Audiological Evaluation of and Prevention Strategies for Chemical-induced Hearing Loss

Adrian Fuente, Ph.D.
a.fuente@uq.edu.au
and
Thais C. Morata, Ph.D.
tmorata@cdc.gov

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.
Acknowledgement

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
<table>
<thead>
<tr>
<th>Therapeutic class</th>
<th>Ototoxicity recognized</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heavy metals</td>
<td>11th century</td>
<td>mercury</td>
</tr>
<tr>
<td>Antimalarial drugs</td>
<td>1843</td>
<td>quinine, chloroquine</td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory drugs</td>
<td>1877</td>
<td>salicylate (aspirin), fenprofen, ibuprofen, indomethacin, naproxen, phenylbutazone, sulindac</td>
</tr>
<tr>
<td>Anthelmintics</td>
<td>late 19th century</td>
<td>oil of chenopodium (worm seed oil)</td>
</tr>
<tr>
<td>Arsenicals</td>
<td>early 20th century</td>
<td>atoxyl, salvarsan</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>1945</td>
<td>streptomycin, amikacin, gentamicin, kanamycin, neomycin, netilmicin, paromomycin, tobramycin</td>
</tr>
<tr>
<td>Other antimicrobial agents</td>
<td>1960s</td>
<td>chloramphenicol, colistin, erythromycin, minocycline, polymyxin B, vancomycin</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>1960s</td>
<td>ethacrynic acid, bumetanide, furosemide</td>
</tr>
<tr>
<td>Industrial solvents and chemicals</td>
<td>1970s</td>
<td>toluene, organotins, carbon monoxide, potassium bromate</td>
</tr>
<tr>
<td>Topical disinfectants</td>
<td>1970s</td>
<td>chlorhexidine</td>
</tr>
<tr>
<td>Antineoplastic drugs</td>
<td>1970s</td>
<td>bleomycin, carboplatin, cisplatin, dichloromethotrexate, nitrogen mustard, vinblastine, vincristine</td>
</tr>
<tr>
<td>Chelating agents</td>
<td>after 1980</td>
<td>deferoxoxamine</td>
</tr>
</tbody>
</table>
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

- Metals
- Solvents
- Asphyxiants
- Pesticides
- PCBs
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

Key minimum information to be gathered

- Age
- Gender
- Lifestyle
- Education

OHL

Occupational exposures

Genetics

Diet

General health

Socio-economic factors
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). Interactions between factors often occur.
# Animal studies

<table>
<thead>
<tr>
<th>NOAEL</th>
<th>LOAEL</th>
<th>Exposure duration</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Styrene - only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>250 ppm - 500 ppm</td>
<td>Gavage or Inhalation 3 w - 4 w</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>-combined with noise (N)</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>Toluene - only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>900 -1000</td>
<td>Inhalation14 h/d, 14 w or 6 h/d, 2-4 w</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>-combined with noise (N)</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>Xylene - only</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>-combined with noise (N)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trichloroethylene - only</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>-combined with noise (N)</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-

<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</td>
<td>65, S</td>
<td>++</td>
<td>Morata et al, 2002, Johnson et al, 2007</td>
</tr>
<tr>
<td><strong>N</strong>: S+N mean 89 dBA</td>
<td>89, S and N</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td><strong>S</strong>: Mean ca 5 ppm</td>
<td>32 S</td>
<td>++</td>
<td>Mascagni et al, 2007</td>
</tr>
<tr>
<td><strong>N</strong>: 73 dB(A)</td>
<td>60 controls (age matched)</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td><strong>S</strong>: Mean 8 ppm</td>
<td>44, S; 49 S in mixt</td>
<td>++</td>
<td>Morioka et al., 1999</td>
</tr>
<tr>
<td><strong>N</strong>: &lt; 85 dB</td>
<td>33 controls</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td><strong>S</strong>: Mean 11-38 ppm</td>
<td>220 S</td>
<td>+++</td>
<td>Sliwinska-Kowalska et al, 2003</td>
</tr>
<tr>
<td><strong>N</strong>: 70-93 dBA (&gt;85 S+N)</td>
<td>70 S and N</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td><strong>S</strong>: Mean ca 22 ppm</td>
<td>16 S</td>
<td>-</td>
<td>Hoffman et al, 2006</td>
</tr>
<tr>
<td><strong>N</strong>: not given</td>
<td>16 controls</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>S</strong>: &lt; 26 ppm.</td>
<td>170 dir exp</td>
<td>-</td>
<td>Sass-Kortsak et al, 1995</td>
</tr>
<tr>
<td><strong>N</strong>: 80 to 89 dBA</td>
<td>86 indir exp</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>S</strong>: &lt; 26 ppm.</td>
<td>43 controls</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>N</strong>: not given</td>
<td>18 S</td>
<td>+</td>
<td>Möller et al, 1990</td>
</tr>
<tr>
<td><strong>S</strong>: Mean 5-38 ppm</td>
<td>18 S</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td><strong>N</strong>: 70-93 dBA (&gt;85 S+N)</td>
<td>157 controls</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td><strong>S</strong>: &lt; 25 ppm.</td>
<td>157 controls</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td><strong>N</strong>: not given</td>
<td>23 S and N</td>
<td>++</td>
<td>Morioka et al, 2000</td>
</tr>
<tr>
<td><strong>S</strong>: Mean &lt; 30 ppm</td>
<td>23 S and N</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td><strong>N</strong>: S + N =76 dBA</td>
<td>12 controls</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td><strong>S</strong>: &lt; 35 ppm.</td>
<td>59 S</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td><strong>N</strong>: &lt; 85 dBA</td>
<td>94 controls</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td><strong>S</strong>: &lt; 54 ppm</td>
<td>20 S</td>
<td>-</td>
<td>Calabrese et al, 1996</td>
</tr>
<tr>
<td><strong>N</strong>: not given</td>
<td><strong>Bal</strong></td>
<td><strong>Bal</strong></td>
<td></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>
</table>
| **Current exposures**
| T= Toluene, N= Noise | | |
| **T:** low 3 ppm  N 82 dBA | 152 low T 181 high T | - | Schäper et al., 2003 |
| **T:** high 26 ppm  N 81 dBA | | | |
| **T:** 20 ppm  N: Not given | 49 TOL 59 controls | (+) | Vrca et al., 1996 |
| **T:** ~ 97 ppm  N: Not given | 40 T 40 controls | (+) | Abate et al., 1993 |
| **T + N 9-37 ppm**
| **N:** 88-98 dBA | 50 T+N 50 N 40 controls | ++ with N | Bernardi, 2000 |
| **T + N** | | | |
| **T + N** | | | |
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 – human studies

\( \text{CS}_2 \)

- 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
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 which evidence now suggests 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 18th century...
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
# Metals – Animal studies

<table>
<thead>
<tr>
<th>Metals - only</th>
<th>NOAEL</th>
<th>LOAEL</th>
<th>Exposure duration</th>
<th>Reference-G</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead (blood lead level)</td>
<td>-</td>
<td>30 µg/dl</td>
<td>In diet: birth to 13 years of age</td>
<td>Rice 1997</td>
</tr>
<tr>
<td></td>
<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>Mercury - only</td>
<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></td>
<td>10 µg/kg/d HgCH₃Cl</td>
<td>Orally: gestation to 4 y of age</td>
<td>Rice 1998</td>
</tr>
<tr>
<td>Trimethyltins - only</td>
<td>-</td>
<td>0.2 mg/kg bw</td>
<td>single i.p. injection Guinea pigs</td>
<td>Liu and Fechter, 1994</td>
</tr>
<tr>
<td></td>
<td>2 mg/kg bw</td>
<td>3 mg/kg bw</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 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>Carbon monoxide - only</td>
<td>1 500 ppm</td>
<td>Inhalation 3.5-9.5 h</td>
<td>Chen and Fechter 1999</td>
</tr>
<tr>
<td>-combined with noise (N)</td>
<td>300 ppm + 95 or 100 dB</td>
<td>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 Leq8h impulse noise</td>
<td>500 ppm + 87 dB SPL Leq8h impulse noise</td>
<td>Inhalation and N: 6 h/d, 10 d</td>
<td>Lund et al 2003</td>
</tr>
<tr>
<td>Hydrogen cyanide - only</td>
<td>50 ppm</td>
<td>Inhalation: 3.5 h</td>
<td>Fechter et al 2002</td>
</tr>
<tr>
<td>-combined with noise (N)</td>
<td>10 ppm + 100 dB</td>
<td>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)
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
Audiological evaluation of chemical-induced hearing loss
Dysfunction of the peripheral auditory system

Evidenced by pure-tone audiometry

- Mixture of Solvents
- Toluene
- Styrene
- Carbon Disulphide
- Lead
- Mercury
Dysfunction of the Central Auditory System

Electrophysiological Measurements:

- Mixture of Solvents
  - Toluene
  - Styrene
  - Carbon Disulphide
- Lead
- Mercury
Directions for further research
(NoiseChem)

- Occupational hearing loss surveillance
  - Pure tone audiometry (often insufficient)

- Consensus conference
  - Called for evaluation with more complex audiometric test batteries
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?
Let’s start from the basics
What would you do in this case?

33-year-old male patient
Sensorineural hearing loss induced by xylene
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)
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
Directions for further research (NoiseChem)

- Occupational hearing loss surveillance
  - Pure tone audiometry (insufficient)

- Consensus conference
  -Called for evaluation with more complex audiometric test batteries
Test battery approach to assess different auditory functions

- Detection of sounds
- Speech discrimination in quiet and in noise
- Temporal processing, including temporal resolution
- Binaural integration (inter-hemispheric transfer, dichotic listening)
- Binaural interaction
- Auditory closure and sound segregation
- OHC function, OAEs
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

3 studies evaluated audiological tests for solvent-exposed populations


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

DOI: 10.1097/JOM.0b013e3181bae17c
DPOAEs (average amplitude in dB)
Group comparisons

<table>
<thead>
<tr>
<th>Group</th>
<th>DPOAEs amplitudes in dB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>4.8</td>
</tr>
<tr>
<td>Group 2</td>
<td>3.3</td>
</tr>
<tr>
<td>Group 3</td>
<td>2</td>
</tr>
</tbody>
</table>
Dichotic Digit Test total score (%)
Group comparisons

- Group 1: 86.5%
- Group 2: 66.1%
- Group 3: 61.5%
Multivariate linear regression analysis

Test results significantly predicted by solvent exposure

- Conventional pure-tone audiometry
- High frequency pure-tone audiometry
- Dichotic Digit Test

Test results not significantly predicted by solvent exposure

- DPOAEs (age, gender, race)
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

**Frequencies**

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

**dB HL**

- 0
- 5
- 10
- 15
- 20

**Exposure Groups**

- Exposed
- Non-exposed

*Mann-Whitney U test p<.05  
**Mann-Whitney U test p<.01*
Pitch Pattern Sequence

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

Non-exposed
Exposed

FS right ear**
65.47, 55.05

FS left ear**
66.03, 57.89

FS combined score**
66.98, 56.55

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

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

**Wilcoxon test p<.01**
Self-reported hearing performance - Amsterdam Inventory for Auditory Disability and Handicap
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
AUC ROC

Area under ROC curve = 0.7022
Binaural hearing thresholds and methyl hippuric acid

Spearman’s Rho = 0.37 (p=0.04)
HINT

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

% correct

98.7  99.2  98.9

95.7  93.5  94.6

DD right ear  DD left ear**  DD average**

Non-exposed  Exposed

** p<.007
Auditory Brainstem Response
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.
Current best practices guidelines, standards and legislation

http://www2a.cdc.gov/nioshtic-2/default.asp
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.”
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
US Army Regulation 1998-2012

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.

Position Papers


Vyskocil, A. Weight of evidence approach
http://www.irsst.qc.ca/en/utOto.htm
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.”
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)*

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

Laws and Standards

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

Brazil/ Decree no. 3048/ May 6, 1999

Australia/New South Wales

Australia-New Zealand AS/NZS 1269:2005 Occupational Noise Management/Informative Appendix on Ototoxic Agents requiring hearing tests for those exposed to ototoxic agents

Dec 2011 Code of Practice Managing Noise and Preventing Hearing Loss at Work
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
Remediation

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
Thank you! Any questions?

Adrian Fuente a.fuente@uq.edu.au

Thais Morata tmorata@cdc.gov