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

Nicotine

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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

Nicotine

Quebec's Occupational exposure limits: TWAEV: 0,5 mg/m³

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

Ototoxicity - Analysis of human studies

No study was identified.

Ototoxicity - Analysis of animal studies

Only one study in guinea pigs was identified. No ototoxic effect was observed using electrocochleography and light microscopy after 20 days of intraveinous exposure up to 20 mg/kg/d nicotine.

Interaction with noise - Analysis of human studies

No study was identified.

Interaction with noise - Analysis of animal studies

Only one study in guinea pigs was identified. No ototoxic interaction with noise was observed using electrocochleography and light microscopy after 20 days of intraveinous exposure to up to 20 mg/kg/d nicotine.

Discussion

No human study was identified. In guinea pigs, no ototoxic effect or interaction with noise were detected. However, the route and dose of nicotine exposure were different from those experienced by humans. In summary, there is neither evidence of ototoxicity of nicotine nor if its interaction with noise.

Nicotine

Nicotine
• TWAEV : 0,5 mg/m³ D-TWAEV : 0,071 mg/kg/d

Population

Species : Guinea pig # : NR Sex : Not reported
Age : NR

Exposure

Route : Intraveinous
Duration : 20 d
C/D reported : 1-20 mg/kg/d
CSU/DSU :
Ratio : 14-282
ASM :
BM :
NSM :
NL :
Remarks :

Tests

Test type • Effects reported	Details on test • Remarks
Electrocochleography (Compound action potential : CAP)	Tone bursts at 0.6 and 6 kHz
• Cochlear microphonic (CM) and compound action potential (CAP) threshold results were not affected by nicotine exposure	• Test performed 21 days after the end of exposure
Light microscopy	
• - No significative effects on hair cells damage between the animals treated with saline or with different doses of nicotine	• Cochleae were dissected 21 days after exposure

Mechanism of action

Authors' conclusion

No nicotine ototoxicity was detected by the methods used in this study

Our conclusion

No signs of nicotine ototoxicity

Nicotine

Nicotine
• TWAEV : 0,5 mg/m³ D-TWAEV : 0,071 mg/kg/d

Population

Species : Guinea pig # : NR Sex : Not reported
Age : NR

Exposure

Route : Intraveinous
Duration : 20 d
C/D reported : 1-20 mg/kg/d
CSU/DSU :
Ratio : 14-282
ASM :
BM :
NSM :
NL : 126 dB SPL at 4 kHz
Remarks : Animals were exposed to noise for 30 minutes, ½ to 4 hours after the last nicotine injection

Tests

Test type • Effects reported	Details on test • Remarks
Electrocochleography (Compound action potential : CAP)	Tone bursts at 0.6 and 6 kHz
• Cochlear microphonic (CM) and compound action potential (CAP) threshold results were not affected by nicotine exposure	• Test performed 21 days after the end of exposure
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