BEFORE

THE UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH
NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCE
NATIONAL TOXICOLOGY PROGRAM

COMMENTS OF THE

AMERICAN HERBAL PRODUCTS ASSOCIATION

ON THE

NATIONAL TOXICOLOGY PROGRAM'S

DRAFT BACKGROUND DOCUMENT FOR

ARISTOLOCHIC ACID-RELATED EXPOSURES

January 11, 2008

The American Herbal Products Association (AHPA) is the national trade association and voice of the herbal products industry. AHPA is comprised of domestic and foreign companies doing business as growers, processors, manufacturers and marketers of herbs and herbal products. AHPA serves its members by promoting the responsible commerce of products that contain herbs, including conventional human foods and dietary supplements.

Background

The National Toxicology Program (NTP) announced in a November 13, 2007 Federal Register notice the availability of a draft document on aristolochic acid-related exposures ("Report on Carcinogens Draft Background Document for Aristolochic Acid-Related Exposures: (1) Aristolochic acid & (2) Botanical Products Containing Aristolochic Acid;" referred to herein as "the draft document"). The November 13 notice reported that the draft document is scheduled to be reviewed by an expert committee on January 24-25, 2008. The notice also invited the submission of comments on the draft document. AHPA and its members have an interest in the issues addressed in the draft document and therefore submit the following comments.

The draft document occasionally uses the words "adulterated" and "contaminated" differently than defined

The Glossary of Terms in the draft document provides the following definitions:

- Adulterant: A substance that is knowingly substituted for another.
- Contaminant: A substance that is unintentionally added to a product or switched with another.

It is obvious that the only significant difference between these terms is the matter of intention. Consistent with these terms and as stated elsewhere in the draft document (in section 2.4.3), adulteration is a deliberate act and contamination is accidental.

In spite of the clarity of these definitions, however, there are several places throughout the document where the word "adulterated" or the terms "adulterated or contaminated" or "adulterant or contaminant" are used to describe scenarios in which there is absolutely no reason to suspect that deliberate substitution occurred. AHPA believes that in every such instance, these terms should be replaced with the word "contaminated" or "contaminant," respectively, and hereby requests that these replacements be made.

To take this point a step further, AHPA questions the need for the inclusion of the words "adulterant" or "adulteration" anywhere in the draft document. As is discussed in

the draft document, there is some potential for accidental substitution of one plant ingredient for another due to the fact that different plants have similar Chinese language names. Thus, a plant that contains aristolochic acid, especially from the genus *Aristolochia*, can be inadvertently substituted for a plant that does not contain aristolochic acid if nomenclatural confusion arises. But there is no evidence, and in fact there has been no suggestion that some nefarious and intentional substitution has ever occurred. AHPA suggests that the removal of any mention of adulteration would therefore provide a more accurate narrative.

Botanicals in which aristolochic acid is known to occur should be clearly differentiated from botanicals that do not contain aristolochic acid

This issue of nomenclatural confusion, as discussed above, was a focus of the regulatory actions of the U.S. Food and Drug Administration in 2000 and 2001. FDA's import alert on this matter provides two separate tables, described as "Attachment A – Botanicals known or expected to contain aristolochic acid," and as "Attachment B – Botanicals which may be adulterated with aristolochic acid." Attachment A lists only species in the genera *Aristolochia* and *Asarum*, and a species identified by FDA as *Bragantia wallichii*, and it is this list that identifies plants that are known or suspected to contain aristolochic acid. The plants listed on Attachment B consist primarily[1] of those that may be inadvertently confused with one or another species of *Aristolochia*, but which do not themselves contain aristolochic acid.

It should be recognized, however, that the plants on FDA's Attachment B do not contain aristolochic acid if they are properly identified. AHPA believes that it is important to emphasize this fact in several places in the draft document. AHPA notes, however, that the title of the draft document's Table A-2 in Appendix A is, "Botanical products for oral use, available as of March 4, 2003, that list ingredients that may be adulterated with aristolochic acid." Similarly, Appendix B in the draft document is titled, "Botanical products containing aristolochic acid," even though Table B-2 within that Appendix (titled, "Botanicals which may be adulterated with aristolochic acid") lists only plants that do not contain aristolochic acid.

AHPA is concerned that the terminology of the cited appendix and tables may lead readers and reviewers to fail to clearly understand that the species listed in Tables A-2 and B-2 do not contain aristolochic acid. AHPA therefore requests that these be

[1] There are also several species of *Asarum* on this second list.

revised, for example, to reflect the additional words provided below in underline font and the deletions in strikethrough text. Note that these suggested modification also take into account the earlier suggestion to replace the word “adulterated” with the word “contaminated” wherever it occurs.

- Table A-2: Botanical products for oral use, available as of March 4, 2003, that list ingredients that do not contain aristolochic acid but that may be ~~adulterated~~ contaminated with botanicals that contain aristolochic acid
- Appendix B: Botanical products containing aristolochic acid and botanical products that do not contain aristolochic acid but that may be contaminated with botanicals that contain aristolochic acid
- Table B-2: Botanicals which do not contain aristolochic acid but that may be ~~adulterated~~ contaminated with botanicals that contain aristolochic acid

Recent legislation regarding serious adverse event reports should be noted
The draft document in its section 2.5.1, in discussing U.S. regulation of dietary supplements, states, “Manufacturers are not required to record, investigate, or report to the FDA adverse events associated with use of the [dietary supplement] product.” While this may have been true when the draft document was written, that statement is no longer accurate. As of December 22, 2007, marketers of dietary supplements are required to receive and record all received adverse event reports associated with dietary supplements that they sell in the United States; to maintain all such records for 6 years; to allow FDA to inspect all such records; and to submit to FDA any such reports that meet the definition of a “serious adverse event.”

AHPA appreciates the opportunity to comment on the draft document. Please contact me if additional clarification or input is needed on this matter.

Respectfully submitted,

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