Ototoxicity of industrial chemicals alone or in combination with noise**

p-tert-Butyltoluene

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Introduction

There is increasing epidemiological evidence that exposure to some solvents, metals, asphyxiants and other substances is associated in humans with a risk of hearing loss. On the contrary, the interaction of chemicals and noise has received little attention. This project was undertaken to develop a database of toxicological data from the primary literature, allowing the identification of ototoxic substances and substances that interact with the noise present in the work environment. Critical toxicological data were compiled for chemical substances included in the Quebec regulation (Regulation Respecting Occupational Health and Safety).

Methods

The data were evaluated only for realistic exposure concentrations up to:
- the short-term exposure limit value, or
- the ceiling value, or
- 5 times the 8-h time weighted average exposure limit value (TWAEV) for human data, or
- 100 times the 8-h TWAEV or the ceiling value for animal studies.

We took into consideration the number of studies and for each study the following parameters: studied species, number of subjects or animals, exposure route, characteristics of control groups, exposure levels, audiometric and statistical tests, dose/effect relationship and when available, mechanisms of action.

Using a systematic weight of evidence approach, the information from both human and animal studies was examined. At first, a weight of evidence qualifier was given for both the ototoxicity and the interaction with noise: "strong", "medium", "weak", "absent" or "no study found". Note that weight of evidence qualifier "absent" should not be regarded as evidence that a substance is not ototoxic or that it does not interact with noise.

We built a weight of evidence table (see Table 1) that allowed us to combine the information from both human and animal studies on ototoxicity of chemicals and their interaction with noise. Human data were given more weight in the overall assessment. For example, a "strong" evidence from animal studies combined with an "absence" of evidence from the available human studies yielded a "medium" evidence overall.

Regarding the final conclusion about the ototoxic potential of substances or their interaction with noise, a substance bearing an overall qualifier of "strong evidence" of ototoxicity or interaction with noise was considered as an "ototoxic substance" or as a substance for which there is an "evidence of interaction" with noise. Those with "medium evidence" overall were rated "possibly ototoxic" or "possible interaction". We considered the ototoxic potential of those with only "weak evidence" as "non conclusive". Finally, those for which there was absence of evidence bore the mention "no evidence" of ototoxicity or interaction with noise.

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3 École d'orthophonie et d'audiologie, Université de Montréal
### Table 1
Weight of evidence approach for the assessment of ototoxicity and interaction with noise of industrial chemicals

<table>
<thead>
<tr>
<th>Human studies</th>
<th>Animal studies</th>
<th>Overall</th>
<th>Conclusion about ototoxicity</th>
<th>Conclusion about the interaction substance / noise</th>
</tr>
</thead>
<tbody>
<tr>
<td>S</td>
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<td>O</td>
<td>I</td>
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<tr>
<td>S</td>
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<td>I</td>
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</tr>
<tr>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

**Strength of evidence about ototoxicity or interaction substance / noise**

S = Strong, M = Medium, W = Weak, A = Absent, X = No study found

**Conclusion about ototoxicity**

O = Ototoxic substance, PO = Possibly ototoxic substance, NC = Non conclusive, NE = No evidence, X = No documentation

**Conclusion about the interaction substance / noise**

I = Evidence of interaction, PI = Possible interaction, NC = Non conclusive, NE = No evidence, X = No documentation
Abbreviations

TWAEV : 8 h time weighed average exposure [limit] value in Quebec
D-TWAEV : Calculated inhaled dose for pulmonary ventilation of 10 m³/d and body weight of 70 kg
Ceiling : Ceiling exposure [limit] value in Quebec
D-Ceiling : Calculated inhaled dose for pulmonary ventilation of 10 m³/d and body weight of 70 kg
STEV : Short term exposure [limit] value in Quebec
C/D reported : Reported concentration or reported dose
CSU/DSU : Reported concentration expressed in standard units of mg/m³ or reported dose expressed in standard units of mg/kg/d
Ratio : For concentrations CSU/TWAEV or CSU/Ceiling and for doses DSU/ D-TWAEV or DSU/D-Ceiling
ASM : Air sampling method
BM : Biological monitoring results
NSM : Noise sampling method
NL : Noise levels
SPL : Sound pressure level
### Conclusion about ototoxicity

**No evidence**

#### Strength of evidence

<table>
<thead>
<tr>
<th>From human studies:</th>
<th>No study found</th>
</tr>
</thead>
<tbody>
<tr>
<td>From animal studies:</td>
<td>Absent</td>
</tr>
<tr>
<td>Overall:</td>
<td>Absent</td>
</tr>
</tbody>
</table>

### Conclusion about interaction with noise

**No documentation**

#### Strength of evidence

<table>
<thead>
<tr>
<th>From human studies:</th>
<th>No study found</th>
</tr>
</thead>
<tbody>
<tr>
<td>From animal studies:</td>
<td>No study found</td>
</tr>
<tr>
<td>Overall:</td>
<td>No study found</td>
</tr>
</tbody>
</table>

#### Ototoxicity - Analysis of human studies

No study identified.

#### Ototoxicity - Analysis of animal studies

Two studies on two strains of rats exposed by inhalation were identified. No hearing loss has been found as shown by auditory brainstem responses measurements. Only minor neurofunctional changes were observed at high concentration of p-tert-butyltoluene. No morphologic examination was performed.

#### Interaction with noise - Analysis of human studies

No study identified.

#### Interaction with noise - Analysis of animal studies

No study identified.

### Discussion

No human study was identified. Two animal studies showing no ototoxic effect were identified. No human or animal study on ototoxic interaction between p-tert-butyltoluene and noise was identified. In summary, there is neither evidence of ototoxicity of p-tert-butyltoluene nor of its interaction with noise.
p-tert-Butyltoluene

<table>
<thead>
<tr>
<th>Specie(s)</th>
<th>Rat Long Evans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>3 months</td>
</tr>
<tr>
<td>Number</td>
<td>11 - 13</td>
</tr>
<tr>
<td>Sex</td>
<td>Males</td>
</tr>
<tr>
<td>Route</td>
<td>Inhalation</td>
</tr>
<tr>
<td>Duration</td>
<td>6 h/d; 7 d/w; 4 w</td>
</tr>
<tr>
<td>C/D</td>
<td>20 and 40 ppm</td>
</tr>
<tr>
<td>CSU/DSU</td>
<td>20 - 40</td>
</tr>
<tr>
<td>ASM</td>
<td></td>
</tr>
<tr>
<td>BM</td>
<td></td>
</tr>
<tr>
<td>NSM</td>
<td></td>
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<tr>
<td>NL</td>
<td></td>
</tr>
<tr>
<td>Remarks</td>
<td>LC50 = 165 ppm for 8 hours and 248 ppm for 4 hours in rat</td>
</tr>
</tbody>
</table>

**Effects reported**

- No shift in hearing threshold but amplitude of the first wave was increased at high stimulus levels (16 kHz; 95 dB)
- Test performed 5 months after the end of exposure

**Auditory brainstem responses**

- Tone pips of 4, 8 and 16 kHz

**Our conclusion**

No adverse effect at 40 ppm in te rats
**p-tert-Butyltoluene**

### Population

<table>
<thead>
<tr>
<th>Species</th>
<th>Rat Wistar</th>
<th># : 9</th>
<th>Sex</th>
<th>Males</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

### Exposure

- **Route**: Inhalation  
- **Duration**: 6 h  
- **C/D reported**: 50 and 150 ppm  
- **CSU/DSU**:
  - Ratio: 50  
  - ASM:       
  - BM:       
  - NSM:       
  - NL:       

**Remarks**:
- LC50 = 165 ppm for 8 hours and 248 ppm for 4 hours in rat

### Tests

**Test type**
- Effects reported

**Auditory brainstem responses**
- No effect on the amplitude.
- Significant changes in the waveforms for at least 120 hours at 50 ppm and 288 hours at 150 ppm

**Details on test**
- Clicks of 100 dB at 8 kHz
- Test performed 2, 6, 24, 48, 120 and 288 hours after the end of exposure

### Mechanism of action

### Authors' conclusion

Minor neurofunctional changes

### Our conclusion

No adverse effect at 150 ppm in the rats
BIBLIOGRAPHY
