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

Mercury, Alkyl compounds (as Hg)

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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 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

Mercury, Alkyl compounds (as Hg)

Quebec's Occupational exposure limits: TWAEV: 0,01 mg/m³. STEV: 0,03 mg/m³

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

Ototoxicity - Analysis of human studies

Two studies on Japan inhabitants were identified. Ototoxic effect of organic mercury was reported using pure tone audiometry and Békèsy's audiometry. However, the levels of exposure were not reported and age was not taken in consideration.

Ototoxicity - Analysis of animal studies

No study was identified.

Interaction with noise - Analysis of human studies

No study was identified.

Interaction with noise - Analysis of animal studies

No study was identified.

Discussion

Ototoxic effect of organic mercury was reported in two studies in Japan inhabitants. However, the levels of exposure were not reported and age was not taken in consideration. No animal study was identified. In the absence of other studies, it is not possible to draw any conclusion regarding the ototoxicity of alkyl mercury compounds. No human or animal study on ototoxic interaction between alkyl mercury compounds and noise was identified.

Oganic mercury compounds

Mercury, Alkyl compounds (as Hg)
• TWAEV : 0,01 mg/m³ D-TWAEV : 0,00143 mg/kg/d

Population

Species : Human # : 34-144 Sex : Males and females

Age : 7-74

Exposure

Route : Oral
Duration : NR
C/D reported : NR
CSU/DSU :
Ratio :
ASM : NR
BM :
NSM :
NL : NR
Remarks : Intoxication of habitants in Japon – Minamata disease. Exposure concentration non reported

Tests

Test type • Effects reported	Details on test • Remarks
Pure tone audiometry	at 0.5, 1 and 2 kHz
• Hearing loss (10-90 dB)	• Age was not taken in consideration
Bekesy test	Site of lesion
• 9 cases from 34 subjects evaluated had retrocochlear lesion (type III pattern of Jerger's classification)	• Reflex adaptation

Mechanism of action

Authors' conclusion

Ototoxic effect of organic mercury in human caused by cochlear lesions

Our conclusion

Ototoxic effect of organic mercury was reported in human, but the exposure to mercury was not reported and age was not taken in consideration for pure tone audiometry

Oganic mercury compounds

Mercury, Alkyl compounds (as Hg)
• TWAEV : 0,01 mg/m³ D-TWAEV : 0,00143 mg/kg/d

Population

Species : Human # : 17 M + 18 W Sex : Males and females

Age : 20 - 74 years

Exposure

Route : Oral

Duration : NR

C/D reported : NR

CSU/DSU :

Ratio :

ASM : NR

BM :

NSM :

NL : NR

Remarks : Intoxication of habitants in Japon – Minamata disease recognized during 1968-78. Exposure concentration not reported

Tests

Test performed during 1986-1987

Test type • Effects reported	Details on test • Remarks
Pure tone audiometry	at 0.5, 1 and 2 kHz
• 16 out of 58 ears showed deterioration of hearing (28%) while 4 ears showed improvement (7%)	• No control for age

Mechanism of action

Authors' conclusion

Ototoxic effect of organic mercury in human

Our conclusion

Ototoxic effect of organic mercury cannot be evaluated as the age was not taken into consideration

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