Hearing loss prevention and Ototoxicants in the workplace

Thais C. Morata, Ph.D.

tmorata@cdc.gov

Engineering and Physical Hazards Branch

The findings and conclusions in this presentation are those of the author and do not necessarily represent the views of the National Institute for Occupational Safety and Health.
The review reported here was prepared for the Nordic Expert Group with Dr. Ann-Christin Johnson from the Karolinska Institute in Stockholm, Sweden.

www.nordicexpertgroup.org
Complexity, often used to characterize something with many parts in intricate arrangement
Great appeal for the state, quality, or an instance of being **simple**; freedom from complexity, intricacy, or division into parts

Danger of simplism, making unrealistically simple judgments or analyses
Health research is characterized by the study of single agents as if they occurred alone.

95% of the resources in toxicology are committed to single chemical investigations, as well as with noise!
What about greater-than-additive scenarios???

Synergism: occurs when both agents have an effect individually and a more than additive effect when together. \(1 + 1 > 2\)

Potentiation: is when one agent has an effect but the second does not but enhances the effect of the former agent on combined exposure. \(1 + 0 > 1\)
Ototoxicity of therapeutic drugs

- Antimalarial
- Non-steroidal anti-inflammatory
- Aminoglycosides
- Antimicrobial
- Loop diuretics
- Antineoplastic
- Chelating agents

**Mostly:**
- Vastly studied
- Effects restricted to cochlea
- Use monitored, i.e., knowledge of intake

**Approaches:**
- Substitution
- Antioxidants
Ototoxicity of environmental chemical exposures

**Mostly:**

- Relatively few studies
- Effects not restricted to the cochlea
- Use poorly monitored, i.e., poor knowledge of exposure history
- Confounded by noise

**Approaches:**

- Substitution/control of exposure
- Antioxidants
Before the 1980’s

No systematic research effort on auditory effects of environmental/occupational chemicals, but isolated reports:

- Poisoning: accidents or abuse
- Occupational exposures (painters, printers, metal, chemical, leather industry workers, etc.)
- Environmental exposures (air, food and water contamination)
During the 1980’s

The involvement of other groups: as the Swedish NIOH (later the NIWL), Johns Hopkins University, INRS, US NIOSH, etc., resulted in more evidence of auditory effects of chemicals and interactions.

Proposed Strategies for the Prevention of Leading Work-Related Diseases and Injuries, p.9 NIOSH, 1988:

• “Determine through investigations the degree of which noise interacts with other agents in the work environment (solvents, metals, prescription drugs, etc.) to affect hearing.”
Occupational hearing loss research
Endogenous & exogenous factors

Age
Gender
Lifestyle
Education

OHL
Occupational exposures
Genetics
Diet

General health
Socio-economic factors

Key minimum information to be gathered
Which chemicals have been evaluated and shown to be ototoxic?

Solvents, PCBs, asphyxiants, pesticides, metals

Recognition that hearing loss is caused by more than just noise (case reports, laboratory, clinical, epi studies).
Intoxication route

Blood burden: $C_{art}$ TOL

inhalation

Cochlear arteries

Stria vascularis

Pierre Campo, 2012
## Animal studies

<table>
<thead>
<tr>
<th>NOAEL</th>
<th>LOAEL</th>
<th>Exposure duration</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Styrene - only</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>250 ppm – 500 ppm</td>
<td>Gavage or Inhalation</td>
<td>Chen et al., 2007; Lataye et al., 2005</td>
</tr>
<tr>
<td>300</td>
<td>600</td>
<td>Inhalation 4 w</td>
<td>Mäkitie, et al 2002</td>
</tr>
<tr>
<td><strong>-combined with noise (N)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>400 + 85 dB Leq8h</td>
<td>Inhalation and N 4 w</td>
<td>Lataye et al., 2005</td>
</tr>
<tr>
<td>300 + 100-105 dB SPL</td>
<td>600 + 100-105 dB SPL</td>
<td>Inhalation and N 4 w</td>
<td>Mäkitie et al., 2003</td>
</tr>
<tr>
<td><strong>Toluene - only</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>900 -1000</td>
<td>Inhalation 14 h/d, 14 w or</td>
<td>Pryor et al 1983a; Johnson et al 1988</td>
</tr>
<tr>
<td>700</td>
<td>1 000</td>
<td>Inhalation 14 h/d,16 w</td>
<td>Pryor et al 1984b</td>
</tr>
<tr>
<td><strong>-combined with noise (N)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>500 + 87 dB Leq8h</td>
<td>-</td>
<td>Inhalation and N 90 d</td>
<td>Lund and Kristiansen 2008</td>
</tr>
<tr>
<td>500+90 dB Leq8h</td>
<td>1 000 + 90–100 dB Leq8h</td>
<td>Inhalation and N 10 d</td>
<td>Brandt-Lassen et al 2000</td>
</tr>
<tr>
<td><strong>Xylene - only</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>450 p-XYL</td>
<td>900 p-XYL</td>
<td>Inhalation 13 w</td>
<td>Gagnaire et al 2001</td>
</tr>
<tr>
<td><strong>-combined with noise (N)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Trichloroethylene - only</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>2 000</td>
<td>Inhalation 3 w</td>
<td>Rebert et al 1991</td>
</tr>
<tr>
<td>800</td>
<td>2 500</td>
<td>Inhalation 13 w</td>
<td>Albee at al 2006</td>
</tr>
<tr>
<td><strong>-combined with noise (N)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>3 000 + 95 dB SPL</td>
<td>Inhalation and N: 18 h/d, 3 w</td>
<td>Muijser et al 2000</td>
</tr>
</tbody>
</table>
## Human studies – Styrene OEL 20-100

<table>
<thead>
<tr>
<th>Exposure levels</th>
<th>Styrene groups</th>
<th>Evidence of HL shown</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S</strong>: Mean 3.5 ppm&lt;br&gt;<strong>N</strong>: S+N mean 89 dBA</td>
<td>65, S&lt;br&gt;89, S and N; 81 controls</td>
<td>++</td>
<td>Morata et al, 2002, Johnson et al, 2007</td>
</tr>
<tr>
<td><strong>S</strong>: Mean ca 5 ppm (biol. monit)&lt;br&gt;<strong>N</strong>: 73 dBA</td>
<td>32 S&lt;br&gt;60 controls (age matched)</td>
<td>++</td>
<td>Mascagni et al, 2007</td>
</tr>
<tr>
<td><strong>S</strong>: Mean 8 ppm&lt;br&gt;<strong>N</strong>: &lt; 85 dB</td>
<td>44, S; 49 S in mixt&lt;br&gt;33 controls</td>
<td>++</td>
<td>Morioka et al., 1999</td>
</tr>
<tr>
<td><strong>S</strong>: Mean 11-38 ppm&lt;br&gt;<strong>N</strong>: 70-93 dBA (&gt;85 S+N)</td>
<td>220 S&lt;br&gt;70 S and N&lt;br&gt;157 controls</td>
<td>+++</td>
<td>Sliwinska-Kowalska et al, 2003</td>
</tr>
<tr>
<td><strong>S</strong>: Mean ca 22 ppm (biol. monit)&lt;br&gt;<strong>N</strong>: not given</td>
<td>16 S&lt;br&gt;16 controls</td>
<td>-</td>
<td>Hoffman et al, 2006</td>
</tr>
<tr>
<td><strong>S</strong>: &lt; 26 ppm.&lt;br&gt;<strong>N</strong>: 80 to 89 dBA</td>
<td>170 dir exp&lt;br&gt;86 indir exp&lt;br&gt;43 controls</td>
<td>-</td>
<td>Sass-Kortsak et al, 1995</td>
</tr>
<tr>
<td><strong>S</strong>: &lt; 25 ppm.&lt;br&gt;<strong>N</strong>: not given</td>
<td>18 S&lt;br&gt;Comp to reference pop.</td>
<td>+&lt;br&gt;++ Bal</td>
<td>Möller et al, 1990</td>
</tr>
<tr>
<td><strong>S</strong>: Mean &lt; 30 ppm&lt;br&gt;<strong>N</strong>: S + N =76 dBA</td>
<td>23 S and N&lt;br&gt;12 controls</td>
<td>++</td>
<td>Morioka et al, 2000</td>
</tr>
<tr>
<td><strong>S</strong>: &lt; 35 ppm.&lt;br&gt;<strong>N</strong>:&lt; 85 dBA</td>
<td>59 S&lt;br&gt;94 controls</td>
<td>+</td>
<td>Muijser et al, 1988</td>
</tr>
<tr>
<td><strong>S</strong>: &lt; 54 ppm&lt;br&gt;<strong>N</strong>: not given</td>
<td>20 S</td>
<td>-&lt;br&gt;++ Bal</td>
<td>Calabrese et al, 1996</td>
</tr>
</tbody>
</table>
Solvents - Possible Mechanisms

- **Synergistic** interaction with noise in animal model
- **Effect on isolated OHC**
  - Dose-response shortening of OHC, more pronounced in apical end of cochlea
  - Free intracellular Ca\(^{2+}\) increased
- **Intoxication Route via Organ of Corti**
  - Toluene/Styrene concentrations highest in stria vascularis
  - Lower concentrations in supporting cells near to Organ of Corti
- **Inhibit the auditory efferent system**
  - modifying the response of the protective acoustic reflexes
- **ROS formation**
  - apoptotic cell death
Human studies on occupational exposure to Styrene

- 12 studies - 10 different groups of workers
- Different designs and out-come measures used
- Majority of studies showed effects on hearing
  - PTA not the best indicator AND Central effects also present
- Styrene exposure levels in all studies were low
- Noise not a necessary factor
  - BUT interactions with noise occur
- Styrene IS a risk factor for hearing loss

**Conclusion** LOAEL is inconclusive but suggested to be below 20 ppm (current exposure and low noise level at time of studies).
## Human studies – Toluene OEL 50-100 ppm

<table>
<thead>
<tr>
<th>Exposure levels</th>
<th>Toluene groups</th>
<th>Evidence of HL shown</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current exposures</td>
<td>Toluene groups</td>
<td>Evidence of HL shown</td>
<td>References</td>
</tr>
<tr>
<td><strong>T</strong>: low 3 ppm</td>
<td>152 low T</td>
<td>-</td>
<td>Schäper et al., 2003</td>
</tr>
<tr>
<td><strong>N</strong>: 82 dBA</td>
<td>181 high T</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T</strong>: high 26 ppm</td>
<td>49 TOL</td>
<td>(+)</td>
<td>Vrca et al., 1996</td>
</tr>
<tr>
<td><strong>N</strong>: 81 dBA</td>
<td>59 controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T</strong>: 20 ppm</td>
<td>40 T</td>
<td>(+)</td>
<td>Abate et al., 1993</td>
</tr>
<tr>
<td><strong>N</strong>: Not given</td>
<td>40 controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T</strong>: ~ 97 ppm</td>
<td>50 T+N</td>
<td>++ with N</td>
<td>Bernardi, 2000</td>
</tr>
<tr>
<td><strong>N</strong>: Not given</td>
<td>50 N</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T + N</strong>: 9-37 ppm</td>
<td>50 T+N</td>
<td>++ with N</td>
<td>Morata et al., 1997</td>
</tr>
<tr>
<td><strong>N</strong>: 88-98 dBA</td>
<td>50 N</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>N</strong>: 88-98 dBA</td>
<td>40 controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T + N</strong>: 50 ppm (in 109 workers; biol. monit.)</td>
<td>124 T (in mixture)</td>
<td>+ with N</td>
<td></td>
</tr>
<tr>
<td><strong>N</strong>: 71-93 dBA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative expo index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T + N</strong>: 176-2 265 year-ppm</td>
<td>58 TOL+N</td>
<td>++ with N</td>
<td>Chang et al., 2006</td>
</tr>
<tr>
<td><strong>N</strong>: 79-87 dBA</td>
<td>58 N</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>N</strong>: 83-90 dBA</td>
<td>58 controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T + N</strong>: 100-365 ppm</td>
<td>50 N</td>
<td>+++ with N</td>
<td>Morata et al., 1993</td>
</tr>
<tr>
<td><strong>N</strong>: 88-98 dBA</td>
<td>51 T+N</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>N</strong>: 88-98 dBA</td>
<td>50 controls</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Human studies on occupational exposure to Toluene

- 7 studies
- Different designs and outcome measures used
- Majority of studies showed effects on hearing
  - PTA not the best indicator, since central effects also present
- Toluene exposure levels in studies were moderate to high
- Noise was always present (above or below 85 dBA)
- Toluene IS a risk factor for hearing loss at least with noise

Conclusion LOAEL is approximately 50-100 ppm (current exposure and low noise level at time of studies).
Other solvents – Human studies

Mixtures (Toluene & Xylene often included)

- In animal studies additive effects have been shown for solvent pairs in high doses.
- In humans many studies with solvent mixtures have shown HL at low current exposure levels.
  - Due to differences in exposure content and levels, evidence available is not sufficient for the identification of the NOAELs and LOAELs in humans.
Other solvents – with human studies

CS₂
- Central auditory effects shown in rats
  - NOAEL 200 ppm (5 w) or 400 ppm (11 w)
  - LOAEL 800 ppm
- Central auditory effects and hearing loss shown in workers after chronic exposure
  - LOAEL above 14 ppm current exposure
Ototoxicity

Auditory cortex

Auditory nerve

Cochlea

CS₂

toluene

styrene

xylene

n-hexane

noise

Sliwinska-Kowalska, 2003
Metals

Mercury

• neurotoxicity and sensorineural hearing deficits
• excitatory effects on central auditory structures
• potassium channels may be targets

Lead

• dysfunction of the eighth cranial nerve in rats
• cochlear effects were reported in studies with monkeys
• central auditory effects in humans

Organotins - trimethyltin

• hair cell damage and vascular damage in the cochlea
• disrupts function at the synapse between the inner hair cell and the Type 1 spiral ganglion cell
Study finds Beethoven died of lead poisoning

By Rick Weiss
Washington Post

By focusing the most powerful X-ray beam in the Western Hemisphere on six of Ludwig van Beethoven's teeth, researchers found evidence he was poisoned by lead. The evidence includes lead content higher than in normal amounts found in modern-day dentists. The researchers believe the lead poisoning occurred over many years. Among the possibilities are his liberal indulgence in wine consumed from lead cups or perhaps a lifetime of medical treatments, which in the 19th century were laced with lead.
## Metals – Animal studies

<table>
<thead>
<tr>
<th>NOAEL</th>
<th>LOAEL</th>
<th>Exposure duration</th>
<th>Reference-G</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lead (blood lead level)- only</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>30 μg/dl</td>
<td>In diet: birth to 13 years of age</td>
<td>Rice 1997</td>
</tr>
<tr>
<td>35 μg/dl</td>
<td>55 μg/dl</td>
<td>In diet: prenatal to ~10 years of age</td>
<td>Lilienthal and Winneke, 1996</td>
</tr>
<tr>
<td><strong>Mercury - only</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>0.4 mg/kg bw HgCl₂</td>
<td>Gavage: daily in 12 weeks (rats)</td>
<td>Fazakas et al 2005</td>
</tr>
<tr>
<td></td>
<td>10 μg/kg/d HgCH₃Cl</td>
<td>Orally: gestation to 4 y of age</td>
<td>Rice 1998</td>
</tr>
<tr>
<td><strong>Trimethyltins - only</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 mg/kg bw</td>
<td>0.2 mg/kg bw</td>
<td>single i.p. injection</td>
<td>Liu and Fechter, 1994</td>
</tr>
<tr>
<td></td>
<td>3 mg/kg bw</td>
<td>Guinea pigs</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>single i.p. injection Rats OHC-loss</td>
<td>Crofton et al., 1990</td>
</tr>
</tbody>
</table>
Metals – Human studies

Lead
- NOAEL is not known
- LOAEL is blood lead concentrations of 12-64 μg/dl
- No interaction greater than additive between lead (57 μg/dl) and noise found
  - One study only
- Auditory effects begin to appear at blood lead levels found in the general population
  - Western Europe (37 μg/dl) and North America (17 μg/dl)

Mercury
- LOAELs; Concentration in air of 0.008 mg/m3 and mean blood mercury levels of 0.5 μg/l showed effects in central auditory tests

Trimethylnitins
- No human studies
Other chemicals

- **Asphyxiants**
  - Interfere with cell “breathing”
  - Not ototoxic alone (animal models) BUT potentiate other ototoxic agents and noise
  - Maybe by ROS formation

- **Carbon monoxide - CO**
  - Smoking

- **Hydrogen cyanide**
  - Other nitrils
Carbon monoxide – animal studies

<table>
<thead>
<tr>
<th>NOAEL</th>
<th>LOAEL</th>
<th>Exposure duration</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carbon monoxide - only</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 500 ppm</td>
<td></td>
<td>Inhalation 3.5-9.5 h</td>
<td>Chen and Fechter 1999</td>
</tr>
<tr>
<td><strong>-combined with noise (N)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>300 ppm + 95 or 100 dB</td>
<td>500 ppm + 95 or 100 dB</td>
<td>Inhalation 3.5-9.5 h, 5 d N 2 or 4 h, 5 d</td>
<td>Chen and Fechter 2000; Fechter et al 2000</td>
</tr>
<tr>
<td>300 ppm + 87 dB SPL Impulse noise</td>
<td>500 ppm + 87 dB SPL Impulse noise</td>
<td>Inhalation and N: 6 h/d, 10 d</td>
<td>Lund et al 2003</td>
</tr>
<tr>
<td><strong>Hydrogen cyanide - only</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 ppm</td>
<td></td>
<td>Inhalation: 3.5 h</td>
<td>Fechter et al 2002</td>
</tr>
<tr>
<td><strong>-combined with noise (N)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 ppm + 100 dB</td>
<td>30 ppm + 100 dB</td>
<td>Inhalation: 3.5 h N: 2 h</td>
<td>Fechter et al 2002</td>
</tr>
</tbody>
</table>

Additional stressors make it worse - 
Exposure to CO, noise AND Toluene caused even more HL than CO and noise alone (Lund, Kristiansen and Campo, 2008)
https://toxsci.oxfordjournals.org/content/58/2/315.full
Carbon monoxide

- **Animal studies**/consider safety factor
  - Interaction and potentiation with noise shown
    - NOAEL without noise 1500 ppm
    - NOAEL with noise 300 ppm
    - LOAEL with noise 500 ppm

- **Human studies**
  - Few studies of auditory effects
  - Type of interaction between carbon monoxide and noise has not been established
  - The LOAEL is inconclusive,
    - One study suggested a LOAEL of ~ 20 ppm without excessive noise exposure
Other chemicals

- **Pesticides**
  - Many different substances
  - Limited evidence because of the heterogenicity

- **PCBs**
  - Only investigated in animal studies
  - Some PCBs give auditory effects in the offspring after dosage during gestation
    - NOAEL: 0.25 μg/kg body weight/day or 1mg/kg depending of PCB mixture
    - LOAEL: 1 μg/kg body weight/day (1 mg/kg body weight/day or 3 mg/kg depending of PCB mixture)
Is there evidence for the ototoxicity of chemicals in occupational settings?

- Strongest evidence for
  - Styrene
  - Toluene
  - Mixtures of solvents
  - Lead
  - Carbon monoxide

- Dose - response relationship challenging in human studies

- Strong support from animal studies
  - Increased risk with more exposure factors
Morata et al., 2002
Hearing Difficulties:
- Sound detection
- Sound discrimination
- Speech discrimination, especially in the presence of background noise

Dysfunction of the peripheral auditory system

Evidenced by pure-tone audiometry

- Mixture of Solvents
- Toluene
- Styrene
- Carbon Disulphide
- Lead
- Mercury
Hearing Difficulties:
- Sound detection
- Sound discrimination
- Speech Discrimination in quiet and in noise, or under challenging conditions
- Sound Localization
Chemical-induced hearing loss

Chemicals

Oto-and neuro-toxicity

Tests of peripheral auditory function
Tests of central auditory function
Impact on daily-life, Quality of life
Which clinical procedures should be used when evaluating chemical induced-hearing loss?
Sensorineural hearing loss induced by xylene

From Fuente et al., 2012
Sensorineural hearing loss induced by mixtures of solvents

62 year old male painter
30 years in automobile industry
Combined exposure to organic solvents and low intensity noise (80-85 dB LeqA)

From Polizzi et al., 2003
In summary

• Pure-tone audiometry should be carried out.

• Chemical-induced hearing loss may be blurred by noise or age-related hearing loss. Thus, consider what else can be done to distinguish among causes.
Central auditory dysfunction induced by chemical exposure
Test battery approach to assess different auditory functions

- Pure-tone audiometry
- Acoustic reflex
- TEOAEs (including efferent suppression)
- DPOEAs
- ABR
- Hearing-in-Noise Test
- Dichotic digits
- Filtered Speech
- Random Gap Detection
- Auditory Test of Temporal Resolution
- Pitch Pattern Sequence
- Masking Level Difference
- Amsterdam Inventory for Auditory Disability and Handicap

Fuente et al.
Audiological test battery

Study 1

- Conventional pure-tone audiometry (250-8000 Hz)
- High-frequency pure-tone audiometry (12-16 kHz)
- Distortion product otoacoustic emissions
- Dichotic digit test
Peripheral and Central Auditory Dysfunction Induced by Occupational Exposure to Organic Solvents.
Fuente, Adrian; Slade, Martin; Taylor, Tanisha; MD, MPH; Morata, Thais; Keith, Robert; Sparer, Judy; MS, CIH; Rabinowitz, Peter; MD, MPH

Journal of Occupational & Environmental Medicine. 51(10):1202-1211, October 2009. DOI: 10.1097/JOM.0b013e3181bae17c
DPOAEs (average amplitude in dB)

Group comparisons

Group 1: 4.8 dB
Group 2: 3.3 dB
Group 3: 2 dB

DPOAEs amplitudes in dB
Dichotic Digit Test total score (%)
Group comparisons

Group 1: 86.5
Group 2: 66.1
Group 3: 61.5
Summary Study 1

- Differences for hearing thresholds were found between groups

- Workers with higher solvent exposure obtained poorer results for Dichotic Digits and lower amplitudes for DPOAEs in comparison to workers with lower exposure

- All of the audiological test results, with the exception of DPOAEs, were best predicted by solvent exposure and other covariates such as age and gender.
Audiological test battery

Study 2

- Pure-tone audiometry (250-8000 Hz)
- Hearing-in-noise test (speech discrimination in noise and in quiet -auditory figure/ground; auditory closure)
- Dichotic digit test (binaural integration)
- Filtered speech (speech discrimination of degraded speech material, auditory closure)
- Pitch pattern sequence (auditory temporal processing -temporal ordering)
- Random gap detection (auditory temporal processing -temporal resolution)
- Masking level difference (temporal interaction)
Hearing thresholds – Right ear

- Mann-Whitney U test *p<.05
- Mann-Whitney U test **p<.01

Frequencies

125 Hz  250 Hz  500 Hz*  1 kHz**  2 kHz**  3 kHz**  4 kHz*  6 kHz  8 kHz

dB HL

Exposed
Non-exposed
HINT

HINT SRT

Exposed

Non-exposed

dB SNR

Noise Front** Noise Right** Noise Left** Composite**

Exposed

Non-Exposed
Filtered speech

**Mann-Whitney U test p<.01**

<table>
<thead>
<tr>
<th></th>
<th>Non-exposed</th>
<th>Exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>FS right ear**</td>
<td>65.47</td>
<td>55.05</td>
</tr>
<tr>
<td>FS left ear**</td>
<td>66.03</td>
<td>57.89</td>
</tr>
<tr>
<td>FS combined score**</td>
<td>66.98</td>
<td>56.55</td>
</tr>
</tbody>
</table>
Pitch Pattern Sequence

**Mann-Whitney U test p < .01**
Dichotic digit test

<table>
<thead>
<tr>
<th></th>
<th>Right ear</th>
<th>Non-exposed</th>
<th>Exposed**</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Correct</td>
<td>99.01</td>
<td>93.23</td>
<td>93.48</td>
</tr>
<tr>
<td>% Correct</td>
<td>97.66</td>
<td>93.23</td>
<td>88</td>
</tr>
</tbody>
</table>

**Wilcoxon test p<.01**
Summary Study 2

- Solvent-exposed subjects obtained statistically lower scores than the control group for HINT, random gap detection, filtered speech, pitch pattern sequence and dichotic digit tests

- An abnormal right-ear advantage was observed in solvent-exposed workers

- All of the audiological test results were best predicted by solvent exposure and other covariates such as age and gender
Study 3 Noise dosimetry
Methyl Hippuric Acid in urine
Audiological test battery

Study 3

- Pure-tone audiometry (250-500 Hz)
- Distortion product otoacoustic emissions
- Auditory brainstem response
- Hearing-in-noise test (speech discrimination in noise and in quiet -auditory figure/ground; auditory closure)
- Dichotic digit test (binaural integration)
- Pitch pattern sequence (auditory temporal processing -temporal ordering)
- Auditory test of temporal resolution (auditory temporal processing -temporal resolution)
- Masking level difference (temporal interaction)
Pure-tone thresholds

- Xylene-exposed group (n=30)
- Non-exposed group (n=30)

Significant differences (p<.05)

Absence threshold (dB HL)

Frequency (kHz)

0.25  0.5  1  2  3  4  6  8

Right Ear

Left Ear
Binaural hearing thresholds and methyl hippuric acid

Spearman’s Rho = 0.37 (p=0.04)
HINT

Ototoxicity
Ann-Christin Johnson

Exposed Non-exposed

Hint 1** Hint 2 Hint 3** Hint Comp**

dB SNR

Hint 1**  Hint 2  Hint 3**  Hint Comp**

Exposed  Non-exposed
Pitch Pattern Sequence

% correct

<table>
<thead>
<tr>
<th></th>
<th>Non-exposed</th>
<th>Exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPS right ear</td>
<td>98.2</td>
<td>89.6</td>
</tr>
<tr>
<td>PPS left ear</td>
<td>97.4</td>
<td>89.0</td>
</tr>
<tr>
<td>PPS average**</td>
<td>97.8</td>
<td>89.3</td>
</tr>
</tbody>
</table>

**p<.007
Dichotic Digit Test

**p<.007

<table>
<thead>
<tr>
<th></th>
<th>Non-exposed</th>
<th>Exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>DD right ear</td>
<td>98.7</td>
<td>95.7</td>
</tr>
<tr>
<td>DD left ear</td>
<td>99.2</td>
<td>93.5</td>
</tr>
<tr>
<td>DD average**</td>
<td>98.9</td>
<td>94.6</td>
</tr>
</tbody>
</table>
Auditory Brainstem Response

**p<.05
Summary Study 3

Xylene exposed workers exhibited poorer

- Hearing thresholds
- Speech discrimination in noise
- Binaural integration (dichotic digits)
- Temporal ordering (pitch pattern sequence)
- ABR results
In conclusion

• Chemicals affect the peripheral and central auditory system.

• Workers exposed to chemicals may or may not present with hearing thresholds below 25 dB HL. However, thresholds in mid-and high-frequencies may fall below expected levels according to age.

• Workers exposed to chemicals encounter poorer listening performance in daily-life activities than their peers who are not exposed to chemicals.
In the clinical setting

- A detailed case history including history of recreational and occupational noise exposure, the type of chemicals the person has been exposed to and duration of exposures

- Possible middle-ear problems should be ruled out

- Standard pure-tone audiometry including 3 and 6 kHz

- If available, high-frequency pure tone audiometry
In the clinical setting

• Evaluation of the central auditory system with electrophysiological measures (if available) and/or behavioural procedures:
  • Dichotic listening (e.g. dichotic digit test)
  • Temporal processing (e.g. pitch pattern sequence)
  • Auditory closure (e.g. filtered speech)
  • Speech in noise (e.g. HINT)
    • Important to consider the test-retest reliability of the procedure

• Impact on daily-life listening performance, quality of life (e.g. self-report questionnaires) and look for mismatch of complaints and PTA results
For hearing conservation programs

- Detailed medical history, alcohol intake, tobacco.
- Detailed exposure history to chemicals and noise
- Standard pure-tone audiometry including 3 and 6 kHz
- If available, high frequency pure-tone audiometry and OAEs
- At least one test to evaluate the central auditory system should be carried out:
  - Dichotic digit test (approx, 5 mins)
Take home message

• Questions about exposure to chemicals should be included in the case history.

• Clinical audiologists should consider the oto-and neuro-toxic properties of chemicals and thus a comprehensive test battery should be used to evaluate chemical-induced hearing loss.
  • Pure-tone audiometry - ALWAYS compare the hearing thresholds against what is expected to the age of the person.
  • Otoacoustic emissions
  • ABR
  • Dichotic digit test
  • Filtered speech
  • Frequency pattern test
  • Speech-in-noise tests (e.g. HINT)
Take home message

• Workers exposed to ototoxic chemicals should be incorporated in hearing conservation programs regardless their noise exposure levels.

• Procedures such as pure-tone audiometry, otoacoustic emissions and the dichotic digit test can be used to monitor the auditory system.

• Self-reported questionnaires about listening performance can also be used to screen possible adverse effects of chemicals on the auditory system.

1998-2016

TLVs® and BEIs®:

“Exposure to certain chemicals may also result in hearing loss. In settings in which there may be exposure to noise as well as toluene, lead,... periodic audiograms are advised and should be carefully reviewed.”
Position Papers


ACOEM Evidence-based Statement Noise-induced Hearing Loss, JOEM 2003, 2012:

“Clinicians evaluating cases of possible noise-induced hearing loss should keep in mind the following clinical concerns:...
Coexposure to ototoxic agents, such as solvents, heavy metals and tobacco smoke, may act in synergy with noise to cause hearing loss”.
US Army Regulation 1998-2016

Dept. of the Army Pamphlet 40-501 Hearing Conservation Program: Requires consideration of ototoxic chemical exposures for program inclusion, particularly when in combination with marginal noise (¶ 3-3).


Fact Sheet 51-002-0903 suggests Action Level for chemicals for inclusion in Hearing Conservation Program.

The European Community directive on noise (2003/10 EC noise) requires that the interaction between noise and work-related ototoxic substances, and noise and vibration be taken into account in the risk assessment of exposed populations. (Article 4 of Section II)


Countries (Australia, New Zealand, Brazil) started to accept link between chemical exposure and hearing loss in compensation cases.

Occupational exposure to chemicals

• Ototoxic chemicals DO increase the risk for hearing loss

• OELs for chemicals do not account for ototoxicity

• New EU Noise directive
  • Acknowledge ototoxic substances in risk assessment

• Consideration ought to be given for the inclusion of workers exposed to ototoxic chemicals should in Hearing Loss Prevention Programs
Laws and Standards

Change in Toxicity label due to ototoxic effects

"I TOLD YOU WE SHOULD HAVE READ THE SOLVENT INSTRUCTIONS CAREFULLY!"
Combined exposure to noise and ototoxic substances

• Review of literature
• Strength of evidence
• Gaps in research and regulations and
• Perspectives considering individual countries, the Global Harmonised System and REACH

Information dissemination is very important

- Which chemicals are ototoxic?
- Acknowledge ototoxic substances in standards, but HOW??


http://www.av.se/dokument/inenglish/legislations/eng1118.pdf
The problem is complex, but... can the solution be simple?
Remediation

Develop simple and clear messages

CLEAN IT UP and QUIET IT DOWN!

• Reduce hazardous exposures, thinking of the big picture
  • Engineering controls, Buy-Quiet, Design Quiet
  • Protective equipment (e.g. respirators, gloves)
• Education of the potentially affected population
Research, policy and practice

- Information to scientists
- Information to policy makers
- Information to general public
- Publication of guidelines, best practices in different formats
- Regulation
- Awards and Incentives
Thank you! Any questions?

Thais C. Morata, Ph.D.
tmorata@cdc.gov