HESI EIC Proposal: Building Novel Methods and Science for Ototoxicity Detection and Prevention

Laura Maurer, ExxonMobil Biomedical Sciences Inc.
Purpose and Scope

Purpose:

• Improve ototoxicity characterization for risk assessment

Scope:

• Ototoxicity (which describes damage to the inner ear and/or associated nerves) is a hazard posed by exposure to select pharmaceuticals, metals, and industrial chemicals, as well as physical hazards such as audible sound (noise)
  • Occupational and consumer exposures
  • Potentially lower PoD than some other exposure-related outcomes

• Opportunities for improvement in current hazard and risk assessment across multiple disciplines
  • Epidemiology
  • Toxicology
  • Risk characterization and communication
Ototoxicity as an Emerging Issue

- Ototoxicity has long been recognized as a public health issue
  - **Prevalence**: Hearing loss in the U.S. is the 3rd most common chronic physical condition in adults
    - Hearing difficulty in U.S. working population: 12%
    - Occupational exposures contributes to approximately 24% of hearing difficulty among U.S. workers
    - Examples of occupational exposures: noise, solvents, metals
    - Examples of non-occupational exposures: noise, antibiotics

- Novel concepts relating to a long-recognized issue:
  - **Co-exposures** to physical and chemical agents
  - **Non-occupational** exposures to noise
    - Technology advances
  - Ototoxicity is not just hearing loss
    - Involves vestibular system (controls sense of **balance**)
    - Vertigo, dizziness, nausea
Standards and regulations for mitigation of auditory impairments in the workplace

**Occupational Safety and Health Administration (OSHA) Noise Standard**
- Employer required to implement a hearing conservation program when noise exposure is at or above 85 decibels averaged over 8 working hours (85db = permissible exposure limit)
- Hearing conservation programs: strive to prevent initial occupational hearing loss, preserve and protect remaining hearing (PPE provision and usage, engineering controls, etc)

**American Conference of Governmental Industrial Hygienists (ACGIH)**
- Added “ototoxicant” notation in threshold limit values (TLVs) for chemicals
- Audible sound TLV

**National Institute for Occupational Safety and Health (NIOSH) Special Bulletin (2018)**
- Call for preventing hearing loss caused by chemical and noise exposure
- Data suggesting that combination of chemical and noise exposures contribute to hearing loss in the workplace
  - In general, these studies used high levels of noise and high concentrations of solvents
Mechanisms of injury – physical and chemical exposure

Solvents, Noise, Antibiotics, Metals:
  Auditory Damage

Solvents, Noise, Antibiotics:
  Vestibular Damage

TINNITUS
Tinnitus is the perception of noise or ringing in the ears. A common cause of tinnitus is inner ear hair cell damage.

SYMPTOMS
- Ringing
- Buzzing
- Roaring
- Clicking
- Hissing
- Humming

Sound Waves

Auditory Nerve → To the Brain

Cochlea

Brain

Ear Drum

Ear Canal

Earlobe

Healthy Hair Cell

Damaged Nerve Cell

Inside Cochlea

VERTIGO
Vertigo - sensation of spinning or tilting or that one's surroundings are rotating

NORMAL
- Cochlea (Cristae) → Gel Membrane → Rats → Sensory Hair Cells → Nerve Fiber

VERTIGO
- Impaired Otoliths (Cristae)

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Opportunities for Advancement of the Science: Epidemiology

Current State

• Studies often rely on recall to assess exposures in the workplace
  • Confounding factors (noise, other co-exposures)
  • Methods for measuring hearing loss need improvement
  • Measurement of hearing loss relies on varied and nonspecific methodology

Opportunities

• Move toward battery of hearing tests to more precisely determine level and type of ototoxicity present
  • Call for improved methodology of hearing loss metrics in the form of an audiological test battery

• Work with clinical community on definitive diagnostics

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Opportunities for Advancement of the Science: Toxicology

Current State

• Range of species, diets, exposures used to investigate ototoxicity
  • Strain differences in hearing and responses to nonauditory effects of noise
    • Not often addressed in studies

• Ototoxicity is almost exclusively explored in terms of hearing loss
  • Relatively less understood: loss of balance/dizziness/vertigo
    • Inner ear controls both functions

Opportunities

• Use fit-for-purpose animal models for different classes of exposures (ie: metals, antibiotics, solvents) to systematically gather dose-response information
  • Co-exposures that confound human studies

• Use animal models to investigate cellular and functional consequences of exposures to encompass both outcomes in a controlled environment
  • Occupational and non-occupational

Opportunities for Advancement of the Science: Risk Characterization and Communication

**Current State**

- Difficulty in systematically understanding and communicating individual risks
- Limitations on context
  - Recent use of NHANES data to correlate hearing loss and urinary metabolites of chemicals\(^1\)

**Opportunities**

- Compile literature in systematic review format
  - Stratify by important co-exposures
- Publish/provide the necessary perspective for use of large datasets which may be useful, but not always fit-for-purpose for ototoxicity

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Stakeholders/Potential Collaborators

• Pharmaceutical industry
• Chemical industry
  • ACC – leverage ongoing ototoxicity work on chemical-specific panels
  • Chevron (Shanna Clark, PhD)
• NIOSH
• Academia
  • University of Michigan (Rick Neitzel, PhD)
• Department of Defense
  • USAF
    • WPAFB Human Performance Wing (David Mattie, PhD and SSgt Leguin, PhD)
  • USN
    • Navy Medical Research Unit – Dayton (LCDR Cody Schaal, PhD CIH CSP)
First Year: Problem Formulation and Scoping – Hazard and Exposure Assessment

- Project 1: Begin to systematically understand and clarify data gaps in hazard assessment (specifically, dose-response information including low-dose, as well as modes or mechanisms of action)
  - Milestones/Deliverables: Literature review to inform toxicology study designs/answer above scoping questions
- Project 2: Provide the necessary perspective for use of large biometric databases (NHANES) with ototoxicity as an endpoint
  - Milestones/Deliverables: Assessment of dataset and conclusion generation; dissemination of findings at conferences/meetings

First and Second/Third Year:

- Publications of Project 1 and Project 2
- Project 3: Assessment of current, historically utilized clinical metrics for ototoxicity against new, improved methods (potential for greater precision in determining type and level of ototoxicity with new battery of tests)
  - Milestones/Deliverables: Dissemination of findings at conferences/meetings with intent to publish
- Project 4: Development and initiation of fit-for-purpose animal studies to address the most significant data gaps identified in Project 1
  - Milestones/Deliverables: Dissemination of findings at conferences/meetings with intent to publish