Report on FDA CFSAN's Redbook

Introduction:

For the past several decades**,** FDA's Center for Food Safety and Applied Nutrition, Office of Food Additive Safety, and its predecessor organizational units, have made available to the regulated industry and other interested stakeholders technical and policy guidance regarding the development and submission of toxicity data generated to support the approval of certain food ingredients for commercial use. At the present time, this guidance, currently entitled "Toxicological Principles for the Safety Assessment of Food Ingredients," and known less formally as the "Redbook," applies only to a subset of the universe of food ingredient or supplement chemicals: direct food additives, color additives, food contact substances and those substances classified as generally recognized as safe (GRAS). Substances falling into the first three of these categories are subject to a pre-market approval process which includes a toxicity/safety assessment performed or overseen by agency staff. Most of the new substances argued to be GRAS undergo a rigorous data review by a qualified external expert panel. The guidance articulated in the Redbook is *generally* applicable to all of these assessments, whether conducted internally or externally.

Food safety is a hot-button issue for many people these days. The level of public awareness has increased exponentially as a result of readily available multi-media stories of food contamination instances and other scares. The ease with which information can be made available allows the general public (and the scientific community) to learn quickly of incidents which may or may not have untoward public health implications. One moment, it's arsenic in rice and juices; the next, it's horse, donkey and buffalo meat masquerading as beef in processed meats; tomorrow, who knows? While one might be tempted to parse these events as representing "contamination" or deliberate, but illegal, addition, the enlightened public is asking questions about the integrity of food, in general, with significant attention being given to foods of all kinds, both fresh and processed. This places the onus on FDA to articulate and implement the most up-to-date scientific approaches which will most accurately assess the safety of substances added to food.

The time is right for FDA to ask the question of whether or not its existing tools used in the regulation of food are "up to snuff." They are to be commended for acknowledging this and for beginning to take steps to update and upgrade. In this particular instance, the spotlight is on the Redbook and whether or not it currently represents articulation and application of the best science to garner an understanding of the toxicity profile of certain food ingredients.

What follows is my assessment of the Redbook as it currently exists. I will include not only my observations, but also offer some suggestions/recommendations that could be considered in updating/improving this important tool. To the degree possible, I'll make use of the framework created by the questions posed in the task order. I will be making frequent reference to the work and practices of the European Food Safety Agency

(EFSA) and the US Environmental Protection Agency, specifically its Office of Pesticide Programs (EPA OPP). I do this for three reasons: 1) Both of these organizations have responsibility for implementation of food and food safety legislative mandates, as does FDA CFSAN, and 2) EPA OPP shares with FDA CFSAN a role in implementation of those portions of the Federal, Food, Drug and Cosmetic Act (FFDCA) relevant to the regulatory paradigm for food additives, and 3) Both EFSA and OPP are much more open in that ALL of their substance-specific assessments, generic science policy guidance and regulatory actions are easily accessible on/through their respective websites. EPA OPP now also puts all of this information on Regulations.gov. EFSA publishes all its scientific outputs, including its scientific opinions, in the EFSA Journal. Regulatory decisions are made at the European Commission level and are documented on its website. In recent years, both EFSA and OPP have had resources available to pursue efforts dedicated to the development and provision of new or updated science-based guidance and to take a step back and craft brand new approaches to the work they do in light of the promise and availability of new tools for assessing the potential for toxicity of chemical substances. I strongly urge CFSAN/OFAS to exploit more rigorously these resources by studying, reviewing, adapting and adopting relevant outputs of EFSA and OPP. Continue the practice of seconding an EFSA staffer to the Office. Continue to support the reciprocal. Expand the collaboration with EFSA to include working-sharing, including on individual petitions, whenever possible. This can work well if a sponsor wishes to introduce its product into the global market and chooses to seek pre-market approval from more than one authority at the same time. As noted above, OPP has been engaged in worksharing with PMRA and CalEPA for years, and to a lesser extent with EFSA. Also, consider establishing an OFAS/ OPP staff reciprocal extended detail program. There may also be some value in building relationships with the parallel bureaucracy in the Canadian government. Admittedly, I haven't spent the time necessary to figure out and recommend any specifics on how to do this, as I found that their website is difficult to explore.

Another general recommendation I would offer is for the Office to make better use of in-person public meetings of its FACA-sanctioned Food Advisory Committee: 1) to solicit expert input into the development of updated and new approaches and guidance and 2) later, to carry out the necessary formal external scientific peer review of all components of a new Redbook. This can be done in segments, reflecting progress made at points in time and the mix of expertise needed to address each of the different topics. There may be value in contacting the Executive Secretary of EPA's FIFRA Scientific Panel for information on how they balance the panel's activities related to consultation during product development and peer review of a final draft version of the product. Acknowledging the circumstances surrounding current resources (human and otherwise), the agency should explore other possible collaborative arrangements to develop appropriate protocol and guidance documents. These might be interagency workgroups (i.e., US Feds only) or US plus foreign government experts (e.g. those who sit on EFSA Scientific Committees) or government plus academic experts. Maximize communication with the OECD U.S. National Guidelines Coordinator and ICCVAM/NICEATM. The agency may want to explore a partnership with the ILSI Research Foundation for assistance in convening appropriately-appointed committees to help develop certain material. I offer a cautionary note because I'm unsure of the agency's current degree of

comfort about working with committees made up of representatives from industry as well as government, academia, and sometime, the public interest group community. There, of course, is precedent for this, as FDA staff have participated in many projects managed by the Research Foundation, ILSI North America and ILSI HESI.

Topics:

1. Form and format

FDA CFSAN/OFAS is best served by having a single, easily-accessible and searchable, document on its website which describes its regulatory/guidance principles and practices related to toxicology in the areas of foods and food safety for which it has legislative authority. Whether or not this information remains embodied in something called the Redbook may be immaterial unless this nickname is so imbedded in the agency's and its stakeholders' psyches that it would be difficult to abandon it. (Personally, I would keep it, since it's unique to FDA CFSAN). However, since the Redbook addresses only human and animal health, but not environmental/ecological issues, its title should acknowledge this scope, e.g. "Toxicological Principles for the Safety Assessment of Human Food and Animal Feed Ingredients."

Assuring and improving access to relevant materials by reconstructing the CFSAN website in addition to updating the written documentation available on it would be very helpful. The fewer clicks a searcher must make, the better. That is, consolidate the information into as few web pages as possible, taking greater advantage of current technology. [Note: Since I began working on this assignment to evaluate the currency and value of the existing Redbook, FDA announced its efforts to re-construct/revise its website FDA.gov/food (March 15, 2013). I must admit I have not had time to examine the new views to see how they may match up with the thoughts I had about possible useful changes).

All guidance must serve both the Agency staff and its stakeholders. "Outsiders," such as the regulated community, public interest groups and interested citizens, deserve this transparency. But, so do the Agency staff. Creating and sharing clear and credible legislative, regulatory and science policy guidance internally works to insure credible and consistent assessments and decisions over time. This is particularly important given that preliminary feedback on some of the information gathered during the staff interviews suggests that there is little or no regular cross-staff communication or collaboration going on.

Currently, the Redbook addresses information regarding U.S. legislative mandates and scope and the decision logic for data needs and generation (e.g., Concern Levels, Data Packages; specific testing protocols). However, I could find nothing in it or in any other document on the FDA website that describes data *evaluation/interpretation* practices and guidance, other than for carcinogenicity in Chapter II, Section C5. Absent the existence of such guidance, it would appear to an outsider as if each individual petition is treated separately and *ad hoc*, and that there is little or no attempt to advocate

or exercise consistency when reviewing/assessing the same types of data across substances. There is an urgent need to create/publish such information for the benefit of Agency scientific staff, regulated entities and other stakeholders, particularly in light of the observation that there is little or no regular cross-staff communication. This is a glaring deficiency and a significant credibility issue. (I am sensitive to the fact that this would require significant human resources, but I will offer some suggestions for gaining some efficiencies in this endeavor later).

At the present time, the Redbook is geared towards meeting the requirements and policies of the U.S. FDA. It should stay that way. As I point out in several places below, it might be advantageous to roll certain relevant information regarding food substances other than those currently covered by the Redbook into the Redbook (i.e., GE foods, medical foods, infant formula, dietary supplements, allergens). Attempting to cover international food ingredient safety assessment would be of little value to the agency or to its regulated community and other stakeholders. That doesn't mean that practices of other bodies should never be mentioned or incorporated into FDA's own practices (I recommend later that the agency consider using, as their own, products created in other fora but modified to suit its purposes); but the Redbook should not become a compendium of international practices. The Redbook should focus on being an excellent guidebook for the U.S. regulatory program, incorporating the best science available. This "best science" may reflect a consensus of the international scientific community, but it should be discussed in the context of the U.S. regulatory paradigm.

2. Accessibility of information

The Redbook, as currently available on the website, is scattered (that is, some of the material is accessible on the main page, but other, older, information is available only by clicking away to another page). This serves only to exacerbate the impression that the Redbook is out-of-date.

I would recommend that folks NOT be redirected away from the main page to see portions of the Redbook, with one possible exception: the interpretative guidance to be described in a new Chapter VI. If the interpretative guidance documents turn out to be rather long (as are EPA's "Purple Books"), it might be better to have short introductory material in the Redbook chapter and a link to a separate pdf document containing the detailed guidance. There should be only one main document, on one webpage, all sections reflecting the Agency's current thinking/approach. I would set the 1993 material aside as an historical entity, and put any still-current material from 1993 and 2000 into one updated entity, not called Redbook 2000, just the Redbook. The 2000 date is misleading, anyway, as most of the document has been updated since then, with only a small part not updated since 1993. Remove the 2000 and just advertise/present THE currently-applicable Redbook with dates of last update next to each section. The 1993 and 2000 versions can be made available elsewhere as pdfs, but only for historical purposes.

3. Scope and coverage of guidance

As noted in the Introduction to the Redbook, the guidance applies only to a subset of the universe of ingredients in, or supplements to, food: direct food additives, color additives, food contact substances and those substances which are classified as generally recognized as safe (GRAS). This is somewhat understandable, as the Agency does not have the regulatory authority to impose equivalent pre-market approval requirements for other categories such as genetically-engineered foods, dietary supplements and contaminants.

However, the agency might wish to include some text in the Introduction about these other categories, articulating its opinion that, if animal or human studies are conducted on behalf of a substance in these other categories, they should be designed, conducted and reported in a manner consistent with the guidance provided in the Redbook for the other categories (if that is the Agency's opinion, of course). Reference also can be made back to the more detailed information on this aspect of testing that is available on the websites specific to GE foods and dietary supplements.

Alternatively, the agency might choose to include more extensive and detailed sections in the Redbook on GE foods, dietary supplements and the other categories that provide some, if not, all of the material on philosophy and particulars of testing strategy, study design, conduct and reporting that now can/should be found on the web pages which access the relevant guidance documents for the safety assessment of these other categories.

4. Topics covered in the Redbook

The Redbook 2000 contains the historical/legislative background for the regulatory paradigm for a subset of food ingredients, the decision logic and criteria for determining what toxicity-related data should be developed for a specific substance, study design and conduct, reporting requirements, statistical analyses and collection and review of histopathology data, among others. These are appropriate topics and should be retained, although the content of each chapter needs significant review and possible wholesale updating and/or revision. Furthermore, as mentioned above, a new chapter should be added which provides guidance on 1) how the data gathered on the parameters/endpoints measured in each study will be evaluated and interpreted and 2) how all of the information contained in a substance-specific data set is integrated into an overall assessment, hopefully by employing a credible weight-of-evidence (WoE) approach. It's no longer adequate, or scientifically-sound, simply to pick the lowest NO(A)EL, plunk a safety factor on it, and call it a day (or an ADI or TDI, as the case may be).

Proposed outline for updated/revised Redbook:

Table of Contents

Chapter I. Introduction

Chapter II. Agency Review of Toxicology Information Submitted in Support of the Safety Assessment of Food Ingredients

Chapter III. Recommended Toxicity Studies

Chapter IV. Guidelines for Toxicity Studies

Chapter V. Human Studies

There is a need to update this chapter considerably. Much discussion and debate has occurred since it was drafted and many changes have been made in the policies/ regulations regarding the Protection of Human Subjects. The Basic HHS Policy for Protection of Human Research Subjects was revised in early 2009 and implemented in July of that year. It can be found in the Code of Federal Regulations TITLE 45. PUBLIC WELFARE- DEPARTMENT OF HEALTH AND HUMAN SERVICES. PART 46 PROTECTION OF HUMAN SUBJECTS (Available at http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html).

I would recommend soliciting input into its revision from the current Director of the Office for Human Research Protections (OHRP). In addition, there would be value in having a conversation with the Designated Federal Officer for EPA's Human Studies Review Board. Members of that Board may also contribute valuable insights.

The task order for this Redbook review included the following two questions:

- What, if any, recommendations or other information would enhance the utility of the Redbook for the safety assessment of food ingredients that are purported to have a health benefit on the human body? What is the scientific basis for your position?

- Should the role of clinical studies be expanded for food ingredients? If so, could this be accomplished without risk to human subjects?

I don't have sufficient technical expertise in this area to comment intelligently on these two questions. However, I envision these as being two of several questions the agency could present to an expert panel to be convened under FACA rules for a public discussion of relevant Human Studies topics. Candidates for such a panel could include current members of EPA's Human Studies Review Board, one of whom is Bern Schwetz. The list of members is available at http://www.epa.gov/hsrb/members.htm

NEW: Chapter VI. Interpretative Guidance for Toxicity and Human Studies

This was noted above as the most glaring deficiency. Study specific and/or endpoint specific interpretative guidance is a must. So, too, is a description of preferred practices for an integrated assessment of the database as a whole, the step leading to the derivation of health-based values, such as the ADI or TDI. Consider drawing upon materials developed by WHO and/or FAO and used by JECFA such as "Environmental Health Criteria 240 Principles and Methods for the Risk Assessment of Chemicals in Food" (2009), EPA's "Purple Books," the endpoint-specific risk assessment guidelines issued by the Risk Assessment Forum, and relevant EFSA publications, easily accessed on its website http://www.efsa.europa.eu/

Chapter VII. Emerging Issues in Safety Assessment of Food and Color Additives Used in Food and Food Contact Substances

Topics in this chapter may be different from those included in Chapter VII of the 1993 draft document, although most, if not all, of these topics could remain because they continue to evolve in new contexts. This section currently discusses approaches to testing that may be useful in assessing the safety of macro-additives, bioengineered additives, additives that are enzymes and microbially-derived additives. This section also discusses the use of alternatives to whole (vertebrate) animal testing in safety evaluation and the potential for direct food additives and color additives used in food to cause both heritable and somatic genetic toxicity.

I am not particularly familiar with the literature on any of the first four topic areas in this chapter (macro-additives, bioengineered additives, additives that are enzymes and microbially-derived additives), so I cannot recommend specific sources of information to use in updating these topics. However, the agency could seek expert input, using the Food Advisory Committee or a specially-convened public workshop as the vehicle(s) for discussing of the current state-of-the-science.

[Note: The section on microbially-derived additives stated that "a comprehensive review of the safety concerns relating to microbial sources will be issued in another publication." I couldn't find such a document on the FDA website. Was it ever written and issued? If not, here's a place to start the updating of discussion on this category of food additives].

I would recommend moving the section on heritable and somatic genetic toxicity into the section in Chapter IV on *Short-term Tests for Genetic Toxicity* as part of the introductory material. There is value in including the rationale for testing closer to the discussion of the actual tests. In any case, this section needs updating as much new research has been done (e.g., the development of transgenic animals for use in gene-tox and carcinogenicity testing and the 'omics) and several new and updated assessments of the value of specific tests and test batteries in predicting carcinogenicity and somatic and germ cell mutations in whole animals and humans have been published since 1993.

The chapter section on *Advances in the Development of Alternatives to Whole Animal (Vertebrate) Testing* requires a wholesale update. This is the spot where the *detailed* discussion of ICCVAM- and ECVAM-validated tests should be inserted. The agency has an obligation to communicate which, among those that have been validated, it will now accept as complements to, or substitutes for, traditional whole animal studies—if any.

TOX21 and its promise/potential is an obvious topic to be added here. The 2007 NRC report entitled *Toxicity Testing in the 21st Century- A Vision and a Strategy* has prompted a flurry of activity in the research community, inside and outside of government, to develop new, more efficient toxicity-testing strategies to evaluate the hazards associated with exposure to drugs, food additives, pesticides, and industrial and other chemicals. The report is having an enormous impact on the scientific community in reviewing and rethinking the entire approach to testing of chemicals and other entities to better understand their impacts on human and environmental health. The implementation of the REACH program in Europe has served as the final wake-up call to sponsors and regulators alike on a global basis that data-gathering on the many thousands of substances of interest has been too little and too slow. Presuming the agency agrees that a revisiting of its testing paradigm is necessary, it should point out that while the development of several potentially-useful technologies are underway, they have yet to be fully validated as predictive tools-- BUT, when they are, the agency will give full consideration to how, and when, they can be incorporated into its testing "toolbox."

In the United States, one of the many initiatives launched in response to the challenges the NRC report offered is Tox21, a collaboration among multiple federal Agencies – EPA, NIEHS, NIH and FDA. The task is to develop, validate and translate innovative, high-throughput screening (HTS) chemical testing methods to characterize key steps in toxicity pathways. The (near-term) goals are to investigate the use of these new tools to prioritize substances for further in-depth toxicological evaluation, identify mechanisms of action for further investigation, and develop predictive models for *in vivo* biological response. Determination of the suitability to substitute someday for traditional whole animal testing remains a far-off goal.

So what role could Tox21 play in assessing the safety of food ingredients, sooner rather than later? The first element, in my view, is to nominate direct food additives, including GRAS substances, for testing in the system. This would be a near-term task. Although, admittedly, I didn't review the entire list of 10000+ substances currently in the database, I did screen a large enough subset to conclude that there were few, if any, direct food additives in it. I saw color additives, some known contaminants, and some chemicals which fall into the category of food contact substances, but are on the list primarily because they are TSCA chemicals. Of course, there were no proteins at all, so macro-additives, bioengineered additives, enzymes and microbially-derived additives that are proteins are all excluded. Nonetheless, there is still a large candidate pool to focus attention upon.

The Tox21 "players" talk about using the results of this effort to "prioritize substances for further in-depth toxicological evaluation." A variation on that theme arose frequently during the discussions at the three workshops sponsored in 2011 and 2012 by the Pew Charitable Trusts, the Institute of Food Technologists, and the journal Nature on FDA's food additive regulatory program. A number of participants in those workshops called for the agency to consider instituting a *re*-evaluation program for approved food additives, similar to the registration renewal program EPA OPP carries out for all registered pesticides. EPA's program was mandated by Congress. Such a program for FDA's universe of food additives hasn't been---yet. Many of the workshop participants were unconvinced that FDA ever looked at an additive again after it was first approved.

Tox21 also is envisioned to contribute to the characterization of mode/mechanism of action and/or adverse outcome pathways (as discussed in NRC, 2007). During the second Pew/IFT/Nature workshop, one of topics on the agenda was Substances with Similar Biological Effects. Context began with a discussion of the legislative mandate in the Food Additives Amendment of 1958 that states that safety decisions must consider "the cumulative effects of such additive in the diet of man or animals taking into account any chemically or pharmacologically related substances in such diet." The agency adopted a rule explaining how it would set maximum allowable levels for substances that cause similar or related pharmacological effects. In addition to attempting to articulate and clarify the many possible definitions of "similar biological effects," "cumulative effects," "cumulative dietary exposure assessment," etc., there was an acknowledgment that Tox21 outputs, along with ToxCast and QSAR tools could/would be useful in predicting substances that may have similar chemical structure or similar biological effects. In the short term, if/when deciding to do a cumulative assessment for two or more chemicals, not simply an additional use of the same additive, checking to see if there are relevant data in the Tox21 database would be an obvious step to take.

Chapter VIII. Glossary: Acronyms and **(Their)** Definitions

Update, as appropriate. It's likely that new terms would be added, as other sections of the Redbook are updated.

5. Detailed assessment of scientific currency of existing Chapters IV and V.

In light of the earlier recommendation to revise the Redbook into a single document, Chapters IV and V should be combined.

(2000 version) **Chapter IV.A. Introduction: Guidelines for Toxicity Studies**

IV.A. Introduction should be revised to note process changes and to list ALL study types in one chapter.

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

Other than removing the parenthetical references to Redbook version this or that in the introductory paragraph, this section remains up-to-date and consistent with currently-accepted practices.

IV.B.2. Guidelines for Reporting the Results of Toxicity Studies

This section should be reviewed to determine if the elements required in this version of the reporting guidelines are still required or if additions/deletions are desired. Also, the introductory paragraph should note that there are study-specific templates available for the submitter's use which are related to the submission of toxicology data. The link to the webpage where they are located should be added to the introductory paragraph of this section. As FDA states the "templates provide optional tools for industry in submitting summary toxicology data from the respective studies in support of petitions and notifications for safe use of food and color additives. The purpose of this guidance is to assist industry in preparing toxicology reports using standardized formats and vocabularies that are consistent with current Agency recommendations for toxicological information. Their use will expedite the evaluation process of toxicology information by the Agency since data will be presented in a consistent, predictable, format for evaluation." There should be active encouragement of their use. In fact, a push for mandatory use and electronic submission would be useful both to the agency and to the sponsor. This could be coupled with an implementation of a SEND process, tailored for CFSAN (and CVM).

At this time, templates are available for nine of the studies. Templates should be created for the remaining study types on the list and any new study types to be added (e.g., allergenicity). Accomplishment of this task could be facilitated by evaluating, adapting and adopting the templates that EPA's Office of Pesticide Programs uses and asks their petitioners to use as well. This tool also has proved to be a boon to OPP in carrying out its internal reviews and its workshare programs with Health Canada's Pesticide Management Regulatory Agency (PMRA) and CalEPA's Department of Pesticide Regulation. The information is presented in a uniform format, while retaining the flexibility for each regulatory authority to capture and articulate its specific science policy positions in the summary and conclusions section. OPP's study profile templates for *all* of the health effects studies listed in a new combined Redbook Chapter IV (except for allergenicity) can be accessed at http://www.epa.gov/pesticides/regulating/studyprofile_templates/studyprofile_templatelist.htm#series-870.

IV.B.3. Pathology Considerations in Toxicity Studies

Recent years have seen updates and revisions to pathology review procedures, nomenclature, etc. This section should be reviewed and revised, as needed, to reflect any changes officially adopted by the pathology community that engages in the review of animal studies conducted by, or submitted to, government authorities. Toxicologic pathology organizations around the world have developed harmonized nomenclature through the International Harmonization of Nomenclature and Diagnostic Criteria for Lesions in Rats and Mice (INHAND) initiative, which will promote international agreement and consistency needed to improve the safety assessment of drugs, biologics and chemicals (Mann et al, 2009). Participants in the INHAND initiative are

collaborating with FDA CDER on employing the harmonized terminology in SEND (INHAND, 2012).

IV.B.4. Statistical Considerations in Toxicity Studies

The content of this section appears to be adequate, representing practices still in vogue. Nonetheless, as with the rest of the document, this section should be reviewed and revised, as necessary, to reflect currently-preferred practices, if they are different from those described.

IV B 5. Diets for Toxicity Studies

The content of this section appears to be factually-accurate for the time frame in which it was written. Much attention has been directed at the contents of rodent diets since the issue of endocrine disruption/disruptors has burst onto the scene. Also, there is quite a literature on the value (or, not) of dietary restriction. This section should be reviewed and revised, as necessary, to address these two issues as well as to capture any changes in approach/opinion/ preferences OFAS may have implemented since the last version was written.

IV. C.

This next section of the current Chapter IV (section C) and all sections of current Chapter V address the recommended protocols for each study type that will or may be conducted to satisfy regulatory requirements. Herein lies the most resource-demanding aspect to updating of the Redbook. In light of the publication of the 2007 NRC report entitled *Toxicity Testing in the 21st Century: A Vision and a Strategy*, a groundswell of activity is underway in government, industry, consulting laboratories, academia and science-based public interest groups and other NGO's such as ILSI to develop and implement toxicity testing strategies that move away from a dependence upon "observing outcomes in whole animals, such as clinical signs or pathologic changes, to a new toxicity-testing system that evaluates biologically significant perturbations in key toxicity pathways by using new methods in computational biology and a comprehensive array of *in vitro* tests based on human biology" (NRC, 2007). Needless to say, this transition will take some time---perhaps, decades. Nonetheless, in order to implement a state-of-the-science testing/regulatory program, it will be necessary for CFSAN/OFAS to commit itself to embracing and integrating the new science, as many of these new tools will become validated and incorporated into comparable regulatory programs elsewhere (e.g., OPP and EFSA). CFSAN OFAS should commit resources NOW to support its scientific staff in becoming knowledgeable of the ongoing activities, including the ability to actively engage in some of these activities, in real time, rather than just observing from the sidelines. As each significant step forward is confirmed and validated, the staff should ask the question "If, when and how should this technology/information be incorporated into our testing/regulatory paradigm?" This should occur on a reasonably frequent recurring basis, for instance, annually.

In the meantime, as this wholesale de- and reconstruction of the testing paradigm unfolds, what else might be done? A somewhat lesser demand on resources might be to study, and possibly implement, a revised, more efficient testing strategy that still depends

largely on whole animal studies. EPA OPP is engaged in a partnership with the agricultural chemical industry and academia, initially via an ILSI-managed project, but now independent of ILSI via one of its own advisory committees (Pesticide Program Dialogue Committee (PPDC)) to examine this question. The PPDC provides a forum for a diverse group of stakeholders to provide feedback to the pesticide program on various pesticide regulatory, policy and program implementation issues. It's not a scientist-only constituency.

The outputs of the ILSI project included four papers published in a 2006 issue of Critical Reviews in Toxicology (Barton, et al, Carmichael, et al., Cooper et al, and Doe, et al.-full citations are in the reference section). The Doe, et al paper focused on developing a tiered approach to systemic toxicity testing. Developing the scheme was not just a hypothetical, academic exercise. Since that time, a handful of already-registered agricultural pesticides were re-tested using the proposed new, more efficient, approach with the results being compared to those from the traditional studies originally submitted to support registration to determine if, in fact, the newer data would reveal the same toxicity profile that the original data did. During a conversation I had at the recent SOT meeting with a representative of one of the pesticide registrants which is running a side-by-side analysis, their manuscript is nearly finished and should be submitted for publication any moment, if it hasn't been already. I am awaiting feedback on whether or not other registrants are actually participating as well.

The ILSI project was introduced to the PPDC at its October 2005 meeting. The presentation can be accessed at
http://www.epa.gov/oppfead1/cb/ppdc/2005/october05/session6-1.pdf.
Additional discussion on new testing strategies began after the publication of the 2007 NRC report (see presentation to May 2008 PPDC meeting, accessible at
http://www.epa.gov/oppfead1/cb/ppdc/2008/may2008/session1.pdf.
The PPDC 21st Century Toxicology/New Integrated Testing Strategies Workgroup was empanelled by April 2009 and is now working with the Program to develop and implement new approaches. The relevant presentation to the full PPDC is available at
http://www.epa.gov/oppfead1/cb/ppdc/2009/apr2009/session1.pdf.
OPP also has a webpage on its website entitled "Strategic Direction for New Pesticide Testing and Assessment Approaches" (available at
http://www.epa.gov/pesticides/science/testing-assessment.html).
OPP's efforts are accessible and should be exploited (in the positive sense of the word). The Senior Science Advisor to the Office Director should be consulted about collaboration. There is lots of potential for resource-sharing, outside feedback and faster times to the finish line.

The third, and lowest, level of resource commitment with the shortest timeframe focuses on review and potential revision of ALL of the study-specific sections to assess their currency. This task should be viewed as an interim, but necessary measure, given the longer time it will take to carry out either of the two options described above. It should begin immediately. Anything cited as being in the "will-be added" group needs to be added ASAP. The stated preference for use of protocols consistent with OECD GLs/study designs should be retained (or OPPTS or ICH GLs, if no OECD GL exists). These sets of guidelines have been subjected to intensive expert input and peer review.

This approach is also consistent with EFSA's philosophy. The guidance should continue to acknowledge the possibility that a variation in study design may be more suitable in a specific instance, but that it is the responsibility of the petitioner, not the Agency, to make the case. If there is internal agency disagreement with some aspect of the OECD/EPA/EFSA guidelines, then the Agency must make the scientific and policy case for the modification(s). Ask (and, answer) the question as to whether or not any additional (whole) animal studies should be added to the list, such as developmental neurotoxicity, *in vivo* components of the Endocrine Disruptor Screening Program, allergenicity. Also, is the agency ready to sanction inclusion of specific validated *in vitro* tests as companions to, or substitutes for, traditional/historical whole animal studies? If so, which ones, when and how? NIEHS's NICEATM maintains on its ICCVAM webpage (http://iccvam.niehs.nih.gov/) a "library"of all tests submitted for validation, including those which have completed the validation process domestically. ECVAM does the same for efforts undertaken in Europe. (http://ihcp.jrc.ec.europa.eu/our_labs/eurl-ecvam)

IV.C.1. Short-Term Tests for Genetic Toxicity

CFSAN/OFAS currently recommends a genotoxicity test battery for food ingredients whose cumulative estimated daily intake exceeds 50 ppb in the diet (150 µg per person per day) consisting of: a test for gene mutations in bacteria *and* an *in vitro* test with cytogenetic evaluation of chromosomal damage using mammalian cells *or* an *in vitro* mouse lymphoma thymidine kinase$^{+/-}$ gene mutation assay (the mouse lymphoma assay is preferred) *and* an *in vivo* test for chromosomal damage using mammalian hematopoietic cells.

This section should be reviewed to assure that the protocols described are consistent with the most recent OECD version, if the decision is made to continue to employ this four-test menu.

However, it might be appropriate to include alternative options for satisfying components of this data requirement. OECD has issued two new guidelines (GL 487- In Vitro Mammalian Cell Micronucleus Test (July 2010) and GL 488- Transgenic Rodent Somatic and Germ Cell Gene Mutation Assays (July 2011)) since it did the 1997 update of the set in the current menu.

Another approach to consider would be to incorporate the integration of the cytogenetic tests into repeated dose (rodent) toxicity studies to satisfy the *in vivo* cytogenetic data requirement. This procedure has been discussed and internationally accepted as noted in papers by the International Workshop on Genotoxicity Testing (Rothfuss et al, 2011) and the International Committee for Harmonization (ICH) for pharmaceuticals. The ICH harmonized guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use S2(R1) (2011) describes how it can be integrated into repeated dose rodent studies. There would be efficiencies gained in that fewer tests would need to be done, and fewer animals would be used.

IV C 2. Acute Oral Toxicity Tests

The discussion in this section should be revised to exclude any advice related to the now-out-of-favor LD_{50} study-other than not to do it. OECD's long-standing, traditional LD_{50} study was deleted in 2002. Two new guidelines have been added to the OECD arsenal and accepted via ICCVAM (GL 423-Acute Oral Toxicity-Acute Toxic Class Method and GL425-Acute Oral Toxicity-Up-and down method). If FDA has not already issued an opinion on whether or not these 'new' GLs can be used, they should do so ASAP.

IV.C.3.a. Short-Term Toxicity Studies with Rodents

The OECD guideline 407 repeated dose 28-day oral study in rodents was updated in 2008. This section should be revised, as necessary, to reflect those updates.

IV.C.4.a. Subchronic Toxicity Studies with Rodents

No specific changes recommended at this time. It is adequately consistent with the current OECD guideline 408 issued in 1998 and other prevailing scientific opinion.

IV.C.4.b. Subchronic Toxicity Studies with Non-Rodents

No specific changes recommended at this time. It is adequately consistent with the current OECD guideline 409 issued in 1998 and other prevailing scientific opinion.

IV.C.5.a. Chronic Toxicity Studies with Rodents

In 2009, OECD issued a revised TG 452-chronic study in rodents in parallel with revisions to its TG 451-Carcinogenicity Studies and TG 453-Combined Chronic Toxicity/ Carcinogenicity studies. This action was taken, in part, with the objective of obtaining additional information from the animals used in the study and providing further detail on dose selection. These revisions also were considered in order to reflect recent developments in the field of animal welfare and regulatory requirements.

The protocols described in the current Redbook for these three studies should be reviewed and revised, as appropriate, to reflect the changes made in the OECD guidelines.

IV.C.5.b. One-Year Toxicity Studies with Non-Rodents

CFSAN/OFAS should consider dropping this guideline altogether, as has EPA and other regulatory authorities. Analyses by scientists in OPP as well as others at ZEBET (the national centre for alternatives in Germany at the BfR (Federal Institute for Risk Assessment) have concluded that little information of value is gained from the results of 1-year studies in dogs over that available from the subchronic study.

Dellarco, et al (2010) describes a 2005 "retrospective analysis of results from 13-week and 1-year dog studies for 110 conventional pesticide chemicals, representing more than 50 classes of pesticides. The data were evaluated to determine if the 13-week dog study, in addition to the long-term studies in two rodent species (mice and rats), were sufficient for the identification of no observed adverse effect levels (NOAELs) and

lowest observed adverse effect levels (LOAELs) for the derivation of chronic reference doses (RfD). Only pesticides with adequate 13-week and 1-year duration studies were included in the present evaluation. Toxicity endpoints and dose-response data from 13-week and 1-year studies were compared. The analysis showed that 70 of the 110 pesticides had similar critical effects regardless of duration and had NOAELs and LOAELs within a difference of 1.5-fold of each other. For the remaining 40 pesticides, 31 had lower NOAELs and LOAELs in the 1-year study, primarily due to dose selection and spacing. In only 2% of the cases, were additional toxic effects identified in the 1-year study that were not observed in the 13-week study and/or in the rodent studies. In 8% of the cases, the 1-year dog had a lower NOAEL and/or LOAEL than the 13-week study, but there would have been no regulatory impact if the 1-year dog study had not been performed because adequate data were available from the other required studies. A dog toxicity study beyond 13-weeks does not have significant impact on the derivation of a chronic RfD for pesticide risk assessment." [The detailed paper entitled "A Comparison of the Results of Studies on Pesticides from 12- or 24-Month Dog Studies with Dog Studies of Shorter Duration" was authored by Karl P. Baetcke, Whang Phang, and Vicki Dellarco and presented for external peer review to the FIFRA Scientific Advisory Panel (SAP) on May 5-6, 2005. It is available on the SAP website at http://www.epa.gov/scipoly/sap/meetings/2005/050505_mtg.htm#materials].

The ZEBET analysis (Box and Speilmann, 2005) focuses on the results from a retrospective study analyzing data on 216 pesticides kept on record by the Bundesinstitut für Risikobewertung, BfR (German Federal Institute for Risk Assessment), the competent regulatory authority in Germany. The study was conducted by BfR scientists. They concluded that chronic studies are of limited value since they only provide essential information that cannot be obtained in subchronic studies in about 5% of cases.

These conclusions are supported by other retrospective analyses using data on pharmaceutical drugs carried out in the context of the International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH). Over 90% of drugs elicited no toxic symptoms in 12-month studies in dogs in addition to those that had been recorded previously in studies conducted for 90 or 180 days in dogs and rats. In light of their analysis, the ICH harmonized guideline on the Duration of Chronic Toxicity Testing in Animals (Rodent and Nonrodent) (S4), is defining studies of 6 months' duration in rodents and 9 months' duration in non-rodent as "chronic," noting that in the EU, studies of 6 months' duration in non-rodents are acceptable.

IV.C.6. Carcinogenicity Studies with Rodents

See IV.C.5.a. discussion.

IV.C.7. Combined Chronic Toxicity/Carcinogenicity Studies with Rodents

See IV.C.5.a. discussion

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

See IV.C.5.a. discussion

IV.C.9.a. Guidelines for Reproduction Studies

A review and possible revision of this guideline is warranted as OECD issued an update of its 2-generation reproduction study in January 2001 (TG 416).

CFSAN/OFAS also may wish to consider replacing the 2-generation study requirement with the (life stage F_1) extended one-generation study described in TG 443 which was adopted in October 2012. This protocol is based on the ILSI-HESI ACSA project proposal as published in Cooper et al., 2006 (and, described above).

IV.C.9.b. Guidelines for Developmental Toxicity Studies

A review and possible revision of this guideline is warranted as OECD issued an update of its prenatal developmental toxicity study in January 2001 (TG 414).

IV.C.10. Neurotoxicity Studies

A review and possible revision of this guideline may be warranted to determine consistency with OECD TG 424 or other consensus GLs on this endpoint. Review of the OECD Guidance Document for Neurotoxicity Testing issued in November 2004 is also recommended.

[New] IV. C. 11 Metabolism and Pharmacokinetic Studies

This protocol currently must be accessed through the 1993 version of the Redbook. As recommended above, it should be added to an updated Chapter IV. This is one of the two test protocols yet to be updated by CFSAN. While this older protocol is not contradictory to more updated ones, it should be reviewed and possibly revised. OECD TG 417-Toxicokinetics was originally adopted in 1984. It was updated in 2010. It may provide some new and useful insights.

[New] IV.C.12 Immunotoxicity

While OECD does not have a stand-alone guideline for immunotoxicity, EPA OPPTS does (Health Effects Test Guidelines OPPTS 870.7800 Immunotoxicity). While the EPA OPPTS guideline does not include the discussion of the decision logic on which studies should be done when based upon the Concern Level, etc., it does include greater detail on study conduct. CFSAN/OFAS should consider including these procedural details when updating this guideline. Also, the literature should be searched to identify potential *in vitro* or new less complex *in vivo* study designs that could substitute for, or complement, the standard tests.

[New] *IV.C. 13 Allergenicity*

While this endpoint is more likely to be associated with exposure to proteins, and thus, more aligned with issues related to biotechnology and genetically-engineered foods, there may be a place for including testing protocols for it within the Redbook--IF the agency decides that it wishes to have the Redbook cover testing and assessment principles for food ingredients beyond the current categories.

Neither OECD nor EPA has guidelines for this endpoint, but there are other parties who have been studying this issue for years and have developed approaches to its testing. EFSA and FAO/WHO both have written extensively on this topic. Furthermore, a joint FAO/WHO committee has proposed a decision tree approach to the evaluation of the allergenicity of genetically modified foods (FAO/WHO, 2002). This approach was based upon one developed earlier by an expert committee supported by the International Food Biotechnology Council and the Allergy and Immunology Institute of the International Life Sciences Institute (IFBC/ILSI) (Metcalfe et al., 1996).

Summary of Recommendations:

1. **Keep the Redbook--**
    a. **As a single, easily-accessible and searchable document on the FDA/Food website, but expand it to include a chapter on Interpretative Guidance and, elsewhere, insert appropriate information on testing and interpretation of data on additional types of food (GE, medical foods, infant formula, dietary supplements allergens) into the relevant sections of the document.**
    b. **Retain focus of Redbook only on U.S. regulatory program; do not dilute impact by attempting to describe the international situation as well.**
2. **Revise Redbook to:**
    a. **Combine current Chapters IV and V**
    b. **Add new Chapter on Interpretative Guidance**
3. **Exploit the resources of EPA OPP, EFSA, OECD, WHO, FAO and ICH**
    a. **Adapt and adopt their existing guidance on relevant topics**
    b. **Continue (EFSA) and establish (EPA) staff exchanges**
    c. **Establish a workshare program with EFSA**
    d. **Explore collaboration with parallel bureaucracy in Canadian government**
4. **Make better, more frequent, use of the Food Advisory Committee to help develop updated/new guidance and, also, serve as external peer reviewers.**
5. **Explore other collaborative mechanisms for developing updated/new guidance, using the Food Advisory Committee only for external peer review in these cases**
6. **Play a more active role in Tox21 activities. Start by nominating direct food additives, including some GRAS substance such as diacetyl, for screening (e.g., those listed on EAFUS).**
7. **Complete templates for all study types-**
    a. **Make them mandatory as part of data submission**
    b. **Implement a SEND program.**
8. **Consider revising the current testing paradigm, with the long-term goal of replacing all whole animal testing with other tools. (See Item 5. Detailed assessment of scientific currency of existing Chapters IV and V for specifics).**

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