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Re: American Botanical Council REVISED Public Comment on NTP Draft Toxicology Report on Ginkgo Biloba Extract:

“NTP TECHNICAL REPORT ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF GINKGO BILOBA EXTRACT (CAS NO. 90045-36-6) IN F344/N RATS AND B6C3F1/N MICE (GAVAGE STUDIES)”  
[NTP TR 578 NIH Publication No. 12-5920]

Dear Members of the NTP Toxicology Reports Peer Review Panel:

We the undersigned are writing to you to provide our collective comments about the above-referenced draft report, the “NTP Technical Report on the Toxicology and Carcinogenesis Studies of Ginkgo Biloba Extract” (the Draft NTP Report). [1, 2]

We are writing to you under the aegis of the American Botanical Council, an independent nonprofit research and education organization, tax-exempt under IRS Code 501(c)(3). We, the undersigned, represent numerous levels of expertise in various fields related to herbal science, including extensive history within the herb manufacturing and research community; clinical herbal medicine and herb-related safety issues; herbal pharmacology, pharmacodynamics, and pharmacokinetics; toxicology and pharmacovigilance and of dietary supplements and other consumer products, among others.

These comments are a revised version of our previous comments sent on the posted deadline of January 25 and reflect our further collective opinion on various matters in the Draft NTP Report. Insofar as the initial Draft NTP report was released shortly prior to the Winter Holidays, we believe that some additional time was needed for us to produce our comments, i.e., in addition to our initial comments being filed per the stated deadline. In the intervening days, we have had the opportunity to
further revise and clarify our initial submission. We sincerely appreciate the NTP’s flexibility in allowing us to submit these revised comments. These comments are intended to replace the letter we sent to NTP on January 25.

We appreciate the opportunity to respectfully submit the following comments, questions, concerns and/or possible criticisms regarding the Draft NTP Report on the studied Shanghai Chinese Ginkgo Biloba Extract:

In general, we believe we have observed a number of anomalies, deficiencies, and other potential shortcomings of the Draft NTP Report that raise reasonable questions.

Our primary concern is the nonconformity of the Shanghai Chinese Ginkgo Biloba Extract (GBE) test material with ginkgo extract in the U.S. market. We have further concerns about the chemical purity of the Shanghai Chinese GBE, the relevance of this testing protocol to humans, the use of corn oil as a vehicle for the of the Shanghai Chinese GBE, the section on quercetin, and other concerns.

Nomenclature

**GBE.** For the purposes of these comments, we will refer to the general term denoting commercial extracts of the leaf of ginkgo (*Ginkgo biloba* L., Ginkgoaceae) as simply “Ginkgo Biloba Extract”, using the acronym “GBE”. This generic ingredient is found in dietary supplements in the United States and similar products sold elsewhere.

**Shanghai Chinese GBE.** In these comments we will refer to the specific 2 batches of GBE procured by the NTP for its testing program from the Shanghai Xing Ling Science and Technology Pharmaceutical Company Ltd. of Shanghai, China as the “Shanghai Chinese Ginkgo Biloba Extract” or “Shanghai Chinese GBE”. We prefer to include the name “Shanghai” in our terminology as, based on the chemical profiles noted in the draft NTP report – i.e., 31.2% flavonol glycosides, 15.4% terpene lactones, and 10.45 +/- 2.40 ppm ginkgolic acid, we have strong reason to believe that this particular GBE produced by this company and utilized by NTP for its rodent toxicology and carcinogenesis testing is not characteristic of other GBE material produced in China and available to manufacturers of dietary supplements in the U.S. Shanghai Chinese GBE (lot 020703) was used during the 3-month and 2-year studies. A different batch (lot GBE-50-001003) was used only for analytical and testing methods development. Analytics (identity, purity, stability and moisture) were conducted by the analytical chemistry laboratory Midwest Research Institute (Kansas City MO). In addition, according to the NTP data, the study laboratory at Batelle Columbus Operations (Columbus, OH) confirmed the identity of the Shanghai Chinese GBE test article by infrared spectroscopy.

We strongly believe that because this Shanghai Chinese GBE is significantly different in its stated chemical profile than the standard GBEs prevalent in the market, that NTP should refer to this Shanghai China GBE throughout its forthcoming final toxicological and carcinogenesis report in an appropriately specific manner – i.e., not in terms that are generic and possibly confusing regarding the results of this study and its relationship (or lack thereof) to other GBEs in the marketplace.

**Egb 761®.** Further, we will refer to the term “EGB 761®” or “EGb 761” as the proprietary, patented extract of *Ginkgo biloba* by the Willmar Schwabe Pharmaceutical Co. of Karlsruhe, Germany, which is characterized by the following profile for the publicly known constituents: 22-27% ginkgo flavonol glycosides (GFG), 5.4-6.6% terpene lactones (TL), and < 5ppm of ginkgolic acids (GA).
Ginkgo Extract in the U.S. Dietary Supplement Marketplace

We are aware of the relative popularity of GBE in dietary supplements in the U.S. market [3] and the probable reason why NTP has chosen to conduct toxicological and carcinogenesis studies on this material. However, NTP’s choice of using the of the Shanghai Chinese GBE does not reflect market conditions in the U.S. Based on our significant long-term collective history and experience with the U.S. herbal dietary supplement market, the chemical parameters of the Shanghai Chinese GBE, as documented by NTP, do not comport to the chemistry of the GBE in many (or possibly any of the ginkgo dietary supplement products in the U.S. market, including, but not limited to EGb 761).

The Universally-Recognized Standard for GBE: EGB 761®

It is a well-known fact among herb and phytomedicinal researchers, market experts, regulators, and others in the herb and phytomedicine fields that the Schwabe ginkgo extract EGB 761 was the first chemically standardized ginkgo extract in the marketplace in Europe and in the world phytomedicine market. In addition, for over 30 years the overwhelmingly vast super-majority of pharmacological and clinical trials on GBE have been conducted on EGB 761. As noted in the NTP draft report, the Schwabe EGB 761 is standardized to ca. 6% terpenes and 24% ginkgo flavonol glycosides, and is minimized to the potentially allergenic compound ginkgolic acid to a level not to exceed 5ppm. In addition, a GBE of similar chemical profile, i.e., with respect to the terpene and flavone fractions, is produced by a number of other companies, e.g., Indena SpA of Milan, Italy. Indena’s GBE is sold throughout the world to various manufacturers for use as phytomedicines and dietary supplements. To the best of our knowledge, one of the brands under which the Indena GBE is sold is Kaveri® Lichtwer Pharma; Klosterfrau HealthCare Group, Germany), incorrectly attributed by NTP as being a brand for EGb 761 on page 21.

Official status of chemical profiles consistent with EGb 761. The profile of chemical constituents in EGb 761 has been recognized in numerous official and authoritative monographs and compendia. These include the following:

- **American Herbal Pharmacopoeia** (2003)
- **German Commission E Monograph** (1994)
- **German Pharmacopoeia** (DAB 2000) (This was replaced by Ph. Eur. Monograph in 2008)
- **European Scientific Cooperative on Phytotherapy** (ESCOP 2003)
- **United States Pharmacopeia** (USP 32; the Ginkgo Extract monograph in the USP is different from other monographs since January 2007 [USP30] as the terpene lactones have a range from 5.4-12%; the revisions are as of November 2011 and are not yet approved.)
- **World Health Organization** (WHO, 1999).

Chemical Profile of the Shanghai Chinese GBE Tested by NTP

Based on the information provided in the NTP Draft Toxicological and Carcinogenesis Report on GBE [2], as well as 2 sets of analyses conducted by outside contracting laboratories as noted in the Report and subsequently obtained from NTP by ABC [4,5], the chemical profile of the Shanghai
Chinese GBE employed by NTP in the Draft NTP Report describing rodent toxicology studies does not conform to the definition of ginkgo extract chemical parameters and specifications published in all the official or unofficial pharmacopeial monographs and/or related compendia, as well as, as already noted above, to GBEs found in the marketplace.

The NTP states in the Draft NTP Report (p.35) that the Shanghai Chinese GBE and EGb 761 are similar in chemical composition. The analytical results of the Shanghai Chinese GBE (given on p.7) show 31.2% ginkgo flavonol glycosides (GFG), 15.4% terpene lactones (TL) and 10.45 ppm ginkgolic acids; however, EGb 761 contains 22-27% GFG, 5.4-6.6% TL, and < 5ppm of ginkgolic acids (GA). Although these differences may appear to be superficially similar, there is a significant difference in the content of the TLs (250% higher) and GA (twice the normally allowed limit in various pharmacopeias).

Multiple Batches of the Shanghai Chinese GBE Used in the Study

We are concerned about what appears to be the lack of adequate analysis in the actual test material of the Shanghai Chinese GBE. According the information released by NTP, there are 2 lots of Shanghai Chinese GBE employed in the entire Draft NTP Report study protocol: Shanghai Chinese GBE (lot 020703, Shanghai Xing Ling Science and Technology Pharmaceutical Company Ltd.) was used during the 3-month and 2-year toxicology and carcinogenesis studies on rodents. However, an apparently different batch of the Shanghai Chinese GBE (lot 50-001003) was used only for analytical methods development. (The latter lot was used to develop the analytics [i.e., the identity, purity, stability, and moisture content of the Shanghai Chinese GBE] which were conducted by the analytical chemistry laboratory of the Midwest Research Institute [Kansas City, MO] while the study laboratory at Batelle Columbus Operations [Columbus, OH] was charged with confirming the identity of the Shanghai Chinese GBE by infrared spectroscopy.) With respect to analytical techniques, in our opinion, the use of infrared spectroscopy is an inadequate and inappropriate test for confirming the identification of a multi-chemical botanical extract, i.e., unless this particular technique is adequately validated, which does not seem to be the case in the NTP report and corollary analyses of the Shanghai Chinese GBE.

Insofar as the NTP has conducted analytical testing on what is described as a different lot number of the Shanghai Chinese GBE than the lot number of the Shanghai Chinese GBE used on the test rodents, it is not clear to us whether the analytical testing data accurately and adequately describe the actual test material used on the rodents in this battery of toxicological testing – a consideration that is especially important in multi-chemical natural products. This bears emphasis not only with respect to the actual parameters of the primary ginkgo chemical fractions (GFG and TLs, et al.) but also regarding the presence of possible contaminants, including, but not limited to, heavy metals, pesticides, solvent residues, etc. (Please see below.)

Review of the NTP Chemical Analyses with Respect to Possible Adulterants, Contaminants, and Solvent Residue Levels

The possibility of the presence of contaminants, including heavy metals, pesticides, excessive levels of residual extraction solvents, etc. is a potential problem that sometimes can occur with some commercial botanical extracts unless they are appropriately processed under highly robust quality-control parameters.

It is thus prudent and appropriate to conduct adequate analytical testing for these potential contaminants – or at least those which may reasonably be expected to occur, lest their potential presence at inappropriate levels might contribute to the toxicological effect of an extract, particularly when such extract is provided at significantly high dosage levels, as is the normal protocol for toxicological studies on test animals.
Although we appreciate NTP’s attempts to chemically characterize the Shanghai Chinese GBE used in this study, we are concerned that lot GBE 50-001003 of the Shanghai Chinese GBE which was utilized for the analytical testing and not used for the rodent toxicological studies is more fully characterized for the presence of pesticides, aflatoxins, and other possible contaminants than lot 020703 of the Shanghai Chinese GBE that was used for the toxicological studies. We find this disparity worthy of comment and concern, as the Shanghai Ginkgo GBE test material does not appear to have undergone the same level of analysis for such potential contaminants. This raises the question as to whether both test batches of the Shanghai Chinese GBE are reasonably identical or whether there may be marked differences in the levels of potential contaminants, which might contribute to adverse outcomes.

**Shanghai Chinese GBE in Corn Oil Used to Treat Test Animals**

The Shanghai Chinese GBE in corn oil used to treat test animals does not represent products in the U.S market. A critical evaluation of the Materials and Methods of the Draft NTP Report section has identified several key considerations important for investigations into the causative agent(s) responsible for the carcinogenic effects observed in this study. For example, GBE extract in corn oil may influence biological effects of the mixture and influence the profile of degradation products. These changes will impact the toxicological profile of the resulting compound.

The draft report does not contain any information on the criteria applied for the selection of corn oil as vehicle for the test substance. Corn oil has frequently been used in toxicity studies as dosing vehicle for lipophilic chemicals such as halogenated hydrocarbons. However, no such requirement is recognizable for GBEs that usually are produced by extraction with aqueous alcohols or acetone. This is a problematic issue as lipophilic constituents (e.g., ginkgolic acids) may be enriched in the carrier whereas water-soluble compounds will not be dissolved at all and therefore might not be absorbed. Subsequently, this may lead to a completely different toxicokinetic profile than is usually seen with other forms and delivery matrix for GBE. Furthermore, corn oil is not an inert compound and it may influence test results. Corn oil is a digestible vehicle that carries a high energy content which may lead to caloric oversupply and obesity causing metabolic distress particularly to the liver which has been identified as an important target organ in the studies described in the draft report. It is well known that the level of dietary fat intake represents both an initiator and a promoter of many adverse conditions that lead to a health risk. For example a relationship between dietary fat intake and oxidative status can influence the gene expression for drug-metabolizing enzymes. [6]

A quick literature search identifies that using corn oil as a carrier is a variable that needs consideration. It has been reported that administration of trihalomethanes in corn oil can influence the site and magnitude of toxic and carcinogenic responses in rodents, e.g., by inducing metabolizing enzymes or altering tissue composition. [7] Rahman et al. examined the effects of various levels of corn oil and lard fed during the initiation stage of azoxymethane (AOM)-induced hepatocarcinogenesis in male Fischer 344 rats. [8] They observed an enhancing effect of a corn oil diet on hepatocarcinogenesis compared with a lard diet.

Another shortcoming in the use of corn oil as vehicle is its well-established contribution to the production of pancreas adenoma in rats. [9] These facts are well known and led to a NTP-designed study with the aim to evaluate the role of several oils in altering cancer rates in male rats. [10] The investigators came to the conclusion that "the use of corn oil as a gavage vehicle may have a confounding effect on the interpretation of chemically-induced proliferative lesions of the exocrine pancreas and mononuclear cell leukemia in male F344m rats". In this context, it is noteworthy that over an 8-year period a 5-fold increase in the incidence of mice with spontaneous hepatoblastoma and a moderate increase in the incidence of chemically induced hepatoblastoma in B6C3F1 mice occurred in 2-year NTP studies in which corn oil was generally used as vehicle. [11]
It is well established that vegetable oils, such as corn oil, will degrade with time and that oxidative byproducts of oil degradation can influence the chemical composition of a solution. The periodic analyses of the corn oil vehicle performed by the study laboratory evaluated only peroxide concentrations. Peroxide testing alone is not a valid measure for rancidity or oxidative byproducts in oil matrix. [12] At a minimum rancidity testing should include testing for secondary oxidation byproducts such as aldehydes and ketones (anisidine value). The Draft NTP Report does not indicate that antioxidants were used to stabilize the test solution, which would increase the probability of antioxidant byproducts developing within the test material. In addition, The Shanghai Chinese GBE in corn oil was not evaluated for potential interactions between oxidative by-products of the corn oil and components of the Shanghai Chinese GBE that could result in new degradation by-products. The investigators should provide evidence that during prolonged storage of the Shanghai Chinese GBE in corn oil no harmful degradation products have been formed.

There are historical examples where the presence of decomposition products of corn oil significantly influenced the results of toxicological studies. For example, an NTP study on the toxicology and carcinogenesis of commercial grade 2, 4- and 2, 6-toluene diisocyanate (TDI) [13] noted the formation of a decomposition product of the test material (2, 4-diaminotoluene). The latter compound is considered to be responsible for the carcinogenic effects observed in this study on TDI. Therefore, in the data summary audit of this study it is concluded that "the accuracy of the TDI dose mixtures were uncertain because of reactivity with water and the unknown nature of the decomposition products that resulted from preparation of the TDI-corn oil mixtures". In addition, the formation of peroxides was only periodically analyzed for the corn oil vehicle but not the dose formulation. Hence, it cannot be excluded that an enhanced lipid peroxidation occurred over the prolonged storage period.

The significance and validity of toxicological studies and in particular carcinogenicity studies with the use of corn oil as substance vehicle is dubious. The investigators should explain which considerations led to the selection of corn oil as substance vehicle and how they account for potential adverse effects of corn oil on its own, possible interferences with the test compound, lack of adequate rancidity testing, and minimal understanding of the potential interaction of degradation compounds and native compounds in the Shanghai Chinese GBE test material, any or all of which may invalidate the study results.

**Dosage of the Shanghai Chinese GBE Test Material**

In the context of implied human relevance, there are also concerns with the selection of doses utilized in the study. It is understandable that an escalating dose protocol to determine potential toxicity and carcinogenicity would be utilized, but if it is likely that the reader might not understand the limitations of the model, it is incumbent of the researcher to specifically point them out. As it relates to this study, there are multiple variables that amplify the uncertainty of any relevance to human consumption of the Shanghai Chinese GBE.

In this murine toxicity study, doses of the Shanghai Chinese GBE test doses given to both mice and rats were 5- to 55-fold larger than the highest level of consumption in humans (240mg/day) and 6.8- to 108-fold greater than the more normal level used by humans (120mg/day). (calculations per Reagan-Shaw method, 2007).[14] Although this nature of dose escalation might be justified to account for metabolic differences in the murine model as compared to humans, in this particular case there are other test material differences that actually result in compounding the significance of other factors that substantially increase uncertainty. Of significant issue are the variables related to the presence and concentration of multiple constituents in the NTP-utilized experimental Shanghai Chinese GBE test material as compared to other available GBE material of GMP quality. When compared to GBE found in other commercially available products, the constituent concentration variation can be more than 100% as well as the fact that other undeclared ingredients may be present.
Given these variable differences and discrepancies, attempts to ascertain or imply the human carcinogenic or toxicological potential of the tested Shanghai Chinese GBE material and/or its relevance to other more representative GBE products in the market place would be entirely speculative, and not substantiated by data from this single study. It would be scientifically prudent for the authors to specifically acknowledge these significant limitations in their discussion of the results and advise the reader that the principle utility of the data is simply to benchmark a single experimental protocol to inform future study design that would use relevant dose and product formulations. This is especially important where in the discussion of study results the authors cite human epidemiology and pharmacokinetic studies in the context of explaining results from this murine study.

Perspectives on Quercetin

The NTP Draft Toxicology Report on GBE states that Ginkgo was nominated for study by the National Institute of Environmental Health Sciences in part because quercetin, a major ingredient in GBE, is a known mutagen. However, the Draft Report does not clarify that critical evaluations of the toxicology of quercetin have concluded that quercetin, at estimated dietary intake levels, does not produce adverse health effects. [15] Furthermore, the report fails to discuss the limited relevance of data on the mutagenicity of quercetin derived from animal models to humans consuming GBE which contain naturally occurring quercetin glycosides that have been shown to be poorly absorbed.

The current NTP Technical Report on the Toxicology and Carcinogenesis of Ginkgo biloba [2] and the 1992 NTP Technical Report on the Toxicology and Carcinogenesis of Quercetin [16] both refer to the poor absorption of quercetin glycosides. Specifically, studies measuring urinary levels of kaempferol and quercetin before and after oral administration of GBE have concluded that the flavonol glycosides kaempferol and quercetin display low bioavailability and are metabolized mainly through glucuronidation. [17] It has been established that GBE’s contain almost exclusively quercetin glycosides and only trace amounts of flavonol aglycones. [18] After limited absorption, flavonol glycosides undergo extensive first-pass metabolism and reach the blood and tissues as neither aglycones nor glycosides. The glycosides are quickly deglycosylated and immediately conjugated with glucuronate or sulfate with or without methylation. The flavonol conjugates are likely to possess biological properties different from those aglycones used in experimental animal models. [19] Therefore, conclusions drawn from in vitro and in vivo studies with the quercetin aglycone may not appropriately be applied to foods and botanical preparations that contain quercetin glycosides.

The current NTP Draft Toxicology Report on Ginkgo Biloba Extract [2] makes several references to the presence of quercetin in the Shanghai Chinese GBE. On page 32 the report states, “Quercetin, a flavonol, was identified in the Ginkgo biloba extract used in the NTP 2-year bioassay”, which is followed in the Draft NTP Report by a review of toxicological data on quercetin. On page 36 the Draft NTP Report states, “Quantitation assays of α-glycosides in the hydrolyzed extracts using HPLC/UV indicated that the test material [i.e., the Shanghai Chinese GBE] contained 16.71% quercetin, 12.20% kaempferol, and 2.37% isorhamnetin”, which reinforces the fact that humans exposed to GBE are exposed to glycosides of quercetin, which will have a different biological effect than quercetin aglycones. These distinctions are important to highlight in the text of the Draft NTP Toxicology Report on Ginkgo biloba extract to help readers place existing data related to quercetin in appropriate context when considering exposure to GBE. These distinctions also raise the issue whether the inclusion of the quercetin toxicology data (pp. 32-33) data should be included in the NTP Draft Toxicology Report on Ginkgo Biloba Extract at all.

Quercetin is a common food component that occurs in onions, apples, brassica vegetables (broccoli,
cabbage et al.), and other healthy foods that are regularly consumed by humans. The average daily consumption of quercetin from food is 25 mg. [16] Critical evaluations of toxicological data have concluded that quercetin at estimated dietary intake levels does not produce adverse health effects. Clinical trials conducted using supplemental quercetin at doses up to 1000 mg that demonstrate potential for a wide variety of health benefits and are without reports of serious adverse events. The Draft NTP Report would benefit from additional clarifying details on the limited relevance of quercetin toxicological data to exposure to GBE to help future users of this report to appropriately interpret the current findings.

Conclusion

In summary, as noted above and explained in this letter, the draft “NTP Technical Report on Toxicology and Carcinogenesis Studies of Ginkgo Biloba Extract” has numerous anomalies and shortcomings, including, but not limited to the nonconforming Shanghai Chinese GBE test material itself, the presence of possibly two different lots of the Shanghai Chinese GBE test material, the use of corn oil as a delivery vehicle, this test’s relevance to humans, etc. Even though NTP notes in its Foreword that the results of its toxicological and carcinogenesis tests are not applicable to humans [“Extrapolation of these results to other species, including characterization of hazards and risks to humans, requires analyses beyond the intent of these reports.”], we believe that this point it not adequately emphasized throughout the Draft NTP Report.

Further, we believe that it is possible that the findings observed in the draft NTP report may be due to a non-genotoxic effect caused by the induction of metabolizing enzymes and the very high load of the test material which may have eventually led to the formation of tumors in the test animals.

The undersigned writers of these comments recognize the general safety and potential health benefits of properly manufactured GBE that meets the parameters established by official pharmacopeial monographs. Such health benefits are relevant in both clinical medicine as well as in self-care, as documented by numerous published clinical trials. We are deeply concerned that any final report from NTP based on the toxicology of the Shanghai Chinese GBE used in the NTP studies – which we have adequately shown is not consistent with the proprietary ginkgo extract that has been employed in most of the published pharmacological and clinical trials, and which is not consistent with the specifications established and officially recognized in numerous government monographs on ginkgo – will have an erroneous, undeserved, and unwarranted adverse effect on professional and public perceptions of the relative safety of the appropriately manufactured ginkgo extract. To help reduce such potential confusion, we strongly recommend that NTP modify its nomenclature used throughout the report and even in its title and refer to the Shanghai Chinese GBE test material in a way that clarifies the distinction between it and other GBEs.

Furthermore, based on the available evidence, we believe that the results of the NTP’s extensive toxicology studies on the Shanghai Chinese GBE are not relevant and not appropriate for extrapolation to the officially recognized EGb 761 and probably other GBE formulations that are very similar chemically to the parameters of EGb 761. We believe that the NTP’s final report on the Shanghai Chinese GBE should emphasize that the results noted in the study pertain only to the Shanghai Chinese GBE and that there is no direct evidence that they relate to EGb 761 and/or other possibly similar ginkgo extracts.

Also, as noted above, we believe that there are legitimate concerns regarding the inclusion and presentation of the quercetin toxicology data in this Draft NTP Report. We recommend that it be modified in such a way as to adequately explain the limitations of the research with respect to the quercetin content of GBE.
We thank you for your consideration of our comments.

Respectfully submitted,

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