Ototoxic effects of industrial chemicals**

Cyanides (as CN)

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Introduction

There is accumulating epidemiological evidence that exposure to some solvents, metals, asphyxiants and other substances in humans is associated with a risk of hearing loss. This project was undertaken to develop a toxicological database allowing the identification of possible ototoxic substances present in the work environment. Critical toxicological data were compiled for chemical substances included in the Quebec Occupational Health Regulation.

Methods

The data were evaluated only for realistic exposure concentrations up to:
- the short-term exposure limit, or
- the ceiling value, or
- five times the 8-h time weighted average exposure limit value (TWAEV) for human data, or
- up to 100 times the 8-h TWAEV or the ceiling value for animal studies.

Using a systematic weight of evidence approach, the information from both human and animal studies was examined.

At first, information from each source was given a weight of evidence qualifier for ototoxicity: strong, medium, weak, absent or "no study found". We took into consideration the following parameters: studied species, number of subjects, exposure route, characteristics of control groups, exposure levels, audiometric and statistical tests, dose/effect relationship.

Note that weight of evidence qualifier “absent” can rarely be considered as the proof that a substance is not ototoxic. Furthermore, studies on ototoxicity remain relatively rare. Therefore, we consider more prudent, given our current knowledge, to adopt the mention “no evidence” rather than “non ototoxic”, which would suggest that we have proof of absence of ototoxicity.

The effects of chemical substances on hearing have been documented and information on action mechanisms was recorded when available.

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. Table 1 shows how the information from both types of studies was combined to yield an overall assessment and corollary conclusion about the ototoxicity of the investigated chemicals. Human data were generally given more weight in the overall assessment. It is important to mention that this was a matter of professional judgment and that examination of specific cases could possibly lead to revisions in the assessments.

When good quality human studies showed absence of evidence of an ototoxic effect, the overall assessment was one degree lower than that resulting from the animal studies. For example, a "strong" evidence from animal studies combined with an "absence" of evidence from the available human studies yielded a "medium" evidence overall. When no human studies were available, or when existing human studies were not considered credible because of inadequate methodology, the overall assessment was deemed the same as that from animal studies.

Regarding the final conclusion about the ototoxic potential of chemical substances, all substances bearing a "strong evidence" of ototoxicity overall were considered "ototoxic". Those with "medium evidence" overall were rated "possibly ototoxic". We considered the ototoxic potential of those with only "weak evidence" as "non conclusive". Finally, those for which there was absence of evidence overall bore the mention "no evidence", which signifies that we have found no indication in scientific literature suggesting or demonstrating that the substance is ototoxic. However, this provides no assurance that the substance is not ototoxic.

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** Production of this document was supported by the IRSST (Grant 099-542)

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Table 1. Weight of evidence approach for the assessment of ototoxicity of various industrial chemicals

Strength of evidence about ototoxicity in assessed studies			Conclusion about ototoxicity
Human	**Animal**	**Overall**	
S	S	S	O
S	M	S	O
S	W	S	O
S	A	S	O
S	X	S	O
M	S	S	O
M	M	M	PO
M	W	M	PO
M	A	M	PO
M	X	M	PO
W	S	M	PO
W	M	W	NC
W	W	W	NC
W	A	W	NC
W	X	W	NC
A	S	M	PO
A	M	W	NC
A	W	W	NC
A	A	A	NE
A	X	A	NE
X	S	M	PO
X	M	W	NC
X	W	W	NC
X	A	A	NE

Indication of ototoxicity:

S = strong; M = medium; W = weak; A = absent; X = no study found

General conclusion about ototoxicity:

O = ototoxic substance; PO = possibly ototoxic substance; NC = non conclusive; NE = no evidence

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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

Cyanides (as CN)

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

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

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).

ANALYSIS OF HUMAN STUDIES

No study was identified.

CONCLUSION

No human study was identified. Two animal studies showed a transient ototoxic effect of cyanide. In the absence of other studies, it is not possible to draw any conclusion regarding the ototoxicity of cyanides.

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 :
Remarks : Potassium cyanide used

Tests

Test type • Effects reported	Precisions on test • Remarks
Electrocochleography	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

Action mechanism

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 :
Remarks : Potassium cyanide used

Tests

Test type • Effects reported	Precisions on test • Remarks
Electrocochleography	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

Action mechanism

Authors' conclusion

Possible accumulation of ototoxicity after repeated administration

Our conclusion

Ototoxic effect after repeated injection in rats

BIBLIOGRAPHY

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