Collaboration on Ototoxicity Risk Assessment (CORA)

A call for participation and scientific partnership

Presented by: Rick Neitzel, PhD
University of Michigan

Agenda

1. Current State of the Science
2. Safety Assessment Standards
3. Related Efforts
4. CORA Scope, Mission, Project Plan
5. 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[1]:** 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 difficultly among the working population
  - Examples of occupational exposures: **noise, solvents, metals**
  - Examples of non-occupational exposures: **noise, antibiotics**
- <u>Ototoxicity risk is complex and multifactorial:</u>
  - **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

HESI

[1]: National Institute for Occupational Safety and Health: OCCUPATIONAL HEARING LOSS (OHL) SURVEILLANCE (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

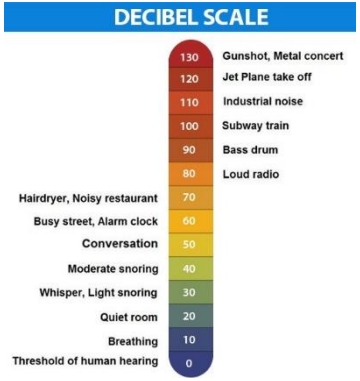
Risk Assessment

- 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



NIOSH RELs and ACGIH TLVs for Noise

Duration	REL and TLV
16 hours	82 dB
8 hours	85 dB
4 hours	88 dB
2 hours	91 dB
1 hour	94 dB
1/2 hour	97 dB
15 minutes	100 dB

REL – recommended expose 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)

OSHA PELs for Noise

Duration	PEL
8 hours	90 dB
4 hours	95 dB
2 hours	100 dB
1 hour	105 dB
1/2 hour	110 dB
15 minutes	115 dB

PELs – permissible exposure limits – limit set to protect adult worker exposed 40 hours per week for 40 years

HESI.

Similar approaches seen around globe…

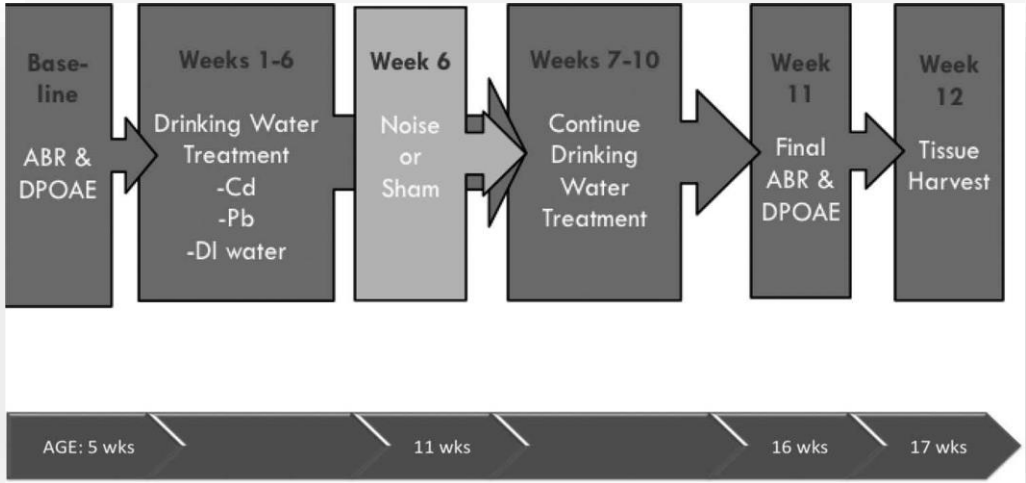
- ILO – International Labor Organization
  - Published safety standards in *Protection of Workers Against Noise and Vibration in the Working Environment* in 1977, updated in 1984
  - Recommend limit of noise for **8 hours** of exposure: **85-90 dBA**
- EU-OSHA – European Union OSHA
  - The European Directive 2003/10/EC sets the maximum limit at **87 dB(A) for an eight-hour workday**

J Toxicol Environ Health A. Author manuscript; available in PMC 2019 Sep 21.
Published in final edited form as:
J Toxicol Environ Health A. 2018; 81(20): 1041–1057.
Published online 2018 Sep 21. doi: 10.1080/15287394.2018.1521320

PMCID: PMC6349363
NIHMSID: NIHMS1001254
PMID: 30239325

Assessing ototoxicity due to chronic lead and cadmium intake with and without noise exposure in the mature mouse

Krystin Carlson,* Jochen Schacht,† and Richard L Neitzel*



Let's look at a model showing WHY noise + chem exposure evaluation is important

- 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

HESI.

Assessing Ototoxicity due to Chronic Lead and Cadmium Intake with and without Noise Exposure in the Mature Mouse - Results

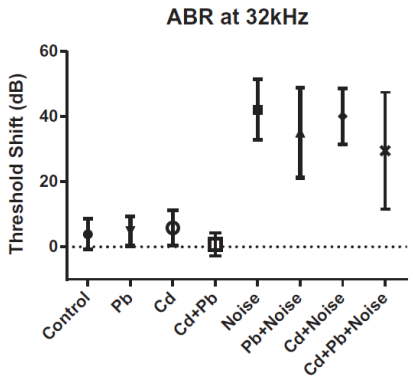


Figure 4. Mean and standard deviations for ABR Threshold shifts at 32 kHz for single treatment and mixture groups with 3 mM Pb, 300 µM Cd, and 105 dB.

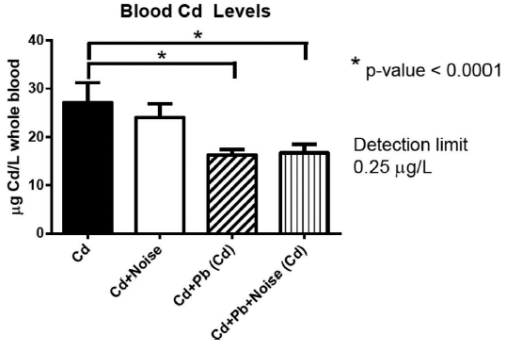


Figure 5. Blood Cd levels (µg/L) by treatment groups for single treatment and mixture groups with 3 mM Pb, 300 µM Cd, and 105 dB.

Table 7. Cochlea cytogram missing outer hair cell counts.

		Apex		Middle		Base	
Treatment Group	N	Avg	SD	Avg	SD	Avg	SD
Control	15	0.2	0.2	0.2	0.3	0.3	0.4
3 mM Pb*	11	0.2	0.2	0.3	0.2	0.1	0.1
300 µM Cd*	12	0.2	0.3	0.2	0.2	0.2	0.2
102 dB Noise	7	0.2	0.2	0.3	0.3	3.1	2.3
105 dB Noise*	10	0.2	0.2	0.4	0.2	5.8	4.4
108 dB Noise	8	0.3	0.1	1.6	2.6	13.8	16.7
Cd+ Pb	9	0.1	0.3	0.2	0.2	0.7	1.2
Pb+ Noise	9	0.3	0.3	0.3	0.3	2.9	2.3
Cd+ Noise	9	0.2	0.1	0.5	0.4	11.6	9.6
Cd+ Pb+ Noise	6	0.1	0.1	0.3	0.3	7.3	5.0

*Group treatment levels used for mixtures (3 mM Pb, 300 µM Cd, & 105 dB Noise)

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.

HESI.

Co-exposure effects on hearing a topic of current study by others as well…

S Afr J Commun Disord. 2019; 66(1): 568.
Published online 2019 May 9. doi: 10.4102/sajcd.v66i1.568
PMCID: PMC6556967
PMID: 31170785

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

Faatima Nakhooda,[1] Benn Sartorius,[2] and Samantha M. Govender[1]

DOI: 10.1136/oemed-2018-105471 • Corpus ID: 59275676

Exposure to noise and ototoxic chemicals in the Australian workforce

Kate Lewkowski, J. Heyworth, +9 authors L. Fritschi • Published 2019 • Medicine • Occupational and Environmental Medicine

Preventive hearing tests in workers exposed to noise and organic solvents

Mariola Śliwińska-Kowalska [1]

More details

Med Pr 2020;71(4):493–505

DOI: https://doi.org/10.13075/mp.5893.00993

HESI.

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-Panel/

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.

HESI.

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

HESI.

CORA Project Plan

Phase 1

Problem Formulation & Scoping

- **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 ototox risk assessment

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

HESI

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:

	Number of distinct organizations	Number of members	Areas of expertise
Academia	4	4	Noise exposure assessment, heavy metals ototoxicity, occupational co-exposure to solvents and noise/ noise-induced hearing loss, etc.
Government	4	8	Toxicology, occupational health, chemical and noise exposure assessment, jet fuels, ototoxicity, noise interactions, guidance documents, etc.
Industry	6	8	Industrial hygiene, product stewardship, non-clinical ototoxicity, ototoxicity prevention/diagnosis, etc.

HESI.

Seeking Additional Collaborators for Project 1…

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.)

HESI.

Questions and Comments

Contact Us

Rick Neitzel, PhD

Committee Co-Chair, University of Michigan

rneitzel@umich.edu

Laura Maurer, MPH, PhD

Committee Co-Chair, ExxonMobil Biomedical Sciences, Inc

laura.maurer@exxonmobil.com

Jennifer Pierson, MPH

Senior Scientific Program Manager, HESI

jpierson@hesiglobal.org

Raechel Puglisi, MPH

Scientific Program Associate, HESI

rpuglisi@hesiglobal.org