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

Lead and inorganic compounds (as Pb)

A. Vyskocil[1]*, T. Leroux[3], G. Truchon[2], F. Lemay[1], F. Gagnon[1], M. Gendron[3], S. Botez[1], N. El Majidi[1], A. Boudjerida[1], S. Lim[1], C. Émond[1], C. Viau[1]

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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* Corresponding author : adolf.vyskocil@umontreal.ca
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[1] Institut de recherche en santé publique de l'Université de Montréal. Département de santé environmentale et de santé au travail, Université de Montréal.
[2] Institut de recherche Robert-Sauvé en santé et en sécurité du travail (IRSST), Montréal
[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

Weight of evidence of studies			Conclusion about ototoxicity	Conclusion about the interaction substance / noise
Human studies	**Animal studies**	**Overall**		
S	S	S	O	I
S	M	S	O	I
S	W	S	O	I
S	A	S	O	I
S	X	S	O	I
M	S	S	O	I
M	M	M	PO	PI
M	W	M	PO	PI
M	A	M	PO	PI
M	X	M	PO	PI
W	S	M	PO	PI
W	M	W	NC	NC
W	W	W	NC	NC
W	A	W	NC	NC
W	X	W	NC	NC
A	S	M	PO	PI
A	M	W	NC	NC
A	W	W	NC	NC
A	A	A	NE	NE
A	X	A	NE	NE
X	S	M	PO	PI
X	M	W	NC	NC
X	W	W	NC	NC
X	A	A	NE	NE
X	X	X	X	X

Strength of evidence about otoxicity 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 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

NSM: Noise sampling method

NL: Noise levels

SPL : Sound pressure level

Lead and inorganic compounds (as Pb)

Quebec's Occupational exposure limits: TWAEV: 0,05 mg/m³

Conclusion about ototoxicity	Strength of evidence
Ototoxic substance	From human studies: **Strong** From animal studies: **No study found** Overall: **Strong**
Conclusion about interaction with noise	Strength of evidence
No evidence	From human studies: **Absent** From animal studies: **No study found** Overall: **Absent**

Ototoxicity - Analysis of human studies

Eleven 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, four studies did not demonstrated ototoxicity (Murata 1995; Lille 1988; Counter 2002; Yokoyama 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) in which noise levels ranged between 40 and 50 dB.

Ototoxicity - Analysis of animal studies

No study was identified.

Interaction with noise - Analysis of human studies

One study in workers was identified (Wu 2000). A significant correlation was found between a high, long-term lead exposure index (defined by duration of employment and ambient lead concentration) and decreased hearing ability. In contrast, such a correlation between short-term lead exposure (defined by blood lead level) and hearing ability was not significant. Neither noise exposure level alone nor the simultaneous noise and short- or long-term lead exposure were correlated significantly with decreased hearing ability.

Interaction with noise - Analysis of animal studies

No study was identified.

Discussion

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. There is no evidence of interaction after combined exposure to lead and noise in industrial population in one study. Further studies are necessary to draw any conclusion about interaction with noise.

Lead

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

NSM :

NL :

Remarks :

Tests

Test type • Effects reported	Details on test • Remarks
Auditory brainstem responses	Clicks
• Brainstem components latencies prolongation in correlation with PbB and age	

Mechanism of action

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

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

NSM :

NL :

Remarks :

Tests

Test type • Effects reported	Details on test • 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. - No significant correlation between hearing loss and PbB at any frequency	
Auditory brainstem responses	Clicks
• Mean brainstem components latencies within the normal range	

Mechanism of action

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

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)

NSM :

NL :

Remarks :

Tests

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

Mechanism of action

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

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

NSM :

NL :

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

Tests

Test type • Effects reported	Details on test • Remarks
Auditory brainstem responses • - 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	Clicks

Mechanism of action

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

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)

NSM :

NL : 42 dB (40 - 50 dB)

Remarks :

Tests

Test type • Effects reported	Details on test • Remarks
Pure tone audiometry • - Higher hearing threshold in exposed workers than controls at 1 - 8 kHz. - Positive correlation between hearing threshold and lead in blood (PbB) at 8 kHz. - 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

Mechanism of action

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

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
NSM :
NL :
Remarks :

Tests

Test type • Effects reported	Details on test • Remarks
Pure tone audiometry • 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

Mechanism of action

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

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

NSM :

NL :

Remarks :

Tests

Test type • Effects reported	Details on test • Remarks
Auditory brainstem responses	Clicks

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

Mechanism of action

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

Lead and inorganic compounds (as Pb)
• TWAEV : 0,05 mg/m³ D-TWAEV : 0,0071 mg/kg/d

Population

Species : Human # : 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)

NSM :

NL :

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

Tests

Test type • Effects reported	Details on test • Remarks
Auditory brainstem responses • Prolongation of brainstem components latency in exposed group	Clicks

Mechanism of action

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

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)
NSM :
NL :
Remarks :

Tests

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

Mechanism of action

Authors' conclusion

No conclusion about ototoxicity

Our conclusion

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

Lead

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
NSM :
NL :
Remarks :

Tests

Test type • Effects reported	Details on test • Remarks
Auditory brainstem responses • - 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 - 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	Clicks

Mechanism of action

Authors' conclusion

Brainstem auditory pathway is probably influenced by lead

Our conclusion

Ototoxic effect possible at PbB < 650 µg/L

Lead

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

NSM :

NL :

Remarks :

Tests

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

Mechanism of action

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

Lead

Lead and inorganic compounds (as Pb)
• TWAEV : 0,05 mg/m³ D-TWAEV : 0,0071 mg/kg/d

Population

Species : Worker # : 118 M + 102 F Sex : Males and females

Age : M = 37.0 years ; F = 36.4 years

Exposure

Route : Inhalation

Duration : M = 67.5 months; F = 37.4 months

C/D reported : Ambient lead concentration = 0.19 mg/m³

CSU/DSU :

Ratio : 3.8

ASM :

BM : Lead in blood (PbB) : 569 µg/L (M : 670 µg/L , F : 453 µg/L)

NSM :

NL : 86.0 dB(A) (8 h) (s.d.: 5.7)

Remarks :

Tests

In this study, the hearing loss definiton is based upon hearing threshold at 4 kHz in the worst ear. This definition does not reflect many possible affects of noise exposure on hearing

Test type • Effects reported	Details on test • Remarks
Pure tone audiometry • - Neither noise exposure level alone nor the interaction between noise exposure level and short- or long-term exposure was correlated significantly with decreased hearing ability - Dose-response relationship observed between PbB and hearing ability in M + F exposed workers - In combined short term exposure, age and alcohol drinking were associated with hearing threshold at 4 kHz - In long term lead exposure in noisy environment, age, sex and alcohol drinking were associated wiht hearing threshold at 4 kHz	Pure tones at 0.5, 1, 2, 4, 6 and 8 kHz • Test performed after acoustic pause for more than 14 hours

Mechanism of action

Authors' conclusion

Dose-Reponse relationshipobserved between lead in blood level and hearing loss in high Pb exposed group but no association between PbB + noise level and hearing loss

Our conclusion

Ototoxic effect at 0.19 mg/m³ Pb in workers

Lead

Lead and inorganic compounds (as Pb)
• TWAEV : 0,05 mg/m³ D-TWAEV : 0,0071 mg/kg/d

Population

Species : Worker # : C = 14; E = 29 Sex : Females

Age : C = 25.9 ± 2.5 years; E = 27.6 ± 2.7 years

Exposure

Route : Inhalation

Duration : 7.9 ± 3.4 years

C/D reported : From 0.4 to 1.2 mg/m³

CSU/DSU :

Ratio : 8-24

ASM : According to the report by the manager

BM : Lead in blood : 557 ± 138 µg/L

NSM :

NL :

Remarks :

Tests

Test type • Effects reported	Details on test • Remarks
Brainstem auditory evoked potentials	20 clicks per second at a level of 80 dB
• No significant differences were observed in BAEP between the two groups	• Tested in the right ear

Mechanism of action

Authors' conclusion

It remains to be elucidated which part of the nervous system is most sensitive to subclinical lead absorption

Our conclusion

No ototoxic effect was observed in female workers with mean blood lead concentration of 557 µg/L

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