points are not connected, since FDA did not select the 8 mg limit because of uncertainty about what products contain.

The IG's commentary implies that without GMPs there is no requirement for products to meet label claim. This is false. Under FDA regulations, all foods including dietary supplements are required to provide what the labels say they provide. Products that fail to do so are misbranded and illegal. In addition, DSHEA added a new provision reiterating that dietary supplements are misbranded if they fail to have the identity and strength they are represented to have.

Page 34, commentary on FDA's reliance on adverse event reports rather than controlled research

The commentary relating to the new ingredient notification process is not relevant to ephedra, since ephedra is not a new ingredient. It was on the market well before the passage of DSHEA, and in fact some of the initial adverse event reports date from 1992. FDA had access to an abundance of clinical evidence on ephedrine alkaloids, which was discussed in depth at the 1995 and 1996 advisory committee meetings, but chose to rely primarily on some adverse event reports in its regulatory approach to ephedra.

Page 35, commentary on product usage associated with adverse events

The commentary relating to a pharmaceutical manufacturer's establishment of recommended usage levels is not relevant to the topic under discussion. The issue here is not the labeled directions, but the actual usage pattern of the individual for whom the adverse event was reported. People do not always use products—even prescription products—in the manner directed in labeling, and adverse event reports often do not provide information on the actual usage patterns associated with the adverse event.

Page 35, comment on denominator data

The importance of denominator data is overstated, especially since it has been noted elsewhere that a single well-documented report may be sufficient as a basis for action (as in the case of the plantain/digitalis problem).

APPENDIX B, pages 36-38

The list of 31 actions taken by FDA on safety of dietary supplements actually pertain to only a handful of products:

- Ephedrine alkaloids
- GHB, GBL and related products
- Digitalis/plantain mixup
- 5-hydroxy-L-tryptophan
- Triax metabolic accelerator
- Aristolochic acid

These represent a unique selection of products, most of which are not typical of dietary supplement ingredients. The vast majority of dietary supplements are notably absent from this list, since they by and large have an excellent safety record and do not generate any significant reason for concern. Almost half of total dietary supplement sales are accounted for by vitamins and minerals, which do not appear in this list. While CRN recognizes that there is some potential for toxicity from an excess of some vitamins and minerals, actual reports of adverse events—in the clinical literature or elsewhere—are relatively rare. CRN has recommended voluntary dosage limitations for those nutrients such as vitamin A that are known to cause adverse effects when used in excess. Another quarter of the market is made up of a variety of botanical ingredients, most of which have an excellent safety record and most of which do not appear to any significant extent as the subject of adverse event reports. These include botanicals such as garlic, ginseng, and echinacea.

Products containing ephedrine alkaloids are probably the most physiologically active of the botanical products marketed in this country. Yet millions of consumers have used ephedra-containing products safely for weight loss and for sports nutrition, and have vigorously expressed their concern about state or Federal efforts that might restrict access to such products. Experts differ in their evaluation of the significance of the adverse events that have been reported in association with such products and in their recommendations regarding the regulatory actions that should be taken. Industry, FDA, and consumers will all benefit when there is a regulatory resolution to the longstanding issue of establishing appropriate parameters for the safe marketing of these products. In December 2000, CRN submitted to FDA an extensive evaluation of the safety of ephedra, prepared by toxicological experts at the firm of Cantox, and we are hopeful that this rigorous scientific evaluation will help FDA bring this issue to closure.

GHB and GBL are not legitimate dietary supplements, but are industrial chemicals or drugs masquerading as dietary supplements. GHB was on the market as a “designer drug” for years before DSHEA was passed, and is not a legitimate dietary supplement. GBL is an industrial chemical marketed as a floor stripper, and has been only temporarily using the dietary supplement category as a convenience. In fact, CRN understands that many purveyors of GBL have apparently now re-adopted the category of “floor stripper” in preference to the dietary supplement category. It is inappropriate to consider such products as in any way typical of the dietary supplement category.

The digitalis/plaintain issue was a clear case of a mix-up, which happens with foods and even with prescription drugs from time to time. As soon as the mix-up was identified, the product was the subject of an FDA warning and a recall. This was a good example of quick action

based on an adverse event report, involving cooperation between FDA and the industry to promptly warn consumers and recall the product.

The triax problem evidently is a case of a company overtly adding a drug to a dietary supplement. CRN is not aware whether FDA action on this ingredient was triggered by an adverse event report.

The 5-hydroxy-tryptophan issue arose because of the purported similarity of a substance in this product to the contaminant responsible for the EMS outbreak related to L-tryptophan in the late 1980's, and was not triggered by the adverse event reporting system.

Aristolochic acid has long been recognized as a substance of concern, especially in Europe. FDA's current action was in reaction to European precedents and was not triggered by the adverse event reporting system.

The nature of the actions FDA has taken on the basis of safety concerns over the past six years, and the types of products involved in them, only serve to emphasize CRN's point that the overwhelming majority of dietary supplements are safe within a broad range of use, and the incidence of significant adverse events is limited to a relatively narrow spectrum of products. It is critical that discussion of the overall adverse event reporting system for dietary supplements be considered in this context.

Groft, Stephen (NCCAM)

From: Kenneth Fisher [kfisher@erols.com]
Sent: Sunday, October 14, 2001 10:35 AM
To: steve groft; Axelrod, Corinne (NCCAM)
Subject: Notes from the NAS/NRC Supplements meeting

1. I spoke with Chris Lewis-Taylor. She is just back from her honeymoon and suggested we use the phone and not Email as it is overfull. She would be glad to confer with us later this mnth. She suggested we call when we know Dr. LowDog will be here. Chriss would prefer late afternoon at our office as she lives in Kensington. I told her about 2 hours would be useful; she said okay. We need to fax the Interim Report to her because of the Email issue. I suggest a cover note from Steve saying we'll be in touch by phone.

2. There is a new book (symposium) available that is mostly supplements, altho titled "Examining the Science Behind Nutraceuticals". I will order it if Corinne doesn't have it. It is a good source of needed references. Let me know, Young One.

3. I have a copy of a brief talk about the drug approval process, but it is a summary of 21CFR312. We may need to get the current CFR Chp 21 as it is also a good reference. OTC drug reporting of AEs is voluntary, except for Rx drugs converted to OTC. In this case, reports are required quarterly for the first year, and then annually for 3 years, then voluntary. I asked for the reference in the OTC part of the CFR but we may need to go on the web to find it as it may be in FDA Guidance and not the CFR yet.

. Talks by FEMA and CIR reps suggest to me that we need to check and see if any flavoring agents or cosmetics are also dietary supplements. Might be a tedious job, but I have some idea on how to do it.

5. The PoisonControl Centers was a topic of discussion in regard to deriving a framework for safety evaluation. The American Association of Poison Control Centers has an office in DC and has a web site (address unknown yet). They publish a listing of reports annually in the Journal of that Society. Also they have a database containing the names of substances which have elicited reports. It is for sale, and FDA has the ephedra portion of the database only. It was suggested that it is much more extensive than the AER of FDA. We need to check it out, but I didn't get a contact person's name. Maybe Chris L-T can help in this regard.

6. DSHEA Section 13 specifically states that the ODS is the DS Central for "coordination of research in NIH" and "principal advisor" to DHHS for aspects of dietary supplements. We need to review this and revise the CAM Central ideas to reflect what's already in the Law. Might need to confer with Paul Coates on this matter.

7. Steve: I need to talk with you about what the NAS/NRC wants me to do, just so we're not compromising the efforts of both groups (WHC and NRC).

I'll be in Tuesday morning. Is the final report done yet?

kdf

TABLE 22B. Demographic Profile of Exposure Cases by Generic Category of Substances and Products: Pharmaceuticals

Substances Implicated In the Exposure	No. of Exposures	Age (yr)			Reason				Treated in Health Care Facility	Outcome					
		<6	6-19	>19	Unint	Int	Other	Adv Rxn		None	Minor	Moderate	Major	Death	
Analgesics															
Acetaminophen only															
Adult formulations	25,978	6,412	9,084	9,657	13,257	12,346	15	272	14,610	8,258	3,531	1,451	457	38	
Podiatric formulations	26,161	23,324	2,608	273	26,604	343	10	82	3,075	7,141	308	63	22	0	
Unknown formulations	8,963	2,572	2,852	3,222	4,342	4,433	6	98	5,237	2,413	1,390	662	261	47	
Acetaminophen in combination with:															
Aspirin (with other ingredients)	5,423	2,016	1,476	1,756	3,096	2,061	1	246	2,432	1,649	968	248	22	4	
Aspirin (no other ingredients)	12	5	3	4	7	4	0	1	4	3	2	1	0	0	
Codeine	5,741	1,090	1,150	3,214	2,505	2,755	4	444	3,084	1,364	1,349	439	98	3	
Oxycodone	3,553	434	446	2,385	1,460	1,745	3	317	1,836	678	850	265	81	15	
Propoxyphene	5,120	594	629	3,611	1,824	3,024	0	223	3,295	1,162	1,338	519	193	18	
Other narcotics	11,626	1,212	1,721	7,987	4,465	6,175	7	874	6,409	2,211	2,741	979	320	40	
Other drugs, adult formulations	15,213	2,222	3,760	8,528	5,383	9,323	10	406	9,701	3,523	3,842	1,604	312	12	
Other drugs, pediatric formulations	322	224	60	34	289	25	0	8	44	74	54	8	2	0	
Aspirin alone															
Adult formulations	4,022	1,545	1,184	1,206	2,280	1,632	9	90	1,902	1,202	619	317	38	7	
Pediatric formulations	482	385	73	21	444	34	0	4	90	194	25	7	0	0	
Unknown formulations	9,350	1,938	3,355	3,699	3,512	5,560	6	205	6,231	2,490	1,949	1,276	213	38	
Aspirin in combination with:															
Codeine	353	49	37	244	126	209	0	16	228	67	94	36	18	1	
Oxycodone	234	29	30	161	98	120	0	15	123	43	45	27	5	2	
Propoxyphene	41	7	5	27	21	17	0	3	22	8	11	3	2	0	
Other narcotics	33	10	7	13	23	9	0	1	17	9	7	1	1	1	
Other drugs, adult formulations	1,785	377	371	949	823	852	1	96	956	403	382	180	30	2	
Other drugs, pediatric formulations	3	1	1	1	3	0	0	0	1	1	0	0	0	0	
Narcotics															
Codeine	1,258	497	273	437	873	290	2	89	369	311	210	50	16	3	
Meperidine	600	59	74	415	253	259	0	82	316	96	134	72	25	2	
Methadone	1,047	79	108	792	342	580	4	84	705	87	190	204	117	17	
Morphine	1,218	146	125	843	562	529	8	100	706	189	245	169	61	10	
Oxycodone	1,632	187	111	1,201	792	652	2	163	804	268	324	181	71	12	
Pentazocine	204	15	17	156	77	87	0	38	95	25	57	14	7	0	
Propoxyphene	560	53	47	416	193	325	0	35	361	99	113	83	33	12	
Other/unknown	3,267	468	431	2,141	1,377	1,404	4	435	1,690	503	702	419	159	44	
Nonaspirin salicylates	1,065	536	143	359	792	231	0	41	377	342	146	63	5	0	
Other nonsteroidal anti-inflammatory drugs															
Colchicine	146	45	22	78	94	32	0	19	82	43	17	17	6	6	
Ibuprofen	54,643	33,886	10,376	9,356	41,986	11,678	21	854	13,013	17,073	4,149	854	105	3	
Indomethacin	682	203	82	357	302	200	0	77	264	180	120	30	4	0	
Other	18,181	5,300	3,716	8,322	10,809	5,910	10	1,381	6,710	5,174	2,532	738	115	3	
Unknown	8	3	0	4	6	1	0	1	2	1	1	0	0	0	
Phenacetin	2	1	0	1	2	0	0	0	0	0	0	0	0	0	
Phenazopyridine	913	693	77	133	819	47	0	47	221	396	96	14	1	0	
Salicylamide	75	67	1	7	70	3	0	2	23	35	3	0	0	0	
Other	4,058	771	466	2,553	2,069	1,419	1	545	1,792	751	1,102	377	89	0	
Unknown	102	16	37	39	30	63	1	6	61	22	18	5	0	0	
*Category totals	214,066	87,471	44,858	74,602	131,190	74,386	125	7,410	86,908	58,488	29,754	11,376	2,889	340	
Anesthetics															
Inhalation anesthetics															
Nitrous oxide	232	16	105	96	108	85	2	35	114	23	46	32	12	2	
Other	199	18	25	138	160	23	3	12	87	15	57	28	3	1	
Unknown	2	0	0	0	0	0	0	2	2	0	0	1	0	0	
Ketamine and analogs	294	12	113	156	52	227	5	4	247	24	67	88	24	0	
Local and topical anesthetics															
	6,966	4,731	652	1,390	6,421	164	35	335	1,184	2,531	821	144	31	0	

(Continued on following page)

TABLE 22B. Demographic Profile of Exposure Cases by Generic Category of Substances and Products: Pharmaceuticals (Cont'd)

Substances Implicated In the Exposure	No. of Exposures	Age (yr)			Reason				Treated in Health Care Facility	Outcome				
		<6	6-19	>19	Unint	Int	Other	Adv Rxn		None	Minor	Moderate	Major	Death
Other	41	8	7	22	24	6	0	10	27	5	9	6	2	0
Unknown	6	2	3	1	3	1	1	1	3	0	3	1	0	0
*Category totals	7,740	4,787	905	1,803	6,768	506	46	399	1,664	2,598	1,003	300	72	3
Anticholinergic drugs	4,689	1,576	630	2,308	2,868	1,462	11	299	2,384	1,227	869	600	132	4
Anticoagulants														
Heparin	95	19	11	52	83	5	0	7	50	22	8	9	5	1
Warfarin (excluding rodenticides)	1,699	666	84	883	1,336	263	6	82	725	511	69	105	84	1
Other	439	129	23	269	371	35	0	33	140	153	26	10	5	0
Unknown	6	3	0	2	4	2	0	0	5	2	0	1	0	0
*Category totals	2,230	817	118	1,206	1,704	306	6	122	920	688	103	125	94	2
Anticonvulsants														
Carbamazepine	6,132	1,741	1,305	2,864	3,812	1,958	5	277	3,768	1,338	1,614	927	285	0
Phenytoin	4,045	786	345	2,720	2,310	1,319	3	337	2,575	910	955	559	115	1
Succinimides	98	48	29	20	91	6	0	1	22	41	9	1	0	0
Valproic acid	8,743	1,027	2,202	5,100	3,672	4,691	1	297	5,762	2,391	2,095	1,012	336	8
Other	4,378	544	727	2,847	2,115	1,928	4	311	2,472	1,075	968	472	140	5
Unknown	14	8	1	4	10	4	0	0	9	3	1	1	0	0
*Category totals	23,410	4,154	4,609	13,555	12,010	9,906	13	1,223	14,608	5,758	5,642	2,972	876	14
Antidepressants														
Cyclic antidepressants														
Amiripityline	7,787	969	980	5,456	2,410	5,048	6	192	6,157	1,241	1,794	1,727	1,021	62
Amoxapine	48	4	8	35	16	30	1	1	35	4	10	7	10	0
Desipramine	334	44	57	219	133	180	0	19	240	79	61	66	23	2
Doxepin	1,854	134	156	1,463	490	1,288	5	50	1,494	274	434	423	243	18
Imipramine	1,704	437	551	668	966	659	1	68	1,036	518	346	227	95	8
Maprotiline	37	6	6	24	16	20	0	1	26	5	5	8	7	0
Nortriptyline	1,332	163	206	894	536	728	0	57	935	291	298	203	108	9
Protriptyline	21	9	4	7	15	5	0	1	15	8	6	2	0	0
Other cyclic antidepressants	751	74	87	545	376	325	3	43	434	169	198	110	48	1
Unknown cyclic antidepressants	15	0	0	12	2	12	0	1	11	0	1	4	4	1
Cyclic antidepressant formulated with a benzodiazepine	70	10	6	50	25	41	0	2	44	12	14	11	7	1
Cyclic antidepressant formulated with a phenothiazine	198	30	18	146	80	106	0	7	148	33	32	47	20	0
Lithium	4,361	277	734	3,146	1,567	2,264	8	428	3,381	941	1,020	898	253	6
MAO inhibitors	372	46	8	288	215	102	0	52	227	69	52	87	21	0
SSRIs	28,563	4,743	7,030	15,278	10,568	16,335	23	1,485	18,023	8,561	6,296	2,518	473	22
Trazodone	10,501	767	1,590	7,480	2,916	7,077	8	442	7,552	2,307	3,292	1,284	218	9
Other	12,088	1,806	2,364	7,258	4,757	6,634	4	634	8,203	3,275	2,719	1,709	551	14
Unknown	24	0	5	15	4	20	0	0	17	1	7	1	2	0
*Category totals	70,060	9,519	13,810	42,983	25,092	40,874	59	3,483	47,978	17,788	16,585	9,332	3,104	153
Antihistamines														
Diphenhydramine, (OTC)	17,632	9,245	2,902	5,070	12,492	4,724	9	357	6,264	4,716	3,327	1,401	175	6
Diphenhydramine, (Rx)	332	105	71	143	194	127	0	10	167	87	61	41	9	0
Diphenhydramine, unknown if OTC or Rx	5,936	2,092	1,240	2,400	3,353	2,347	4	195	2,741	1,309	1,239	702	105	14
H ₂ receptor antagonists	5,721	3,429	655	1,484	4,854	654	1	196	1,152	1,834	426	88	9	0
Other	22,497	10,110	5,590	6,197	16,805	4,825	19	770	7,457	6,984	3,193	1,198	156	8
*Category totals	52,118	24,981	10,458	15,294	37,698	12,677	33	1,528	17,781	14,930	8,246	3,430	454	28
Antimicrobials														
Antibiotics														
Systemic	36,763	20,232	5,848	9,529	28,951	3,584	22	4,107	6,073	8,166	3,259	781	54	2
Topical	7,314	5,460	497	1,168	7,109	67	1	133	203	1,480	341	19	3	0
Unknown	879	286	207	341	488	226	0	161	282	153	190	22	2	0
Antifungals														
Systemic	1,180	625	147	361	952	96	0	129	261	305	114	26	1	1
Topical	8,137	6,132	430	1,379	7,889	52	9	181	283	1,718	596	37	1	0

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TABLE 22B. Demographic Profile of Exposure Cases by Generic Category of Substances and Products: Pharmaceuticals (Cont'd)

Substances Implicated In the Exposure	No. of Exposures	Age (yr)			Reason				Treated in Health Care Facility	Outcome				
		<6	6-19	>19	Unint	Int	Other	Adv Rxn		None	Minor	Moderate	Major	Death
Unknown	13	7	0	6	12	0	0	1	2	5	3	0	0	0
Anthelmintics														
Diethylcarbamazine	250	130	15	96	241	6	0	2	13	65	10	2	0	0
Piperazine	508	391	42	69	408	10	2	6	50	170	24	2	1	0
Other	731	400	84	199	691	12	5	22	163	189	118	22	3	0
Unknown	23	15	2	5	21	1	0	1	4	5	1	1	0	0
Antiparasitics														
Antimalarial	437	129	69	213	332	67	1	36	195	151	40	34	7	1
Metronidazole	1,253	307	192	669	768	238	0	245	327	247	183	43	1	0
Other	108	62	15	28	102	2	0	4	20	28	10	0	0	0
Antituberculars														
Isoniazid	412	86	160	152	187	189	0	31	301	102	53	42	86	2
Rifampin	49	16	10	21	34	8	0	7	24	13	11	2	0	0
Other	14	3	1	10	11	1	0	2	5	4	1	1	0	0
Unknown	3	2	0	1	2	1	0	0	1	1	1	0	0	0
Antivirals														
Systemic	1,575	480	200	807	1,030	346	0	191	558	394	159	69	23	1
Topical	48	29	7	10	47	0	0	1	3	14	4	0	0	0
Unknown	53	17	9	25	34	6	0	13	13	12	2	2	0	0
Other	174	129	18	24	147	14	0	13	35	65	14	2	0	0
Unknown	9	2	2	4	6	2	0	1	3	0	2	0	0	0
*Category totals	59,933	34,940	7,955	15,117	49,542	4,928	40	5,287	8,819	13,295	5,136	1,107	182	7
Antineoplastics	1,257	392	83	678	1,075	63	4	113	427	381	129	48	14	2
Asthma therapies														
Aminophylline/theophylline	1,641	357	190	1,048	1,110	395	2	110	962	401	286	313	65	10
Terbutaline and other beta-2 agonists	9,536	7,297	1,255	900	8,746	449	13	317	2,282	3,103	1,488	534	15	0
Other beta agonists	2,412	560	577	1,149	1,105	1,050	3	236	1,270	468	576	376	37	0
Other	3,306	2,254	562	441	3,010	216	3	71	500	1,228	188	47	5	0
Unknown	10	2	4	4	5	4	0	0	5	1	1	2	0	0
*Category totals	16,905	10,470	2,588	3,542	13,976	2,114	21	734	5,019	5,201	2,539	1,272	122	10
Cardiovascular drugs														
ACE inhibitors	7,160	2,836	488	3,600	5,984	951	4	209	2,410	3,083	452	381	50	4
Alpha blockers	1,455	540	90	775	1,194	186	2	68	681	602	151	121	18	0
Antiarrhythmics	1,046	199	51	754	916	73	0	53	383	391	75	72	23	9
Antihypertensives	6,683	2,308	2,066	2,173	5,142	1,302	11	183	3,659	2,001	1,248	1,038	171	5
Beta blockers	9,502	2,556	972	5,622	7,124	2,078	10	259	4,684	3,817	827	890	195	26
Calcium antagonists	8,844	2,304	554	5,665	6,831	1,723	5	252	4,667	3,622	801	883	243	61
Cardiac glycosides	2,810	812	128	1,799	2,247	285	1	234	1,404	964	191	408	153	20
Hydralazine	152	42	14	95	117	31	0	4	73	61	22	16	3	0
Long-acting nitroate	582	232	15	314	517	54	0	8	186	266	40	33	3	0
Nitroglycerin	2,194	1,313	139	681	1,900	246	9	34	641	1,024	152	65	10	1
Nitroprusside	36	3	2	25	15	0	0	21	32	4	8	5	4	0
Other vasodilator	301	136	24	131	276	19	0	4	91	133	27	10	0	0
Unknown types of vasodilators	2	0	0	1	1	0	0	1	0	0	0	0	0	0
Vasopressor	7	2	2	3	6	0	0	0	5	2	2	0	0	0
Other	3,060	1,294	344	1,296	2,689	216	3	144	706	941	262	95	13	1
Unknown	22	6	1	13	11	10	0	1	12	3	0	1	0	0
*Category totals	43,856	14,583	4,890	22,947	34,970	7,174	45	1,475	19,633	16,904	4,258	4,018	886	127
Cold and cough preparations	99,873	63,951	18,650	15,868	86,784	9,889	49	2,974	18,717	27,445	14,501	2,900	199	5
Diagnostic agents	454	85	37	270	387	9	3	52	178	72	99	27	2	0
Diuretics														
Furosemide	1,687	829	145	658	1,495	152	1	33	488	541	212	73	7	0
Thiazide	1,869	814	183	809	1,556	240	2	67	580	655	159	76	9	1
Other	1,404	636	132	588	1,168	165	2	64	419	528	134	53	9	0
Unknown	302	141	27	123	247	34	1	19	107	109	32	17	3	0
*Category totals	5,262	2,420	487	2,178	4,466	591	6	183	1,594	1,833	537	219	28	1
Electrolytes and minerals														
Calcium	4,045	3,407	284	306	3,912	72	3	55	189	949	120	20	2	0
Fluoride	3,911	3,398	341	150	3,850	24	2	33	213	1,238	357	13	0	0
Iron	3,654	2,265	530	781	3,005	534	9	96	1,257	1,282	447	110	9	1

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TABLE 22B. Demographic Profile of Exposure Cases by Generic Category of Substances and Products: Pharmaceuticals (Cont'd)

Substances Implicated In the Exposure	No. of Exposures	Age (yr)			Reason				Treated in Health Care Facility	Outcome				
		<6	6-19	>19	Unint	Int	Other	Arly Rxn		None	Minor	Moderate	Major	Death
Magnesium	447	161	68	194	377	35	4	30	122	85	71	25	5	1
Potassium	1,163	556	112	453	1,015	112	2	29	308	425	87	43	6	0
Sodium	2,426	1,600	442	328	2,306	87	18	13	295	615	370	39	4	0
Zinc	2,574	1,776	192	543	2,430	49	0	07	205	495	237	41	0	0
Other	857	557	92	190	681	96	1	77	178	245	85	21	3	0
Unknown	6	1	1	4	3	2	0	1	3	4	1	0	0	0
*Category totals	19,083	13,723	2,062	2,949	17,579	1,011	39	421	2,770	5,338	1,775	312	29	2
Eye/ear/nose/throat preparations														
Nasal preparations														
Tetrahydrozoline	75	53	3	17	67	3	0	5	27	33	10	1	0	0
Other decongestant	2,317	1,033	403	790	2,023	166	8	115	431	756	336	82	6	0
Other	568	388	42	120	544	7	0	17	22	134	78	7	0	0
Unknown	12	4	2	4	10	1	0	1	2	3	2	0	0	0
Ophthalmic preparations														
Contact lens products	3,209	1,872	287	889	3,155	24	13	17	311	527	535	97	1	0
Glaucoma therapies	125	48	3	67	113	1	0	11	26	37	18	6	0	0
Tetrahydrozoline	1,666	1,128	177	321	1,455	76	98	33	571	793	161	36	3	0
Other ophthalmic														
sympathomimetics	471	232	65	150	402	10	1	58	119	159	73	17	1	0
Other	1,119	531	136	406	1,036	27	7	48	149	176	148	35	3	0
Unknown	34	8	7	13	23	4	2	3	7	6	6	0	0	0
Otic preparations														
Combination products	1,172	844	117	186	1,165	2	0	4	114	354	291	12	0	0
Other	2,188	1,100	214	764	2,164	11	0	8	216	380	648	56	3	0
Unknown	25	9	2	14	24	1	0	0	3	3	7	0	0	0
Steroids-topical for eye/nose/throat														
723	390	103	197	679	18	1	24	56	111	119	8	0	0	0
Throat preparations														
Lozenges without local anesthetics														
738	581	81	71	705	13	0	20	27	169	37	4	0	0	0
Lozenges with local anesthetics														
259	167	48	43	236	15	0	8	20	61	14	4	0	0	0
Other	310	157	93	51	254	47	0	7	70	102	39	4	0	0
Unknown	6	5	0	1	6	0	0	0	1	1	0	0	0	0
*Category totals	15,017	8,550	1,783	4,104	14,061	426	130	379	2,172	3,805	2,522	369	17	0
Gastrointestinal preparations														
Antacids														
Salicylate-containing	2,325	1,799	256	238	2,157	80	1	84	196	688	102	18	1	0
Other	18,014	16,397	703	807	17,694	160	26	128	447	3,637	396	38	6	0
Antidiarrheals														
Diphenoxylate/atropine	1,064	517	147	369	815	183	1	63	465	397	154	59	12	0
Non-narcotic	690	514	59	105	636	20	1	31	78	188	30	10	0	0
Paregoric	44	29	6	6	36	5	0	3	12	13	10	0	2	0
Other narcotic	182	128	15	34	161	8	0	12	36	95	13	2	0	0
Antispasmodics														
Anticholinergic	928	294	194	402	524	341	1	56	485	282	184	93	19	0
Other	9	4	1	3	8	0	0	0	2	6	0	1	0	0
Laxatives	13,509	9,512	1,269	2,444	12,257	747	127	354	1,615	2,591	2,014	195	6	0
Other	7,933	5,941	484	1,355	7,140	443	6	326	1,394	2,211	506	207	22	1
Unknown	1,885	998	146	674	1,571	209	0	103	402	694	113	33	6	0
*Category totals	46,583	36,133	3,280	6,437	42,999	2,196	163	1,160	5,132	10,802	3,522	656	74	1
Hormones and hormone antagonists														
Androgens														
502	185	61	220	321	116	2	58	166	106	57	29	7	0	0
Corticosteroids	9,483	5,538	1,172	2,447	8,491	368	8	603	818	1,937	572	100	7	0
Estrogens	3,463	2,539	183	668	3,279	108	3	72	332	889	94	29	3	0
Insulin	1,428	116	100	1,105	1,048	330	7	34	558	416	104	248	43	4
Oral contraceptives	8,730	7,294	784	558	8,165	435	6	120	627	1,910	277	9	2	0
Oral hypoglycemics	5,351	2,137	402	2,636	4,296	862	1	162	3,349	2,355	422	812	129	9
Progestins	1,147	607	169	337	1,004	61	2	78	164	277	54	8	3	0
Thyroid preparations	6,930	4,156	625	1,987	6,435	394	3	89	1,179	1,872	231	83	11	0
Other hormones	1,986	976	360	564	1,504	379	8	93	534	562	257	43	8	0
Other hormone antagonists	321	110	40	152	258	41	1	21	87	94	21	10	2	0

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TABLE 22B. Demographic Profile of Exposure Cases by Generic Category of Substances and Products: Pharmaceuticals (Cont'd)

Substances Implicated In the Exposure	No. of Exposures	Age (yr)			Reason				Treated in Health Care Facility	Outcome				
		<6	6-19	>19	Unint	Int	Other	Adv Rxn		None	Minor	Moderate	Major	Death
Unknown hormone or antagonists	10	3	0	6	6	1	0	2	5	1	1	1	1	0
*Category totals	39,351	23,661	3,896	10,680	34,807	3,095	41	1,332	7,819	10,419	2,090	1,372	216	13
Miscellaneous drugs														
Allopurinol	278	163	13	102	240	18	0	18	67	106	19	8	0	0
L-dopa and related drugs	668	200	17	437	566	62	0	35	225	196	95	50	5	0
Dietary supplements/ homeopathic	13,722	6,313	1,894	5,097	8,482	3,396	271	1,410	5,413	3,008	1,796	1,641	744	10
Disulfiram	410	13	15	333	115	223	3	64	223	47	82	67	14	0
Ergot alkaloids	479	230	52	181	328	94	0	53	289	168	77	45	5	0
Methysergide	3	2	0	1	2	1	0	0	2	1	0	0	0	0
Neuromuscular blocking agents	21	0	3	16	10	5	0	5	17	3	3	6	0	0
Nicotine pharmaceuticals	750	221	80	409	481	77	2	189	127	150	153	55	0	1
Other	11,788	5,093	1,247	4,903	9,823	1,000	41	887	2,826	3,058	1,730	522	65	4
*Category totals	28,119	12,235	3,321	11,479	20,047	4,876	317	2,661	9,189	6,737	3,955	2,394	833	15
Muscle relaxants														
Carisoprodol (formulated alone)	5,267	285	505	4,193	1,295	3,776	2	131	4,002	661	1,807	858	280	9
Cyclobenzaprine	4,441	834	686	2,671	1,776	2,519	2	108	2,948	1,015	1,193	647	183	6
Methocarbamol	1,199	168	185	768	479	653	1	51	692	269	296	84	33	1
Other	2,139	443	310	1,250	962	1,036	1	119	1,317	494	458	299	135	2
Unknown	49	7	13	27	15	33	0	1	33	10	13	3	0	0
*Category totals	13,095	1,737	1,699	8,909	4,527	8,017	6	410	8,992	2,449	3,767	1,891	631	18
Narcotic antagonists	219	11	20	173	72	104	1	39	140	31	45	34	13	2
Radiopharmaceuticals	16	2	0	13	8	3	0	5	9	0	4	0	1	0
Sedative/hypnotics/ antipsychotics														
Barbiturates														
Long-acting	3,478	727	322	2,273	1,994	1,346	2	90	1,833	703	751	425	213	7
Short-acting	961	81	108	703	315	598	2	36	670	156	274	132	50	1
Unknown type	4	0	0	4	0	3	0	1	4	0	1	0	1	0
Benzodiazepines	40,299	4,663	4,016	28,946	11,301	27,544	291	792	29,087	6,965	13,299	4,942	1,354	65
Chloral hydrate	305	74	33	184	123	143	0	34	223	25	102	58	27	2
Ethchlorvynol	59	4	1	53	12	44	0	2	49	5	11	19	11	0
Glutethimide	8	3	1	4	4	4	0	0	5	4	1	0	0	1
Meprobamate	139	9	10	112	43	91	0	2	103	17	34	27	14	0
Methaqualone	38	0	7	27	6	31	0	0	29	1	8	8	1	0
Phenothiazines	6,952	1,041	976	4,549	3,033	3,330	13	497	4,696	1,529	1,583	1,342	258	8
Sleep aids (OTC)	1,533	100	228	1,115	327	1,167	1	25	1,151	278	428	247	40	2
Other	17,793	1,502	3,167	12,176	5,578	11,178	14	848	12,755	3,415	5,368	2,745	673	23
Unknown	240	14	32	165	65	152	12	9	179	29	53	40	6	1
*Category totals	71,809	8,218	8,901	50,311	22,801	45,631	335	2,336	50,784	13,127	21,913	9,985	2,648	110
Serums, toxoids, vaccines	2,003	361	307	1,107	1,432	32	1	530	610	160	301	90	5	0
Stimulants and street drugs														
Amphetamines	16,684	4,593	6,995	4,614	9,945	6,006	167	438	8,743	4,274	3,028	2,324	389	18
Amyl/butyl nitrites	105	12	8	74	44	58	2	0	50	13	27	10	2	1
Caffeine	6,264	1,039	3,162	1,846	2,477	3,423	16	312	2,927	847	1,909	807	26	0
Cocaine	4,286	91	584	3,352	465	3,691	40	21	3,730	643	833	1,080	374	70
Diet aids														
Phenylpropanolamine	1,125	400	341	349	623	437	0	58	599	355	169	141	11	1
Phenylpropanolamine and caffeine	180	67	60	49	93	78	0	8	108	59	32	25	1	0
Other, OTC	235	116	46	65	147	50	0	38	81	75	29	25	0	0
Other, Rx	178	55	46	68	80	81	1	13	124	55	39	28	1	0
Unknown	152	46	38	57	78	42	1	28	75	40	24	15	0	0
Heroin	1,669	12	175	1,387	117	1,503	12	24	1,484	146	267	521	230	30
LSD	1,252	20	830	335	156	1,002	72	11	902	48	219	446	42	0
Marijuana	1,930	125	878	819	367	1,457	44	36	1,304	164	449	420	65	0
Mescaline/peyote	173	43	45	79	125	40	2	5	58	8	58	22	2	0
Phencyclidine	465	21	140	271	90	343	14	4	400	34	82	167	44	1
Phenylpropanolamine look- alike drugs	19	3	4	9	6	13	0	0	11	3	3	4	1	0
Other stimulants	198	44	59	91	77	115	0	5	133	46	49	43	3	0
Other hallucinogens	1	0	0	1	1	0	0	0	1	0	0	0	0	0

(Continued on following page)

TABLE 22B. Demographic Profile of Exposure Cases by Generic Category of Substances and Products: Pharmaceuticals (Cont'd)

Substances Implicated In the Exposure	No. of Exposures	Age (yr)			Reason				Treated in Health Care Facility	Outcome				
		<6	6-19	≥19	Unint	Int	Other	Adv Rxn		None	Minor	Moderate	Major	Death
Unknown hallucinogens	10	1	4	3	1	3	5	0	7	0	0	2	0	0
Other street drugs	25	0	7	18	4	20	1	0	18	3	8	6	1	0
Unknown stimulant/street drugs	59	2	24	27	10	36	10	0	45	7	7	14	3	0
Category totals	35,010	6,690	13,446	13,514	14,906	18,398	387	1,001	20,800	6,820	7,232	6,100	1,195	121
Topical preparations														
Acne preparations	2,207	1,217	500	435	2,022	61	4	119	153	520	349	35	2	0
Boric acid/porates	214	100	19	85	199	11	1	3	29	44	26	4	0	0
Calamine	3,516	2,579	211	669	3,467	30	3	14	175	810	215	9	0	0
Camphor	8,486	6,501	580	1,273	8,282	144	18	38	979	2,995	1,315	78	7	0
Camphor/methyl salicylate	1,126	938	66	111	1,101	5	2	17	110	413	193	8	0	0
Diaper products	33,901	32,078	915	800	33,810	24	9	52	315	6,729	846	22	1	0
Hexachlorophene														
antiseptic	157	108	16	31	152	2	0	3	20	29	16	5	0	0
Hydrogen peroxide	7,772	3,421	819	3,291	7,583	104	34	50	432	1,461	1,377	57	1	0
Iodine or iodide antiseptics	1,628	540	295	702	1,406	148	8	61	396	400	300	65	3	0
Mercury antiseptics	267	211	14	34	254	6	0	6	30	87	14	2	1	0
Methyl salicylate	9,250	6,898	809	1,386	9,063	70	15	100	804	2,501	2,037	59	8	0
Podophyllin	54	16	10	24	47	4	0	3	20	9	10	2	2	0
Silver nitrate	221	17	96	90	191	14	2	12	39	25	57	9	0	0
Topical steroids	6,825	4,896	437	1,317	6,675	42	11	95	165	1,207	376	33	0	0
Topical steroid with antibiotics	1,276	946	108	196	1,240	6	1	28	46	279	117	8	0	0
Wart preparation	1,524	971	221	296	1,470	25	3	26	146	421	263	28	2	0
Other liniment	2,585	1,447	209	829	2,365	18	4	197	187	478	640	35	2	0
Other topical antiseptic	3,913	2,677	376	762	3,723	90	7	85	442	1,121	493	55	9	0
Category totals	84,922	65,561	5,701	12,331	83,050	804	122	909	4,488	19,529	8,644	514	38	0
Veterinary drugs	3,316	1,729	243	1,170	3,249	47	7	11	259	872	426	46	5	0
Vitamins														
Multiple vitamin tablets: adult formulations														
No iron, no fluoride	2,578	1,782	281	481	2,256	169	3	143	283	563	177	26	4	0
With iron, no fluoride	5,866	3,004	614	1,130	5,225	506	2	118	642	1,862	302	41	5	2
With iron, with fluoride	60	57	2	1	59	0	0	1	6	10	7	0	0	0
No iron, with fluoride	24	24	0	0	24	0	0	0	2	6	4	0	0	0
Multiple vitamin tablets: pediatric formulations														
No iron, no fluoride	7,262	6,340	869	46	7,154	94	1	10	224	1,860	170	9	0	0
With iron, no fluoride	15,760	14,057	1,594	93	15,536	200	4	17	1,440	5,289	705	34	2	0
With iron, with fluoride	672	645	22	4	668	4	0	0	34	162	17	2	0	0
No iron, with fluoride	1,404	1,321	68	12	1,388	7	6	2	36	397	20	0	0	0
Multiple vitamin liquids: adult formulations														
No iron, no fluoride	79	43	9	23	62	8	0	9	17	13	6	2	0	0
With iron, no fluoride	119	66	11	36	96	10	0	13	23	30	10	1	0	0
With iron, with fluoride	4	2	1	1	3	0	0	1	0	0	0	0	0	0
No iron, with fluoride	2	1	0	1	2	0	0	0	0	0	0	0	0	0
Multiple vitamin liquids: pediatric formulations														
No iron, no fluoride	214	201	9	4	210	1	0	3	10	56	5	2	0	0
With iron, no fluoride	508	482	20	5	502	3	0	3	30	145	30	1	0	0
With iron, with fluoride	92	91	1	0	92	0	0	0	3	23	2	0	0	0
No iron, with fluoride	405	394	7	4	403	0	0	2	10	104	10	1	0	0
Multiple vitamins, unspecified adult formulations														
No iron, no fluoride	18	10	3	5	11	4	0	3	2	5	1	0	0	0
With iron, no fluoride	2,008	1,471	285	293	1,857	100	2	36	322	602	112	21	2	0
With iron, with fluoride	4	3	1	0	3	1	0	0	2	2	0	0	0	0
No iron, with fluoride	25	24	1	0	25	0	0	0	0	4	0	0	0	0

(Continued on following page)

TABLE 22B. Demographic Profile of Exposure Cases by Generic Category of Substances and Products: Pharmaceuticals (Cont'd)

Substances Implicated In the Exposure	No. of Exposures	Age (yr)			Reason				Treated in Health Care Facility	Outcome				
		<6	6-19	>19	Unint	Int	Other	Adv Rxn		None	Minor	Moderate	Major	Death
Multiple vitamins, unspecified pediatric formulations														
No iron, no fluoride	41	37	3	1	41	0	0	0	0	10	0	0	0	0
With iron, no fluoride	85	73	11	1	84	1	0	0	11	33	5	0	0	0
With iron, with fluoride	10	9	1	0	10	0	0	0	0	0	0	0	0	0
Other vitamins														
Vitamin A	1,555	1,288	75	176	1,491	30	2	32	95	358	43	7	2	0
Niacin (B3)	2,088	454	345	1,166	1,065	217	3	800	278	136	780	58	2	0
Pyridoxine (B6)	445	268	68	96	352	65	0	28	95	128	30	11	4	0
Other B complex vitamins	1,535	1,068	112	309	1,346	105	2	76	189	344	71	12	2	0
Vitamin C	2,470	1,908	281	242	2,285	128	3	52	126	540	119	13	1	0
Vitamin D	228	133	18	66	208	8	0	12	29	60	9	5	1	0
Vitamin E	1,869	1,524	100	214	1,776	58	1	34	99	423	58	7	1	0
Other	610	433	55	111	525	24	1	60	88	134	53	10	0	0
Unknown	651	448	91	94	562	53	2	32	89	195	33	6	0	0
*Category totals	48,741	38,651	4,938	4,615	45,321	1,862	32	1,487	4,485	13,494	2,779	269	26	2
Unknown drug	11,452	3,416	2,409	4,845	6,056	3,629	723	639	6,516	2,332	1,593	1,206	388	7
Total number of pharmaceutical substances	1,020,598	480,824	162,084	344,988	719,535	255,015	2,765	38,602	350,803	262,523	150,049	62,964	15,173	987
% of pharmaceutical substances		47.1%	15.9%	33.8%	70.5%	25.0%	0.3%	3.8%	34.4%	25.7%	14.7%	6.2%	1.5%	0.1%
% of all substances	43.1%	20.3%	6.8%	14.6%	30.4%	10.8%	0.1%	1.6%	14.8%	11.1%	6.3%	2.7%	0.6%	0.0%



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Vla: T. Low Dog
10-5-01

April 6, 2001

Michael F. Mangano, Acting Inspector General
HHS Office of Inspector General
Room 5246 Cohen Building
330 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Mr. Mangano:

The Council for Responsible Nutrition (CRN) appreciates the opportunity to provide comments on the draft report of the IG on adverse event reporting for dietary supplements. This opportunity seems especially critical to us, in that we see a number of serious problems and even errors of fact in the report as it now stands.

CRN is a trade association representing about 110 manufacturers of dietary supplement products. Our members are committed to providing consumers with safe and beneficial dietary supplements manufactured to high quality standards. We recognize the importance of an adverse event reporting system that provides regulators and the industry with signals alerting them to the existence of potential problems with any consumer product. This is especially important with regard to products that are ingested, including conventional foods, dietary supplements, and pharmaceutical products. We have worked with the Food and Drug Administration on issues relating to the safety of dietary supplements for many years, and have made recommendations to the agency and to Congressional committees regarding improvements needed in the adverse event reporting system. We recognize several of our suggestions in some of the recommendations that are already covered in the IG's report. CRN worked with the appropriations committees in the last Congress to build support for the additional funds FDA needs to improve its handling of adverse event reports, with some success.

While CRN recognizes the need for an effective adverse event reporting system, we also strongly believe the approach to collecting and evaluating such reports relating to dietary supplements should be viewed in the context of other food-related systems. We are extremely troubled by the view repeatedly expressed in the IG's report that the appropriate comparison is to prescription drug reporting systems. This is entirely inappropriate. The correct comparison is to the systems currently in place for other self-selected consumable products, including foods such as medical foods and infant formula, as well as OTC drugs.

*What is the reporting system for
OTC meds. need to get this*

We are equally concerned about the negative view of dietary supplements that we believe pervades the IG's report. The popularity of dietary supplements and the belief that they are generally safe are viewed as risk factors, rather than as evidence that the vast majority of products are indeed both beneficial and benign. We believe in this respect the IG's report represents a failure to fairly evaluate the product category.

Because dietary supplements are not subject to a requirement for premarket approval based on proprietary research submitted by the manufacturer, the IG's report concludes that there is little scientific basis for the purported benefits of these products. This is an entirely false assumption. In fact it is the abundance of publicly available scientific research that drives both the manufacturers' and the consumers' interest in dietary supplements, and this needs to be fully acknowledged in the report.

The report paints a negative picture of the dietary supplement industry, implying that many companies are fly-by-night operations that FDA has difficulty locating. In fact, the vast majority of dietary supplements are manufactured by large corporations that are well known to the agency since they are regularly inspected. *Nutrition Business Journal* estimates that the largest 65 manufacturers in the business account for about 75% of the products on the market. The products these companies make are properly labeled, as required by regulations, but unfortunately labels are not routinely submitted by individuals reporting an adverse event. The report indicates that FDA lacks a product label in 77% of the adverse event reports in the database, but fails to make the point that the lack of a label may largely explain the agency's difficulty in tracking products

These general concerns will be reflected in many of our specific comments, keyed to specific page numbers in the IG's report. The specific comments are attached.

CRN and its member companies are very hopeful that our comments will be taken seriously and will result in significant changes in the overall tone and content of the IG's draft report on adverse event reporting for dietary supplements. We believe extensive changes are essential, before the report is made public, and we would welcome the opportunity to review the next draft before a decision is made to release it. The faults in the present draft are so severe that we believe releasing it in its current form would be a major disservice to the dietary supplement industry and could impede rather than advance productive discussion of the important issue of improving the adverse event reporting system for dietary supplement products. We are prepared to work with the IG's office in any way possible to provide the information necessary to support vitally needed improvements in the current draft.

Sincerely,

A handwritten signature in cursive script that reads "Annette Dickinson".

Annette Dickinson, Ph.D.
Vice President, Scientific and Regulatory Affairs

INSPECTOR-GENERAL'S REPORT ON ADVERSE EVENT REPORTING FOR DIETARY SUPPLEMENTS

COMMENTS SUBMITTED BY THE COUNCIL FOR RESPONSIBLE NUTRITION APRIL 6, 2001

EXECUTIVE SUMMARY

Page 1, end of "background" paragraph

This paragraph notes that "unlike prescription drugs, FDA does not require supplements to undergo premarket approval for safety and efficacy. Instead it relies mostly on its adverse event reporting system to identify safety problems." This statement is the first of many instances in which the prescription drug reporting system is taken as the appropriate comparison category for dietary supplements. CRN believes this comparison is inappropriate. At the least, the IG should add an additional statement such as: "FDA also relies on adverse event reporting to identify and quantify potential safety problems in food products including medical foods and infant formula. FDA also has periodically imposed specific reporting requirements to ensure adequate monitoring of some food ingredients. This was the case in the past with sulfites and aspartame, and is currently being required for products containing olestra."

Page 2, paragraph on "limited product information"

The final sentence of this paragraph states: "Product samples are especially helpful because dietary supplement ingredients are not standardized." This is a curious statement. Product samples are always helpful, even with foods or standardized pharmaceutical products, because adverse events can be due to errors in formulation or accidental contamination. The value of product samples accompanying any adverse event report has nothing to do with whether ingredients are "standardized."

Page 2, paragraph on "limited manufacturer information"

This paragraph states that FDA receives 90 percent of adverse event reports about prescription drugs from their manufacturers. It should also acknowledge that the reason for this is that prescription drug manufacturers are subject to a mandatory reporting requirement. There is no mandatory reporting requirement for adverse events associated with OTC drugs or with foods, including medical foods and infant formula. This should also be acknowledged.

Page 3, paragraph on “limited clinical information”

This paragraph says there is little clinical research on the safety and efficacy of supplements, because premarket clearance is not required. This is a false statement. In fact, there is an abundance of clinical research on the safety and efficacy of supplements, ranging from vitamins and minerals to omega-3 fatty acids to botanical ingredients. Indeed, it is the existence of this rich and ever-expanding scientific research base that drives marketers to provide ingredients such as these in the form of dietary supplements. It is this abundant and publicly available database that provides the foundation of both the consumer and the commercial interest in the product category.

Page 3, paragraph on “limited information on consumer use”

This paragraph suggests that it is essential that FDA have a mechanism for tracking the number of consumers using a particular supplement, in order to determine the incidence and seriousness of adverse events. In fact, it is not always necessary to know the denominator of consumer usage in order to justify action based on safety concerns. One example cited in the IG’s report is the plantain warning and product recall, based initially on a single adverse event report due to a misidentified ingredient, namely a variety of digitalis instead of the intended ingredient plantain.

Page 3, heading asserting that FDA “rarely takes safety actions” based on adverse event reports

This heading is not supported by the text, which in fact says that FDA took 31 actions between January 1994 and June 2000. This number of actions cannot be characterized as “rare” events. The fact is that most dietary supplements have a broad range of safe intakes and the number of products presenting a significant safety concern is small. This in itself explains to a large extent why numerous actions are not required or taken by FDA.

RECOMMENDATIONS

Page 4, recommendation 1

The IG’s first recommendation is that manufacturers of dietary supplements should be required to report adverse events to FDA. The paragraph notes that such reporting is currently mandatory for pharmaceutical products marketed under a new drug application. Again, the IG’s report proceeds on the assumption that the appropriate comparison is between dietary supplements and prescription drugs. This is not the case. It should be acknowledged that mandatory reporting is currently not required for OTC monographed drugs or for conventional foods, including medical foods and infant formula. As the report stands, it is made to appear that only dietary supplements are free of the requirement for mandatory reporting, and this is not correct.

It is CRN's belief that a potential requirement to report serious adverse events is an issue that bears further discussion. CRN would be opposed, however, to a general requirement to report all events, including minor effects. In order to facilitate further discussion, further definition of serious adverse events -- and even of adverse events *per se* -- will be needed. For example, adverse events need to be distinguished from simple product complaints, such as complaints about taste or color, even recognizing that changes in organoleptic qualities of a product may sometimes be an indicator of a potential safety issue. Also, serious events need to be distinguished from minor events. CRN and other industry trade associations are currently reviewing proposals from third-party organizations that could provide services relating to collecting and evaluating serious adverse event reports.

The third part of the first recommendation is that an FDA phone number should appear on all dietary supplements labels. It should be noted that there is no such requirement for any other consumer product category, including OTC drugs and prescription drugs. It is CRN's belief that there is no basis for imposing any such requirement uniquely on dietary supplement products. Many dietary supplement manufacturers currently provide an 800 number to facilitate consumer inquiries, including reports of adverse events. CRN believes providing an 800 number is a commendable company policy which should be encouraged.

Pages 4 and 5, recommendation 2

It is suggested that dietary supplement manufacturers be required to register with FDA, and that individual products should also be registered. This is a suggestion that bears further discussion, provided the topic is simple registration and not the precursor of a cumbersome registration or licensing system such as exists in some countries.

It should also be noted that FDA currently has a vast amount of information available on dietary supplement manufacturers and products, since the agency has in the past several years received thousands of notifications from hundreds of companies regarding structure/function statements used in labeling, as required by DSHEA. These notifications have been compiled in a database made available commercially by AAC Consulting, and that database provides a valuable source for cross-referencing many products and manufacturers.

The IG's report also suggests that FDA should notify manufacturers upon receipt of an adverse event report, to alert the company and to obtain more product information. CRN has suggested this, in comments submitted to FDA on program priorities and in testimony presented in Congressional hearings. We believe it deserves serious consideration. The company would then be in a position to provide important information on the actual formulation of the product as well as substantive data relating to any potential safety concerns.

It is suggested that FDA develop an improved computer database for tracking and analyzing adverse events. CRN has also suggested this in the past, and we worked with

appropriations committees in the last Congress for additional FDA appropriations for this purpose, with some success.

Page 5, recommendation 3

The IG's report suggests that FDA issue guidance on the type of safety information needed in a 75-day notice. Several industry members have supported the need for additional guidance in this area, and CRN believes guidance could be helpful, provided the guidance does not result in creating a burden equivalent to the current food additive approval system.

The report suggests that a set of monographs be developed on the safety and benefits of dietary supplements. CRN believes this is a good idea, in concept, provided a drug standard of proof is not applied and providing the monograph is not taken as the equivalent of a preapproval system such as the one that exists for OTC monographed drugs.

In the Nutrition Labeling and Education Act, it was recognized that health claims for foods do not need to be based on a drug-like level of proof. For example, foods are not typically subject to the type of controlled trials that are undertaken for drugs. However, epidemiological data regarding healthful dietary patterns in large populations can provide the basis for scientifically sound public recommendations as well as health claims relating to the importance of certain nutrients or types of foods. In other cases, there may be substantial clinical data regarding the effects of some specific nutrients or food components, as in the case of the role of calcium in reducing the risk of osteoporosis. The food model rather than the drug model should be utilized in evaluating dietary supplements, if and when monographs are developed.

It is noteworthy that FDA has already contracted with IOM (Institute of Medicine) for the development of monograph concepts relating to the safety of dietary supplements, and the Research-Based Dietary Ingredient Association has likewise contracted with LSRO (Life Sciences Research Office) for a set of monographs on the safety and benefits of certain ingredients used both in dietary supplements and in functional foods. Thus, the value of third-party reviews of dietary supplement safety and benefits is a concept which is being recognized both by industry and by the agency.

The IG report suggests that FDA collaborate with NIH in setting a research agenda including dietary supplement safety issues. This is an excellent idea and is already to some extent ongoing.

The report suggests that the industry and USP should standardize dietary supplement ingredients, particularly botanicals. It is unclear in this context what the IG envisions by the term "standardization." Dietary supplements are formulated to meet the health needs and preferences of a wide variety of people. Even in the vitamin area, ingredients and formulations are not "standardized," and there is a demand for products ranging from multivitamins to single nutrients, and from low potencies (only a fraction of the RDI) to

high levels of some nutrients (vitamin E at 400 IU, vitamin C at 1000 mg). In the botanical arena, there could be a legitimate purpose served by products providing different levels of intake or different combinations of ingredients. CRN does not believe there is a need to "standardize" all ingredients and products. However, it may well be desirable to define certain terms used in product labeling to improve consumer understanding of products that are "standardized" to contain a certain percent of an active ingredient, for example.

The IG's report recommends that FDA expedite the development of GMPs. It should be noted that the industry fully supports GMPs, has worked diligently to provide FDA with a model for dietary supplement GMPs, and is anxious to see appropriate GMPs finalized. Also, most of the industry associations have already committed that their members are observing the GMPs set forth in the initial FDA publication in 1997, and some associations are sponsoring audit programs to verify this. CRN fully supports GMPs, and has taken an active role in creating and promoting the version currently under discussion. However, the IG's report may overestimate what can be accomplished merely by GMPs. The law already requires that products provide 100% of label claim, for example, and companies that flaunt that requirement are not likely to be brought into line merely because an additional regulation is in place supporting the requirement. The GMPs, in and of themselves, will not in fact be able to provide assurance of the precise contents of each batch manufactured. As is the case now with all other legal and regulatory requirements, any assurance provided will be the result of a combination of factors, including the companies' commitment to following GMPs and FDA's commitment to enforcing them.

Page 5, recommendation 4

The recommendation that FDA put more useful information on its website about adverse events may have value, provided it is made very clear what the limitations of adverse event reports are, particularly with regard to demonstrating any real association between a product and an event. It would be useful to consider limiting any publicly available adverse event information to some type of summary form, categorized by product types or generic ingredients. It should be noted that, in the food area, FDA has not published reports that identify adverse events by company or even product name, but rather has grouped events related to ingredients of potential concern (aspartame, sulfites, olestra). Similarly, reports prepared by the Poison Control Centers are summarized in broad categories and do not identify specific products or companies. This could provide a useful pattern for dietary supplement reports as well.

INTRODUCTION

Page 8, second line

This line says that reported events range in severity "from nausea and cardiac arrest to death." This is awkward phrasing. A suggested edit might incorporate two minor and

two major effects, such as: “Reported events range in severity from nausea or dizziness to cardiac effects or death.”

Page 8, section on DSHEA

This is a good basic summary of DSHEA.

Page 8, section on “Our Inquiry”

The first sentence says “FDA’s adverse event reporting system for dietary supplements is a particularly important safety valve for consumers due to the lack of other complementary oversight systems.” This statement implies that dietary supplements are unique among FDA-regulated products in the lack of complementary oversight systems. This is not the case. Dietary supplements are a category of foods, and are no more lacking in oversight than are other foods, including conventional foods, functional foods, infant formula, and medical foods. It is entirely appropriate that the oversight systems should be the same for all these food categories.

This paragraph of the IG’s report also falsely suggests that dietary supplements are not subject to manufacturer inspections. This is not the case. Dietary supplements are subject to manufacturer inspections, and the inspections that are conducted are often extensive, requiring several days to complete. These inspections are based on the same GMPs that apply to conventional foods, until such time as new dietary supplement GMPs are adopted.

This paragraph also suggests that the increased popularity of dietary supplements, by itself, is a risk factor for adverse events. This is not a logical statement. Foods, after all, are used by one and all, and their popularity or universal usage does not itself confer risk.

IMPORTANCE OF THE SYSTEM

Page 11, last paragraph

The IG’s report says FDA has received only 38 new dietary ingredient notifications covering 32 ingredients. AAC Consulting has a commercially available database showing more than 100 new ingredient notifications, to date.

Page 12, chart on regulatory mechanisms

The box summarizing regulatory requirements should show that dietary supplements are subject to food GMPs until new dietary supplement GMPs are developed. Likewise infant formula is subject to food GMPs until new ones are developed.

Page 12, first paragraph under “popularity of dietary supplements”

This paragraph emphasizes: “Today, dietary supplements are widely available in grocery stores, retail pharmacies, health food stores, and on the Internet.” Except for the internet aspect, this is not a new phenomenon, as the paragraph implies. Dietary supplements have been “widely available” in grocery stores, retail pharmacies, and health food stores for at least 60 years, if not longer.

Pages 13-14, warning labels on dietary supplements

The report notes that some dietary supplements bear warning statements about potential contraindications, even though FDA does not specifically require such warnings. The extensive efforts of industry associations to encourage appropriate warnings are dismissed with the statement, “Some industry groups have established standard warnings for certain products, but manufacturers’ use of these standard warnings is voluntary.” It would be more appropriate for the report to fully acknowledge the extent of the industry’s efforts, especially with regard to controversial products such as ephedra. Although FDA has not yet finalized a regulation relating to ephedra, the industry has largely complied with trade association recommendations to include a very extensive warning statement on products containing ephedra. The warning is modeled on the OTC drug warning label for ephedrine-containing products. Some states have also passed laws requiring extensive warning statements for ephedra-containing products. Some associations have recommended warning statements for other products, and some have recommended dosage limits for ingredients that may present safety concerns. The associations which have been pro-active in this regard include the Council for Responsible Nutrition, the American Herbal Products Association, the Consumer Healthcare Products Association, the National Nutritional Foods Association, and the Utah Natural Products Alliance. These efforts deserve more attention and more credit than they are given in the present draft IG report.

This may also be an appropriate place to include some comment regarding the importance of consumer compliance with label directions. All dietary supplements recommend a specific level or range of use for the product, and many of the reported adverse event reports involve misuse or abuse of the product by the consumer.

Page 15, first paragraph

An FDA-commissioned paper by A. Walker is cited to the effect that adverse event reports capture only about 1 percent of actual adverse reactions. Is this paper available? CRN would appreciate the opportunity to review it.

Page 15, comparison to other adverse event reporting systems

The IG’s report suggests that the large number of reports received by the Poison Control Centers provides a more realistic view of true consumer experience than the much

smaller number received by FDA. It should be noted, however, that all calls received by the Poison Control Centers are considered "reports," even if they involve no adverse event and possibly no ingestion at all. For example, if a mother finds her toddler on the floor with an open bottle of tablets and calls the Poison Control Center for advice, that is considered a report, even though the child may have no symptoms and may not in fact have even swallowed any of the tablets. It is also notable, and should be mentioned in this report, that the vast majority of reports received for dietary supplements by Poison Control Centers involve accidental exposures in young children rather than deliberate consumption by any age group, and result in no symptoms or minor symptoms. The report currently gives the incorrect impression that the thousands of reports received by the Poison Control Centers represent significant adverse events not captured by the FDA system, and this is not necessarily the case. If the State of Texas has received large numbers of reports, this is in part due to active solicitation of reports relating to ephedra-containing dietary supplements. CRN is aware that the state forwarded some of these reports to FDA, but is not aware of the reasons why all reports apparently were not forwarded. Perhaps only significant reports were forwarded.

Page 16, top of page

The first paragraph on this page says that manufacturers do not share adverse event information with FDA. The implication is that ONLY dietary supplements are exempt from mandatory reporting of adverse events. In fact, this is true of conventional foods as well as OTC drugs. Only prescription drugs or NDA drugs are required to report adverse events to FDA. The report should clarify these facts.

Page 16, paragraph on "presumed safety"

This paragraph states: "The presumed safety of dietary supplements may cloud the consumers' ability to link an adverse event with a supplement product." Is the implication that an attack should be mounted on "presumed safety"? The fact is that the vast majority of dietary supplements are safe when used as directed in labeling, or when used in the manner that is common among most consumers.

Page 16, paragraph on "self-care products"

This paragraph asserts that "another factor that may contribute to under-reporting of supplement adverse events is that they are self-care products." It should be acknowledged that many other products, including OTC drugs, are also self-care products. People also utilize conventional foods specifically for health purposes. It is a well established and valid assumption that people can and should take substantial responsibility for their own health care. This is a critical and positive aspect of overall health care in the U.S. By definition, "self-care" occurs mostly without the guidance of the physician. The IG's report inappropriately casts aspersions on the whole concept of self-care. This is in contrast to the findings of Congress at the time of the enactment of DSHEA, which recognized that better nutrition and supplementation can contribute to consumer health and can even help control escalating health care costs. DSHEA

emphasized that “consumers should be empowered to make choices about preventive health care programs based on data from scientific studies of health benefits related to particular dietary supplements.”

Page 19, first paragraph

The IG’s report indicates that FDA may need to test products to determine the actual ingredients and levels of each ingredient in the product. It would be appropriate to recognize at this point that there are in some cases a variety of methodologies available for analyzing some ingredients, and that there is a need for validated methods as well as good laboratory practices in order to ensure that appropriate results are obtained. Some of the publicity about variable levels of some ingredients has been based on inappropriate methods of analysis. The industry is currently supporting several efforts to establish validated analytical methods, including the INA/MVP program (Institute for Nutraceutical Advancement/Methods Validation Program), a new initiative being undertaken by AOAC, the ongoing efforts of the USP, and a new certification program recently launched by NSF.

Page 19, second paragraph

The IG’s report implies that the new dietary supplement GMPs will permit access to records not currently available for food products generally. It should be noted, however, that DSHEA does not include any specific change to the current law regarding access to records for foods generally, including dietary supplements.

Page 19, paragraph on “limited manufacturer information”

The IG’s report says nonreporting of adverse events by dietary supplement manufacturers “contrasts starkly” with the number of reports from pharmaceutical and device manufacturers, as if this were the correct comparison. In fact, the correct comparison is to reporting for OTC drugs and for foods, since these categories – like dietary supplements – are also self-care products and have no statutory requirement to report. It is hardly surprising that FDA receives numerous reports from those industries required by law to provide such reports.

Pages 19-20, characterization of the industry

The report paints a negative picture of the dietary supplement industry, implying that many companies are fly-by-night operations that FDA has difficulty locating. In fact, the vast majority of dietary supplements are manufactured by large corporations that are well known to the agency since they are regularly inspected. *Nutrition Business Journal* estimates that the largest 65 manufacturers in the business account for about 75% of the products on the market. The products these companies make are properly labeled, as required by regulations, but unfortunately product labels are not routinely submitted to FDA by individuals reporting an adverse event. The report indicates that FDA lacks a product label in 77% of the adverse event reports in the database, but fails to make the

point that the lack of a label may largely explain the agency's difficulty in identifying manufacturers and tracking products.

The IG's report incorrectly states that products sold through multi-level organizations may be especially difficult to track. CRN's membership includes many of the major multi-level marketers, and they indicate that their products bear the name and location of the company headquarters, not of a local distributor.

This is not to say that in all cases the company named on the label of a product will be the actual manufacturer of the product. Labeling regulations for all foods, including dietary supplements, require that the label show the name and address of the manufacturer, packer or distributor. This can become an issue when any company manufactures a food, drug, or dietary supplement which is marketed through another company. For example, major chains such as Safeway, CVS and Walmart typically sell their own store brands of many products, including dietary supplements, and these products are almost always manufactured by another firm. The chain may prefer that its name appear on the label as the distributor of the products, so that consumer complaints or inquiries will come to the chain rather than going to the actual manufacturer. In such cases, however, it is unlikely that FDA would face a major difficulty in obtaining the name of the actual manufacturer from the chain distributing the product.

Page 21, number of new ingredient notifications

The report says only 38 new ingredient notifications have been received, but AAC Consulting has a commercially available database indicating that more than 100 have been filed.

Page 21, section on consumer use

Once again, it is taken as a given that the correct comparison is between dietary supplements and prescription drugs. Dietary supplements are widely distributed and intended for self-selection, as are conventional foods and OTC drugs. The denominators of usage for dietary supplements, conventional foods, and OTC drugs are generally unknown, but large. Prescription drug practices are not the appropriate comparison.

Page 22, number of actions taken by FDA

CRN suggests that 31 safety actions from January 1994 to June 2000 is not a small number and does not support the IG's assertion that FDA "rarely" takes such actions. Also, the fact that FDA took only 31 actions during a period when more than 100 million people were taking dietary supplements is not necessarily low, let alone "strikingly low." During that period, it is likely that around 60 million of those people were specifically taking a multivitamin, and it is not at all surprising that not a single FDA action was taken against a multivitamin. In fact, it would be striking if any actions were taken against the multivitamin category, given the longstanding record of safe use of such products by a large fraction of the population.

The IG's report repeatedly presumes that the dietary supplement category is inherently risky and that the very prevalence of consumer use is a risk factor. This presumption is not justified, and the final report must be revised to more fairly reflect the actual safety profile of the most commonly used dietary supplement products. Over the decades, hundreds of millions of consumers have used dietary supplements on a regular basis. Many of those consumers are longterm satisfied users who have never experienced an adverse event associated with the dietary supplements that are an integral part of their efforts to construct a healthy lifestyle.

Pages 25-30: Recommendations

See CRN comments on the summary IG recommendations, in pages 2-5 of these comments.

APPENDIX A, FDA experience with ephedra-containing products

Page 31, ephedra discussion

The approved dosage of synthetic ephedrine for use in OTC drugs as a bronchodilator is incorrectly stated as "up to 25 mg a day." The correct statement would be that ephedrine is approved for use in OTC drugs as a bronchodilator at levels up to 25 mg per dose, with a maximum daily intake of up to 150 mg.

Pages 34-35, IG's commentary on criticisms of FDA's proposed rule on ephedra

These two pages cite some criticisms that have been raised regarding FDA's proposed rule on ephedra-containing products, and provide commentary from the IG's office. Curiously, in most cases the IG's commentary appears to CRN to be unrelated to the substance of the criticism cited. Examples are mentioned below.

Page 34, comment on meeting label claim

The IG's "commentary" in this section is unrelated to the criticism about FDA's selection of the 8 mg maximum dose. The criticism cited is that FDA's proposed limit of 8 mg is based in large part on the agency's analysis of the adverse event reports. The IG's commentary is related to the possibility that products may not always meet label claim, and therefore FDA needs product samples to permit analysis of the product actually used by consumers. These two points are not connected, since FDA did not select the 8 mg limit because of uncertainty about what products contain.

The IG's commentary implies that without GMPs there is no requirement for products to meet label claim. This is false. Under FDA regulations, all foods including dietary supplements are required to provide what the labels say they provide. Products that fail to do so are misbranded and illegal. In addition, DSHEA added a new provision

reiterating that dietary supplements are misbranded if they fail to have the identity and strength they are represented to have.

Page 34, commentary on FDA's reliance on adverse event reports rather than controlled research

The commentary relating to the new ingredient notification process is not relevant to ephedra, since ephedra is not a new ingredient. It was on the market well before the passage of DSHEA, and in fact some of the initial adverse event reports date from 1992. FDA had access to an abundance of clinical evidence on ephedrine alkaloids, which was discussed in depth at the 1995 and 1996 advisory committee meetings, but chose to rely primarily on some adverse event reports in its regulatory approach to ephedra.

Page 35, commentary on product usage associated with adverse events

The commentary relating to a pharmaceutical manufacturer's establishment of recommended usage levels is not relevant to the topic under discussion. The issue here is not the labeled directions, but the actual usage pattern of the individual for whom the adverse event was reported. People do not always use products – even prescription products – in the manner directed in labeling, and adverse event reports often do not provide information on the actual usage patterns associated with the adverse event.

Page 35, comment on denominator data

The importance of denominator data is overstated, especially since it has been noted elsewhere that a single well-documented report may be sufficient as a basis for action (as in the case of the plantain/digitalis problem).

APPENDIX B, pages 36-38

The list of 31 actions taken by FDA on safety of dietary supplements actually pertain to only a handful of products:

- Ephedrine alkaloids
- GHB, GBL and related products
- Digitalis/plantain mixup
- 5-hydroxy-L-tryptophan
- Triax metabolic accelerator
- Aristolochic acid

These represent a unique selection of products, most of which are not typical of dietary supplement ingredients. The vast majority of dietary supplements are notably absent from this list, since they by and large have an excellent safety record and do not generate any significant reason for concern. Almost half of total dietary supplement sales are accounted for by vitamins and minerals, which do not appear in this list. While CRN recognizes that there is some potential for toxicity from an excess of some vitamins and

minerals, actual reports of adverse events -- in the clinical literature or elsewhere -- are relatively rare. CRN has recommended voluntary dosage limitations for those nutrients such as vitamin A that are known to cause adverse effects when used in excess. Another quarter of the market is made up of a variety of botanical ingredients, most of which have an excellent safety record and most of which do not appear to any significant extent as the subject of adverse event reports. These include botanicals such as garlic, ginseng, and echinacea.

Products containing ephedrine alkaloids are probably the most physiologically active of the botanical products marketed in this country. Yet millions of consumers have used ephedra-containing products safely for weight loss and for sports nutrition, and have vigorously expressed their concern about state or Federal efforts that might restrict access to such products. Experts differ in their evaluation of the significance of the adverse events that have been reported in association with such products and in their recommendations regarding the regulatory actions that should be taken. Industry, FDA, and consumers will all benefit when there is a regulatory resolution to the longstanding issue of establishing appropriate parameters for the safe marketing of these products. In December 2000, CRN submitted to FDA an extensive evaluation of the safety of ephedra, prepared by toxicological experts at the firm of Cantox, and we are hopeful that this rigorous scientific evaluation will help FDA bring this issue to closure.

GHB and GBL are not legitimate dietary supplements, but are industrial chemicals or drugs masquerading as dietary supplements. GHB was on the market as a "designer drug" for years before DSHEA was passed, and is not a legitimate dietary supplement. GBL is an industrial chemical marketed as a floor stripper, and has been only temporarily using the dietary supplement category as a convenience. In fact, CRN understands that many purveyors of GBL have apparently now re-adopted the category of "floor stripper" in preference to the dietary supplement category. It is inappropriate to consider such products as in any way typical of the dietary supplement category.

The digitalis/plaintain issue was a clear case of a mixup, which happens with foods and even with prescription drugs from time to time. As soon as the mixup was identified, the product was the subject of an FDA warning and a recall. This was a good example of quick action based on an adverse event report, involving cooperation between FDA and the industry to promptly warn consumers and recall the product.

The triax problem evidently is a case of a company overtly adding a drug to a dietary supplement. CRN is not aware whether FDA action on this ingredient was triggered by an adverse event report.

The 5-hydroxy-tryptophan issue arose because of the purported similarity of a substance in this product to the contaminant responsible for the EMS outbreak related to L-tryptophan in the late 1980's, and was not triggered by the adverse event reporting system.

Aristolochic acid has long been recognized as a substance of concern, especially in Europe. FDA's current action was in reaction to European precedents and was not triggered by the adverse event reporting system.

The nature of the actions FDA has taken on the basis of safety concerns over the past six years, and the types of products involved in them, only serve to emphasize CRN's point that the overwhelming majority of dietary supplements are safe within a broad range of use, and the incidence of significant adverse events is limited to a relatively narrow spectrum of products. It is critical that discussion of the overall adverse event reporting system for dietary supplements be considered in this context.