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

ACC Toluene & Xylene Panel
Wednesday, February 19, 2020

American® Chemistry Council

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ANTITRUST CHECKLIST FOR AMERICAN CHEMISTRY COUNCIL MEETINGS

This antitrust checklist, a part of ACC's Antitrust Compliance Guide, is for use by ACC staff and member company representatives in the conduct of ACC-sponsored meetings. Prohibited discussion topics apply equally to social gatherings incidental to ACC-sponsored meetings. The checklist is not exhaustive and does not address antitrust issues relating to activities other than ACC meetings. Participants in ACC meetings also should be thoroughly familiar with the Antitrust Compliance Guide.

DO

Do ensure strict performance in areas of:

OVERSIGHT/SUPERVISION:

- Have an ACC staff representative at each ACC-sponsored meeting;
- Consult with ACC counsel on all antitrust questions relating to ACC-sponsored meetings;
- Limit meeting discussions to agenda topics (unless additional topics have been approved by the ACC staff representative); and
- Provide each member company representative and ACC employee attending an ACC-sponsored meeting with a copy of this checklist, and have a copy available for reference at all ACC-sponsored meetings.

RECORDKEEPING:

- Have an agenda and minutes which accurately reflect the matters which occur; and
- Provide agendas and minutes to ACC legal counsel for review and approval in advance of distribution.

VIGILANCE:

- Protest against or stop any discussion or meeting activities which appear to violate this checklist. Member company representatives should disassociate themselves from any such discussion or activities and leave any meeting in which they continue.

DON'T

Don't, in fact or appearance, discuss or exchange information on:

PRICES, INCLUDING:

- Individual company prices, price changes, price differentials, markups, discounts, allowance, credit terms, etc.;
- Individual company data on costs, production, capacity, inventories, sales, etc.; and
- Industry pricing policies, price levels, price changes, differentials, etc.

PRODUCTION, INCLUDING:

- Plans of individual companies concerning the design, production, distribution or marketing of particular products, including proposed territories or customers; and
- Changes in industry production, capacity or inventories.

TRANSPORTATION RATES:

- Rates or rate policies for individual shipments, including basing point systems, zone prices, freight equalization, etc.

MARKET PROCEDURES, INCLUDING:

- Company bids on contracts for particular products; company procedures for responding to bid invitations; and
- Matters relating to actual or potential individual suppliers or customers that might have the effect of excluding them from any market or influencing the business conduct of firms toward them.

Revised 9/4/2012 (single page version)
Reformatted 1/89 MDB; 6/96 SKR; 4/97 PGM

American Chemistry Council – Responsible Care

- 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.
- The Panel represents producers of toluene & xylene.
- 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.

World Health Organization

- Around 466 million people worldwide have disabling hearing loss and 34 million of these are children.
- It is estimated that by 2050 over 900 million people will have disabling hearing loss.
- Hearing loss may result from genetic causes, complications at birth, certain infectious diseases, chronic ear infections, the use of particular drugs, exposure to excessive noise, & ageing.
- 1.1 billion young people (aged between 12–35 years) are at risk of hearing loss due to exposure to excessive noise levels in recreational settings.
- https://www.who.int/news-room/fact-sheets/detail/deafness-and-hearing-loss

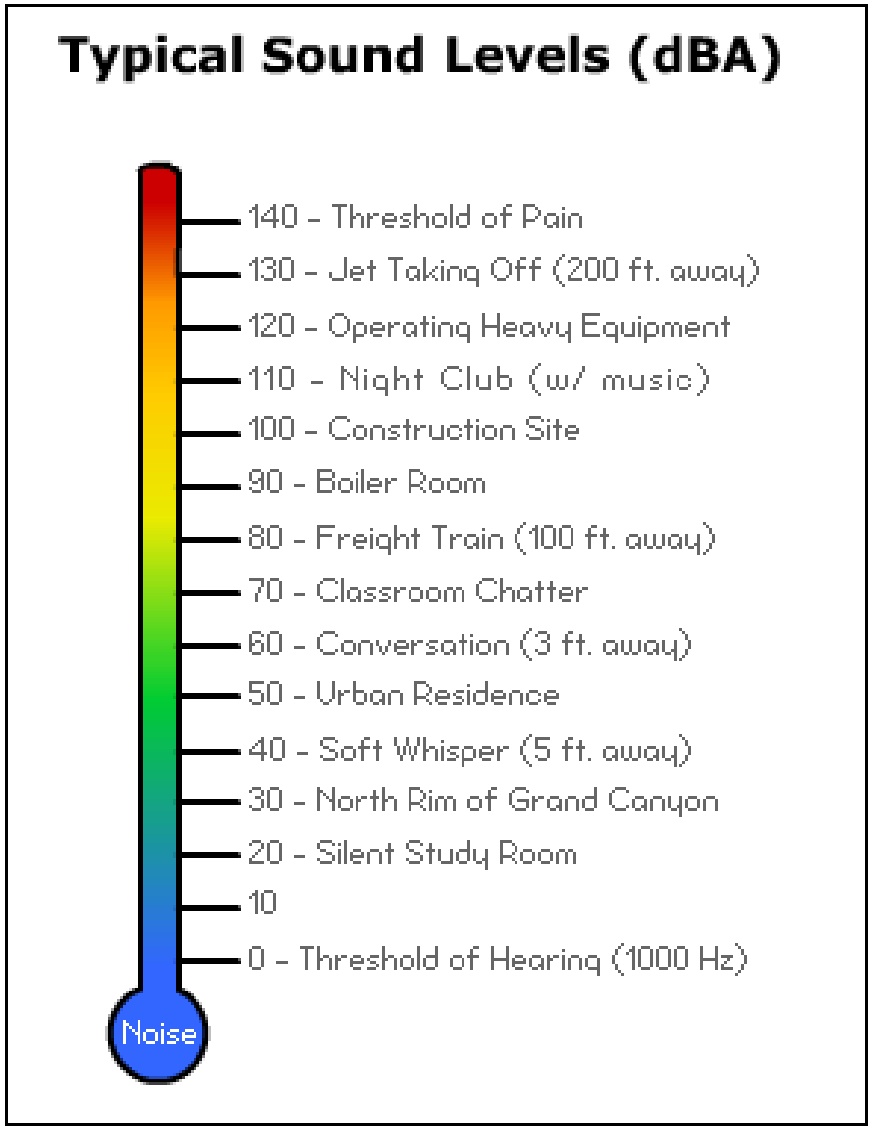
Global Interest in the Issue

- The involvement of several groups: US NIOSH, OSHA, ACGIH
- Academic Universities
- European Project Noise Chem
- The Swedish NIOH (later the NIWL)
- French INRS
- Polish Nofer
- Australia
- Canada
- Norwegian etc.

National Institute for Occupational Safety and Health (NIOSH)

- Occupational hearing loss is one of the most common work-related illnesses in the United States.
- Each year, about 22 million U.S. workers are exposed to hazardous noise levels at work.
- Over 30 million U.S. workers are exposed to chemicals, some of which are harmful to the ear (ototoxic) and hazardous to hearing.
- The NIOSH Recommended Exposure Limit (REL) for occupational noise exposure is 85 decibels (dBA),as an 8-hour time-weighted average (TWA)
- Occupational Safety & Health Administration (OSHA)'s standard uses a permissible exposure limit (PEL) of 90 dBA for all workers for an 8 hour day with a 5 dBA exchange rate.

https://www.osha.gov/SLTC/noisehearingconservation/loud.html



Industries that use potential ototoxicants 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

https://www.cdc.gov/niosh/docs/2018-124/pdfs/2018-124.pdf?id=10.26616/NIOSHPUB2018124

Introduction & Problem Identification

- OSHA standards require employers to maintain exposures to the specific substance at or below the respective Permissible Exposure Limits (PEL)s.
- However, there is concern that synergistic effects from the combined “ototoxicant” chemical & noise exposure could result in hearing loss when exposures ***are at or*** below the PELs.
- Some studies have suggested that some ototoxic chemicals, such as certain solvents, might exacerbate noise-induced hearing loss even though the noise level is ***at or*** below PEL.

What is the Issue?

- Hearing loss is a multi-faceted adverse health effect.
- Recent studies have indicated multiple viable causal hypothesis and a variety of potential Modes-of-Actions (MOA)s.
- The interaction between noise and ototoxic agents & their combined interaction is very complex.
- No consensus has 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.

What is Ototoxicity?

- Ototoxicity – Hearing Loss (HL)
- Ototoxicity is a disorder affecting the auditory system
- Ototoxicity is the property of being toxic to the ear (oto-)
- Adverse effects of the cochlea, auditory nerve, and sometimes the vestibular system
- The effects of ototoxicity can be reversible and temporary, or irreversible and permanent.
- Noise-Induced-Hearing-Loss (NIHL)
- Chemical-Induced- Hearing-Loss/Solvent-Induced-Hearing-Loss
  - (CIHL)/(SIHL)

What type of Ototoxicity/Hearing Loss (HL)?

- Two categories of hearing loss:
  - Noise-induced hearing loss (NIHL)
  - Chemical-Induced-Hearing Loss
- Examples: Pesticides, Solvents, Metals & Pharmaceuticals (as a side effect of some antibiotics, & other therapeutics such as anti-neoplastics and some antibiotics such as aminoglycosides are one of the most well-known drugs that can cause HL.
- HL may be interpreted as a threshold effect, and the threshold can be modified (upwards or downwards).

What is the Issue?...

- How useful are the current risk assessment approaches/frameworks to address the complex interactions between concurrent co-exposures to chemical and non-chemical stressors?
- A concern is an insufficient number of case studies have applied the present approaches to address this emerging and complex issue.
- How can these approaches be adapted to meet the new challenges?

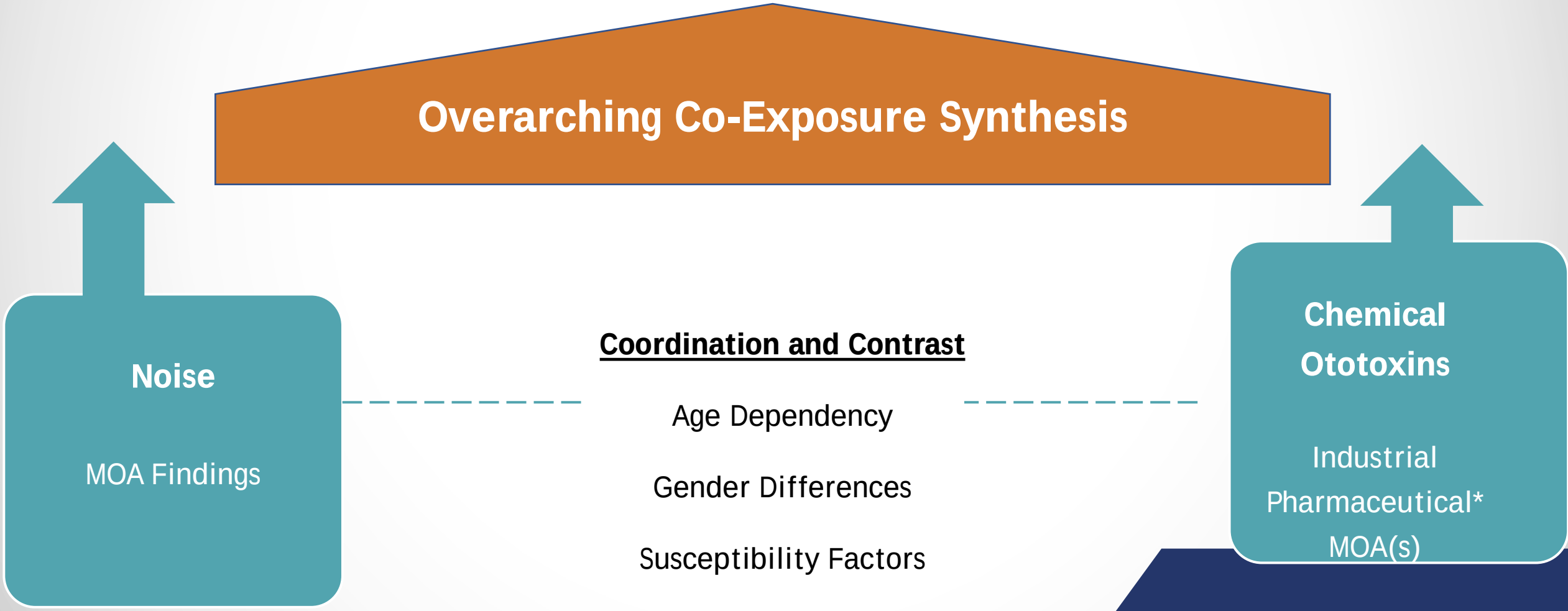
What are the Overall Goals?

- Worldwide collaboration on appropriate/consistent nomenclature
- Consensus on the Terms of Reference (TOR)
- What is the process to identify “ototoxic chemicals?
- Synergism vs Potentiation
- How can the available approaches such as Cumulative Risk Assessment (CRA) be adapted to meet the challenges to evaluate complex interactions between chemical and non-chemical stressors
- Biomarkers of Exposure vs Biomarkers of Effect
- Promote development of case-studies

What do we know so far from animal and Epi Studies?

- Well-controlled laboratory animal studies published in the peer-reviewed scientific literature are insufficient alone to inform mechanisms relevant to human workplace exposures.
- Complex concurrent co-exposures are encountered by humans (including not only heterogeneous career exposures (Johnson and Morata, 2010).
- Dietary and medical history may include ototoxic exposures and medications among potential confounders.

Approach


Overarching Co-Exposure Synthesis
Noise
MOA Findings
Coordination and Contrast
Age Dependency
Gender Differences
Susceptibility Factors
Chemical Ototoxins
Industrial Pharmaceutical* MOA(s)

Specific Goal 1

- Conduct a preliminary (screening-level) assessment.
- Clearly articulate problem formulation.
- Agreed-upon TOR (i.e., additive, synergistic, potentiation or other TOR).
- Evaluate the individual effects and the interactions as the two stressors are different in nature & their interaction is highly complex.

Problem Formulation Scoping

1. Adopt glossary or adapt new terms of reference (TOR) for noise & ototoxin co-exposures (Table I)*
2. Establish answers to scoping questions (Table II)*
3. Revise/expand the general concept figure (example at right from *Lentz et al. 2015*)*)

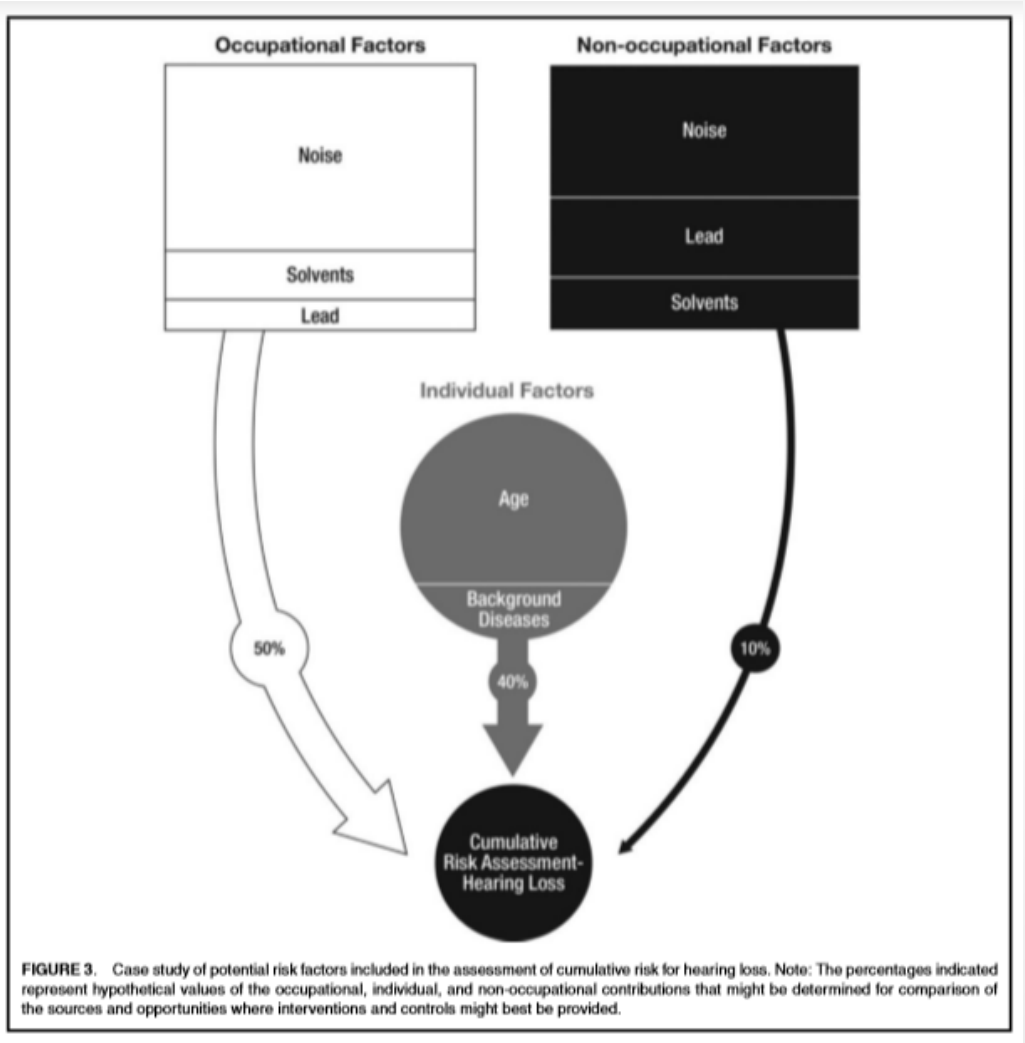


FIGURE 3. Case study of potential risk factors included in the assessment of cumulative risk for hearing loss. Note: The percentages indicated represent hypothetical values of the occupational, individual, and non-occupational contributions that might be determined for comparison of the sources and opportunities where interventions and controls might best be provided.

Lentz et al. (2015) Aggregate Exposure and Cumulative Risk Assessment—Integrating Occupational and Non-occupational Risk Factors, *Journal of Occupational and Environmental Hygiene*, 12:sup1, S112-S126.

Specific Goal: 1…

- Validate TOR appropriate for noise & ototoxin coexposure

c.f. Lentz et al. (2015) glossary at right:

- Does aggregation for hearing health stressors still work, if MOA varies?
- Is a unique, multi-mode (multiple AOP) scheme needed? If so, for what MOAs?
- Do certain susceptible subpopulations warrant an exception to the hearing health framework?

TABLE I. Glossary of Key Terms

Key Term	Definition
Aggregate risk	The sum of risks associated with exposures from multiple pathways and routes
Biomarkers	Internal measures or markers of exposures or effects for a chemical or agent in the body
Cumulative risk	The combined risk from exposure to chemical and no-nchemical stressors, including the possibility that such exposures may modify the toxic effects observed or their severity through interactive processes

Lentz et al. (2015) Aggregate Exposure and Cumulative Risk Assessment—Integrating Occupational and Non-occupational Risk Factors, *Journal of Occupational and Environmental Hygiene*, 12:sup1, S112-S126.

Efforts to Date

- Reviews (*e.g. Lentz et al. 2015*):

TABLE II. Critical Factors and Key Questions to Inform and Guide Aggregate and Cumulative Risk Assessments

Critical factors	Key questions
• Advances in exposure science	• Which mixtures are most important from a public or occupational health perspective?
• Increased technical capabilities associated with exposure monitoring and analytical techniques	• What is the nature (i.e., duration, frequency, and timing) and magnitude (e.g., exposure concentration and dose) of relevant cumulative exposures for the population of interest?
• Application of toxicokinetics and toxicodynamics data to characterize the consequences and variability of mixed exposures to environmental stressors	• What is the mechanism (e.g., toxicokinetic or toxicodynamic) and consequence (e.g., additive, less than additive, more than additive) of the mixture's interactive effects on exposed populations?[63]

Lentz et al. (2015) Aggregate Exposure and Cumulative Risk Assessment—Integrating Occupational and Non-occupational Risk Factors, *Journal of Occupational and Environmental Hygiene*, 12:sup1, S112-S126.

What is the Problem Formulation (PF)

- Several studies have suggested that some ototoxic chemicals, such as certain solvents, may exacerbate noise-induced hearing loss even though the noise level is below the OSHA Permissible Exposure Levels (PELs).
- PF: To determine and delineate the effects of chemicals on Hearing Loss (HL) from the effects of noise.

What are the Potential Modes-of-Action (MOA)s?

- Excessive exposure to noise is a physical hazard.
- Excessive noise can cause mostly mechanical & metabolic damage to the peripheral auditory receptor, the cochlea, and more rarely, to the auditory neural pathways.
- Some evidence suggests that some chemicals after entering the bloodstream can cross either the blood-labyrinth barrier into the cochlea or cross the blood–brain barrier to reach the central nervous system.
- Chemical-induced hearing loss can therefore result in potential effects on several target sites within the auditory system.
- Campo and Morata. 2013

What do we know from Animal Studies?

- High exposure concentrations in animal studies.
- Long-duration and frequency of exposures to aromatic solvents have been shown to cause irreversible hearing impairment, with the cochlear hair cells as the initial targets.
- Most of these animal studies were performed with rats, whose cochleae are sensitive to aromatic solvents.
- Campo, Morata, Hong, 2013

What do we know from Epidemiological (Epi) and Clinical Studies?

- Some clinical and epidemiological studies have reported an association between exposure to solvents (styrene, toluene, xylenes, solvent mixtures, & jet fuels) in the workplace, & increased prevalence of hearing loss, as well as poor hearing thresholds beyond the traditional 4 kHz noise-related audiometric notch (Campo et al 2013).

- Retrospective study of Air Force Reserve Personnel found HL to be associated with age + Noise & low-med solvent exposure to Toluene, Xylene, & Styrene < their respective OELs was not associated with HL (Hughes and Hunting, 2013).

What do we know from Epidemiological (Epi) and Clinical Studies?

- Many of the epi studies did not identify an increase in adverse effects on auditory function due to Toluene exposures at <50 ppm with noise levels at 83 dBA;
- Australia Toluene OEL is 50 ppm ; Noise: 85 dBA for 8 h
- EU occupational exposure limit value (50 ppm) in place of long-term inhalation DNEL value for workers

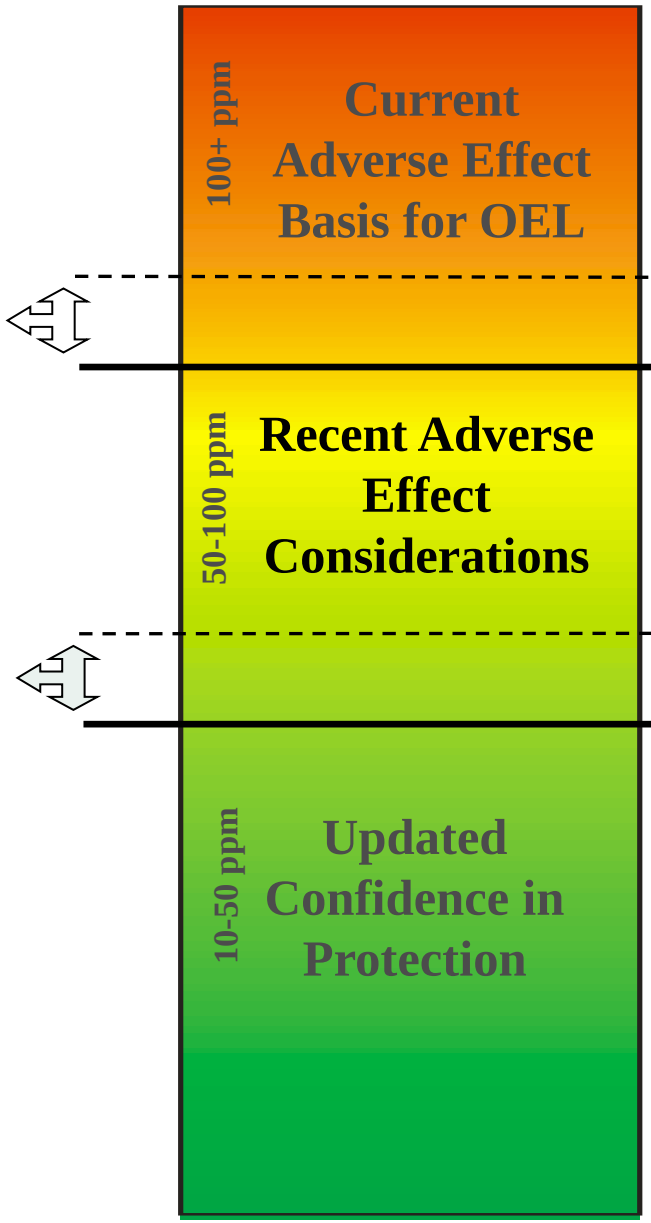
Toluene

- OSHA Permissible Exposure Limit (PEL) - General Industry
- 200 ppm TWA; 300 ppm Ceiling; 500 ppm Peak(10 minutes)

- NIOSH Recommended Exposure Limit (REL)
- 100 ppm TWA;150 ppm STEL

- American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV)
- 20 ppm(2007) and New Feb 2020- 20 ppm TLV with “OTO” notation

The difference between example occupational exposure reference levels is not represented realistically with a bright line, due to vintage and genre (regulation versus recommendation). For any given example concentration, the difference in exposure populations (e.g. shift assumptions, geographic location, underlying public health contribution / genetic susceptibility) may or may not make a significant biological difference (i.e., variability within 3X up to an order of magnitude).



US OSHA (1972) 200 ppm, NIOSH 100 ppm (CNS)

- CNS Effects: 100+ ppm human volunteer 6-7 hours reported headache, dizziness, fatigue, sleepiness, feelings of intoxication, reduced performance in neurological tests.
- Hearing loss (HL) in animals at "high" (>250 ppm) concentrations

◊ 1991-2007

- CNS Meta analysis (2005) of 22 studies: no neurobehavioral effects (average exposures 33-89 ppm)
- Color vision changes (2000 avg 44ppm; 36 ppm@ 18 yr)
- HL in humans at lower (than animal) concentrations with co-exposure to noise (>50 ppm)
- Reproductive (human epi) average 88 ppm (range 50-150): n = 55 spontaneous abortion RR 2.8 (1992 study)

◊ 2007-present

ACGIH (2007) 20 ppm*

TLV Basis: CNS impairment, visual impairment, hearing impairment (*OTO 2020), reproductive system/pregnancy loss

Need better understanding of nuances of combined exposures, reversibility, AOP / MOA

Collaboration to ensure HL risk communication not only for workers but in the community to enable **EARLIEST POSSIBLE INTERVENTION**

Bullets from ACGIH (2020) Draft TLV Documentation

Limitations from the available Epi Studies

- Different OELs in different countries
- Lack of detailed exposure histories, presence of confounding factors (ototoxic drugs, tobacco and alcohol use, aging, & exposures outside workplace);
- Sample sizes, study designs, insufficient characterization of the occupational exposure levels for chemicals & noise; Lack of detailed info on all other solvent exposure levels
- Difficult to ascertain the type of interaction between the agents
- Lack of clear dose–response relationship
- Difficult to determine the lowest exposure concentrations necessary for an effect to be detected for the solvents
- Limited info on the non-occupational noise/background/nature of the sound Intensity/Magnitude & Impulse
- Some studies indicated that with concomitant exposures, solvents may exacerbate noise-induced impairments even when noise intensity was below the European occupational limit value.

What do we know so far…

- A key gap in extrapolating 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 are enhanced.

- The first step, however, in accomplishing this objective is to review the available approaches to determine whether the available approaches for combined or concurrent exposures can be adapted appropriately to evaluate ototoxicity from co-exposures to chemical and non-chemical stressors.

Discuss if the available approaches for combined or concurrent exposures can be adapted appropriately to evaluate ototoxicity from co-exposures to chemical and non-chemical stressors?

Challenges and/or Limitations of the Data Set

- Present approaches have not yet addressed the complexity of the interaction of effects.
- The concentration-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.
- While, effects of overexposure to noise are better studied, there is still the need to integrate the D-R information from both areas of toxicity.
- In animal studies the use of high concentrations of solvents for short intervals of time does not accurately reflect occupational exposure conditions.
- Available epi studies often lack detailed exposure histories and the recognition 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

US EPA Cumulative Risk assessment (CRA) Framework Strengths & Limitations

- In the case of US EPA's, CRA guidance notional combinations of stressors (such as "chemicals" and "noise") are mentioned, absent concrete examples, particularly in light of the current ototoxicity literature.
- Intuitively, this approach would seem applicable to and appropriate for assessing the current scenario of concurrent co-exposure to a chemical hazard and a physical hazard both of which arguably result in independent auditory deficits.

Challenges of using the US EPA CRA Framework

- The assumption of using such an approach for concurrent 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 each respective hazard apparently affect different anatomical sites comprising the auditory system.

For Discussion

- 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-Exposure Concentration” (in relation to 20 ppm OEL) Animal Studies
- No / de minimis toluene 400 ppm effect for 5 or 10 days absent noise
- Threshold exceeded at 5 consecutive days 400 ppm to become irreversible + 93 dBA Neither “solvents” nor “noise” are easily defined and are complex on their own
- Papers contrast shapes of concentration -response of curves (toluene/styrene correlation)

For Discussion….

- 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

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
- This metric 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

- Fuente A, Qiu W, Zhang M, et al. Use of the kurtosis statistic in an evaluation of the effects of noise and solvent exposures on the hearing thresholds of workers: An exploratory study. J Acoust Soc Am. 2018;143(3):1704.

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

- Work environments typically not normal or Gaussian (G) but may be described as “complex non-Gaussian (non-G)” noise
- Kurtosis of the amplitude distribution, a statistical metric that is sensitive to the peak and temporal characteristics of a noise, could be a very good descriptor of the resulting auditory damage induced by complex noise exposures.

- N= 20 for noise and 20 for noise + solventsExposed to a mixture of solvents: acetone, ethyl acetate, methyl ethyl ketone (MEK),benzene, toluene, butyl acetate, ethyl benzene, xylene, & styrene
- Mixture of solvents -Additive effects
- No dose-response relationship for hearing thresholds were observed with either of the factors considered [i.e., dose of solvent exposure alone and combined with CNE and CNE(b)]

- Fuente A, Qiu W, Zhang M, et al. Use of the kurtosis statistic in an evaluation of the effects of noise and solvent exposures on the hearing thresholds of workers: An exploratory study. J Acoust Soc Am. 2018;143(3):1704.

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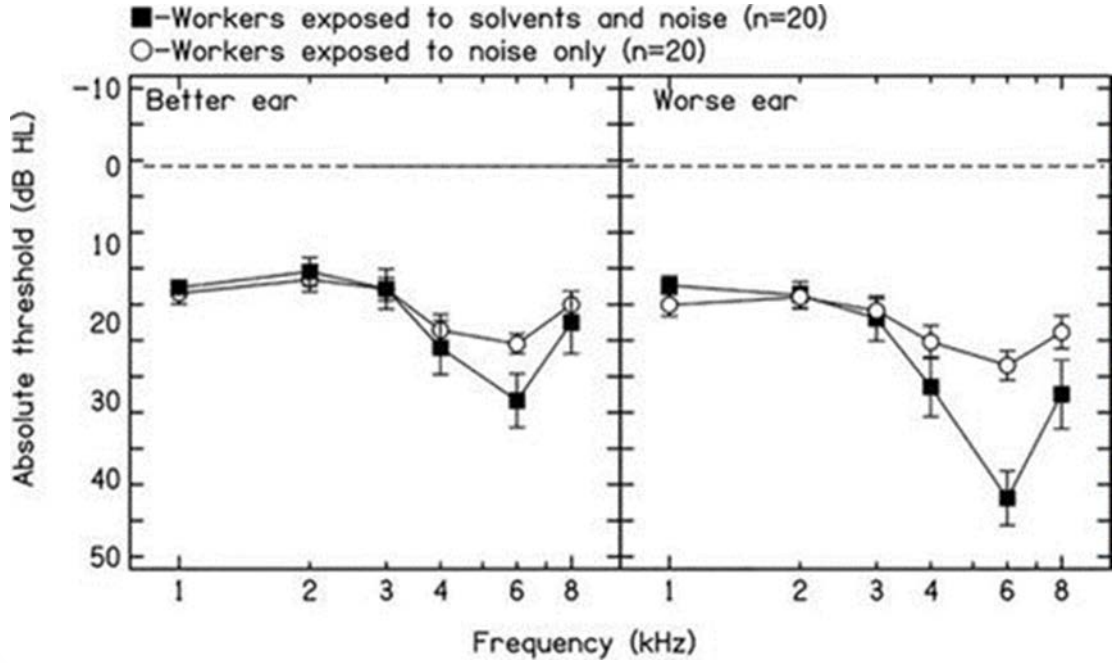


Fuente A, Qiu W, Zhang M, et al. Use of the kurtosis statistic in an evaluation of the effects of noise and solvent exposures on the hearing thresholds of workers: An exploratory study. J Acoust Soc Am. 2018;143(3):1704.

Discussion

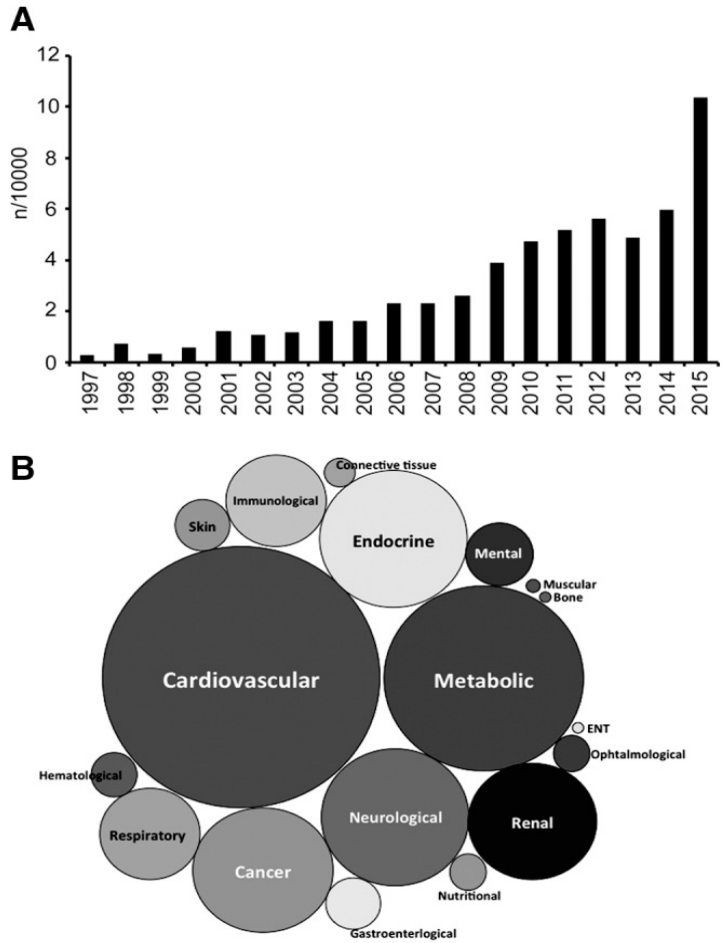
- Please comment on the use of the CNE metric to evaluate the hearing thresholds due to concurrent co-exposures to noise and solvents
- Is a separate metric needed for < 88 dBA by year?
- Is gender difference something that needs to be revisited given other papers suggesting significant modifying factors of a lifetime of different background frequencies?

Use of Biomarkers to make correlations with Disease

- According to WHO: A biomarker is any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease
- To be a clinically relevant biomarker:
  - Specificity for a certain disease (diagnostic), (ii) have prognostic value, and (iii) correlate with disease activity.

WHO. Biomarkers in Risk assessment: Validity and Validation. Geneva: WHO, 2001 [Google Scholar]

*Frijhoff J, Winyard PG, Zarkovic N, et al. Clinical Relevance of Biomarkers of Oxidative Stress. *Antioxid Redox Signal*. 2015;23(14):1144–1170. doi:10.1089/ars.2015.6317



Frijhoff J, Winyard PG, Zarkovic N, et al. Clinical Relevance of Biomarkers of Oxidative Stress. *Antioxid Redox Signal*. 2015;23(14):1144–1170. doi:10.1089/ars.2015.6317

Use of Non-Specific Biomarkers to assess HL

- Pudrith (2019) evaluated NHANES data using urinary metabolite data for the years during which audiometry readings were also collected
- Reported data on 21 urinary metabolites and correlated with HL to parent compounds using auditory oxidative stress biomarker
- Conclusions*:* Urinary metabolites may help to explain susceptibility to oxidative stress-induced hearing

National Health and Nutrition Examination Survey (NHANES) review audiometric data

- CDC during 2011–2012 conducted NHANES to analyze the most recent available data collected both by questionnaire and audiometric tests of adult participants aged 20–69 years in the) to determine the presence of hearing loss
- Noise-induced hearing loss is a significant, often unrecognized health problem among U.S. adults.
- Limitations : Audiometric notches were used as a proxy for noise-induced HL
- Other factors could have contributed to the HL: Reliance on self-reported rather than measured noise exposures, complexity of categorizing hearing loss; and co-occurrence of risk factors, including genetic predisposition, and aging.

Carroll YI, Eichwald J, Scinicariello F, et al. Vital Signs: Noise-Induced Hearing Loss Among Adults - United States 2011-2012. *MMWR Morb Mortal Wkly Rep*. 2017;66(5):139–144. Published 2017 Feb 10. doi:10.15585/mmwr.mm6605e3 (open access)

Limitations and Challenges

- Lack of validation for oxidative stress as a biomarker to correlate disease
- The oxidative stress biomarker is not very specific bioassay marker to assess biomarker of effect
- Endogenous and Exogenous sources of oxidative stress
- Are these effects of auditory oxidative stress reversible?
- Uncertainties in the data need to be presented
- Limited to no occupational exposure information
- How to define adverse effect from the results of the bioassay?
- Is auditory oxidative stress a good metric to understand the complex interaction between a physical hazard combined with a chemical substance?

Data Requirements

- Facilitate collaboration for conducting systematic reviews for ototoxicity from co-exposures to both chemicals & audible sound
- 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.

Data Requirements

- 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).

Data Requirements

- While some human correlation and epidemiologic observational studies are available (e.g., Pudrith et al. 2019) for the 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:
- Controlling/accounting for confounders
- Background information on the participants genetic, medical and/or work history
- Information on the appropriate ototoxic metabolites,
- Stronger correlations on the urinary metabolite profile and solvent exposure with hearing loss metrics.

Data Requirements

- An ideal database should include data on ototoxicity & neurotoxicity,
- 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 collaborations and partnerships to further the development and use of New Alternate Methodologies (NAMs) in the arena of ototoxicity
- Uncertainty, Specificity, and sensitivity analysis.

Challenges and/or Limitations of the Data Set

- Present approaches need to be modified to study the complex interactions
- High concentrations of solvents for short intervals of time does not accurately reflect occupational exposure conditions.
- The question of human relevance has not been 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
- 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
- Large uncertainties in epi studies and no clear dose-response
- Fortunately, effects of overexposure to noise are better studied
- However, the integration of dose-response information from both areas of toxicity is an area for future investigation and debate.

Proposed Strategy

Advance Terms of Reference (TOR) Alignment

- Revisit cumulative risk and aggregate exposure work done to date
- Conduct outreach to key companies and groups for glossary
- Ensure consistent with key regulatory considerations

Build Network of MOA / AOP SMEs and Validators

- Develop science-based standard MOA descriptions
- Compile valid and potentially related in vitro indicators that support each MOA
- Engage researchers directly for view on WOE / feedback on applied regulatory risk assessment

Refine Screening Problem Formulation

- Leverage existing expertise
- Advance synthesis of pros/cons of various aggregate approaches
- Participate in future revisiting of systematic review output
- Seek relevant biomonitoring metrics to correlations

Agree on Solutions & Best Practices

- Assess relevance of dose-response data
- Continue to develop sector-specific best practices/guidelines
- Explore novel real-time noise tracking data universe
- Identify and advance additional solutions given first-world self-monitoring, citizen science, and crowdsourcing
- Support development of appropriate safeguards and novel treatments

Support Safeguards

- Build out strategy and value proposition for effective hearing health programs and safeguards
- Reinforce prevention of hearing loss as key to total worker health
- Counter myths and conduct outreach for broader validation
- Communicate solutions and best practices to key stakeholders

Next Steps

- Conduct scoping-level problem formulation at Alliance for Risk Assessment "Beyond Science and Decisions" Workshop
- Outline terms of reference (TOR) and recruit additional subject matter experts to comment on workshop output
- Secure necessary resources for systematic review, including data quality assessment and WOE on MOA(s)
- Continue to evaluate emerging literature and weigh animal data evidence alongside relevant community or worker health data
- Focus on total worker health approaches and agile implementation of prevention/hazcom as priorities

Thank you!

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