AHPA
AMERICAN HERBAL PRODUCTS ASSOCIATION

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Re: Written Comments on TR 585

Dear Dr. Xie,

This correspondence serves as written comments on NTP TR 585, currently titled in draft form as "NTP Technical Report on the Toxicology Studies of Green Tea Extract in F344/NTac Rats and B6C3F1/N and Toxicology and Carcinogenesis Studies of Green Tea Extract in Wistar Han [Crl: WI (Han)] Rats and B6C3F1/N 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 585" and uses the term "NTP TR 585" to mean any eventual final Technical Report on these studies.

AHPA has significant concerns regarding Draft TR 585 in relation to the specific green tea extract test article used in the 3-month and 2-year gavage studies that are the subject of this NTP report, as well as to the presentation of the conclusions drawn for these studies.

Concerns regarding the green tea extract test material

AHPA's concerns with regard to the test article itself include:

- In its description of the material used in these studies Draft TR 585 neglects to identify the part of the tea plant (i.e., *Camellia sinensis*) used as the starting material to manufacture the extract. While it may be assumed that the plant part used was the tea leaf, numerous of the compounds found in the leaf are also found in low levels in other parts of the plant,

[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.

such as the seed or seed oil.[2] Clarification of this detail is therefore needed.

- This description also fails to provide any information to identify the solvent used in the production of the extract, even though this information may be relevant to evaluating the safety of any specific green tea extract.[3]

Concerns regarding extrapolation of study results to other extracts

AHPA is also concerned that the presentation in Draft TR 585 of the conclusions for these studies is written in a manner that implies that the same effects observed in these studies would be observed in similar studies with any other green tea extract. But based on the description of the test material, it appears to have been a unique extract of green tea (presumably leaf) that may or may not be similar to other green tea leaf extracts marketed in the United States.

The comments already presented are relevant to this point, as extracts of different parts of the same plant species are different extracts, as are extracts of the same plant part where the solvents differ. Other factors that have not been addressed in the description in Draft TR 585 of the test material must also be examined to evaluate the similarities or differences between this test article and other green tea leaf extracts. For example, unique green tea extracts can be manufactured by controlling for numerous factors, including for example: the specific tea cultivar and season of collection; the quality and condition (i.e., fresh or dried) of the leaf at the time of extraction; the quantitative ratio of leaf to solvent; the use of other substances in the extraction process, such as a soluble calcium source; etc.

The wide variety of green tea leaf extracts in the U.S. marketplace is not only speculative but has been well documented. For example, a review of 19 such products[4] demonstrated, *as is noted in Draft TR 585,* "a wide variation in concentrations of catechins and caffeine in different green tea extract products."[5] It is clear that the NTP researchers are aware of this marketplace variation, and NTP therefore cannot represent the green tea extract used in these studies as

[2] Fazel M, Sahari MA and Barzegar M. Determination of Main Tea Seed Oil Antioxidants and their Effects on Common Kilka Oil. *Int Food Res J*. 2008;15(2):209-217.
[3] Sarma DN, Barrett ML, Chavez ML, et al. Safety of green tea extracts: a systematic review by the US Pharmacopoeia. *Drug Safety* 2008;31(6):469-484.
[4] Seeram NP et al. Catechin and caffeine content of green tea dietary supplements and correlation with antioxidant capacity. *J. Agric. Food Chem*. 2006;54:1599-1603.
[5] See Draft TR 585 at page 103.

similar to any other specific green tea leaf extract, and should in fact make every effort to clarify that these tests are relevant only to the specific test article.

U.S. Senate on NTP's extrapolation of study results to other extracts

AHPA is not alone in urging NTP to be accurate in its descriptions of the herbal test articles used in its studies and to refrain from explicit or implicit extrapolations of the results of these studies to other extracts of the same herbal source ingredient. The United States Senate Appropriations Committee included the following statement in its report accompanying the fiscal year 2014 Labor, Health and Human Services and Education Appropriations spending bill:

> "The Committee urges NTP to be highly precise when describing the results of its studies on particular extracts of an herbal species to avoid any possible confusion about the relevance of such studies to other extracts of the species."

AHPA requests and encourages the NTP Peer-Review Panel to take this Senate urging into account as it reviews Draft TR 585.

AHPA's specific recommendations

AHPA is recommending by these comments specific revisions to Draft TR 585 prior to issuance of the final NTP TR 585. These recommendations are:

- The title of NTP TR 585 should be changed to accurately reflect that the green tea extract used in these studies is a unique ingredient that may or may not be similar to other green tea leaf extracts marketed in the United States. AHPA specifically suggests that the title be changed to read as follows, with proposed additions in bold underline font:

  > "NTP Technical Report on the Toxicology Studies of **a Specific Brand of** Green Tea **Leaf** Extract in F344/NTac Rats and B6C3F1/N and Toxicology and Carcinogenesis Studies of Green Tea Extract in Wistar Han [Crl: WI (Han)] Rats and B6C3F1/N Mice (Gavage Studies)."

- All statements in NTP TR 585 that claim or infer that the tested green tea extract is similar to other green tea extracts should be removed. This can be accomplished by clearly identifying the test article in any instance that it is mentioned with such terms as "the specific brand of green tea extract" or "the tested green tea leaf extract," and by using a more generic term, such

as “green tea leaf extracts,” whenever the subject is the broader ingredient category of all green tea extracts.

- Specific examples of the need for the clarification requested in the last bullet point follow:
  - “These data indicate that **the tested brand of** green tea extract exhibits the potential to be a reproductive toxicant in male and female F344/NTac rats.”[6]
  - “These data indicate that **the tested brand of** green tea extract exhibits the potential to be a reproductive toxicant in male and female mice.”[7]
  - “**The tested brand of** green tea extract was mutagenic in *S. typhimurium* strains TA98 and TA100 in the presence of induced rat liver S9; no mutagenicity was observed in these strains without S9 or in the *E. coli* strain WP2 *uvr*A/pKM101, with or without S9. *In vivo*, no increases in the frequencies of micronucleated erythrocytes were seen in peripheral blood of male or female B6C3F1/N mice in the 3-month study.”[8]
  - “Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenic activity** of **the tested brand of** green tea extract in male or female Wistar Han rats administered 100, 300, or 1,000 mg/kg. There was *no evidence of carcinogenic activity* of **the tested brand of** green tea extract in male B6C3F1/N mice administered 30, 100, or 300 mg/kg. There was *equivocal evidence of carcinogenic activity* of **the tested brand of** green tea extract in female B6C3F1/N mice based on occurrences of squamous cell neoplasms of the tongue.”[9]

The recommendations for revisions to Draft TR 585 presented here are not intended to be exhaustive, such that additional revisions may be needed to ensure that NTP TR 585 is completely accurate. In addition, these comments are limited to only the subjects specifically addressed herein. Draft TR 585 comments on numerous other issues, including, for example, consumer use and current research on green tea. Absence of comments by AHPA on these and any

[6] See Draft TR 585 at page 6.
[7] See Draft TR 585 at page 7.
[8] See Draft TR 585 at page 7.
[9] Ibid.

other portions of Draft TR 585 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 me if any additional information is required to clarify the recommendations made in these comments.

Sincerely,
[Redacted]

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