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VIA ELECTRONIC SUBMISSION

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NIEHS/NIH
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Re: NTP Technical Report on the Toxicology Studies of Green Tea Extract in F344/NTac Rats and B6C3F1/N Mice and Toxicology and Carcinogenesis Studies of Green Tea Extract in Wistar Han[Crl:WI(Han)] Rats and B6C3F1/N Mice (Gavage Studies) [NTP TR 585]

The Council for Responsible Nutrition (CRN) is the leading trade association for the dietary supplement and nutritional products industry, representing manufacturers of dietary ingredients and of national brand name and private label dietary supplements[1].

[1] Members of CRN, founded in 1973, produce a large portion of the dietary supplements marketed in the United States and globally. Our member companies manufacture popular national brands as well as the store brands marketed by major supermarkets, drug stores and discount chains. These products also include those marketed through natural food stores and mainstream direct selling companies. CRN represents more than 100 companies that manufacture dietary ingredients and/or dietary supplements, or supply services to those suppliers and manufacturers. Our member companies are expected to comply with a host of federal and state regulations governing dietary supplements in the areas of manufacturing, marketing, quality control and safety. Our supplier and manufacturer member companies also agree to adhere to additional voluntary guidelines as well as to CRN's Code of Ethics. Learn more about us at www.crnusa.org.

CRN submits these comments on the National Toxicology Program's (NTP's) draft technical report on the Toxicology Studies of Green Tea Extract in F344/NTac Rats and B6C3F1/N Mice and Toxicology and Carcinogenesis Studies of Green Tea Extract in Wistar Han[Crl:WI(Han)] Rats and B6C3F1/N Mice.

Test Article Characterization

The method of extraction for the test article [green tea extract (GTE) from Amax NutraSource, Inc. (lot #GTE50-A030203)] was not described in the draft report. This information is essential because the extraction method, including the solvent(s) used and conditions of extraction (e.g., temperature or pH), determines which substances are extracted. For example, hydroalcoholic extracts of green tea have been implicated in case reports of hepatotoxicity[2]; therefore, the solvent(s) and method of extraction must be considered when assessing the toxicity of the test article and its relevance to other GTE preparations in the marketplace. If solvent(s) other than water was/were used to prepare the test article, characterization of the test article should include testing for residual solvent(s), as the presence of solvent(s) could affect the toxicity of the material and/or be solely responsible for any observed toxicity. Testing for solvent(s) content was not included in the draft NTP report.

The source for the tea leaves used in the preparation of the GTE was not identified in the report. Where the tea is cultivated may have implications on the levels of contaminants such as pesticides, polycyclic aromatic hydrocarbons (PAHs), and heavy metals potentially present in the GTE, which could in turn have impact on the outcome of the studies.

[2] Sarma DN, Barrett ML, Chavez ML, Gardiner P, Ko R, Mahady GB, Marles RJ, Pellicore LS, Giancaspro GI, Low Dog T. Safety of green tea extracts : a systematic review by the US Pharmacopeia. Drug Saf. 2008;31(6):469-84.

Contaminant testing included measurement of heavy metal levels, as well as ochratoxin and zearalinine levels; however, matrix interferences prevented the analysis of aflatoxins B1, B2, G1, and G2. Pesticide levels also were not quantified due to matrix interference. Additionally, testing for microbiological contaminants or PAHs was not reported. It is necessary to conduct adequate analytical testing for these potential contaminants to demonstrate their absence or compliance within acceptable limits, as these substances may contribute to and/or be responsible for toxicological effects if ingested in sufficiently high doses. In the absence of adequate analytical data, the NTP should not exclude the possibility that the unidentified contaminants or residues contributed to or were solely responsible for the observed effects.

Analysis of Dose Formulations

In the section describing the analysis of dose formulations used in the study and for stability testing, it is unclear which component(s) of the test material (e.g., a specific polyphenol, all major polyphenols, or caffeine) served as the basis for determining % target concentrations. If the GTE concentration measures were based on the value for one component only, it should not be concluded that the dose formulations used in the study met the target concentrations for all GTE components within 10% or that the dose formulations were stable.

Reproductive Effects in 3-Month Studies

Based on several observed effects on reproductive parameters in the 3-month studies, the NTP stated in the draft report that GTE exhibits the "potential to be a reproductive toxicant" in male and female F344/NTac rats and B6C3F1/N mice. However, similar to the reported effects in lymphoid tissue, the NTP should consider the possibility that the observed effects on reproductive parameters were secondary alterations as a response to stress.

In female rats exposed to 1,000 mg GTE/kg body weight/day and female mice exposed to 500 mg GTE/kg body weight/day, increased time in extended diestrus was observed. Additionally, increased estrous cycle length was noted in female rats. These findings are consistent with a stress response, as the most sensitive reproductive parameter to stress is a disturbance of the estrous cycle[3]. No other reproductive parameters were affected by GTE administration.

In male rodents, the most sensitive reproductive parameter in response to stress is a decrease in accessory sex organ weight (prostate and seminal vesicles); however, these tissues were not weighed in the 3-month studies on GTE. Epididymal weights, which also are an indicator of stress, were significantly decreased in male rats administered 1,000 mg GTE/kg body weight/day. Other significant reproductive effects observed were lower cauda epididymis and testis weights in male rats (1,000 mg/kg body weight/day), and decreased spermatid per testis count in male mice (500 mg/kg body weight/day).

In the absence of data from reproductive toxicity studies conducted on the specific GTE tested by the NTP, the possibility that the effects observed in the 3-month studies, particularly in female rats and mice, could be partially or fully attributed to stress should not be excluded.

Reduced Incidence of Neoplasms in 2-Year Studies

It is noteworthy that in the 2-year studies, GTE administration resulted in statistically significant reductions in the incidence rate of tumors for several tissues/organs, as well as the overall rate of malignant neoplasms in the animals. While the data are presented in the

[3] Everds NE, Snyder PW, Bailey KL, Bolon B, Creasy DM, Foley GL, Rosol TJ, Sellers T. Interpreting stress responses during routine toxicity studies: a review of the biology, impact, and assessment. Toxicol Pathol. 2013;41(4):560-614.

appendices, they are neither noted nor discussed in the Results or Discussion sections. These findings clearly suggest that GTE may have protective effects against certain cancers under the experimental conditions and are worthy of mention in the Discussion and Conclusions sections of the report for a more balanced and objective representation of the study outcomes.

Respectfully submitted,

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