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May 8, 2015

## VIA ELECTRONIC SUBMISSION

Division of Dockets Management  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

**RE: Toxicological Principles for the Safety Assessment of Food Ingredients; Public Meeting on Updates and Safety and Risk Assessment Considerations; Request for Comments. 79 *Fed. Reg.* 64603-64604 (October 30, 2014). Docket No. FDA-2014-N-1497.**

The Council for Responsible Nutrition<sup>1</sup> (CRN) applauds FDA's efforts to update the widely used guidance titled "Toxicological Principles for the Safety Assessment of Food Ingredients" or "the Redbook." CRN respectfully submits the following general comments, as well as comments in response to the specific topics mentioned in the October 30, 2014 *Federal Register* notice. We are joined in these comments by the Consumer Healthcare Products

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<sup>1</sup> The Council for Responsible Nutrition (CRN), founded in 1973 and based in Washington, D.C., is the leading trade association representing dietary supplement and functional food manufacturers, marketers and ingredient suppliers. CRN companies produce a large portion of the functional food ingredients and 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 150 companies that manufacture dietary ingredients, dietary supplements and/or functional foods, 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 and food 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](http://www.crnusa.org).

Association (CHPA)<sup>2</sup>, the leading U.S. trade association for manufacturers and distributors of nonprescription medicines and dietary supplements.

## General Comments

As described in the *Federal Register* notice, FDA intends to expand the scope of Redbook to include chemical safety assessments for all products over which FDA's Center for Food Safety and Applied Nutrition (CFSAN) has statutory authority, including dietary supplement ingredients. We agree that the toxicological principles outlined in the current Redbook can apply across the various regulatory categories. However, we urge FDA to provide clear and specific guidance for applying these principles within each particular context, paying particular attention to the relevant safety standards as required by the Federal Food, Drug, and Cosmetic Act (FD&C Act).

The FD&C Act, as amended by the Dietary Supplement Health and Education Act of 1994 (DSHEA), exempts dietary ingredients from definition of food additives and prescribes a safety standard specifically for the evaluation of new dietary ingredients (NDIs).<sup>3</sup> All dietary supplements and dietary ingredients, new and old, are subject to an adulteration provision prohibiting products that present a “significant or unreasonable risk of illness or injury.”<sup>4</sup> However, for NDIs that require notification, the notifying party must show that these ingredients “will reasonably be expected to be safe.”<sup>5</sup> In passing DSHEA, Congress explicitly concluded that this standard is more appropriate for these presumptively safe ingredients than the “reasonable certainty of no harm” standard applicable to food additives<sup>6</sup> and the “generally recognized as safe” (GRAS) standard applicable to other conventional food ingredients.<sup>7</sup> Thus, absent a change to the statute, safety assessments for dietary supplement ingredients must conform to the appropriate safety standard provided in the FD&C Act.

We also echo the concerns noted by Senators Hatch and Harkin in their December 8, 2014 letter to Commissioner Hamburg regarding the proposed expansion.<sup>8</sup> FDA developed and has applied the Redbook exclusively to food and color additives, whereas the agency issued a separate and very detailed draft guidance for NDIs; we recommend that the revised NDI guidance be issued prior to any changes to the Redbook.<sup>9</sup> Thus, the proposed expansion of the Redbook could cause confusion as to the requirements for NDIs, given the potential for two separate guidance documents that cover the same category of ingredients. We further agree with the senators that the requirements of the Administration Procedures Act may limit how broadly

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<sup>2</sup> CHPA, founded in 1881, is a national trade association representing manufacturers and distributors of dietary supplements and over-the-counter medicines ([www.chpa.org](http://www.chpa.org)).

<sup>3</sup> FD&C Act § 201(s).

<sup>4</sup> FD&C Act § 402(f)(1)(A).

<sup>5</sup> FD&C Act § 413(a)(2).

<sup>6</sup> 21 C.F.R. § 180.1(a) (providing that “there is a reasonable certainty that the substance is not harmful”).

<sup>7</sup> FD&C Act § 201(s).

<sup>8</sup> Sen. Hatch, Orrin, and Sen. Tom Harkin. Letter to FDA Commissioner Margaret Hamburg. 8 Dec. 2014.

<sup>9</sup> Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues, Docket No. FDA-2011-D-0376, 76 Fed. Reg. 39111 (July 5, 2011).

FDA expands the principles delineated in the Redbook, given the lack of notice-and-comment rulemaking on this potentially significant change to long-standing FDA policy.

However, if FDA proceeds with an expansion of the Redbook to include dietary supplement ingredients, the agency must include references to the appropriate safety standard. While similar toxicological principles may apply to all safety assessments, the standard battery of toxicity tests used to approve food and color additives should not be applied to dietary supplement ingredients, i.e., the “reasonable certainty of no harm” standard should not be used to evaluate dietary ingredients. Likewise, given the known safety history of many dietary ingredients, the type of information needed to perform an assessment will vary. Therefore, it is imperative that the distinction between safety standards is clearly articulated throughout the Redbook, along with the appropriate testing and related procedures.

## **Topics in the October 30, 2014 Federal Register Notice**

### ***1. What components of the Redbook should receive priority for review and update?***

*Update testing methodologies and harmonize with internationally recognized testing guidelines.*

Throughout the Redbook, the guidelines on toxicological testing methodologies and procedures should be harmonized with internationally recognized standards such as those adopted by the European Food Safety Authority (EFSA), Food and Agriculture Organization/World Health Organization (FAO/WHO), International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and the Organization for Economic Cooperation and Development (OECD). Harmonization is necessary to provide consistency on the conduct and interpretation of toxicity studies, and to enhance the efficiency of the regulatory review process nationally and globally.

The development of alternative toxicity testing methods with faster output and reduced animal usage has progressed rapidly in recent years, and new testing protocols are being validated and accepted by regulatory and authoritative bodies for hazard identification and safety assessment. For instance, the OECD has published over 30 updated or new testing methods pertaining to human health effects since 2007. Aligned approaches will avoid confounding or conflicting results, which have led to regulatory, professional, and consumer misperceptions, as well as redundant and unnecessary testing.

Specific examples of updated testing methods that we recommend for consideration are listed below in our comments to Questions 2 and 3.

## ***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?***

### *Tools for priority setting*

The current Redbook focuses almost exclusively on traditional toxicity testing in animal models and some *in vitro* tests for genetic toxicity. However, there are approaches available that can be used as a tool for prioritization screening of substances (i.e., to determine which substances should be prioritized for further toxicity testing). These approaches should be incorporated in the Redbook to reflect current and best science, reduce use of animals, and increase efficiency. Examples of approaches for consideration include, but are not limited to constituent analytical characterization; the threshold of toxicological concern (TTC) approach; and predictive models such as structure-activity relationships (SAR), quantitative SAR (QSAR), and read-across approaches. Several of these tools are already widely used by FDA and/or other regulatory and authoritative bodies. For instance, the TTC approach is utilized by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and EFSA in the evaluation of flavoring substances; and the threshold of regulation for substances used in food contact articles also applies the principles of TTC. Additionally, SAR modeling is accepted by FDA for food contact substances<sup>10</sup>, and QSAR programs are currently used by CDER (Chemical Informatics Program) for toxicity predictions<sup>11</sup>.

### *Tiered testing approach*

The current version of the Redbook recommends specific sets of toxicological studies for food ingredients based on their Concern Level and estimated cumulative human exposure, referencing separate guidance documents for each product category. Many of these traditional test batteries use a large number of animals.

The updated Redbook is an opportunity for FDA to clarify its position on predictive approaches to address data gaps and reduce the need for animal testing. We recommend that FDA consider adopting a science-based, tiered testing approach in determining necessary toxicity studies for the safety assessment that balances the data requirements against potential risk. Using a tiered approach, optimally selected testing can be identified, designed and conducted upon reviewing other relevant data (from different sources, e.g., structurally-related

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<sup>10</sup> Sotomayor RE, Arvidson KB, Mayer JN, et al. Regulatory Report: Assessing the Safety of Food Contact Substances. Available at: <http://www.fda.gov/Food/IngredientsPackagingLabeling/PackagingFCS/ucm064166.htm>.

<sup>11</sup> Kruhlak NL. FDA/CDER Current Practices for Q(SAR) Analysis Under ICH M7. ICGM Webinar, ILSA Limited Events. 2014. (FDA Presentation). Available at: <http://www.lhasalimited.org/Public/Library/Lhasa%20Library/Lhasa%20-%20Presentations/FDA%20CDER%20Current%20Practices%20for%20QSAR%20Analysis%20under%20ICH%20M7.pdf>.

substances, history of use, and other predictive models, consistent with internationally recognized standards), in lieu of conducting a full battery of traditional toxicity studies. The outcome from lower tier testing may help determine the need for and design of toxicity studies at higher tiers with a focus on the effects of concern.

Integrated testing approaches have been accepted in various risk assessment areas by other regulatory and authoritative bodies such as the Center for Drug Evaluation and Research (CDER) of FDA<sup>12</sup>, the Environmental Protection Agency (EPA)<sup>13</sup>, EFSA<sup>14</sup> and OECD.<sup>15, 16</sup>

### *Toxicological testing for substances developed with emerging technologies*

There are many emerging technologies utilized in the food ingredient category, as well as in other categories regulated by CFSAN, and the toxicity testing approaches and methodologies for the substances derived from these technologies can differ substantially from traditional toxicity studies intended for conventional chemicals that are listed in the current Redbook. Simply conducting a full battery of traditional toxicity studies without addressing potential concerns unique to emerging technologies could lead to unnecessary usage of a large number of animals and other resources while still overlooking potential hazards.

In recent years, scientific considerations relevant to the safety assessment and toxicological testing of various emerging technologies have been published by the agency or other competent authoritative bodies. We encourage FDA to reference other guidelines that have been issued by the agency or other regulatory/authoritative bodies. Some examples of such

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<sup>12</sup> U.S. FDA. International Conference on Harmonisation; Proposed Change to Rodent Carcinogenicity Testing of Pharmaceuticals; Request for comments. *Fed Reg.* 2013;78(52):16681-16684 (March 18, 2013).

<sup>13</sup> U.S. EPA. Strategic Direction for New Pesticide Testing and Assessment Approaches. Available at: <http://www.epa.gov/pesticides/science/testing-assessment.html#pesticide>.

<sup>14</sup> EFSA Panel on Food Additives and Nutrient Sources Added to Food (ANS). Guidance for Submission for Food Additive Evaluations. *EFSA Journal* 2012;10(7):2760. Available at: <http://www.efsa.europa.eu/en/efsajournal/doc/2760.pdf>.

<sup>15</sup> OECD. New Guidance Document on an Integrated Approach to Testing and Assessment (IATA) for Skin Corrosion and Irritation, No. 203. 2014. Available at: <http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono%282014%2919&doclanguage=en>.

<sup>16</sup> OECD. Guidance on Grouping of Chemicals, No. 194, 2014. Available at: [http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono\(2014\)4&doclanguage=en](http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2014)4&doclanguage=en).

guidelines include those pertaining to nanotechnology,<sup>17,18</sup> probiotics,<sup>19</sup> and selected microorganisms.<sup>20</sup>

#### *History of human exposure data*

Currently, the Redbook contains chapters on clinical studies and epidemiology studies as part of hazard characterization consideration; however, the use of human experience or history of human exposure to identify potential hazard or the absence of such is not addressed. Relevant history of use is an important aspect of assessing the safety of food ingredients. We recommend the selective, science-based inclusion of history of human exposure evidence in the Redbook.

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

Comments in response to this question are organized by chapters and sections in the current Redbook.

#### *Chapter IV.B.1. General Guidelines for Designing and Conducting Toxicity Studies*

##### II. Test Animals. D. Number and Sex

Currently, the Redbook recommends at least 20 rodents per sex per group for subchronic toxicity studies (10 may be acceptable for a study that is considered to be range-finding in nature or when longer term studies are anticipated). The rationale for this recommendation is to help ensure that the number of animals that survive until the end of the study will be sufficient (10 per sex per group) for a meaningful evaluation of toxicological effects and for histological evaluation. Typically, however, all animals in food ingredient studies survive to the end of the intervention period; therefore, the recommended 20 animals per sex per group may be excessive. To reduce the number of animals used, we propose that FDA harmonize its recommendations with OECD 408<sup>21</sup> guidelines to use 10 rodents per sex per group.

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<sup>17</sup> U.S. FDA. Guidance for Industry: Safety of Nanomaterials in Cosmetic Products. 2014. Available at: <http://www.fda.gov/Cosmetics/GuidanceRegulation/GuidanceDocuments/ucm300886.htm>.

<sup>18</sup> EFSA. Guidance on the risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain. *EFSA Journal*. 2011;9(5):2140. Available at: <http://www.efsa.europa.eu/en/efsajournal/pub/2140.htm>.

<sup>19</sup> Joint FAO/WHO Working Group Report on Drafting Guidelines for the Evaluation of Probiotics in Food. Guidelines for the Evaluation of Probiotics in Food. 2002. Available at: [http://www.who.int/foodsafety/fs\\_management/en/probiotic\\_guidelines.pdf?ua=1](http://www.who.int/foodsafety/fs_management/en/probiotic_guidelines.pdf?ua=1).

<sup>20</sup> EFSA. Introduction of a Qualified Presumption of Safety (QPS) Approach for Assessment of Selected Microorganisms Referred to EFSA - Opinion of the Scientific Committee. *EFSA Journal*. 2007;587: 1-16. Available at: <http://www.efsa.europa.eu/en/efsajournal/pub/587.htm>.

<sup>21</sup> OECD. OECD Guidelines for the Testing of Chemicals. Test No. 408: Repeated Dose 90-Day Oral Toxicity Study in Rodents. 1998. Available at: [http://www.oecd-ilibrary.org/environment/test-no-408-repeated-dose-90-day-oral-toxicity-study-in-rodents\\_9789264070707-en](http://www.oecd-ilibrary.org/environment/test-no-408-repeated-dose-90-day-oral-toxicity-study-in-rodents_9789264070707-en).

### III. Test Substance

Although an outline of required information pertaining to the identity, physical properties, and manufacturing of a substance subject to toxicological testing is included in the current version of the Redbook, additional guidance with further detail and clarity on identification and characterization of a test substance is warranted. For instance, the composition of a source material used to derive a plant-derived food ingredient can vary with growing and harvesting conditions, and the chemical makeup of such ingredients can be further influenced by manufacturing methods, including but not limited to solvents and purification processes. Additionally, natural substances often comprise a complex mixture of compounds that may or may not exert biological effects and thus identification and quantification of constituents whenever possible is an important aspect of the toxicological assessment of an ingredient.

We recommend that FDA provide detailed guidance in the Redbook on the importance of and approach to substance identification and characterization, and encourage FDA to consider guidelines that have been issued by other regulatory/authoritative bodies on this topic.<sup>22</sup> For substances of natural origin, the Redbook should include guidance on verification and documentation of the source material and addressing aspects of the manufacturing process that might influence the chemical composition of the substance. Where available, internationally accepted compendia and spectroscopic and/or chromatographic analytical methodologies that are used for characterizing the chemical profile of an ingredient should be referenced to establish consistency of test material characterization and strengthen the utility of the Redbook.

### IV. Experimental Design. C. Dose Groups: 1. Selection of Treatment Doses

Currently, the Redbook indicates that the high dose should be sufficiently high to induce toxic responses in test animals. However, food ingredients are generally of low toxicity, even at relatively high doses. For macronutrients that are used in relatively high amounts (e.g., oils, fibers), doses greater than 1,000 mg/kg bw/day as recommended in OECD 408<sup>23</sup>, or a limit of 5% in the diet as currently recommended in the Redbook, may be needed to achieve a safety margin of 100. Thus, we recommend allowing for exemptions to the limit of the high dose in the testing on a case-by-case basis.

#### *Chapter IV.C.1. Short-Term Tests for Genetic Toxicity. Genetic Toxicity Test Battery*

The current Redbook recommends a genetic toxicity test battery for food ingredients with a cumulative estimated daily intake exceeding 50 ppb in the diet (150 mcg per person per day) to

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<sup>22</sup> EFSA. Guidance for submission for food additive evaluations. *EFSA Journal*. 2012;10(7):2760. Available at: <http://www.efsa.europa.eu/en/search/doc/2760.pdf>

<sup>23</sup> OECD. OECD Guidelines for the Testing of Chemicals. Test No. 408: Repeated Dose 90-Day Oral Toxicity Study in Rodents. 1998. Available at: [http://www.oecd-ilibrary.org/environment/test-no-408-repeated-dose-90-day-oral-toxicity-study-in-rodents\\_9789264070707-en](http://www.oecd-ilibrary.org/environment/test-no-408-repeated-dose-90-day-oral-toxicity-study-in-rodents_9789264070707-en).

generally include 2 *in vitro* tests and 1 *in vivo* test. To reduce unnecessary animal use, we recommend that FDA adopt EFSA's step-wise approach<sup>24</sup>, which begins with a battery of *in vitro* tests (bacterial reverse mutation assay and micronucleus assay); *in vivo* testing is recommended only in the case of inconclusive or positive *in vitro* results.

Additionally, FDA should consider allowing the inclusion of more recent methodology of obtaining *in vivo* genetic toxicology data as part of routine repeat-dose studies, as opposed to standalone studies. For example, the ICH S2(R1)<sup>25</sup> guidance allows for samples to be collected to evaluate micronucleus formation from peripheral blood, which can be harvested as a terminal endpoint in a 28-day or 90-day repeat-dose toxicity study. This allows for a more robust evaluation of micronucleus formation (counting of more events), without a separate standalone study and thus also reduces the number of animals used.

#### *Chapter IV.C.3 Short-Term Toxicity Studies with Rodents and Chapter IV.C.4 Subchronic Toxicity Studies with Rodents*

In the short-term toxicity chapter, the Redbook currently recommends collection of clinical pathology blood samples at 2 weeks and at termination. For the subchronic toxicity chapter, the Redbook recommends collection of samples at 2 weeks, 45 days, and at termination.

We recommend the elimination of interim blood collections for clinical pathology evaluations of rodents in the aforementioned sections and suggest alignment with comparable OECD guidelines.<sup>26,27</sup> Interim blood collections on rodents can cause undue pain and distress in the animals. The comparable OECD guidelines do not call for such interim collections and suggest evaluation of clinical pathology changes only at the termination of the study. The interim collections suggested by the Redbook can confound the data interpretation (changes associated with pain and distress, not true compound-related toxicology) and may compromise the health of the animals and possibly reduce survival.

#### *Chapter IV.C.6 Carcinogenicity Studies with Rodents & IV.C.7 Combined Chronic Toxicity/Carcinogenicity Studies with Rodents*

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<sup>24</sup> EFSA. Scientific opinion on genotoxicity testing strategies applicable to food and feed safety assessment. *EFSA Journal*. 2011;9(9):2379. Available at: <http://www.efsa.europa.eu/en/efsajournal/pub/2379.htm>.

<sup>25</sup> ICH. Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use S2(R1). 2011. Available at: [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Safety/S2\\_R1/Step4/S2R1\\_Step4.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S2_R1/Step4/S2R1_Step4.pdf)

<sup>26</sup> OECD. OECD Guidelines for the Testing of Chemicals. Test No. 407: Repeated Dose 28-day Oral Toxicity Study in Rodents. 2008. Available at: [http://www.oecd-ilibrary.org/environment/test-no-407-repeated-dose-28-day-oral-toxicity-study-in-rodents\\_9789264070684-en](http://www.oecd-ilibrary.org/environment/test-no-407-repeated-dose-28-day-oral-toxicity-study-in-rodents_9789264070684-en).

<sup>27</sup> OECD. OECD Guidelines for the Testing of Chemicals. Test No. 408: Repeated Dose 90-Day Oral Toxicity Study in Rodents. 1998. Available at: [http://www.oecd-ilibrary.org/environment/test-no-408-repeated-dose-90-day-oral-toxicity-study-in-rodents\\_9789264070707-en](http://www.oecd-ilibrary.org/environment/test-no-408-repeated-dose-90-day-oral-toxicity-study-in-rodents_9789264070707-en).

Interim blood collection for hematology and serum chemistry evaluation are recommended as part of the current Redbook guidance on carcinogenicity studies, to include 10 animals per sex per group at 2 weeks and 3, 6 and 12 months. However, it is inappropriate to perform these collections on a subset of animals designated for carcinogenicity evaluations, as this differential treatment of animals within a group does not represent good scientific practice. In addition, blood collections for clinical pathology evaluations may have already been performed in short-term, subchronic, or other chronic toxicity studies. Therefore, blood collections in carcinogenicity studies are redundant. It may only be appropriate to collect limited plasma studies in carcinogenicity studies at the  $T_{max}$  at 2 weeks to confirm exposure.

Instead of interim blood collection in carcinogenicity studies, evaluations for clinical pathology should be recommended for standalone chronic toxicity studies or in a chronic toxicity arm of a combined chronic toxicity/carcinogenicity study. The blood collection scheme should be flexible to allow for evidence-based collection of data and should be minimized to reduce pain and distress to the animals.

We propose that FDA consider harmonization with OECD guidelines for carcinogenicity (OECD 451)<sup>28</sup> and combined chronic toxicity and carcinogenicity (OECD 453)<sup>29</sup> studies to represent current thinking on study design and endpoints evaluated as part of chronic toxicity and/or carcinogenicity studies. Moreover, a clear distinction should be made between routine chronic toxicity endpoints and carcinogenicity endpoints.

We also recommend that FDA consider the use of transgenic mouse models of carcinogenicity as an alternative to traditional 2-year carcinogenicity mouse studies. The transgenic mouse models are of shorter duration (6 months), use fewer animals, and have been employed in the evaluation of pharmaceuticals.<sup>30</sup>

#### *Chapter IV.C.8 In Utero Exposure Phase for Addition to Carcinogenicity Studies or Chronic Toxicity Studies with Rodents*

The current Redbook suggests including an *in utero* exposure phase for compounds that are in Concern Level III. It should be noted that the guidance already recommends the conduct of developmental and reproductive toxicology studies for compounds in Concern Level III, which addresses *in utero* exposure. Therefore, Chapter IV.C.8 is duplicative in terms of its

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<sup>28</sup>OECD. OECD Guidelines for the Testing of Chemicals. Test No. 451: Carcinogenicity Studies. 2009. Available at: [http://www.oecd-ilibrary.org/environment/test-no-451-carcinogenicity-studies\\_9789264071186-en](http://www.oecd-ilibrary.org/environment/test-no-451-carcinogenicity-studies_9789264071186-en).

<sup>29</sup> OECD. OECD Guidelines for the Testing of Chemicals. Test No. 453: Combined Chronic Toxicity/Carcinogenicity Studies. 2009. Available at: [http://www.oecd-ilibrary.org/environment/test-no-453-combined-chronic-toxicity-carcinogenicity-studies\\_9789264071223-en](http://www.oecd-ilibrary.org/environment/test-no-453-combined-chronic-toxicity-carcinogenicity-studies_9789264071223-en).

<sup>30</sup> ICH. Proposed Change to Rodent Carcinogenicity Testing of Pharmaceuticals - Regulatory Notice Document. 2015. Available at: [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Safety/S1/S1\\_Regulatory\\_Notice\\_Document\\_10Mar2015.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S1/S1_Regulatory_Notice_Document_10Mar2015.pdf)

scope and contradicts the principle of the 3Rs for the reduction of animal usage. We recommend that this section be eliminated from the Redbook.

#### *Chapter V. Additional Studies. B. Metabolism and Pharmacokinetic Studies*

This chapter should be updated to include appropriate validated metabolic and immunologic techniques. For example, specific guidance on the conduct and use of toxicokinetic studies, similar to that published by OECD<sup>31</sup> should be included. The OECD 417 guidelines advocate flexibility in the design of toxicokinetic studies and recommend that “[a]ll available information on the test substance and relevant metabolites and analogues should be considered by the testing laboratory prior to conducting the study in order to enhance study quality and avoid unnecessary animal use. This could include data from other relevant test methods (*in vivo* studies, *in vitro* studies, and/or *in silico* evaluations).” Incorporation of guidance on toxicokinetics studies, comparable to OECD 417, would provide a valuable resource for industry and would be of relevance to using a tiered testing approach as discussed above in our response to Question 2.

#### *Other*

In addition to updating existing chapters, we recommend the inclusion of a chapter providing guidance on the conduct and interpretation of a combined repeat-dose toxicity study with reproductive/developmental endpoints, similar to that published by OECD<sup>32</sup>.

#### ***4. How should we balance the desire for transparency and consistency in risk assessment as described in the Redbook, with the goal of flexibility in applying the most appropriate analysis for specific contexts?***

Flexibility, as stated in the Introduction of the current Redbook, must be maintained and emphasized. Under the section, “Flexibility in Guidance for Toxicity Testing,” it is stated that “FDA’s guidance for toxicity studies for food ingredients continue to emphasize that there is no substitute for sound scientific judgment. This guidance presents recommendations—not hard and fast rules.”

The objective of toxicological testing is to identify the hazard(s) and characterize the dose-response relationship(s). The types of toxicological studies and their design required to adequately characterize the hazard of a substance is a scientific judgment rather than a standard model, and should take into account what is already known about the properties and toxicity

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<sup>31</sup> OECD. OECD Guidelines for the Testing of Chemicals. Toxicokinetics, Test No. 417. 2010. Available at: [http://www.oecd-ilibrary.org/environment/test-no-417-toxicokinetics\\_9789264070882-en](http://www.oecd-ilibrary.org/environment/test-no-417-toxicokinetics_9789264070882-en).

<sup>32</sup> OECD. OECD Guidelines for the Testing of Chemicals. Test No. 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test. 1996. Available at: [http://www.oecd-ilibrary.org/environment/test-no-422-combined-repeated-dose-toxicity-study-with-the-reproduction-developmental-toxicity-screening-test\\_9789264070981-en](http://www.oecd-ilibrary.org/environment/test-no-422-combined-repeated-dose-toxicity-study-with-the-reproduction-developmental-toxicity-screening-test_9789264070981-en).

potential of the substance, its intended conditions of use, and current standard practices for toxicity testing. It should be clearly recognized in the Redbook that scientific judgment should apply when determining the types of studies and protocols in safety assessment, allowing industry the ability to use existing high quality data, when appropriate, and the flexibility in the conduct of testing guided by sound scientific principles while ensuring products meet their applicable safety standards.

The Institute of Medicine's (IOM) Tolerable Upper Intake Levels (ULs) represent an example of a flexible approach to assessing safety. IOM's UL assessment strategy is based on risk assessment, which "requires that information be organized in rather specific ways but does not require any specific scientific evaluation methods. Rather, risk assessors must evaluate scientific information using what they judge to be appropriate methods; and they must make explicit the basis for their judgments, the uncertainties in risk estimates, and when appropriate, alternative interpretations of the available data that may be scientifically plausible." In addition to the statements on flexibility in the current Redbook, FDA should consider including similar language in the Introduction section of the revised Redbook.

CRN and CHPA again thank FDA for providing the opportunity to voice our comments regarding the update of the Redbook and we look forward to answering any questions FDA may have. Please do not hesitate to contact us.

Respectfully submitted,

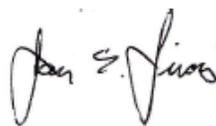
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