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Results from the Listening Sessions that CFSAN/CVM/OFVD Conducted as Part of the Chemical Safety Assessment Review

OFVD/CFSAN/CVM held five listening sessions on the chemical safety assessment program. One session was with CFSAN epidemiologists and biostatisticians to learn how these disciplines can be better integrated into the chemical safety assessment process at CFSAN. Two different sessions were held with representatives from the food industry and trade associations. Two different sessions were held with representatives from different consumer organizations. The topics discussed were in three broad areas: Science Issues, Forecasting Emerging Areas of Concern, and Collaboration/Communications Issues

Results from the Epidemiology Listening Session

Science Issues

- Epidemiology data are often used in CFSAN contaminant risk assessment – but not being evaluated by epidemiologists. Epidemiologists (and others) are not always in at the end of a risk assessment to know what happens/how epidemiology data were used.
- Although epidemiologists have participated in a couple of different chemical safety review working groups, there is no consistent way of involving them in safety reviews in CFSAN. That means they get handled by different Center offices in different ways which means epidemiologists may or may not be involved.
- CFSAN needs to develop a consistent process (SOPs) for handling chemical safety issues that would consider whether epidemiologists should be involved and get them involved sooner. Process/template should include some type of checklist for the scientific disciplines that need to be engaged in the issue.
- Every office/branch wants its own epidemiologist(s). Better to keep the epidemiologists together in a service-type of office in order to have better access. Also, this would lend itself to a critical mass of the discipline for the most robust assessments/evaluations of data.
- CFSAN doesn't need a list of the experts to engage (people come and go over time) but rather a process and organizational structure that starts the process going without wasting time or other resources and gets the right disciplines/people engaged for the issue.
- Epidemiology functions used to be part of a service office within CFSAN (OSAS) that could be tapped from any part of CFSAN. Epidemiologists in CFSAN are not available in the same way they used to be. There is too much separation of epidemiologists within CFSAN (scattered in separate offices), which results in inconsistent products.
- Epidemiologists in the CFSAN have different views/approaches – need one consistent approach.
- CFSAN needs to reduce the tendency to pigeon-hole people in different disciplines – need integration of multiple disciplines for successful chemical safety review. Need

cross fertilization across scientific disciplines in reaching decisions on complex issues, such as a multi-disciplinary team working on an issue.

- CFSAN needs to do a “weight of the evidence” evaluation for chemical safety hazards, i.e., epidemiology data need to be integrated with toxicology data – hard to do if we don’t have the evidence/data.
- CFSAN has been most successful in addressing chemical safety crises when the issue has had a key individual, high up in the Center, coordinating – someone with a good skill set – good people skills to bring/keep people together and break down office barriers (to reach across offices to pull in needed disciplines/expertise).
- Toxicologists, risk assessors, lawyers/regulators, and epidemiologists look at and value evidence differently, and they sometimes work at cross-purposes (there can be grey areas in epidemiologic results when lawyers/regulators want black and white answers). Case studies and lessons learned could be used in trainings to help staff in different disciplines understand the requirements of good science for each other’s methods and the importance of involving epidemiologists from the very beginning.
- Process issues – CFSAN is at risk of picking literature (for epidemiology work) that might not stand up to scrutiny. Need to do triaging in literature reviews. The Center needs to establish an SOP that can serve as a resource for doing literature searches. The SOP could provide stages and steps for “check-in” across Center and agency (make sure everyone is on the same page).
- CFSAN needs to look at what are the probable limitations for epidemiology data (if assessing something with a small effect, epidemiology data may not be useful/available).
- CFSAN needs to better integrate epidemiology data (not just stand alone) in the whole picture when doing a safety assessment/risk assessment.
- CFSAN needs a centralized/large epidemiology database (meta data base) so that CFSAN isn’t reinventing the wheel every time it has a chemical safety issue. Epidemiology data change over time – need to keep it (database) current. - Effort needs to be made to capture institutional memory of epidemiologists before they retire. Important to know: What were the strengths and weaknesses of the evidence available to that review? When was the current review completed?
- CFSAN should consider using iRISK as a repository on hazards – need to discuss how it could be used to integrate epidemiology data.
- A catalogue or list of epidemiology data resources and a description of the periods and types of data contained in the collections would be a helpful resource for epidemiologists participating in chemical risk assessment. Really need to pay attention to idea of creating databases/repository of epidemiology data and experiences to ensure that CFSAN isn’t re-inventing the wheel for risk assessment and other purposes every time we face a chemical hazard safety assessment.

- CFSAN should institute a policy of conducting “post mortems” on all risk assessments to discuss data gaps, challenges, what epidemiology data can be used to validate the risk assessment.
- CFSAN needs to view “crises” as public health opportunities (to advance knowledge, increase awareness, improve regulatory oversight where gaps exist, improve technology, etc.)

Dealing with emerging issues and questions of concern in chemical safety review

- Which chemical compounds are selected to “go under the microscope” for safety review seems to be largely driven by media interest, rather than as a result of FDA creating a framework for considering which compounds to evaluate.
- Chemical safety issues coming from outside in a “frenzied mechanism” don’t allow for methodical approach (e.g., BPA, antibiotic resistance).
- CFSAN should have a developed and prioritized plan for reviewing emerging issues, for example, endocrine disruptors.
- CFSAN has old issues that become emerging issues (again). Should CFSAN revisit issues on a cyclical basis? How does/should CFSAN manage cyclical reviews?
- CFSAN needs to be proactive in collecting epidemiology data on issues – a ‘watch list’ – ahead of time. CFSAN needs to get ahead of the curve (particularly for epidemiology data).
- CFSAN needs a list of ‘hazards’ to be managed by the Center – a list of hazards and a process for dealing with them. CFSAN knows certain emerging chemical safety issues that can ‘hit us’ if we don’t pay attention. Need a way (criteria) to evaluate/rank importance of chemical safety issues for review.
- CFSAN is losing institutional knowledge to retirement and increasing mobility of scientific experts. CFSAN seems to be starting from scratch repeatedly. How can CFSAN make the process one that will evolve or mature over time and use the wealth of knowledge gained from prior efforts?
- There appears to be no/little institutional memory or back-up for chemical safety issues/evaluations. Need a repository – not just a list, but an active repository that is managed and monitored on a regular basis.
- CFSAN should call together a group of 5-10 people every three-to-four months or so to do “big thinking” on epidemiological issues (what’s coming down the pike re: tattoos/mycobacterium; caffeine/young people)
- An ongoing working group approach could help proactively identify priority chemical safety evaluation needs, with subgroups to work on each evaluation, data needs, and ways to acquire the necessary data.

Data/Collaboration/Communication Issues

- One can't get useful data from CAERS regarding individual ingredients (data geared to whole products only) e.g., caffeine levels, other ingredients. If trolling data for ingredients – looking for signals for melatonin – need to be able to look for data on specific ingredients (not whole food).
- CFSAN needs to better integrate all human data (CAERS, human studies, etc.); numbers in CAERS data are too small; hard to find the data; and use the data? for epidemiology evaluation.
- CAERS is good for seeing signals of acute effects, but not for chronic effects (more likely with low-level chemical contaminants). Need something other than CAERS to track/provide signals for detecting chronic effects from chemical contaminants.
- Poison control centers may be a good source for data – but FDA doesn't have access to poison control center data, which are very costly. CDC has a relationship with poison control centers but can't give us the data – this needs to be fixed. Consumer Complaints (ORA) can't get at information on product labeling or product ingredients. General lack of good epidemiology data in complaints and MedWatch reports (re: onset date and duration of illness). CFSAN needs to talk with ORA on whether we can get better data for complaints and we need to give the field better information/guidance on what data to collect in taking complaints/picking up samples.
- RFR may require reporting on adverse events– but it is based on whole foods (not single ingredients). The problem is with products with multiple ingredients and finding a way to correlate a potential safety concern to the individual ingredient.
- Problem – systems are not user friendly/easy to submit adverse event report information to FDA. Need to find a way to make it easier to report and improve consistency of data provided.
- Problem with under-reporting of adverse events (when looking for signals of chemical safety (or other) issue).
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- The group is aware of/thinks there are legal and policy constraints against integration both in terms of data sharing and integration of efforts.

Feedback from Consumer Listening Sessions

Science Issues

- FDA needs a major shift to chemical safety. Agency is “stuck in the past;” needs to be “vital protector/defender” of public health.
- FDA doesn't seem to be keeping up – agency is stuck on “old ways” of thinking and doing things. For example - why are risk assessments based on a 165-lb man? FDA

needs to be able to consider other populations and alternate end points. FDA is using old methods to evaluate new products/technologies.

- Consumers want risk assessments to answer the questions of: a) how dangerous is it (the chemical); b) how controllable is it by me or others; and c) what is FDA doing about it?
- Risk assessments need to deliver “pure analysis” (apart from risk management). Keep risk assessment and risk management separate.
- Responsibility for risk assessments should be combined in the Federal Government – a single agency or entity – use EFSA model (one agency does risk assessment, another does risk management).
- Risk assessments need to be more transparent and be better at factoring in long term effects and chronic disease endpoints. FDA needs to assess how to integrate information coming from “Tox 21” into risk assessments.
- FDA needs to more clearly articulate risks in its risk assessments; currently a confidence gap for FDA in the area of chemical safety. FDA does not act aggressively enough when the evidence is clear. FDA needs too high a degree of scientific certainty before it will consider/accept scientific evidence and act on it,
- For all new technologies, CFSAN needs better new measurement tools and understanding of what those tools mean. Toxicology tests are expensive (and raise concerns among groups like PETA). Need to be able to measure and have the right measurements for all the new technologies.
- FDA not sensitive enough to “sensitive populations” when doing risk assessments. Risk assessments need to be better at taking into account sensitive populations; pay attention to early life exposure and lifelong impacts (from early exposure); also need to better address impact on behavior and cognitive functioning (not just cancer risk); impact on the life cycle. Risk Assessments need to be different for chemicals/food additives depending on whether they are derived from chemicals themselves or from organisms that produce the chemical/additive (re: synthetic biology platforms).
- As precipitated by issues surround “GE” tomatoes – how do we assess whole food safety (versus just as an ingredient in food)? This is a daunting task but FDA will soon be faced with it and needs the capacity to evaluate. For example, nutritional impacts will be increasingly important
- There is a gap in confidence, i.e., that FDA will not always decide in the public interest with respect to contaminants. FDA needs to be on the vanguard in protecting public health when the science is clear and when the science is unclear.
- View transparency as declining – used to be able to get information through FOIA (now, it takes “years” to get data on a FOIA request). For example- information on nano-technology (nano-chemicals) needs to be in the public domain (Federal agencies are over using confidential business information – leads to lack of transparency).
- Urge FDA to release as much science on these things as FDA can. Want transparency and “real” data (not just summaries).

- Don't assume that NGO's will use info to play "gotcha" with FDA/industry.
- If a contaminant/chemical is truly dangerous, it should be banned. Risk assessment, risk management, and risk communication should involve fairly clear messages; FDA needs a strong risk management approach and clear messages.
- For nanotechnology, the focus now is on how to measure/detect nano particles. How do you do risk assessment if you can't even detect the substance you're interested in? In food contact substance area, with respect to nanotech, FDA is asking the right questions. Need to pay attention to food items coming in from other countries that use this technology.
- Would like to see FDA do more testing of more products (not aware of what routine monitoring is currently being done).
- FDA has taken misguided direction with respect to GE fish (GE and antibiotic resistance issues) Want FDA to take a more scientific approach rather than just saying it sees no difference between genetic engineered and other products.
- FDA should put resources into recognizing engineered organisms are different – FDA needs to treat them differently and not regulate them under the coordinated framework.
- FDA should assess unintended effects (re: GE products) through feeding studies with whole foods.
- FDA should be more like the EU and require data on GE products (e.g., evaluate their safety thoroughly and not treat GE/GM products as if they were the same as regular food).
- There are very good biostatisticians on the foods and veterinary medicine advisory committees but FDA doesn't listen to them.

FDA gets too much money from user fees which makes the agency too sensitive to industry concerns for release/characterization of data (perception is that FDA doesn't want to upset industry).

Dealing with emerging issues and questions of concern in chemical safety review

- FDA is largely reactionary – doesn't act until others raise an alarm and does not appear to be ahead of the curve to external stakeholders. FDA is more reactive than proactive.
- Concern about multiple agencies doing risk assessments for the same compounds – with conflicting results (e.g., FDA and EPA for methylmercury and arsenic); and Salmonella Enteritidis in eggs (FDA/USDA) – can't agree on the burden of illness.
- FDA can't possibly do thousands of separate risk assessments on thousands of compounds alone and in combination. Need to find others ways to address; determine what will actually be useful. This is particularly evident with changing exposures and different platforms that vastly expand the number of products to be reviewed by FDA (e.g., synthetic biotechnology products.)

- May need to prove there is a risk first before designing a risk assessment to address. Maybe put the burden of proof (that there is/is no risk) on those who want to prove the safety of new technologies (not just what the compound is, but how it is created).
- Some areas of specific concern for consumers are:
 - Arsenic – extent to which it is in the food supply (extensive); what are the risks
 - Approval of certain food additives – Quorn, Olestra
 - Chemical agent that shows up in baked goods (acrylamide)
 - Ractopamine is an international issue (beta-agonist).
- Cross-cutting issues – endocrine disrupting compounds – BPA, phthalates, maybe nanotech – because they attach to receptors on cells. Need to think differently than for other classes of products in considering toxicology. The normal monotonic function and linear dose response approach (classical toxicology) doesn't apply to these compounds. FDA needs to place more emphasis and training on how to evaluate non-monotonic mechanisms.
- Looking at mixtures of compounds and potential synergistic and other interactive effects.
- Overlap for safety between chemicals for food additives and same chemicals used for drug manufacturing, e.g., synthetic biology (yeast in foods) – developing things we've never seen before (e.g., orange 'flavors' for cleaning products – what happens if/when they cross over for food use).
- Animal drug issues re: how they are being used in food producing animals i.e., how animals are being treated; how drugs are being used and administered. Concern over beta agonists – are drug companies suppressing information on tests showing they aren't good for the animals (e.g., heat stroke).
- How can FDA assign GRAS status for things we've never seen before? Need a way to understand new "platforms" before a product is approved – need to think along lines of "what else can this be used for". Why are products on the market if you have no basic methodologies to measure/test them for safety?
- Need to consider whether/how addition of a chemical substance affects health.
- Concerned about titanium dioxide in foods (nano-particles) – about 37% of these particles are smaller than 100 nanometers (e.g., size to pass through human gut). Recommend that FDA work with CDER, which has done substantive work on this issue (in medical products).
- All the consumer organizations are primarily policy organizations so tend to be reactive or identify new concerns to bring to the agencies.
- CFSAN takes a long time studying before coming out publicly on an issue (average of 2 years).
- Keep focus on what will be the conversation on emerging chemical safety concerns in the future; focus on what consumer reactions likely to be in the future.

- Work to push issues into the public consciousness and get FDA's attention.
- Concerned with chronic health issues – do testing for antibiotics and arsenic in apple juice.
- Interested in doing more testing (re: biotech) if we could better measure nanotech.
- Consumer groups listed the following as activities they conducted to help forecast emerging issues:
- Often get tip offs from whistleblowers in industry and government to spark interest/investigation.
- Pick certain areas to work on actively (such as food additives); currently only organization they know of working on seafood toxins/drug residues in seafood imports (using information from the States and subject of media calls). What is the only organization working on these? The consumer organization?
- Respond to media requests to comment/review studies conducted by others.
- Participate on committees and review related information. Info related to?
- Keep certain issues on “the radar screen” and pay attention to issues brought forward by others.
- Daily survey of what is going on in the external environment related to chemical safety; daily monitoring efforts.
- Survey scientific literature (teams of writers for organization publication) and use as resource for articles. Scan/review journal articles for what is currently happening; also scan consumer reporting of information and State reporting systems.
- Pay attention to WHO activities; monitor FDA import alerts

Communication/Collaboration Issues

- Cooperation not good in the animal drug areas (lots of pressure on the trade issue vs safety side of things); animal drug issues will be the most contentious issues in the future.
- Leadership the US (re vet drugs) is crippled by the over involvement of other (not public health oriented) agencies and the drug companies.
- There's too much politics involved. Not the fault of FDA – it gets directions from above, primarily State Department. Also, the US Government tries to coerce other countries into agreeing with them on Codex issues.
- FDA has good scientists – but they are interfered with at higher levels of management.
- For some process things, FDA does well (e.g., US/EU, US/Trans Pacific trade agreements).
- Office of Technology Assessment? should take on many of the issues involving new technologies (but is hampered by politics).

- Too many things end up in the market place before we know if we really need them and whether they are safe.
- Just providing labeling information is too much for consumers. Need FDA to set limits or standards to drive change.
- There's a difference between naturally occurring hazards (chemicals) and those that are man-made. For something like "radon" then just providing information is fine, but for other chemicals FDA needs to set limits to help drive the market.
- With respect to arsenic in rice, believe that if FDA sets limit that 76% or more of rice would 'pass' (be above MRL).
- Advisories or recommendations should only be used when data are limited, for example, when first examining a potential health hazard. Consumer organizations do recognize that setting limits is difficult and time consuming.
- It is difficult to effectively communicate risk with consumers and specifically if you want them to make decisions.
- Bottom line – FDA should not be allowing things in the market place that aren't safe.

Feedback from the Food Industry Listening Sessions

Science Issues

- Society has arrived at current point of strong chemophobia. People are afraid of chemical hazards in general.
- General lack of trust and specifically in government regulators and the industry. Big money in Fear -- message is "big companies are bad."
- General public has a lack of scientific knowledge -- doesn't understand scientific terms. Tend to discount data too quickly. There is a belief that no level of a contaminant, additive, etc. in food is safe -- confusing for consumers when they get mixed messages from government and from consumer groups.
- Safety science is slow to keep up with increases in analytical capabilities. Very low levels of chemicals are identified but data to demonstrate safety are not available.
- Industry is incorporating new "Tox 21" methodology in some of its assessments. Industry is focusing a more critical eye on these and other new technologies. However, these technologies may go the way of genetic toxicology testing. Initially thought to be very predictive of carcinogenicity and mutagenicity but now not considered as predictive as once thought.
- May incorporate Threshold of Toxicological Concern for trace elements

- Exposure data are not always reliable. Need better estimates of consumption than National Health and Nutrition Examination Survey (NHANES). Example- NHANES data on chewing gum is not good.
- CFSAN Generally Recognized as Safe (GRAS) notification and FCN programs work well. we'll need to spell out
- CVM GRAS notification not working well -- difficulty making scientific decisions that are science based and requests for data are sometimes unfathomable. Easier to go through the petition program.
- In ingredient reviews, there are different assessments for different countries with no explanation of why the differences occur. The more recent the review, the more confidence the public has in it, so if another country has a more recent assessment, public sees as more valid than an older US assessment,
- FDA needs standards against which to measure safety -- similar to the 1962 effectiveness standards.
- Food industry is giving out smaller grants for food safety issues . Food industry is using weight of the evidence approaches. Using small expert panels to look at science issues.

Dealing with emerging issues and questions of concern in chemical safety review

- Food industry recognizes the importance of being proactive and increasing awareness of emerging issues. Goal is to “get better at what we do.”
- One company has a safety and environmental group that is tasked with reviewing the literature on an ongoing basis.
- Industry also develops partnerships with academic institutions where research is being conducted on food-related topics. Increasing affinity for industry to work with academics.
- Industry does not conduct basic science research; rather, it relies on suppliers to interface with scientific groups. Asks all suppliers to let it know if they are using Nano.
- Use consultants for specific topics, especially for novel and unique approaches to chemical safety assessment.
- Participate in global groups to keep ahead of trends.
- Some companies have monthly calls on “horizon scanning.”

- Some companies have a more formalized “Advanced Issues Management Group” or AIM.
- Project “No Surprise” looks at economic adulterants, which this triggers discussion of what other foods these might be present in. It also tracks law suits.
- Discussion with NGOs about a hit list of hot button items,
- GMA has a formalized process- --two consultants that report on the “hot topic of the day,”
- Industry looks at weather reports – to predict economic adulterants- i.e., mycotoxins and climate change,
- Believes that Adsorption, Distribution, Metabolism, Excretion () information is important and that if one understands ADME, one can predict toxicity in many cases. Discussing how to reshape ADME to make it more predictive.
- Flavor and Extract Manufacturers Association (FEMA) does a 10 year re-review process- cyclic review- of its products.
- Industry relies on JECFA/EFSA evaluations.
- Gaps in databases make it difficult to keep up to date. Part of FDA resources should be working with trade associations to develop joint databases, to give the databases more credibility. Evens out the playing field if all parties have access to the same data.
- New software tools for tracking emerging issues need to be developed.
- Green chemistry is not an issue with the food industry as it is with the chemical industry.

Communication/Collaboration Issues

- Industry recognizes the importance of accurate risk communication.
- Industry realization that even if it did the science “right” it will not be able to convince the public because the public does not trust industry studies although these studies may be conducted with higher standards than journal articles or academic studies.
- Food companies spend a lot of time “managing outrage” rather than issues regarding true public health hazards. For example 80-90% of industry “reactive efforts” are not for safety reasons but for corporate image.
- Public doesn’t understand the rigor that FDA goes through as it makes a decision.

- FDA loses a lot of public trust when it says it doesn't have enough resources to do something, and it is difficult to re-build this trust.
- Example is BPA – tell public that the science shows no concern but the FDA still has some concern, which is taken to mean that science is no longer credible.
- FDA statement on arsenic that was released after the Consumer Union article was not reassuring to the public.
- FDA needs to look at its words more carefully; lower credibility when FDA uses phrases such as “need a better understanding” or “FDA is aware of.”
- Lack of a credible voice for the public; many reporters don't check facts or sources before publishing their stories.
- Confusing to the public when there are different international standards for the same products. For example, the level of allowable arsenic in India is 1000 ppb.
- FDA needs to monitor social media. Industry uses social media to track “brands” and what is being said about certain brands.
- Inability of scientists to be good communicators, thus what is being communicated on chemicals in the food supply is misunderstood. Leaves consumers open to negative advertising.
- Industry needs to brand itself better- maybe also the FDA- for example CDC is branding itself by showcasing all the good things that it does.
- Initial focus should be global leadership spearheaded by FDA.