

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

Mercury, inorganic compounds

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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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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 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

Mercury, inorganic compounds

Quebec's Occupational exposure limits: TWAEV: 0,025 mg/m³

Conclusion about ototoxicity Non conclusive	Strength of evidence From human studies: Weak From animal studies: Absent Overall: Weak
Conclusion about interaction with noise No documentation	Strength of evidence From human studies: No study found From animal studies: No study found Overall: No study found

Ototoxicity - Analysis of human studies

Two human studies using auditory brainstem responses tests were identified. One study, showed that an ototoxic effect of inorganic mercury cannot be excluded. Reported mean urinary mercury concentration was 325 µg/g creatinine. The level of exposure to noise was not reported (Discalzi 1993). The second study did not demonstrate any ototoxic effect. Reported mean urinary mercury concentration was 350 µg/g creatinine (Lille 1988).

Ototoxicity - Analysis of animal studies

One study in rats was identified (Fazakas 2005). Using cortical auditory evoked potentials test, no ototoxic effect was observed after subchronic oral exposure to mercury chloride.

Interaction with noise - Analysis of human studies

No study was identified.

Interaction with noise - Analysis of animal studies

No study was identified.

Discussion

Two human studies reported contradictory results. One subchronic study in rats showed no ototoxic effect of mercury chloride. In the absence of other studies, it is not possible to draw any conclusion regarding the ototoxicity of inorganic mercury compounds. No human or animal study on ototoxic interaction between inorganic mercury compounds and noise was identified.

Mercury, inorganic compounds**Mercury, inorganic compounds**

• TWAEV : 0,025 mg/m³ D-TWAEV : 0,0036 mg/kg/d

Population

Species : Worker

: C = 6 M + 2 F; E = 6 M + 2 F

Sex : Males and females

Age : C = 34.7 years; E = 34.5 years

Exposure

Route : Inhalation

Duration : E = 11.7 years

C/D reported : NR

CSU/DSU :

Ratio :

ASM :

BM : Mercury in urine: 325 µg/L

NSM :

NL : NR

Remarks : Urine mercury concentrations were measured at the end of workshift of the days before test

Tests**Test type**

• Effects reported

Details on test

• Remarks

Auditory brainstem responses

Clicks at 100 dB SPL

• Interpeak latencies were significantly more prolonged

Mechanism of action**Authors' conclusion**

Abnormalities associated with exposures to mercury

Our conclusion

Ototoxic effect in workers cannot be excluded. Other data are necessary

Mercury chloride**Mercury, inorganic compounds**

• TWAEV : 0,025 mg/m³ D-TWAEV : 0,0036 mg/kg/d

Population

Species : Rat

: 10

Sex : Males

Age : 12 weeks

Exposure

Route : Gavage

Duration : Every day for 12 weeks

C/D reported : 0.4 mg Hg/kg/d

CSU/DSU :

Ratio : 28

ASM :

BM :

NSM :

NL :

Remarks :

Tests**Test type**

• Effects reported

Details on test

• Remarks

Cortical auditory evoked potentials

1 Hz; 40 dB

• No effect

• Test performed after the end of exposure
Lack of details in results

Mechanism of action**Authors' conclusion**

No ototoxic effect at 0.4 mg/kg/d in rats

Our conclusion

No ototoxic effect at 0.4 mg/kg/d in rats

Mercury, inorganic compounds**Mercury, inorganic compounds**• TWAEV : 0,025 mg/m³

D-TWAEV : 0,0036 mg/kg/d

Population

Species : Human

: 6 M + 3 F (5 occupational exposure +
4 accidental exposure)

Sex : Males and females

Age : mean of 29 years

Exposure

Route : Not reported

Duration : 1 - 40 years (occupational exposure)

C/D reported : NR

CSU/DSU :

Ratio :

ASM :

BM : Mercury in urine: 0.35 mg Hg/g creatinine (0.02 - 1.6)

NSM :

NL : NR

Remarks :

Tests**Test type**

• Effects reported

Details on test

• Remarks

Auditory brainstem responses

Clicks 60 dB SL

• No effect

Mechanism of action**Authors' conclusion**

No ototoxicity of inorganic mercury

Our conclusion

No ototoxicity of inorganic mercury

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