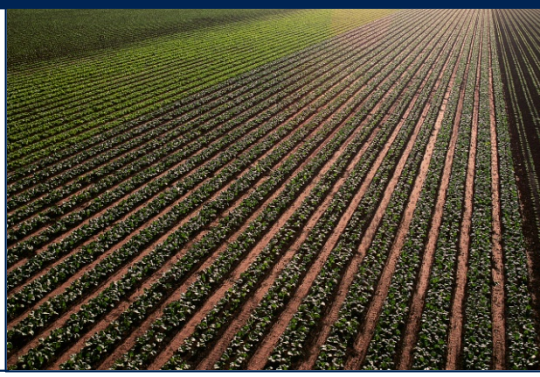
FDA Foods Program Review of Chemical Safety Capacity and Management:

Results of External Interviews





FINAL
July 1, 2013

Contract No. HHSF223201210011B
BPA No. 2

Disclaimer: It should be noted that the statements made by former FDA or other Federal employees in this report are the expression of individual views and opinions and do not necessarily reflect the facts or agency policy or guidance, and cannot be construed as official representations of (as examples) statutes or regulations.

Prepared for:
FDA/CFSAN
5100 Paint Branch Pkwy
College Park, MD 20740

Prepared by:
Versar, Inc.
6850 Versar Center
Springfield, VA 22151

Table of Contents

1. INTRODUCTION

This document compiles and presents the results of interviews with eight individuals, including: (1) FDA alumni and (2) senior managers from other Federal agencies with chemical safety assessment and management programs. These external interviews were conducted to augment the results from interviews of almost 90 FDA scientists, providing additional insight and perspectives on FDA's Foods and Veterinary Medicine Program's (FVMP's) chemical safety program. Obtaining the input of these individuals is consistent with the overall goal of this effort – to help FDA to be better positioned to meet current and future chemical safety challenges.

FDA recognizes the importance of the perspectives of these external scientists/participants, utilizing the institutional memory of FDA alumni, while also strengthening interactions with other Federal agencies and academia. FDA provided two lists of names of potential participants for the interviews: FDA Alumni (seven previous FDA employees) and other Federal agencies with chemical safety assessment and management programs (six names).

All potential participants were contacted via email to schedule appointments for interviews. The interviews could be conducted in person, by phone, or by filling out the questionnaire and submitting it via email. A total of nine interviews were conducted, five interviews with FDA alumni (three by phone and two via email) and four interviews with other Federal agency managers (all by phone). Interviewees were asked a series of ten questions addressing topics on science issues, communication and collaboration, and expertise and training.

This compilation presents the responses for each individual interview, organized by the two groups, and then sorted by the question. As a result, responses to the same questions from the respondents within each group can be seen side by side, to facilitate analysis of the similarities and differences in the responses.

2. RESPONSES FROM FDA ALUMNI

The interview results are presented by individual question below.

2.1 Chemical Safety Questions for FDA Alumni

Question 1
How has CFSAN's risk assessment and safety evaluation methods/program changed since you were at FDA?

FDA Alumni #1

I haven't been in contact with what has happened since I left FDA. What I can say is, before I left, among the trends that were happening was increased uses of computational methods, computational toxicology, structure activity, predictive methods, and a few years ago, when there actually was some money, some greater use of existing data for things like what was actually being used in the market place. One of the quirks, of the food additive program at least, is that the regulations are generic and anybody can use them once the regulation is published. One of the things the Agency had to do was try to keep track of what was actually in the food supply and how much of it. There were various methods and mechanisms in the past that were trying to do that, but recently, there had been an attempt to use existing data and information to get a much better picture of what was there. I think there was more attention being paid to things like allergenicity and immunological effects and so forth. Those are things that were happening when I left and I presume they continued, but I don't know that because I really haven't been keeping in touch.

FDA Alumni #2

Probably not a heck of a lot. This is probably true of several of these initial questions. I think the basic drift of what FDA does there is still the same. The risk assessment and safety evaluation methodologies and programs are pretty much intact conceptually and in practice as they were when I was there. There are advances in science. Science is not static, so there are going to be new developments in knowledge-bases created and I am hopeful that they've kept up with all that, but the basic structure and what they are there to do is the same and the methodologies are pretty much the same. The real job of FDA is to execute the statute; it is to essentially to administer the Federal Food, Drug, and Cosmetic Act. That law hasn't changed, but the way in which that statute is administered is under scientific concepts and scientific procedures. It is a science-based law. So obviously, as science changes, the knowledge-bases that you use to execute the statute are going to be enriched by that new science, but the basic drift of what you are trying to do there, to ensure the safety of the food supply, is the same. So, in that sense, nothing has changed. But you can point to changes in new science if there are new methodologies out there, like DNA sequencing for example, or the ability to understand something about the genomic basis, making biotechnology derived food additives safer from the likelihood there being allergens present. Things like that. It is all to be expected and you would want that there. If you look at some of the techniques they use, they are, I think, and should be,

making use of all the modern science that is available. But the basic job is the same – looking at the statute and asking if these things safe under the statute.

FDA Alumni #3

It has changed enormously. The responsibilities have changed almost a 100%, in that, during the time I was at FDA, our ultimate responsibility was formal rulemaking to establish regulations in the Federal Register. We did formal rulemaking on 300 Generally Recognized as Safe (GRAS) substances while I was there. We moved 30 color additives from the provisional color list to the permanent color list, which was no easy task. We were sued several times and finally went to DC Circuit Court of Appeal. We did well over a 100 indirect food additives. All of this had to go through a notice and comment, formal rulemaking resulting in a final regulation in the CFR. Today CFSAN does practically none of that. There are good reasons for that. I am certainly not criticizing that they don't do it. Partly, it's because the GRAS substances that were on the early GRAS list had already been converted over so they didn't have to worry about that. All the colors got permanently vested, that is those that were not carcinogenic, and had to be de-vested. Now the artificial sweeteners and artificial fats have really already been done. There is not much interest in industry in coming up with additional ones because there are enough on the market and it is a very competitive market.

The big legal change has been with indirect food additives where Congress passed a law in the '90s that provided for notification of indirect food additives. I think that since that law was passed, the Agency (if you look on its Website) has accepted the notices for over a 1,000 indirect food additives. The interesting thing about the law is it only allows the company that submitted its notification to take advantage of FDA granting notification and that is really unprecedented because the idea always had been that, whenever FDA approved anything in the food arena, it was open to any company. But with food contact notification, that is not the case. Every company has to get its own notification and that is one of the reasons why they have done so many because they have multiple notifications for the same substance, but there are an awful lot of food contact substances that migrate into food that need notification and that program, as far as I can see, has been going along well, consistent with the law, and apparently pretty consistent with what the industry finds acceptable.

A huge change was made in GRAS affirmation or GRAS regulation. The Agency decided around 1999 or 2000 that they weren't going to do GRAS affirmation anymore. I think they sent it to Congress, but I am not a 100% sure that they did. They made it clear that GRAS affirmation was something that they no longer were going to pursue and they proposed a regulation, which hasn't been finalized yet. So, for the past 12 or 13 years, it has remained as a proposed regulation and not a final regulation. At any rate, it has been quite successful. Hundreds of GRAS substances that have been noticed, not affirmed, but noticed. So there is no need for formal rulemaking for those indirects and no need for formal rulemaking for the GRAS substances. Both are noticed. The programs as far as I can see are going along well without any huge problems. I think we had far more problems in terms of lawsuits, Congressional hearings, and nasty letters than CFSAN is getting now over its various notification programs. I am sure they are getting challenges from consumer groups and that sort of thing, but that is inevitable. It is not a bad thing; it is not always a good thing, but it is something you always have to deal with.

FDA Alumni #4

CFSAN uses Risk Assessments (RA) and now relies more on formal risk assessments rather than best estimates.

FDA Alumni #5

In my experience, the RA and Safety Assessment (SA) methods were so varied and so inconsistently applied and managed that it is difficult to state concisely how they have changed. They suffered from a lack of systematic application and transparency. I recall each office and program doing it their own way.

Question 2
2a. Does it appear to be keeping up with the current and emerging state of the art and, is it recognized as such by the external scientific and stakeholder communities?

2b. If not, what are the shortcomings?

FDA Alumni #1

2a. I think classically, the Program had always been very well-regarded. In fact, the typical ways of assessing food additives was sort of invented at FDA in the past. As things got away from the classical, it got harder, given the resources available, to keep up entirely. I think one of the things that was reassuring is that it was really well-regarded by regulatory counterparts in Europe, Canada, and Asia, with people who kind of did the same work. Other stakeholder groups will have different opinions depending on where they are coming from. In general, the Program does pretty well and the shortcomings will be discussed in the next few questions.

2b. One has been the Program, and this is true of CFSAN as a whole and is certainly true of the Food Additives Program. In CFSAN, there are chemical safety programs for food additives, food ingredients, assessing chemical safety in cosmetics, the dietary ingredients in dietary supplements, and contaminants. There are a number of chemical safety programs in CFSAN and I don't know to what extent you are looking at all of them, but the food additives program is the one I am most familiar with and has probably been a little bit insular, not taking advantage perhaps of some of the ways and approaches and things that were being used even within the Center, let alone elsewhere, as we will talk about later when we talk about interagency coordination in the future. I'll talk about the others in the next question. I think it is easier.

FDA Alumni #2

2a. Yes, but here is a potential problem. For the folks (I am thinking of the toxicologists, chemists, consumer safety officers, environmental scientists, and other who are working on food additives in particular, which is where my expertise area is and where my experience was at FDA), there needs to be scientists conversant with the cutting edge of science. The work they do is kind of back behind the cutting edge a little bit. They are not doing research as in the university setting. They are administering the statute under the current basic knowledge that is available that science provides. Science is always moving forward and the cutting edge is always advancing. But, in order to do their job right, they have to stay as close to the cutting edge of science as possible and be conversant with it. That means, as government employees, they have to go to work every day and take care of that "inbox," but they also have to stay knowledgeable and stay sharp on what is new in science. That means that the Agency has got to provide for their training and their exposure to the outside world, send them to conferences, allow them the time to read and keep up with their field of expertise so they know the current science and can apply it to their work. Even when I was there, it was a struggle, but now maybe even more so because of the question of resource constraints. I don't think the Agency is able to allow its scientists the freedom to go to as

many conferences as they would like to go to, to be talking to their industry colleagues, and their academic counterparts to understand what is happening out there and the scientific cutting edge and then apply that to their work. There is a real danger there, I think, that they could fall behind. I think you see it sometimes where people say aren't you aware of this new phenomena or this new scientific tool, well maybe and maybe not. In general terms, I would say there is a danger there. On the whole, they try very hard to keep up. I don't have any hard evidence to say this is an example. I think, just from my experience, I would say I have seen situations where the scientists at FDA have had to really struggle to stay right on top of the cutting edge of their knowledge-base that they use in making their decisions. It's a struggle and really is something the Agency needs to pay attention to.

2b. I don't know if I can give examples. NCTR, for example, that is an Agency science lab but it is doing research down there in Little Rock, AR. I don't know to what extent the rank and file toxicologists in CFSAN are really talking to NCTR counterparts down there. In some cases, they may be but I don't know they have the luxury to have the kind of in depth conversations they need to have. I would say there is a question mark over that for me. I would hope that they are talking to their internal counterparts down at NCTR. Beyond that, there is probably a lot going on out in the real world, out in the industry and out in the academic world, and maybe the bigger world outside in Europe and elsewhere, where there are conferences going on and information is being exchanged and I am not sure that the FDA scientists are as plugged into that as they ought to be. In the shortcomings, I hesitate to try to point to specific examples. I could probably come up with a few as we talk here and go forward, but thinking more in terms of the generic drift of things, what I noticed when I was there was it was very hard to find funds to send toxicologists or chemists to the kinds of conferences they needed to be at in order to stay conversant with everything that was going on around them.

FDA Alumni #3

2a. I would say, since FDA's existence, it always struggled to do that. You can always argue that it never quite gets there. I don't see any greater gap today than what we have commonly had. It is always a struggle to get where the public wants you to be and where you want to be.

2b. I am not privy to know what is going on in a detailed way inside the Agency, but in a general way, I think one of the deficiencies that they may have today that wasn't apparent when I was there, is the interaction between the research people and the review people. When I was there, the research people and the review people were in the same office and, within the Division of Toxicology, there was a large research group of about 100 people and a large regulatory group of about 50 people. Today, they are totally separate. When I was there, we were really got a lot of value out of the labs and the research people. They did a lot of critical things for us, e.g., when we had a big problem with BHA, which is the number one food additive in the world. They did critical work when we had problems with trypsin inhibitors, which could have been a big problem for infant formula. They did ground breaking critical work. Those are two examples but there are many examples where they really pitched in and helped out a great deal. I think it gave us credibility too. Unless they

are working together, they tend to drift further and further apart. I think that may be happening.

FDA Alumni #4

2a. It does appear that the CFSAN staff are keeping up with new development in risk assessments.
2b. No response given.

FDA Alumni #5

2a. No. I think that the RA and SA procedures have not adapted to changing science and they have not kept up with the state of the science, both domestically and internationally.

2b. FDA/CFSAN scientists are not able to effectively interact with the leading scientists in the area and to incorporate new and better methods into safety and regulatory decision making. This is both because of institutional inertia and the legal framework that they have to operate in.

Question 3
3a. What do you see as some of the emerging issues and questions in chemical safety review?

3b. How well do you think CFSAN facilitates the needed developments in the science to address and answer these issues and questions?

3c. Has this changed since you were here?

FDA Alumni #1

3a. I assume you have talked about this a lot in the internal discussions as well. I'll back up when I talk about the traditional assessment of food additives being invented at FDA. Until very recently, the assessment of food additives and food ingredients was essentially classical toxicology. That is that food additives were intended to be invisible. So when you were looking at animal toxicity tests, you were able to put in high enough safety factors so there really were no effects at all. There were effects on the food, but not on the animal or the person by the time you had this very large safety factor. That worked very, very well. I think the things that are out there now are different and challenging. One is what I will call generally the toxicology-nutrition interface, and that has to do with the dietary ingredients in conventional foods; it has to do with things like trying to assess what is going on with salt and fat. The food additives law probably is not the very best tool to use to deal with dietary guidance. It is a tool and can be used, but you are now talking about compounds that do have effects. Then the question becomes, what is an adverse effect and how do you distinguish between signal and noise? That's new.

Obviously, the other one is probably the one that provoked this study – what I will call very generally the non-toxicological endpoints. That includes the things that are enzyme-mediated or hormone-mediated, i.e., the endocrine disruptors. The things that, rather than classical toxicology or pathology looking at livers and kidneys, act in different ways from immunological effects, as well as the immune boosters and so forth and food allergenicity. I'll lump those all under the notion of sort of the non-classical toxicity endpoints and they have in common that there are effects. And so how do you distinguish the effects, the nutrition ones anyway, that are perfectly reasonable, from those that are adverse effects? That is one challenge and one that goes along with that has to do with the highly increased sensitivity of methods. So you are detecting things, and again, that comes to signal and noise. What's noise and what's signal and where do you put your attention? How do you set priorities? Those kinds of questions are the ones that are challenges in front of anyone doing chemical safety review today.

3b. When thinking about this question, I think the first issue is who should do this work. Clearly, traditionally the industry or academia, the outside, has been responsible for developing most of the testing because it was to their advantage to do that since they were the ones looking for approvals. Clearly, we do have a fair amount of internal capabilities. Obviously, I am sure bisphenol A (BPA) is part of the reason you are doing this study. I will say perhaps one of the positive things that has come out of the long, nightmarish issue

of BPA has been the better coordination with NCTR. NCTR obviously has lots of capabilities and, through much of its history, there has been a lot of concern that their focus and their work was not serving the regulatory needs as well as it might. BPA was a case where the communication was very, very good, in the sense of saying, let's do tests that actually we can rely on in a regulatory standpoint. NCTR certainly is one, and to the extent that worked well with BPA and to the extent that can be replicated in other cases, it would be very, very helpful. I'm sure part of the problem is that they serve, not only CFSAN, but also the rest of the Agency and, again, it is a matter of priority setting.

The internal CFSAN labs are another case where the Center/Agency needs to do a better job of trying to make sure that there is the best possible communication between the scientists in the lab and the regulators to make sure that what the lab scientists are doing is actually very relevant to regulatory decision making. I'm not sure I have any good ideas to how that could happen. If I did, I would have helped make it happen when I was there. It has been a long-standing problem.

Another thing I was thinking about. One of the issues that arose with bisphenol A, and a lot of other compounds as well, was that there is a lot of work in the literature, work that was done in academe, for a particular purpose of figuring out the mechanisms of action of these compounds. The Agency was saying we really couldn't rely on those studies, among other things, because these were investigations that were designed to answer hypotheses about endocrine disruption. They weren't validated. They were useful for hypotheses generation, but weren't the kinds of things we could rely on to make a regulatory decision. It occurs to me that perhaps one of the things that the Agency and CFSAN and other possibly could do is do more to try to see if some of those tests can be validated and can be useful from a regulatory point of view. I assume, when doing your interviews, the group ICCVAM might have come up. They're about animal alternatives. When I was there, the group was not very well resourced and there wasn't a whole lot of agency leadership behind it. It was a group that came up with a couple of *in vitro* tests and did the work to see if they could be validated so they could be used in a regulatory sense. Maybe that is too narrow. Animal alternatives obviously are a good thing, but perhaps there should be more of that on the Agency, just in the sense of animal tests. Are there other animal tests that could be validated? Are there other tests that are particularly relevant to things like hormone-mediated or immunology? Everybody in the whole world has been looking for an animal model for allergenicity, but perhaps that is something the Center/Agency could do in terms of trying to say, are there methods out there that are being used in academia, being used in the published literature that actually could work for regulatory decision making if they were properly validated. Maybe that is something the Agency could take on at least in part with a group like ICCVAM that would be interagency and governmental. Clearly, the agencies themselves don't really have the resources to go out a do a lot of this testing. It is appropriate, but it is easy to get lambasted for relying on industry tests. The government can't do all the testing, and therefore, needs a way to know what tests are valid and what tests are useful and how they can be best used for regulatory decision making. Maybe that is an example. ICCVAM could be broadened and given more leadership backing in the Agency.

3c. Again, I don't know. I haven't been in contact enough to answer that.

FDA Alumni #2

3a. There has been a lot of controversy that has been swirling for years on BPA; for example, the compound that is present in these plastic food containers and lid liners, where there is concern voiced about endocrine disruption. These phenomena are sometimes exhibited in studies that are done when the dose, response is not monotonic. At least it is claimed in the studies that, when you drop the dose, the response drops; that happens, but you get down to a low enough dose the response starts going back up again. It is counter intuitive. It isn't very well documented in reproducible studies, but is claimed. There is a whole lot of controversy about whether that is a true phenomenon and whether or not it should be incorporated into the review process that scientists use on a routine basis, or whether it is just a one-off or a phenomenon that could be more of a general phenomenon. I think here is a case where this is an emerging issue. FDA needs to be on top of it and have a really good feel for whether or not it is a material thing that should be considered in the study.

Biotechnology and allergenicity are other areas that are emerging. These are all places where science is changing the appearance of things and this knowledge base needs to be incorporated into the review process. Let me reinforce a point here though and that was that FDA operates behind the cutting edge. It has to because it is making decisions that have to be based on an administrative record and has to be supported by that record in a court of law possibly. And so the decisions that they make cannot be the same that would happen in a university lab where you are exploring the cutting edge of science and there is very little agreement about whether these facts are really facts or not. FDA has to operate behind that cutting edge because they need to operate in an area of science that is a little bit more cut and dry so that the force and effect of law can come into play on their decisions. There has to be a reliability and a sense that this is solid science and it's been validated. Un-validated science is interesting stuff and FDA has to be aware of it, but it can't use un-validated science in making its decisions. So while the cutting edge is important to be aware of and to begin to at least be knowledgeable about in your situ evaluations. You can't use it on a routine basis to make those decisions.

Biotechnology and allergenicity issues, the whole idea of genetic expression looking for carcinogens on microscopic dots on slides where you are looking for the gene expression, micro dots when you are looking for gene expression. These are indicators potentially of genetic tendencies for compounds to elicit carcinogenetic effects. The gold standard for making decisions about whether something is a carcinogen is still the 2-year bioassay in rodents. If you try to inject unsettled or un-validated science into the decision making process, you are really going to mess it up because, for one thing, it will be much more expensive because you will have to do a lot more studies that are not well-settled or understood. You will have to go through the validation process while you are doing the application review. That is really going to slow things down. Using settled science is actually much more effective in reaching decisions. While the Agency has to be aware of all these techniques and procedures, they can't always just inject them automatically into the current safety risk assessment process today. They have to think about how to do it in the

future. Perhaps today is not the time to force the use of them just because they are new and novel.

3b. I think there is good intention. The Agency really does try. It gives good lip service to the need. Kind of like what I am doing saying, "yeah, you got to do these things." Whether it really effectively does it or not is sometimes an open question. It is not so much that the intention isn't really there, but the funding isn't there. The "inboxes" of these people are so high they don't have the time and the money is not there to fund the laboratories at FDA that need to be doing these things or to send the desk-bound scientists to conferences so that they can learn this material. It really is a question of resources, in large part, as far as I can tell.

3c. It's been the same. I don't see a change particularly. This is a struggle that has been going on ever since I can remember. It is an everyday challenge to a regulatory agency that is science-based to keep its regulators well enough funded so they can hire the best scientists out there, that are competent to review the kinds of things that are coming in the door from industry and stay conversant with the cutting edge of their field, and still have the time to do in a timely way the job the country is hiring them to do. It's a real challenge.

FDA Alumni #3

3a. That is really a good question. When I was there, the really big emerging issue was risk assessment of carcinogenic substances. That was new, it was controversial, and it was emotional. I personally wrote several papers that were semi-scientific and maybe even semi-political about the place for risk assessment of carcinogens and, for that matter, everything else. That was not just a national issue, it was an international issue and different countries and different zones in the world took different positions and there was a lot of acrimony. Much of this has since died down. I don't think it is that big of an issue now, which is a good thing. Probably today the biggest thing facing food safety people is allergenicity; hypersensitivity of food substances might be the biggest thing on the radar screen right now.

3b. I don't know. I don't know what their research program is right now and I don't know how well integrated it is with the needs, as viewed by the regulatory or review people. When I was there, I think it was really good. It was good, in large part, because the people running the program were making sure that what they were doing was really relevant to our mission. I don't know if that is going on today.

3c. Yes, when I was at FDA, it was integrated – research and review. They really weren't doing anything that was inconsistent with our mission. That was because it was so well integrated organizationally. The current organization is quite different. The researchers are totally separated, organizationally, from the reviewers and the regulatory people. That doesn't mean that they are not interacting, but it does mean that it is more difficult for them to interact. I made sure as Director of my office that there was good interaction and there was. It wasn't a problem for me because all my senior people wanted it that way.

FDA Alumni #4

3a. The primary issue is predicting the next chemical-related public health threat among the many possibilities

3b. CFSAN is, like industry, typically behind in anticipating developing issues.

3c. It has not changed.

FDA Alumni #5

3a. One is the undue influence of outside interest group pressure and dramatic changes in the operational climate (mostly political). Another is the globally-emerging advances in science that allow both a better and more accurate RA and SA and better, more timely and more efficient approaches to prioritization of focus and action.

3b. Not very well. I don't think the management structure is very adaptive to changes in science. There should be an institutionalized mechanism for frequent and deliberate assessment and incorporation of advancing science into the RA/SA activities.

3c. No. In many cases, they are still using the same approaches and methods as when I came to the agency in 1968.

Question 4
4a. Does CFSAN have the scope and depth of expertise it needs to fulfill its chemical safety regulatory obligations and meet today's (and future) chemical safety challenges?

4b. In what areas does CFSAN have greatest expertise?

4c. Where does CFSAN most need to increase its scope and depth of expertise to improve our programs?

FDA Alumni #1

4a. Probably never have and never will in order to do it completely as well as one would wish.

4b. It has very good expertise in things like analytical chemistry, classical toxicology, and microbiology. I think one of the issues here is, for the last couple of decades, in terms of resources, priorities, and attention for the Agency, or at least CFSAN, it's been the years of bacteriology or microbiology. That is perfectly legitimate and appropriate that most resources should be put on foodborne illness where you do have people getting sick and dying. So there is a lot of expertise in that area, some of which is very helpful for the chemical safety. Microbiological issues do come up. Analytical chemistry and toxicology in general and microbiology are probably places where, at least when I left, CFSAN was well represented.

4c. As new issues come up, things like immunology and allergenicity, there is some expertise there, but it is not all that deep. I'll put in a plug for biochemistry and reaction mechanisms. I think when we were back in the classical way of dealing with chemicals in food, at least chemicals added to food, you could put in a big safety factor and there would be no effects at all. You could make a really good case for saying you have lots and lots of animals and they don't show any kinds of effects at all; you're done. You really don't have to worry too much about the mechanism of what was going on because there were no effects. Now that we're in the situation of the enzyme-mediated, the hormone-mediated and the nutritional interface, I think mechanism of action, intermediary metabolism, and comparative physiology between animals and humans are areas that probably are going to be more required. Again, this is a matter of resources. I guess I have never been a big fan of saying you have to have experts in every area in-house, partly because you usually can't afford more than one expert and if you have one expert all by themself, isolated, they are not an expert for long. Once you get some experts, the next thing that comes over the transom you need somebody else. So I think that, to that extent, and especially now with the resource constrained area, the best thing you can do is hire bright people that have a breadth of experience and know enough to say we need help. I think the idea of hiring through contract expertise when you need it. Obviously, it is a two-edged sword and has to be done carefully, but it I think is one way to deal with the size of the programs we are talking about and the unlikelihood that they are going to expand enormously. It is unrealistic to suggest that we are going to be able to completely staff up in every possible area. It is important to be able to continually hire people who are attuned to what is going on in academia and

what's going on in the science and essentially churn the scientific expertise in the Agency. Buy what you need and when you need it, at times.

FDA Alumni #2

4a. I think the short answer is yes, for the moment, but I really worry about the ability of the Agency to hire the best scientists in the coming years. I know that some of the people I hired during my tenure at FDA have left the Agency earlier than my colleagues and my immediate peer group. We were of a different generation and our whole mind-set was you accrue a job and spend you whole career there. Many of us did. Now, people don't do that as much. I am really fearful that the Agency has not been able to retain the scientists because if you give them enough headaches, you sequester their pay, you don't show any indication of progressing their salaries or career development, the best ones are going to leave and that is what's happening. I think today you probably could say it has the scope and depth of experience that it needs to fulfill its responsibilities, but when you get to the "and future chemical safety challenges," I would put a question mark over the future because the answer might be that I'm not sure and I am fearful that it is not.

4b. Toxicology is strong and always has been strong and should continue to be strong, but then again, I worry. Chemists are strong. Its scientists are as good as anybody anywhere. But I really fear that that will not be the case five to ten years from now unless there is something done to ensure that they continue to be able to hire the best qualified candidates and keep them.

4c. I don't know that I really have an answer to that. I don't think there is a specific scientific area that is vulnerable. I think they all are vulnerable. As I said, not being able to hire and keep the best scientists, that is a problem across the board. But I don't see any particular holes in, let's say, the toxicology area or biochemists or physical scientists, or whatever. If you look over that organization, you will see expertise in all the areas where you will probably need it. You'll find an MD when you need an MD. There is a particular breed of individuals that is really important to create, train, and maintain and that is the consumer safety officer type of job. Those are folks that are scientifically trained, but their job involves project management, the creation of teams, and the effective use of those teams to get to the decision point the Agency has to get to in administering the statute. These consumer safety officers, even though they are scientists in their own right, their job really is to build the administrative record that allows the Agency to reach and defend its decisions. It is science plus the ability to pull a team together and make it work effectively. Then make sure the administrative record is solid, to work with the attorneys at the Agency to make sure the legal briefs that support that administrative record and decision that is being made are properly done, and connect with the science, knit together the law and science. This is a unique kind of individual who needs to do all those things. They have to be good at interpersonal skills. They have to read well, they have to write well, and they have to be good scientists. Those are hard people to find and you almost have to create them out of thin air. You have to hire good people, train them, and keep them. That is probably a potential weak spot. If you cannot keep people like that, you won't be doing an effective job.

FDA Alumni #3

4a. I think it does. They have had a lot of retirements in the last few years and they lost a lot of people with institutional memory and also a lot of functionality. These people are extremely hard to replace. Furthermore, a lot of the leaders in CFSAN, mainly division directors, are getting pretty close to retirement and the question is, do they have people behind them that are ready to step in and take their jobs. Do they have adequate knowledge and training to do that? I simply don't know. They haven't been doing that much hiring in recent years.

4b. They have super expertise in the area of indirect food additives or food contact substances. They've got good teams within that division and, knowledge-wise, they know as much as any group in the world as to what the food contact substances are, how they get into food, what they break down into, and what their safety is. They are extremely knowledgeable and the people in the GRAS group that have GRAS notices on quite a number of substances have to be quite knowledgeable in the area of substances that are generally recognized as safe and what is being used in the food industry. Once that GRAS notification/regulation was proposed and the program got underway the industry, I think it was a lot more willing to share what they were doing and what they wanted to do with the Agency because the notification process is not as overwhelming as the GRAS affirmation process was. In fact the GRAS affirmation process was so difficult that, at a Congressional hearing, we were asked, "How long does it take to GRAS affirm a substance?" And we said, "We can't give you an average because we've got about 200 submissions and only 3 or 4 have ever been GRAS affirmed." So going from GRAS affirmation to GRAS notification was an enormous change. As you can well imagine, there were groups out there that don't like that and don't think it provides the same level of safety as GRAS affirmation. I don't think that is true at all. If you look at what they have GRAS noticed, it looks to me that the program is working quite well and working quite well in assuring food safety.

4c. My personal opinion is what I have been talking about earlier and that is to try and bring the research people together more with the regulatory people to explore the issues that have come to their attention or issues that have prevented them from doing notices or regulations. If anybody knows what the problems are, it is them, because those problems come to them. There are two ways of dealing with it. One is you figure out how to go ahead of a notification and regulation. The other is that you reject the submission. Sometimes that is trivial; you are rejecting it for reasons that are so clear cut that action is trivial. There are other occasions where your rejection says something really profound and requires additional knowledge to resolve. An example of that, and I might be reaching too far, are the sugar alcohols, where there has been continuing concern at FDA, more so at FDA than the rest of the world, that sugar alcohols may pose a risk of cancer. There are all kinds of things they can do in research that would help to resolve concerns that they have. As far as I know, they are not using the labs in that kind of way. I may be wrong. I think bringing the labs in more to deal with problems that CFSAN has, is facing, and needs to resolve would be a very good thing. That doesn't necessarily mean the lab people would like it, because the lab people like to do their own thing whenever they can. It is not that easy of a thing to do unless you have a bunch of people that are really dedicated to do it. As you lose those people, things kind of drift apart, and I think that has happened. I think that is probably the biggest weakness that is theoretically fixable. There are weaknesses that are not theoretically

fixable. An example of that would be risk assessment. You are not going to convince everybody that risk assessment should be done on carcinogens.

FDA Alumni #4

4a. No. CFSAN needs to hire/acquire both depth and breadth of expertise. More trained toxicologists/chemists.

4b. Analytical expertise and capability.

4c. Food toxicology/food chemistry.

FDA Alumni #5

4a. Yes. My experience is that they have adequate scientific staff and skills necessary to fulfill their RA/SA responsibilities. They are not always properly assigned, trained and managed.

4b. CFSAN has great expertise in chemical analysis and assessing exposure to chemicals.

4c. I'm not sure this is the right question. CFSAN has very skilled scientists. It lacks an effective and adaptable management structure and legal/regulatory climate in which to work. This results in damaging influences from outside interests and a "moving of the target" when this climate changes. CFSAN would benefit from a greater interactive climate with leaders in the field domestically and internationally, as well as from all stakeholders (industry, academia and public interest). I have often thought that a RA/SA advisory committee might help, but the advisory committee (AC) process is excessively bureaucratic in nature.

Question 5

5a. How can CFSAN keep the Redbook and other guidance up to date with the pace of new science?

5b. Is there an alternative to the lengthy guidance procedure that you could suggest?

5c. Does CFSAN still need a Redbook?

FDA Alumni #1

5a. Yes, that was an interesting question. It's not easy. I think that the attempt made some years ago to say we won't try to do a whole book but we'll put chapters up individually up on the Web and do it one piece at a time was in the right direction. But it still turned out to be an undertaking that took longer than it should so that it was less useful than it could have been. Then again, it was much more resource intensive and that gets to the next two parts of that question.

5b. The lengthy guidance procedure is a pain, but it was there for a purpose, in the sense to make sure there was lots of input and guidance didn't turn into regulations and requirements without due process as it were. But it did make it so that it was discouraging to put out guidance because it was so resource intensive.

5c. This gets to the first part of the question as well. I know that the stakeholders and people on the outside certainly want a "Redbook." I don't think we have a chance to do a new Redbook *per se*. But I think it is really important both for the stakeholders and the Agency and for the internal scientists to write down and articulate their thinking in guidance and put it out there. Because there is nothing like having to write it down and make a coherent argument to see where you are perhaps making assumptions that you didn't even know were assumptions. I think it is very helpful for both the scientists internally and the stakeholders to find ways to put out agency thinking and guidance. If putting out anything that was even remotely like the Redbook, in the front part of the Redbook is where people talked about their concern levels and so forth. That was almost as important as the second part of the Redbook because it laid out agency thinking. I think that the way we might now need to do it would be to do it in much smaller chunks. An enormous investment of lots and lots of time and effort so that it becomes such a big project that it never gets done because it is so hard. I think it is very important both for the Agency and the outside world to maybe chunk it down to the smallest divisible piece of useful guidance or useful thinking of the Agency and, in some way to be able to, get it out. I don't know whether the Agency needs a Redbook, but it needs something like the chapters in the Redbook. I think it is very important for the Program to have out there their best possible guidance, with all the provisos that it is going to change or if you do a draft guidance on a subject and you find that you are barking up the wrong tree, then only be too happy to say, never mind, let's wait a couple of years and try this again because obviously we weren't ready for prime time. Not to make it such a big project and make it so difficult that it just doesn't get done. I think that is a shortcoming. I think the programs, in general, have fallen behind in terms of getting their thinking on issues, even when they are not quite to the place where you know exactly

where you are on some of these but getting it out there. Although meetings and workshops are fine and might be very good for another purpose (keeping in contact with academics and people outside the government), there is nothing like writing it down and let everybody see what you've got. I don't think there is any other way to do that other than just putting out guidances in as timely manner as possible.

FDA Alumni #2

5a. This is a real challenge and this goes back to a lot of what I already said. The Redbook is a good achievement. When I got to FDA in 1977, there were all kinds of hoops that industry had to go through to satisfy the Agency that the required amount of work was done to support the safety decision on whether or not to approve a food or color additive – that was all kind of unwritten. It was folklore, it was orally transmitted wisdom, it was something an industry petitioner might learn when coming to the Agency and having a meeting and asking, what do I need to do? A senior person at the time would sit back in a chair and say why don't you do a subchronic feeding study in two rodent species and histopathology on 30 organ tissues at decent doses and let's see what you get. Then, based on that, the answer after 1.5-2 years would be, this study didn't seem to tell us what we wanted to know, why don't you do a chronic feeding study. Industry would tear its hair out. So the Agency put together the Redbook in 1979/1980. It was the first attempt to put down in writing the basic scheme of things that the Agency was looking for in terms of toxicological and other information to help industry understand what it what that they had to do to satisfy the safety criteria the Agency was administering under the statute. Having it in writing was a boon. You could look at it and see what you have to do. It started the discussion and it held the Agency. The Agency wasn't totally bound by that document but, in a way, it was hanging out there. This is pretty much what we want to see. So it was good because industry had a target to shoot for and the Agency had a basic guideline they could wave around and say if you really want to know what you have to do here it is in this book. The problem is that it's a very extensive document. It is hard to find the time, these scientists who are writing this document are also supposed to be taking care of the huge "inbox" they have. Keeping it up to date was an impossibility. As a result, they moved away from publishing a hard copy volume and reissuing it from time to time front to back and moved to updating it periodically from time to time on the internet. I think that is a good thing. They put it on the internet and say, here is the document and, by the way, in a year we will have Chapter 9 rewritten and will update what to do with respect to toxicology.

How can CFSAN keep the Redbook and other guidance up to date with the pace of new science? So keep your scientists current, keep them conversant with the cutting edge of science and then update the Redbook from time to time based on that science, but do it on the internet and do it chapter by chapter.

5b. I don't think there is particularly. You could always say it is case-by-case, but I think there really needs to be a document like the Redbook that lays it out there and says here is the basic scheme of things. I'm not so sure there is an alternative. The alternative is not to have something written and not to have it be comprehensive. Then I think you would go right back to the way it was in the 1970s. People will be at sea. They won't know what the

Agency requires for any particular thing. At least it is a starting point. The Redbook is really, more or less, a starting point. Toxicological Principles is the title of it. It's a starting point; it is not necessarily the end point for every package that comes into the door. You really do need a document like that. If not hard copy, you need it up on the Web and updated from time to time.

5c. Yes, absolutely; it has to have something in writing for the purpose of laying out the basic concept. Here is what we would like to see; if you are going to try to get a new food additive in the food supply this is the basic package of information that you are going to have to put together.

FDA Alumni #3

5a. That is a good question. Obviously, they have to look at the problems that have come to them and then they have to look at what their guidelines are, which would include the Redbook. They have to see if they can't make advances that will help to resolve some of those issues and problems. It really needs to be done, not just by the reviewer or regulatory people, but also by the lab people. If the lab people are not pursuing a comparable agenda, the lab people are not going to help very much, but it would be a start. It is not an easy thing to get them to work together. It is not natural for them to work together. It takes leadership.

5b. The notification of indirect food additives or food contact substances and notification of GRAS substances does depart very significantly from the lengthy guidance in the Redbook. It does so, in my judgment, in a satisfactory way, but it does depart. I think it's an evolutionary process. I would say that some resources need to be dedicated to try to keep the Redbook updated and making sure that it is relevant with respect to what's going on today. Originally, the Redbook was produced, it was first announced in the Federal Register in the '80s, so the basic Redbook is over 30 years old. That doesn't necessarily mean that it is out of date toxicologically, but it does mean that updating should be done. That might sound easy, but it is not easy at all. Every time CFSAN has tried to update it, it has pretty much been a disaster.

5c. That's a good question. It certainly doesn't need it the way that it did back when the Redbook was produced. The Redbook does two critical things. It says what kinds of studies should be done to determine whether a food additive is safe. The other thing it does is that is has essentially a mathematical scheme, whereby you can determine what priority for retesting approved additives should have. The reason we did that was because we were constantly being hit by Congress about why we were doing something about this food additive. We have hundreds of food additives and so we wanted to be able to determine what priority for retesting each food additive had. The Redbook and the subsequent reviews of the additives did that for us. So when we were called in to testify before Congress and were asked, "Why aren't you doing more with this compound?" We could say, "Well it is 298 on our priority list and we are working on 1, 2, 3, 4 right now and, if you want us to work on more, you are going to have to give us more money."

FDA Alumni #4

5a. Invest more in allowing scientists to engage with professional associations at the forefront of food toxicology (e.g., Tox Forum; ACS; IFT).

5b. One-pagers that list essentials (similar to what was done with agents in the food defense program).

5c. I think the Redbook is valuable and of value to the regulated industry as a reference of agency thought.

FDA Alumni #5

5a. Very poorly! I think the Redbook is the poster child for what is wrong and may even be an embarrassment for the agency in the SA/RA community.

5b. Perhaps a reinvented Redbook is a better alternative. It should be a "living" document that communicates the current scientific thought for SA. Instead of being totally CFSAN-centric in its content and updates, perhaps a RA/SA advisory committee would help to keep industry guidance up-to-date. It might also benefit from constructive engagement with the global scientific and regulatory community. The current process for development and issuance of guidance is arcane and outdated (so-called Good Guidance Practices).

5c. No. However, the regulated stakeholders do need an effective way to communicate with the agency and to determine what is really needed to assess risk and conduct safety assessments. This is not a one-size-fits-all issue, even though FDA often applies it that way through the Redbook. Unfortunately, the Redbook is basically dogma and safety assessments are measured against the Redbook. Even though the Redbook is described as guidance approximating the requirements, it allows very little deviation.

Question 6

6a. How can CFSAN be more proactive in identifying compounds or issues of emerging safety concern (for example, contaminants, endocrine disruptors, dietary ingredients in conventional food)?

6b. Has this changed since you were at CFSAN?

FDA Alumni #1

6a. I am going to say a word that is probably a dirty word to me because I spent some of my least productive moments at FDA thinking and working on this, but the word is "bioinformatics." I think we do really need to have to make much, much better use of information and data that are out there and use modern, informatics methods for getting that information in. Clearly, there is room for a lot of things here. There is certainly room to say that people need to be following the literature. If you have good scientists and people not long from academe or industry, or out there or keeping in touch. You'll have people reading the literature and knowing what's going on. But to try to go to meetings and be involved are all important items, but we do need to make the best possible use of external databases and external information. I think most emerging issues are pretty identifiable if people are active and involved in both the literature and the scientific community. I think we need to find better ways to prioritize, to say which are the ones that are potentially really going to impact public health and potentially impact the regulatory decision making, and why. Years and years ago, in attempting to keep an eye on compounds in the literature, there were large contracts with National Academies and so forth, but I think there is lots of information and data that industry generates and people generate and I think we could use. Maybe that's a place when they were asking about what kind of expertise do we need. We do need people that are comfortable with that terrible phrase of "data mining," but at least knowing how to use data and data information and databases that are out there to say, "Oh, this is not only an emerging issue but it is going to be relevant and important for us to have to deal with sooner rather than later.

6b. Once again, I will say that I don't know. As I mentioned before, before I left, people were, for at least that brief shining moment of time when there was a fair amount of money for the Program, trying to begin to do some of this. I hope that this has continued.

FDA Alumni #2

6a. This is really an important point here. What we have been talking about up until now is really premarket safety evaluation. It is what the Agency does when something has never been in the food supply before or a particular use of a substance that has never been approved before is going to be approved or decided by the Agency not to be approved. That is what I call a premarket decision. That has to be distinguished between a post market decision about whether or not to be concerned about something that is already out there in use and has presented risks that nobody anticipated or that are now emerging based on new science or new studies that may have been done. Administratively that is very different stuff. When FDA approves a new food additive it must use all the scientific knowledge and

all the information available on that substance. It has to comb the literature and know all the most recent studies that have been done on it. It has to understand the science of that and then apply the best science under its regulatory regime to make those decisions. When something is already out there in the marketplace, the question of how does the Agency approaches that: what triggers a response, what triggers Agency action, what triggers a re-review of safety, what triggers a ban or a court action or some sort of legal step that results in a substance being taken off the market or at least questioned? Those are really two different regimes of statute. Once something is on the books, it is much more difficult to take action against it, unless there is a pile of evidence. The pile of evidence has to be really well put together. The Agency is charged with maintaining the safety of the food supply, but a lot of people in the industry expect the Agency to be there to help get new things approved and when the Agency is spending time looking at old things that are already out there, people get nervous because they see it as the Agency wasting a lot of time just trying to stir up trouble and think the things out there are safe anyway so why should we be paying a salary to people that are looking back on things that have already been decided upon. There is not a lot of support for re-reviewing things where decisions have already been made in the past.

So when it says here be more proactive in identifying compounds or issues of emerging safety concern, one answer to that question is whether the Agency should be proactive. How can it be more proactive? First of all, it is just a basic statement; the Agency should be proactive in identifying those compounds. It has to be continually combing the literature for new information that might point to a risk that nobody anticipated and it has to do that systematically and has to do it with a priority-based system. There is so much information out there and so much happening every day that, if the Agency simply combs the literature, there wouldn't be any time to review food additive petitions. So, based on what I have said already, trying to find the time to do all these things it is very, very difficult. The key here is setting priorities. The key here is to take the universe of things that could potentially be a problem and organizing it in some kind of way that allows the potential problems to rise to the top, either because there is a lot of exposure or because the chemical structure of the materials might raise a suspicion, or because new information published in a university or European journal or somewhere in China, wherever, pops up and says whoops there is a potential problem with this substance. If that new information on the hazards or toxicity of new chemicals, is coupled with exposure, coupled with what we know about the chemical structure of the material, then our prioritization system should allow that substance to bubble to the top of the list. If you have a 1000 things on the list, but you know something about the top five and why they are there, then you can put your limited resources on the top five. So that is part of the answer to "how can it do this?" It can be proactive but it can't be proactive on every substance and every conceivable situation; it simply doesn't have the resources, so it has to set priorities. You need to have a systematic way to comb through all the knowledge-base and let things that are potentially problematic bubble to the surface.

6b. That has not changed since I was there. One of the things we tried to do in the '70s or early '80s was to essentially create a priority system like that for all the things that could potentially be a problem. The metaphor I used to use is, if you have a bowl of water with 150 corks floating on the water and you have to hold as many of those corks underwater as

you possibly can, the ones that really matter are floating to the top. You've got to suppress the noise level so that you can focus on things that are really problematic.

FDA Alumni #3

6a. The question supposes that there is a need and utility in CFSAN being more proactive, as opposed to dealing with the myriad of what consumer groups come up with and confront with, and I am not sure there is much value in CFSAN being proactive in that regard. Having said that, they are already very much involved in WHO's JECFA (Joint Expert Committee on Food Additives) which is a worldwide organization. Innumerable things come up at those meetings that give them a heads up on what might be the problem compound of tomorrow.

They could obviously add to that, but something like that would be a model. Because what the Indians think of as a food additive problem isn't necessarily going to be what the Germans think of as a food additive problem. You get a broadened perspective when you serve on those committees. I am sure they must still be going to those JECFA meetings and contributing to their program. Of course, there is the EU, as well as Australia, New Zealand, and Japan, all of which are very active in the food additive business. I think the Agency is quite familiar with those activities and are quite likely to provide a heads up. Canada, Britain, and the U.S. always work closely together on those matters. I don't know if they still do, but basically, working with the right groups around the world is probably the best way to get an early heads up. Sometimes, it will do you a lot of good and sometimes it won't matter a whole lot.

6b. I don't know because I am not that familiar with what they are doing internationally. We were very active internationally and I don't know if they are today or not. At that time the Director of the Center was an international person and was constantly traveling, as was the Office Director for Nutrition. Both people had their fingers on the pulse of what was going on around the world.

FDA Alumni #4

6a. As in 5a, allowing more interaction between CFSAN scientists and others in the scientific community.

6b. No.

FDA Alumni #5

6a. Again, the best and most robust process might be through an advisory committee structure. However, AC procedures suffer from the same arcane and bureaucratic requirements that hamper the agency in being adaptive and agile in a rapidly changing global scientific community. (For example, Europe has an "Adaptation to Technical Progress" system that allows regulators to incorporate scientific advances into their systems. They also have robust and credible scientific committees to advise their scientific programs). Whatever

process is contemplated, it must be transparent and not the current "black-box" approach that keeps stakeholders at a distance.

6b. Yes – It has gotten much worse.

Question 7

7a. How effective does it appear that the coordination and collaboration between CFSAN and other federal agencies on cross-cutting issues?

7b. What can be done to improve coordination and collaboration?

7c. Has this changed since you were here?

FDA Alumni #1

7a. I think that is a shortcoming. The programs have been fairly insular; they have been fairly self-sufficient in the past and there wasn't too much of a need. I think that is probably true within FDA, CFSAN and other centers. CFSAN and CVM perhaps have a fair amount of discussion, but with other centers, I think there is a need to be more aware of what's happening in other agencies. I think that sometimes people have been afraid of doing that too much because every agency, and to some extent every center, works under a different set of laws, rules, and has a different mind-set, quite properly. You can come to very different conclusions. One compound could be said to be okay for pesticides and not be added to food or vice versa and that would be perfectly rationale. But, because people do come at these from different regulatory mind-sets, sometimes it makes conversation more difficult. When various people are dealing with the same kinds of issues and often with the same compounds, I don't know that coordination is so much the issue (but occasionally it might be), but certainly communication is. There shouldn't be any surprises and there shouldn't be any excuses when somebody is taking a regulatory action that impacts someone else. Obviously, the White House, Office of Science and Technology Policy (OSTP), Office of Management and Budget (OMB), and various folks our out there to make sure that doesn't happen. But that is sort of at the back end of the process.

7b. I'm not sure I have a good answer on how to make this better, but there should be better communication almost at the working level or early levels. There are examples of this in specific places which come up in the next questions and so I will defer it for the moment. I think lack of communication at the scientific level, as opposed to the policy, regulatory, and the OSTP and OMB side, is a shortcoming and should be improved. I think one of the things is that we should make much, much more use of cross-agency details or job swaps at the working level so people can get an idea of what is going on. Sometimes there are hurdles to sharing data and information or even doing some of the details. There should be ways around those and that is an opportunity we haven't taken very good advantage of and is something we should try to do more of – again, at the level of the scientist, the working level and maybe mid-level management.

7c. I have no idea, once again.

FDA Alumni #2

7a. There is a mixed signal here. As a general matter, there should be coordination and collaboration between CFSAN and other agencies. There has to be conversation and cross-talk between agencies to some extent. You can have stove pipes in the Federal government where things are happening and some agency that are completely unknown by another agency and it becomes a problem. I think FDA has done pretty well in this area, by and large. Like when you get into questions like mercury in seafood, for example. They have been involved in Executive Branch Task Forces where they have been working with people from the National Oceanic and Atmospheric Administration (NOAA) and EPA and Bureau of Standards. FDA and other agencies to talk about mercury, where does mercury come from?, how do you measure it?, where does it show up in fish?, Is it in fresh water fish, seafood? Is it coming out of power plants? That is an example, and I think FDA has been consistently talking to its sister agencies. But it is difficult because you are a bureaucratic organization and bureaucratic organizations have a chain of command. They have limited budgets and their overriding priorities, so there is a tendency to focus inward. It's a constant struggle. It's a tension. It has to be maintained and you have to work against it. I would say the answer to the question is yes, FDA should interact with other Federal scientific and regulatory agencies on significant chemical safety and risk assessment issues. I think the collaboration is effective; it could be more effective, but I think it is being done.

7b. I think to improve it you would have to have the Agency heads somehow come together and be able to share information and let it filter down to the various agencies. I don't think you can destroy the stovepipes particularly. The Federal government is fairly complex and I don't think you can make a homogeneous mass of the whole thing. Some of the stovepipes have to be there simply the way the government works. Each of these organizations operates under different legal mandates. The Toxic Substances Control Act (TSCA) explicitly rules out food chemicals, so you've got EPA scientists working on things that are simply not going to be handled in the same way; they have different safety standards, different approach, and different legal framework than the Food, Drug, Cosmetic Act. You've got to have those divisions. At the same time, if FDA scientists were working on a food ingredient that happens to be the subject of research and evaluation at EPA under TSCA, the scientists could be talking to each other in a productive way. Sometimes that is facilitated by the Agency heads getting together. Back in the days when TSCA was fresh and new, our Commissioner at that time was talking to his counterpart over at EPA and there were task groups put together; people were brought together from EPA and FDA to talk about it and that happened.

To improve the coordination, you could keep the higher level people talking to each other and then make it possible for the task forces and cross cutting organizations, let's say ad hoc committees, to form and go away as needed to keep people in these various agencies talking to each other as necessary.

7c. It is pretty much the same. Generically, I don't think that problem is any different than it has ever been. You have the same set of statutes and the same agencies; you have reorganizations from time to time. Probably, if anything, it is a question again of resources. If the agencies are strapped for resources, they are going to turn inward. They have certain

vital responsibilities and then there are other things you can do as additional things. What happens when budgets get tight the additional things fall aside because you have to focus on the vital responsibilities that, under the law, you have to administer. There is a tendency to turn inward when budgets get tight. If the budgets get sufficiently squeezed, the agencies will retract and do less of this kind of interagency collaboration. It is probably not a good thing.

FDA Alumni #3

7a. I know what it was like when I was there, but I have no idea now. We interacted a tremendous amount with EPA over pesticides and with USDA over meat, poultry, and eggs, and had a lot of interaction with ATF over wine, whiskey, and that sort of thing. A lot of our colors and food additives were in wine. The sulfite issue that we faced here a few years ago was a big wine issue and a big salad bar issue. Those were the main agencies we interacted with, but we also interacted with NIH a lot and, to some extent, with the National Science Foundation (NSF). But mainly it was with the other regulatory agencies. Today, I don't know if it is interaction, but they pay attention to what each other are doing, between NIH and FDA-CFSAN. I would think that they are still interacting a great deal with EPA on pesticides in particular. It wasn't just pesticides, but things like PCB and other environmental problems that ultimately became food problems. We pretty much had to work together, whether we wanted to or not. Sometimes we did and sometimes we didn't.

7b. I guess the most important thing is to develop good personal relationships at appropriate levels so you can pick up the telephone and call the person you need to talk to at the other agency. There is no way FDA is going to change USDA's philosophy, program, or mind-set, but you can work together nevertheless. You can best work together when you know each other and pick up the phone and talk safely and don't have to be too on guard about what you are saying.

7c. I don't know what kind of communicative pathways they have now. I know that certain people who retired fairly recently who had excellent contacts at USDA and some at EPA. When these people retired the Agency lost a lot of institutional memory and contacts in other agencies. Whether they have rebuilt them or not, or to what extent they have rebuilt them, I don't know. They have some very good people who are more than capable of doing that sort of thing, but what is actually going on in this point in time I don't know.

FDA Alumni #4

7a. Difficult to tell from the outside. It appears that CFSAN TRIES to interact with other federal agencies, but may actually be better with regulatory colleagues in other countries (e.g., Health Canada).

7b. Establish an interdepartmental working group on chemical threats in food and agriculture.

7c. No.

FDA Alumni #5

7a. Not very effective. But this is not surprising. It is very difficult to coordinate and collaborate among programs unless there is a strong management commitment and involvement (leadership). This was even true among FDA centers when I was at the Agency (esp. foods and drugs). Different agencies have different mandates and constituents. However, the RA/SA programs can benefit and an effort should be made.

7b. This difficult goal requires management commitment and leadership. Perhaps a lead scientific manager for each program and help.

7c. No.

Question 8
8a. How do you think CFSAN should interact on significant chemical safety and risk assessment issues with NIEHS, CDC, EPA, USDA, other federal agencies, and international bodies?

8b. What worked well in this regard when you were at CFSAN?

8c. What improvements are needed, and how can we best achieve these improvements?

FDA Alumni #1

8a. This is a little bit like the previous question. In some cases, for example, CFSAN works very closely with CDC on food borne illness issues. It has, in the past, worked much less closely with them and coordinated with them much less well on chemical safety issues. That was beginning to change in very recent years and may have continued to do so, but I'm not sure.

8b. These are examples of how I would think CFSAN should interact on significant chemical safety. One that worked quite well at the working level, again, was genetic engineering. Clearly when the first biotech foods and genetically engineered foods were coming up, FDA, USDA, and EPA were all very involved in it. Admittedly, some of the direction and coordination came from the OSTP level because everybody knew that this was going to be controversial, to say the least. What came out of it, and I don't know whether it is still working as well as it once did, was not only a fair amount of coordination at the political and leadership level, but a lot of communication at the working level. There were regular phone calls among the scientists and groups and people knew each other. You knew who was working on these and you could pick up the phone and talk within the ability of what was "talkable aboutable." It helped enormously. It didn't always work perfectly well, and I can think of a couple of examples where it didn't work well at all, but it was one case where, in most situations, it worked well and was actually very helpful, possibly heading off what could have been embarrassing or whatever to one agency or the other because people were in pretty constant communication.

Another one that worked quite well don't know if it still is because there were a lot of reorganizations at least on the USDA side, at least the Food Additive Program and maybe other parts of the chemical safety program with The Food Safety Inspection Service (FSIS) and the parts of food additives in meat and poultry as well as food additives in the rest of the food supply when another case when the jurisdiction was kind of divided and there was very good communication and discussion between the two sides to make sure one didn't do something. Avoiding a phrase that took me a while to understand, avoiding the predictable surprise. The predictable surprise being, yeah, you should have known you were going to be shocked about this and should have been able to avoid it by having one agency or the other come to a conclusion or make an announcement or do something that is in contradiction to what somebody else has done or was done without the knowledge of the interested parties. It can work. There is so much crosscutting. I think one of the things that again would be useful with the details and the job swaps is just a matter of getting to know the counterparts,

who to call, and who's working on something. One of the issues, and it does involve question 9 on transparency. One of the hurdles sometimes of having discussions with the other agencies, is there is far more than there is with the Food Additives Program there are often issues with what is releasable and what can be discussed and shared because of confidentiality of issues. There are ways to get around those and I think those should be explored, just as there are agreements with our regulatory counterparts on sharing information, internationally there certainly are, there is the potential for agreements and for sharing information across agencies. I think those should be pursued and made as easy as possible because there is no point one agency having a room full of data on a chemical while another agency is looking at the same chemical but doesn't have access to the data. I think that is an area that [FDA] could spend a fair amount of time trying to improve and I think a lot of it is (it reminds me a little of what people talk about in terms of Congress these days), that it worked better when everybody had to live in Washington and go get drunk together on a weekend. I am not suggesting that everybody should go get drunk together, but I am suggesting that people get to know their counterparts and be able to have discussions about reviews. When it happened to me, it was more useful than not and they in the Agency should do more of it or as much as possible.

International bodies – I think we have done that a fair amount with our regulatory counterparts in Canada and Europe. I think people were making more contacts with regulatory counterparts in the Far East, Japan and China. Obviously there are the CODEX efforts. I think those are important. Again, in a world where you can't do everything you want to, you have to figure out where you can do the most good in terms of keeping contacts open. I think that is another case where details and job swaps, to the extent they could be managed, would also be very, very helpful.

8c. I probably talked about the improvements needed. Again, I know that that is the most important part of this. All I can do is repeat that encouraging and making possible contacts, again, not only at the political level and not only at the leadership level, but at the working level and the middle management level and finding ways to make sure counterparts get comfortable with each other and be able to talk about the science. Not necessarily the regulatory decision making again everybody comes at it from a different point of view and has different legal and regulatory constraints to work under but at least what kind of data are coming in, what do the studies show, and how do you deal with the new non-traditional endpoints and how can we make, at least our approach to the science, as consistent as possible within the constraints that we have with our different missions and different legal and regulatory constraints.

FDA Alumni #2

8a. I think that kind of goes with the previous one. The answer is first, they should interact and they should do it by involving their scientific staffs, much as I said earlier, scientists working at CFSAN need to be going to conferences and international meetings, they need to be present at WHO meetings, they need go to meetings where CDC is unveiling information or NIEHS is talking about toxicological testing priorities and EPA is coming out with a big rulemaking on nanoparticles, for example. The scientists working in that area need to be at

those meetings to listen, take notes, and talk to their counterparts in those agencies; they need to be there. The Agency has to cut aside time for them to be present and involved. The higher ups in those agencies need to be talking to each other to allow for that kind of cross-talk between the scientists in the agencies. I think it should happen and I think it does happen. My recollection is that, when I was at FDA, there was quite a bit of it. There could probably be more, but with the proviso that there are different statutory schemes operating in these different areas. CDC and NIEHS have different mandates under law than FDA. EPA has a different mandate under law in all kinds of different areas, like clean water, clean air, TSCA, Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), etc. than does FDA under the FD& C Act and the Public Health Service Act. So, if you pay attention to those statutory mandates, you can come to the incorrect conclusion that all these agencies ought to be regulating these chemicals in exactly the same way and that is not true. There are different risks and different risk standards applied under law for good reason. Sometimes it's a little arbitrary. Congress does things that are not easily explainable, but there is good common sense behind a lot of these things. Food, for example, is required for life, so your standard for how you come at a question about whether something should or should not be in food is different than a question at EPA about whether or not something ought to be present in the air, or water, or on the back lot of an industrial setting. These are different exposure scenarios, different societal risk assessment paradigms, because the statutes are accordingly different. You can't expect EPA standards to be the same as FDA standards in all these areas. At the same time, you want your FDA scientists and your EPA scientists talking about the science of these situations so they are aware of each other's work.

8b. I gave some examples from when TSCA was new and the Commissioner sent FDAers over to EPA. I remember going over to EPA and sitting at meetings and listening about TSCA and priority setting methodologies they were using and we borrowed some of those ideas and brought them back to FDA and were using some priority concepts there to look at food chemicals. We were quite well aware that we were a different statutory scheme and so we had to handle it differently. That was working. I think under nanotechnology it is working well; FDA is involved. Even in the BPA area and endocrine disruption, there is plenty of FDAers that have been involved with EPA. JECFA, FDAers are constantly being called upon by the China experts on food additives and at the FAO/WHO in Europe to participate as experts in all kinds of different areas. FDA has all kinds of people involved with all kinds of CODEX meetings and that just needs to continue. There is no way the Agency can do its job well without having people involved in those kinds of things.

8c. I am not sure there are any particular improvements needed from a conceptual point of view. I think FDA understands that they have to be involved in all these things and tries very hard, but here again, it is a question of resources. There is a need to make sure that resources are available to have the depth of staff to do these kinds of meetings and participate in these committees and still carry on the work that is required at home. That is the big job; again, it all comes down to resources. If you start at the Agency, you may satisfy an ideological goal. Again, government shouldn't be too big, but on the other hand, if you do that then the government is not going to do the work that the people will expect from it either.

FDA Alumni #3

8a. Well, the short answer is, the best they can. They've got to interact with all those groups. Sometimes, they are going to be taking the lead, and other times, they are just going to observing what is going on and trying to factor it into their responsibilities and mission. Sometimes, it is right in the middle between those two extremes. You can't do those things unless you have people that have that assignment. You can't do it well unless you have people that are really properly oriented toward doing that kind of job. I know there is a lot of interaction with the NIEHS people because of the National Toxicology Testing Program they run where they keep finding those carcinogens and some of those carcinogens are in the 21 CFR. They're food contact substances and, in some instances, food additives. It raises a host of Delaney type questions.

8b. Well again, it really came down to personal contacts. We did have some Memoranda of Agreement with USDA and maybe one with CDC. Those can be helpful. You can't really accomplish very much unless you have contact people who are good at what they do. There have been times in the past when we had superb contact people that knew everybody in every agency. If anybody could get things on track, these people could do that.

8c. You can never stop improving. Going back to what we discussed earlier, the thing that should be seriously looked into that can help in almost every category is getting the lab people on board relative to mission needs. That could certainly help the functioning of the Center, particularly in times of crisis. For example, BHA was a crisis for us, and the labs were instrumental in helping us out of that problem. They did a lot of things, but that comes to mind because it was such a crisis.

FDA Alumni #4

8a. As in 7b, forming an interdepartmental working group to discuss issues would be a good start.

8b. A similar idea for TSE's, and chemical issues between Health Canada/Quads countries seemed to be successful.

8c. Aside from formalizing interactions, I don't know.

FDA Alumni #5

8a. Again, this is very challenging but also very important. Most of my experience was with NIEHS and there was a significant disconnect there. NIEHS was much more academic and detached and suffers from undue influence from the director level (often politically motivated). Each agency varied mostly because of their mandate and constituency. It is hard to coordinate on everything without grinding the process to a stop and introducing mixed agendas. Perhaps retrospective case studies among the agencies would best inform future actions. Also, highlighting benefits and the availability of special expertise might be an incentive. Alternatively, all of the RA/SA activities could be centralized so that the one body would service all needs.

8b. I think the interactions worked best (but not necessarily well) for the most significant and visible RA/SA events. Things digressed from there.

8c. Again, this is a very difficult area. Some mechanism for sharing expertise and exposing scientists to new and emerging areas would help.

Question 9
9a. What is the current state of scientific transparency and engagement internally and between FDA's chemical safety scientists and programs and the external scientific community?

9b. How satisfied do you feel stakeholders are with the current state?

9c. What, if anything, needs to be done to improve transparency and engagement?

FDA Alumni #1

9a. This is one case where we say FDA and not CFSAN. Is there any particular significance to that? I will talk mainly about food additive and food ingredients because that is what I am most familiar with. In a sense, the food additive and food ingredient side of the house is probably one of the most transparent programs out there. There is much less confidentiality and much less information that is not available to the public in the Food Additives Food Ingredients Program because of the way the law and regulations are written than there is in almost any other program; certainly far more than drugs and far more than pesticides at EPA. I think that's probably for the Food Additive Food Ingredient Program less of an issue than it is for any other programs. It is relatively transparent and is probably almost as transparent as it could be.

Engagement is a different issue from transparency. Regarding transparency, as I said, it's more transparent than almost any other program. That's premarket approval, at least, certainly. Given the need to keep some confidentiality, after all, if you do want industry to talk to you and want the industry to talk to you as early as possible so that we do have a heads up on emerging issues and new things that are coming up, you have to be able to promise confidentiality where it is appropriate, so there has got to be a balance. But, to the extent possible, I think the food additive and ingredients added to food are the only ones where, once something does come in formally and officially, then virtually all safety information is immediately able to be disclosed publicly. That is pretty unique and very good, I might say.

Engagement, I think it is probably better than it was at one time, at least in terms of the stakeholders that are most involved on the premarket side and the industry. It is not as nearly as good as it could be with other stakeholders, be it academia, be it consumer groups, be it just about anybody else that might be interested.

The external scientific community…to the extent that the program and the science are not as engaged as they might be with the external scientific community. I'm not sure this is really a different question than it is the scientific community that needs more engagement with I suspect are the other regulatory bodies, the ones we have already talked about. Academia, maybe this refers to the next question on training. There is a lot to be said about keeping people in tune with scientific meetings. Maybe that is another case where, in a place where you had unlimited resources, you would send people off to details in academic labs, but I don't know there is very much more to be done in that area than there is now. The main

stakeholders would have most interest and concern about engagement and would be the ones that would be either on the industry side, the people petitioning for approvals for example, consumer groups, consumers in general, and maybe the media and press. The engagement – externally, is probably fine; internally, I probably already mentioned that, when you are talking about whether we need better communication between scientists, between FDA, CFSAN and other agencies, that also speaks to needing better communication at the working scientific level, between CFSAN and the other centers, for that matter.

9b. I'm sure nobody is completely satisfied. It is probably the typical tension one gets in a regulatory agency. I'm sure the industry would prefer far more confidentiality, on one hand, and far more engagement, in the sense of willingness to share reviews with them while they are in process. The consumer groups, I'm sure, say we need to be more transparent and have more opportunities for them to engage with the Agency in their decision-making.

9c. I must admit that at the beginnings of peer review, certainly Versar was involved in some of those and some of those I knew about before I left. I think the whole idea of peer review is a good one. I think the time and place when you use it need to be well selected, but I think it is something that is helpful for transparency and engagement. Again, it comes back to what I said about the guidance too; it is useful for the Agency, the Center, and the Program to write down how they came to their tentative conclusions and test it with other people who are appropriate and have the expertise to be able to give an opinion, advisory committees as well. I think that, with advisory committees and maybe less so with peer review and other kinds of engagement, you need to again look for a balance. One of the things that happened with the advisory committees is that everyone was so concerned about making sure the advisory committee and the people serving them didn't have conflict of interests and it was very transparent, who they were and who they had worked for. By the time you got finished going over all those hurdles, it became so difficult to put together; it was easier not to do it at all. Of course, this defeated the entire purpose and defeated the purpose from the point of view of the people who really wanted the safeguards. The safeguards were important and they are important. The same has to do with contracting, it has to do with peer reviews. But somehow we got to make sure there is a balance. You can make use of these methods and ways to vet some of your tentative conclusions or the ways you are thinking of interpreting data and new information with presumably and hopefully objective expert outsiders. That is very good for the Agency and good for the Program; need to find ways to make use of it, but not in a way that is so onerous and time consuming that it is easier to say let's not do it at all. I am not sure how much flexibility there is since some of these the requirements are pretty well set in stone. People should be thinking hard about how to make as much possible use of outside and very public review of the conclusions or tentative conclusions.

FDA Alumni #2

9a. It is probably less than it could be. Again, it goes back to staying plugged into what is going on in the real world. I think there is a tendency potentially for FDA scientists to become more inward focused and provincial, simply because they have a big "inbox" and not any resources to go out and be put on the wide angle lenses and talk to their colleagues in other areas. It is done, but it is not done enough. So there is a chance FDA scientists will not

have access to the current knowledge base when they make their decisions. They try very hard. They do their literature searches and stay up to data on a lot of things. There is a level of conversation and interaction that has to take place. The engagement with the external scientific community that takes place at conferences that are hosted by academic bodies, intergovernmental bodies, or non-profits, where scientists are brought together to discuss important issues. FDA needs to have a presence there. They don't always have as strong of a presence as they should, partly because they don't have the resources to do it.

9b. I think stakeholders are conflicted. I may be guessing here. There is a very good basis for stakeholders to believe, and I agree with this belief, that the Agency needs to be strong so that it is reliable and can be responsive to the stakeholder's needs. But there is an undercurrent of we don't want the Agency to be too strong because then the regulatory side becomes harder to deal with. From the stand point of policing, we would like a weaker agency, but from the stand point of responsiveness to our requests, we want a stronger agency. I think the industry stakeholders sometimes can be conflicted.

I think the consumer stakeholders, by and large, are pretty satisfied. If you look at the polls that sometimes surface, consumer stakeholders are often satisfied with FDA. They think the Agency, and CFSAN in particular, is pretty responsible. It is a believable and responsible agency in the eyes of the consumer stakeholders. There is always an undercurrent of urban legend and concern about FDA decisions and whether or not they're objective, if they are being played by industry and so forth. There is always that out there. The nature of the job is controversy. If the Agency is not receiving criticism from somebody, it is probably not doing its job right. So it is a given that FDA will receive criticism from stakeholders one way or another. Either not approving a food additive fast enough, not denying it soon enough, or not banning a substance that should be banned – it's faulted by somebody and that is to be expected and is part of the territory. I think, in general, stakeholders see the Agency as credible and are thankful that it is there. You can see that when people pull something off the shelf the one thing they don't worry about is whether somebody has looked at the safety of something. Sometimes that can be problematic because there are occasionally products out there that mix caffeine and alcohol that might not be particularly safe and people buy them because they have the presumption that it wouldn't be on the market if FDA hadn't been looking at it. If it weren't safe, it wouldn't be here. The whole confidence issue is really important. In that sense, I think the consumer stakeholders are satisfied with the current state.

9c. I think there are opportunities for FDA scientists and regulators to be talking to people outside the Agency. There are venues; they tend to be conferences, international bodies, interagency meetings, National workshops, or international bodies like CODEX or JECFA. But the Agency people have to be present at those. If they cannot be present, then they cannot engage. You can't do it easily by reading a literature search at your desk. It helps, thankfully, that a lot of things are nowadays available electronically that were a lot harder to get in years gone by. Thankfully, technology has helped, but you still need to be talking to people. That can only be done if you can afford the time and money to send your scientists off and allow them to do that.

FDA Alumni #3

9a. Well, it probably isn't that great because I don't think that many people are publishing. When I was there, even our lawyers were publishing in the scientific area. I was writing lots of papers. Rulis, who was in charge of Food and Color Additives, was writing lots of papers. Most of what we were doing was relevant to risk assessment, but that was the big issue of the day. If you are not publishing, then you are not taken seriously. Even when you are publishing, you may not be taken that seriously. But if you don't publish, there is not much chance that you are going to be taken seriously.

9b. I don't think it's any worse. If anything, it is probably better. They are probably more satisfied overall. You will find exceptions, of course. But in general, stakeholders are pretty happy with CFSAN. That is not to say that some don't hate CFSAN to death, but in relative terms CFSAN is looked upon favorably by stakeholders.

9c. It seems to me, from my experience, that you have to be prepared to deal with issues as they arise. Issues that create real problems from the Center Director's Office all the way down to the individual reviewer. You never know what is going to happen. There are a number of things on your plate that you know are problems and they have been festering for months or years and you are doing what you can do. But if you are in the job long enough, you are going to get blindsided and you are going to need help. If you have got an organization where the review people and the research people are pretty well coordinated, you can get a lot more help that you could otherwise.

FDA Alumni #4

9a. This is an area of great opportunity for improvement, particularly between OFAS and the outside. Chemicals management/approvals is, at this time (and has been), a "black box" to the outside.

9b. With the exception of those who actively engage CFSAN, stakeholders are not satisfied

9c. Public meetings and more activity within advisory committees would help.

FDA Alumni #5

9a. Very poor. But I think this lack of transparency is controlled by the legal and regulatory framework. I think that transparency is probably the most important aspect of CFSAN RA/SA. The process needs to be open to all stakeholders (for better or worse). This perhaps invites a free-for-all, especially with aggressive activists and a litigious climate. However, it could function somewhat as a peer review system and keep agency scientists more accountable for their actions and decision making. Right now, it is very much a "black box" system that, in some cases, angers stakeholders and questions the competency of RA/SA scientists.

9b. Very dissatisfied in my experience.

9c. I think a public meeting or conference to discuss the issue might help define the key issues and explore how a more transparent system might work. It can't be completely open but there has to be a better way.

Question 10
10a. What training types/topics would be most beneficial to the CFSAN programs?

10b. Are there outside entities CFSAN could partner with for more training opportunities?

FDA Alumni #1

10a. No matter what, you'll end up in the same place of resources. Training is obviously very important. I don't know I can suggest particular topics. I would go back to reassert one of the things I mentioned in another context, and that is details and job swaps. Making more use of those would be useful. That is not only with other agencies, but to the extent it is possible with academia, even with industry in some cases. I think, clearly, giving people an opportunity to publish and also to maintain expertise by going to meetings and all the things one would hope you could do. It is difficult to do as much training as possible.

10b. It would be nice to be able to leverage, to get training opportunities at low cost for the government, because you will never be able to do everything you really want to do. I'm not sure I have any good ideas about that. It's great to be able to say partner with industry, particularly in the premarket area. There is always a lot of difficulty with that, in terms of I got to give you the training to make sure your decisions are favorable. It would be useful to think about sabbaticals in both directions with academe. Again, churning the employee base is good, to the extent that when you are in a place when you may not be able to hire a whole lot and have resource constraints. The possibility of bringing someone in from academia for a year and/or sending body out temporarily would be very worthwhile for the Agency, as well as for the person. I suppose, overall, one of the huge challenges obviously facing the Program is priority setting. There is a lot you want to do, but what are the things you can do that will be most helpful and useful. It comes back to I don't think you could ever staff up so that you have people with up-to-date expertise in every narrow area that could conceivably come up in the next thing that comes over the transom. The training that could be most helpful would be one that keeps people broadly aware of what is going on in their general field and knowing where are the experts that might be available if you really needed some advice and help in a particular narrow area. I vote for broad training and broad opportunities that you keep up with your area in a broad, generic way that keeps you in touch with people in your area and, again, makes the most possible use of details, sabbaticals, temporary assignments and such to be able to both have a feeling of the constraints of the issues that other people and agencies and people who are dealing with the same questions you are. How are they doing? How are they approaching those issues, and from the point of view of the personal contacts, so you do get comfortable with being able to share views and know who to talk to and when to talk to them. Get advice and help with what you have to deal with.

FDA Alumni #2

10a. I think I would divide it into two parts again. One is pure science – the expertise that is used by a particular scientist in CFSAN, whether it be chemistry, toxicology, biochemistry,

or biotechnology. These scientists need training in their field that brings them out to the cutting edge so that they are conversant with the best science out there and the changing techniques that are available in science. So they need to have opportunity to stay plugged in and that may mean going to an academic style offering. For example, the American Chemical Society runs training workshops at international meetings or there would be a contract offered to NC State University to run a packaging course on new polymers used in food contact material. FDA chemists are getting updated in his or her field at a class like that. There are a lot of opportunities in academia that are out there that FDA scientists could take advantage of. There ought to be FDA scientists sitting in conferences and going to toxicology forum meetings and Society of Toxicology meetings, and speaking and giving papers and participating in workshops. Things like that.

The other thing is the issue of coalescence of science, policy, and law. There needs to be internal training constantly by the Agency of its personnel to help people understand what it is they're doing there. You don't want toxicologists or chemists to be ignorant of the fact that their science is really applied in an area where there is an overlap between policy, the law, and science. They are not operating in a vacuum of science. They are operating in an environment that has policy implications and it must occur under law. They have to be trained to think that way. This something unique to the U.S. If you go to Europe and look at an organization like the European Food Safety Authority (EFSA), until recently. EFSA is approaching something like FDA is. In years gone by, the Europeans were struggling with this because they didn't have a good understanding on how to coalesce the areas of law, science and policy in ways that allowed them to make regulatory decisions that were scientifically sound, legally sufficient, and sensible from a policy point of view. It didn't have individuals that were trained in all three areas. They had compartments where policy people were not necessarily scientists. If they need help on a decision they would go to the scientists, and the scientists they went to had no idea what the policies ought to be. They would get into endless scientific discussions, but could never get to what is practical in the real world. This is something unique at FDA. You train people to work in all three areas at the same time. That kind of training is internal to FDA. They will never learn this on the outside. The people that FDA hires come into that agency from academia. They don't get those courses in academia. They may know something about the law or policy, and how to read and write and how to work together in a committee, but they don't get the explicit training on how that is done as a way of life at FDA. I think it is extremely important for FDA to do internal training of its people to teach their employees to knit together and work effectively in an environment where all three of those areas are constantly on their desk and in their mind. That is what is really unique about FDA, and sometimes, it is a concern for me that we are not training people to do that kind of work as effectively as we could.

10b. I don't know. A lot of that training is unique to FDA. It's internal. When I was there, we worked internally to develop training internally. We had people from the General Counsel's Office come to talk about the law, people from the compliance area come to talk about policy issues, and the scientists would get together and put together an internal training course for their people.

Outside entities oftentimes do not understand the culture or the constraints under which FDA actually works. It is not very easy to get an outside entity to say anything useful to you in that particular area. In the pure science area, there probably is. You could send your scientists off to some kind of graduate course in nutrition or cutting edge course in genetics or biotechnology that would help them understand how genetic sequencing could be used in ways to enhance the safety assessment paradigm. Those are the areas where you could get external academic resources or schools to help teach FDAers what they need to know. In terms of the internal culture of how the science, policy, and law come together, it is really hard to find anybody outside that can do that in a reasonable way. If you go across lines to different agencies, that is not necessarily going to be very helpful. It could be informative but might not be helpful because, as I said, you have different statutory mandates, different standards of safety, and different procedures that operate under law in these different agencies.

FDA Alumni #3

10a. Wherever you have a new area opening up, like nanotoxicity or genetic recombinant problems with food, what the Europeans call the "Frankenfoods." This is high technology. Agency reviewers need to know as much about it as they can and need to be trained in those areas. It is hard to recruit people that have the specific expertise that you need, but it is possible to take people with good scientific backgrounds and train them in a specific area where you do have a need. As technologies evolve, you need to make sure your staff is able to keep up with the new developments.

10b. That's a good question. There has got to be, but I don't have any good suggestions. Certainly for the toxicologists, there are with the Society of Toxicology, American College of Toxicology, and the International Society for Toxicology and Pharmacology. They have annual meetings and almost always have training sessions prior to the annual meetings. They have 3 or 4 training sessions before they officially begin their annual meetings. Some of those look very, very good. That is one thing the Center could focus on. The other thing is that these societies would certainly take under serious consideration any suggestions that come from the Center that they would like to have training sessions on such and such an area. So interacting with the professional societies, I think, would be the most cost efficient and time efficient way of achieving that.

FDA Alumni #4

10a. Public speaking, risk communications.

10b. Taking advantage of FDA Centers of Excellence other government training opportunities would be a good place to start.

FDA Alumni #5

10a. How the regulated industry works and the impacts of the current regulatory systems on innovation. How the public perceives the regulatory process. RA/SA systems in domestic and international settings. All exposures that might heighten agency staff awareness of other perspectives and alternative approaches to problem solving. Also, regular and mandatory training on new and emerging science for RA/SA.

10b. Yes – many. Virtually all stakeholders – industry, academia, NGO, legal and international provide opportunities for partnering. The RA/SA community is robust and varied and offers opportunities to keep FDA/CFSAN as a leader in this area. But they will have to understand that they cannot accomplish this with the insular mindset that now exists.

3. RESPONSES FROM OTHER FEDERAL AGENCY MANAGERS

The interview results are presented by individual question below.

3.1 Chemical Safety Questions for Other Federal Agency Managers

Question 1
Are you aware of differences between FDA methods and your agency?

Other Federal Agency Manager #1

Most of the government does risk assessment pretty much the same. We both have a weight of evidence approach that look at the data. We both look at cancer and non-cancer end points, we both have guidelines that are somewhat similar in how they do it. One of the biggest changes is that we try to do a little more mathematical modeling. We do benchmark dose or biologically-based dose responses if we can. I am not sure if CFSAN does that.

Also, my impression from being up here is that our peer review is fairly extensive on risk assessments. I don't know if FDA has the same level of scrutiny as this agency has over peer review.

Other Federal Agency Manager #2

I am aware that there are differences, I suspect I am not aware of all of the differences.

Other Federal Agency Manager #3

NIEHS/NTP…doesn't do risk assessments, we do hazard evaluation. Part of my agency might, but we don't do risk assessment. But I am aware of the differences between say FDA methods and EPA methods.

Other Federal Agency Manager #4

[When it comes to how they do it, it is similar but different. They certainly look at the same kind of studies and try to find out what the NOELs are that are proper and protective. However, rather than deriving RfDs and cancer slope factors they tend to use more of a margin of exposure or margin of safety-type approach, acceptable daily intake. There are certainly similarities there but there are different mathematical computations.] Right.

Question 2
2a. What is the current state of scientific transparency and engagement between FDA's chemical safety scientists and programs and your agency?

2b. How satisfied is your agency with the current state?

2c. What, if anything, needs to be done to improve transparency and engagement?

Other Federal Agency Manager #1

2a. Since I got up here, CFSAN has reached out quite a bit, basically to network with me and start to move the two organizations closer together. I am not sure with my predecessor if there was much direct interaction with FDA, but like I said earlier that at the lower level of the organization there was obviously contact. We have tried to work closer together. We are both interested in arsenic. We are reevaluating arsenic and I know that FDA has had a lot to do with arsenic issues in apples and rice.

We are currently grappling with something called non-monotonic dose responses or endocrine active chemicals. There has been a pretty close collaboration with some of the CFSAN scientists. As we did our State of the Science Review, they were actually there helping write it and being on the working groups, and being directive on the conclusions we are reaching on that. Perchlorate is another example. I think where there is a chemical that crosses over or a scientific issue that crosses over I think that there has been a movement that we work more closely together. As the sequestration steps in and our resources get more and more constrained it is probably more important to work with FDA.

One other topic we have work with them as well is there is an inter-governmental effort that we call Tox 21 it is trying to implement some of the recommendations the Academy's 2007 Report. Initially it was just NIH and EPA working together. There were two NIH organizations, one was the National Genomics Center and the other was the National Toxicology Program. EPA partnered to try and accelerate the newer high throughput screening methodologies. We worked hard to bring FDA into that agreement. After 2 or 3 years of begging and pleading we got them to join the MOU. A lot of that was with the CDER folks, but more recently there has been more engagement with CFSAN folks on that. I think that is another place where the government is trying to gain some efficiencies by tapping into complementary expertise that cross organizations.

2b. I think it's okay. I think we all need a little more time to nurture this. CFSAN has talked with me about having a Memo of Understanding that would maybe formalize these interactions a little bit more. I think that would be something that would be good to do if we could just have the time to fit that into the schedule. Clearly, there are a lot of commonalities with what we do and the need to have efficiencies and risk assessment across the government is pretty high. That we are not all evaluating the same data. We can come to different conclusions, but when we look at the data we should be looking at it with the same kind of lens, I think. We could gain some efficiency that way.

2c. If we could have a more formalized Memo of Understanding or whatever we called it between agencies. I think that would be helpful. How do we collaborate specifically with risk assessment issues that are common in nature? With the non-monotonic and some of the Tox 21, arsenic, and so forth we have some basis to build upon.

Other Federal Agency Manager #2

2a. I would say it's uneven. When there is a chemical that both FDA and EPA regulate there has been collaboration between our respective organizations on the assessments of that specific chemical. In the past but not so much recently there have been collaborations on broader issues involving risk assessment policy. Again, it is uneven. For example I think our organizations are currently working together on the issues of whether chemicals have a non-monotonic dose response pattern when the effect involves the estrogen, androgen, or thyroid hormonal systems. EPA is seeking advice on that issue from the National Academy of Sciences and FDA is providing comment on White Paper that EPA is developing. About 15 years ago I was involved with a variety of science policy issues about how to evaluate for example substances that inhibit cholinesterase or how to assess exposure to substances in the food supply. We worked with FDA to review the policy documents that we developed at EPA. Apart from those examples I think almost all of the work has been on specific chemicals. Fluoride, as I mentioned, triclosan in recent years, lindane in the past, malathion and so forth.

2b. When we do work together it seems to work well. I have the sense that there are more opportunities for us to do that. One example involves the universe of antimicrobial substances that are regulated as pesticides under the Federal Insecticide Fungicide and Rodenticide Act and for which EPA issues product licenses called registrations. Some of those products are also regarded as food additives under Section 409 of the Food, Drug, and Cosmetic Act and the Office of Food Additive Safety issues food additive regulations for them. Our assessment at EPA and FDA's assessment are basically asking the same questions to a large extent. Is the addition of this particular substance to the food supply going to be okay for public health purposes? Our organizations have not worked together very much on harmonizing data requirements, harmonizing assessment methods, harmonizing regulatory review procedures, and so forth.

2c. In the Pesticide Office we have done a lot to work with other organizations and from that I have seen a certain series of steps that need to happen. Some of them have happened and some of them haven't across the many areas where FDA and EPA potentially overlap. The first step is to agree on risk assessment methodology broadly speaking. That has many different elements. Things like, what kind of data will somebody look at? How to evaluate the data? What are the policies for interpreting results and assessing risks? For example, how to estimate exposure in terms of how much will get through the food supply. Whether to take into account exposure from sources other than food in assessing chemical safety and so on. After the risk assessment methodology, everything from data requirements to science policies get dealt with there are also issues relating to regulatory process. They have to do with sharing data, sharing assessments, coordinating timing of reviews, maybe even potentially sharing workload so that we don't do the same work in two different

organizations and essentially duplicate each other's efforts. As I say, there have been instances where we have worked together very effectively and I am aware of some instances where we are not working together very much at all.

Other Federal Agency Manager #3

2a. Not great.

2b. Well, I would like to see it improve. I would say it is very one-sided. They get very upset if we don't provide them with the information as soon as we generate it or know about it, but they don't reciprocate.

2c. They need to be open. They need to send information. They need to ask questions. If we provide them information we need to know what they do with it. Frankly, CFSAN is a disaster. It's got people in, never mind, certainly the 20th Century. They are still applying a lot of methodologies and looking at things in many ways I think that science has moved beyond the ways that they are doing things.

Other Federal Agency Manager #4

2a, b, c. We are dealing with transparency in IRIS. That's been a major challenge for us. About how to open up the process to make it so people would know what we do and how we do it. The Agency had not been accustomed to such transparency. So I have been pushing and it looks like I am finally getting approval to do so. To open up the process and have public stakeholder meetings. At least two during the IRIS process. One at the beginning, when we identify and scope out the literature that we are going to review. Then we will publish an evidence table. It is simply a table listing the papers that we reviewed or attempt to review, and what we think the key evidence is and people can debate that. That should be a public meeting. And so I don't know if FDA does that or not. It seems to me that if they don't they haven't run into the issues we have run into. In other words, stakeholders and industry are mainly complaining that they don't know what we are doing until the end. Then we've sometimes not used the models they would have used. We need to debate the models. We sometimes have omitted some papers or assigned some less weight to a paper. And so it seems these issues should be debated up front, early in the process. And so that it what we are going to do now. Identify the data gaps, if there are any, and in almost all cases there are gaps. So these are things now that we are going to debate now in the beginning. Then two years from now when we are reporting out we will be on the same page. No surprises. I don't know if FDA does that or not, but if they don't it seems to me that they are going to run into the same issues that we ran into. We are opening our process up and I think it is going to work very well.

Question 3
3a. For example, has your agency been asked to participate/peer review any assessments/guidance from FDA?

3b. Has your agency asked FDA the same thing?

Other Federal Agency Manager #1

3a. I am only personally aware of one and that's the Methyl Mercury in Fish Advisory. In the year that I have been up here that is the only one I am aware of. There might be other ones.

3b. As part of our assessment process, the IRIS assessment. IRIS is our Integrated Risk Information System. It is our sort of highest level chemical risk assessment that is done by the Office of Research and Development. It has looked at nearly 600 chemicals since its existence. It publishes an IRIS assessment which sets the reference dose for either non-cancer or the cancer slope factor for a carcinogenic event. There is a very rigorous assessment development process that includes both stakeholder engagement, peer review, but also a formal interagency review process so every one of those assessments goes out for an interagency review. FDA is one of the members who would be in that chain of evaluation.

We do risk assessments in other offices, for example the pesticides office does a risk assessment, but I can't speak for the extent to which they reach out to FDA or whether it is a higher medium production volume chemical that is run through the Office of Pollution Prevention and Toxics. I can only speak for what goes on in ORD in the context.

Other Federal Agency Manager #2

3a. I am aware of some instances where we have. I work a lot with FDA on issues relating to nanomaterials and FDA issued in the last year a couple of proposed guidances relating to cosmetics and food additives. We have reviewed those guidances through inter-agency working group, but I am guessing that there are other guidance documents that FDA develops for which we do not get an opportunity to review or comment. I can't say for sure that I know that we have missed stuff, but I suspect there is more than just that.

3b. There are lots of different parts of EPA and I can only speak for the Office of Pesticide Programs. I think that we more often than we hear from FDA, ask about that, but I am also fairly sure that we have not shared every guidance document that we've developed with FDA.

Other Federal Agency Manager #3

3a. There have been sometimes. We have certainly had FDA people involved in some of our peer reviews and so on.

3b. That's it. Our agency has involved them in some of our peer reviews and so on.

Other Federal Agency Manager #4

3a and b. I can't say yes or no. I can't answer that. I mentioned this to the IRIS program and they are not aware of much interaction that is directed to us from FDA. They are aware that we ask them but it's not clear if we have been invited to participate. I know that I have not been. I just don't know but it is clear that interactions are pretty low.

Question 4
4a. How effective is the coordination and collaboration between FDA and your agency on cross-cutting issues?

4b. If not, what are the impediments?

4c. What can be done to improve coordination and collaboration?

Other Federal Agency Manager #1

4a. For the time that I have been here, it's been pretty good. The non-monotonic is a really good example of where we have come together to work closely together. What would improve the coordination? I think if we could meet periodically as senior managers of the organization and share what are our upcoming priorities. In the IRIS program, we are trying to set up our priorities for the next two to three years. What chemicals that will be going through that process. It is a 7-step process to go through the assessment. We are trying to map out when we expect each step to take place. So if we were to meet at sort of senior manager levels periodically and have a discussion about our priorities and whether we can meet any common understandings, that might be a way to foster communication between the two groups. Again it only takes time.

4b. Time, distance, and knowing each other. If we can develop a better network at the senior level I think it would help. To make sure we made the right connections when they were worthwhile making. There are always surprises that come up, the immediate risk assessment, that we might have to do a Superfund site or FDA is going to have to do a food supply. Those are the unexpected things but there is a whole lot of stuff that we could reasonably anticipate that we are going to be dealing with and it would be easier to collaborate on.

4c. The same thing, get to know each other and spend some time. Understand priorities.

Other Federal Agency Manager #2

4a. It varies. There are certain types of issues where I think our coordination is pretty effective. The way that the laws are set up, EPA reviews pesticides and decides how much pesticide residue in food may be allowed. We establish what are called tolerances or maximum residue limits for residues of particular pesticides on particular types of food. FDA has the responsibility for enforcing those tolerances. That is to say they check food and if they find a residue for which there is no tolerance or they find a residue that is in excess of the permitted amount FDA has the responsibility to take enforcement action on. Sometimes they will find residues in foods that they want to discuss with us and determine whether there is a serious food safety issue. I think our two organizations work well together to sort those questions out to get timely answers. FDA uses our advice, in my opinion, quite appropriately as they make their decisions about how to proceed on the enforcement front.

Then there are other areas. I mentioned the antimicrobial area as an example, where I think there is a great opportunity for coordination and we are not realizing it. We'd probably do things faster and with less effort and better, if our two organizations worked more effectively together

4b. My sense is that there is a variety of impediments. One that has over the years that has been a source of frustration for us is the way in which FDA handles information provided by companies who are subject to regulation. Basically FDA treats any submission from a company as confidential and will not provide the information to us at EPA. I gather that has its roots in the statutory provisions but I have got to say that I think FDA could be more active in terms of addressing those questions. For example, some number of years ago, 10 or 15 years ago, we received information saying that a particular chemical that was both a pesticide and used as a drug had been implicated in causing cancer. We thought that was information that would be relevant to our judgments about safety of the pesticide. We asked FDA if they would share the data. They wouldn't. We asked FDA if they could confirm that they had the data and they wouldn't. We were left pretty much in the dark about whether that was in fact real. So that is one issue.

Then I think there are simply cultural issues. Two organizations tend to develop different styles and different approaches on a variety of regulatory science issues and don't readily want to change anything. Often times change is what is needed in order to collaborated more effectively. Change both what you do, who you tell, when you tell them, and all that stuff.

4c. In my experience it takes a commitment from the top of both agencies. I sense that the collaboration will be worth the extra work. It can also be driven by external parties. In the case of antimicrobials the regulated industry could help the coordination and collaboration effort by being more forthcoming in terms of its communications with FDA about what they are doing at EPA and with EPA about what they are doing with FDA. Then it requires an ongoing attention to the issue. It is not enough simply to have a pronouncement from the top of the two organizations and say yes, we want to collaborate if there isn't sustained attention.

Other Federal Agency Manager #3

4a. Fair.

4b. Again, I think they have many people who are not up to date on the newest science.

4c. More open-mindedness. Again, if we are talking CFSAN. I should say, again, that most of the comments I am making have to do with the National Toxicology Program and some of my extramural efforts, not my intramural program.

Other Federal Agency Manager #4

4a, b, c. The coordination and collaboration are minimal in both directions but I think it will improve because of my relationship with NIEHS and FDA is in the same department. I have a good working relationship with FDA and before coming here I met with them. I met with the science advisor and with the FDA Commissioner to talk about collaboration and partnership since I have been here. I am actually going to go out and visit with them and try to develop collaboration and partnerships. I am going to reach out to them and be proactive. The indication is that they are going to be receptive to that. They need to meet half way and it is clear they want that.

Question 5
At what levels and in what manner does the FDA program interact on significant chemical safety and risk assessment issues with your agency?

Other Federal Agency Manager #1

I think that goes back to the IRIS a lot and the interagency review, which I think that happens at a fairly high level. I am not sure who the FDA reviewers are in that process, but I would think that has fairly high level attention within CFSAN.

Other Federal Agency Manager #2

Again speaking only about the pesticide world, our Assistant Administrator works closely with the FDA Deputy Commissioner for Foods. Over the years I have dealt with the Deputy Commissioner and I also know some of the folks in various positions throughout FDA and have worked with them. I encourage my boss who doesn't have as long a history or as many contacts to reach out and be in touch with his counterparts at FDA. We have done that to some extent. There are scientist to scientist collaborations. There are lawyer to lawyer collaborations on issues, but they are really not systematic. They are driven more by a personal individual history, from working together for 25 years and knowing that I can get in touch with him. And I know some other folks at FDA in the same way. I have fewer contacts with the FDA CFSAN management chain than I used to have.

Other Federal Agency Manager #3

Well the best interactions are when it actually comes out of the Commissioner's Office and there are questions that are occurring there. So there is a good example when they came to us about concern about arsenic in rice and rice products. They've involved us in their determinations and analysis. That is a good example.

Other Federal Agency Manager #4

I was a bit surprised that culture has not been that interactive. When I talk to my people they are not so eager to do so, but I am insistent that we change the culture, to interact with our government stake holders. So I have met with OMB last week to talk to them. They were very grateful that we reached out to them and offer to them to see things and to discuss issues early. They were very grateful for that. In fact that was my meeting a few minutes ago, the debrief about that meeting. It is really about who is at the top giving the time, who has the responsibility for these positions. Sometimes you can have 7 or 8 people who are very collaborative-oriented in nature and others who like to keep things close or within their own groups. I know managers at NIEHS and ATSDR. People that we know and FDA, we could develop some of these productive collaborations and sharing because benefits could be derived for the American people by doing that. I am going to work on it and it should pay some dividends.

Question 6
How does your agency program's risk assessment and safety evaluation method stay current with emerging state of the art in risk assessment?

Other Federal Agency Manager #1

We have a Risk Assessment Forum. It is an internal deliberative body which has representatives from the different program offices in EPA as well as Office of Research and Development. They take on specific tasks. They may be looking at cumulative risk or may be looking at thresholds or other problems within the risk assessment activity.

We have a whole part of the organization within ORD, the National Center for Environmental Assessment. They run the IRIS program and they also run the Integrated Science Assessments which look at the 7 national ambient air quality standards that are set for pollutants such as ozone, NO2, SOx, carbon monoxide, lead, particulate matter. It is a whole organizational unit devoted to doing risk assessments and they have the component, which is targeted toward improving the methodology in risk assessment. We have six large national research programs. One of them is on Chemical Safety for Sustainability that supports a fairly significant research effort to develop modern computational toxicology tools to improve risk assessment processes.

Then at the highest level at the Agency we have a Science and Technology Policy Council, which takes on the real significant issues in risk assessment and tries to come up with Agency consensus on those activities.

Finally, either through our requests or through Congressional requests, we have input from the National Academy on risk assessment methods. They issued several books, "Science and Decisions" being one of the more provocative ones. They looked at the formaldehyde risk assessment and gave us a whole bunch of recommendations on how to improve the IRIS process.

Then we have internally, like the Academy, just established a new Standing Advisory Board within our Science Advisory Board that is going to look at the whole IRIS program and do peer reviews on probably four or five IRIS assessments per year so we have got some continuity in that review process.

In a lot of ways, risk assessment has been somewhat of a static field for a while but I think that it is evolving and advancing with the new methodologies that are being brought into the field and practiced now. There has been a lot of change happening and a lot of desire to deal with some of the more difficult issues like acceptability, sensitivity, environmental justice issues, cumulative risks, community health. A lot of different ways we do that.

Other Federal Agency Manager #2

We have an Office of Research and Development within EPA that is constantly working in the frontiers of scientific issues and our regulatory scientists are quite well connected with, informed about, and participate in the research arena. Also our science staff are active in the professional societies for their discipline, the Society of Toxicology, the folks who do exposure, like

industrial hygienists and so on. We also work a lot with people in the regulated community, the scientific arms of those organizations and they are often times bringing to our attention new ideas and new techniques and technologies. And finally we have an advisory committee that does scientific peer review and we use them to help keep our science up-to-date with state of the art.

Other Federal Agency Manager #3

As I said, we don't really do risk assessment. We may do hazard evaluations. We are actually leading the efforts really for the federal government in developing systematic review which is a completely transparent way to generate all the data, so that anyone else could follow what you did. We are very interactive and open about that. Holding public meetings, taking comments, and sharing with our federal partners. That is how we are moving forward to having an open and transparent process of hazard evaluation.

Other Federal Agency Manager #4

We provide and assist our people to get training periodically. There are regular training programs, but also I am very much concerned that we not only keep current but we lead in this area. We know what the needs are in risk assessment because we do it. I really want us to identify the needs in risk assessment and get the research done. In fact for us to identify the gaps and to go to our government partners and request that the science be done or get our own labs to do the science. For example, I think epigenetics could be a very useful tool to accumulate the risk assessment, but we are not pushing that. Well I am, but the Agency is not. That should be something that everybody, I'm sure FDA and NIH would be interested in. If we led the charge. It's an environmental issue largely. The environment-induced epigenetic changes would be a way, I think, of looking at cumulative risk exposure and risk assessment. These are the kinds of things we need to advance. For example, I appreciate that NIEHA/NTP is out front on this systematic review and weight of evidence methodologies and developing them. When I came here I felt we should identify that as a need and we were going to be on top of. We are now engaged in it. Those are the kinds of things that we as an agency, who use risk assessment, need to develop these tools. We need to make the investment. Not just keep using the same old tools that we used 20 years ago because the volume of science and papers that we have to go through and to analyze them in an objective way is challenging. We need robust tools to do these things. The science is more complex than it used to be. We need vigorous debate and discussion with the scientific community about these issues. No one person can know all these things or no one small group can. You need expertise from many different fields to come in and experts can disagree on some of these issues. But we need to at least have public debate about them. I am insisting that our people get engaged on these discussions.

Animal studies are costly and time consuming. Some of the other studies could certainly be adequately predictive that if you had to make an investment in an animal study or human study you would know that they are likely to be absolutely needed. Rather than make the investment in an animal study and find out that they are not particularly relevant to the risk assessment.

Question 7
7a. What does your agency see as some of the emerging issues and questions in chemical safety review?

7b. How does your agency facilitate the needed developments in the science to address and answer these issues and questions?

7c. Is your agency proactive in identifying compounds or issues of emerging safety concern (for example, endocrine disruptors?)

Other Federal Agency Manager #1

7a. We are probably on the forefront of bringing computational toxicology. We define it as blending the tools of molecular biology with computational sciences to really bring a lot more information to bear in an integrated way as we do hazard assessments or risk assessments. Over the last 5-7 years, we have focused a lot on the hazards component of developing high throughput technologies to look for toxicity pathways or adverse outcome pathways. We are now trying to shift some of our attention so that we can look at exposure in the same way because information on exposure tends to be even more lacking than information on hazard. So unless we have both parts of that equation, we are not really able to improve the risk assessment process. We see those computational tools both in the toxicology and the exposure side as being important. We see that nanotechnology continues to be an emerging issue.

A whole range of integrated testing strategies and intelligent testing strategies of how do we go from a checklist of assays that we routinely ask our company to run and for which we may only use one or two in a risk assessment process. How can we be more efficient to select particular kinds of bioassays for a chemical based upon what we understand from some of the computational tools might be the real risk factors for it? And how do we bring these new tools, how do we get them validated for regulatory acceptance in either prioritization processes or replacement processes for existing methodology.

7b. We have these national research programs. Chemical Safety has about 140 scientists in the research program. We fund intramural research on these topics. We fund extramural research through our STAR grant program to fill data gaps, advance the state of the science. We are constantly asking our partners and our clients in the program offices in the regions around the country what are their key issues and how can we bring science to most effectively answer some of those. And then we involve a lot of advisory bodies. We have boards of scientific counselors that evaluate the quality of the work that we are doing and the state of the art that it represents. We have science advisory board panels that review our strategic directions and make sure that we are really pointed correctly. Both through our intramural program and extramural program and our advisory board, we really strive to make sure we are asking the right questions and that we are actually doing the right science to answer those questions.

7c. Yes, we do have an endocrine disruptor screening program that has been trying to chip away at that. It has somewhat struggled because it is not a program that you can run a lot of chemicals through effectively right now. That is where some of the computational tools that we are developing and hoping to prioritize chemicals for getting into that.

We are still quite active in looking at nanotechnology. We see one of our particular niches as the fate and transport of nanomaterials through the environment. It is not something a lot of other organizations are looking at. They may be looking at some of the health effects or the hazards of nanomaterials, but not necessarily environmental fate and transport.

We are always trying to look at issues that are arising in program offices or regions or even through international emergencies. Like what happened with the Deepwater Horizon when we had to, in a very short time, address the safety of dispersants being used in the deep waters of the Gulf of Mexico when that environmental tragedy happened.

Other Federal Agency Manager #2

7a. Probably the biggest issue is how to use new technologies to improve, simplify, speed up risk assessment for chemicals. We refer to it as 21st Century Toxicology. It includes use of genomics, proteomics, metabolomics, *in vitro*, and *in silico* methods to screen chemicals and focus risk assessment on the particular adverse outcome pathways that lead to apical effects in humans to a greater extent than has been done in the past. To use that to cut back on the amount of testing in laboratory animals typically used to screen food additives and pesticides. I think that the other thing that will come out of that is better modeling of pharmacokinetics and pharmacodynamics that will enable better translation of external exposures into internal doses in terms of predicting effects in human beings and understanding better the variability across the human population in terms of potential sensitivities to the adverse effects of chemicals.

7b. I think the answer to that one is tied up with No. 6 that was asked before and so I really don't have much else to add to that.

7c. I like to think so. On the endocrine disruptor issues we have a statutory mandate to screen certain classes of chemicals for their potential to interact with the endocrine system. We have been working over the last 20 years or so, more like 15 years, to develop a battery of studies that would screen a chemical effectively for that and then a battery of additional studies that could be used to follow-up on chemicals that display endocrine disruptor activity that would produce data that we could use for risk assessment purposes. The topic I mentioned earlier about non-monotonic dose response is related to the endocrine disruptor issues and we have been using the National Academy of Sciences and have been working with FDA on trying to understand what the scientific literature shows about the existence of that phenomenon and develop some guidance that would be useful for possibly reconsidering the kinds of studies that people conduct to assess chemical safety. I think we have also tried to work with other agencies on new issues like triclosan and its endocrine disrupting effects. I think we are trying to work through with FDA and CPSC and OSHA on how to assess the safety of nanomaterials. But that is an area, frankly, where I believe a lot

more coordination could pay-off. There is some coordination, but not as much on the scientific front as I think could possibly occur.

Other Federal Agency Manager #3

7a. I think some of the key issues are mixtures and susceptible populations.

7b. We fund hundreds and hundreds of thousands of dollars of grants every year that are looking at some of these issues. As well as we have programs that we look at through both our intramural and our NTP program.

7c. I would say we are the leaders in that.

Other Federal Agency Manager #4

7a, b, c. I think we probably haven't done a good job of that. I think that is what I mean when I say we need to identify the information gaps. When I was Director of NIEHS I made a pitch to Congress and the Director NIH to get money to start a nano-toxicology group at NTP. We were given some monies by NIH to do that. That is probably where most, at least within the government, of the nanotechnology work has now been done. But again because I recognize that the government, NSF, and others and industry was making a huge investment, back in 2004 or 2005, in nanotechnology for medics, communication, and others. But there was almost nothing being invested in looking at the toxicity of some of these particles. I think that is a situation where it is obvious that is our future needs for research and there still is. The gap between investments in developing the technology and investments to look at the possible safety and all that. Very little has been done. So that is an area. Also endocrine disruptors, I don't know what effects they are having, but it is one of the mechanisms that maintains homeostasis in a biological system particularly as complex as one in humans. So we need to make an investment to understand the biology of those chemicals and how they are acting and at what levels. I would say those are at least two examples of areas where research investments need to be made and are to some extent. Endocrine disruptors are probably adequate but nanoparticles are not. Those are the kinds of things that I think typically we at regulatory agencies get focused on, their process, and using one tool over and over and over and not giving a lot of thought about how to advance the state of art and the science. I'm going to emphasize that because I am certainly interested in doing the risk assessment, but I am also interested in improving the assessments so they are more relevant, more accurate for humans, and less costly, and less time consuming.

Question 8
How does your agency assure that it has adequate internal and external expertise when needed?

Other Federal Agency Manager #1

We go through periodic work force planning exercises where we look at what's the future, what are our future strategic directions, what's our current work force expertise, what kind of gaps do we have? In that we use our advisory boards. The Board of Scientific Counselors (BOSC) looking sort of retrospectively and the SAB looking prospectively to evaluate the quality of the science that we do and the scientists that we employ. As we go through the tightening of the domestic budgets, there is going to be a real oppressing issue for us. Because if we are in a hiring freeze, like we are now, it does become a challenge to make sure we have the right expertise. I think this is only going to become more troubling for a lot of federal agencies as the resources get tighter and tighter. We actually do have this work force planning activity to periodically go through and assess where we're at in the work force, skills and knowledge, and abilities.

Other Federal Agency Manager #2

I referred earlier to the advisory committee and that is probably for the pesticide world the main resource that we use to get external support for tough scientific questions. It has a very broad charter and allows us to draw on any expert in any field, provided they meet the conflict of interest requirements, to offer advice about what EPA ought to be doing. We have typically had somewhere between 6 and 10 advisory committee meetings a year on a wide diversity of topics. Internally we turn to our colleagues in other parts of EPA. There are superb scientists in our Office of Research and Development and many of the things we do on the pesticide front are similar to the kinds of work that goes on for example in the Air Program, the Water Program, and the Superfund Program. There may well be people with expertise on particular chemicals or issues that can come into play and help support our risk assessments. I imagine the same thing is true with regard to FDA, and broader HHS.

Other Federal Agency Manager #3

Well, everything that we do goes through extensive…Depending on the program, we have science advisory boards and boards of scientific counselors to ensure that we are doing things that have appropriate expertise and reviews. So for example, we first, in both the NTP and the extramural program if we are going to start in a new area, have a concept. In the case of the extramural program, we present a concept to our National Advisory Council and in the case of NTP to the Board of Scientific Counselors before we embark in a new area. If it's an area where we don't have the appropriate expertise we get it involved either by hiring or by contracting with people to get it done appropriately. Everything we do goes through lots of rounds of both internal and external peer review and in many cases across federal agency review. I would say on all of our boards, our council board and NTP's board…On our council's board we have ex-

official members from other federal agencies and on the NTP board we have the same kind of situation and we form expert panels to look at specific topics.

Other Federal Agency Manager #4

That was another issue that I identified and that's in our proposed enhancements that we are going to roll out in a week or so. We just created a permanent standing Science Advisory Board made up of about 20 to 25 people. The way we typically did our reviews before were with contract-managed peer reviews. I think you need consistency and so having a standing committee gives you that. Also we need to consult with a panel of scientists constantly. As we are developing these assessments, why can't we consult with them about systematic review, weight of evidence, models for extrapolation of risk at low levels and doses that are non-linear. There are lots of challenging science questions that we need science advisory advice. I think having a standing committee would be a way of getting that input into our decision making. It is not directly related to any specific decision but it is related to the science. How are we going to apply the science under different scenarios? I intend to make use of our Science Advisory Board. I am impressed by the quality of the membership, and they can help us in many ways. One of the issues that I am faced with a lot from different groups (NASA, Department of Defense) is the issue about background levels. Methanol is in a lot of things. Formaldehyde, there are background levels. When we find a cancer slope factor or inhalation risk factor, RfC, that is below background, how do you deal with it? These are the discussions we need to have with the scientific community. How are we going to deal with it? Agencies don't want us to report out RfCs that are below background. There may be a risk at background. We know UV light; we are at a risk at background. There are some exposures there is a risk at background level. What do we do? It seems to me that is a risk management decision, but we scientific debate and discussion about those kinds of issues. I intend to involve our Science Advisory Board on many of these issues and to get good advice on how we apply the science to risk assessment.
[Prompt: To what degree have you published things in scientific literature to have this dialogue? Obviously it is not an immediate dialogue but to put into the literature, here is our current thought and wait for other people to react to it. Initiate research.] We have done that in the past to some extent and I have urged us to do that more often and I think that is a way to promote our young scientists' career also. I think that is one thing I think we should do more of. I had a discussion last week. With every assessment we should get out a publication and let the community see how we are doing things and let's debate it. I think that's a good way to do it. Hopefully the level of publication is going to go way up for just that reason.

Question 9
9a. What training types/topics have you found are most beneficial for your risk assessment program?

9b. Are there outside entities that you have partnered with for more training opportunities?

9c. How does your agency make sure that professional development needs are being met to ensure development and retention of qualified scientists?

9d. Are there training opportunities that your agency might do in collaboration with the FDA?

Other Federal Agency Manager #1

9a. Our NCEA, that runs the IRIS program, they do have a formal series of training modules that they offer. They will actually go out to countries or organizations and do that training. I would direct you to look at that.

With the changes that are happening in computational toxicology there is also a "communities of practice" that we set up that meet by teleconference once a month and talk about advances in different methodologies or technologies, a sort of best practices kind… We have set up a few of these "communities of practices" that seem to be pretty effective at bringing people up to speed.

We try to put out newsletters to people on Listserves on what events are going on and what are the opportunities for the outside world to engage with us.

9b. Other than scientific societies, I am not sure we would actually call them partnerships. I am not too aware of any of those. They may exist.

9c. We have the annual performance reviews. There are career development plans that are put together for people so that they can list their training needs or desires and can work with their supervisors to try to get those met by either internal or external process.

We think it is really important to send our scientists to cutting edge scientific meetings where they not only make presentations but they can hear what is going on in the field, they can take CE courses that are present there, and just in general network with scientists, which is an undervalued opportunity for attending meetings.

We try to encourage our scientists to work with scientific societies and with other national or international organizations interested in environmental health and human protection. ILSI has the World Health Organization, the United Nations Environment Programme, international program on chemical safety, and regulatory partners around the world whether it's Health Canada, Environment Canada, European Chemical Agency, or

European Food Safety Agency. We do try to make professional outreach be part of attracting scientists, as well as retaining them.

9d. Probably, that is something if we had some higher level interactions we might be able to be able to hone what some of those opportunities might be.

Other Federal Agency Manager #2

9a. We have undertaken to create a library of documents that describe steps in risk assessment. The first thing, of course, is to figure out what data to require and when to require it. The second is to characterize what information should be in a report about a study. The third set of type of documents has to do with the evaluation of the results. The fourth kind of document is how to integrate information across different types of studies. So for example, looking at data on reproductive toxicity or looking at data that would be relevant to assessing carcinogenicity. So those are things we have done. We have developed videos that we use with our new staff that explains these documents to them to familiarize them with the documents and talk about the subject areas broadly. For example we've got videos on the subject area of absorption, distribution, metabolism, and excretion (ADME), how to review an ADME study, how to use that study in a broader risk assessment for a particular chemical. Then once the new staff has had the opportunity to work through all that, then they work through mentoring programs and through internal peer review systems that help them understand and see how to do their work. A staff reviewer that gets a study, reviews it and produces a report following the guidance on evaluating that particular kind of data will then take it to a second line supervisor who will give them feedback on whether that report is done well or poorly. If there are issues raised then it will go to a group of senior scientists who will look at the issues and discuss them. Eventually after a while, new staffers develop enough familiarity and expertise in the field and they can begin to take on some of the secondary peer review roles or tertiary quality control activities. Those are the ways we train our staff and it seems to be successful in producing consistent reviews.

9b. Most of our training is external. We regard attendance to professional societies as also beneficial and helpful and effective in professional development. I don't think of it explicitly as training but I think it certainly does contribute to the quality of the work that the scientists do.

9c. We do what we can internally. The thing that I believe keeps people in the government in the science disciplines is doing interesting work and work that makes a difference and rewarding them to an extent that the government pay scales permit as much as we can. As staff get better and better we ask them to tackle more and more interesting issues. Fortunately or not we have a lot of interesting issues to deal with and I suspect the same is true at FDA.

9d. I would bet there are. I don't have any specific ideas at the moment other than to consider whether there might be opportunities for staff exchanges.

Other Federal Agency Manager #3

9a. I am not sure what that question even means. We try to be sure that our scientists, our employees are trained and up to date on the science. We have a very vigorous, active seminar program. We bring in some of the top people in the field. We support people to attend national meetings where they can take continuing education courses. I am not sure if that is what you are talking about. And we bring in expert panels and before we start a systematic review effort we start reading about it. We prepare by having our staff look into it. All of this is intended to make sure that we analyze the available information before we bring together a panel of experts to provide guidance.

9b. Again, I am not sure what these questions mean. Yes, our scientists go to appropriate scientific meetings: Society of Toxicology, Society of Toxicological Pathology, Society of Risk Assessment, Endocrinology Society, and whatever the appropriate. There are opportunities for not only to listen to all the science and participate but take training. If you mean a specific company or group that we bring in, not necessarily. We may go to a consulting firm if we want to provide communications training or something.

9c. We encourage participation in appropriate scientific meetings, both local and national. We vigorously encourage our scientists to be involved in these national organizations, not only to go to the meeting.

9d. I suppose so. I would need more specific examples of what kind of training you are talking about. Certainly the systematic review as we go forward and develop that. If FDA is interested in looking at this as a way for them to do their assessments, we would certainly be happy to work with them on that.

I feel that some of the questions were very hard for me to answer because we don't do risk assessments. It is very frustrating when some of the newest data is not used. People will say, oh, well they did not do Good Laboratory Practices or something. But I can tell you that GLP no way ensures that you have a good study. It just assures that there has really been good recordkeeping. I look at many of the guideline studies and they were fine when they were developed in the 70s, but they are not asking some of the questions that we understand now, today because the science has progressed.

Other Federal Agency Manager #4

9a, b, c, d. I think probably all of the above. I guess there are some for profit, some contractors. Some contractors or groups are experts in doing certain things and we've hired consultants to come here and do training for 10, 20, or 30 people at once. Recently we had a trainer come in and give us training in science writing. So we could write our reports so they would be more lucid. I think that was a small contractor from a university who did that. Certainly some of the societies give really good courses taught by experts in the field and not necessarily from universities but from private industry as well as universities. We encourage those and we support that kind of training. I would guess most of our training is

done through the professional societies. Our scientists go to those and so I would say we use all of the above.