

Morgan, Lewis & Bockius LLP
1111 Pennsylvania Avenue, NW
Washington, DC 20004
Tel: 202.739.3000
Fax: 202.739.3001
www.morganlewis.com

Morgan Lewis
C O U N S E L O R S A T L A W

Stephen Paul Mahinka
Partner
202.739.5205
smahinka@morganlewis.com

May 15, 2014

VIA PDF

Dr. Yun Xie
NTP Designated Federal Official
DNTP
National Institute of Environmental Health Sciences
P.O. Box 12233, MD K2-03
Research Triangle Park, NC 27709

Dear Dr. Xie:

On behalf of non-U.S. parties, Morgan, Lewis & Bockius LLP (“Morgan Lewis”), an international law firm, respectfully submits the following comments in response to the U.S. Department of Health and Human Services’ National Toxicology Program’s (“NTP” or “Agency”) request for comments on the Availability of 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 Rats and B6C3F1/N Mice, as set out at 79 *Federal Register* 15135 (March 18, 2014).

Morgan Lewis respectfully requests that NTP revise the draft to incorporate the changes proposed below regarding the following issues before finalizing the draft NTP Technical Report on the Toxicology and Carcinogenesis Studies of Green Tea Extract (“NTP Report” or “draft report”): (1) NTP should include reference to a 2011 chronic toxicity and carcinogenicity study performed by Yoshida, et al., and the NTP Report on green tea extracts should clearly reflect and include the results of this study, that there were no signs indicative of hepatotoxicity on serum

Dr. Yun Xie
May 15, 2014
Page 2

biochemical and histopathological examinations, or of carcinogenic potential in male or female rats; and (2) NTP should incorporate a clear statement that the scope of this NTP Report is limited to concentrated mixtures of green tea extract found at significant levels predominantly in dietary supplements, rather than the much lower levels of green tea extract ordinarily in many currently marketed foods and beverages, to clarify what is only implicitly indicated in the draft report.

I. NTP should include reference to a 2011 chronic toxicity and carcinogenicity study performed by Yoshida, et al., and the final NTP report on green tea extracts should clearly reflect the results of these studies, that there were no signs indicative of hepatotoxicity or of carcinogenic potential in male or female rats.¹

While the draft NTP Report includes an extensive summary of the current published literature on the safety of green tea and catechins, the notable exclusion of the paper by Yoshida, et al., is concerning and failure to include it in the final report would render the report non-comprehensive and misleading. This study, included as Appendix A to these Comments, includes both a 12-month chronic toxicity study and a 24-month carcinogenicity study in Wistar Hannover GALAS rats. These well-controlled studies, which involved 600 animals, evaluated the impact of dietary consumption of green tea catechins at concentrations of 0, 0.02, 0.3, 1, and 3% of the total diet in the test animals. The highest exposure level of 3% corresponds to a consumption of 1922.9 and 2525.7 mg/kg/day, and was more than two-fold greater than the 1000 mg/kg dose administered in the draft NTP report. Further, given that the substance was included in the food of the test animals, the mechanism of delivery was much less traumatic than the oral gavage route used in the NTP report, which, as the report reflects, may have seriously affected the accuracy of the results.

¹ Yoshida, M., Takahashi, M., Inoue, K., Nakae, D., and Nishikawa, A. (2011). Lack of chronic toxicity and carcinogenicity of dietary administered catechin mixture in Wistar Hannover GALAS rats. *Journal of Toxicological Sciences*. 36(3):297-311.

Dr. Yun Xie
May 15, 2014
Page 3

Consistent with the draft NTP report, Yoshida, et al., found that administration of green tea catechins resulted in a suppression of weight gain, but only at the highest doses. These results were found in females only for the chronic toxicity study, but were seen in both sexes in the carcinogenicity study. This weight loss was not a result of decreased appetite, as both males and females in the highest dose category had a tendency for *increased* food intake. The authors indicate that this increase in food intake is likely due to the decreased caloric intake, given that supplementation with catechins offers little caloric value, rather than being a toxic side effect of administration. A similar conclusion regarding decreased caloric intake also may be applicable to the discussion in the draft NTP report of the lack of weight gain in the test animals, given the volume of solution administered via gavage in the NTP study.

As discussed extensively in the draft NTP report, hepatotoxicity has been purported as a potential effect of green tea catechin consumption. Indeed, the draft NTP report found increased hepatic necrosis and inflammation, as well as mucosal necrosis in the stomach. Despite higher doses of catechins administered, Yoshida, et al., did not find similar effects in the liver or stomach. Liver weights were increased in males only, in the 3% group within the chronic toxicity study, but there was no effect on liver weight in the 24-month carcinogenicity study. In both of the Yoshida, et al., studies, slight centrilobular hypertrophy of hepatocytes was found in males in the 3% group and, in the chronic toxicity study, this was associated with increased activity of CYP3A2 but was not associated with any serum clinical chemistry or other histopathological findings consistent with hepatotoxicity. The hypertrophy was not detected in the females.

As highlighted by Yoshida, et al., the World Health Organization and the Food and Agriculture Organization have previously issued guidance on the interpretation of liver

Dr. Yun Xie
May 15, 2014
Page 4

hypertrophy.² The summary report from the 2006 Meeting of Pesticide Residues states the following:

In the absence of histopathological damage and relevant clinical chemistry changes, at the dose that induces only hepatocellular hypertrophy and/or liver size/weight changes, hypertrophy should not be identified as an adverse effect or used for establishing health-based guidance values.

In light of this guidance on interpretation, the liver findings in both the Yoshida, et al., 2-year carcinogenicity study and 1-year chronic toxicity study properly would not be considered adverse events. Further, there were no other dose-related, non-neoplastic lesions detected in either study. Tumors and lesions detected in treatment groups were consistent with levels found in control animals, suggesting no carcinogenic potential from long-term catechin administration via dietary intake.

The paper by Yoshida, et al., is in stark contrast to some of the purported findings in the draft NTP Report, and the reason for these differences should be included in the NTP's analysis in its final report. Route of administration is critical. The Yoshida, et al., study delivered catechins in a manner more consistent with dietary consumption as conventional food or beverages, such as ingestion of green tea, whereas the draft NTP Report used gavage of a concentrated powder diluted with water, which is more consistent with consumption as dietary supplements.

The differences found between the draft NTP report and the Yoshida, et al., paper are not completely unexpected. A recent study published by Navarro, et al. (included as Appendix B), reviewed 97 case reports of herbal dietary supplements implicated in human hepatotoxicity for catechins, even if the presence of green tea extract was not always indicated on the product label.

² Joint FAO/WHO Meeting of Pesticide Residues. (2006). Guidance on the interpretation of hepatocellular hypertrophy. Summary report.

Dr. Yun Xie
May 15, 2014
Page 5

The study found that, among patients with confirmed hepatotoxicity, “there was no statistically significant association between the presence of catechin or the dose consumed and liver injury causality score, severity, or pattern of liver injury.” The authors concluded that they were unable to establish an association or causal link between green tea catechin dietary supplement use and development of hepatotoxicity.³ This likely reflects the complexity of differences among dietary supplements, and their interaction with the liver and metabolic systems.

Finally, it is vital that the NTP include a discussion of the doses tested in contrast to typical consumption levels. As pointed out by Yoshida, et al., the lowest dose tested, 0.02% of the diet is consistent with consumption of one tea beverage serving. Given that both studies found the most severe effects at doses more than 100 times this level, the relevance of the toxicologic findings to the consumer are not properly framed in the draft report and should be modified to reflect this issue in the final report.

II. NTP should incorporate a clear statement in the final report that the scope of its study and the final NTP Report is limited to dietary supplements only, rather than food and beverages generally, to clarify what is only implicit in the draft report.

The final NTP Report on the Toxicology and Carcinogenesis Studies of Green Tea Extract should clearly indicate that the report is limited to concentrated mixtures of green tea extracts at significant levels used predominantly in dietary supplements, rather than the much lower levels of green tea extract ordinarily in many conventional foods and beverages, to clarify what is only implicitly indicated in the draft report. Although the draft NTP Report implies that its assessments relate to green tea extract as used in dietary supplement products, the NTP should include statements that more clearly indicate that its report focuses on green tea extract use in

³ Navarro, V., Bonkovsky, H., Hwang, S., Vega, M., Barnhart, H., Serrano, J. (2013). Catechins in dietary supplements and hepatotoxicity. *Digestive Diseases and Sciences*. 58:2682-2690.

Dr. Yun Xie
May 15, 2014
Page 6

dietary supplements products only.⁴ As the discussion above demonstrates, the levels of the substance and the route of administration is critical with respect to potential effects, and the final report should not indicate that its results and conclusions extend beyond the dietary supplement usage context.

Further, we note that people who live in many countries, in particularly in Asia, historically consume green tea extract from brewed green and green tea beverages every day. As these are considered food uses under U.S. law, a clear statement of the scope of NTP's report as limited to dietary supplement uses would also be useful in avoiding unnecessary confusion with respect to NTP's analysis and findings when read by those in non-U.S. regulatory contexts.

We believe inclusion of the Yoshida, et al., study and the clarifications discussed above will further the efforts of the Agency to review and finalize toxicology and carcinogenesis reports on green tea extract, and we respectfully request that NTP consider and include these proposed clarifications. The clarifications set out in these Comments should aid the NTP in providing a final report that is comprehensive, clearly defined in its scope, and thus most beneficial to the development of public health policy.

⁴ See p. 35 of the draft NTP report, "Oral gavage was chosen as the route of exposure because it was considered most relevant to human exposure to green tea extract dietary supplements." See also p. 103 of the draft NTP report, "Green tea extract is the purported active ingredient [sic] of many weight-loss and nutritional supplements."

Dr. Yun Xie
May 15, 2014
Page 7

Please let us know if we can provide any further information with respect to our
Comments.

Sincerely,
[Redacted]

Stephen Paul Mahinka, Esq.
Partner
Morgan Lewis & Bockius LLP
1111 Pennsylvania Ave. NW
Washington, D.C. 20004
202-739-5205
smahinka@morganlewis.com

Kathleen M. Sanzo, Esq.
Partner
Morgan Lewis & Bockius LLP
1111 Pennsylvania Ave. NW
Washington, D.C. 20004
202-739-5209
ksanzo@morganlewis.com

Jessica L. Vaughn, Ph.D.
Regulatory Scientist
Morgan, Lewis & Bockius LLP
1111 Pennsylvania Ave. NW
Washington, D.C. 20004
202-739-5332
jvaughn@morganlewis.com

Christine Forgues, M.S.
Regulatory Scientist
Morgan, Lewis & Bockius LLP
1111 Pennsylvania Ave. NW
Washington, D.C. 20004
202-739-5055
cforgues@morganlewis.com