Toxicology Challenges in Lifestage-Specific Safety Assessments

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Conflict of Interest Statement

Dr. Kluever does not have any conflicts of interest

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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

US FDA Center of Food Safety and Applied Nutrition

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)

Definitions-
What are Lifestages?

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)

Definitions-
What are Lifestages?

"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

US EPA (2014). Framework for Human Health Risk Assessment to Inform Decision Making
https://www.epa.gov/sites/production/files/2014-12/documents/hhra-framework-final-2014.pdf

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2014 Food Advisory Committee (FAC) Meeting

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

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/FoodAdvisoryCommittee/UCM428847.pdf

FAC on Susceptible Populations Key Recommendations

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.

FAC on Susceptible Populations Key Recommendations

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.

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Infants as an Example for Lifestage-Specific Safety Assessment

Infant Safety Assessment at CFSAN: *Lifestage-specific*

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

Lawrie, 1998; National Research Council, 1993; Neal-Kluever et al, 2014

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 disproportionally 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
Felter et al, 2015, *Crit. Rev. Toxicol*. **43**:219-244

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

Chemical	Relative to Adult	Determinants	References
Dioxins	Faster elimination	Lower body fat in infants	Kreuzer et al, 1997
Methylated Xanthines	Slower elimination	Deficient CYP1A2	Ginsberg, 2004

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 disproportionally 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

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Challenges in Infant Safety Assessment

1. When to test?
2. What to test?
3. How to test?
4. How to interpret the data?

Challenges: When to Test?

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

Challenges: What to Test?

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

Addressing Challenges in Study Selection

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

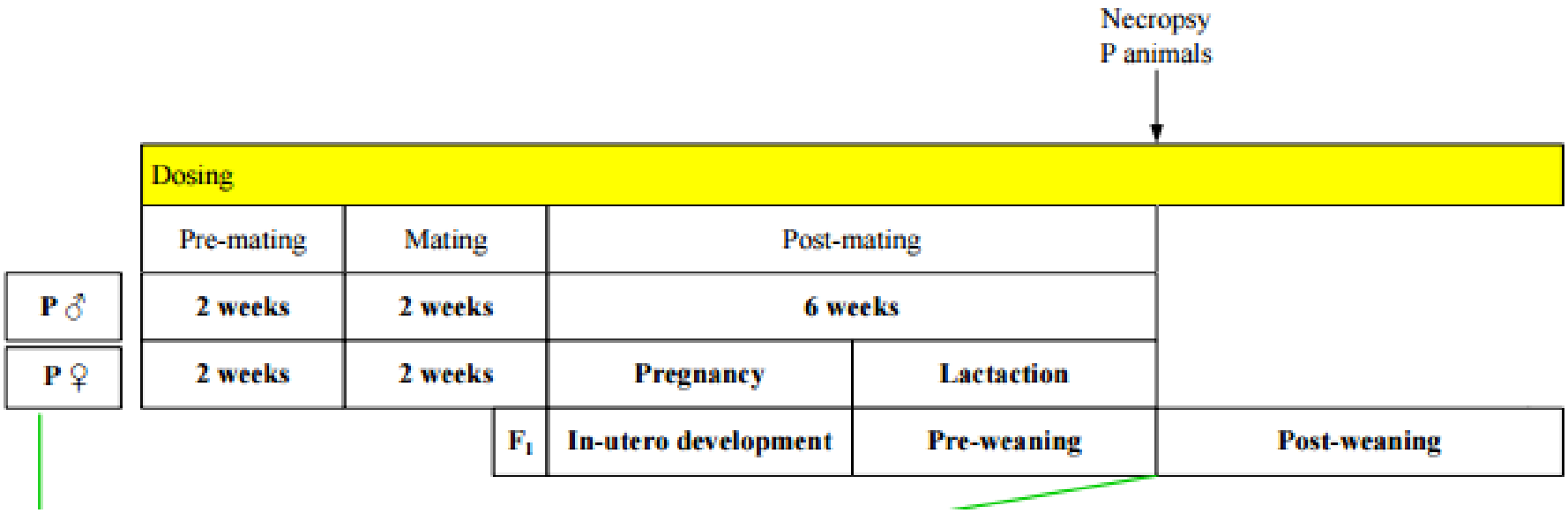
Challenges: How to Interpret the Data?

Nearly all DART study designs have several major areas of uncertainty

1. Uncertainty regarding test article exposure to pups

OECD Test No 443: Extended One-Generation Study

Figure 1: Scheme of the Extended One-Generation Reproductive Toxicity Study



Pups are not directly exposed to the test article until weaning in most generational studies

http://www.oecd-ilibrary.org/docserver/download/9712211e.pdf?expires=1459362714&id=id&accname=guest&checksum=A4F898CA316F8106C46FE9AB2259A0E5

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
Timing of Completion of Nephrogenesis for Various Species

Species	Timing of nephrogenesis completion
Man	35 weeks gestation
Sheep	Before birth
Guinea Pig	Before birth
Dog	Postnatal week 2
Pig	Postnatal week 3
Mouse	Before birth
Rat	Postnatal week 4–6

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

Zoetis T and ME Hurtt (2003). *Birth Defects Res B* **68**:111-120

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.

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