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Ototoxicity
Something More than Noise

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Noise and Hearing Loss Overview

- Historically employees exposed to noise have been known to be at increased risk for hearing loss; primary risk factor
- OSHA regulates in general industry – 29 CFR 1910.95
- 85 decibels on the "A" scale [dBA] as an 8-hour time weighted average (TWA) as the Action Level; this "adjusts" to 83 dBA for 10 hour/82 dBA for 12 hour shifts
- Exposure over the AL requires a Hearing Conservation Program, including audiometric testing – initial and annual
- 90 dBA TWA as the Permissible Exposure Limit (PEL) – exposure in excess requires use of hearing protection and use of feasible engineering controls (does not adjust for longer shifts)
- This was the extent of the "risk" for noise induced hearing loss and it's control for many years and for many organizations

Ototoxicants Overview

- Ototoxicity = ear poisoning (oto = ear and toxicity = poisoning)
- In our context this is due to **exposure to chemicals (including drugs)** that cause **damage [resulting in hearing loss]** to the inner ear and/or vestibulo-cochlear nerve (this send balance and hearing information from inner ear to the brain)
- Ototoxicity and its effects can be **temporary or permanent**
- Ototoxic chemicals are classified as **neurotoxicants, cochleotoxicants, or vestibulotoxicants based on the part of the inner ear they damage**, and they can reach the inner ear through the blood stream and cause injury the inner ear ("hair cells") and connected neural pathways

Recent History of Ototoxic References

- For Decades (1970's or even earlier) it has been known that certain drugs – example: streptomycin –can cause hearing loss
- November 2008 the European Agency for Safety and Health at Work – (EU-OSHA) published *Combined exposure to noise and ototoxic substances*; presented the potential for independent and additive or synergistic effects of chemicals alone or combined with noise on hearing *
- NIOSH/ OSHA posted article on March 15, 2018; **

"OSHA's occupational noise exposure standard at 29 CFR 1910.95 only requires audiometric testing at the noise action level (i.e., an 85-decibel 8-hour time-weighted average). However, wearing hearing protection and using audiometric testing to detect early signs of hearing loss, even in workers exposed below the action level and ototoxic chemicals below the PEL, may prevent hearing loss from their additive/synergistic effects."

- **However, to date no change to regulations (noise/air contaminants); but mentioned as an issue in OSHA Technical Manual**

*https://osha.europa.eu/en/publications/literature_reviews/combined-exposure-to-noise-and-ototoxic-substances
**https://www.cdc.gov/niosh/docs/2018-124/default.html

Recent History of Ototoxic References

- **ACGIH TLV** Committee added Ototoxicant (OTO) Notation as a Notice of Intended Change in 2018 to highlight the potential for the chemical to cause hearing impairment alone or in combination with noise (even below 85 dBA) – adopted in 2019

  - “Chemical” with potential to cause hearing impairment alone or combined with noise exposure, even below 85 dBA TWA;

  - Substances may act synergistically with noise or potentiate noise effects; best case additive effects; worse case synergistic effect

  - Focus attention on controls (engineering, administrative and PPE) to reduce airborne concentrations and other means to prevent excessive combined exposures with noise to prevent hearing disorders

  - Place affected employees in a HCP – combined noise & CO, HCN, lead, solvent mixture exposures; and when have exposure to ethylbenzene, styrene, toluene or xylene even in absence of noise exposure

Source: ACGIH - TLV’s and BEIs Booklet – 2018 - 2020

Ototoxic Medications

Commonly Used Medications with Ototoxic Potential

Aminoglycoside Antibiotics	***Antineoplastic Drugs***
Amikacin	Cisplatin
Gentamicin*	Carboplatin
Neomycin*	Nitrogen mustard
Kanamycin	Methotrexate*
Netilmicin	Vincristine
Streptomycin*	Dactinomycin
Tobramycin*	Bleomycin
Other Antibiotics	***Antimalarial Drugs***
Erythromycin*	Quinine*
Vancomycin	Chloroquine
Chloramphenicol	Hydroxychloroquine*
Furazolidone*	Primaquine*
Polymyxin B and E	Quinidine*
Trimethoprim-sulfamethoxazole	Pyrimethamine
Loop Diuretics	***Salicylates***
Ethacrynic acid*	Aspirin
Furosemide*	Nonsteroidal anti-inflammatory agents
Bumetanide*	

*Also potentially vestibulotoxic

Source: Black & Pesznecker, 1993; Brummett, 1993; Gagnaire & Langlais, 2005 Jung, Rhee, Lee, Park, and Chol, 1993; Matz, 1993;Schweitzer, 1993; Sulkowski et al., 2002

Medications and Industrial Chemicals with Ototoxic Potential

Ototoxins that Primarily Cause Auditory (Cochlear) Toxicity	Ototoxins that Primarily Cause Vestibular Toxicity	Ototoxins that Primarily Cause Auditory and Vestibular Toxicity
Carbon monoxide	Alcohol (ethanol)	6-Amino nictonamide (6-AN)
Carboplatin	Barbiturates	Lead
Chloramphenical	Carbon disulfide	Nitrogen mustard
Cisplatin (cis-platinum)	Hexane	Nonsteroidal anti-inflammatory agents (NSAIDs)
Erythromycin	Lipid solvents	Polymixin
Loop Diuretics - Ethacrynic acid, Furosemide, Bumetanide, torsemide	Manganese	Aminoglycoside antibiotics (Amikacin, Gentamicin, Kanamycin, Neomycin, Streptomycin, Netilmicin, dihydrostreptomycin, Tobramycin
Salicylates	Marijuana	Quinine and cinchona bark preparations
Vincristine and vinblastine	Mercury	Quinine and derivatives chloroquine, quinidine, quinine, tonic water
	Minocycline	Tobacco
	Styrene	Vancomycin
	Tin	
	Toluene	
	Trichloroethylene	
	Xylene	

Source: Black & Pesznecker, 1993; Brummett, 1993; Gagnaire & Langlais, 2005 Jung, Rhee, Lee, Park, and Chol, 1993; Matz, 1993;Schweitzer, 1993; Sulkowski et al., 2002

New NIOSH/OSHA Guidance on Ototoxicity Posted

- "There is growing concern among occupational health and safety professionals that ototoxicant-induced hearing loss may go unrecognized since the measure for hearing loss does not indicate the cause," the document states.

- "For example, audiometric tests are powerful tools that show hearing impairments (i.e., threshold shifts); however, the typical audiogram does not differentiate between noise and ototoxic causes."

- “Hearing loss can be even greater with exposure to both ototoxic chemicals and noise than exposure to either noise or the ototoxic chemical alone. Many ototoxic substances have a greater-than-additive (e.g., synergistic) effect on hearing loss with noise exposure and in particular with impulse noise. 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 OSHA's Permissible Exposure Limit (PEL).

https://www.osha.gov/dts/shib/shib030818.html

ACGIH TLVs with OTO Notations as of 2021

- Styrene - 10 ppm TWA adopted 2020; reduced from 20 ppm TWA (1995)]; OTO Notation added; OSHA PEL 100 ppm since 1970s
- TLV Basis: Central nervous system (CNS) effects & **Hearing impairment**; URT irritation; peripheral neuropathy; visual disorders
- Toluene –OTO Notation adopted 2021; 20 ppm TWA (2007): OSHA PEL 200 ppm TWA
- Documentation/Basis – CNS & Visual effects and **Hearing impairment**; female reproductive system damage and pregnancy loss
- Xylene –100 ppm TWA; Notice of Intended Change (NIC) - 20 ppm TWA (2018); OTO Notation added 2020; OSHA PEL 100 ppm TWA
- Documentation/Basis – Upper respiratory tract (URT) irritation & **Hearing impairment**
- Ethyl Benzene – 20 ppm TWA (2011); NIC OTO (2020); OSHA PEL 100 ppm TWA
- Documentation/Basis – URT irritation, kidney/liver damage & **Hearing impairment**

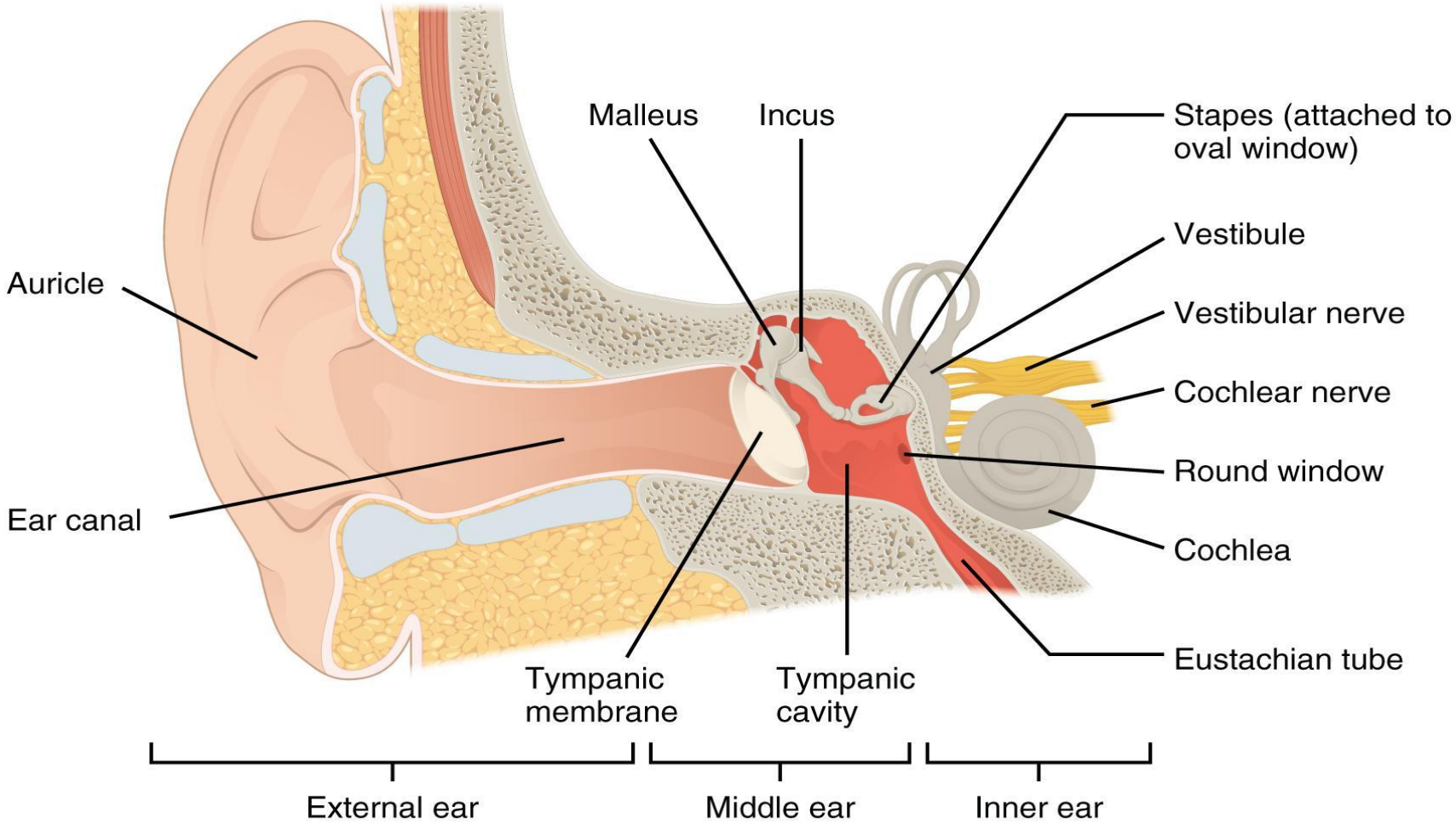
Ototoxic Effects

- Deafness due to Ototoxic Exposures – Clinical Characteristics
- Bilateral Hearing Loss – both ears – same loss (+/-) would be expected and is most common
- High Frequency Hearing Loss – generally like noise induced hearing loss – 4,000 hertz (Hz) and spreading; toluene may effect into the lower frequency – maybe even 500 Hz
- Reversible or progressive – in some cases can “recover” hearing; in others once loss is started it continues even if ototoxic exposure discontinued
- With Tinnitus (“ringing in the ears”), vertigo (balance) – depends on ototoxic exposure and its “area” of effect; example – ethanol and weaving, stumbling drunks; vestibulotoxicant

Ototoxic Substances and Noise

- Dual Exposures
- Noise and Ototoxic materials – can have a number of “effects” (not yet completely understood):
  - Singular – each on its own causes hearing loss – no interaction
  - Additive – best case for combined effects
  - Potentiate – carbon monoxide
  - Synergistic – toluene, others (lead?) – worse case
- Noise Levels
  - Effects even if exposures are <85 dBA TWA
  - Impact noise/sounds may even cause greater loss of hearing than normal when concurrent exposure to ototoxic material

The Ear and Hearing – Basic Review



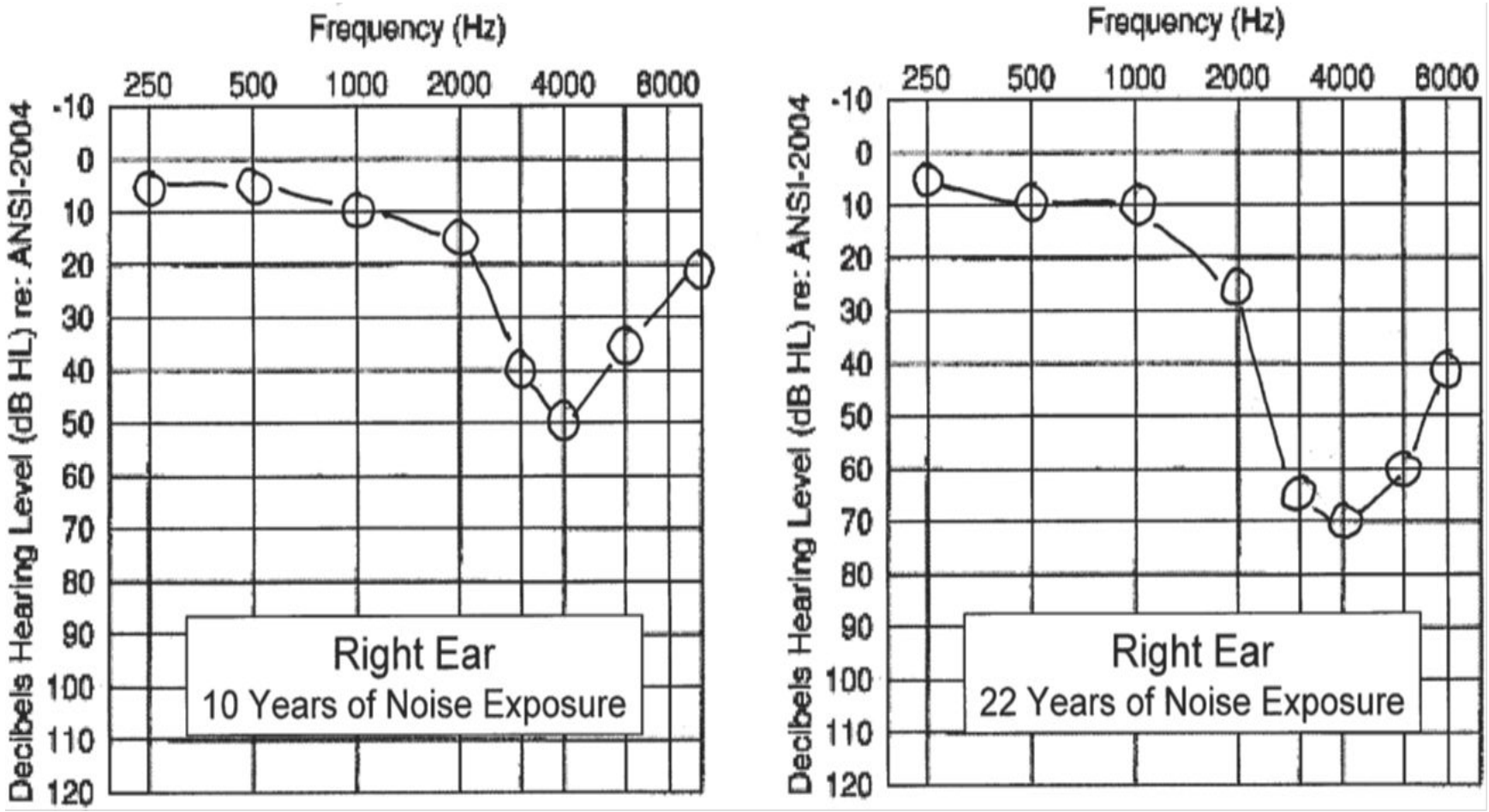
How Do We Lose Our Hearing

Mechanisms for Noise-Induced Hearing Loss

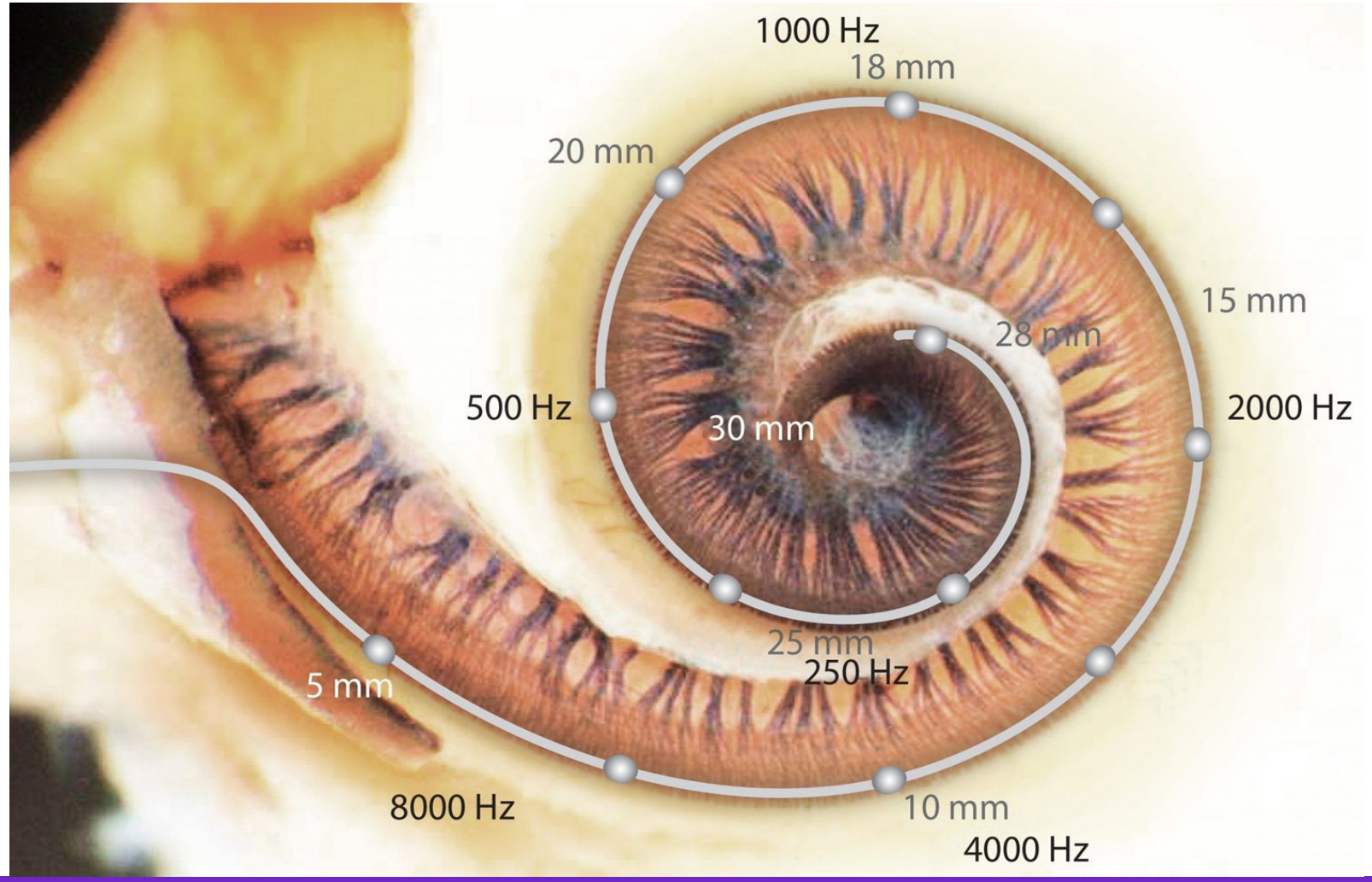
1. Mechanical (until almost the end):

- Sound waves cause the eardrum to vibrate
- Bones in middle ear transmit vibrations to cochlea
- Receptors (hair cells) in cochlea convert vibrations to electrical energy
- Brain interprets these electrical impulses as sound
- "Mechanical" Damage due to sound pressure destroying the hair cells

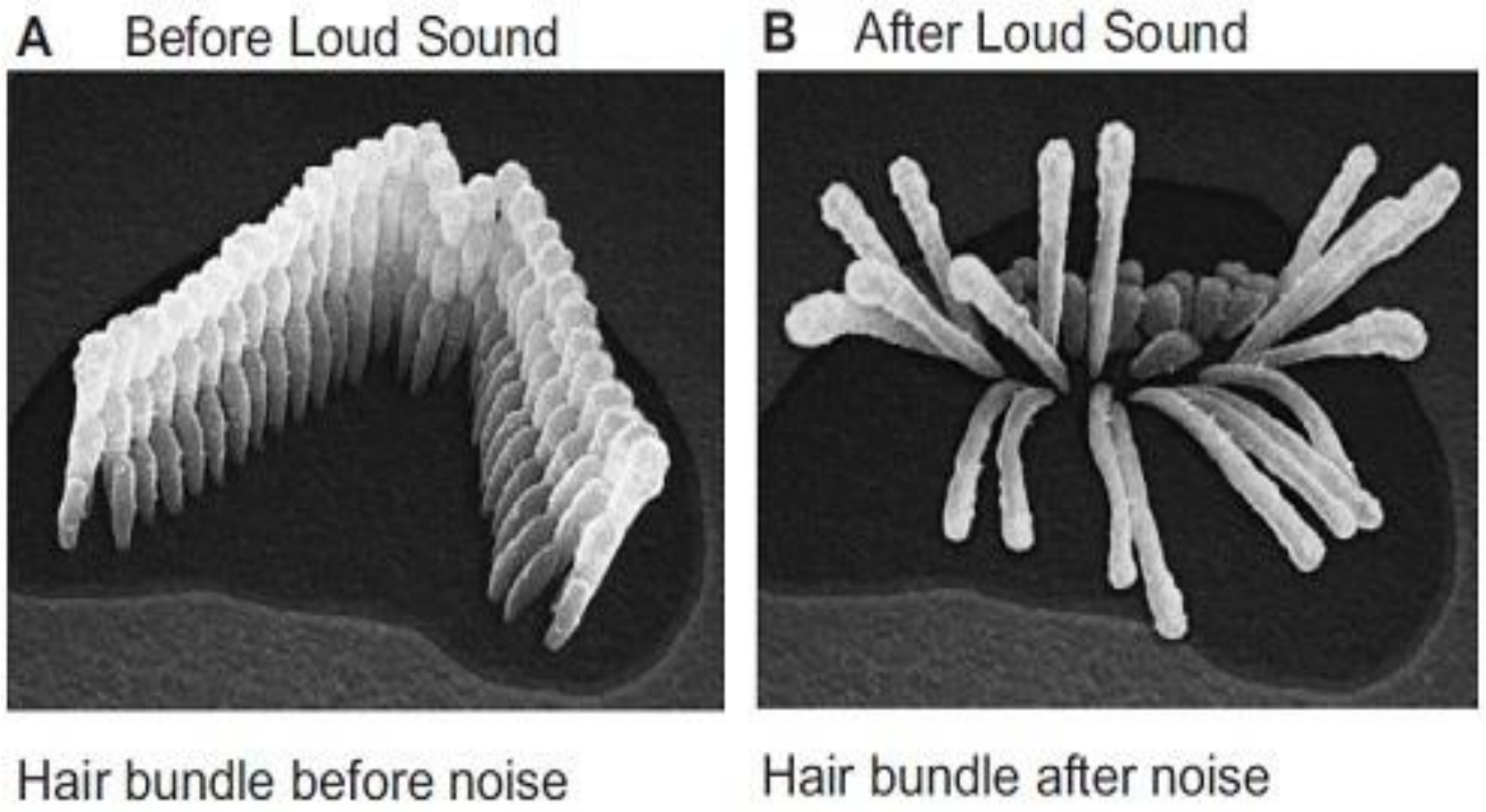
Noise Induced Hearing Loss



The Ear and Hearing – Basic Review

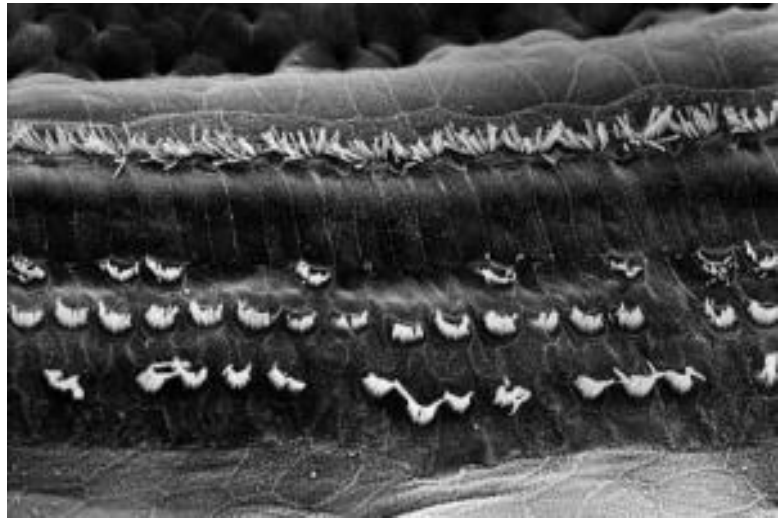


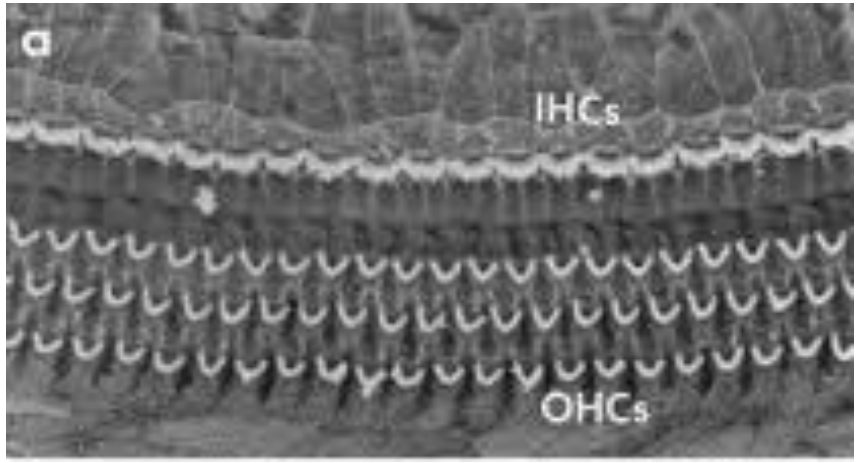
Cochlea Hair Cell Damage



Organ of Corti Hair Cells - Normal to Stage 1 Destruction

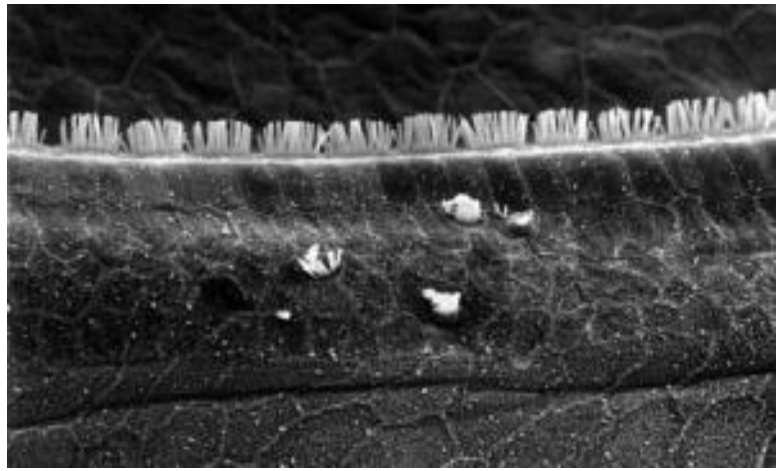
Normal aspect of the surface of the organ of Corti.





The first row of OHCs is the most affected. Little damage can be seen in the 2nd and 3rd rows, and the IHCs are intact. In the clinical population, this level of damage would manifest as a light or moderate hearing loss

Organ of Corti – Stage 2 and 3 Destruction

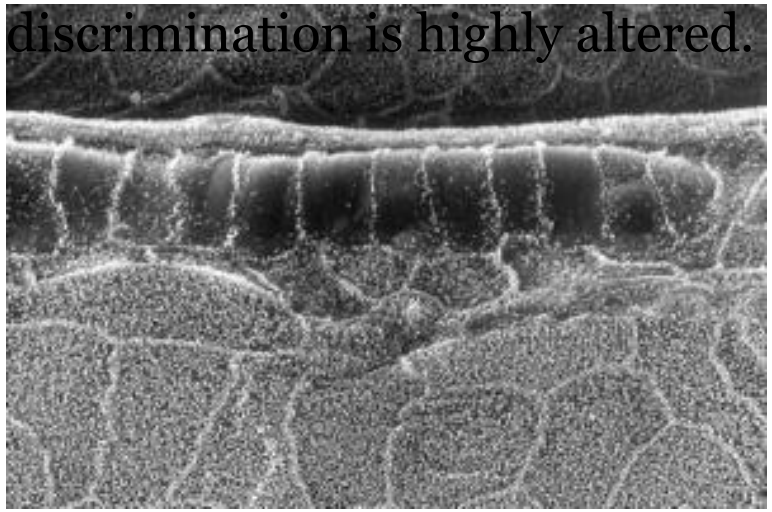


With a further increase in exposure dose IHCs have also been destroyed.

In this case, there is obviously a profound (complete) hearing loss.

A higher dose eradicates nearly all OHCs, causing the loss of the cochlea's active mechanism. The IHCs are still unaffected.

In a clinical population this level of damage manifests as a hearing loss of around 50-60 dB, and frequency discrimination is highly altered.



Clinical Manifestations - Ototoxicants

- Symptoms depend upon the person and type and dose of the agent; can vary from mild tinnitus to total hearing loss.
- Hearing Loss Should be Bilateral (both sides) – but one-sided loss is potentially possible; Sensorineural deafness
- Constant or fluctuating tinnitus; high pitched tinnitus is often the earliest symptom
- Vertigo – "dizziness", loss of balance – hair cells in the vestibule or vestibular nerve effected – probably only an ototoxic affect
- May not be able to differentiate hearing loss due to noise or ototoxicants in regular audiometric testing

Diagnosing Ototoxic Hearing Loss

Need specialized audiometric tests

1. Extended high-frequency pure-tone audiometry (EHF-PTA) - 8k to 20k
2. Distortion-product optoacoustic emission (DP-OAE)

Not your common audiometric tests – need specialized equipment;

What Does Otoxicity Mean for us in IH/Safety, Risk Management

Single Exposure to OTO

- Pay attention to “Confirmed” OTO substances – TLV notation and others “known”; weight accordingly
  - OTO designated in TLV versus “known” in literature
  - Example: Styrene (OTO) versus Xylene (NIC-OTO) versus n-hexane (known)?
- At what level is the OTO effect occur?
  - Perhaps OTO effect occur only at levels of exposure significantly above the TLV
  - So no OTO notation – as long as exposures below TLV (OEL)

Pharmaceuticals *Ototoxicity at therapeutic doses is limited	Aminoglycosidic antibiotics (e.g. streptomycin, gentamycin) and some other antibiotics (e.g. tetracyclines), Loop diuretics* (e.g. furosemide, ethacrynic acid) Certain analgesics* and antipyretics* (salicylates, quinine, chloroquine) Certain antineoplastic agents (e.g. cisplatin, carboplatin, bleomycin)
Solvents	Carbon disulfide, n-hexane, toluene, p-xylene, ethylbenzene, n-propylbenzene, styrene and methylstyrene, trichloroethylene
Asphyxiants	Carbon monoxide, hydrogen cyanide and its salts
Nitriles	3-Butenenitrile, cis-2-pentenenitrile, acrylonitrile, cis-crotononitrile, 3,3'-iminodipropionitrile
Metals and Compounds	Mercury compounds, germanium dioxide, organic tin compounds, lead

https://www.osha.gov/dts/shib/shib030818.html

The OTO Effect

- At what level is the OTO effect occur?
  - Styrene – "levels as low as 3.5 – 22 ppm – statistically significant hearing loss compared to non-exposed controls" – NIC was 2 ppm – now TLV 10 ppm?
  - N-butanol – ototoxic effect is "built" into TLV – so stay below – no issue
  - Read Documentation – use as guide; base decisions on data or lack of data
- Since exposure to OTO noted substances alone can cause hearing loss, at what levels of exposure should we require a HCP/audiograms?
  - ❖ >TLV? Or >50% TLV (AL)? **Start at >20% TLV for OTO designated per 2017 NIC TLV;** require a HCP/audiograms .

OTO Exposure

- **<u>Exposure to OTO noted substances with concurrent noise exposures</u>**; additive/synergistic effect (hearing loss) – what do we do?
  - ❖ Reduction of TLV (like additive approach)? How much?
- At what levels of exposure should we recommend a HCP/audiograms?
  - ❖ >TLV? Or >50% TLV (AL)? **Start at >20% TLV for OTO designated per 2017 NIC TLV;** require a HCP/audiograms**.**
  - ❖ **Reduce "allowable" noise levels? Use 80 dBA instead of 85 dBA? Start HCP at 80 dBA TWA exposure.**
  - ❖ Reviewers of audiograms be alert for **synergistic effects of OTO and noise.** If see this may want to consult with audiologists to do other tests like Distortion Product Otoacoustic Emissions (DPOAEs).
  - ❖ **Require mandatory use of HPD at 80 dBA TWA.**

Controlling OTO Chemicals

- What is **“good IH practice”** in controlling OTO chemicals?
  - ❖ Elimination, substitution, isolation or other engineering controls to reduce chemical and concurrent noise exposures to control both to lowest levels – Control one or both completely – then no issue; if nothing else reduce both as much as possible to reduce risk.
  - ❖ Use work procedures, job rotation, respiratory protection to reduce exposures until exposure “controlled” or if engineering controls not completely effective.
  - ❖ Since may be additive or synergistic need to reduce one or both to eliminate (synergistic) or reduce (additive) the exposure situation.
  - ❖ Make specific and comprehensive control plans

Ototoxics and Hearing Loss Claims

Prescription Drugs Usage – Non-Occupational

Ototoxic Chemical Exposures - Occupational

How to differentiate between hearing loss from noise and from ototoxics:

1. Routine Audiogram – 0.5 k to 8k
2. Extended high-frequency pure-tone audiometry (EHF-PTA) - 10k to 20k. Hearing will degrade below 8k over time. Used to detect early signs of hearing loss.
3. Distortion-product otoacoustic emission (DP-OAE)
4. Important for Cancer Patients and Chronic Ototoxic Drug Users.

Workers Compensation Considerations – i.e. Cost-Benefit

Apportionment – Settlement if medical ototoxicants are used.

Summary/Take-aways

- Hearing Loss can Occur from Other Exposures than Noise Levels above 85 dBA TWA; concurrent exposures to ototoxicants can cause Hearing Loss at Noise Exposures Below 85 dBA TWA or to ototoxicants alone
- Use of TLV vs OSHA likely to allow for earlier intervention if needed
- Examination of the list of Ototoxic compounds and determine acceptable airborne concentrations would be good practice to reduce non-noise hearing loss
- Consideration of implementing HCP with noise levels <85 dB if ototoxic compounds detected at target concentrations (80 dBA TWA)
- Hazcomm training should include information on Ototoxic and medical causes of hearing loss
- Medical Questionnaires when performing audiometric testing should include list of medicines and other recreational chemicals known to be ototoxic
- Maintain HCP – include “Marginal” Exposure Groups - Current Trend is to cut participation in HCP to save $; “penny wise and pound foolish”

Questions

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