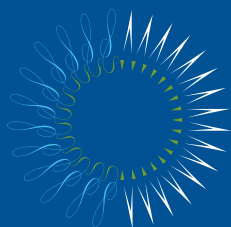


# WORKSHOP ON ENHANCING FDA'S EVALUATION OF SCIENCE TO ENSURE CHEMICALS ADDED TO HUMAN FOOD ARE SAFE

*The Pew Charitable Trusts*

*Washington, DC*

*April 5-6, 2011*



**PEW**  
HEALTH GROUP



nature

Dear workshop participants,

Welcome to the expert workshop titled *Enhancing FDA's Evaluation of Science to Ensure Chemicals Added to Human Food are Safe* at the Pew Conference Center in Washington, DC. The workshop is cosponsored by the journal *Nature*, the Institute of Food Technologists (IFT) and the Pew Health Group, with planning support from the U.S. Food and Drug Administration (FDA) and the National Institute of Environmental Health Sciences (NIEHS).

You are joining experts from government, industry, academia and public interest organizations to participate in a facilitated discussion regarding FDA's evaluation of scientific studies on substances intentionally added to human food and factors that enhance the usefulness of FDA's risk assessment and risk management decisions. These issues were brought to the forefront by leading scientific journals (including *Environmental Health Perspectives* and *Nature*) and by the Bipartisan Policy Center in its report *Improving the Use of Science in Regulatory Policy*. In addition, the workshop will contribute to FDA's *Advancing Regulatory Science Initiative*, specifically the priority to better evaluate the safety of food additives by adapting science at FDA to meet the challenges of increasingly complex issues and products. Finally, new developments in science such as Tox21 and nanomaterials present opportunities to enhance the scientific basis for making regulatory decisions.

We are not seeking to reach a consensus at this workshop or to dwell on controversies involving specific chemicals. Rather, we want to advance the discussion, develop a shared understanding of the current system FDA uses to assess the safety of chemicals added to human food, and explore opportunities to strengthen that system in a manner consistent with FDA's regulatory science initiative. For the workshop to succeed, you must share your ideas and experiences and listen openly to your peers, especially during small group discussions. To help, experienced facilitators will support the workshop as well as each small group to ensure that everyone is heard.

We anticipate publishing a summary of the workshop, although no comments will be attributed to any specific individual. To ensure that it is fair and accurate, we will share a draft of the summary with you about eight weeks after the workshop so you can review and comment on it. Separately, the Pew Health Group plans to develop recommendations based on the discussions and will share these with you as a draft for comment before they are released. If you have any comments or questions, please contact Tom Neltner of the Pew Health Group at [tneltner@pewtrusts.org](mailto:tneltner@pewtrusts.org).

We want to extend a special thanks to FDA and NIEHS for their active participation in planning this conference. As you will see in the workshop, their guidance improved the agenda and the materials!

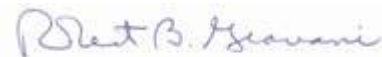
Sincerely,



Erik Olson  
Director, Food Programs  
Pew Health Group



Philip Campbell  
Editor-in-Chief  
*Nature*



Robert B. Gravani  
President  
Institute of Food Technologists

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## WORKSHOP AGENDA

All sessions are in the North and South America rooms on the second floor, except as noted.

Tuesday, April 5, 2011

- 8:30 a.m.     **Continental Breakfast**
- 9:00           **Welcome and Workshop Overview**  
 Moderated by Tom Neltner of Pew Health Group and Abby Dilley of RESOLVE
- Shelley Hearne, Managing Director, Pew Health Group
  - Joe Hotchkiss, Fellow, Institute of Food Technologists
  - Linda Birnbaum, Director, National Institute of Environmental Health Sciences
  - Mike Taylor, Deputy Commissioner for Food, Food and Drug Administration
- 10:10          **Introduction to Small Group Discussions for Round 1** – See page 15  
 Moderated by Abby Dilley of RESOLVE
- 10:30          **Break**
- 10:45          **Small Group Discussions – Round 1: Considerations in Identifying and Validating Endpoints, Including Adverse Effects**
- **Endocrine Disruption** – Oklahoma Room on third floor
    - Moderator: Tom Zoeller                                 Facilitator: Abby Dilley
    - FDA Representative: Kristi Jacobs
  - **Behavioral Impacts** – New Mexico Room on third floor
    - Moderator: Routt Reigart                                 Facilitator: Robin Roberts
    - FDA Representative: Jason Aungst
  - **Nanomaterial Characterization** – Hawaii Room on third floor
    - Moderator: Stephen Roberts                                 Facilitator: Jen Peyser
    - FDA Representatives: Scott Thurmond and Greg Noonan
  - **Tox21 & NHANES Screens** – European Union Room on second floor
    - Moderator: Gail McCarver                                 Facilitator: Dana Goodson
    - FDA Representatives: Suzanne Fitzpatrick and Gene Leclerc
- 12:00 p.m.     **Lunch**  
 Lunch will be provided in each small group discussion room to allow the discussions to continue with minimal disruption.
- 12:45          **Small Group Reports from Round 1**  
 Moderated by Abby Dilley of RESOLVE
- 1:45           **FDA's Safety Assessment Process and Use of Computational Toxicology**  
 Mitchell Cheeseman, Acting Director, U.S. FDA, OFAS
- 2:10           **Introduction to Small Group Discussions for Round 2** – See page 26  
 Moderated by Abby Dilley of RESOLVE
- 2:15           **Break**
- 2:30           **Small Group Discussions – Round 2: Evaluating Study Design and Data for Regulatory Decisions**

- **Dose Response** – Hawaii Room on third floor
  - Moderator: Tracey Woodruff                      Facilitator: Abby Dilley
  - FDA Representatives: Michelle Twaroski and Ron Lorentzen
- **Transparency** – Oklahoma Room on third floor
  - Moderator: John Vandenberg      Facilitator: Jen Peyser
  - FDA Representatives: Kelly Randolph and Supratim Choudhuri
- **Study Reproducibility** – New Mexico Room on third floor
  - Moderator: Joe Hotchkiss                      Facilitator: Robin Roberts
  - FDA Representative: David Hattan
- **Use of Hypothesis-based Research** – European Union Room on second floor
  - Moderator: Glenn Sipes                      Facilitator: Dana Goodson
  - FDA Representatives: Kristi Jacobs and Gene Leclerc

3:45            **Small Group Reports from Round 2**  
 Moderated by Abby Dilley of RESOLVE

4:45            **Beyond FDA: EFSA, JECFA and OECD**  
 Moderated by Vincent Hegarty, Michigan State University
 

- Jean-Lou Dorne, European Food Safety Authority, Emerging Risks Unit
- Angelika Tritscher, WHO Joint Secretary to JECFA and JMPR

5:15            **Wrap-up of Day 1 / Preview of Day 2**  
 Moderated by Abby Dilley, RESOLVE
 

- Tom Neltner, Pew Health Group
- Maricel Maffini, Pew Health Group
- Will Fisher, Institute of Food Technologists

5:30            **Adjourn Day 1**

5:30            **Reception Hosted by Pew Health Group** – Outside North America Room

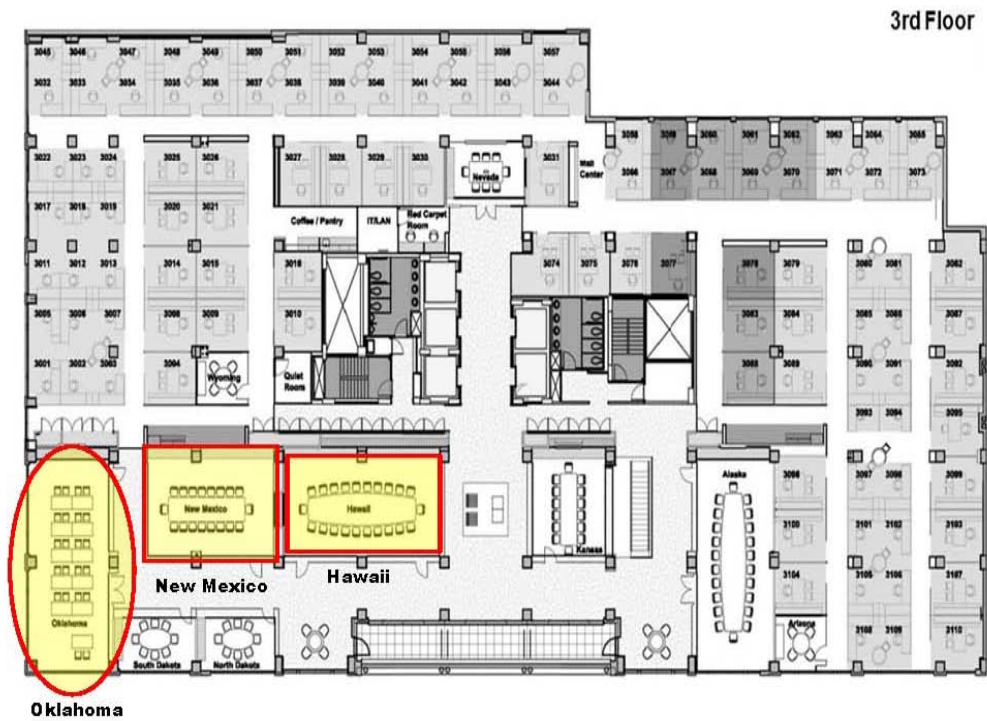
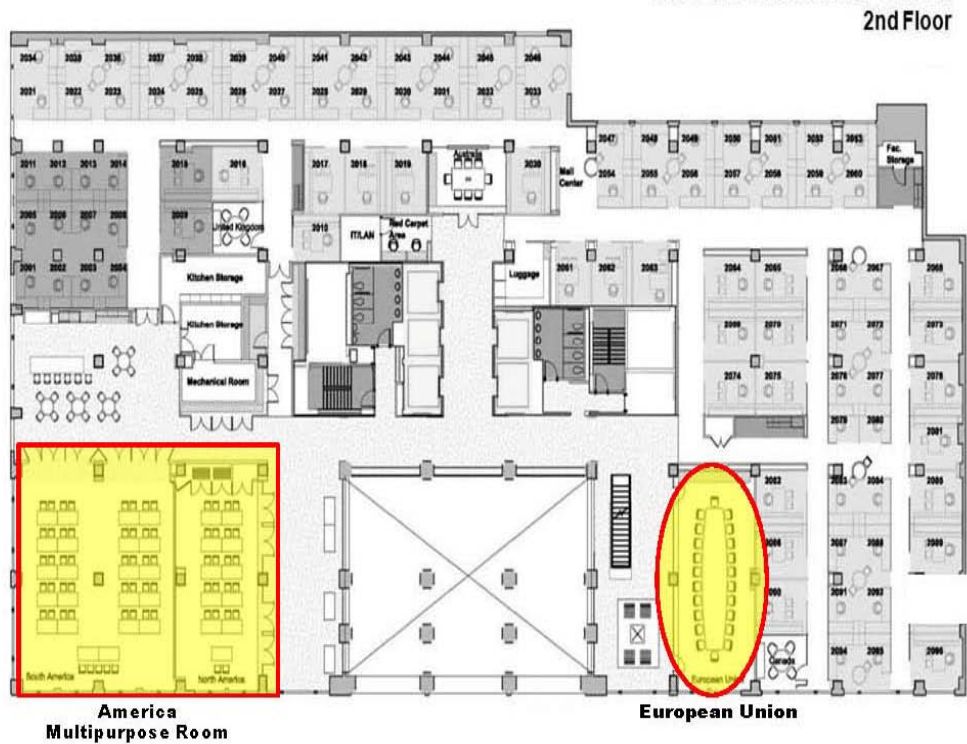
6:30            **Adjourn Reception**

Wednesday, April 6, 2011

- 8:30 a.m.      **Continental Breakfast**
- 9:00            **Overview of Day 2 Agenda**  
Moderated by Tom Neltner of Pew Health Group and Abby Dilley of RESOLVE
- 9:10            **Alternative Methods**  
Moderated by Maricel Maffini of Pew Health Group and Abby Dilley of RESOLVE
- Rodger Curren, President, Institute for *In Vitro* Sciences
  - Panel:
    - Leon Bruner, Chief Science Officer, Grocery Manufacturers Association
    - Jennifer Sass, Senior Scientist, Natural Resources Defense Council
    - Raymond Tice, Chief, NTP Biomolecular Screening Branch, NIEHS, and member of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)
- 10:15           **Introduction to Small Group Discussions for Round 3** – See page 32  
Moderated by Abby Dilley of RESOLVE
- 10:30           **Break**
- 10:45           **Small Group Discussions – Round 3: Developing and Reviewing Test Guidelines**
- **Developing Test Guidelines for Review A** – European Union Room on second floor
    - Moderator: Glenn Sipes                      Facilitator: Dana Goodson
    - FDA Representative: David Hattan
  - **Developing Test Guidelines for Review B** – Hawaii Room on third floor
    - Moderator: Stephen Roberts                      Facilitator: Jen Peyser
    - FDA Representative: Jason Aungst
  - **Reviewing and Approving Test Guidelines C** – Oklahoma Room on third floor
    - Moderator: Joe Hotchkiss                      Facilitator: Abby Dilley
    - FDA Representative: Supratim Choudhuri
  - **Reviewing and Approving Test Guidelines D** – New Mexico Room on third floor
    - Moderator: Gail McCarver                      Facilitator: Robin Roberts
    - FDA Representative: Michelle Twaroski
- 12:00 p.m.      **Lunch**  
Lunch will be provided outside of the North America Room. You may use any other room to eat, including the small group discussion rooms.
- 12:45           **Small Group Reports from Round 3**  
Moderated by Abby Dilley of RESOLVE
- 1:45            **Introduction to Small Group Discussions for Round 4** – See page 38
- 1:50            **Break**

- 2:00      **Small Group Discussions – Round 4: Identifying and Evaluating Potential Solutions**
- **Improving Hypothesis-based Research** – Hawaii Room on third floor
    - Moderator / Facilitator: Dana Goodson
    - FDA Representatives: Kristi Jacobs and Gene Leclerc
  - **Improving Guideline-based Studies** – New Mexico Room on third floor
    - Moderator / Facilitator: Robin Roberts
    - FDA Representative: David Hattan
  - **Refining the Regulatory Decision-making Process** – Oklahoma Room on third floor
    - Moderator / Facilitator: Jen Peyser
    - FDA Representatives: Suzanne Fitzpatrick and Michelle Twaroski
- 3:00      **Small Group Reports from Round 4**  
Moderated by Abby Dilley, RESOLVE
- 4:00      **Review and Next Steps**  
Moderated by Abby Dilley, RESOLVE
- Tom Neltner, Pew Health Group
  - Maricel Maffini, Pew Health Group
  - Will Fisher, Institute of Food Technologists
- 5:00      **Adjourn**

## CONFERENCE CENTER FLOOR PLAN





## WORKSHOP OVERVIEW

The primary objective for this workshop is to gather insight and guidance from national and international thought leaders on the best methods to enhance the Food and Drug Administration's (FDA's) evaluation of science to ensure that chemicals added to human food are safe. While the goal is not to reach consensus, identifying and evaluating potential ideas to enhance the development and review of the scientific basis of FDA's assessment of chemicals added, directly or indirectly, to food are priorities.

Over the past 50 years, FDA has developed a complex regulatory program to ensure the safety of chemicals added to food based on the Food Additives Amendment of 1958. This law and later amendments established a number of categories of additives with specific requirements for each. FDA must give premarket approval for all chemical uses defined as food additives (including food contact substances which are food additives), color additives and animal drugs. The Environmental Protection Agency (EPA) must do the same for pesticide residues. Certain chemical uses expressly approved by FDA or the U.S. Department of Agriculture before 1958 were grandfathered as "prior-sanctioned substances." There are two remaining categories that do not require agency premarket approval: dietary supplements and uses of chemicals (other than pesticides, color additives or animal drugs) determined by the food manufacturer to be "generally recognized as safe" or "GRAS."

For food additives, food contact substances, color additives and GRAS substances, safety means that there is reasonable certainty in the minds of competent scientists that the chemical is not harmful under the intended conditions of use. A determination that a chemical is GRAS may be based on either scientific procedures or the common use in food prior to 1958. While an expert panel is not required, there must be evidence that the GRAS substance's safety is common knowledge throughout the scientific community who know about the safety of chemicals directly or indirectly added to food. If using scientific procedures, the determination must be based only on published studies, though they may be corroborated by unpublished studies and other information. If a food manufacturer wants to rely only on unpublished studies, the chemical use cannot be GRAS. To rely on unpublished data, the firm must submit a food additive petition or food contact notification to FDA and secure the agency's premarket approval.

Since food manufacturers can add GRAS substances to food without notifying FDA of their determination, FDA developed regulations to control the basis of these decisions defining the scientific procedures that firms must follow. It also created a program to encourage food manufacturers to voluntarily notify FDA of their determinations.

The result is a regulatory program where scientific decisions on safety are made by FDA or food manufacturers, or both depending on the situation. It also provides an incentive for scientific studies to be published, because food manufacturers can more quickly get a product on the market if a chemical's use directly in food is GRAS.

As the regulatory program developed, toxicology grew into a large and sophisticated field of science to assess the impact of chemicals on human health. In response to concerns about significant problems at private contract testing facilities and to improve transparency and reproducibility of results, FDA adopted a Good Laboratory Practices (GLP) rule in 1978 setting rigorous standards for the documentation and management of animal studies for use in regulatory decision making. To provide some structure and standardization to the assessment, FDA publishes its "Toxicological Principles for the Safety Assessment of Food Ingredients" guidance, commonly known as the "Redbook" (not to be confused with other Redbooks such as the National Research Council of the National Academies' Redbook on risk assessment published in 1983).

In the Redbook, FDA essentially established the current system to conduct safety assessments to

- determine the need for toxicity studies
- design, conduct and report the results of toxicity studies
- conduct statistical analysis of data
- review the histological data
- submit information to FDA as part of its safety assessment of food ingredients.

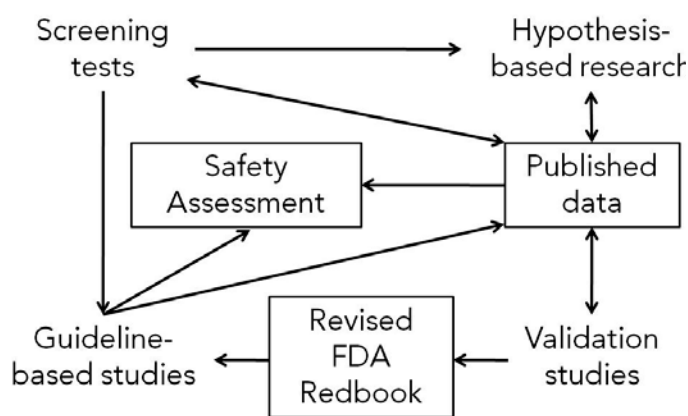
In the past few years, a controversy emerged during scientific discussions regarding the safety of bisphenol A as a food contact substance in polycarbonate containers and as part of epoxy linings in metal food containers. Several academic researchers maintained that endocrine disruption studies provided sufficient evidence for FDA to determine that there is no longer a reasonable certainty in the minds of competent scientists that the substance is not harmful – the standard of safety required for both food additives and GRAS substances. These scientists believed FDA favored good laboratory practice (GLP) studies using standardized protocols consistent with the Redbook over peer-reviewed studies using the latest methodologies and science published in respected journals by academics. Industry representatives defended the system explaining the need for quality assurance, transparency and reproducibility, and raising questions about the limitations of peer review. An editorial published in *Nature* called for regulators to take into account new methods as rapidly as they can be validated. The journal published on-line a response by two FDA food additive scientists who explained the role of GLP in improving study reliability, that safety regulation depends on a scientific consensus, and the importance of study design and considering dose and exposure in assessing and managing risk. In addition, they stated their view that experimental—particularly academic—laboratories often lack the financial and physical resources to perform experiments needed to support regulatory decision making on safety.

Against this backdrop, the Pew Health Group decided to convene this workshop to foster a common understanding of the system for determining the safety of chemicals added to food, address emerging issues and identify opportunities to enhance it. The Institute of Food Technologists—the nation's professional association for food experts—and the *Nature* journal agreed to cosponsor the event. FDA and NIEHS provided essential planning support.

While the workshop will deal with all aspects of safety assessment, this event will focus on the evaluation of potential human health hazards posed by chemicals added directly or indirectly to human food. A later workshop will focus in more detail on exposure assessment—the other half of a risk assessment. While important to any decision, to help make the discussions more productive we narrowed the workshop's focus to exclude

- pet food or animal feed
- animal drugs
- pesticide residues
- contaminants
- environmental impacts.

FIGURE 1  
CURRENT SYSTEM TO DEVELOP THE TOXICOLOGY TO  
MAKE SAFETY ASSESSMENTS FOR HUMAN FOOD



The Pew Health Group developed a framework, described below and in Figure 1, to explain the current system FDA uses to develop the toxicological studies needed to determine whether food additives are safe. Like all frameworks, it simplifies the process and leaves out various nuances.

In general, there are four types of toxicological studies represented by the four corners of Figure 1. Each type serves a distinct role in the system:

1. Screening tests identify potential human health hazards from chemicals.
2. Hypothesis-based research explores whether potential human health hazards exist and determines their significance.
3. Validation studies take the methods and protocols from hypothesis-based research to evaluate whether they reproducibly measure adverse effects with an array of chemicals so they can be incorporated into test guidelines such as the Redbook.
4. Guideline-based studies use validated protocols described in the Redbook to assess the hazards in a standardized manner.

Table 1 (see page 11) provides more detailed descriptions of each term.

While the results of all types of studies may be published, the majority of the published studies, especially in peer-reviewed journals, are hypothesis-based research by academic researchers.

Safety assessments rely on both guideline-based studies and hypothesis-based research. Typically, the results of screening tests and validation studies are not pivotal for the final safety assessment since they are not intended to identify adverse effects. If the study is pivotal to a GRAS determination, then it must be published in some form.

With this common understanding of the system, the workshop's goal is for participants to engage in robust discussion of the four key issues to provide potential opportunities for improvement in the generation and evaluation of scientific information. The areas are

1. What are the considerations in identifying and validating adverse health effects?
2. What are the best methods to evaluate study designs and data for regulatory decisions?
3. How should validation studies be developed and test guidelines be reviewed?
4. What problems have been identified with our current regulatory process, and what potential solutions should be considered?

**TABLE 1**  
**TERMS AND DEFINITIONS**

For purposes of this workshop, we are defining the terms as follows:

- **Generally Recognized as Safe:** A substance generally recognized among qualified experts as having been adequately shown to be safe under the conditions of its intended use.
- **Guideline-based studies:** Studies that use agency-approved protocols or test guidelines to evaluate the potential hazards of a substance. These studies are commonly done in laboratories that specialize in performing the protocols using Good Laboratory Practice for the purposes of supporting a regulatory safety determination.
- **Hypothesis-based research:** Research that begins with an investigator's original hypothesis and consists of experimental protocols designed by the investigator to test the hypothesis. This research is commonly done in an academic setting.
- **Published data:** Study or research results published in peer-reviewed literature or in some other publicly accessible form.
- **Revised FDA Redbook:** FDA's "Toxicological Principles for the Safety Assessment of Food Ingredients" guidance recommending test guidelines for toxicology studies and describing under what situations they should be performed.
- **Safe:** There is reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use.
- **Screening tests:** Tests designed to identify potential hazards or actual exposures. Though these tests generally are not sufficient to identify adverse effects, they may serve as the basis for hypothesis-based research and guideline-based studies.
- **Validation studies:** Studies to assess whether results are reproducible in different laboratories at different times by different investigators and whether observed effects are adverse or can predict adverse effects.

## PARTICIPANT EXPECTATIONS, GROUND RULES AND ROLES

To create an atmosphere of open dialogue and maximize participation in the generation of creative and constructive ideas, we have consulted a number of stakeholders, organized the agenda, developed and provided background documents and materials, engaged professional facilitators and tapped several key people to play specific roles.

Proceedings from the workshop will be compiled into a workshop summary and submitted for publication. The workshop summary will capture the substance of the ideas with no attribution. All workshop participants will have the opportunity to review and comment on a draft of the article. The Pew Health Group plans to develop recommendations for improvements to the regulatory review process, provide these to FDA and submit them for publication.

The dialogue and generation of ideas will depend on the full participation of all workshop attendees. Our *expectation* is that *all participants* will come fully prepared, having read the materials and participated in or reviewed the webinar, and will contribute to the discussions. We also ask that participants in the small group sessions stay in the session for the full time and not move from group to group. The generation and development of ideas will be enhanced if the conversation is sustained among all participants throughout the session.

As you will see from the participant list, we have a large, diverse group, with representation of different areas of expertise, responsibilities and perspectives. To benefit from these qualities, it is essential to establish ground rules and designate specific responsibilities and roles.

Our *ground rules* to encourage productive dialogue in this workshop include the following:

- **Full participation**
  - All participants should engage in the discussion.
  - Keep comments concise to allow time for everyone to participate.
  - Carry out one conversation in the room so that everyone can hear and distractions are limited.
- **Constructive dialogue**
  - Dialogue involves listening as well as talking.
  - Shape comments and ideas to advance the discussions.
  - Stay on task and on topic.
- **Respectful engagement**
  - While strong opinions are certainly expected and appropriate, they can be best heard and discussed in a respectful manner.
  - Participants are asked to respect different points of view and, when disagreeing, disagree without being disagreeable.

All participants are asked to abide by the ground rules. If other or additional ground rules would be helpful, please suggest them.

In addition to ground rules, various participants will serve in *specific roles* to support and document the discussion.

*Facilitators:* Facilitators will be tasked with encouraging constructive engagement and dialogue. The facilitator's general role is to

- get people talking and encourage broad participation
- stay impartial and be fair to all people and opinions
- help participants understand each other and be understood
- be an active listener

- move the discussion along and keep it on track
- help identify common themes and areas of agreement
- help a group capture and remember its discussion
- help a group identify next steps.

In the plenary sessions, the facilitators will

- assist the moderators of each session
- keep speakers on time
- help facilitate the question-and-answer sessions
- provide explanations of transitions to next agenda items
- give instructions for work group sessions.

In the small discussion groups, the facilitators will

- lead the discussions through a list of questions and topics
- keep discussions productive and moving forward
- clarify points and themes
- capture some of the conversation on flip charts
- help the groups summarize and organize the moderator's report to the full group in the plenary sessions.

In the plenary sessions, a *moderator* will help the facilitator lead the session, frame its purpose as part of the workshop goals, introduce speakers and organize the discussion.

In the small group discussion sessions, each small group will have representatives from Pew Health's Group's team of expert advisors to serve as *moderators* who will help focus the substantive deliberations by assisting with the framing of the issues—not driving the discussions but providing information and context. The FDA representatives will be available to provide information on FDA's current processes as needed.

Each small group also will have *moderators* who provide the highlights from the small group discussions to the plenary participants. While the large group sessions will be recorded electronically, the small group sessions will not.

Also in the small group discussion sessions, *note takers* will capture the discussion in writing, and these documents will be used to formulate the meeting summary. In the meeting summary, comments will not be attributed to specific individuals or organizations.

## OVERVIEW OF SMALL GROUP DISCUSSION PROCESS

The workshop's plenary sessions provide an excellent opportunity to introduce topics and summarize discussions. But with more than 80 participants, the plenary sessions are not conducive to an open and thoughtful discussion. For that reason, we are providing participants with four rounds of small group discussion forums designed to take us stepwise through specific issues. After each round, representatives of the groups will summarize the discussions in a plenary session and take questions from participants.

Each small group should consist of 15 to 20 people and include the following:

- session moderator familiar with the specific issue to introduce the topic selected from the Pew Health Group's team of expert advisors
- facilitator to lead the discussion
- scientist from FDA
- note taker to record the key points on a flip chart.

While we will record the plenary sessions in order to have an accurate summary of the presentations, we will not record the small group discussions. We want an open and thoughtful discussion, and that requires a chance to explore new ideas and issues. Participants in the session can elaborate on key points or clarify as needed. The session moderator or a designated group member will report on the discussions.

We ask that you stay in your assigned small group discussion. If you need to leave, please do not go to another session, since we want to avoid the disruption that occurs when people come in and out of the discussion.

There will be four rounds of small group discussions, two on each day. We will have four small group discussions in the first three rounds and three in the final round. The four rounds are

1. considerations in identifying and validating endpoints, including adverse effects
2. evaluating study design and data for regulatory decisions
3. developing and reviewing test guidelines
4. identifying and evaluating potential solutions.

In essence, we will start by looking at detailed aspects of toxicological studies. We then will expand the focus in a stepwise manner toward a broader understanding of the system FDA uses to assess the science to ensure that chemicals added to human food are safe.

To help you prepare, as well as to serve as a reference during the workshop, we are providing you with a short description of the topics to be discussed in each round and then a more detailed explanation of each small group discussion topic. Please look over the information and the assignments before the sessions.

## SMALL GROUP DISCUSSIONS – ROUND 1: CONSIDERATIONS IN IDENTIFYING AND VALIDATING ENDPOINTS, INCLUDING ADVERSE EFFECTS

Round 1 of the small group discussions will focus on considerations in identifying and validating relevant endpoints, including adverse effects. In essence, we are asking the following question: **What should guideline-based, nonclinical studies measure to assess the human health effects of a substance?**

To help focus the discussion, we selected four hot topics designed to engage participants. They are

- endocrine disruption
- behavioral impacts
- nanomaterial characterization
- Tox21 and NHANES screens.

At first glance, you may notice that not all of these topics involve health effects. We have included an array of relevant topics, including health effects, characterization of a class of materials that may raise unique hazards, and methods used to screen for markers of exposure to highlight different aspects of the issue.

The discussion of endocrine disruption and behavioral impacts will focus on the contentious issue of whether or not endpoints with positive results in hypothesis-based research constitute or sufficiently predict adverse effects to justify incorporation into guideline-based studies. We selected these two topics because they represent distinct aspects of endpoint identification and validation and would allow us to address the underlying questions. Note that FDA does not have a definition of adverse effect related to chemicals added to food.

The discussion on nanomaterial characterization will look at a different issue: What is the substance being studied? Currently, guideline-based studies do not assess whether or how much of a substance is between 1 and 100 nanometers in a single dimension. Recent research into these nanoscale materials indicates that some substances exhibit unusual physical and chemical properties that may be important toxicologically.

The Tox21 and NHANES discussion will focus on the use of these screening tests as a trigger for more focused hypothesis-based research and, perhaps, guideline-based studies. Tox21 screens use *in vitro* methods to evaluate the impact of a wide array of chemicals and mixtures on cells. NHANES screens for human exposures by measuring chemicals in a large sample of the general population. In other words, Tox21 is a screen for a substance's potential hazard, and NHANES is a screen for human exposure. Both methods are important to understand the potential health risk posed by a substance. While a positive result in either screening system does not mean the result is an adverse effect, it does indicate the need for additional study that will lead to regulatory decisions.

**TABLE 2**  
**TERMS AND DEFINITIONS**

For purposes of this workshop, we are defining the terms as follows:

- **Hypothesis-based research:** Research that begins with an investigator's hypothesis and consists of experimental protocols designed by the investigator to test the hypothesis. This research is commonly done in an academic setting.
- **Guideline-based studies:** Studies that use agency-approved protocols or test guidelines to evaluate the potential hazards of a substance. These studies are commonly done in laboratories that specialize in performing the protocols using Good Laboratory Practice for purposes of supporting a regulatory safety determination.
- **Screening tests:** Tests designed to identify potential hazards or actual exposures. Though these tests generally are not sufficient to identify adverse effects, they may serve as the basis for hypothesis-based research and guideline-based studies.
- **Study validation:** Studies to assess whether results are reproducible in different laboratories at different times by different investigators and whether observed effects are adverse or can predict adverse effects.



By examining all three types of issues—adverse health effects, raw material characteristics and results of screening methods to conduct additional studies to identify adverse effects—we can ensure that nonclinical, guideline-based studies are more adequately designed and are more useful and relevant to human health.

## ROUND 1-A: ENDOCRINE DISRUPTION

- Room: Oklahoma Room on third floor
- Moderator: Tom Zoeller
- Facilitator: Abby Dilley
- FDA Representative: Kristi Jacobs

This small group discussion session will consider whether endocrine disruption represents an adverse effect that should be specifically measured and reported in nonclinical, guideline-based studies. If so, what types of endocrine disruptive effects should be considered?

For the purpose of this discussion, we are using EPA's definition of endocrine disruption: "a mode or mechanism of action potentially leading to other outcomes, for example carcinogenic, reproductive, or developmental effects, routinely considered in reaching regulatory decisions. Evidence of endocrine disruption alone can influence priority setting for further testing, and the assessment of the results of this testing could lead to regulatory action if adverse effects are shown to occur."

FDA makes safety determinations based on reasonable certainty of no harm considering probable consumption; cumulative effect (including pharmacologically related substances); and safety factors. Although the agency does not have a statutory or regulatory definition of "harm" or "adverse effect," it has more than 50 years of precedent as the basis for these decisions.

For the purpose of the discussion, we will use EPA's definition of adverse effect from its Integrated Risk Information System (IRIS) glossary: "a biochemical change, functional impairment, or pathologic lesion that affects the performance of the whole organism, or reduces an organism's ability to respond to an additional environmental challenge."

Although hormone disruption occurs at any age, it could have greater impact—including permanent impact on an individual's health—during critical periods such as gestation, infancy and puberty when the body is undergoing significant changes. We will focus the discussion on these developmental stages because of their sensitivity to hormonal perturbation.

While the issue of reliability and reproducibility in measurement of endocrine disruption in different laboratories is significant, for purposes of the discussion we assume that all assays can be replicated. We will discuss reproducibility in a later session.

The discussion group should report in the plenary session the participants' observations on the following questions:

1. Using endocrine disruption as a case example, what are the challenges and strengths of determining adverse effects?
2. Can effects that occur before the manifestation of overt adverse effects be used as early indicators of harm? What kinds of early indicators of harm have been associated with adverse effects? How can they be validated?
3. How important are critical periods of exposure and long-term effects, and how can these items be detected in the assay used?
4. Endocrine disruption affects many systems, including the reproductive system. Are endpoints other than reproductive toxicity adequately represented in the Redbook?

### BACKGROUND

Current protocols suggest that at least three doses of a substance are used for toxicity testing:

- A dose high enough to induce toxicity
- A dose low enough to not induce toxicity

- An intermediate dose high enough to induce effects that eventually may lead to adverse impacts, such as changes in enzyme levels or a slight decrease in body weight.

The selection of these doses allows the evaluation and reporting of irreversible, gross adverse effects on the study animals, and increases the likelihood of identifying the No Observed Adverse Effect Level (NOAEL).

Guideline-based, nonclinical studies do not require testing or assessment of changes in hormone function but assess only the overt manifestation of those changes. In addition, the current protocols do not require the animals to be exposed to chemicals at doses below the NOAEL or at specific times of development that hypothesis-based studies indicate may be significant.

The laboratory conducting the guideline-based study is not prohibited from assessing more sensitive potential endocrine disruption impacts in addition to the endpoints included in the protocol, but it is not required to do so under the current guidelines. Since the assessment involves more extensive testing and longer-term studies, the laboratory may require significantly more resources. Often no organization provides the laboratory with these resources.

## ROUND 1-B: BEHAVIORAL IMPACTS

- Room: New Mexico Room on third floor
- Moderator: Routt Reigart
- Facilitator: Robin Roberts
- FDA Representative: Jason Aungst

This small group discussion session will consider what types of behavioral changes represent adverse effects, and whether or not they can and should be measured and reported in nonclinical, guideline-based animal studies.

FDA's Redbook defines neurotoxicity as "any adverse effects on the structure or functional integrity of the developing or adult nervous system." The agency considers biochemical, morphological, behavioral and physiological abnormalities as adverse effects.

For the discussion purposes, we will limit the focus to subtle behavioral changes that are likely to be manifested as significant changes in learning, memory, anxiety, hyperactivity, aggressiveness or reproductive behavior and may be more difficult to assess in laboratory animals. This narrow focus should allow a more thorough discussion that will be useful to the broader assessment.

The discussion group should report in the plenary session the participants' observations on the following questions:

1. What are the challenges to assessing behavioral impacts in guideline-based studies on animals? What behavioral impacts that may be noticed in humans would not be identified in these studies with the current protocols?
2. What are the limitations of FDA's screening method in identifying the need for additional neurological testing?
3. What are the limitations of FDA's case-by-case approach in developing a protocol for a substance when screening methods indicate potential neurological toxicity?
4. Are there standard protocols to assess animal behavior that are routinely used in hypothesis-based research that could be added to FDA's guidelines?

### BACKGROUND

FDA commonly uses clinical and epidemiological studies as the basis for evaluating specific chemical uses. A recent example involved caffeine in alcoholic beverages. FDA also set standards for lead contamination based on the learning disorders associated with very low levels of exposure. But clinical studies on additives are uncommon and, like epidemiological studies, are typically done after the substance is in use in human food.

The Redbook guidance recommends that substances undergo a screen to identify any potential adverse impacts on the nervous system. The screen consists of a structure-activity relationship analysis, review of published literature and empirical testing. In 2000 when the Redbook was revised, FDA acknowledged that testing was the primary means of obtaining neurotoxicity screening information.

FDA identifies five options for empirical testing to be conducted as part of other toxicity studies. The options are

1. Short-term (14- to 28-day) rodent and non-rodent studies to screen adult animals exposed to a test chemical across a range of relatively high doses for brief periods of time
2. Subchronic (90-day) rodent and non-rodent studies to screen adult animals across a range of relatively lower doses
3. Long-term (one-year) rodent and non-rodent studies to screen adult animals across a range of relatively lower doses

4. Reproductive/developmental studies to screen for potential developmental neurotoxicity in perinatally exposed offspring
5. Other types of toxicity studies presented to FDA for consideration.

FDA recommends that the testing include a histopathological examination of all areas of the brain, spinal cord and peripheral nervous system. It also recommends a systematic clinical evaluation assessing the incidence and severity of the following endpoints:

- seizure, tremor, paralysis or other signs of neurological disorder;
- level of motor activity and alertness;
- animals' reactivity to handling and other stimuli
- motor coordination and strength
- gait
- sensorimotor response to primary sensory stimuli
- excessive lacrimation or salivation
- piloerection
- diarrhea
- polyuria
- ptosis
- abnormal consummatory behavior
- any other signs of abnormal behavior or nervous system toxicity.

If the screening is positive, FDA recommends in-depth neurological testing designed in consultation with FDA to determine whether the test chemical has any other, possibly more subtle, effects on the structural and functional integrity of the nervous system in mature and developing organisms. It also recommends a closer examination of dose-response relationships using intermittent and continuous exposures, and the most relevant and sensitive endpoint.

Academic researchers have developed a variety of behavioral test protocols for animals to address specific neurological problems. But FDA has not validated these endpoints, and the protocols have not been integrated into the Redbook.

## ROUND 1-C: NANOMATERIAL CHARACTERIZATION

- Room: Hawaii Room on third floor
- Moderator: Stephen Roberts
- Facilitator: Jen Peyser
- FDA Representatives: Scott Thurmond and Greg Noonan

This small group discussion session will consider the need to accurately characterize the physical and chemical properties of nanomaterials in hypothesis-based and guideline-based studies, and the challenges to doing so.

EPA has adopted a definition of nanomaterials as an ingredient that contains particles that have been intentionally produced to have at least one dimension that measures between approximately 1 and 100 nanometers. We will use this definition for the purpose of this session.

We want to narrow the discussion to the physical and chemical properties of the nanomaterials and avoid, at this time, focusing on the potential adverse effects of the substance. While identifying potential adverse effects is critical, the main question is whether the substance is a nanoscale material, especially under the conditions in which it will be used. Failure to accurately characterize the raw material used in a study may result in little insight regarding its toxicity.

At this time, we are not distinguishing between engineered and non-engineered nanomaterials for two reasons:

1. The line between the two types is subjective—relying heavily on the intent of the manufacturer; and
2. Like the rest of the food additives program, the hazard assessment is not contingent on whether it is synthetic or natural.

The discussion group should report in the plenary session the participants' observations on the following questions:

1. What physical-chemical properties should be considered as important attributes in seeking to accurately characterize the hazard potential of a nanomaterial?
2. Once the nanoscale physical properties of the raw materials are accurately characterized, are existing guideline-based toxicology studies sufficient to evaluate the potential adverse effects of nanomaterials?
3. Should the nanoscale physical and chemical properties of a naturally occurring raw material be evaluated, even if the materials are not engineered to be nanomaterials?
4. Are there situations where the raw material should be better characterized?

### BACKGROUND

The manufacture of nanomaterials is an emergent field with the potential to have great impact on the food system. Key areas appear to be enhancing food safety and quality, reducing the environmental impact of processing and packaging, and reduction of food losses. With some materials already in the market, very little is publicly known about the safety of these products. The biological attributes (positive and negative) of nanomaterials largely depend on their physical and chemical properties. Some of these materials may have been specifically developed as nanomaterials, while others are naturally occurring. Proteins and enzymes are naturally occurring nanomaterials.

In 2006, OECD started a Working Party on Manufactured Nanomaterials that addressed the safety testing of a reference group of nanomaterials. In its latest report, OECD identified the following data gaps in the published literature that are necessary for safety determinations

1. Nanomaterial information/identification
2. Physical-chemical properties and material characterization

3. Environmental fate
4. Environmental toxicity
5. Mammalian toxicology
6. Material safety

In 2007, FDA's Nanotechnology Task Force released a report in which it acknowledged the challenges posed by nanomaterials used in food. The report mentioned the "emerging and uncertain nature of the science" and the necessity to improve scientific development to assist FDA in decision making. The lack of basic information for many nanomaterials and the apparently unique characteristics of each of these materials make safety assessment a challenging process. FDA is in the process of developing guidance for nanomaterials.

The situation for nanomaterials is similar in some aspects to biotechnology, where scientific advances allowed food manufacturers to develop variants on foods. In response, FDA developed specific guidance regarding the scientific considerations for foods derived from new plant varieties. It took a similar approach for enzyme preparations.

## ROUND 1-D: Tox21 & NHANES SCREENS

- Room: European Union Room on second floor
- Moderator: Gail McCarver
- Facilitator: Dana Goodson
- FDA Representatives: Suzanne Fitzpatrick and Gene Leclerc

This small group discussion session will consider how the results of the Tox21 and NHANES screens should be used as a trigger for additional studies. In essence, how should positive results from screening tests be used as part of a system to assess the toxicity of a chemical or mixture of substances?

The biomonitoring studies conducted as part of U.S. Center for Disease Control's (CDC) National Health and Nutrition Examination Survey (NHANES) provide a nationally representative sampling of synthetic chemicals in the blood or urine of the general population, excluding very young children. After more than a decade of testing, we now have an extensive database of information regarding exposure to the chemicals tested. But exposure without a solid understanding of the hazard or the route of exposure provides limited insight into human risk.

Unlike NHANES, Tox21 screens are still in development. When in place, they will use *in vitro* methods to evaluate the potential hazards of a wide array of chemicals and mixtures on cells. A positive result or combination of results is unlikely to be considered an adverse effect on its own. Instead, it can serve as a trigger for more detailed studies.

The discussion group should report in the plenary session the participants' observations on the following questions:

1. What criteria should be used to determine when a substance should undergo additional guideline-based study?
2. How should FDA handle positive results from NHANES and Tox21 screens in its assessment or reassessment of substances added to food?
3. Should FDA supplement its current guidance to establish chemical levels of concern based on NHANES and Tox21 screening results?
4. How can screening results be used to supplement computational toxicology tools?

### BACKGROUND

In the Redbook, FDA identifies the appropriate guideline-based toxicity studies based on an assessment of a substance's potential toxicity using structure-activity relationships and cumulative human exposure. In the context of food, exposure is equal to consumption.

FDA places chemicals, but not food contact substances, in one of three levels of concern based on a cumulative exposure estimate and a structure-activity relationship, and recommends specific protocols for each level of concern. For food contact substances, the studies are based on the exposures.



Concern Level	Recommended studies
I	Two studies: Genetic toxicity tests and short-term toxicity tests with rodents.
II	Four studies: Genetic toxicity tests; short-term toxicity tests with rodents; subchronic toxicity studies with rodents; and subchronic toxicity studies with non-rodents.
III	Genetic toxicity tests: Short-term toxicity tests with rodents; subchronic toxicity studies with rodents; subchronic toxicity studies with non-rodents; one-year toxicity studies with non-rodents; chronic toxicity or combined chronic toxicity/carcinogenicity studies with rodents; carcinogenicity studies with rodents; reproduction studies; developmental toxicity studies; and metabolism and pharmacokinetic studies.

Exposure	Recommended studies
Less than 1.5 µg/person/day	No safety studies recommended.
Between 1.5 and 150 µg/person/day	Genetic toxicity tests.
Between 150 and 3000 µg/person/day	Genetic toxicity tests; subchronic toxicity studies with rodents; and subchronic toxicity studies with non-rodents.
More than 3000 µg/person/day	Handle as food additive in Table 1.
Exposure is based on cumulative exposure for all but levels less than 1.5 µg/person/day. At that level, the exposure is based on incremental exposure.	

The technological and scientific advances of the last decade contributed to the creation of highly sensitive analytical tools that allow investigators to measure very small amounts of chemicals from many sources (e.g., water, air, and body fluids and tissues). Similar technological advances make it possible to analyze and quantify events inside single cells (e.g., gene expression and protein activity).

NHANES data are used to determine the prevalence of major diseases and risk factors for diseases. In the late 1990s, NHANES began measuring synthetic chemicals in the urine of a nationally representative sample of 5,000 Americans. It does not take blood samples from children younger than one year and urine samples from children younger than six. The measured chemicals were selected based on

- scientific data suggesting exposure in the U.S. population
- serious health effects known or suspected to result from some levels of exposure
- the need to assess the effectiveness of public health actions to reduce exposure to a chemical
- the availability of a biomonitoring analytical method with adequate accuracy
- the availability of adequate blood or urine samples
- incremental analytical costs to perform biomonitoring analysis for the chemical.

The NHANES survey data have the potential to trigger new epidemiological studies and hypothesis-based research. In particular, human chemical exposure data provide real-life information regarding chemical levels that can help design toxicological studies to mimic current human exposure.

Tox21 is a collaboration among the EPA, the National Institutes of Health (NIH) and FDA to research, develop, validate and translate innovative chemical testing methods that characterize toxicity pathways. It will use high-throughput screening tests to evaluate mechanisms of toxicity with the purpose of

1. Identifying mechanisms of chemically induced biological activity

2. Prioritizing chemicals for more extensive toxicological evaluation
3. Developing more predictive models of *in vivo* biological response.

Tox21 is a new program with the capacity to generate large amounts of data regarding chemicals' interactions with cellular pathways. The types of additional studies that Tox21 screening could trigger will depend on how the weight of evidence is defined.

## SMALL GROUP DISCUSSIONS – ROUND 2: EVALUATING STUDY DESIGN AND DATA FOR REGULATORY DECISIONS

Round 2 of the small group discussions will shift from a narrow focus on study endpoints to the overall study design. This expanded focus will allow us to build on the previous discussions and deal with specific challenges that have been raised about both guideline-based studies and hypothesis-based research. To help focus the discussion, we selected four topics designed to engage participants. They are:

1. dose response
2. transparency
3. study reproducibility
4. use of hypothesis-based research.

FDA's presentation immediately before this round should help prepare you for this discussion by explaining how it assesses the safety of food additives and makes its regulatory decisions. You may want to review the three documents that FDA provided at the end of this binder as background to the discussion.

The first session will focus on whether the methods to develop doses for nonclinical, guidance-based studies need to be modified on the basis of research indicating low-dose effects.

The second session will focus on the challenge of transparency in both hypothesis-based research and guideline-based studies as well as FDA's review of the science. Most stakeholders agree that the results of the studies would be more credible and useful if FDA and independent analysts had access to the raw data, laboratory notes and detailed analysis so they could make their own evaluation. But accomplishing this would be a challenge. In both types of studies, independent analysts cannot access the information. FDA gets access only if a study is

- conducted by or on behalf of the submitter requesting premarket authorization
- funded by the federal government and the funding agency requests the information.

The third session will focus on how to ensure that studies evaluated by FDA are reproducible in other laboratories. If the study results are not reproducible, they have limited use in guideline-based studies and should not be the basis of a validated endpoint or toxicity study design. Guideline-based studies comply with GLP standards to provide assurance to FDA that the results are reproducible. Hypothesis-based researchers rely on their peers to evaluate their publications and attempt to reproduce their data. However, funding for study replication is limited.

The fourth session moves beyond the three key issues and takes a broader look at how FDA can make better use of hypothesis-based research directly in its regulatory decisions. FDA often relies on this type of research for clinical studies, epidemiological studies or studies that expand on guideline-based studies. This session is designed to help researchers better understand FDA's needs and to help FDA better understand researchers' capabilities.

## ROUND 2-A: DOSE RESPONSE

- Room: Hawaii Room on third floor
- Moderator: Tracey Woodruff
- Facilitator: Abby Dilley
- FDA Representatives: Michelle Twaroski and Ron Lorentzen

This small group discussion session will consider how to interpret and incorporate studies that indicate nonlinear dose response relationships into regulatory decision-making.

The discussion group should report in the plenary session the participants' observations on the following questions:

1. In a toxicity screen, should animals be evaluated for adverse effects at lower doses when no adverse effects are noted at the highest dose?
2. When human exposure data are available, should toxicity studies be conducted using doses that reflect estimated exposure, in addition to the high doses?
3. Are dose responses such as stepwise or non-monotonic curves common enough to warrant modifying the standard approaches?
4. If so, under what circumstances should alternative approaches be used?

### BACKGROUND

Traditional toxicology assumes that higher doses produce the greater effects and that dose-response curves are always monotonic; in other words, that the slope of a response does not change direction. Therefore, if there are no adverse effects at high doses, it is common for toxicologists to assume that lower doses are safe. Recent hypothesis-based research indicates that certain body functions such as the endocrine system may respond to exposure in a stepwise or non-monotonic manner. Depending on the timing of the exposure, this response may result in adverse effects as discussed in earlier small groups.

The Redbook recommends that chemicals be screened using at least three doses. If there are no adverse effects at the highest dose, the lower doses do not need to be evaluated for adverse effects. If the highest dose has a response, then the study must find a minimum dose where no adverse effects are observed. This dose is the No Observed Adverse Effect Level (NOAEL). If the lowest dose has an adverse effect, then it may be used but with an additional margin of safety added to the calculation.

## ROUND 2-B: TRANSPARENCY

- Room: Oklahoma Room on third floor
- Moderator: John Vandenberg
- Facilitator: Jen Peyser
- FDA Representatives: Kelly Randolph and Supratim Choudhuri

The small group discussion session will consider methods to increase transparency of the data and analyses in both hypothesis-based research and guideline-based studies.

The discussion group should report in the plenary session the participants' observations on the following questions:

1. Does the fact that hypothesis-based research and guideline-based studies are not always published impair FDA's ability to make a sound decision regarding the safety of a food additive? If so, how?
2. Would making the data and analysis of pivotal studies on a substance added to food available to FDA improve the quality of its assessment?
3. Would it improve the quality of the assessment if the data and analysis were available to independent analysts to evaluate?
4. How much data would need to be made available?

### BACKGROUND

In both guideline-based studies and hypothesis-based research, independent analysts generally cannot access the raw data without the permission of the researcher or laboratory principal investigator. FDA gets access if the study is:

- conducted by or on behalf of the submitter requesting premarket authorization
- funded by the federal government and the funding agency requests the information.

Guideline-based studies are typically conducted pursuant to GLP rules. When reporting results, the GLP rule states that the laboratory must provide a description of the transformations, calculations or operations performed on the data, a summary and analysis of the data, and a statement of the conclusions drawn from the analysis.

The author of a report from a GLP-compliant study does not have to publish it or submit it to a peer-reviewed journal. In this situation, when the FDA or a food manufacturer makes a GRAS determination, it may not be aware of the unpublished report performed by someone else that would impact its determination. As a result, it would be unable to consider the results in its analysis.

Hypothesis-based researchers seldom make the raw data available, even when published in peer-reviewed journals. Usually they reveal the data only in extreme cases of suspicion of fraud, in which the journal where the data were published and the institution where the suspected work was performed conduct an in-depth investigation. Some peer-reviewed journals are providing researchers with the option of posting the data on a website to support a published article, but this is not common practice.

Typically, hypothesis-based researchers submit only positive results to a peer-reviewed journal for publication. If the results are negative or uncertain, the researcher is typically under no obligation to publish the results and is unlikely to find a journal interested in publishing the results. Negative or uncertain results are usually not journal-worthy.

As part of its Science for Policy Project, the Bipartisan Policy Center convened a diverse group of leading academic, public interest and industry scientists. In August 2009, the scientists and the Center published *Improving the Use of Science in Regulatory Policy: Final Report*. They reached a consensus that “agencies and their scientific advisory committees should cast a wide net in reviewing studies relevant to regulatory policy, and should make their methods for filtering and evaluating those studies more transparent.”

## ROUND 2-C: STUDY REPRODUCIBILITY

- Room: New Mexico Room on third floor
- Moderator: Joe Hotchkiss
- Facilitator: Robin Roberts
- FDA Representative: David Hattan

This small group discussion session will consider how to ensure that studies evaluated by FDA are reproducible in other laboratories. If a study's results are reproducible, they are more credible. Such results can become the basis of new guidelines and can support regulatory decisions on safety.

The discussion group should report in the plenary session the participants' observations on the following questions:

1. How should FDA determine if a study (either guideline-based or hypothesis-based) is reproducible?
2. What level of certainty in a study's reproducibility will support the use of the results in making a regulatory safety decision?
3. How is reproducibility considered in FDA's evaluation of a study design or method for inclusion as an FDA-recommended guideline-based study?
4. What is the role of federal agencies such as FDA and NIEHS to encourage labs to reproduce published data?

### BACKGROUND

A common practice in hypothesis-based research is to publish data that have been reproduced in the laboratory at least twice. In addition, hypothesis-based investigators maintain that study results published in a peer-reviewed journal undergo rigorous review as part of the peer-review process. When their peers in other laboratories publish results reaching the same or similar conclusions, they maintain that the results are reproducible.

FDA generally considers guideline-based studies complying with GLP rules to be reproducible because of the large number of animals involved in the study and the strict data reporting required by GLP. These studies also have been shown to be reproducible a significant number of times. However, neither hypothesis-based nor guideline-based GLP-compliant studies guarantee their reproducibility.

## ROUND 2-D: USE OF HYPOTHESIS-BASED RESEARCH

- Room: European Union Room on second floor
- Moderator: Glenn Sipes
- Facilitator: Dana Goodson
- FDA Representatives: Kristi Jacobs and Gene Leclerc

This small group discussion session will consider how FDA can make better use of hypothesis-based research when it considers the safety of a substance to be added to food. The discussion should go beyond the issues of reproducibility and transparency to evaluate both sides of the issue: changes FDA should consider and changes researchers should consider.

The discussion group should report in the plenary session the participants' observations on the following questions:

1. What changes should FDA consider in its review of hypothesis-based research?
2. What changes should researchers consider in study design, data reporting and availability to FDA so the agency can more effectively consider the study?
3. How can these changes best be implemented?
4. What would be the role of funding agencies to promote changes that enhance the usage of hypothesis-based research for regulatory decision making?

### BACKGROUND

FDA reviews hypothesis-based research when it considers the safety of a substance added to food. Regardless of the source of the study, FDA uses eight criteria derived from a compilation of its Redbook, OECD and EPA guidelines to determine the adequacy of data for safety assessment.

1. Route of administration
2. Sample size and statistical analysis
3. Validity of endpoint measured
4. Plausibility or relevance to human health
5. Dose response
6. Sex of the animals
7. Repeatability
8. Environmental contamination

In general, hypothesis-based research is not conducted with the intention of being used for regulatory purposes, but rather to explore new ideas and publish original data. The content of the article is judged by peers, and the format is dictated by the peer-reviewed journals. The peer reviewers determine whether or not there is sufficient value and originality in the findings to publish them. Thus, there are no homogeneous criteria, nor is there a "one-size-fits-all" approach to experimental design and data reporting.

When scientific peer-reviewed publications are used to evaluate the toxicity of chemicals, the lack of harmonization in such areas as doses, routes of administration, endpoints and species can make it necessary to develop criteria that will be uniformly applied to select between adequate and inadequate studies. As an example, the National Toxicology Program Expert Panel that reviewed the reproductive and developmental toxicity of bisphenol A decided that hypothesis-based research studies would be acceptable for inclusion in the review process if the experimental design included

- a minimum of six animals per treatment
- dosing via the mother or directly under individual housing conditions
- consideration of effects related to litter of origin in the design and statistical procedures
- statistical analyses that account for repeated measurement if similar tests were conducted at multiple ages in order not to inflate degrees of freedom



- a preference for oral route of administration, with other routes relevant when circulating parent compound is measured
- proper positive and negative controls.

Currently, NTP does not have evaluation criteria to review hypothesis-based publications. Although it is not clear how these criteria were selected by members of the Expert Panel, this example provides a starting point to discuss how both FDA criteria and hypothesis-based research can be enhanced to make better use of the data for regulatory decisions.

## SMALL GROUP DISCUSSIONS – ROUND 3: DEVELOPING AND REVIEWING TEST GUIDELINES

Round 3 of the small group discussions will focus on developing and reviewing test guidelines. These guidelines establish the objectives, general design and endpoints of guideline-based studies. When FDA determines that a test method has been validated and provides useful understanding of the safety of a food additive, it includes the protocol in its Redbook guidance and explains how it should be used. Once this is done, food manufacturers, expert panels and consultants conducting their own safety assessment or preparing a petition to FDA are expected to conduct guideline-based studies consistent with the guidance.

While FDA is our priority, we also want to keep in mind the other organizations that review and approve relevant test guidelines. The most important are the Organisation for Economic Co-operation and Development (OECD) and, to some extent, the Joint FAO/WHO Expert Committee on Food Additives (JECFA).

FDA's presentation at the end of Day 1 and its document on the Redbook in the back of the binder should help you better understand how it reviews and approves test guidelines. The panel presentation on alternative methods to animal testing at the beginning of Day 2 should provide insights into how the system handled a new set of test guidelines.

In Round 3, we are continuing to expand our focus, moving stepwise from specific endpoints in Round 1 to study design in Round 2 and, now, to the incorporation of new or improved study designs into FDA's guidance. Unlike Rounds 1 and 2, we will not focus on a handful of hot topics. In this round, we want to look broadly at all aspects of the issue. To make the discussion more productive, we have divided the issue into two parts:

1. **Developing test guidelines for review:** How are new or improved draft test guidelines developed, validated, funded and submitted to FDA (or another organization) for its consideration?
2. **Reviewing and approving test guidelines:** How does FDA (or another organization) review, manage and approve new or improved draft test guidelines?

Given the breadth of the topic and the importance of having small enough groups to ensure that all participants will be heard, we will have two small group discussions going on simultaneously in each of these two parts.

All groups should also consider whether implementing a step-by-step procedure following the OECD model would be useful and practical under FDA's Good Guidance Practices, and which steps can be taken to make these procedures efficient.

### BACKGROUND

The Redbook is an FDA Level 1 guidance document under 21CFR 10.115 Good Guidance Practices. At 21 CFR 10.115, FDA describes the procedures to participate in the development of guidance documents. Any person, institution, stakeholder or agency can

1. Provide input on guidance documents
2. Suggest areas of guidance development
3. Submit drafts of proposed guidance documents
4. Suggest revision or withdrawal of any guidance document.

Once a year, FDA publishes in the *Federal Register* a list of possible topics for future guidance document development or revision. Before and after preparing a draft for a new Level 1 guidance document like

the Redbook, FDA seeks public comments in response to the notice, reviews them and incorporates them into the final guidance document as appropriate.

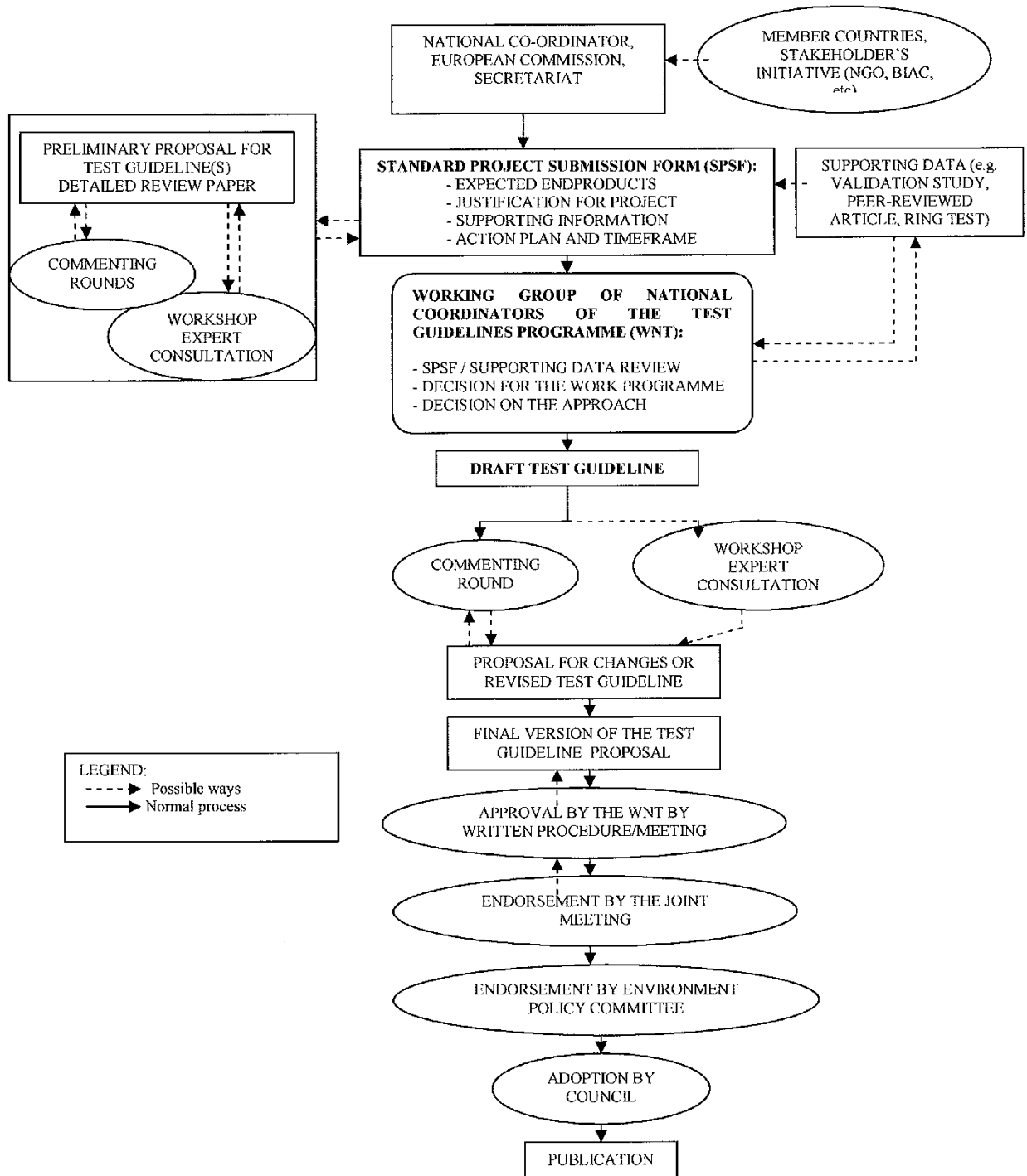
OECD has defined procedures for the creation of new guidelines and updating of current test guidelines under the Test Guidelines Program; these procedures are described in “Guidance Document No. 1 for the Development of OECD Guidelines for Testing of Chemicals.” See Figure 2 for a flowchart of the procedures.

Governments, industry, public interest groups, the scientific community, the European Commission or the OECD Secretariat can submit proposals to develop or update test guidelines. The submission form contains a detailed description of the project and supporting documentation (such as regulatory need, validation status, relevance and reliability) and describes the work plan (deadlines, deliverables and milestones). OECD guidelines and documents are available at no charge online.

The information provided at the time of proposal submission describes

- foreseen or existing regulatory need for such a test (or update)
- contribution to international harmonization of data requirements
- scientific arguments indicating the importance of the test or the modifications
- animal welfare considerations indicating the advantages of the proposed test/procedure with respect to animal use/discomfort without loss of essential information
- a rationale indicating the advantages of the proposed test/procedure with respect to reduced costs without loss of essential information
- supporting documentation; e.g., on the performance of the test method, validation status, or the reliability and relevance of the method.

FIGURE 2  
OECD TEST GUIDELINES DEVELOPMENT FLOW DIAGRAM



## ROUNDS 3-A & 3-B: DEVELOPING TEST GUIDELINES FOR REVIEW

### Group 3-A

- Room: European Union Room on second floor
- Moderator: Glenn Sipes
- Facilitator: Dana Goodson
- FDA Representative: David Hattan

### Group 3-B

- Room: Hawaii Room on third floor
- Moderator: Stephen Roberts
- Facilitator: Jen Peyser
- FDA Representative: Jason Aungst

This small group discussion session will consider how new or improved draft test guidelines are developed, validated and submitted to FDA (or another organization) for possible adoption. In essence, it is focusing on the process before FDA formally considers a proposal.

The discussion group should report in the plenary session the participants' observations on the following questions:

1. What are the barriers to developing and validating new or improved draft test guidelines?
2. How is the development and validation of new or improved draft test guidelines funded?
3. Who leads the effort?
4. How can the process be improved to more efficiently and effectively get the best proposals to FDA in a format that it needs?

## ROUNDS 3-C & 3-D: REVIEWING AND APPROVING TEST GUIDELINES

### Group 3-C

- Room: Oklahoma Room on third floor
- Moderator: Joe Hotchkiss
- Facilitator: Abby Dilley
- FDA Representative: Supratim Choudhuri

### Group 3-D

- Room: New Mexico Room on third floor
- Moderator: Gail McCarver
- Facilitator: Robin Roberts
- FDA Representative: Michelle Twaroski

This small group discussion session will consider how FDA (or another organization) reviews, manages and approves new or improved draft test guidelines. In essence, it is focusing on the process after it is formally submitted to FDA. It should also consider how FDA considers changes on its own accord based on its monitoring of scientific developments.

The discussion group should report in the plenary session the participants' observations on the following questions:

1. What are the key steps in FDA's review and approval process?
2. What are the different methods that FDA uses to review and approve new or improved test guidelines?
3. How does FDA differ from other organizations?
4. How could this process be enhanced?

## SMALL GROUP DISCUSSIONS – ROUND 4: IDENTIFYING AND EVALUATING POTENTIAL SOLUTIONS

Round 4 of the small group discussions will consist of priority-setting sessions to improve any aspects of FDA's evaluation of science to ensure that chemicals added to human food are safe. We want to shift from evaluating specific aspects of the system to assembling the ideas from previous sessions, grouping them into categories, combining them as appropriate, and getting a structured insight into participants' priorities for the ideas.

To help focus the discussion, we divided the system into three areas:

1. Improving hypothesis-based research
2. Improving guideline-based studies
3. Refining the regulatory decision-making process.

We recognize that there is significant overlap between the topics. The discussion should not be strictly limited to the specific topic. Also, we may adjust the topics and even add a concurrent session based on the discussions and ideas developed throughout the workshop. Talk with the facilitators and session moderators if you have ideas and comments.

## ROUND 4-A: IMPROVING HYPOTHESIS-BASED RESEARCH

- Room: Hawaii Room on third floor
- Moderator / Facilitator: Dana Goodson
- FDA Representatives: Kristi Jacobs and Gene Leclerc

This small group discussion session will consider improvements to hypothesis-based research so the results are

- more likely to be seriously considered by food manufacturers, expert panels and consultants conducting their own safety assessment or preparing a petition to FDA;
- more useful to FDA when it conducts its safety assessment or evaluates a GRAS determination;
- more likely to result in validated test guidelines that are approved by FDA and incorporated into the Redbook.



## ROUND 4-B: IMPROVING GUIDELINE-BASED STUDIES

- Room: New Mexico Room on third floor
- Moderator / Facilitator: Robin Roberts
- FDA Representative: David Hattan

This small group discussion session will consider improvements to guideline-based studies to ensure that the results

- best reflect the significant hypothesis-based research that has been validated
- systematically provide FDA with the best information it needs to conduct a safety assessment on chemicals added to food.

It will also consider how validation studies could be conducted more quickly and efficiently to demonstrate reproducibility so they can be incorporated into the guidelines.

## ROUND 4-C: REFINING THE REGULATORY DECISION-MAKING PROCESS

- Room: Oklahoma Room on third floor
- Moderator / Facilitator: Jen Peyser
- FDA Representatives: Suzanne Fitzpatrick and Michelle Twaroski

This small group discussion session will consider refinements to FDA's regulatory decision-making process so the results

- best ensure that chemicals added to food are safe
- reflect the best and most relevant science available
- are transparent, fair, consistent and credible
- include review of substances originally considered safe but whose safety is now being reevaluated.

## APPENDIX A: GLOSSARY

ADI	Acceptable Daily Intake. The amount of a substance that may be consumed daily over a lifetime without experiencing health risks.
Adverse Effect	A biochemical change, functional impairment, or pathologic lesion that affects the performance of the whole organism, or reduces an organism's ability to respond to an additional environmental challenge. (EPA IRIS Glossary) (FDA does not have published definition.)
BPA	Bisphenol A
CCFA	Codex Committee on Food Additives
CDC	Centers for Disease Control and Prevention in Department of Health and Human Services (DHHS)
CFR	Code of Federal Regulations
CFSAN	Center for Food Safety and Applied Nutrition in FDA
Clinical studies	Laboratory studies that occur in human subjects.
Codex	Codex Alimentarius
CVM	Center for Veterinary Medicine in FDA
DHHS	United States Department of Health and Human Services
ECVAM	European Centre for the Validation of Alternative Methods (European Union)
Endocrine disruption	A mode or mechanism of action potentially leading to other outcomes; – for example, carcinogenic, reproductive, or developmental effects, routinely considered in reaching regulatory decisions. (EPA Definition)
EPA	United States Environmental Protection Agency
Epidemiological studies	Population-based studies that assess the health effects of exposure to an agent.
FAO	Food and Agriculture Organization in the United Nations
FDA	United States Food and Drug Administration in the Department of Health and Human Services (DHHS)
FDA Redbook	FDA's Toxicological Principles for the Safety Assessment of Food Ingredients Guidance recommending test guidelines.
Food additives	Chemicals added that provide a technical effect to the food product, including those intentionally added, migrated from food contact substances and residual from processing.
GLP	Good Laboratory Practice
GRAS	Generally Recognized as Safe. GRAS substances must be generally recognized, among qualified experts, as having been adequately shown to be safe under the conditions of their intended use.
Guideline-based studies	Studies that use agency-approved protocols or test guidelines to evaluate the potential hazard of a substance. These studies are commonly done in laboratories that specialize in performing the protocols using Good Laboratory Practices for purposes of supporting a regulatory safety determination.
Hypothesis-based research	Research that begins with an investigator's hypothesis and consists of experimental protocols designed by the investigator to test the hypothesis. This research is commonly done in an academic setting.
IFT	Institute of Food Technologists
JECFA	Joint FAO/WHO Expert Committee on Food Additives
Nanomaterial	Materials with at least one dimension in the range between 1 and 100 nanometers.
NCGC	NIH Chemical Genomics Center in NIH
NHANES	National Health and Nutrition Examination Survey in CDC
NHGRI	National Human Genome Research Institute in NIH

NIEHS	National Institute of Environmental Health Sciences in NIH
NIH	National Institutes of Health in Department of Health and Human Services (DHHS)
NOAEL	No Observed Adverse Effect Level. The level of exposure to a substance that provides no significant adverse observed effects in laboratory tests.
NOEL	No Observed Effect Level. The level of exposure to a substance that provides no significant effects in laboratory tests.
Nonclinical studies	Laboratory studies that occur <i>in vivo</i> (in animals) or <i>in vitro</i> (in cells or test tubes).
NTP	National Toxicology Program (NIEHS)
Neurotoxicity	Any adverse effects on the structure or functional integrity of the developing or adult nervous system (FDA Redbook)
OECD	Organisation for Economic Co-operation and Development
OFAS	Office of Food Additive Safety in FDA's CFSAN
ppb	parts per billion
ppm	parts per million
QSAR	Quantitative Structure-Activity Relationship
Redbook	FDA's Toxicological Principles for the Safety Assessment of Food Ingredients Guidance recommending test guidelines.
Safe	There is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use.
SAR	Structure Activity Relationships
Screening tests	Tests designed to identify potential hazards or actual exposures. Though these tests generally are not sufficient to identify adverse effects, they may serve as the basis for hypothesis-based research and guideline-based studies.
Tox21	Computational Toxicology Research Program
USDA	United States Department of Agriculture
Validation	A process based on scientifically sound principles by which the reliability and relevance of a particular test, approach, method or process are established for a specific purpose.
WHO	World Health Organization

## APPENDIX B: RESOURCES

You may find the following references helpful .. If you have additional links, please send the materials to Maricel Maffini of the Pew Health Group at [mmaffini@pewtrusts.org](mailto:mmaffini@pewtrusts.org).

### Legal References

- Food Additives: Code of Federal Regulation Title 21 Part 170. [www.access.gpo.gov/nara/cfr/waisidx\\_09/21cfr170\\_09.html](http://www.access.gpo.gov/nara/cfr/waisidx_09/21cfr170_09.html)
- Good laboratory practice for nonclinical laboratory studies. Code of Federal Regulation Title 21 Part 58. [www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=58](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=58).
- FDA's policies and procedures for developing, issuing and using guidance documents. Good Guidance Practices. Code of Federal Regulation Title 21 Part 10 Section 115. [http://edocket.access.gpo.gov/cfr\\_2010/aprqtr/pdf/21cfr10.115.pdf](http://edocket.access.gpo.gov/cfr_2010/aprqtr/pdf/21cfr10.115.pdf)

### U.S. FDA References

- Advancing Regulatory Science for Public Health. A Framework for FDA's Regulatory Science Initiative. [www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm228137.htm](http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm228137.htm)
- U.S. FDA *Redbook 2000*: Toxicological Principles for the Safety Assessment of Food Ingredients. Guidance for Industry and Other Stakeholders. [www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/Redbook/default.htm](http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/Redbook/default.htm)
- U.S. FDA Guidance, Compliance and Regulatory information. Guidance for industry:
  1. Summary table for recommended toxicological testing for additives used in food. [www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/ucm054658.htm#ftn3](http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/ucm054658.htm#ftn3)
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- U.S. FDA Nanotechnology Task Force Report 2007. [www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/NanotechnologyTaskForceReport2007/default.htm](http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/NanotechnologyTaskForceReport2007/default.htm)
- U.S. FDA Warning letters to makers of caffeinated alcoholic beverages. [www.fda.gov/Food/FoodIngredientsPackaging/ucm190366.htm](http://www.fda.gov/Food/FoodIngredientsPackaging/ucm190366.htm)

### OECD References

- OECD Series on Testing and Assessment. Guidance document for the development of OECD guidelines for the testing of chemicals. No. 1, 2009. [www.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/jm/mono\(2006\)20/rev1&doclanguage=en](http://www.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/jm/mono(2006)20/rev1&doclanguage=en)
- OECD Series on Testing and Assessment. Guidance document on the validation and international acceptance of new or updated test methods for hazard assessment. No. 34, 2005. [www.oecd.org/officialdocuments/displaydocumentpdf?cote=env/jm/mono\(2005\)14&doclanguage=en](http://www.oecd.org/officialdocuments/displaydocumentpdf?cote=env/jm/mono(2005)14&doclanguage=en)
- OECD Series on the Safety of Manufactured Nanomaterials. List of manufactured nanomaterials and list of endpoints for phase one of the sponsorship programme for the testing of manufactured nanomaterials: Revision. No. 27, 2010. [www.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/jm/mono\(2010\)46&doclanguage=en](http://www.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/jm/mono(2010)46&doclanguage=en)

### National Health and Nutrition Examination Survey

- Information about NHANES. [www.cdc.gov/nchs/nhanes.htm](http://www.cdc.gov/nchs/nhanes.htm)

### Computational Toxicology Research Program Tox21

- [www.epa.gov/ncct/Tox21/](http://www.epa.gov/ncct/Tox21/)

### Bipartisan Policy Center, Science for Policy Project

- Improving the Use of Science in Regulatory Policy.  
[www.bipartisanpolicy.org/sites/default/files/BPC%20Science%20Report%20fml.pdf](http://www.bipartisanpolicy.org/sites/default/files/BPC%20Science%20Report%20fml.pdf)

### National Academy of Sciences Report

- Science and Decisions: Advancing Risk Assessment.  
[www.nap.edu/catalog.php?record\\_id=12209](http://www.nap.edu/catalog.php?record_id=12209)

### Integrated Risk Information System

- Glossary. [www.epa.gov/ncea/iris/help\\_gloss.htm](http://www.epa.gov/ncea/iris/help_gloss.htm)

### Scientific Literature

- The weight of evidence. *Nature* 464:1103, 2010.  
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<http://ehp03.niehs.nih.gov/article/fetchArticle.action?articleURI=info%3Adoi%2F10.1289%2Fehp.0900884>
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- Myers et al. *Environmental Health Perspectives* 117:A483, 2009. Good Laboratory Practices: Response to Becker et al.  
<http://ehp03.niehs.nih.gov/article/fetchArticle.action?articleURI=info%3Adoi%2F10.1289%2Fehp.0900884R>

## APPENDIX C: WORKSHOP SPONSORS

### INSTITUTE OF FOOD TECHNOLOGISTS

The Institute of Food Technologists (IFT) is a nonprofit scientific society. IFT's individual members are professionals engaged in food science, food technology and related professions in industry, academia and government. IFT's mission is to advance the science of food, and its long-range vision is to ensure a safe and abundant food supply, contributing to healthier people everywhere.

For more than 70 years, the IFT has been unlocking the potential of the food science community by creating a dynamic global forum where members from more than 100 countries can share, learn and grow. IFT champions the use of sound science across the food value chain through the exchange of knowledge, by providing education and by furthering the advancement of the profession. IFT has offices in Chicago, Illinois, and Washington, DC. For more information, please visit [ift.org](http://ift.org).

### NATURE

Focusing on the needs of scientists, *Nature* (founded in 1869) is the leading weekly international scientific journal, covering all fields of science. It draws more citations than any other interdisciplinary science journal, according to the 2009 Journal Citation Report Science Edition, and its website has nearly 2 million unique users every month. In addition to peer-reviewed papers, *Nature* publishes news, features and opinion pieces covering subjects of interest to scientists. It also publishes daily online science news that attracts a large and growing following.

*Nature* is part of a family of journals, all published by Nature Publishing Group, that includes the Nature research journals and Nature Reviews journals, plus a range of prestigious academic journals, including society-owned publications. Online, [nature.com](http://nature.com) provides over 5 million visitors per month with access to NPG publications and online databases and services, including Nature News and NatureJobs, plus access to Nature Network and Nature Education's Scitable.com. NPG also publishes *Scientific American*, aimed at the science-literate public. Founded in 1845, *Scientific American* is the oldest continuously published magazine in the United States and the leading authoritative publication for science in the general media. Together with [scientificamerican.com](http://scientificamerican.com) and 16 local language editions around the world, it reaches over 3 million consumers and scientists.

### PEW HEALTH GROUP OF THE PEW CHARITABLE TRUSTS

The Pew Charitable Trusts is driven by the power of knowledge to solve today's most challenging problems. Pew applies a rigorous, analytical approach to improve public policy, inform the public and stimulate civic life. We partner with a diverse range of donors, public and private organizations, and concerned citizens who share our commitment to fact-based solutions and goal-driven investments to improve society.

The Pew Health Group is the health and consumer-product safety arm of The Pew Charitable Trusts. PHG seeks to improve the health and well-being of all Americans by advocating for policies that reduce potentially dangerous health risks in food, medical, financial, and consumer products and services.

As part of this effort, Pew's Food Additives Project is using scientific evidence to undertake a comprehensive assessment of the existing regulatory system to determine whether it ensures that chemicals added to food are safe as required by law, and is assessing policy recommendations to address any gaps. The Food Additives Project is not an advocacy campaign. It organized the Workshop on Enhancing FDA's Evaluation of Science to Ensure Chemicals Added to Human Food are Safe to provide informed bases for potential future efforts to elicit policy change in our food safety system.

## APPENDIX D: KEY AGENCIES SUPPORTING WORKSHOP

The following agencies provided guidance in developing the agenda and these materials.

### U.S. FOOD AND DRUG ADMINISTRATION'S OFFICE OF FOOD ADDITIVE SAFETY

The Office of Food Additive Safety (OFAS) is in FDA's Center for Food Safety and Nutrition (CFSAN). CFSAN provides services to consumers, domestic and foreign industry, and other outside groups regarding field programs; agency administrative tasks; scientific analysis and support; and policy, planning and handling of critical issues related to food and cosmetics. Most Center staff members work in the Center's headquarters in College Park, Maryland. The Center also operates research facilities in Laurel, Maryland, and in Dauphin Island, Alabama.

OFAS is FDA's one-stop shop for questions about the safety of ingredients in human food, food packaging and food processing equipment, including sources of radiation used to treat or inspect food and foods derived from bioengineered plants. It is the lead for FDA's food and color additive petition processes, the consideration of independent determinations of GRAS status, and review of notifications for food contact substances.

### U.S. NATIONAL INSTITUTES OF HEALTH'S NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

The National Institute of Environmental Health Sciences, located in Research Triangle Park, North Carolina, is one of 27 research institutes and centers that constitute the NIH in the U.S. Department of Health and Human Services (DHHS). The mission of the NIEHS is to reduce the burden of human illness and disability by understanding how the environment influences the development and progression of human disease.

The NIEHS traces its roots to 1966, when the U.S. Surgeon General announced the establishment of the Division of Environmental Health Sciences within the NIH. In 1969, the division was elevated to full NIH institute status. Since then, the NIEHS has evolved to its present status as a world leader in environmental health sciences, with an impressive record of important scientific accomplishments.



## APPENDIX E: PLENARY SESSION SPEAKERS

**Linda Birnbaum:** Director of the National Institute of Environmental Health Sciences (NIEHS) and of the National Toxicology Program. Dr. Birnbaum oversees a budget that funds multidisciplinary biomedical research programs, prevention and intervention efforts that encompass training, education, technology transfer and community outreach. The NIEHS supports more than 1,000 research grants.

Dr. Birnbaum has received numerous awards, including the Women in Toxicology Elsevier Mentoring Award, the Society of Toxicology Public Communications Award, EPA's Health Science Achievement Award and Diversity Leadership Award, and 12 Science and Technology Achievement Awards. She is the author of several hundred peer-reviewed publications, book chapters, abstracts and reports. Dr. Birnbaum received her M.S. and Ph.D. in microbiology from the University of Illinois, Urbana. A board-certified toxicologist, Dr. Birnbaum has served as a federal scientist for 30 years, including 10 years at NIEHS as a senior staff fellow at the National Toxicology Program, a principal investigator and research microbiologist, and group leader for the institute's Chemical Disposition Group.

**Leon Bruner:** Senior Vice President for Scientific and Regulatory Affairs and Chief Science Officer for the Grocery Manufacturers Association (GMA). Dr. Bruner is responsible for overseeing GMA's team of scientists who conduct research on nutrition and safety. GMA's scientific research informs its members on nutrition and safety issues, and provides empirical evidence for the association's key policy positions.

During his professional career, Dr. Bruner has developed a strong reputation as an innovator who is able to apply strategic vision, critical thinking and first-class execution in pursuit of business goals. He is an internationally recognized expert in the development and application of non-animal toxicity product testing methods, and is also an expert in product safety and regulatory compliance. He has written numerous peer-reviewed journal articles and several book chapters on those subjects.

Dr. Bruner has contributed to the consumer products industry for more than two decades. Most recently, he served as director, environment, health and safety within Procter & Gamble's Gillette organization. He previously served as vice president of environment, health and safety for Gillette from 2000 to 2007.

Dr. Bruner holds a Doctor of Veterinary Medicine degree and a Ph.D. in pharmacology, both earned at Michigan State University. He also received his bachelor's degree at Michigan State.

**Mitchell Cheeseman:** Acting Director of FDA's Office of Food Additive Safety. Dr. Cheeseman received his Ph.D. in chemistry from the University of Florida in 1990. He has worked for FDA since 1991 in the regulation of direct food additives and food contact substances, color additives, Generally Recognized as Safe (GRAS) food ingredients and bioengineered food.

Dr. Cheeseman's research background includes the application of diverse spectroscopic methods to problems in physical and analytical chemistry, probabilistic risk assessment and the application of structure activity analysis to regulatory decision making. He has numerous publications on FDA's Threshold of Regulation process and the probabilistic risk assessment underlying that policy and process. He also is the author of publications regarding the use of structure activity analysis and short-term toxicity testing in the safety assessment of food additives. He has been an invited speaker and participant at many international meetings, workshops and working groups regarding the use of probabilistic risk assessment in the regulation of chemicals and the Threshold of Toxicological Concern (TTC).

During his career Dr. Cheeseman has been a lead in the development and implementation of FDA's Threshold of Regulation process for food contact substances and FDA's Food Contact Notification Program. In addition, he has pioneered the application of structure activity analysis in FDA's safety review of food ingredients and food contact substances.

**Rodger Curren:** President of the Institute for In Vitro Sciences, Inc. After more than 10 years of specializing in genetic toxicology, Dr. Curren created the *In Vitro* Toxicology Division as part of Microbiological Associates (now BioReliance) in 1988. This activity was subsequently incorporated as the nonprofit Institute for In Vitro Sciences, Inc. Since 1997, the Institute has provided educational and laboratory-based resources to industry, government and animal welfare organizations as well as the general public. Dr. Curren serves on many national and international committees and science advisory boards of organizations focused on the development, validation and practical use of alternative methods to whole animal testing. Among other activities, he is currently president of the American Society for Cellular and Computational Toxicology and is a member of the Scientific Advisory Committee for the European Union's validation authority, ECVAM.

Dr. Curren's efforts in optimizing and promoting new alternative methods have earned him several honors in the *in vitro* field, including the Russell and Burch Award, the Bjorn Ekwall Memorial Award, and the William and Eleanor Cave Award for outstanding achievements in the development, validation and advancement of humane alternatives for product testing.

Dr. Curren received his B.S. in biology from Purdue University, followed by an M.S. from Ohio University and a Ph.D. from the Institute of Microbiology at Rutgers University.

**Abby Dilley:** Senior Mediator at RESOLVE. Ms. Dilley has more than 25 years of experience in designing, facilitating and managing projects addressing scientifically complex and sometimes controversial public health and food-related policy issues. Topics Ms. Dilley has worked on include produce safety issues; pesticide residues in food; agricultural biotechnology policy; risk-based inspection for meat and poultry; public health interventions in reducing and mitigating mycotoxin, particularly aflatoxin exposure; harmonizing risk assessment protocols internationally; and developing recommendations regarding health claims for conventional foods. Ms. Dilley has worked with a very broad range of stakeholders from the public and private sectors, and nongovernment organizational communities at the local, state, regional, national and international levels. She holds a bachelor's degree in biology from Colorado College, and a master's degree in ecology and evolutionary biology from the University of Michigan.

**Jean Lou Dorne:** Toxicologist in the Emerging Risks Unit at the European Food Safety Authority. Dr. Dorne holds a Master's of Science in Toxicology from University of Surrey, a Master's in Philosophy in molecular biology from the Museum d'Histoire Naturelle de Paris and a Ph.D. from the University of Southampton. He has investigated the use of human variability in toxicokinetics for the major metabolic routes and application to risk assessment, for which he was awarded the Young Scientist award by the European Societies of Toxicology. Postdoctoral research includes the development of Monte Carlo models to include human variability in toxicokinetics in risk assessment and the development of new methods for the risk assessment (ecological and human) of mixtures within the European Project. In 2009, he received the Young Investigator Award from the British Toxicology Society. In 2006, he joined the European Food Safety Authority as a Senior Scientific Officer in the unit on contaminants in the food chain. He is now working in the emerging risks unit dealing with the toxicological aspects of emerging chemicals and new methodologies in chemical risk assessment. Dr. Dorne has published more than 45 peer-reviewed articles and five book chapters, and has a book in preparation.

**Will Fisher:** Vice President of Science and Policy Initiatives with the Institute of Food Technologists. Mr. Fisher serves as a liaison with a variety of government agencies, elected officials and organizations

that share a common commitment to the science of food and its application. As the lead executive in charge of science and policy initiatives, he ensures that IFT plays a critical role in identifying, analyzing and prioritizing emerging food issues; recommending appropriate IFT action; overseeing development of programs addressing the science of food and its application; and providing leadership and implementation of science and technology grants and contracts. He oversees the development of timely and effective science reports, positions and policy-oriented documents, ensuring that they appropriately reflect IFT's scientific and policy views.

After attaining both bachelor's and master's degrees at the University of Illinois, Mr. Fisher began his career with General Foods, where he held a number of research and development positions. Upon leaving General Foods, he became Director of R&D for Pillsbury's Godfather's Pizza Division. He moved on to become the Vice President of Technical Services for Arby's and Vice President of Technical Business Development for Hardee's Food Systems. In 1998, he joined Franchise Management International, developer and franchisor of multiple quick-serve restaurant chains, as president. Prior to joining IFT, Fisher was Vice President, Chief Marketing and Sales Officer for NSF International, a not-for-profit, public health and safety world organization headquartered in Ann Arbor, Michigan. He serves on numerous advisory boards and industry committees.

**Shelley Hearne:** Managing Director of the Pew Health Group at The Pew Charitable Trusts and visiting professor at the Johns Hopkins Bloomberg School of Public Health. Dr. Hearne most recently was the founding Executive Director of Trust for America's Health, a national organization dedicated to preventing epidemics and protecting people. Her prior positions include Executive Director of the Pew Environmental Health Commission, Program Officer at The Pew Charitable Trusts, Acting Director of the Office of Pollution Prevention at the New Jersey Department of Environmental Protection and scientist with the Natural Resources Defense Council.

Dr. Hearne has served as the chair of the American Public Health Association's Executive Board and Vice President of the Council on Education for Public Health, the accreditation body for public health schools. She is the author of a broad array of national accountability reports, including *F as in Fat: How Obesity Policies Are Failing in America*, which assessed state obesity rankings and policy initiatives. Dr. Hearne has testified regularly before the U.S. Congress on bioterrorism, pandemic preparedness and health tracking. She is the national recipient of the Delta Omega Curriculum Award honoring innovative public health teaching, and received both the Senator Frank R. Lautenberg Award for Public Health Advocacy and the American Public Health Association's Distinguished Service Award in Environmental Health. Dr. Hearne holds a bachelor's degree in chemistry and environmental studies with honors from Bowdoin College, and a doctorate in environmental health sciences from Columbia University's School of Public Health.

**Joe Hotchkiss:** Professor and Director of the School of Packaging at Michigan State University (MSU). Prior to joining MSU, he was chair of the food science department, Director of the Institute of Food Science and a founding member of the Institute for Comparative and Environmental Toxicology at Cornell University. He has an active research program dealing with food packaging, safety and toxicology. He taught courses in food science, packaging and food toxicology at Cornell. Prior to joining the faculty at Cornell, Dr. Hotchkiss was a Public Health Service Fellow at the U.S. Food and Drug Administration and served on FDA's Food Advisory Committee. Dr. Hotchkiss is a past member of the Food Chemicals Codex Committee of the National Academy of Sciences and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) of the FAO/WHO. Dr. Hotchkiss is a fellow of the Institute of Food Technologists and is a member of IFT's Toxicology and Safety Evaluation and Food Packaging divisions. He currently is an advisor to the Culinary Institute of America, International Life Sciences Institute and the Pew Health Group. He has served on the scientific advisory boards of a number of for-profit companies and frequently consults on matters related to packaging and product safety.

**Maricel Maffini:** Senior Officer in the Food Additives Project in the Pew Health Group at The Pew Charitable Trusts. Before joining the Pew Health Group in August 2010, Dr. Maffini was a research assistant professor in the Department of Anatomy and Cellular Biology at Tufts University School of Medicine in Boston. Her research focused on the fields of carcinogenesis and developmental biology.

Dr. Maffini's cancer studies demonstrated that carcinogenesis is a process akin to development gone wrong instead of a mutation-driven event. Additionally, she studied the association between exposures to environmental estrogen-mimics during fetal life and breast cancer risk in adulthood.

Dr. Maffini holds a Ph.D. in biology from the National University of Litoral, Santa Fe, Argentina. She received the Natalie V. Zucker Research Center for Women Scholars Award as well as awards from the World Bank. Dr. Maffini's work was supported by the Massachusetts Department of Public Health, the U.S. Department of Defense and Susan G. Komen for the Cure. She was a 2007 fellow of the First Science Communication Fellow Program created by Environmental Health Sciences (EHS).

**Tom Neltner:** Director of the Food Additive Project in the Pew Health Group at The Pew Charitable Trusts. Mr. Neltner is a chemical engineer, practicing attorney and a Certified Hazardous Materials Manager, with experience in state government, chemical manufacturing, small business support, academia and public interest advocacy.

Before joining the Pew Health Group in May 2010, he managed the National Healthy Homes Training Center and Network for the National Center for Healthy Housing. The Training Center is funded by the EPA, the U.S. Department of Housing and Urban Development (HUD), and the CDC) to build public health capacity for health and housing professionals. He managed a network of more than 25 training partners across the United States. Most of the training partners are cooperative extension services or schools of public health. As a volunteer for the Sierra Club, he worked on various issues involving chemicals in commerce, including air fresheners, formaldehyde in wood products, lead and cadmium in children's products and certain surfactants.

**Jennifer Sass:** Senior Scientist in the Health and Environment program of the Natural Resources Defense Council and a professorial lecturer at The George Washington University, Department of Environmental and Occupational Health. She oversees the U.S. government regulations of industrial chemicals and pesticides, and assesses the data underlying the regulatory decisions. Dr. Sass has degrees in anatomy and cell biology from the University of Saskatchewan, Canada, and toxicology from the University of Maryland. She has published more than three dozen articles in peer-reviewed journals, has presented testimony before the U.S. Congress and has participated in U.S. government scientific advisory committees.

**Michael Taylor:** Deputy Commissioner for Foods at the U.S. Food and Drug Administration. He is the first individual to hold the position, which was created along with a new Office of Foods in August 2009 to elevate the leadership and management of FDA's Foods Program. Mr. Taylor is a nationally recognized food safety expert, having served in high-level positions at FDA and USDA, as a research professor in academia and on several National Research Council expert committees.

As deputy commissioner for foods, Taylor provides leadership and direction to all food programs in the agency, including those managed by the Center for Food Safety and Applied Nutrition (CFSAN) and the Center for Veterinary Medicine (CVM) as well as the foods-related programs of FDA's inspection and compliance arm, the Office of Regulatory Affairs (ORA).

Mr. Taylor returned to FDA in July 2009 as Senior Advisor to the commissioner. Before that, he served as Research Professor, School of Public Health and Health Services, The George Washington University. His research agenda focused on policy, resource and institutional issues that affect the

success of public health agencies in carrying out their prevention-related missions. Mr. Taylor received his law degree from the University of Virginia and his B.A. degree in political science from Davidson College.

**Raymond Tice:** Chief of the NTP Biomolecular Screening Branch (BSB). The branch is responsible for coordinating the NTP High Throughput Screening (HTS) Initiative and plays a key role in the efforts of the Tox21 Community, which is an outgrowth of a 2008 Memorandum of Understanding between the NTP, the NIH Chemical Genomics Center and EPA's National Center for Computational Toxicology to collaborate on the research, development, validation and translation of new and innovative test methods that characterize key steps in toxicity pathways.

Dr. Tice received his Ph.D. in biology in 1976 from Johns Hopkins University. He was employed by the Medical Department at Brookhaven National Laboratory from 1976 to 1988 and by Integrated Laboratory Sciences, Inc. from 1988 to 2005, where his last position was Senior Vice President for Research and Development. He joined NIEHS in 2005 as Deputy Director of the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and in 2009 became the chief of the NTP Biomolecular Screening Branch.

Dr. Tice has served as President of the Environmental Mutagen Society (EMS) and as Vice President of the International Association of Environmental Mutagen Societies. He is the recipient of NIH Director's Group Awards for activities associated with the NIH Molecular Libraries Initiative and with the development of the ICCVAM Five-Year Plan (2008–2012). In late 2008, he (along with Dr. Christopher Austin of the NIH Chemical Genomics Center and Dr. Robert Kavlock of EPA's National Center for Computational Toxicology) received the North American Alternative Award from the Humane Society of the United States and Procter & Gamble for "outstanding scientific contributions to the advancement of viable alternatives to animal testing." In 2009, Dr. Tice received the EMS Alexander Hollaender Award in recognition of outstanding contributions in the application of the principles and techniques of environmental mutagenesis to the protection of human health. During his career, he has served on more than 50 international expert panels and committees related primarily to genetic toxicology and more recently to the validation of alternative test methods. He has published 130 scientific papers and book chapters, contributed to 23 electronic review publications in support of the NTP chemical nomination process and to 35 NICEATM-ICCVAM publications, and has edited four symposia proceedings. Dr. Tice is a member of the editorial boards of *Mutation Research* and *Environmental and Molecular Mutagenesis*.

**Angelika Tritscher:** WHO Joint Secretary to the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and Joint FAO/WHO Meeting on Pesticide Residues (JMPR). Dr. Tritscher graduated in food science from the University of Würzburg in Germany, and continued with her Ph.D. in biochemical toxicology, focusing on mechanism of hormonal carcinogenesis. She continued her research at the NIEHS focusing on mechanistic aspects and human health risk assessment for dioxins. Returning to Europe, she worked as a toxicologist in the Food Safety Group at the Nestlé Research Center in Lausanne, Switzerland, where she was responsible for organization and management of activities regarding risk assessment of chemicals in food for Nestlé operating companies worldwide. In 2003, Dr. Tritscher joined the World Health Organization, first in the International Programme on Chemical Safety and since July 2008 in the Department of Food Safety and Zoonoses. Her main responsibility is supporting the "chemicals in food" program by serving as WHO joint secretary to JECFA and JMPR, and on expert committees evaluating the safety of chemicals in food, such as additives, contaminants, natural toxicants, pesticide and veterinary drug residues. Other responsibilities relate to exposure assessment of chemicals, including the GEMS/Food program, further development of risk assessment principles and methods, and organization of expert consultations to address specific risk assessment questions, as well as risk benefit assessments. The scientific advice provided through such expert meetings forms the basis for international food safety standards as developed by the Codex

Alimentarius Commission. Dr. Tritscher is involved in many Codex activities representing WHO, and providing the scientific and technical background for risk management decisions. She is a board-certified toxicologist, a member of several national and international professional toxicology societies, and has published more than 50 papers and book chapters.

## APPENDIX F: WORKSHOP PLANNING TEAM

The following people led the design and preparation for the workshop:

- Heather Alger (Pew Health Group)
- Tim Appenzeller (*Nature*)
- Erin Bongard (Pew Health Group)
- Abby Dilley (RESOLVE)
- Will Fisher (Institute of Food Technologists)
- Paul Jung (National Institute of Environmental Health Sciences)
- Maricel Maffini (Pew Health Group)
- Tom Neltner (Pew Health Group)
- Rosie Newsome (Institute of Food Technologists)
- Ralph Simmons (U.S. Food and Drug Administration)

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