



Proposal 6. Ototoxicity, hearing loss, risk assessment, toxicology, epidemiology, risk communication, noise, solvents, medications, synergy, cumulative



## HESI PROPOSAL FORM

### **Instructions:**

- Consult / coordinate with colleagues in other divisions / departments within your institution to solicit and propose ideas on human health and environmental issues of concern.
- Use a separate form for each topic and additional pages, if needed.

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**Proposal title:** Improve Hearing Health via Ototoxicity Risk Assessment

**Key words:** (*minimum of two*) Ototoxicity, hearing loss, risk assessment, toxicology, epidemiology, risk communication, noise, solvents, medications, synergy, cumulative

### **Describe the problem to be addressed. Why is the issue important? To whom is this issue important?**

Increased scientific advances in multiple, interdisciplinary fields provide promising opportunities to improve hearing health in the global population. A primary WHO Sustainable Development Goal is to “ensure healthy lives and promote well-being for all ages”: this worldwide aim will be enhanced by the realization that scientific advances may make it possible to prevent or reverse (currently “irreversible”) hearing loss. Overall wellness measures include hearing health, from birth to old age, and the interrelatedness between hearing health and other wellness measures have been demonstrated around the world (c.f. European Union 2015). As of 2017, reported global statistics suggest that Disability-Adjusted Life Years (DALYs) for all ages includes an upward trend for hearing loss since 1990 (with over 65 million people affected by 2015). The financial burden associated with hearing loss treatment and compensating for (currently irreversible) disability is significant.

A comprehensive synthesis of recent scientific advances is needed as a concrete, essential step toward improving interventions to prevent or reverse hearing loss across the world. While several (U.S., Australian) governmental bodies have begun to address the unique exposure of certain (e.g., military, industrial worker) subpopulations, the proposed HESI-led synthesis would take a more holistic, all-ages approach to establishing ototoxic risk contributions, which includes modern clinical diagnostic techniques, updated toxicological modes of action, epidemiology advances, and new promising technologies that overcome past data collection and interpretation hurdles. 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). Exposures to these chemical and physical agents occur in both the occupational and consumer setting, which creates a complex set of circumstances in which an individual could present with ototoxic outcomes.

Ototoxic outcomes include (but are not limited to) hearing loss and impacts to balance - outcomes which greatly impact one's quality of life and potentially also impact the ability of an individual to function independently. Of note is the relative lack of information on loss of balance and coordination as an ototoxic outcome in comparison to hearing loss: this proposal plans to address both in a comprehensive assessment. The proposal includes plans for engagement with experts across industry, academia, and governmental institutions.

Because of the wide range of exposures and relatively low exposure levels that may result in ototoxic outcomes, it is important to determine safe exposures in which ototoxicity will *not* pose a risk to the consumer or worker. This issue is important across various industries (pharmaceutical, chemical, workplaces with high noise exposure, etc). A common understanding of the risks by industries and governmental organizations is crucial, as robust dose-response information for such exposures has been difficult to harmonize but can drive safe levels for regulation. This proposal puts forth a plan to improve hazard characterization of drivers of ototoxicity and place the subsequent understanding of ototoxic exposures in the proper contexts, resulting in the appropriate communication of risk.

Estimated economic value of this proposal is significant: in 2000, an in-depth study called "The societal costs of severe to profound hearing loss in the United States", published in the *International Journal of Technology Assessment in Health Care* estimated the societal costs of severe to profound hearing loss in the US to be **\$297,000 per person** during that person's life. A recent nonprofit [report](#) estimated that:

*"7% of all adults live with a disabling hearing loss, and more than 2 out of 3 of these people are not treated for their disabling hearing loss. **In the US alone, disabling hearing loss equals \$133 billion a year...** When looking at the general population, untreated hearing loss influences general physical health and wellbeing, and reduces physical activity. People with untreated hearing loss are also more likely to have other chronic diseases than people with normal hearing. There is also a documented relationship between untreated hearing loss and cognitive decline and dementia."*

Improved ototoxic hazard identification contributes to a broader value proposition and measurable global impact, which includes retention of more hearing ability (increased health), earlier detection and intervention (prevention of disease), and cost savings due to health risk avoidance (fewer disabilities and associated claims). Benefits of improved hearing health and reduction to the significant financial and social costs of hearing loss, including secondary effects (depression, isolation, etc.), verge upon immeasurable for future generations.



**Describe the basic project steps or stages to the best of your ability, including an expected timeline, milestones, and deliverables for the first two years.**

This proposal contains elements of three pillars of risk assessment: hazard characterization, exposure characterization, and risk communication. The proposal takes a multidisciplinary approach, with projects aimed at gathering toxicological dose-response data, characterizing existing unexplored biometric information and contextualizing it to be fit-for-purpose, exploring the improvement of clinical methods for detecting ototoxicity, and effectively communicating the findings. The scientific efforts of these projects are designed so that one project does not necessarily depend on the outcome of the others. Additionally, the projects are intended to engage experts across academia, industry, and governmental institutions.

**FirstYear: 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)

Key Scoping Questions: For what human subpopulations (defined by exposure agent or other criteria) are recent ototoxicity animal study dose-response conclusions most applicable/relevant? Are points of departure for ototoxicity suggestive of a “critical effect” lower than current health benchmarks?

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

Key Scoping Questions: For what human subpopulations are recent epidemiology correlations most applicable? Are ototoxicity correlations suggested in biomonitoring or health surveillance databases informative in assessing protectiveness of current health benchmarks, and if so, are occupational health interventions prudent to more holistically improve worker health?

Milestones/Deliverables: Assessment of dataset and conclusion generation; dissemination of findings at conferences/meetings

**FirstandSecondYear:**

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



**Describe the interdisciplinary, collaborative nature of the proposed project, and identify potential partners:** *(identify institutions, organizations, companies, and or consortia)*

The projects as detailed above require expertise from all facets of the issue, and efforts have begun to engage a tripartite group of scientists on the issue in support of this proposal.

The below list reflects potential partners, including some who have either expressed enthusiasm or have already committed to being involved in the projects:

- Pharmaceutical industry
- Chemical industry: ExxonMobil (Laura Maurer, PhD); Chevron (Shanna Clark, PhD); Shell
- NIOSH
- Academia: University of Michigan (Rick Neitzel, PhD)
- Consortia: ACC – leverage ongoing ototoxicity work on chemical-specific panels
- Department of Defense/Air Force/Navy

**What is the potential or anticipated impact of successfully achieving the milestones described above?** *(Describe scientific, regulatory, policy, public health, and/or other impacts.)*

The milestones of this project aim to work toward a greater understanding of modern science related to ototoxicity, which is a key component of overall wellness and prevalent public health issue: exposures in the workplace and in the general public can contribute to ototoxic outcomes. The need to understand the complex etiology of ototoxic outcomes and safe level of associated exposures is a timely and significant issue. Improvements in assessment and proper identification of ototoxic actors can enhance treatment, prevention, and potentially reversibility of currently irreversible health impact. Addressing this need will require a robust, multidisciplinary approach to synthesize existing information and develop new scientific information. This new scientific information is crucial for the formulation of evidence-driven regulation and policies around ototoxicity and noise. Effective communication of the results has the potential to increase impact by framing the information in the proper contexts and providing clarity for a complex public health issue.

**How did you hear about HESI's proposal solicitation? (e.g., HESI email or website, society announcement)**

Email from internal HESI member (Mark Lampi)

**Other comments.**