January 31, 2012

Danica Andrews
Designated Federal Official
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via email: andrewsda@niehs.nih.gov

Re: Written Comments on TR 578

Dear Ms. Andrews,

This correspondence serves as written comments on NTP TR 578, currently titled in draft form as "Technical Report on the Toxicology and Carcinogenesis Studies of *Ginkgo biloba* Extract (CAS No. 90045-36-6) in F344/N Rats and B6C3F1 Mice (Gavage Studies)". These comments are submitted on behalf of the American Herbal Products Association (AHPA).[1] In these comments AHPA refers to this Technical Report in its current "Peer Review Draft" form as "Draft TR 578" and uses the term "NTP TR 578" to mean any eventual final Technical Report on these 2-year gavage studies.

AHPA has significant concerns regarding Draft TR 578, both in relation to the test article used in the 2-year gavage studies that are the subject of this NTP report and to certain of the conclusions drawn from these studies. Concerns with regard to the test article itself include:

- The test article is a unique and specific extract of *Ginkgo biloba* leaf that is not representative of other *Ginkgo biloba* leaf extracts marketed in the United States. It cannot be accurately represented as similar to any other specific *Ginkgo biloba* leaf extract, and its measured chemical constituents cannot be accurately described as reflecting concentrations of these constituents measured in other commercially available and diverse *Ginkgo biloba* leaf extracts.

[1] 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.

- The test article is almost certainly not sold in the United States and there is no evidence outside of the statement in Draft TR 578 that it was ever sold in the U.S.
- The test article was insufficiently characterized with regard to possible environmental pollutants (e.g., heavy metals, mycotoxins, microbiology, polyaromatic hydrocarbons, and pesticides), even though the animal ration used in the studies was analyzed for each of these factors.

Aside from the above concerns regarding the use of a specific *Ginkgo biloba* leaf extract as the test article for these 2-year gavage studies, and the inaccurate characterizations of this specific *Ginkgo biloba* leaf extract as representative of other extracts derived from *Ginkgo biloba* leaf, AHPA has additional concerns with regard to these studies, as follows:

- The choice of corn oil as the vehicle for administering the test article raises significant questions that are not addressed in Draft TR 578 and that call into question the conclusions drawn, even for the specific *Ginkgo biloba* leaf extract used as the test article.
- The stability testing of the test article in its dosage form (i.e., mixed with a corn oil vehicle) was insufficient to conclusively determine that the dose formulations were stable over the full courses of the studies.
- The dose selections in the 2-year studies in mice (both male and female, and for which Draft TR 578 concludes that *clear evidence of carcinogenic activity* was observed) failed to take into account statistically significant and dose-dependent increases in absolute and relative liver weights observed in preliminary 3-month studies conducted to establish doses for the 2-year studies. But an association between a positive result for hepatocellular tumors in mice and an increase in liver weights has been shown, so it is likely in the mouse studies that even the lowest dose tested could have been predicted to produce effects on the liver, including the development of liver tumors.
- The tumorigenic effects observed in the 2-year studies on mice were likely secondary to non-genotoxic, threshold-dependent effects, and the mechanism underlying the responses observed in both the liver and thyroid in the studies may have been related to enzyme stimulation at high dose-level.

- Draft TR 578 concluded that there is some evidence of carcinogenic activity in rats under the conditions of the study with the specific *G. biloba* leaf extract, but this conclusion was based on increased incidence of rat thyroid gland tumors in comparison to concurrent control values that lacked statistical significance.
- The results and conclusion of the 2-year gavage studies in rodents are likely to be irrelevant in assessing the human safety of the specific tested extract, due both to the underlying non-genotoxic mechanism of action related to enzyme induction and to the fact that in this respect significant differences between rodents and humans are evident. While induction of xenobiotic-metabolizing enzymes after administration of ginkgo extracts has repeatedly been reported in rodent studies, no convincing evidence has provided that such happens in humans. Indeed, in a recent human trial with EGb 761® no relevant effect on the in vivo activity of the major CYP enzymes was observed.

AHPA is therefore recommending by these comments numerous revisions to Draft TR 578. The most significant of these recommendations are:

- The title of NTP TR 578 should be changed to accurately reflect that the *Ginkgo biloba* extract used in the 2-year gavage study is a unique ingredient, significantly dissimilar to be other *Ginkgo biloba* leaf extracts marketed as dietary supplements in the United States. AHPA specifically suggests that the title be changed to read as follows, with proposed additions in bold underline font and proposed deletions struckthrough: "Technical Report on the Toxicology and Carcinogenesis Studies of **a Specific** [2] *Ginkgo biloba* **Leaf** Extract ~~(CAS No. 90045-36-6)~~ in F344/N Rats and B6C3F1 Mice (Gavage Studies)".
- All statements in NTP TR 578 that claim or infer that the tested *Ginkgo biloba* extract is or was broadly marketer in the U.S. should be removed, and all statements that claim or infer that the tested ingredient is similar to other *Ginkgo biloba* extracts, and specifically to the EGb 761® brand, should be revised to clearly state the tested ingredient is, in fact, ***dissimilar*** to EGb 761® and to any other *Ginkgo biloba* extract.

[2] The choice of the word "specific" here is somewhat arbitrary. Synonyms, such as "unique" or "uncommon" might optionally be used.

- NTP TR 578 should accurately and bluntly state that the conclusions drawn from the 2-year gavage studies that are the subject of Draft TR 578 are not applicable to EGb 761® or any other conventional ginkgo leaf extract.
- In the absence of a statistically significant response in the increased incidence of rat thyroid gland tumors in comparison to concurrent control values, consideration should be given to whether NTP TR 578 should be revised to record only *equivocal evidence of carcinogenic activity* in male and female rats.

The recommendations for revisions to Draft TR 578 presented here are not intended to be exhaustive, such that extensive additional revisions may be needed to ensure that NTP TR 578 is completely accurate. These recommendations are supported by detailed reviews of Draft TR 578 that are submitted here in two parts. The first part is a review of the specific *Ginkgo biloba* extract used in the 2-year gavage studies that are the subject of Draft TR 578. This review was conducted by AHPA staff in communication with several member companies that sell *Ginkgo biloba* extracts and/or finished dietary supplement products that contain a *Ginkgo biloba* extract.

The second part of this detailed review of Draft TR 578 is in the form of a report prepared for AHPA by Intertek Cantox[3] as a critical review of the 2-year studies with the specific *Ginkgo biloba* leaf extract conducted by the National Toxicology Program (NTP) in F344/N rats and B6C3F1/N mice. In its report, Intertek Cantox reviewed the results of the NTP studies, as well as the conclusions of the NTP pertaining to the 'strength of evidence' for carcinogenic activity of the tested *G. biloba* leaf extract based on the results of the studies. Intertek Cantox also provided some assessment of the relevance of the results of these 2-year gavage studies on a specific *Ginkgo biloba* leaf extract to the safety of oral consumption of this or other *Ginkgo biloba* extracts by humans.

Both the AHPA review of the specific *Ginkgo biloba* leaf extracts used as the test article and the Intertek Cantox review of the 2-year studies are attached to this email and each is incorporated by reference in its entirety in these comments.

These comments are limited to only the subjects specifically addressed herein. Draft TR 578 comments on numerous other issues, including, for example,

[3] Intertek Cantox is a leading international scientific and regulatory consulting firm with specialized expertise in the areas of Food & Nutrition, Pharmaceutical & Healthcare, Chemicals, and Agri, Biotech & Consumer Products.

characterization of how “herbals” are regulated in the United States and historical uses and current research on *Ginkgo biloba*. Absence of comments by AHPA on these and any other portions of Draft TR 578 should not be taken to mean that AHPA agrees with any part of the draft that is not identified in these comments.

Thank you in advance for considering the information provided in these comments. Please feel free to contact us if any additional information is required to clarify the recommendations made in these comments or the accompanying detailed reviews.

Sincerely,

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