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

Cyanides (as CN)

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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

Cyanides (as CN)

Quebec's Occupational exposure limits: Ceiling: 11 mg/m³ (10 ppm)

Conclusion about ototoxicity	Strength of evidence
Non conclusive	From human studies: **No study found** From animal studies: **Weak** 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

No study was identified.

Ototoxicity - Analysis of animal studies

Two studies from the same laboratory performed on rats were identified. Using an electrocochleography test, a transient elevation of auditory threshold was observed after a single cyanide administration and a persistent elevation of auditory threshold was observed after 3 daily doses by the intraperitoneal route (Tawackoli 2001).

Interaction with noise - Analysis of human studies

No study was identified.

Interaction with noise - Analysis of animal studies

No study was identified.

Discussion

No human study was identified. Two animal studies showed ototoxic effect of cyanides. In the absence of other studies, it is not possible to draw any conclusion regarding the ototoxicity of cyanides. No human or animal study on ototoxic interaction between cyanides and noise was identified.

Cyanides (as CN)

Cyanides (as CN)
• Ceiling : 10 ppm | 11 mg/m³ D-CEILING : 1,6 mg/kg/d

Population

Species : Rat Long Evans # : 5 Sex : Not reported
Age : 2 months

Exposure

Route : Intraperitoneal
Duration : Single dose
C/D reported : 7 mg/kg/d
CSU/DSU :
Ratio : 2.6
ASM :
BM :
NSM :
NL :
Remarks : Potassium cyanide used

Tests

Test type • Effects reported	Details on test • Remarks
Electrocochleography (Compound action potential : CAP)	at 2, 12 and 40 kHz
• - Transient elevation of auditory threshold up to 31, 35 and 38 dB at 2, 12, and 40 kHz, respectively within10 minutes after injection. - Complete recovery within 20 minutes	• Test performed prior to and then continuously 35 minutes following the injection
Endocochlear potential recording	
• - Transient suppression of the endocochlear potential within 2 – 4 minutes following injection - Complete recovery within 10 minutes	• Test performed prior to and then continuously 40 minutes following the injection

Mechanism of action

Acute potassium cyanide administration has a prominent disruptive effect at the stria vascularis presumably by disrupting the electron transport chain in this metabolically active structure

Authors' conclusion

Acute administration of potassium cyanide can disrupt transiently auditory function

Our conclusion

Ototoxic effect transient after acute injection in rats

Cyanides (as CN)

Cyanides (as CN)
• Ceiling : 10 ppm | 11 mg/m³ D-CEILING : 1,6 mg/kg/d

Population

Species : Rat Long Evans # : 5 Sex : Not reported
Age : 2 months

Exposure

Route : Intraperitoneal
Duration : Daily for 3 days
C/D reported : 7 mg/kg/d
CSU/DSU :
Ratio : 2.6
ASM :
BM :
NSM :
NL :
Remarks : Potassium cyanide used

Tests

Test type • Effects reported	Details on test • Remarks
Electrocochleography (Compound action potential : CAP)	at 2 - 40 kHz
• Persistent elevation of auditory threshold at all frequencies. The losses are especially large at the high frequencies	• Test performed 24 hours following the injection

Mechanism of action

Authors' conclusion

Possible accumulation of ototoxicity after repeated administration

Our conclusion

Ototoxic effect after repeated injection in rats

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Tawackoli 2001 Tawackoli, W., et al. (2001) Disruption of cochlear potentials by chemical asphyxiants. Cyanide and carbon monoxide. Neurotoxicol Teratol. 23(2): 157-65.