The interaction between chemical and physical agents: the example of ototoxicants and noise

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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

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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 Effects Research

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

- 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
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 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><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 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><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>- 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><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>- 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 20-100

<table>
<thead>
<tr>
<th>Exposure levels</th>
<th>Styrene groups</th>
<th>Evidence of HL shown</th>
<th>References</th>
</tr>
</thead>
</table>
| **S**: Mean 3.5 ppm  
**N**: S+N mean 89 dBA | 65, S  
89, S and N;  
| **S**: Mean ca 5 ppm (bion. monit)  
**N**: 73 dB(A) | 32 S  
60 controls (age matched) | ++ | Mascagni *et al*, 2007 |
| **S**: Mean 8 ppm  
**N**: < 85 dB | 44, S;  
49 S in mixt  
33 controls | ++ | Morioka *et al.*, 1999 |
| **S**: Mean 11-38 ppm  
**N**: 70-93 dB(A) (>85 S+N) | 220 S  
70 S and N  
157 controls | +++ | Sliwinska-Kowalska *et al*, 2003 |
| **S**: Mean ca 22 ppm (bion. monit)  
**N**: not given | 16 S  
16 controls | - | Hoffman *et al*, 2006 |
| **S**: < 26 ppm.  
**N**: 80 to 89 dBA | 170 dir exp  
86 indir exp  
43 controls | - | Sass-Kortsak *et al*, 1995 |
| **S**: < 25 ppm.  
**N**: not given | 18 S  
Comp to reference pop. | +  
++ Bal | Möller *et al*, 1990 |
| **S**: Mean < 30 ppm  
**N**: S + N =76 dB(A) | 23 S and N  
12 controls | ++ | Morioka *et al*, 2000 |
| **S**: < 35 ppm.  
**N**: < 85 dB | 59 S  
94 controls | + | Muijser *et al*, 1988 |
| **S**: < 54 ppm  
**N**: not given | 20 S | -  
++ Bal | Calabrese *et al*, 1996 |
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 outcome 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 T= Toluene, N= Noise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T:</strong> low 3 ppm      N 82 dBA</td>
<td>152 low T 181 high T</td>
<td>-</td>
<td>Schäper et al., 2003</td>
</tr>
<tr>
<td><strong>T:</strong> high 26 ppm     N 81 dBA</td>
<td>49 TOL 59 controls</td>
<td>(+)</td>
<td>Vrca et al., 1996</td>
</tr>
<tr>
<td><strong>T:</strong> 20 ppm</td>
<td>40 T 40 controls</td>
<td>(+)</td>
<td>Abate et al., 1993</td>
</tr>
<tr>
<td><strong>N:</strong> Not given</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T:</strong> ~ 97ppm</td>
<td>50 T+N 50 N 40 controls</td>
<td>++ with N</td>
<td>Bernardi, 2000</td>
</tr>
<tr>
<td><strong>N:</strong> Not given</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T + N</strong> 9-37 ppm</td>
<td>50 T+N 50 N 40 controls</td>
<td>++ with N</td>
<td>Morata et al., 1997</td>
</tr>
<tr>
<td><strong>N</strong> 88-98 dBA</td>
<td></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)+N</td>
<td>+ with N</td>
<td>Morata et al., 1997</td>
</tr>
<tr>
<td><strong>71-93 dBA</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Cumulative expo index</td>
<td>58 TOL+N 58 N 58 controls</td>
<td>++ with N</td>
<td>Chang et al., 2006</td>
</tr>
<tr>
<td><strong>T + N</strong> 176-2 265 year-ppm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>N</strong> 79-87 dBA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T + N</strong> 100-365 ppm</td>
<td>50 N 51 T+N 50 controls</td>
<td>+++ with N</td>
<td>Morata et al., 1993</td>
</tr>
<tr>
<td><strong>N</strong> 88-98 dBA</td>
<td></td>
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</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

$\text{CS}_2$

- 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
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 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 – 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 Guinea pigs</td>
<td>Liu and Fechter, 1994</td>
</tr>
<tr>
<td></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 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

Trimethyltins
• 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>1500 ppm</td>
<td>Inhalation 3.5-9.5 h</td>
<td>Chen and Fechter 1999</td>
<td></td>
</tr>
<tr>
<td>-combined with noise (N)</td>
<td></td>
<td></td>
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</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</td>
<td>Chen and Fechter 2000; Fechter et al 2000</td>
</tr>
<tr>
<td>300 ppm + 87 dB SPL</td>
<td>500 ppm + 87 dB SPL</td>
<td>Inhalation and N: 6 h/d, 10 d</td>
<td>Lund et al 2003</td>
</tr>
<tr>
<td>Leq8h impulse noise</td>
<td>Leq8h impulse noise</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hydrogen cyanide - only</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 ppm</td>
<td>Inhalation: 3.5 h</td>
<td>Fechter et al 2002</td>
<td></td>
</tr>
<tr>
<td>-combined with noise (N)</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)
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
Threshold (dB HL)

Frequency (kHz)

- Control
- Noise
- Styrene
- Styrene & Noise

Best ear

Morata et al., 2002
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 1998-2014

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?
Tool for cumulative risk assessment

An expert system known as “Mixie” is a useful tool that can assist in applying the mixture formula for exposure combinations.

Mixie was developed by the Canadian L'Institut de Recherche Robert-Sauvé en Santé et en Sécurité du Travail (IRSST) and is available at:

What else can we all do?

Tell everybody about it!!!

Improve the exchange of information on evidence-based practices. Share your stories, so many avenues exist today for us to reach out to the general public and health community!

If you need us, tweet us!

The National Institute for Occupational Safety and Health (NIOSH) tweets regularly. Please join the conversation.

twitter.com/niosh
twitter.com/NIOSHNoise
twitter.com/SafeinSoundUS

On Noise
- Workplace Hearing Loss (an overview)
- Are your ears really protected? Find out with NIOSH’s QuickFacts.
- Take Aim at Protecting yourself: Solutions for Preventing Lead Poisoning and Hearing Loss at Indoor Firing Ranges
- Vuvuzelas: What’s the Buzz? (Noise hazards during the World Cup)
- High Speeds, Higher Decibels (Noise in Stock Car Racing)
- These go to 11, But don’t go one louder: Preventing auditory effects of music exposure

Recipient of the 2011 National Hearing Conservation Association Media Award

Join the Discussion!

The NIOSH Science Blog provides a mechanism for NIOSH to reach people in a format that they are increasingly comfortable using. Through the blog and the resources provide within the posts, users have accessed documents and prevention materials that they otherwise may not have. NIOSH encourages users to post comments on articles, and provides a space for readers to post information of use to the NIOSH community such as conference information, recent publications, practical applications, and ideas for future research.

Check out the blogs and send us your idea for the next noise-related post!
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?

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