Toxicology Challenges in Lifestage-Specific Safety Assessments

April Neal Kluever
US FDA/CFSAN/OFAS/DFCN
april.kluever@fda.hhs.gov
Conflict of Interest Statement

Dr. Kluever does not have any conflicts of interest
Toxicology Challenges in Lifestage-Specific Safety Assessments

April Neal Kluever, PhD, DABT
Toxicologist
Food and Drug Administration
Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
Division of Food Contact Notifications
Disclaimer

The data and interpretations expressed in this presentation represent that of the author and not necessarily that of the US FDA.
Outline

1. Background and Definitions
2. Subpopulation Assessment at CFSAN-Food Advisory Committee Recommendations
3. Infants as a case example for lifestage safety assessment
4. Challenges in Infant Safety Assessment
5. Summary
Background and Definitions
Mission: promoting and protecting the public's health by ensuring that the nation's food supply is safe, sanitary, wholesome, and honestly labeled, and that cosmetic products are safe and properly labeled.

- Covers all domestic and imported food except meat, poultry, and frozen, dried, and liquid eggs.
- Covers all domestic and imported cosmetics.
Definitions: What are Subpopulations?

Divisions of the general population on the basis of some discriminating factor/s

- Age (infant, toddler, child, adolescent, adult, elder)
- Physiological state (pregnancy)
- Disease state (diabetes)
A lifestage is defined as a temporal stage of life that has distinct anatomical, physiological, and behavioral or functional characteristics that may contribute to different susceptibility to chemical exposures compared to the general population (Makris et al., 2008).
“Where a statute might use the term ‘subpopulation,’ EPA recognizes this as including consideration of age groups or life stages.”

• Life stages are a type of subpopulation

Outline:

1. Background and Definitions
2. Subpopulation Assessment at CFSAN-Food Advisory Committee Recommendations
3. Infants as a case example for lifestage safety assessment
4. Challenges in Infant Safety Assessment
5. Summary
CFSAN requested advice from the FAC on how to integrate scientific considerations for susceptible populations into its risk assessment procedures and methodologies.

- Proceedings and resource materials published online:
  - http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/FoodAdvisoryCommittee/ucm407113.htm
A separate risk (or safety) assessment may be conducted when there is
1. A clearly bi- or multi-modal distribution to the functioning of an influential enzyme or system such that the expected risks will be distinct.
A separate risk (or safety) assessment may be conducted when

2. A lifestage appears vulnerable based upon critical windows of toxicokinetic immaturity or toxicodynamic sensitivity and this sensitivity has been characterized in dose response studies.
FAC on Susceptible Populations Key Recommendations

A separate risk (or safety) assessment may be conducted when there is

3. A subgroup or lifestage that will receive a disproportionally high exposure to a food, product, or environmental media that contains toxicants that are of particular concern to the subgroup or lifestage.
Outline

1. Background and Definitions
2. Subpopulation Assessment at CFSAN-Food Advisory Committee Recommendations
3. Infants as a case example for lifestage safety assessment
4. Challenges in Infant Safety Assessment
5. Summary
Infants as an Example for Lifestage-Specific Safety Assessment
Infant-specific safety assessments are performed for food contact materials intended for use with breast milk or infant formula.

Lifestage-specific safety or risk assessments may also be performed for other programmatic areas in CFSAN.
Infants Experience a Different Exposure Scenario than other Lifestages

• Increased food consumption compared to other age groups (mg/kg-bw/d)
  
• Restricted variety of food products
  – May consume a sole source of nutrition for up to 6 months (breast milk or infant formula)
  – Do not exhibit the same food consumer patterns as other age groups

Recommendation for Subpopulation Assessment from the CFSAN FAC

A separate risk (or safety) assessment may be conducted when there is:

1. A clearly bi- or multi-modal distribution to the functioning of an influential enzyme or system such that the expected risks will be distinct;

2. A lifestage appears vulnerable based upon critical windows of toxicokinetic immaturity or toxicodynamic sensitivity and this sensitivity has been characterized in dose response studies;

3. There is a subgroup or lifestage that will receive a disproportionately high exposure to a food, product, or environmental media that contains toxicants that are of particular concern to the subgroup or lifestage.
Potential for Altered Exposure Scenario Occurs during Period of Development

Developing Physiology:
- Absorption
- Distribution
- Metabolism
- Excretion

Developing Systems:
- Reproductive
- Endocrine
- Neurological
- Skeletal
- Immunological

For in-depth reviews, see Neal-Kluever et al, 2014, *Food and Chem. Toxicol.* 70: 68-83
Developing Physiology: Infant Pharmacokinetics (or Toxicokinetics)

- Toxicokinetics are about *processes*
- Infants exhibit altered absorption, distribution, metabolism, excretion, and storage of some chemicals compared to other lifestages
  - Rapid changes in the first 6 months after birth
- Altered PK/TK can have a large impact on the toxicity of a chemical and infant susceptibility
## Examples of Altered Toxicokinetics

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Relative to Adult</th>
<th>Determinants</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dioxins</td>
<td>Faster elimination</td>
<td>Lower body fat in infants</td>
<td>Kreuzer et al, 1997</td>
</tr>
<tr>
<td>Methylated Xanthines</td>
<td>Slower elimination</td>
<td>Deficient CYP1A2</td>
<td>Ginsberg, 2004</td>
</tr>
</tbody>
</table>
Developing Systems: Infant Pharmacodynamics (or Toxicodynamics)

- Toxicodynamics are about biological targets
- Infants may express more or less of the biological targets of a chemical than other lifestages

Examples:
- Receptor ontogeny
- High cellular turnover (increased targets for carcinogens)
Recommendation for a Subpopulation Assessment

A separate risk (or safety) assessment may be conducted when there is:

1) A clearly bi- or multi-modal distribution to the functioning of an influential enzyme or system such that the expected risks will be distinct;

2) A lifestage appears vulnerable based upon critical windows of toxicokinetic immaturity or toxicodynamic sensitivity and this sensitivity has been characterized in dose response studies;

3) There is a subgroup or life stage that will receive a disproportionately high exposure to a food, product, or environmental media that contains toxicants that are of particular concern to the subgroup or lifestage.
Steps in Infant Lifestage Assessment

1. Estimation of infant-specific exposure to substance of interest
   - Consideration of infant-specific factors such as weight, intake, and consumer habits

2. Safety or risk assessment in an infant-specific context
Outline

1. Background and Definitions
2. Subpopulation Assessment at CFSAN - Food Advisory Committee Recommendations
3. Infants as a case example for lifestage safety assessment
4. Challenges in Infant Safety Assessment
5. Summary
Challenges in Infant Safety Assessment

1. When to test?
2. What to test?
3. How to test?
4. How to interpret the data?
The FAC provided guidance regarding when a separate safety assessment should be performed.

- It remains an expert decision to determine when additional or specialized toxicological testing is needed to support infant safety.
What are some ways to identify or prioritize chemicals for specialized testing?

- Public literature, Tox21, screening assays, *in silico* prediction approaches, other hazard identification tools.
Challenges: How to Test?

Which study design can best characterize potential hazards for human infants?

Developmental and Reproductive Toxicity (DART) Tests

- Generational developmental and reproductive testing
- Prenatal toxicity testing
- Perinatal/Postnatal toxicity testing
- Other specialized juvenile animal test protocols
Should a large study that captures many endpoints be recommended to support infant safety, or should a smaller and targeted study be recommended?
Addressing Challenges in Study Selection: CFSAN Initiatives

The Gen-DART Project
Assessment of the utility of generational developmental and reproductive toxicity (Gen-DART) testing for infant safety assessment

- Ongoing regulatory research initialized Sept, 2014
- Completed analysis of 40 Gen-DART studies on 37 food additives
- Current efforts underway to expand the study library by harnessing data from exterior sources (ToxRefDB, NTP reports, etc)
Addressing Challenges in Study Selection: CFSAN Initiatives

The JAS Project

Assessment of the utility of juvenile animal study (JAS) protocols for infant safety assessment

- Collaborative effort with the US FDA Center for Drug Evaluation and Research (CDER)
- Research initiated in Nov. 2015
- Pilot capture of data associated with 60 drugs is underway
Addressing Challenges in Study Selection

- Ongoing regulatory research will provide scientific framework for the recommendation of specific study protocols to support infant safety.
- This research may also inform questions on interpretation of study data and extrapolation of potential hazards from the test species to human infants.
Challenges: How to Interpret the Data?

Nearly all DART study designs have several major areas of uncertainty

1. Uncertainty regarding test article exposure to pups
Pups are not directly exposed to the test article until weaning in most generational studies.
How to Address Uncertainty Regarding Test Article Exposure to Pups

1. Direct dosing of pups in DART studies (e.g. oral gavage)
2. Toxicokinetic profiling of chemicals to be tested in DART studies
3. Physiologically-based pharmacokinetic (PBPK) modeling
Challenges: How to Interpret the Data?

Nearly all DART study designs have several major areas of uncertainty

1. Uncertainty regarding test article exposure to pups
2. Uncertainty regarding test model selection
   - All currently validated regulatory test protocols use mice, rats, or rabbits to test for developmental effects.
Species Exhibit Differences in Developmental Trajectories

*Kidney Development*

**Table 2**

<table>
<thead>
<tr>
<th>Species</th>
<th>Timing of nephrogenesis completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Man</td>
<td>35 weeks gestation</td>
</tr>
<tr>
<td>Sheep</td>
<td>Before birth</td>
</tr>
<tr>
<td>Guinea Pig</td>
<td>Before birth</td>
</tr>
<tr>
<td>Dog</td>
<td>Postnatal week 2</td>
</tr>
<tr>
<td>Pig</td>
<td>Postnatal week 3</td>
</tr>
<tr>
<td>Mouse</td>
<td>Before birth</td>
</tr>
<tr>
<td>Rat</td>
<td>Postnatal week 4–6</td>
</tr>
</tbody>
</table>

Data from Kleinman (1982), Fouser and Avner (1993), and Gomez et al. (1999).

How to Address Uncertainty Regarding Species Extrapolation?

1. Examination of human data, if available
2. PBPK modeling
3. Development or validation of additional models or test systems
Summary

- Infants fulfill the CFSAN FAC criteria as a lifestage of interest.
- Infant-specific exposure and safety assessments can be performed if relevant data are available.
- Infant lifestage-specific assessment is an emerging field of regulatory research.
- Regulatory research efforts are underway to optimize the approach to infant safety assessment.
References

Felter et al., 2015. Crit. Rev. Toxicol. 43:219-244
Neal-Kluever et al., 2014. Food and Chem. Toxicol. 70: 68-83