Collaboration on Ototoxicity Risk Assessment (CORA)

A call for participation and scientific partnership

Presented by: Rick Neitzel, PhD
University of Michigan
Current State of the Science

Safety Assessment Standards

Related Efforts

CORA Scope, Mission, Project Plan

Questions & Comments
Background

- **Ototoxicity** - Damage to the inner ear / associated nerves due exposure to a chemical or physical hazard (i.e., pharmaceuticals, metals, industrial chemicals, noise, etc.)

- Ototoxicity is a recognized public health issue
  - **Prevalence**: Hearing loss in the US is the 3rd most common chronic physical condition in adults
  - Hearing difficulty in the US working population is **12%**
  - Occupational exposures contribute to ~24% of hearing difficulty among the working population
  - Examples of occupational exposures: noise, solvents, metals
  - Examples of non-occupational exposures: noise, antibiotics

- Ototoxicity risk is complex and multifactorial:
  - **Co-exposures** to physical and chemical agents
  - **Non-occupational** exposure to noise (i.e., advancing technology)
  - Ototoxicity is **NOT** just hearing loss
    - Vertigo, dizziness, nausea are included

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1. National Institute for Occupational Safety and Health: OCCUPATIONAL HEARING LOSS (OHL) SURVEILLANCE
   [https://www.cdc.gov/niosh/topics/ohl/default.html](https://www.cdc.gov/niosh/topics/ohl/default.html)
Current challenges in utilizing ototoxicity data from…

**Epidemiology**

- Studies often rely on recall to assess exposures
- Co-exposures can be difficult to interpret in many study designs
- Methods for measuring hearing loss need improvement
  - Measurement of hearing loss relied on varied and nonspecific methodology

**Toxicology**

- Range of species, diets, exposures used to investigate ototoxicity in animal models
  - Strain differences in hearing and responses to nonauditory effects of noise (often not addressed in studies)
- Ototoxicity is almost exclusively explored in terms of hearing loss
  - Relatively less understood: loss of balance, dizziness, vertigo although inner ear controls both functions
Opportunities for improvement in the field…

**Epidemiology**
- Move toward battery of hearing tests to more precisely determine level and type of ototoxicity present
- Study design and interpretation to understand co-exposures

**Toxicology**
- Use fit-for-purpose animal models for different classes of exposures (i.e., metals, antibiotics, solvents) to
  - systematically gather dose-response information
  - investigate cellular and functional consequences of exposures
  - Integrate exposures relevant to occupational and non-occupational scenarios

**Risk Assessment**
- 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
  - Potential application of a biometric database (*e.g.*, NHANES)
Regulatory hearing safety standards offer limited guidance on protecting against effects of noise + chemical exposure

Current Safety Assessment Standards – USA – numerical standards focused on NOISE only

- **ACGIH** – American Conference of Governmental Industrial Hygienists - *private organization, existed before OSH Act*
- **OSH Act (1970)** – Established OSHA and NIOSH
  - **OSHA** – Occupational Safety & Health Administration – *legal authority*
  - **NIOSH** – National Institute of Occupational Safety and Health – *research organization, gives recommendations*
    - Special Bulletin in 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

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REL – recommended exposure limit – limit recommend to protect adult worker exposed 40 hours per week for 40 years

TLVs – Threshold Limit Values, 8-hour TWA (Time Weighted Average)

PELs – permissible exposure limits – limit set to protect adult worker exposed 40 hours per week for 40 years
Similar approaches seen around globe...

- **ILO** – International Labor Organization
  - Published safety standards in *Protection of Workers Against Noise and Vibration in the Working Environment* in 1977, updated in 1984
  - Recommend limit of noise for **8 hours** of exposure: **85-90 dBA**

- **EU-OSHA** – European Union OSHA
  - The European Directive 2003/10/EC sets the maximum limit at **87 dB(A) for an eight-hour workday**
Lead (Pb), cadmium (Cd), and noise, singly and in combination, CBA/CaJ mouse

Study Design
- Metals delivered via drinking water for 12 weeks at occupationally and environmentally relevant doses
- Metal exposure was also combined with noise exposure at 2-20 kHz stimulus for 2 hours, or a sham exposure
- Evaluated auditory performance via auditory brainstem responses (ABR) and distortion product otoacoustic emissions (DPOAE) @ baseline, 11 weeks
Assessing Ototoxicity due to Chronic Lead and Cadmium Intake with and without Noise Exposure in the Mature Mouse - Results

Results

- Metal-exposed animals did not develop significant auditory deficits or morphological damage to cochlear hair cells
- Noise-exposed animals, including those exposed to metal and noise, demonstrated significant hair cell loss
- No significant potentiation or synergistic effects were found in groups exposed to multiple agents

Finding:

- Adult mouse model is viable to evaluate a variety of environmental exposure mixtures.
Co-exposure effects on hearing a topic of current study by others as well...

The effects of combined exposure of solvents and noise on auditory function – A systematic review and meta-analysis

Exposure to noise and ototoxic chemicals in the Australian workforce

Preventive hearing tests in workers exposed to noise and organic solvents
Related Efforts - Opportunities for Synergy

International Ototoxicity Management Group (IOMG)
https://www.ncrar.research.va.gov/ClinicianResources/IOMG.asp

American Chemistry Council: Toluene and Xylene Panel
https://www.americanchemistry.com/ProductsTechnology/Toluene-and-Xylene-Panels/
CORA Mission

The collaborative mission of the committee is to better understand the impacts on the inner ear, resulting from co-exposures to noise and known and suspected ototoxic substances, in the pursuit of identifying safe exposure levels which minimize or eliminate the risk of ototoxicity to the consumer or worker.
CORA Scope

- Improve ototoxicity characterization for risk assessment (occupational and consumer exposure settings)

- Research and communicate opportunities for improvement in current hazard and risk assessment across multiple disciplines
CORA Project Plan

**Phase 1**
- **Project 1**: Evaluate current approaches for translational hazard assessment methods for ototoxicity (nonclinical)
- **Project 2**: Explore the potential for application of biometric databases (e.g., NHANES) for use in ototoxic risk assessment

**Problem Formulation & Scoping**

**Phase 2**
- **Publication of Phase 1 Project’s - Project 3 Kickoff**
  - **Project 3**: Evaluation of current clinical metrics for ototoxicity safety relative to novel translational models (*animal, in vitro, in silico, etc.*)

**Phase 3**
- **Publication of Phase 2 Project - Project 4 Kickoff**
  - **Project 4**: Development and initiation of fit-for-purpose animal studies to address data gaps
  - **Future study**: in collaboration with US Navy/Air Force
Current Progress and Collaborators

- Project funded February 2021
- Since funding announced:
  - Kick-off meeting and planning meetings for Phase 1
  - Currently organizing expertise, focusing project scope
- Collaboration’s member representation and expertise:

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<th>Number of distinct organizations</th>
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<th>Areas of expertise</th>
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<td>Academia</td>
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<td>4</td>
<td>Noise exposure assessment, heavy metals ototoxicity, occupational co-exposure to solvents and noise/ noise-induced hearing loss, etc.</td>
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<td>8</td>
<td>Toxicology, occupational health, chemical and noise exposure assessment, jet fuels, ototoxicity, noise interactions, guidance documents, etc.</td>
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<td>Industrial hygiene, product stewardship, non-clinical ototoxicity, ototoxicity prevention/diagnosis, etc.</td>
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Goal: Identify current approaches for translational hazard assessment methods for ototoxicity as it relates to combined noise and chemical exposures.

What does literature and related research tell us about a ‘toxic’ noise level including frequency, co-exposures, and timing of exposure?

Currently seeking collaborators to work with us in:

- Identifying studies on this topic that may not be part of standard peer-review literature e.g., regulatory or other government research, occupational studies, etc.
- Integrating data from diverse sources to identify similarities and differences in current approaches;
- Generating recommendations for fit for purpose application of current methods OR need for new ones.
- Providing multidisciplinary perspectives (clinical, data science, occupational health, regulatory, toxicology, epidemiology, etc.)
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