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# Ototoxic effects of industrial chemicals**

## Lead and inorganic compounds (as Pb)

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## Introduction

There is accumulating epidemiological evidence that exposure to some solvents, metals, asphyxiants and other substances in humans is associated with an increased risk of hearing loss. This project was undertaken to develop a toxicological database allowing the identification of possible ototoxic substances present in the work environment. Critical toxicological data were compiled for chemical substances included in the Quebec Occupational Health Regulation.

## Methods

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

Using a systematic weight of evidence approach, the information from both human and animal studies was examined.

At first, information from each source was given a weight of evidence qualifier for ototoxicity: strong, medium, weak, absent or "no study found". We took into consideration the following parameters: studied specie, number of subjects, exposure way, characteristics of control groups, exposure levels, audiometric and statistical tests, dose/effect relation. Table 1 shows how this information was combined to yield an overall assessment of the ototoxic potential of a given substance. Human data were generally given more weight in the overall assessment. When no human studies were available, which is different from the absence of evidence from the available human studies, the overall assessment was deemed the same as that from animal studies.

We built a weight of evidence table that allowed us to combine the information from both human and animal studies on ototoxicity of chemicals. Table 1 shows how the information from both types of studies were combined to yield an overall assessment and corollary conclusion about the ototoxicity of the investigated chemicals.

Human data were generally given more weight in the overall assessment. When no human studies were available, or when good quality human studies showed absence of evidence of an ototoxic effect, the overall assessment was one degree lower than that resulting from the animal studies. 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 chemical substances, all substances bearing a "strong evidence" of ototoxicity overall are considered "ototoxic". Those with "medium evidence" overall are rated "possibly ototoxic". We consider the ototoxic potential of those with only "weak evidence" as "non conclusive". Finally, those for which there is absence of evidence overall bear the mention "no evidence".

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**Table 1.** Weight of evidence approach for the assessment of ototoxicity of various industrial chemicals

| Strength of evidence about ototoxicity in assessed studies | | | Conclusion about ototoxicity |
|---|---|---|---|
| **Human** | **Animal** | **Overall** | |
| S | S | S | O |
| S | M | S | O |
| S | W | S | O |
| S | A | S | O |
| S | X | S | O |
| M | S | S | O |
| M | M | M | PO |
| M | W | M | PO |
| M | A | M | PO |
| M | X | M | PO |
| W | S | M | PO |
| W | M | W | NC |
| W | W | W | NC |
| W | A | W | NC |
| W | X | W | NC |
| A | S | M | PO |
| A | M | W | NC |
| A | W | W | NC |
| A | A | A | NE |
| A | X | A | NE |
| X | S | M | PO |
| X | M | W | NC |
| X | W | W | NC |
| X | A | A | NE |

**Indication of ototoxicity:**

S = strong; M = medium; W = weak; A = absent; X = no study found

**General conclusion about ototoxicity:**

O = ototoxic substance; PO = possibly ototoxic substance; NC = non conclusive; NE = no evidence

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## Abbreviations

**TWAEV** : 8 h time weighed average exposure [limit] value in Quebec

**D-TWAEV** : Calculated inhaled dose for pulmonary ventilation of 10 $m^3$/d and body weight of 70 kg

**Ceiling** : Ceiling exposure [limit] value in Quebec

**D-Ceiling** : Calculated inhaled dose for pulmonary ventilation of 10 $m^3$/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/$m^3$ 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

# Lead and inorganic compounds (as Pb)

Occupational exposure limits: TWAEV: 0.05 mg/m³

| Conclusion about ototoxicity | Strength of evidence |
|---|---|
| **Ototoxic substance** | From animal studies: **No study found**<br>From human studies: **Strong**<br>Overall: **Strong** |

## ANALYSIS OF ANIMAL STUDIES

No study was identified.

## ANALYSIS OF HUMAN STUDIES

Ten studies in workers and one study in humans accidentally exposed to lead were identified. Pure tone audiometry and auditory brainstem responses (ABR) tests were used. Eight studies demonstrated ototoxicity (Discalzi 1992; Discalzi 1993; Farahat 1997; Forst 1997; Bleecker 2003; Holdstein 1986; Murata 1993; Hirata 1993) one of which in workers with blood lead concentrations (PbB) ranging between 10 and 180 mg/L (Forst 1997). Two of them found a correlation between hearing thresholds and PbB (Farahat 1997; Forst 1997) and one found a correlation between ABR responses and PbB (Bleecker 2003). On the contrary, three studies did not demonstrated ototoxicity (Murata 1995; Lille 1988; Counter 2002), one of which in workers with a mean PbB concentration of 1000 mg/L (Lille 1988). Unfortunately, noise levels were reported only in one well-done study (Farahat 1997).

## CONCLUSION

There is a convincing evidence of lead-induced hearing loss in workers. Correlation between exposure and hearing loss was demonstrated. No animal studies with realistic lead exposure were identified. Given the current evidence from human studies, we recommend considering lead as an ototoxic agent.

## Lead [7439-92-1]

Lead and inorganic compounds (as Pb)
• TWAEV : 0.05 mg/m³ D-TWAEV : 0.0071 mg/kg/d

### Population

Species : Worker # : 357 Sex : Males

Age : 20 - 63 years; mean = 40.7 years

### Exposure

Route : Inhalation

Duration : 0.2 - 26 years; mean = 17 years

C/D reported : NR

CSU/DSU :

Ratio :

ASM :

BM : Lead in blood (PbB) mean: 277 µg/L

Remarks :

### Tests

| **Test type**<br>• Effects reported | Precisions on test<br>• Remarks |
|---|---|
| **Auditory brainstem responses** | Clicks |

• Brainstem components latencies prolongation in correlation with PbB and age

### Action mechanism

Lead exposure affected conduction in the distal auditory nerve

### Authors' conclusion

Lead occupationnal exposure interferes with auditory brainstem response in dose dependent manner

### Our conclusion

Ototoxic effect in workers with a mean lead blood concentration of 390 µg/L

## Lead [7439-92-1]

Lead and inorganic compounds (as Pb)
• TWAEV : 0.05 mg/m³ D-TWAEV : 0.0071 mg/kg/d

### Population

Species : Worker # : 15 M + 15 F Sex : Males and females

Age : 17 - 55 years, median = 35.2 years

### Exposure

Route : Inhalation

Duration : Long term

C/D reported : NR

CSU/DSU :

Ratio :

ASM :

BM : Lead in blood (PbB) : mean = 451 µg/L, range = 112 to 800 µg/L

Remarks :

### Tests

| **Test type**<br>• Effects reported | Precisions on test<br>• Remarks |
|---|---|
| **Pure tone audiometry** | Pure tone at 0.25, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0 and 8.0 kHz |
| • - 60 % of the men and 20 % of the women had elevated auditory thresholds (> 20 dB HL) at 3, 4, 6 and 8 kHz.<br>- No significant correlation between hearing loss and PbB at any frequency | |
| **Auditory brainstem responses** | Clicks |
| • Mean brainstem components latencies within the normal range | |

### Action mechanism

### Authors' conclusion

Lead exposition alone is not the cause of sensory-neural hearing impairment found in those workers. The combinaison of lead intoxication and noise exposure may induce neuro-ototoxicity, particularly in suceptible individuals. However, the noise level was not reported.

### Our conclusion

Auditory loss in workers with a mean lead blood concentration of 450 µg/L but no correlation found.

## Lead [7439-92-1]

Lead and inorganic compounds (as Pb)
• TWAEV : 0.05 mg/m³ D-TWAEV : 0.0071 mg/kg/d

### Population

Species : Worker # : C = 49; E = 49 (37 M + 12 F) Sex : Males and females

Age : C = 33.9 years; E = 34 years

### Exposure

Route : Inhalation

Duration : E = 7.4 years

C/D reported : NR

CSU/DSU :

Ratio :

ASM :

BM : Lead in the blood (PbB): 535 µg/L (average of 3 previous years); 546 µg/L (average of the experimental day)

Remarks :

### Tests

| **Test type**<br>• Effects reported | Precisions on test<br>• Remarks |
|---|---|
| **Auditory brainstem responses** | Clicks |
| • - Prolongation of brainstem components latencies in the exposed group<br>- No correlations between latencies, duration of exposure and PbB concentrations<br>- I-V latencies significantly greater in the subgroup with PbB > 500 µg/L than in subgroup with PbB < 500 µg/L | |

### Action mechanism

Slowing conduction velocity in the brainstem auditory parthways due to Pb exposure

### Authors' conclusion

Ototoxic effect after chronic exposure in workers

### Our conclusion

Ototoxic effect after chronic exposure in workers with 535 µg/L PbB

## Lead [7439-92-1]

Lead and inorganic compounds (as Pb)
• TWAEV : 0.05 mg/m³ D-TWAEV : 0.0071 mg/kg/d

### Population

Species : Worker # : C = 17 M + 5 F; E = 17 M + 5 F Sex : Males and females

Age : C = 34.7 years; E = 34.5 years

### Exposure

Route : Inhalation

Duration : E = 9.3 years

C/D reported : NR

CSU/DSU :

Ratio :

ASM :

BM : Lead in blood (PbB) 475 µg/L

Remarks : Blood lead concentration was measured on the morning of the test day

### Tests

| **Test type**<br>• Effects reported | Precisions on test<br>• Remarks |
|---|---|
| **Auditory brainstem responses** | Clicks |

- - Prolongation of brainstem interpeaks latencies in exposed workers with lead blood level (PbB) > 500 µg/L
  - No correlations between latencies, duration of exposure and PbB

### Action mechanism

### Authors' conclusion

BAEPs may provide a sensitive tool for detecting subclinical central neurotoxicity caused by lead

### Our conclusion

Ototoxic effect in workers with blood lead levels exceeding 500 µg/L

## Lead [7439-92-1]

Lead and inorganic compounds (as Pb)
• TWAEV : 0.05 mg/m³ D-TWAEV : 0.0071 mg/kg/d

### Population

Species : Worker # : C = 45; E = 45 Sex : Not reported

Age : C = 35 years; E = 36 years

### Exposure

Route : Inhalation

Duration : <10 - > 10 years

C/D reported : 0.46 - 23.7 µg/m³

CSU/DSU :

Ratio : 0.01 - 0.47

ASM :

BM : Lead in blood (PbB): E = 369 µg/L; C = 115 µg/L (mean)

Remarks :

### Tests

| **Test type**<br>• Effects reported | Precisions on test<br>• Remarks |
|---|---|
| **Pure tone audiometry**<br>• - Higher hearing threshold in exposed workers than controls at 1 - 8 kHz.<br>- Positive correlation between hearing threshold and lead in blood (PbB) at 8 kHz.<br>- 8 kHz, hearing loss reached significant level with PbB > 300 µg/L and as the exposure duration increased | Pure tone at 0.25 - 8 kHz |

### Action mechanism

### Authors' conclusion

Lead exposure can lead to a increase in hearing threshold level

### Our conclusion

Ototoxic effect at 369 µg/L PbB in workers

## Lead [7439-92-1]

Lead and inorganic compounds (as Pb)
• TWAEV : 0.05 mg/m³ D-TWAEV : 0.0071 mg/kg/d

### Population

Species : Worker # : 171 M + 12 F Sex : Males and females

Age : 19 - 65 years

### Exposure

Route : Inhalation

Duration : NR

C/D reported : NR

CSU/DSU :

Ratio :

ASM :

BM : Lead in blood (PbB): 10 - 180 µg/L

Remarks :

### Tests

| Test type<br>• Effects reported | Precisions on test<br>• Remarks |
|---|---|
| **Pure tone audiometry**<br>• Percentage of abnormal hearing loss (thresholds = 10 dB) is seen to increase with increasing blood lead levels at 3 and 4 kHz. A statistically significant correlation between blood lead level and abnormal hearing threshold occurred at 4 kHz frequency but no significant correlation was demonstrated at other frequencies | Pure tone at 0.5, 1, 2, 3, 4 and 6 kHz |

### Action mechanism

### Authors' conclusion

Lead exposure with PbB ranging from 10 to 180 µg/L may cause hearing loss in workers

### Our conclusion

Conclusion on the ototoxic effect cannot be made as hearing lost of 10 dB is not considered abnormal in workers with the age ranging from 19 to 65 years

## Lead [7439-92-1]

Lead and inorganic compounds (as Pb)
• TWAEV : 0.05 mg/m³ D-TWAEV : 0.0071 mg/kg/d

### Population

Species : Worker # : C = 39; E = 15 Sex : Males

Age : 47 years (mean), 40 - 52 years

### Exposure

Route : Inhalation

Duration : 17 years (mean), 4 - 29 years

C/D reported : 0.01 - 2.69 mg/m³

CSU/DSU :

Ratio : 0.2 - 54

ASM :

BM : Lead in blood (PbB): 424 µg/L; mean: 130 - 670 µg/L

Remarks :

### Tests

| **Test type**<br>• Effects reported | Precisions on test<br>• Remarks |
|---|---|
| **Auditory brainstem responses** | Clicks |

- - Prolongation of brainstem I-V interpeak latencies in exposed workers
  - No correlation between latencies and PbB

### Action mechanism

### Authors' conclusion

Chronic lead exposure reduces the conduction function of the acoustic nerve and the brain stem

### Our conclusion

Ototoxic effect possible at PbB < 670 µg/L

## Lead [7439-92-1]

Lead and inorganic compounds (as Pb)
• TWAEV : 0.05 mg/m³ D-TWAEV : 0.0071 mg/kg/d

### Population

Species : Humain # : C = 20; E = 16 (6 M + 10 F) Sex : Males and females

Age : C = NR; E = 40 (18 - 56) years

### Exposure

Route : Food

Duration : see remarks

C/D reported : NR

CSU/DSU :

Ratio :

ASM :

BM : Lead in blood (PbB): 312 µg/L (average concentration on examination day) and 434 µg/L (10 months average)

Remarks : Adults accidentally exposed through food. Exposure to lead started between a year and two years prior to its detection

### Tests

| **Test type**<br>• Effects reported | Precisions on test<br>• Remarks |
|---|---|
| **Auditory brainstem responses** | Clicks |
| • Prolongation of brainstem components latency in exposed group | |

### Action mechanism

### Authors' conclusion

Auditory brainstem responses test is suggested as a sensitive detector of subclinical lead exposure effects on the nervous system. Impairment of the peripheral portion of the auditory system possible

### Our conclusion

Possible ototoxic effect in humans exposed to low concentrations of lead

## Lead [7439-92-1]

Lead and inorganic compounds (as Pb)
• TWAEV : 0.05 mg/m³ D-TWAEV : 0.0071 mg/kg/d

### Population

Species : Worker # : 10 M + 3 F Sex : Males and females
Age : 37 years (mean)

### Exposure

Route : Inhalation
Duration : 10 years
C/D reported : NR
CSU/DSU :
Ratio :
ASM :
BM : Blood level mean 1000 µg/L (270-2400 µg/L)
Remarks :

### Tests

| **Test type**<br>• Effects reported | Precisions on test<br>• Remarks |
|---|---|
| **Auditory brainstem responses**<br>• Only one abnormality (increased interpeak latency I-V: 4.7 msec) observed in one lead exposed and alcoholic patient | Clicks |

### Action mechanism

### Authors' conclusion

No conclusion about ototoxicity

### Our conclusion

No ototoxic effect in workers with a mean lead blood concentration of 1000 µg/L

## Lead [7439-92-1]

Lead and inorganic compounds (as Pb)
• TWAEV : 0.05 mg/m³ D-TWAEV : 0.0071 mg/kg/d

### Population

Species : Worker # : 20 Sex : Males

Age : 32 - 59 years

### Exposure

Route : Inhalation

Duration : 1 - 18 years

C/D reported : NR

CSU/DSU :

Ratio :

ASM :

BM : Lead in blood (PbB): 120-640 µg/L

Remarks :

### Tests

| **Test type**<br>• Effects reported | Precisions on test<br>• Remarks |
|---|---|
| **Auditory brainstem responses** | Clicks |
| • - Brainstem components latencies were significantly related to hematocrit in exposed workers, not to PbB. No significant differences in the latencies were found between exposed workers and controls<br>- Dose-effect relationship in the I-V interpeak latency of the BAEP was found to be significant despite the absence of significant differences in the BAEP latencies in the lead workers | |

### Action mechanism

### Authors' conclusion

Brainstem auditory pathway is probably influenced by lead

### Our conclusion

Ototoxic effect possible at PbB < 650 µg/L

## Lead [7439-92-1]

Lead and inorganic compounds (as Pb)
• TWAEV : 0.05 mg/m³ D-TWAEV : 0.0071 mg/kg/d

### Population

Species : Worker # : C = 15; E = 36 Sex : Females

Age : C = 22 - 29 years; E = 21 - 35 years

### Exposure

Route : Inhalation

Duration : 7.8 (2 - 17) years

C/D reported : 0.4 - 1.2 mg/m³

CSU/DSU :

Ratio : 8 - 24

ASM :

BM : Lead in blood (PbB): 258-793 µg/L; mean: 556 µg/L

Remarks :

### Tests

| Test type<br>• Effects reported | Precisions on test<br>• Remarks |
|---|---|
| **Auditory brainstem responses** | Clicks |
| • - No significant relationship between brainstem components latencies and lead in blood (PbB) in the exposed group<br>- No significant differences in brainstem components latencies between exposed and control groups.<br>- Working years in exposed workers of this study were not significantly related to PbB or auditory brainstem responses | |

### Action mechanism

### Authors' conclusion

No ototoxic effects at exposure conecntration from 0.4 to 1.2 mg/m³ in the workers

### Our conclusion

No ototoxic effect ranging from 0.4 to 1.2 mg/m³ in the workers

## BIBLIOGRAPHY


**Bleecker 2003** Bleecker, M.L., et al. (2003) Association of chronic and current measures of lead exposure with different components of brainstem auditory evoked potentials. Neurotoxicology. 24(4-5): 625-31.

**Counter 2002** Counter, S.A., et al. (2002) Neuro-ototoxicity in andean adults with chronic lead and noise exposure. J Occup Environ Med. 44(1): 30-8.

**Discalzi 1992** Discalzi, G.L., et al. (1992) Auditory brainstem evoked potentials (BAEPs) in lead-exposed workers. Neurotoxicol. 13(1): 207-9.

**Discalzi 1993** Discalzi, G., et al. (1993) Effects of occupational exposure to mercury and lead on brainstem auditory evoked potentials. Int J Psychophysiol. 14(1): 21-5.

**Farahat 1997** Farahat, T.M., et al. (1997) Hearing thresholds of workers in a printing facility. Environ Res. 73(1-2): 189-92.

**Forst 1997** Forst, L.S., et al. (1997) Occupational lead exposure and hearing loss. J Occup Environ Med. 39(7): 658-60.

**Hirata 1993** Hirata, M. and H. Kosaka (1993). Effects of lead exposure on neurophysiological parameters. Environ Res 63(1): 60-9.

**Holdstein 1986** Holdstein, Y., et al. (1986) Auditory brainstem evoked potentials in asymptomatic lead-exposed subjects. J Laryngol Otol. 100(9): 1031-6.

**Lille 1988** Lille, F., et al. (1988) Effects of lead and mercury intoxications on evoked potentials. J Toxicol Clin Toxicol. 26(1-2): 103-16.

**Murata 1993** Murata, K., S. Araki, et al. (1993). Assessment of central, peripheral, and autonomic nervous system functions in lead workers: neuroelectrophysiological studies. Environ Res 61(2): 323-36.

**Murata 1995** Murata, K., et al. (1995) Autonomic and central nervous system effects of lead in female glass workers in China. Am J Ind Med. 28(2): 233-44.