Heritable Genetic Modifications in Food Animals: A NASEM study

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Eric Hallerman, Committee Chair

Context

- Many promising HGM animal lines are under development.
- Early approvals, determinations of low risk, or non-regulated status:
  - In the United States: PRLR-KO *SLICK* cattle

  - Globally: Argentina, Brazil, Columbia, and Japan: Slick and polled cattle, PRRSV-resistant pig, myostatin-KO red sea bream, leptin receptor-KO tiger puffer and olive flounder
- Other products will presumably be presented to the U.S. Food and Drug Administration (and regulators internationally)→ *What scientific uncertainties will regulators face regarding animal health and consumer safety?*

Committee charge

To identify:

- Methods for generating heritable genetic modifications in food animals;
- Information on hazards to human health related to products of food animals developed using heritable genetic modification techniques;
- Information on hazards to the health of the target food animal species developed using heritable genetic modification techniques;
- Information on any other potential hazards that might reasonably be anticipated to occur, based on relevant experience, for example, with genetically engineered crops;
- Methods for the identification and analysis of intended and unintended genetic alterations (e.g., off-target genome editing effects, insertional mutagenesis, introduction of antibiotic resistance) in the process of developing food animals with heritable genetic modifications;
- Methods for the identification and analysis of potentially hazardous compositional changes in food animal products;
- Challenges to the study of risks of food animals with heritable genetic modifications and approaches to addressing challenges in study design (e.g., appropriate animal models, long-term follow-up, etc.);
- Approaches to risk assessment in the face of uncertainty of the likelihood and magnitude of health hazards; and
- Identify key knowledge gaps and recommend areas of research for the near and medium term (i.e., in a 3-to-10-year period) that should be pursued by the National Institutes of Health, The Department of Health and Human Services, and other funders.

Committee on Heritable Genetic Modifications in Food Animals

- Eric M. Hallerman, Chair, Virginia Polytechnic Institute and State University
- Bernadette M. Dunham, George Washington University
- Lyda G. Garcia, The Ohio State University
- Fred Gould, North Carolina State University
- Darrell R. Kapczynski, U.S. Dept. Agriculture – Agricultural Research Service
- Elizabeth A. Maga, University of California, Davis
- Fiona M. McCarthy, University of Arizona
- Mike J. McGrew, University of Edinburgh
- William M. Muir, Purdue University
- James D. Murray, University of California, Davis
- Jon M. Oatley, Washington State University
- Penny K. Riggs, Texas A&M University
- Thomas E. Spencer, University of Missouri
- Virginia Stallings, Children's Hospital of Philadelphia
- Aspen M. Workman, U.S. Dept. Agriculture - Agricultural Research Service

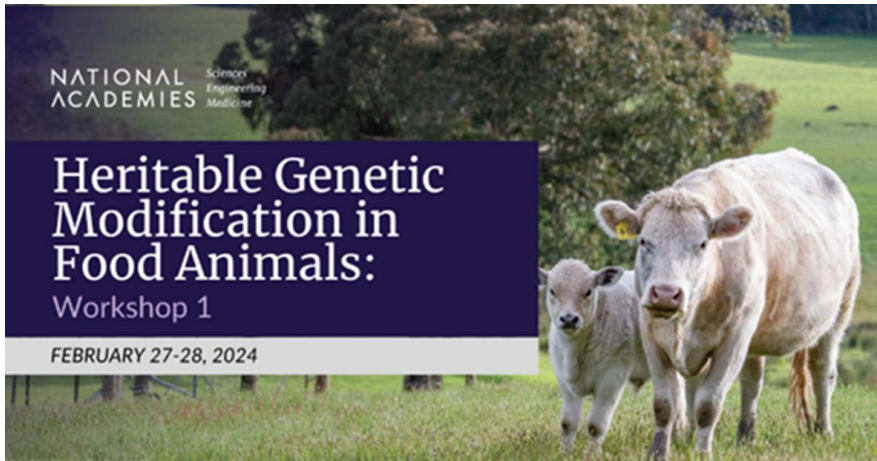
Process

- Organization:
  - Assembly of committee – summer 2023
  - Assessment of COI, public comment on committee membership, seating of committee – fall 2023

- Committee functions:
  - Pubic meeting, October 18, 2023:
    - Committee launch
    - Discussion with sponsors
    - Structure of study

Workshop 1 – *Heritable Genetic Modification in Food Animals: Potentials and Concerns,* Washington, DC, February 27-28, 2024

- 25 presentations, public (exc. last session):
  - Session 1. Methods for generating heritable genetic modifications in food animals
  - Session 2. Horizon scan – What traits might be pursued within the next two years?
  - Session 3. Views of stakeholders – industry, public agencies, consumers and the public
  - Session 4. Animal welfare
  - Session 5. Genome annotation and relation to food safety of HGM animals
  - Session 6. Biological mechanisms that may present novel hazards
  - Session 7. Novel resistance to disease
  - Session 8. Genomics
  - Session 9. Closed session
- Report in press for release in September



Workshop 2 – *Heritable Genetic Modification in Food Animals: Potentials and Concerns,* Washington, DC, July 23-24, 2024

- Open session: Four presentations:
  - Policy developments:
    - Revision of GFI 187 (Food and Drug Administration),
    - Formalization of coordination among FDA and U.S. Department of Agriculture.
  - Allergenicity.
  - Risk assessment.
- Closed session – Committee deliberation and work on draft report.

Structure of study and draft report

1. Introduction

2. Biological mechanisms that may present novel hazards

3. Likelihood of products of agricultural animal biotechnology presenting such hazards

4. Experimental strategies and methodologies to evaluate human safety of modified animals and products

5. Scientific questions that may be addressed

Glossary

1. Introduction

- Technical background:
  - Selective breeding
  - Reproductive technologies: AI, MOET, SCNT
  - Gene transfer
  - Genome editing
- Applications to mammals, poultry, and fishes
- Current state of animal biotechnology – first regulatory determinations
- Context for the report and the committee charge

2. Biological mechanisms that may present novel hazards

- Benefits posed by HGM animals
- Hazards posed by HGM animals:
  - Molecular genetic hazards (on- and off-target effects, unanticipated metabolic outcomes)
  - Altered food composition
  - Novel or heightened allergenicity or food sensitivity
  - Toxicity
  - HGM animals as reservoirs for infectious disease
  - Transfer of antibiotic resistance
  - Mobilization of viruses from HGM animals used for xenotransplantation
  - Horizontal gene transfer

3. Likelihood of products of agricultural animal biotechnology presenting such hazards

- Key concepts of risk analysis
- Application to HGM animal food products:
- Case studies of application of risk analysis to:
  - Transgenics: GalSafe pig, AquAdvantage salmon
  - Genome-edits: SLICK cattle
- Risk management
- Demonstration of safety ≠ risk assessment
- Refinement of risk assessment

4. Experimental strategies and methodologies to evaluate human safety of modified animals and products

- Multiple layers of risk mitigation in development of HGM animal lines
- Molecular outcomes:
  - Identifying on- and off-target editing events
  - Genotyping founders and descendants
  - Need breed-level reference genomes

- Compositional changes:
  - Composition varies widely within and among particular animal products
  - Need much more baseline composition data
- Allergenicity and sensitivity
- The issue of biological vs. statistical significance
- Incorporation of findings into risk assessment framework

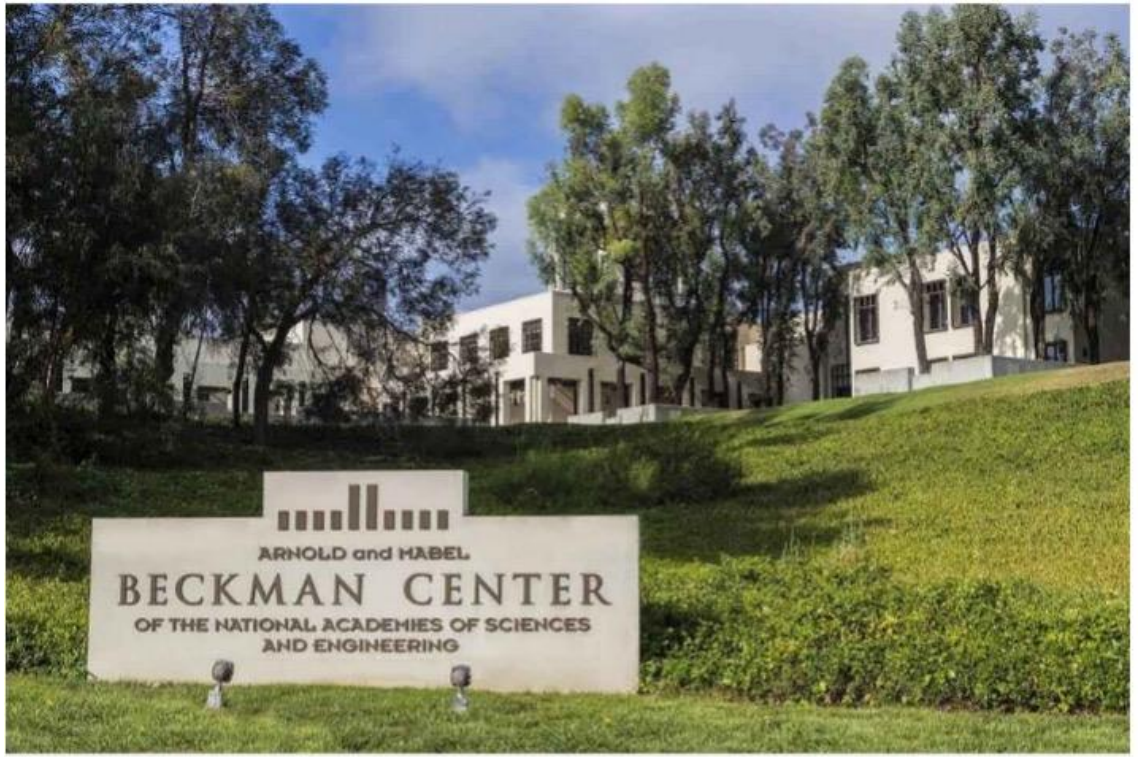
5. Scientific questions that may be addressed

Future research (3-10-year horizon):

- Develop improved genome-editing tools → reduce off-targets
- Breed-specific genomes → detect off-targets
- Strengthened genomic annotation → metabolic and phenotypic effects of HGMs
- Improved food composition database → baseline for comparison
- Enhanced understanding of food allergenicity and sensitivity
- Factors affecting pathogen spillover from (HGM) livestock to wild populations and humans
- Viral dynamics in xenotransplant recipients
- Communication and outreach on HGM animals

Process ahead

- Late September – Workshop 3, closed. Committee will meet to finalize the draft report
- Fall 2024 - Peer review
- Winter 2024 – Revision and submission of final report to NASEM for approval
- Spring 2025 – Publication and publicity



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