

15 April 2015

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room # 1061, Rockville, MD 2085

RE: 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 welcomes the opportunity to provide comments 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".

ILSI North America is a public, nonprofit foundation that provides a forum to advance understanding of scientific issues related to the nutritional quality and safety of the food supply by sponsoring programs, workshops and publications. The ILSI North America Technical Committee on Food and Chemical Safety applauds the U.S. FDA for seeing the need to modernize the Redbook. The core mission of the ILSI North America organization is to foster the advancement of science for the benefit of the health of the public, and specifically through the Food and Chemical Safety Committee, the Committee's work promotes a science-based determination of the chemical safety of foods to support the advancement of public health. We recognize the U.S. FDA has been making improvements to the Redbook over the last two decades, and that this guidance has provided a steadfast, reliable means for industry to know what is expected and equally, what is not expected, when assessing the safety of food substances. The U.S. FDA Redbook is robust and has served its purpose very well. It remains an extremely valuable resource as guidance on toxicological principles for the safety assessment of food ingredients. ILSI North America does not believe it is broken, but that some minor improvements will help it reflect the current state of toxicological science. We support the U.S. FDA Redbook's approach to providing guidance with different options for the risk assessor recognizing one size does not fit all and so we would like to share with the U.S. FDA some ideas for enhancements to the Redbook based on the recent programs and workshops supported by the ILSI North America Food and Chemical Safety Committee and other ILSI branches.

In our written comments, ILSI North America will address 3 of the 4 questions included in Federal Register Notice—"Toxicological Principles for the Safety Assessment of Food Ingredients; Public Meeting on Updates and Safety and Risk Assessment Considerations; Request for Comments" [Docket No. FDA-2014-N-1497]. We would like to thank the agency for holding an open and transparent process in soliciting feedback from stakeholders and trust the agency will see the benefit of an iterative process in the role of stakeholders in reviewing and commenting on proposed revisions to the Redbook throughout this important endeavor.

Question 1: What components of the Redbook should receive priority for review and update?

ILSI North America would like to comment on 3 priorities for review and update of the U.S. FDA Redbook. Please note they are not listed in any order of priority.

- 1) Screening *In-vitro* and Predictive Tools –



In vitro tests in which isolated cell or protein systems are incubated with a fixed concentration of a substance can provide valuable insights into a chemical's mode of action and can be very useful for prioritization for future testing. However, the toxicological significance of *in vitro* findings should be kept in context with the *in vivo* situation (i.e., *in vitro* to *in vivo* extrapolation). By definition, *in vitro* systems are artificial biological systems which lack the body's normal blood flow, and, in many cases, the metabolic capability which are the critical determinants of how long a substance lasts *in vivo* (i.e., pharmacokinetics). Incubation periods that are substantially longer than a substance's *in vivo* half-life should be given limited significance with respect to safety assessments as *in vivo* concentrations are unlikely to be sustained for that long. Additionally, *in vitro* systems can allow for exposures to cell types that may not be exposed to a compound based on the *in vivo* Adsorption, Distribution, Metabolism, and Excretion (ADME) handling of the compound resulting in an irrelevant exposure. With the emerging movement of high-throughput *in vitro* technologies, findings from such artificial systems will become more prevalent and will need to be placed in the right context anchored in the substance's pharmacokinetics for *in vivo* extrapolation.

Recognizing the emergence of high-throughput *in vitro* technologies, ILSI North America Technical Committee on Food and Chemical Safety convened a workshop in January 2013 on "Insights and Perspectives on Emerging Inputs to Weight of Evidence Determination for Food Safety" to consider among experts how these new tools might be integrated into traditional toxicological safety assessments. Workshop proceedings were published in 2013 (Bialk *et al.* 2013) and are included as part of these written comments.

Computational toxicology uses the chemical structure of a compound to determine its biological activity (i.e., toxicity, metabolism, and pharmacology). The initial steps in a safety assessment of a chemical substance may include predictive computational methods (e.g., *in silico* techniques) such as structural alerts, quantitative structure activity relationships (QSAR) and read-across to chemical analogs. Ashby-Tennant structural alerts have been used for decades to predict if a chemical compound may cause genetic mutations that may in turn cause cancer (U.S.FDA Regulatory Report, last updated 2014). In a 1991 study, Ashby and Tennant found that most of the rodent carcinogens tested contained structural alerts - 84% of which caused genetic mutations (Ashby & Tennant, 1991). When the toxicity of a chemical compound is unknown, structural alerts are a valuable tool in predicting the potential for mutagenicity and in some cases, carcinogenicity (U.S. FDA Regulatory Report, last updated 2014). However as highlighted at the ILSI North America Technical Committee on Food and Chemical Safety Weight of the Evidence Workshop, there are limitations associated with the output of QSAR programs, which is only as accurate as the toxicity data entered into the program itself. In addition, the programs can only evaluate substances that are representative of the compounds contained in the predictive library. As a result, metals, polymers, and ions cannot be evaluated with some QSAR programs because data on these compounds are not present in the training programs (U.S. FDA Regulatory Report, last updated 2014).

Independent of these limitations, ILSI North America encourages the U.S. FDA to recognize the role of computational toxicology in the Redbook as a means to screen chemical substances for potential toxicity and in providing insight into toxicological testing (Bialk *et al.* 2013). Equally important is the need for the U.S. FDA to highlight the critical role of continuous validation in ensuring that the output from computational models is consistent and relevant (Bialk *et al.* 2013). ILSI North America supports similar language as that used in the more recent regulatory report on the safety of food contact substances that states: "For FDA to accept any QSAR method for regulatory purposes, the method has to be legitimate, properly validated, and have a representative training set" (last updated 2014). ILSI North America also looks forward to the completion of the Chemical Evaluation and Risk Estimation System (CERES) tool



being developed by the U.S. FDA for the pre- and post-market review of food ingredients and packaging materials which utilizes several of the modern computational and predictive toxicology methods.

As the science of toxicology advances, additional options to animal testing or options that will enhance the animal testing will become available. Currently non-animal testing is only being applied in a few pieces of the safety testing strategy as a screening step, such as genotoxicity. A more complete strategy is needed from the U.S. FDA to use a non-animal testing scheme as a screening tool for ALL traditional animal studies. The U.S. FDA leadership is needed to develop this alternative testing strategy as a viable screening plan.

2) Early life stage subpopulations

The U.S. FDA is being asked to consider sensitive subpopulations as illustrated by the recent U.S. FDA Food Advisory Committee (FAC) meeting on susceptible life stages held on 16-17 December 2014.

It is generally well accepted that infants and young children represent a population that does not always share the same toxicokinetic and toxicodynamic processes as an adult human. Not only does expression of metabolic enzymes vary by individual, but temporally, being less well developed in the fetus than in the young child although some capacity exists (Crestiel 1998). In addition, the immaturity of an infant's physiology (e.g. glomerular filtration rate, nervous system, etc.) may contribute to elimination and functional sensitivities of chemical exposure (Larsen 1998; Peters 1998). However, it has also been observed that infants and young children may eliminate some toxicants more rapidly than adults thus compensating for any increase in organ sensitivity (Renwick 1998). Overall, a general conclusion cannot be made regarding effects of chemical agents on infants and children, as effects in infants and children may be higher or lower in comparison to adults dependent on the timing of the exposure during developmental life-stages, the kinetic and dynamic characteristics of the specific chemical substance, and the exposure situation (ILSI 2003; Ostergaard 1998; Denker 1998; Hasegawa *et al.* 2007). The ILSI Research Foundation's Risk Science Institute held a workshop in 2003 to develop a framework for assessing risks to children from exposure to environmental agents. The proceedings concluded that in order to adequately characterize the risks to infants and children in the derivation of an ADI, methodology (testing protocols) should be applied representing functional outcomes, including delayed neurological, at relevant life stages in animal models and humans (ILSI 2003). Where pre-natal and post-natal toxicity from developmental and multi-generation reproductive studies have been considered in the derivation of the ADI, an intraspecies uncertainty factor for differences in sensitivity is applicable to all populations with the exception of direct oral exposure to infants less than 3 months of age (EFSA 2012; SCF 1998). Infants of this age group are exempted based on the lack of representative oral exposure from infant formula as compared to standard reproductive and developmental studies which often begin dosing of weaned animals at approximately 5 weeks of age. Thus, infant formula is a special case with reference to this unique exposure situation. In addition, during an intake assessment, one must account for the differences between infants, children and adults on a body weight basis resulting in a greater proportional intake in certain food categories (Lawrie 1998).

The ILSI North America Caffeine Working Group sponsored a 2011 review of the reproductive and developmental data for caffeine. It was concluded that planning and analyzing epidemiological studies by utilizing the principles of teratology would markedly improve the caffeine epidemiology studies (Brent *et al.* 2011). Currently no guidelines exist for the conduct of studies on infant formula constituents or for



neonates. However, the IPCS (1987) provided guidance stating that the timing of exposure in animal safety studies should approximate exposure during the same period of life for humans, i.e. after birth, during the time of nursery. An appropriate animal model must be chosen and possess similar physiology and development to that of the human infant and the dose regimen and vehicle must be as similar to human exposure to infant formula as possible. JECFA recently accepted the neonatal piglet model to assess the safety of additives for use in infant (0-12 weeks of age) formula. (Weiner *et al.* 2015 - Carrageenan, Mahadevan *et al.* 2014 – OSA-Modified Starch).

The neonatal pig is a well-established model for infant formula nutrient interactions because of the known variety of food types in the pig diet (Reeds & Odle, 1996; Moughan *et al.* 1992). The safety of numerous ingredients or a specific infant formula formulations have been evaluated in neonatal pigs including; long-chain polyunsaturated fatty acids (Mathews *et al.* 2002; Huang *et al.* 2002); conjugated linoleic acids (Corl *et al.* 2008); and arachidonic acid and eicosapentanoic acid (Hess *et al.* 2008). The piglet serves as an appropriate animal model for assessing safety for the infant based upon: 1) Direct application and relevance pertaining to nutritional requirements, gastrointestinal function, immunological development, cardiovascular disease, and respiratory function in comparison to the juvenile human; 2) Similarity with human infant digestive physiology and nutrient requirements; 3) Similarities in the metabolic functions, intestinal transport times, and characteristics of absorption of nutrients, all of which have made them useful in basic nutritional research; and 4) The fact that the minipig is accepted and used as a surrogate to humans for toxicological assessment (Herfel *et al.* 2009; Hess *et al.* 2008; Bode *et al.* 2010; Jacobs & van der Laan, 2012). In addition to the above, neonatal piglets from birth to four weeks of age models human infants from birth through the infant period to approximately weaning at 4-6 months (Buelke-Sam 2003(a), Buelke-Sam 2003(b), Buelke-Sam and Edward Fisher 2003, Barrow 2012).

In summary, while the neonate/infant subpopulation may potentially be of greater concern for safety, sufficient physiological knowledge and appropriate hazard identification models exist under standard risk assessment procedures. Further guidance from the U.S. FDA as it relates to the special case of infant formula is recommended as part of the Redbook revision.

3) No Observed Adverse Effect Level (NOAEL) vs Benchmark Dose (BMD):

In the use of experimental data for hazard characterization, the NOAEL for the critical effect routinely serves as the Point of Departure (PoD) for derivation of a health guidance value. However, due to the limitations associated with the use of the NOAEL, alternative approaches have been evaluated including the use of the Benchmark Dose method as a means to define the PoD.

The assignment of a NOAEL value from a dose-response curve can be challenging and may result in the assignment of NOAEL at a lower dose than the true NOAEL. The identification of a NOAEL is dependent upon a number of factors including the spacing between doses, the number of subjects tested at each dose, and the sensitivity of the methods in detecting the critical effect. In contrast, the BMD, typically at the lower bound confidence limit, may allow for a more robust evaluation of the entire dose-response curve and may be extended outside of the range of experimental doses. The BMD has also been found to be useful in the evaluation of epidemiological data as confirmed by recent work undertaken by ILSI North America. This work supported by the ILSI North America PHO Task Force focused on the assessment of partially hydrogenated oils (PHOs) effects on LDL-C. The use of meta-regression modeling found that BMD best characterized the effect of trans fatty acids (TFAs) on LDL-C in the low dose region (Haber *et al.* 2015 [SOT 2015 poster and is included as a part of these written comments], Vincent *et al.* 2015 [EB 2015 poster], and to be submitted for publication in a peer-review



journal). In addition, use of the BMD may limit the need for additional toxicity studies, may allow for the use of fewer animals within studies, and present a more systematic method to combine data sets. Although the quantitative and statistical advantages of the BMD approach leads one to conclude its use as a best practice for risk assessment when using epidemiological data, its use is not applicable for all data sets. For example, Tox 21 *in vitro* data is not currently compatible with the BMD determination of *in vivo* toxicological PoDs.

Detailed reviews of the BMD approach have been published by the U.S. Environmental Protection Agency (U.S. EPA)(U.S. EPA 1995; U.S. EPA 2012), the World Health Organization (WHO)(JECFA 2006; WHO 2006; IPCS 2004; IPCS 2005), and the European Food Safety Authority (EFSA) (EFSA 2009; EFSA 2011; EFSA 2012). Highlights of these reviews are provided below.

In June of 2012, U.S. EPA issued their final technical guidance document for the use of BMD stating “...*The benchmark dose (BMD) approach...conveys more information than the No Observed Adverse Effect Level (NOAEL) or Lowest Observed Adverse Effect Level (LOAEL) process traditionally used for noncancer health effects...*”(U.S. EPA 2012). In 1999, 2004 and subsequently in 2005, the International Program for Chemical Safety (IPCS) of the World Health Organization issued guidance on the use of the BMD approach, in which the WHO stated in later guidance documents that “...*When sufficient data are available, use of the benchmark dose (BMD) or benchmark concentration (BMC) approach is preferable to the traditional health-based guidance value approaches*” (JECFA 2006; WHO 2006; IPCS 2004; IPCS 2005). In May of 2009 EFSA’s Scientific Committee concluded that “...*the BMD approach is a scientifically more advanced method to the No-Observed-Adverse-Effect-Level (NOAEL) approach for deriving a Reference Point (RP), and therefore recommended EFSA Scientific Panels and Units to adopt the BMD approach for the risk assessment of chemicals in food* (EFSA 2009; EFSA 2011). EFSA has included the BMD approach in their guidance for food ingredient review based on EFSA’s Scientific Committee’s review: “...[The Committee] *has recently endorsed the benchmark dose procedure and the use of the BMDL₀₅ for continuous data or the BMDL₁₀ for quantal data as a preferred approach to the NOAEL...[and]...expects to increasingly use BMDL values rather than the NOAEL for deriving an ADI...*” (EFSA 2011) While the BMD method is considered to be more scientifically advanced compared to the NOAEL approach (EFSA, 2009 & 2011), health-based guidance values derived using the BMD are expected to be as protective as those derived from the NOAEL approach (EFSA, 2009). On average, ADI values resulting from the BMD method are typically within less than an order of magnitude of those obtained using a NOAEL value (IPCS 2004). Application of the BMD may be of value in cases where human exposure is close to a previously established ADI.

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. The inclusion of U.S. FDA’s position relative to these recent advances in risk assessment methodologies to both inform industry on U.S. FDA’s position related to these topics as well as to promote the use of these practices, where applicable, to improve the quality of food additive and ingredient risk assessment is warranted.

References:

Ashby, J and Tennant, R.W. (1991) Definitive relationships among chemical structure, carcinogenicity



and mutagenicity for 301 chemicals tested by the U.S. NTP. *Mutat. Res.* 257:229-306.

Barrow, P. C. (2012) Use of the Swine Pediatric Model, in *Pediatric Nonclinical Drug Testing: Principles, Requirements, and Practices* (eds A. M. Hoberman and E. M. Lewis), John Wiley & Sons, Inc., Hoboken, NJ, USA.

Bialk, H.M., Llewellyn, C., Kretser, A., Canady, R., Lane, R. and Barach, J. (2013) Insights and Perspectives on Emerging Inputs to Weight of Evidence Determinations for Food Safety: Workshop Proceedings. *Int J Toxicol.* 32(6):405-414.

Bode, G., Clausing, P., Gervais, F., Loegsted, J., Luft, J., Nogues, V., and Sims, J., (2010). The utility of the minipig as an animal model in regulatory toxicology. *J Pharmacol Toxicol Methods.* 62:196-220.

Brent, R. L., Christian, M. S. and Diener, R. M. (2011) Evaluation of the reproductive and developmental risks of caffeine. *Birth Defects Research Part B: Developmental and Reproductive Toxicology.* 92: 152–187.

Buelke-Sam, J. (2003a) Comparative schedules of development in rats and humans: implications for developmental neurotoxicity testing, presented at the 2003 Annual Meeting of the Society of Toxicology, Salt Lake City, UT, 2003.

Buelke-Sam, J. (2003b) Design considerations in juvenile. *Neurotoxicology and teratology.* 25:389.

Buelke-Sam, J and Edward Fisher, J. (2003) An update on animal juvenile toxicity testing: Pharmaceutical use and environmental exposures in children. *Neurotoxicology and teratology.* 25:377-378.

Corl, B.A., Mathews Oliver, S.A., Lin, X., Oliver, W.T., Ma, Y., Harrell, R.J., Odle, J., 2008. Conjugated linoleic acid reduces body fat accretion and lipogenic gene expression in neonatal pigs fed low- or high-fat formulas. *J. Nutr.* 138, 449–454.

Cresteil, Theirry. (1998) Onset of xenobiotic metabolism in children: toxicological implications. *Food Additives and Contaminants.* 15: 45-51.

Denker L. and Eriksson, P. (1998) Susceptibility in utero and upon neonatal exposure. *Food Additives and Contaminants.* 15: 37-43.

EFSA (2009). Guidance of the Scientific Committee on a request from EFSA on the use of the benchmark dose approach in risk assessment. *EFSA Journal:* 1150, 1-72.

EFSA (2011). Use of BMDS and PROAST software packages by EFSA Scientific Panels and Units for applying the Benchmark Dose (BMD) approach in risk assessment. EN-113. [190 pp.]

EFSA (2012). Scientific Opinion: Guidance for submission for food additive evaluations. *EFSA Journal:* 10(7):2760.



Food and Drug Administration (last updated 2014) Regulatory Report: Assessing the Safety of Food Contact Substances.

Herfel, T.M., Jacobi, S.K., Lin, X., Walker, D.C., Jouni, Z.E. and Odle, J. (2009) Safety evaluation of polydextrose in infant formula using a suckling piglet model. *Food and Chemical Toxicology* 47 (7): 1530-1537.

Hess, H. A., Corl, B.A., Lin, X., Jacobi, S.K., Harrell, R.A., Blikslager, A.T. and Odle, J. (2008) Enrichment of Intestinal Mucosal Phospholipids with Arachidonic and Eicosapentaenoic Acids Fed to Suckling Piglets Is Dose and Time Dependent *J. Nutr.* 138: 2164–2171.

Huang, M.-C., Chao, A., Kirwan, R., Tschanz, C., Peralta, J.M., Diersen-Schade, D.A., Cha, S. and Brenna, J.T. (2002) Negligible changes in piglet serum clinical indicators or organ weights due to dietary single-cell long-chain polyunsaturated oils. *Food Chem. Toxicol.* 40, 453–460.

ILSI Risk Science Institute. Workshop to Develop a Framework for Assessing Risks to Children from Exposures to Environmental Agents. Washington, DC. April 2003. *Environ Health Perspect* 111:1524–1526.

International Programme on Chemical Safety (IPCS) in cooperation with the Joint FAO/WHO Expert Committee on Food Additives (JECFA). (1987) Principles for the Safety Assessment of Food Additives and Contaminants in Food, *Environmental Health Criteria* 70, WHO, Geneva.

IPCS (2004) Principles for modelling dose–response for the risk assessment of chemicals (draft). Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria)

IPCS (2005) Chemical-specific adjustment factors for interspecies differences and human variability: Guidance document for use of data in dose/concentration–response assessment. Geneva, World Health Organization, International Programme on Chemical Safety (Harmonization Project Document No. 2).

Jacobs. A., and van der Laan J-W. (2012) Regulatory aspects: Pharmaceuticals, Medical Devices, Food Additives: Minipigs and Global Safety Regulations. In McAnulty, P., Dayan, A.D. Ganderup, N-C., and Hastings, K.L. (Eds) *The Minipig in Biomedical Research* (pp. 565-572), Taylor and Francis Group ISBN 978-1-4398-1118-4.

Joint FAO/WHO Expert committee on food Additives – JECFA (2006), Sixty-fourth meeting, WHO/IPCS Safety evaluation of certain contaminants in food. WHO Food Additives Series 55.

Larsen, J.C. and Pascal G. (1998) Workshop on the Applicability of the ADI to infants and children: consensus summary.

Lawrie, C.A. (1998) Different Dietary patterns in relation to age and the consequences for intake of food chemicals. *Food Additives and Contaminants.* 15: 75-81.



Haber, L.T., Reichard, J., Vincent, M. K., Allen, B.C. and Dourson, M.L. Mode of action and meta-regression analysis of the effect of trans fatty acids on LDL-cholesterol. Poster session presented at Society of Toxicology 54th Annual Meeting; 2015 March 22-26, San Diego C.A.

Mahadevan, B., Thorsrud, B.A., Brorby, G.P. and Ferguson, H. (2014) A 3-Week Dietary Safety Study of Octenyl Succinic Anhydride (OSA)-Modified Starch in Neonatal Farm Piglets. *Food and Chemical Toxicology*. 72: 83-89.

Mathews, S.A., Oliver, W.T., Phillips, O.T., Odle, J., Diersen-Schade, D.A. and Harrell, R.J. (2002) Comparison of triglycerides and phospholipids as supplemental sources of dietary long-chain polyunsaturated fatty acids in piglets. *J. Nutr.* 132, 3081–3089.

Moughan, P.J., Birtles, M.J., Cranwell, P.D., Smith, W.C. and Peraza M. (1992) The piglet as a model animal for studying aspects of digestion and absorption in milk-fed human infants. *World Rev. Nutr. Diet.* 67:40-113.

Ostergaard, G. and Knudsen, I. (1998) The applicability of the ADI (Acceptable Daily Intake) for food additives to infants and children. *Food Additives and Contaminants*. 15: 63-74.

Peters, P. (1998) Developmental toxicology: adequacy of current methods. *Food Additives and Contaminants*. 15:55-62.

Hasegawa, R., Hirata-Koizumi, M., Dourson, M., Parker, A., Hirose, A., Nakai, S., Kamata, E. and Ema, M. (2007) Pediatric susceptibility to 18 industrial chemicals: A comparative analysis of newborn with young animals. *Regulatory Toxicology and Pharmacology* 47(3): 296-307.

Reeds, P. and Odle, J. (1996) Pigs as models for nutrient functional interaction. In: Tumbleson, M.E., Schook, L.B. (Eds.), *Advances in Swine in Biomedical Research*. 2: 709–712.

Renwick, A.G. (1998) Toxicokinetics in infants and children in relation to the ADI and TDI. *Food Additives and Contaminants*.15: 17-35.

Scientific Committee on Food (SCF) (1998) Opinion of the Scientific Committee of Food on the applicability of the ADI (Acceptable Daily Intake) for food additives to infants.

SCF (2003) Opinion of SCF on Carrageenan.

Schilter B, Huggett A. (1998) The ADI as a basis to establish standards for pesticide residues in food products for infants and children. *Food Additives and Contaminants*. 15:83-89.

SCF (1996) Opinion on additives in nutrient preparations for use in infant formulae, follow-on formulae and weaning foods.

U.S. EPA (1995) The use of the benchmark dose approach in health risk assessment. EPA/630/R-94/007. Risk Assessment Forum, Washington DC.

U.S. EPA (2012) Benchmark Dose Technical Guidance. EPA/100/R-12/001



U.S. EPA. (1995) Policy on Evaluating Health Risks to Children.

Vincent, M.K., Haber, L.T., Reichard, J., Allen, B.C. and Dourson, M.L. Meta-Regression Analysis of the Effect of Trans Fatty Acids (TFAs) on LDL-Cholesterol. Poster session presented at Experimental Biology Annual Meeting; 2015 March 28-April 1, Boston M.A.

Weiner, M.L. (2013). Food Additive Carrageenan: PART II: A Critical Review of Carrageenan *In Vivo* Safety Studies. *Critical Reviews of Toxicology*, In press.

WHO. Environmental Criteria 237. Principles for Evaluating Health Risks in Children Associated with Exposure to Chemicals.

Question 2: What aspects of the safety and risk assessment of food ingredients or other CFSAN-regulated products are not addressed and should be considered for incorporation in the Redbook?

ILSI North America would like to provide comments on 3 aspects of the safety and risk assessment of food ingredients to be considered for incorporation into the U.S. FDA Redbook.

1) Role of nutrition data/human data used for safety assessment:

Consideration should be given to the role of human nutrition data used for safety assessment of ingredients. ILSI North America held a workshop in July 2014 to examine the role and use of nutritional studies in evaluating the safety of a food or ingredient. The objective of this workshop was to define a path forward to integrate nutrition studies to complement toxicological studies in determining the safety of food ingredients in certain situations. The importance of development of experimental designs that more fully inform risk assessments was recognized by participants. The workshop highlighted the importance of frameworks like the Bradford Hill criteria in interpreting epidemiology data and also acknowledged the challenges that arise because of the limitations in the datasets. The Key Events Dose-Response Framework, an analytical framework for systematically examining key events that occur between the initial dose of a bioactive agent and the effect of concern should be considered in revisions to the Redbook as a tool for the safety assessment of ingredients. This framework was developed in the late 2000's by a cross-disciplinary working group convened by the ILSI Research Foundation.

2) Dose Response Curve Shape—Non-monotonic dose response (NMDR)

In order to facilitate impartial interpretation of the discussions surrounding research around the emerging concerns of non-monotonic 'low-dose' response; the ILSI North America Technical Committee on Food and Chemical Safety 2014 Summer Fellowship program focused on prioritizing the need to establish mutual understanding of its fundamental terminology. To address the emerging concerns of non-linear 'low-dose' response beyond endocrinology, such as nutrition (e.g. vitaminosis) and nanotechnology, the 2014 Summer Fellowship project sought to identify the vast variation of interpretation of core concepts such as 'low-dose,' 'response,' and non-monotonic dose response. These terms are often limited to qualitative, circumstantial and subjective criteria, and this project sought to present approaches to standardize interpretation of these terms based on a quantitative framework. In doing so, the ILSI North America summer fellow found drastic inconsistencies in core concepts of the 'low-dose hypothesis' and offered a suggestive framework by which stakeholders can consider moving forward. In addition, the



summer fellow highlighted pervasive experimental inadequacies in key aspects of study design, statistics and inconsistent experimental replication, all of which collectively undermine the proposed findings and conclusions from exploratory ‘low-dose’ studies. This work culminates with suggestions to help further facilitate toxicological consideration of future ‘low dose’ studies (Vaughan 2015 [SOT poster 2015] and is included as a part of these written comments).

3) Risk benefit analysis:

The element of benefit of a chemical/compound is a concept currently not addressed in the U.S. FDA Redbook. There is considerable disparity in the way benefits and risks are compared for compounds found in food and often relying on subjective judgment. It is therefore vital that an effective strategy be developed to enable a holistic analysis of the net health impact of chemicals/compounds in food to be assessed and quantified, in a manner analogous to the current assessment of risk. The topic of risk benefit analysis was considered by ILSI Europe in 2007. ILSI Europe coordinated a project, “Benefit-Risk Analysis for Foods (BRAFO)”, funded by the European Commission within Framework Six as a Specific Support Action. BRAFO developed a tiered methodology for assessing the benefits and risks of foods and food components, utilizing a quantitative, common scale for health assessment in higher tiers (Hoekstra *et al.* 2010). The proposed methodology is applicable to a range of situations and can assist in optimizing resource utilization through early identification of those benefit–risk questions where benefit clearly outweighs risk or vice versa. Because of its transparency, this methodology can provide a basis for or guide the harmonization of the evaluation methods across the globe. Examples using this tiered methodology include addition of specific ingredients to food; chlorination of drinking water, fish oil components, folic acid fortification of flour, macronutrient replacement/food substitution; and the isocaloric replacement of saturated fatty acids with carbohydrates. (Verhagen *et al.* 2012; Watzl *et al.* 2012).

References:

Hoekstra, J., Hart, A., Boobis, A., Claupein, E., Cockburn, A., Hunt, A., Knudsen, I., Richardson, D., Schilter, B., Schütte, K., Torgerson, P.R., Verhagen, H., Watzl, B. and Chiodini, A. (2012) BRAFO tiered approach for benefit-risk assessment of foods. *Food and Chemical Toxicology*. 50 (Suppl.4):S684-698

ILSI North America 2014 Workshop on “Role and Use of Nutritional Studies in Evaluating the Safety of Food and Ingredients.”

Vaughan, J. and Kretser, A. (2015) An approach to standardize the concept of “low-dose” and non-monotonic dose response in toxicological research and regulatory science. Poster session presented at Society of Toxicology 54th Annual Meeting; 2015 March 22-26, San Diego C.A.

Verhagen, H., Andersen, R., Antoine, J.M., Finglas, P., Hoekstra, J., Kardinaal, A., Nordmann, H., Pekcan, G., Pentieva, K., Sanders, T.A., van den Berg, H., van Kranen, H. and Chiodini, A. (2012) Application of the BRAFO tiered approach for benefit–risk assessment to case studies on dietary interventions. *Food and Chemical Toxicology*. 50: S710–S723

Watzl, B., Gelencsér, E., Hoekstra, J., Kulling, S., Lydeking-Olsen, E., Rowland, I., Schilter, B., van Klaveren, J., Chiodini, A., 2012. Application of the BRAFO-tiered approach for benefit–risk assessment to case studies on natural foods. *Food and Chemical Toxicology*. 50, S699–S709.



Question 3: How can the Redbook be updated to more fully support the development and submission of safety assessments for substances introduced into food?

ILSI North America would like to provide comments on 5 aspects of how the Redbook can be updated to more fully support the development and submission of safety assessments for substances introduced into food.

- 1) ILSI North America Technical Committee on Food and Chemical Safety Committee 2013 Weight of Evidence Workshop:

As the ability to evaluate the specific biological interactions with chemicals has evolved with the use of high throughput technologies, ILSI North America Technical Committee on Food and Chemical Safety held a workshop, “Insights and Perspectives on Emerging Inputs to Weight of Evidence Determinations for Food Safety” in January 2013 to gain insights from different stakeholders into how computational and emerging *in-vitro* methods, such as high-throughput screening (HTS), could be used to contribute to the weight of evidence that is used by risk assessors to determine safety. While the practice of food safety assessment has continually evaluated and adopted new methods, it is not clear how a number of newly developed non-animal tests, *in vitro* data or computational approaches fit into current approaches to food safety assessment. In particular, it is also not clear where and when these new data types may signal a need for prompt evaluation using more conventional toxicity tests to evaluate safety. One of the key conclusions from this workshop was that although HTS assays may be useful in screening for potential hazards, the methods are currently very limited in determining risk. As the methodology continues to evolve, it will be important to consider the relevance of the results with respect to what occurs *in vivo* and associated dietary exposure.

- 2) Risk21

Productive integration of increasingly complex data sets generated by *in silico* and HTS technologies into chemical safety assessments that improve the confidence of health evaluations is challenging. To help address this challenge, ILSI Health and Environmental Sciences Institute (HESI) formed the Risk Assessment in the 21st Century (RISK21) initiative and their work was presented at the ILSI North America Technical Committee on Food and Chemical Safety Workshop on “Insights and Perspectives on Emerging Inputs to Weight of Evidence Determination for Food Safety”. RISK21 provides a conceptual framework and visual tool whereby both exposure and hazard information are evaluated in a transparent manner, providing a method to synthesize current knowledge and approaches. The framework is based on the premise that risk assessment should be fit for purpose with each step of the process directed at deriving or obtaining information necessary to address the problem at hand. It enables evaluation of all available information, including HTS, molecular data, traditional toxicology studies, and exposure data to aid in prioritization decisions about safety and risk based on the necessary level of precision. RISK21 emphasizes the importance of problem formulation and consideration of exposure at the beginning of the assessment, which can provide insights into the toxicity data that may or may not be necessary. The next steps that are needed to enhance the confidence in these methodologies are fully outlined in the workshop proceedings. Revision of the U.S. FDA Redbook provides the opportunity to prioritize the steps to integrate the new data types into food safety assessment (Pastoor *et al.* 2014; Embry *et al.* 2014a; Simon *et al.* 2014; Embry *et al.* 2014b; risk21.org).



3) Aspect of risk benefit analysis

The consideration of the element of benefit of a chemical/compound provides valuable information for assessing the risk of a chemical/compound and is currently not addressed in the U.S. FDA Redbook. Considerable disparity in the way benefits and risks are compared for compounds found in food are assessed and often rely on subjective judgment. It is therefore vital that an effective strategy be developed to enable a holistic analysis of the net health impact of chemicals in food to be assessed and quantified, in a manner analogous to the current assessment of risk. The topic of risk benefit analysis was considered by ILSI Europe in 2007. ILSI Europe coordinated a project “Benefit-Risk Analysis for Foods (BRAFO)”, funded by the European Commission within Framework Six as a Specific Support Action. BRAFO developed a tiered methodology for assessing the benefits and risks of foods and food components, utilizing a quantitative, common scale for health assessment in higher tiers (Hoekstra *et al.* 2010). The proposed methodology is applicable to a range of situations and aids in optimizing resource utilization through early identification of those benefit–risk questions where benefit clearly outweighs risk or vice versa. Because of its transparency, this methodology can provide a basis or guide for the harmonization of the evaluation methods across the globe. Examples using this tiered methodology include addition of specific ingredients to food; chlorination of drinking water, fish oil components, folic acid fortification of flour, macronutrient replacement/food substitution; and the isocaloric replacement of saturated fatty acids with carbohydrates. (Verhagen *et al.* 2012; Watzl *et al.* 2012)

4) Global harmonization:

Food safety is a global issue and we encourage U.S. FDA to take the leadership on global harmonization of safety assessment for substances. Revision of the Redbook using sound scientific principles and evidence offers an opportunity to demonstrate global leadership and provide a model for global adoption. ILSI North America is one of 17 branches of ILSI across the globe. We work across branches to strengthen scientific understanding in a wide range of issues on food safety to ensure the health of the public. We respectfully highlight the International Conference on Harmonisation (ICH), a global effort undertaken by the major pharmaceutical producing countries to provide a single harmonized guidance for the development and safety substantiation of pharmaceuticals. As a consequence, regulatory agencies from the US, EU and Japan, all recognize and accept safety data submitted for new drugs developed under this ICH guidance. Similar to pharmaceuticals, food safety is also a global priority. The current efforts by the U.S. FDA to revise the Redbook present an excellent opportunity to work toward a global standard for the safety substantiation of new food ingredients. The Organisation for Economic Co-operation and Development (OECD) Guidelines for the Testing of Chemicals is a collection of approximately 150 internationally agreed testing methods used by government, industry and independent laboratories to identify and characterize chemical hazards. There are 34 countries in the OECD (including the United States), many of which are major food producing countries and already recognize and accept safety data generated under these testing guidelines.

5) Evidence-based tier approach:

The utility of the U.S. FDA Redbook is in providing an adaptable guide for the conduct of studies whose purpose is to contribute to the safety assessment of food ingredients. Toxicology studies identify and



assess the possible hazards of a food ingredient, whereas other types of preclinical and clinical studies identify biological responses. Collectively, these studies inform a safety assessment. ILSI North America strongly supports the U.S. FDA's efforts to modernize this guidance document.

As described in the background of the U.S. Redbook, "Safety is generally determined by considering the potential cumulative effect of the substance in consumers and the probable consumption of the substance in the diet. The potential cumulative effects are determined by the outcome of toxicity studies and knowledge of compounds and their structures." Therefore, ILSI North America would like to take this opportunity to emphasize the importance of both aspects of a safety assessment (exposure and hazard assessment), as indicated in the existing wording of the U.S. FDA Redbook.

The Threshold of Toxicological Concern (TTC) is a pragmatic tool that provides a scientifically sound conservative approach to prioritizing the need for chemical specific safety data in the absence of sufficient chemical-specific toxicological data. TTC can assist risk assessors to prioritize the assessment of chemicals and requirements for specific data generation for substances with low-level exposures by demonstrating that no appreciable human health risk would be anticipated to occur. ILSI North America encourages the incorporation of the TTC into the U.S. FDA Redbook as the scientific validity has been established. The TTC evolved from the U.S. FDA's Threshold of Regulation (ToR) which is applied to packaging constituents, and follows the same general principles. The TTC provides sound scientific approach to the prioritization of risk during the safety assessment process allowing for resources to be appropriately allocated against substances with the highest risk.

ILSI North America Technical Committee on Food and Chemical Safety supported a project that focused on refining the TTC approach for risk prioritization of trace chemicals in food (Felter *et al.* 2009). This project brought the concept of length of time of exposure and the incorporation of commonly conducted genotoxicity assays into the TTC concept. To facilitate proper use of the TTC, the ILSI North America Technical Committee on Food and Chemical Safety supported another study that describes issues to be considered by risk managers when faced with the situation of an unexpected substance in food (Canady *et al.* 2013). Case studies were provided to illustrate the implementation of these considerations, demonstrating the steps taken in deciding whether it would be appropriate to apply the TTC approach in each case. While the TTC itself is a risk assessment tool, the type of prioritization and categorization used in the TTC can be translated into guidance on the amount of testing to perform on a new dietary ingredient. For substances which will be present in the diets in such amounts wherein their expected exposure would fall below the TTC for their structural category, it may be appropriate to recommend only a limited screening set of toxicity tests rather than an recommending an extensive battery of tests for a substance with very low levels of human exposure while still allowing for an adequate assurance of safe use. Adoption of tiered assessment principles such as the TTC will help to bring the U.S. FDA Redbook in line with modern toxicological and regulatory paradigms, including the approach utilized by the U.S. FDA in regulation of food packaging substances.

References:

Embry M (2014a): A roadmap for risk: Chemistry & Industry. 78: 28-28.

Embry, M.R., Bachman, A.N., Bell, D.R., Boobis, A.R., Cohen, S.M., Dellarco, M., Dewhurst, I.C., Doerrler, N.G., Hines, R.N., Moretto, A., *et al.* (2014b): Risk Assessment in the 21st century: Roadmap and matrix. *Critical Reviews in Toxicology*. 44: 6-16.



Felter, S., Lane, R.W., Latulippe, M.E., Llewellyn, G.C., Olin, S.S., Scimeca, J.A. and Trautman, T.D. (2009) Refining the threshold of toxicological concern (TTC) for risk prioritization of trace chemicals in food. *Food Chem Toxicol.* 47(9):2236-45

Pastoor, T.P., Bachman, A.N., Bell, D.R., Cohen, S.M., Dellarco, M., Dewhurst, I.C., Doe, J.E., Doerrer, N.G., Embry, M.R., Hines, R.N., *et al* (2014): A 21st century roadmap for human health risk assessment. *Critical Reviews in Toxicology.* 44:1-5.

Canady, R., Lane, R., Paoli, G., Wilson, M., Bialk, H., Hermansky, S., Kobielush, B., Lee, J., Llewellyn, C. and Scimeca, J. (2013) Determining the Applicability of Threshold of Toxicological Concern Approaches to Substances Found in Foods. *Critical Reviews in Food Science and Nutrition.*53:12.

Simon, T.W., Simons, S.S., Preston, R.J., Boobis, A.R., Cohen S.M., Doerrer N.G., Fenner-Crisp P.A., McMullin, T.S., McQueen, C.A. and Rowlands, J.C (2014) The use of mode of action information in risk assessment: Quantitative key events/dose-response framework for modeling the dose-response for key events. *Critical Reviews in Toxicology.* 44: 17-43.

Concluding Statement: In closing, we recognize the U.S. FDA has been making improvements to the Redbook over the last two decades, and that this guidance has provided a steadfast, reliable means for industry to know what is expected and equally, what is not expected, when assessing the safety of food substances. The U.S. FDA Redbook is robust and has served its purpose very well. It remains an extremely valuable resource as guidance on toxicological principles for the safety assessment of food ingredients. ILSI North America does not believe it is broken, but that some minor improvements will help it reflect the current state of toxicological science. We support the U.S. FDA Redbook's approach to providing guidance with different options for the risk assessor recognizing one size does not fit all. Food safety is a global issue and we encourage U.S. FDA to take the leadership on global harmonization of safety assessment for substances.

ILSI North America appreciates the opportunity to provide written comments to the agency on the important effort to update the U.S. FDA Redbook and for considering the scientific data that we have presented in these comments.

Sincerely,

Eric Hentges, PhD
Executive Director
ILSI North America