Preliminary Case Study Summary

Understanding Weight-of-Evidence from Co-Exposures to Noise and Chemicals in the Workplace

- **Presented by: Neeraja Erraguntla, ACC**
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- **About the Sponsors:** The American Chemistry Council's (ACC[1]) Toluene & Xylene Panel (Panel)[2] has a long history of conducting scientific research and communicating critical information to stakeholders, including regulatory agencies in the U.S. and abroad, to better understand the hazards and risks potentially associated with exposures to toluene and xylene. The Panel is committed to Responsible Care®[3].

1. **Provide a few sentences summarizing the Issue.**

Hearing loss is a multifaceted adverse health effect: recent studies suggest multiple viable causal hypotheses and a variety of potential modes-of-action (MOAs). While NIOSH researchers and other subject matter experts previously identified that the interaction between noise and ototoxic agents and their combined interaction is very complex, consensus has not yet been reached on the most applicable / appropriate term(s) of reference (TOR) to explain the cumulative / combined effects of noise with potentially ototoxicant industrial chemicals. Further, current approaches to understand combined exposures have not yet comprehensively addressed the complexity of the effects of co-exposures to a physical stressor such as noise and a chemical that may cause ototoxicity.

Therefore, an important first step should be to encourage worldwide collaboration, understanding and acceptance of whether (and under what conditions could) interactive effects from the concurrent co-exposures to potential ototoxicant industrial chemicals and

[1] ACC represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health and safety performance through Responsible Care®, common sense advocacy designed to address major public policy issues, and health and environmental research and product testing. The business of chemistry is a $553 billion enterprise and a key element of the nation's economy. Chemistry companies are among the largest investors in research and development, investing nearly $10 billion in 2018.

[2] The Panel represents producers of toluene & xylene.

[3] Responsible Care® is the chemical manufacturing industry's environmental, health, safety and security performance initiative. For more than 30 years, Responsible Care has helped American Chemistry Council (ACC) member companies significantly enhance their performance and improve the health and safety of their employees, the communities in which they operate and the environment as a whole.

noise could result in hearing loss, even when exposures are below each agents' respective Permissible Exposure Limit (PEL)[4].

A preliminary (screening-level) assessment with clearly articulated problem formulation is needed to outline agreed-upon TOR (whether synergistic, additive, potentiated, or other TOR) effects as the two stressors are different in nature and their interaction is highly complex. The combination of noise (considered a physical stressor with unique MOA that causes damage exclusively to the cochlea) with chemicals that may impair the cochlea, the vestibulo-cochlear apparatus, the eighth cranial nerve or the central nervous system.

A critical review of the co-exposures to noise and ototoxic chemicals coupled with well-defined and robust exposure characterization is essential to determining the relevance of research and workplace observations in efforts to enhance occupational hearing health. As a first step to accomplish this objective, it is important to have a thorough understanding of the potential mode-of-action and toxicological effects of the chemical in addition to understanding the type of mechanical and metabolic damage that can result from excessive noise in the workplace. Once these parameters and the physical and chemical properties of the chemicals have been defined and accounted for the combined interactions can then be assessed according to recognized systematic review principles and/approaches accounting for uncertainties linked to various confounders, and other factors.

Well-controlled laboratory animal studies published in the peer-reviewed scientific literature are insufficient alone to inform mechanisms relevant to human workplace exposures. The complexity concurrent co-exposures encountered by humans (including not only heterogeneous career exposures (Johnson and Morata, 2010) but the dietary and medical history that may include ototoxic medications and other potential confounders) coupled with nuances of study design suggest that this topic is worthy of a systematic review of the recent and relevant literature, as a means of fostering improvements in occupational health measures.

After considering the resource intensive requirements for conducting a comprehensive systematic review, a limited scoping review of the literature was undertaken as a first step to evaluate the WOE for hearing loss observed following concurrent occupational co-exposure to solvents and noise. The objective of this scoping review is to serve as a commentary on the state of the science while generating and promoting discussions on how to adequately assess the co-exposures of noise and chemicals, in particular when the exposures to ototoxic chemicals are at or below the PELs. To the extent possible, general and well recognized systematic review principles were followed and as applied elsewhere to chemical-specific occupational safety and health questions.

[4] https://www.osha.gov/SLTC/toluene/exposure_limits.html

2. **Describe the problem formulation(s) designed to address. How the method is described useful for addressing the problem formulation?**

Several studies have suggested that some ototoxic chemicals, such as certain **solvents**, might exacerbate **noise**-induced **hearing loss** even though the **noise** level is below the OSHA **Permissible Exposure Levels (PELs)**.

The problem formulation is therefore to discern the effects of chemicals on hearing loss from the effects of noise through a series of questions to understand the background concentrations and to determine "Response Synergism".

This problem is receiving increasing attention globally. In the U.S, there have been efforts to educate and engage stakeholders as shown by recent webinars by the American Conference of Government Industrial Hygienists (ACGIH, 2017 and 2019) in which ACGIH stated:

> "…describe[s] our current knowledge regarding exposures to harmful audible sound in the workplace and in recreational settings and will also review data on the associations between these exposures and two primary health outcomes, hearing loss and cardiovascular disease. The webinar will also describe some of the information on exposures to, and effects of, a range of ototoxic agents.

NIOSH also has weighed in on this issue and provided general guidance on the use of systematic reviews as an approach to answer the different types of occupational safety and health questions through various publications including: informational bulletins, blogs and reports.

Also, as more fully described by Howard et al. (2019), unique challenges exist in applying available systematic review methods to questions regarding occupational safety and health, such as concurrent co-exposures to ototoxic chemicals and audible sound. For systematic review, NIOSH states:

> These questions [related to worker safety] are often oriented to understanding the role that occupational exposures play in causing adverse health outcomes. Answering this question can involve integrating evidence from human studies, animal studies, and in vitro studies rather than conducting controlled clinical trials. The diversity of evidence a lack of randomized control trials create the need to adapt systematic review methods including data quality criteria to occupational safety and health questions.

For example, a recent literature review explored the possibility of hearing loss from concurrent co-exposures to ototoxic chemicals and audible sound in the safety of workers (e.g., Sheikh et al., 2016), and recent work by American, Australian, Canadian and Norwegian, and Swedish investigators demonstrated that co-exposures to excessive noise levels and ototoxic chemicals are widespread. Lewkowski et al. (2019) labeled ten*chemicals as "ototoxic", because they had evidence of auditory effects at exposure concentrations near the Australian relevant 8-hour time-weighted average occupational exposure limits (TWA

OEL)[5] regardless whether the effect occurred with or without noise exposure. These ten chemicals were also included in their survey as modern/relevant ototoxins using the following stated criteria:

"*to establish a priority list of workplace ototoxins, we considered all substances identified as 'ototoxic' and 'possibly ototoxic' from the Institut de recherche Robert-Sauvé en santé et en sécurité du travail (IRSST) group, those with a level category 1 and category 2 level of evidence of ototoxicity to humans by the Nordic Expert Group,and those regarded as having 'good evidence' for ototoxicity on the more inclusive EU-OSHA list."*

In the same review, the authors reported results of a cross-sectional telephone survey of over 5000 workers and reported that over 80% of workers who exceeded the full shift noise limit were also exposed to at least one ototoxic chemical in their workplace. Co-exposures were more common in men in this country, which might explain some of the observed apparent discrepancies in hearing loss recorded for male as opposed to female workers. Other researchers have been able to detect gender-specific differences in the pattern of hearing loss associated with ototoxicity observed at specific sound frequencies, which provides for more targeted future research on hearing health improvement.

Thus, a key gap in applying animal observations to worker experience or hearing health in particular is to ensure that relevant dosing (and tighter dose-response curves) for extrapolation to human workplace experiences is sought, so methods to extrapolate for risk characterization can then be applied. The first step, however, in accomplishing this objective is to conduct a systematic review of the literature, including quality assessment and synthesis, to set the stage for a multidisciplinary discussion.

3. **Comment on whether the present systematic review approaches and the available approaches for combined or joint exposures can be adapted to appropriately to evaluate ototoxicity from co-exposures to chemical and non-chemical stressors? Discuss the overall strengths and weaknesses of the Approaches or provide suggestions to adapted appropriately**

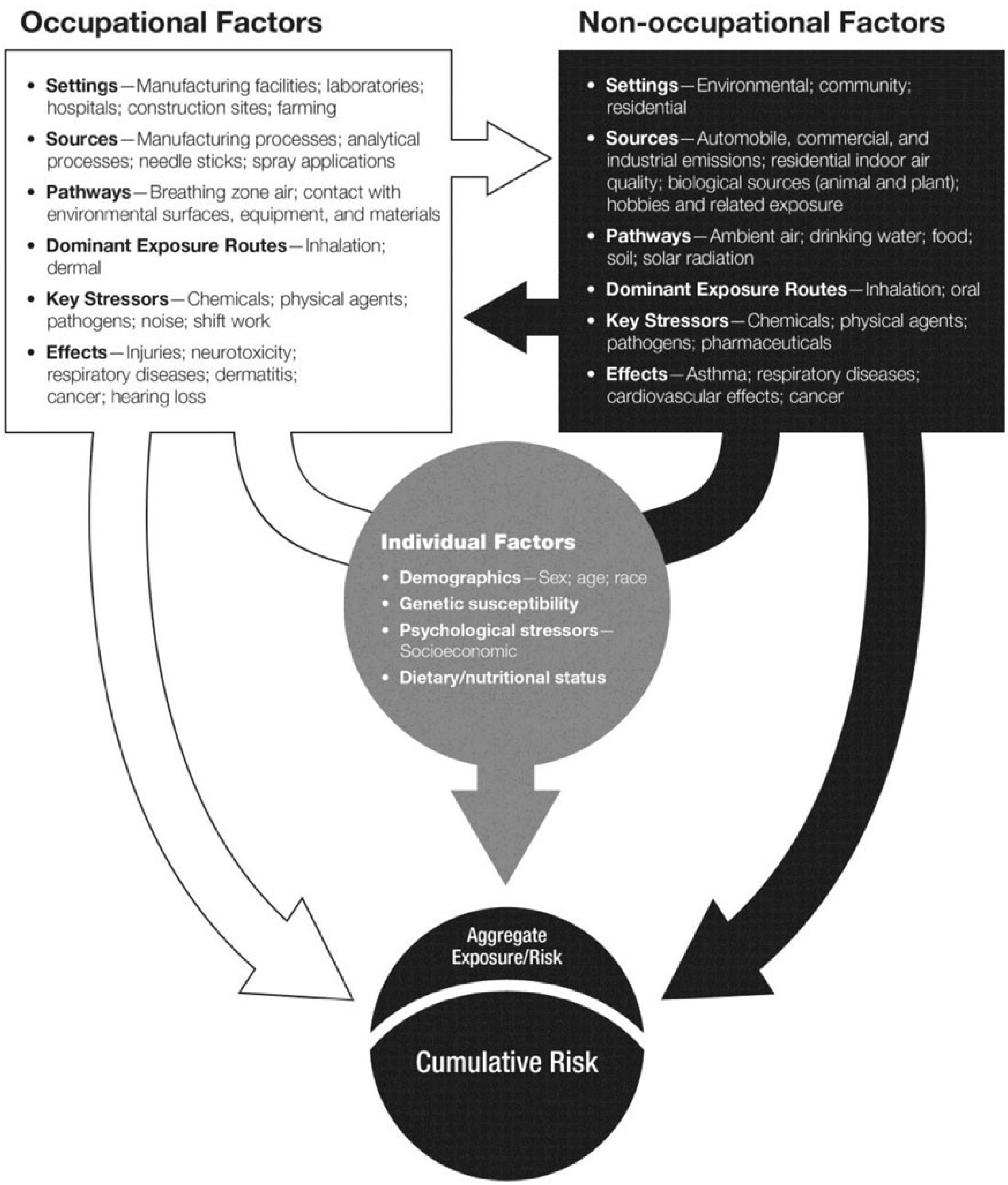
The principles for scoping or systematic review are general enough to be used for evaluating literature associated with concurrent co-exposures to ototoxic compounds and hazardous audible sound. In fact, numerous examples exist of scoping reviews and/or systematic reviews for individual chemicals or their mixtures; but far fewer examples exist for the assessment of cumulative exposures.

[5] https://www.safeworkaustralia.gov.au/system/files/documents/1912/workplace-exposure-standards-airborne-contaminants.pdf

3.1. US EPA’s Cumulative Risk Assessment Framework

By definition, USEPA’s cumulative risk assessment (CMA) framework https://www.epa.gov/sites/production/files/2014-11/documents/frmwrk_cum_risk_assmnt.pdf seeks to comprehensively to address combined risk from multiple stressors from all contributing sources of exposure, typically considering the effects of structurally related chemicals with a common mechanism of action (Rider et al 2012., Lentz et al 2015).

Lentz et al. (2015) provides a good synopsis of the US CMA framework and discusses the need to modify and/or adapt available methods and tools under the CMA to account for complex exposures in the workplace. In addition the authors also provide a few figures that graphically illustrate (Figure 1 and 2 of Lentz et al. (2015)) the unique and complex nature of occupational scenarios. The visual representation in Figure 2 of the paper clearly depicts the 3 different categories (i.e. occupational, non-occupational stressors, and individual factors), that may contribute to both aggregate and cumulative risk and also un-packs the make-up of each of the category. Further, the authors provide examples of the primary settings, sources of risk, exposure routes, key stressors, and effects are included to aid in illustrating considerations that should be included in assessing aggregate and cumulative risk to various hazard.



From Lentz et al. (2015): Illustration of the relationship between key factors considered in cumulative risk assessment.

As with any framework, details are not fleshed out fully and few case studies if any are available for demonstrating applications in real-world settings. In the case of USEPA's cumulative risk assessment framework, notional combinations of stressors (such as chemicals and "noise") are mentioned, but without concrete examples, particularly in light of the current ototoxicity literature.

There is a need to appropriately account for co-exposures to chemical and several- non-chemical stressors and also other occupational and non-occupational risk factors that workers experience. This is a data gap that needs to be addressed by the stakeholders and agencies must look into providing guidance and through partnerships and collaborations with stakeholders

3.1.1. Strengths:

The advantage of such an approach is the capacity to assess the combined effects of multiple stressors, namely chemicals. Intuitively, this approach would seem applicable to the current scenario of concurrent co-exposure to a chemical hazard and a physical hazard both of which arguably result in auditory deficits.

3.1.2. Limitations:

The challenge of using such an approach for co-exposures to chemical and non-chemicals is the implication of a similar mechanism of action. However, to date these two hazards appear to operate through a different mechanisms as different anatomical sites comprising the auditory system are affected.

Campo et al. (2013) in their review discuss the MOAs published by other investigators and describe noise as a physical factor that causes mostly mechanical and metabolic damage to the peripheral auditory receptor, the cochlea, and more rarely, to the auditory neural pathways as opposed to "ototoxic" chemicals for which the MOA indicates that the chemicals can potentially enter the bloodstream and go through either the blood-labyrinth barrier into the cochlea or the blood-brain barrier to reach the eighth cranial nerve and the central nervous system.

As a result, chemical-induced hearing loss can be the result of effects on several sites within the hearing system as opposed to noise-induced hearing loss in which the damage could be more localized to the cochlea.
An initial list of the potentially significant scientific gaps to applying traditional cumulative risk assessment frameworks to the ototoxins-plus-noise challenge may include, but are not limited to, uncertainties related to the following nuances:

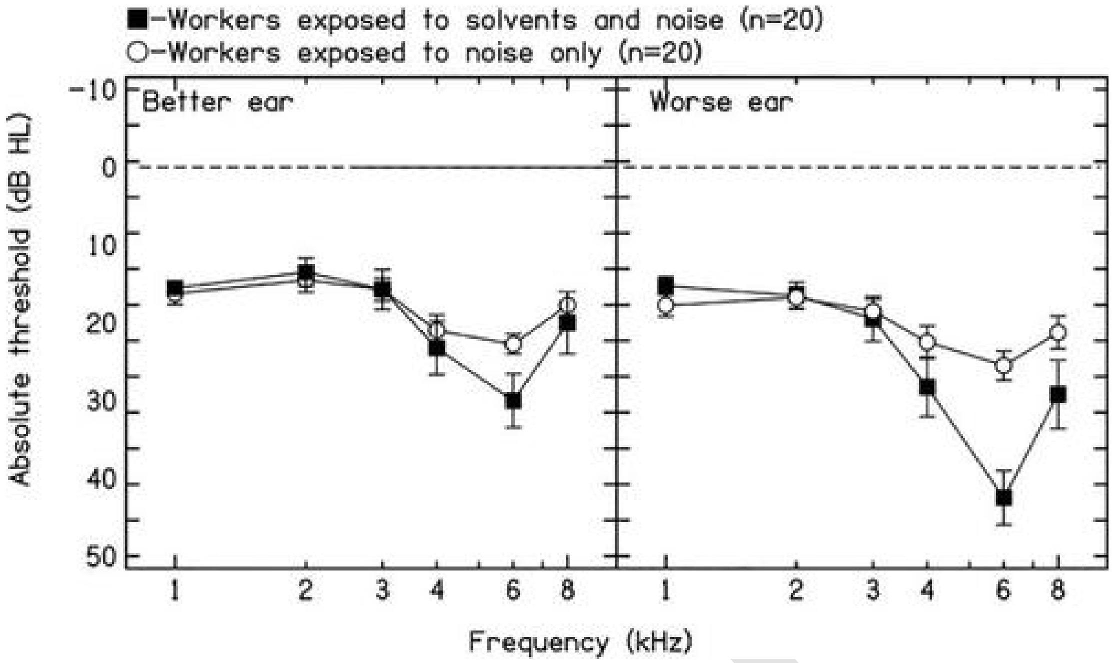
Noise-induced hearing loss (NIHL) hearing loss may be interpreted as a threshold effect, but the NIHL threshold can be modified (upwards or downwards) depending on the ototoxin(s) involved in co-exposure:

- Lowered threshold (increased susceptibility) for some chemical ototoxins

- Increased threshold (decreased susceptibility/protective effect) for others
- Similarly, solvent ototoxicity may be interpreted as reversible and/or as a threshold effect, but the threshold for "solvent"-induced effect can be similarly (as with NIHL) modified (upwards or downwards) depending on the type of noise co-exposure:
- No ototoxicity of carbon monoxide (CO) absent noise
- Toluene "High-Dose" (in relation to 20 ppm OEL) Animal Studies
- No / de minimis toluene 400 ppm effect for 5 or 10 days absent noise
- Threshold crossed at 5 days 400 ppm to become irreversible + 93 dB OBN
- Neither "solvents" nor "noise" are easily defined and are complex on their own
- Papers contrast dose-response shape of curves (toluene/styrene correlation)
- Mixtures studies incompletely defined: even binary studies differ widely
- Different kinds of noise are important: pulsing, vibrational … all relative
- Frequency and amplitude, loudness, all modified by duration/exposure
- Startling noise releases greater stress reaction (chemical) cascade
- Chronic noise has shades of nuance related to "acceptability" of it
- Genetic role of "stress reaction" modifiers may have (not yet quantified) role
- Human reaction to noise / psychological and physiological reaction to noise as a stressor is widely variable: audiogram does not capture these variables
- Ototoxin metabolism has known genetic modifier (e.g. GSH pathway), and PBPK models are available, but yet "stress cascade" impacts on such pathways are not defined, and thresholds remain plausible
- Stress cascade also has a genetic basis in humans, that is one of the many missing links between in vitro oxidative stress markers and whole human

3.2. NIOSH Approach- Use of Combined Noise Exposure Metric (CNE) or the Kurtosis metric as a reasonable estimate

Fuente et al. (2018) conducted an exploratory study to examine the effects of combined exposure to solvents and complex noise on hearing thresholds of workers from eastern China using a kurtosis metric, which takes into consideration the temporal structure of the noise. The authors reported that their ultimate goal was to investigate whether the kurtosis metric can contribute to the study of combined effects Table 1 and Figure 1 of of the Fuente et al. (2018) paper should be reviewed for questions to the panel and/or subject matter experts:



Abstract

Questions to the Committee- Please see Table 1 and Figure 1 of Fuente et al (2018)

1) Please comment on the use of the CNE metric to evaluate the hearing thresholds due to co-exposures to noise and solvents
2) Is a separate metric needed for < 88 dBA by year?
3) Data not available/applicable "NA" in Table 1?
4) Is gender difference something that needs to be revisited given other papers suggesting significant modifying factors of a lifetime of different background frequencies?

3.3. How appropriate is it to use NHANES Biomonitoring Data Collected in conjunction with audiology data to Reverse Estimate that hearing loss occurred due to exposure to chemicals

3.3.1. Strengths

- The NHANES biomonitoring data in the Pudrith (2019) evaluated urinary metabolite data for the years during which audiometry readings were also collected
- Clear inclusion and exclusion criteria were used

3.3.2. Limitations

- What levels of oxidative stress are adverse?
- The oxidative stress biomarker is not very specific bioassay marker to assess biomarker of effect
- There needs to be some context to characterize biomarkers of exposure vs biomarkers of effect?
- There was no information on the use of any pharmaceutical products/medicinal drugs like over the counter aspirin or the use of antibiotics prior to the collection of both urinary metabolites and undergoing auditory assessments
- There is no information on where the participants worked
- Are these effects of auditory oxidative stress reversible?
- Confounding of the potential use of pharmaceutical products and oxidative stress
- Is auditory oxidative stress a good metric to understand the complex interaction between a physical hazard combined with a chemical substance
- Uncertainties in the data need to be presented

4. Outline the minimum data requirements and describe the types of data sets that are needed.

A systematic review for ototoxicity from co-exposures to both chemicals and audible sound would likely require substantial resources and, thus, a scoping review may be considered to be a more reasonable alternative. A minimum data requirement for such a scoping review likely matches the standard operating processes of many existing risk assessment projects.

For human relevance, it is important not to overlook genetic markers associated with ototoxicity susceptibility, as demonstrated in the meta-analysis by Jing et al. (2015). Ototoxicity of many pharmaceuticals is very well-documented. For example, a severe side effect of aminoglycoside antibiotics is ototoxicity. It is therefore, important to document the medical history of the workers during their routine testing and also ensure that this type of information is captured and accounted for adequately in the studies.

Specific base line tests of normal auditory function would be necessary as well as specific histopathology of the auditory system. Some suggestions along this line are available from Fuente et al. (2018) and may have baselines established as in recent military ototoxicity monitoring programs (e.g., Konrad-Martin et al. 2018)

While some human correlation and epidemiologic observational studies are available (e.g., Pudrith et al. 2019) for general population and for solvent-exposed workers) (Fuente et al. 2013) that provide data sets pairing human noise exposure, solvent exposure, they are limited in other ways due to adequate lack of:

- Control for confounders,
- Background information on the participants genetic, medical and/or work history,
- Information on the appropriate ototoxic metabolite,
- Strong correlations on the urinary metabolite exposure with hearing loss metrics.

From the chemical toxicity viewpoint, an ideal database for this case study can include data on ototoxicity and neurotoxicity, and can also include behavioral assays as they may be much more informative than reproductive and developmental toxicity animal studies.

Chronic bioassays specifically designed to evaluate treatment related effects to the auditory system including a reproductive study that monitors effects in offspring, two developmental toxicity studies in different species, and two long term studies in different species may be required.

Minimum data requirements for this chemical toxicity would be one short-term test in experimental animals that monitored for normal auditory function and histopathology.

Domestic and international government agencies should encourage and facilitate collaborations and partnerships to further the development and use of New Alternate Methodologies (NAMs) in the arena of ototoxicity .With such limited data, uncertainty factors may likely be needed to project the safe chemical dose for comparison with the data from sound exposure and so adequate resources must be allocated to include uncertainty and sensitivity analysis.

5. Describe the dose-response relationship in the dose range relevant to human exposure?

The challenge of the current approaches to understand combined exposures have not yet completely addressed the complexity of the effects of co-exposures to a physical stressor such as noise and a chemical that can cause ototoxicity.

The question of human relevance has not be adequately addressed in the studies. The dose-response, lowest observed adverse effect level (LOAEL), and no observed adverse effect level (NOAEL) have only been identified in animal experiments for only a few chemicals.[6].

Fortunately, effects of overexposure to noise are better studied, but still the integration of dose-response information from both areas of toxicity is an area for future investigation and debate. In animal studies the use of high concentrations of solvents for short intervals of time does not accurately reflect occupational exposure conditions. Available epidemiological studies often lack detailed exposure histories and the presence of confounding factors (ototoxic drugs, tobacco, alcohol consumption, aging, and exposures outside the workplace) is a major limitation. There is limited to no dose-response information in the few epidemiological studies that evaluated ototoxicity from co-exposures to noise and solvents especially when the exposures were below their respective OELs.

6. Address human variability and sensitive populations?

Workers in various sectors might fall under "sensitive populations," but are more likely to express variability in response to cumulative exposures. Industries that use potential ototoxicants include manufacturing, mining, utilities, construction, and agriculture. Manufacturing industry subsectors may include:

- Fabricated metal
- Machinery
- Leather and Allied Product
- Textile and Apparel
- Petroleum
- Paper
- Chemical (including Paint)
- Pharmaceutical
- Plastics
- Furniture and Related Product
- Transportation Equipment (e.g. Ship and Boat Building)
- Electrical Equipment, Appliance and Component (e.g., Batteries)
- Solar Cell
- Occupational activities that often have high noise exposure and could add synergistic effects when combined with ototoxicant exposure (i.e., occurring in the above industries) may include:
- Printing
- Painting
- Construction
- Manufacturing occupations in the subsectors listed above
- Fueling vehicles and aircrafts
- Firefighting
- Weapons firing
- Pesticide spraying

7. Address background exposures or responses?

The existing concern is for workers in industries that might have exposures of ototoxic chemicals and noise, and identifying sensitive populations of workers if at all possible. It may also be of concern with certain populations that live near such industries, but it is not the intent of this case study to address these later populations. Recent NHANES analyses may be used in the case study discussion to approximate "background" exposures and responses, to the extent that such studies are available in the open literature.

8. Address incorporation of existing biological understanding of the likely mode of action?

- According to OSHA exposure to ototoxicants may occur through inhalation, ingestion, or skin absorption.
- Health effects caused by ototoxic chemicals vary based on exposure frequency, intensity, duration, workplace exposure to other hazards, and individual factors such as age.
- Effects may be temporary or permanent, can affect hearing sensitivity and result in a standard threshold shift.
- Since chemicals can affect central portions of the auditory system (e.g., nerves or nuclei in the central nervous system, the pathways to the brain or in the brain itself), not only do sounds need to be louder to be detected, but also they lose clarity. Specifically, speech discrimination dysfunction, the ability to hear voices separately from background noise, may occur…
- Ototoxic chemicals are classified as neurotoxicants, cochleotoxicants, or vestibulotoxicants based on the part of the ear they damage, and they can reach the inner ear through the blood stream and cause injury to inner parts of the ear and connected neural pathways.[4]
- Neurotoxicants are ototoxic when they damage the nerve fibers that interfere with hearing and balance.
- Cochleotoxicants mainly affect the cochlear hair cells, which are the sensory receptors, and can impair the ability to hear.
- Vestibulotoxicants affect the hair cells on the spatial orientation and balance organs.

9. Address uncertainty?

There is large uncertainty in extrapolating the complex co-exposures in humans (including not only heterogeneous career exposures, but lifetimes of personal dietary and medical history that may or may not include ototoxic medications and other confounders).

Research on effects of over exposure to noise is better studied. Limited animal studies have evaluated ototoxicity from co-exposures to noise and chemicals at occupational and/or environmental relevant concentrations. Lowest observed adverse effect level (LOAEL) and no observed adverse effect level (NOAEL) have been identified in animal experiments for only a few substances

Further, well-controlled laboratory animal studies published in the peer-reviewed scientific literature are insufficient alone to inform mechanisms relevant to human workplace exposures.

There appears to an interest in establishing correlations for hearing loss using urinary metabolite data from NHANES. There is a need to validate the bioassays such as the auditory oxidative stress bioassays prior to making conclusions of causality. The integration of dose response information from both areas of toxicity is an area for future investigation.

10. Work practically? If the method still requires development, how close is it to practical implementation?

The scoping review will provide a foundation for identifying data gaps needed to be explored further in detail in order to achieve the calculation of risk, which will not be possible at the end of this case study discussion.

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Appendix A

Lewkowski, Kate, Jane S Heyworth, Ian W Li, Warwick Williams, Kahlia McCausland, Corie Gray, Elinor Ytterstad, Deborah C Glass, Adrian Fuente, Si Si, Ines Florath, and Lin Fritschi.

Abstract

Objective To determine the current prevalence of exposure to workplace noise and ototoxic chemicals, including co-exposures.

Method A cross-sectional telephone survey of nearly 5000 Australian workers was conducted using the web-based application, OccIDEAS. Participants were asked about workplace tasks they performed and predefined algorithms automatically assessed worker's likelihood of exposure to 10 known ototoxic chemicals as well as estimated their full shift noise exposure level ($L_{Aeq,8h}$) of their most recent working day. Results were extrapolated to represent the Australian working population using a raked weighting technique.

Results In the Australian workforce, 19.5% of men and 2.8% of women exceeded the recommended full shift noise limit of 85 dBA during their last working day. Men were more likely to be exposed to noise if they were younger, had trade qualifications and did not live in a major city. Men were more likely exposed to workplace ototoxic chemicals (57.3%) than women (25.3%). Over 80% of workers who exceeded the full shift noise limit were also exposed to at least one ototoxic chemical in their workplace.

Conclusion The results demonstrate that exposures to hazardous noise and ototoxic chemicals are widespread in Australian workplaces and co-exposure is common. Occupational exposure occurs predominantly for men and could explain some of the discrepancies in hearing loss prevalence between genders.