

16 November 2016
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room # 1061, Rockville, MD 20852

RE: Addendum to the written comments on Docket No. FDA-2014-N-1497 -- Toxicological Principles for the Safety Assessment of Food Ingredients; Public Meeting on Updates and Safety and Risk Assessment Considerations; Request for Comments

To whom it may concern,

The International Life Sciences Institute (ILSI), North American branch would like to submit an addendum to our written comments (submitted on 15 April 2015) in response to Docket No. FDA-2014-N-1497, announcing the Food and Drug Administration's (FDA) invitation to solicit comments on certain topics related to the guidance titled "Toxicological Principles for the Safety Assessment of Food Ingredients," known less formally as the "Redbook".

Under Question#1, "What components of the Redbook should receive priority for review and update?", ILSI North America provided three priorities for review and update of the US FDA Redbook. One of the priorities included was "No Observed Adverse Effect Level (NOAEL) vs Benchmark Dose (BMD)". ILSI North America cited its work on the assessment of partially hydrogenated oils (PHOs) and the effects on LDL-C and noted this work would be submitted for publication in a peer-reviewed journal. We are pleased to share the three manuscripts which highlight the findings from this work published in *Journal of Food and Chemical Toxicology*. The third manuscript on "Meta-regression analysis of the effect of *trans* fatty acids on low-density lipoprotein cholesterol" applied the BMD for the evaluation of PHOs in the low dose region. The links to the three manuscripts are provided below:

1. **Trans Fatty Acids and Cholesterol Levels: An Evidence Map of the Available Science.** This manuscript is available online:
<http://www.sciencedirect.com/science/article/pii/S0278691516302228>
2. **Mode-of-action evaluation for the effect of *trans* fatty acids on low-density lipoprotein cholesterol.** This manuscript is available online:
<http://www.sciencedirect.com/science/article/pii/S0278691516301739>
3. **Meta-regression analysis of the effect of *trans* fatty acids on low-density lipoprotein cholesterol.** This manuscript is available online:
<http://www.sciencedirect.com/science/article/pii/S0278691516303647>

Based on ILSI North America's work on the safety assessment of PHOs, revisions to the U.S. FDA Redbook guidance related to derivation of an ADI using the recent advances of the BMD should be considered as an option when appropriate data is available. Development of experimental designs that more fully inform risk assessments are needed.

ILSI North America appreciates the opportunity to share these manuscripts with the agency as part of this important effort to update the U.S. FDA Redbook.



Sincerely,

Eric Hentges, PhD
Executive Director
ILSI North America