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

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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**[1]: 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

1 National Institute for Occupational Safety and Health: OCCUPATIONAL HEARING LOSS (OHL) SURVEILLANCE (https://www.cdc.gov/niosh/topics/ohl/default.html) Last updated: Dec 9, 2019

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Current Risk Assessment Paradigm

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

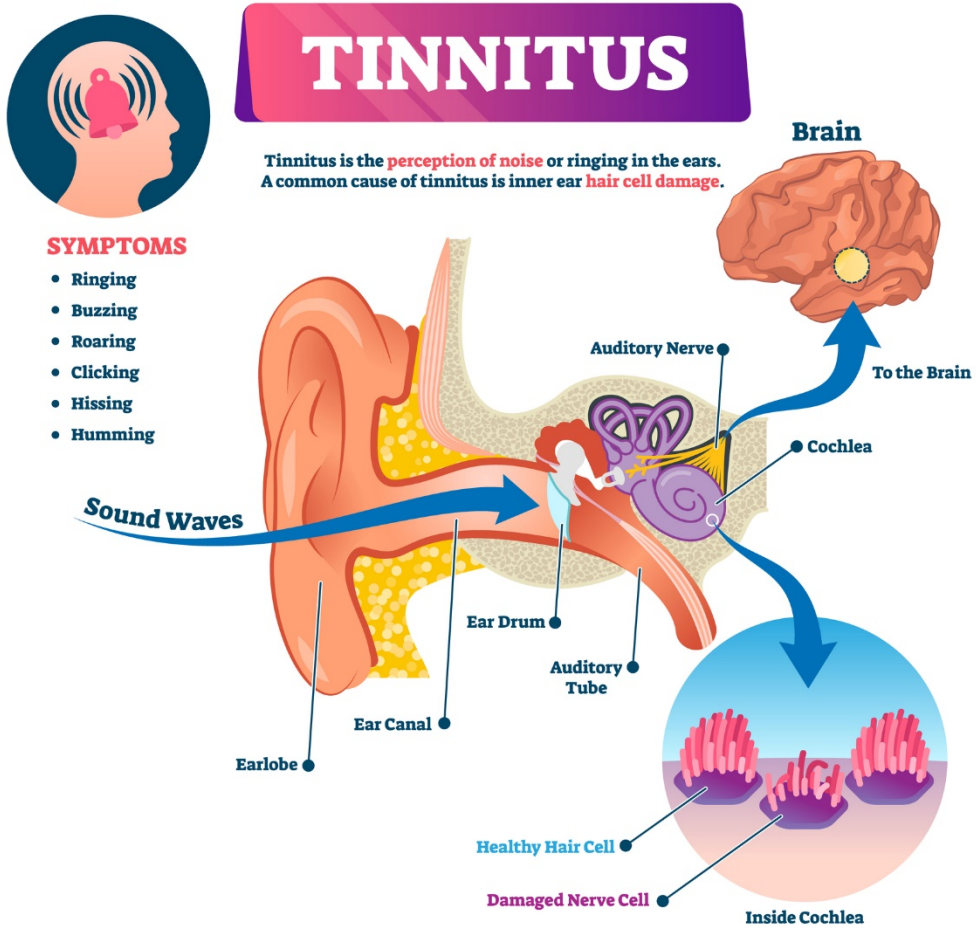
National Institute for Occupational Safety and Health (NIOSH) Special Bulletin (2018)[1]

- 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

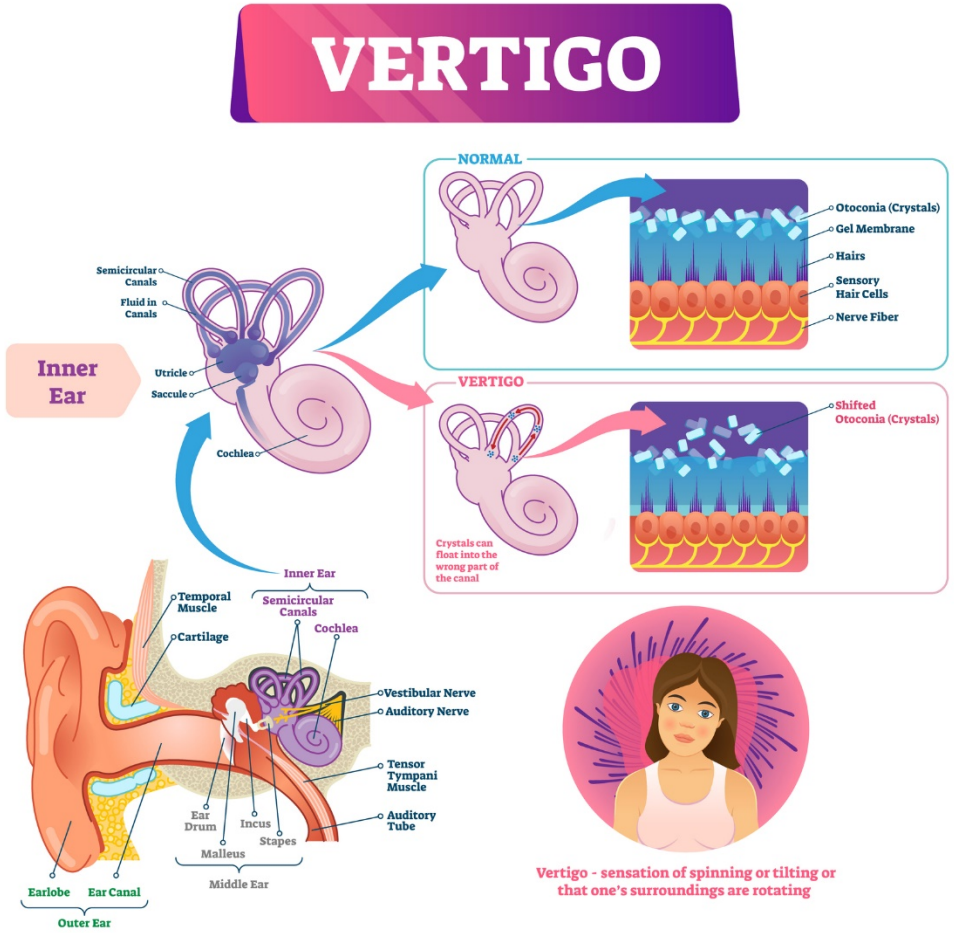
1 DHHS (NIOSH) Publication No. 2018-124

Mechanisms of injury – physical and chemical exposure

Solvents, Noise, Antibiotics, Metals: Auditory Damage



Solvents, Noise, Antibiotics: Vestibular Damage



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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[1]
- Work with clinical community on definitive diagnostics

1 Fuente et al (2013) Auditory dysfunction associated with solvent exposure. BMC Public Health 13, 39 https://doi.org/10.1186/1471-2458-13-39

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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[1]
- 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

1 Turner et al (2005) Hearing in Laboratory Animals: Strain Differences and Nonauditory Effects of Noise. Comp Med. 2005 February ; 55(1): 12–23.

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

1 Pudrith and Dudley (2019) Sensorineural hearing loss and volatile organic compound metabolites in urine. American Journal of Otolaryngology. 40(3): 409-412.
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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)

Project Scoping/Timeline

- **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