Traditional Research Lifecycle

- Planning/Problem Formation
- Research Activities
- Publication

?
Shifting Our Approach

• What happens to the research after a publication?

• How do we know that science is informing public health action and decision making?

• Need for a shift in how we think about the lifecycle of research
Proposed Research Lifecycle

1. Define Knowledge Gap
2. Conduct Research
3. Publish Study Findings
4. Evaluate and Refine Research Needs

Assess Impact Potential
Research Impact Workgroup

- Conducted background research and literature review
- Developed impact framework and metrics
- Engaged stakeholders at FDA to increase awareness and solicit feedback
- Iteratively modified impact framework based on stakeholder feedback and case study analysis
FVM Research Impact Framework

- Advancing Regulatory Science
- Disseminating Scientific Knowledge
- Informing Regulatory Decision Making
- Catalyzing Action
- Advancing Public Health
Applying the Framework

- Workgroup solicited nominations for completed research projects considered to be high-impact.
- 81 nominations received, workgroup selected 11 for initial analysis.
- Pilot retrospective case studies conducted between March and July 2015
- Case study analysis conducted through semi-structured interview and literature review
Success Stories
Measuring Inorganic Arsenic in Fruit Juices

PI: Sean Conklin, CFSAN
Risk Surveillance

March 12, 2008 00:17 ET

CFIA/Warning: Health Hazard Alert-Certain Pear Juices For Toddlers May Contain Arsenic

OTTAWA, ONTARIO--(Marketwire - March 12, 2008) - Audio clips available at www.inspection.gc.ca/english/direct/media/

The Canadian Food Inspection Agency (CFIA) and Loblaws Inc. are warning the public not to consume certain pear juices for toddlers because these products may be contaminated with arsenic.
Need for Regulatory Action

• Based on non-cancer endpoints, FDA established a level of concern of 23 ppb for total arsenic in juice in 2008.

• The ability to quantify public health risk for commercially marketed juice products, therefore, depended on a validated method for detection of inorganic arsenic.
Research Design

• New method for use in surveillance, inspection, and compliance
  – HPLC-ICP-MS

• Stakeholders: FERN laboratories, ORA, industry, consumers, state and federal governments

• Single-lab validation – 2010

• Multi-lab validation ~2013
Dr. Oz Investigates: Arsenic in Apple Juice

When The Dr. Oz Show first heard reports of arsenic in apple juice, we launched an extensive investigation. Using an independent lab for sophisticated, state-of-the-art testing, we uncovered that some of the best-known brands of apple juice contain arsenic. Learn what you need to know to protect your family.

Posted on 9/12/2011 | Comments (0)

Arsenic Apple Juice

Originally aired on 9/14/2011

A shocking investigation by The Dr. Oz Show has revealed that some of the best known brands of apple juice may contain arsenic. See the shocking results.

GUESTS: Dr. Russell Greenfield, Patty Lovera
Stakeholder Interest

Consumer Reports tests juices for arsenic and lead

Consumer Reports tests juices for arsenic and lead

Arsenic in your juice

How much is too much? Federal limits don’t exist.

Consumer Reports Magazine: January 2012

Consumer Reports tests juices for arsenic and lead

How much is too much? Federal limits don’t exist.

Consumer Reports Magazine: January 2012
Informing Regulatory Decision-Making

Cumulative Frequency Distribution for Inorganic As in 2011 Juice Samples Only
FDA Guidance Development

Contains Nonbinding Recommendations
Draft: Not for Implementation

Guidance for Industry
Arsenic in Apple Juice: Action Level

Draft Guidance
This guidance is being distributed for comment purposes only.

FDA intends to take the following sampling and enforcement approach to arsenic in apple juice. FDA intends to initially analyze apple juice samples for total arsenic. FDA intends to speciate samples containing more than 10 μg/kg or 10 ppb total arsenic to determine inorganic arsenic levels. Consistent with 21 CFR 109.6, FDA intends to consider the action level of 10 μg/kg or 10 ppb inorganic arsenic, in addition to other factors, when considering whether to bring enforcement action in a particular case.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Food Safety and Applied Nutrition
July 2013
Disseminating Scientific Knowledge

**New Limits for Arsenic Proposed by F.D.A.**

By BARRINA TAVERISHE  JULY 13, 2013

WASHINGTON — Nearly two years after an apple juice touted off by a segment of the New York Times, the FDA is proposing a limit for arsenic in apple juice.

The Environmental Protection Agency has set a level for arsenic, but the FDA’s new proposal is the first federal standard for a food product. The proposed limit, which will be a federal standard for a food product. The proposed limit, or “action level,” for inorganic arsenic — the harmful form of the chemical that is a known human carcinogen — matches the EPA’s current threshold for inorganic arsenic at 10 parts per billion.

Consumer groups and a handful of Democrats ramped up their calls for a federal standard for arsenic in juice after a study in 2011 showed arsenic is often found in apple juice and that some products exceeded the EPA’s limit for drinking water. Consumer Reports’ testing found a full 10 percent of juices tested were over the EPA limit for water.

The FDA has maintained that juices are safe to drink, in moderation, like any other food or beverage, but after such high-profile attention to

**Food Safety News**

**FDA Proposes Limit for Arsenic in Apple Juice**

By HELEN BOTTENHEIM  JULY 13, 2013

The U.S. Food and Drug Administration on Friday proposed a limit for arsenic in apple juice, two years after testing by Dr. Oz and Consumer Reports spurred widespread consumer concern about the presence of the compound in juice products.

The Environmental Protection Agency already has an arsenic limit for tap water, but the FDA’s new proposal is the first federal standard for a food product. The proposed limit, or “action level,” for inorganic arsenic — the harmful form of the chemical that is a known human carcinogen — matches the EPA’s current threshold for inorganic arsenic at 10 parts per billion.

Consumer groups and a handful of Democrats ramped up their calls for a federal standard for arsenic in juice after a study in 2011 showed arsenic is often found in apple juice and that some products exceeded the EPA’s limit for drinking water. Consumer Reports tested found a full 10 percent of juices tested were over the EPA limit for water.

The FDA has maintained that juices are safe to drink, in moderation, like any other food or beverage, but after such high-profile attention to

**Arsenic in Apple Juice**

Arsenic is present in the environment as a naturally occurring substance or as a result of contamination from human activities. It is found in water, air, soil and foods. In foods, arsenic may be present as inorganic arsenic (the most toxic form of arsenic) or organic arsenic. FDA has been monitoring the levels of arsenic in foods for decades, and in 2011, increased its testing. The latest results confirmed that the amount of arsenic in apple juice is low. The agency has studied consumption levels among children and adults, and completed a scientific assessment. Based on this work, FDA is confident in the overall safety of apple juice for children and adults.

**July 12, 2013**

- News Release: FDA proposes “action level” for arsenic in apple juice. The action level that FDA is proposing is the same as EPA’s limit for arsenic in drinking water. This action level is intended to help keep out of the food supply any occasional lot of apple juice with arsenic levels above those permitted in drinking water. FDA may take this level into account when considering an enforcement action.
- Draft Quantitative Assessment of Inorganic Arsenic In Apple Juice (PDF). This risk assessment provides estimates of arsenic exposure and risk to humans at different hypothetical limits for inorganic arsenic in apple juice.

See also Peer Review Report: Risk Assessment of Arsenic in Apple Juice (PDF) → 209KB
Disseminating Scientific Knowledge

- Peer-reviewed publication
- Presentations at AOAC, ACS, ORS Seminar, and the Florida Pesticide Residue Workshop
## Potential to Advance Public Health

### Table 7. Apple Juice Consumption Estimates

<table>
<thead>
<tr>
<th></th>
<th>NHANES Average (g/kg-day)</th>
<th>3 x Average (g/kg-day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children aged 0-6</td>
<td>4.1</td>
<td>12.3</td>
</tr>
<tr>
<td>All Persons aged 0-50</td>
<td>0.83</td>
<td>2.5</td>
</tr>
<tr>
<td>All Persons</td>
<td>0.62</td>
<td>1.9</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Limit (ppb)</th>
<th>Total Cancer Rate (per million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>2.5 (0.0, 6.8)</td>
</tr>
<tr>
<td>5</td>
<td>4.8 (0.0, 12.8)</td>
</tr>
<tr>
<td>10 and above</td>
<td>8.0 (0.0, 21.3)</td>
</tr>
</tbody>
</table>
Developing a Rapid Detection Methodology for Pesticides

PI: Gregory Mercer, ORA
Identifying the Gap

- FDA is charged with enforcing EPA pesticide tolerances for FDA-regulated foods.
- In 2004, an ORA Science Peer Review found that “…the pesticides program has not evolved to take full advantage of current science and technology.”
- By 2008, FDA had modernized screening to include LC-MS/MS methodologies.
Identifying the Gap

• Because many pesticides were not amenable to LC-MS/MS methods, however, FDA was still heavily relying on selected ion monitoring GC-MS techniques by 2010.

• Each sample was tested with three SIM methods, cumulatively requiring 150 min of run time and screening for 350 pesticide residues.
Research Design

• New sampling method for high-throughput pesticide sample analysis
  – GC-MS/MS

• Retrospective review of sampling data from previous 15 years facilitated a risk-informed reduction in scope of pesticide screening

• Stakeholders: ORA field labs, industry, EPA
• LIB

• Presented at AOAC and Florida Pesticide Residue Workshop
Informing Regulatory Decision-Making

“The findings for FY 2012 demonstrate that pesticide residue levels in foods are generally well below EPA tolerances; the increased import sample violation rate reflects the expansion of the analytical scope of pesticide residues from the implementation of new technologies implemented in FY’s 2010 and 2011.”
• Serial improvements in detection methodologies has expanded FDA pesticide monitoring coverage
• Identification of previously undetected residues can inform EPA establishment or adjustment of tolerance limits
Catalyzing Action

Why Change Your Pesticides Screens?

At The NFL, we parallel our testing protocols to those of FDA. Our goal is to match our compound list to FDA’s compound list. As FDA is continually expanding their list of residues, The NFL will also expand its list to keep current with the FDA. In doing so, our clients are ensured that what we evaluate will meet regulatory scrutiny. The NFL has expanded our pesticide screen, in the same manner that the FDA did, by adding LC/MS/MS to our pesticide testing program. The NFL utilizes the best methods available for the matrix.

- Tech transfer of both LC-MS/MS and GC-MS/MS methodologies to private laboratories
Measuring Hormones in Bovine Muscle Tissues

PI: Pak Chu, CVM
WASHINGTON -- Swiss authorities have detected an illegal hormone known as DES in two shipments of American beef, triggering a major U.S. investigation to pinpoint the source of the banned carcinogen and to determine how much domestic and export beef may have been contaminated.

The Swiss government notified the Clinton administration last summer that DES, or diethylstilbestrol, which is illegal in the U.S. and Switzerland, had been found in two samples of supposedly hormone-free U.S. beef, and that it had barred two U.S. companies from exporting to Switzerland.
Research Design

• Intended to develop a multi-residue method to detect hormones in bovine and fish muscle tissues
  – An extension from a previous single-analyte method for methyltestosterone project
• Aligned with FVM and CVM strategic goals
• Stakeholders: FDA, USDA Food Safety and Inspection Service (FSIS), trade partners, International Renal Care Group

Kande Amarasinghe, Pak-Sin Chu, Eric Evans, Renate Reimschuessel, Nicholas Hasbrouck, and Hiranthi Jayasuriya*

Center for Veterinary Medicine, Office of Research, U.S. Food and Drug Administration, Laurel, Maryland 20708, United States

- Related Publication
  - Method publication currently in progress

- 9 scientific presentations
• Method adopted by USDA FSIS laboratories
• Demonstrated U.S. commitment to ensuring that growth hormones are not used in food products exported to the E.U.
Summary Table I. No. of Samples per Production Class by Compound Class FY 2015 Domestic Scheduled Sampling: Tier 1

<table>
<thead>
<tr>
<th>Methods</th>
<th>No. of Samples per Production Class *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beef cows</td>
</tr>
<tr>
<td>Multi-class</td>
<td>800</td>
</tr>
<tr>
<td>Aminoglycoside (AMG)</td>
<td>800</td>
</tr>
<tr>
<td>Pesticides</td>
<td>275</td>
</tr>
<tr>
<td>Metals</td>
<td>100</td>
</tr>
<tr>
<td>Hormones</td>
<td>300</td>
</tr>
</tbody>
</table>

Table 10: NRP Import Sample Analyses by Chemical Residue Results Jan.–Mar. 2015
Number of import reinspection program analyses arranged by results of chemical residue. Multiple import residue results may be associated with the same sample. Note: No Import sampling chemical violations were found.

<table>
<thead>
<tr>
<th>Chemical Residue</th>
<th>Residue Detected - Not-Violative</th>
<th>Residue Not Detected</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormones</td>
<td>-</td>
<td>382</td>
<td>382</td>
</tr>
</tbody>
</table>
• Subsequent research will modify the LC-MS/MS hormone detection method for use in fish.

**FDA high enforcement priority aquaculture drugs**
CVM has identified a number of drugs and families of drugs historically used in fish without FDA approval that are of high enforcement priority. They should not be used in fish that is to be consumed, unless a sponsor obtains an approval or index listing for them.

- Chloramphenicol;
- Nitrofurans;
- Fluoroquinolones and Quinolones;
- Malachite Green;
- Steroid Hormones.
Impact Factors

• Scientific uncertainty on the research topic, coupled with public expectation that FDA provide clarity

• FDA sponsor with clearly defined research question or knowledge gap, and intent to use findings to support a regulatory action

• Research design demonstrating scientific merit to internal and external scientific stakeholders
Conclusion

- Project builds upon the efforts invested over recent years to prioritize and track research across FVM

- Working towards shifts in culture and processes that will include impact as a consideration across the entire lifecycle of research

- Next steps include development of an impact best practices guide and a triannual publication highlighting examples of impact