

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

## Hydrogen cyanide (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 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 m<sup>3</sup>/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<sup>3</sup>/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<sup>3</sup> 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

## Hydrogen cyanide (as CN)

Quebec's Occupational exposure limits: Ceiling: 11 mg/m<sup>3</sup> (10 ppm)

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

### Ototoxicity - Analysis of human studies

No study was identified.

### Ototoxicity - Analysis of animal studies

One inhalation study on rats was identified. No ototoxic effect was found using pure tone audiometry and histology after a single exposure up to 50 ppm for 3.5 hours.

### Interaction with noise - Analysis of human studies

No study was identified.

### Interaction with noise - Analysis of animal studies

In one study a potentiation of noise induced hearing loss by hydrogen cyanide was observed in rats after a combined exposure using electrocochleography and light microscopy.

### Discussion

No human study was identified. Only one animal study showing no ototoxic effect of hydrogen cyanide inhalation was identified. The same study showed a potentiation of noise-induced hearing loss by hydrogen cyanide. In the absence of other studies, it is not possible to draw any conclusion regarding the ototoxicity of hydrogen cyanide or its interaction with noise.

**Hydrogen cyanide****Hydrogen cyanide (as CN)**• Ceiling : 10 ppm | 11 mg/m<sup>3</sup>

D-CEILING : 1,6 mg/kg/d

**Population**

Species : Rat Long Evans

# : 3 - 16

Sex : Males

Age : 2 - 3 months

**Exposure**

Route : Inhalation

Duration : 3.5 h

C/D reported : 10, 30 and 50 ppm

CSU/DSU :

Ratio : 1 - 5

ASM :

BM :

NSM :

NL :

Remarks :

**Tests****Test type**

• Effects reported

## Details on test

• Remarks

**Pure tone audiometry**

• No effect

Tone burst at 2, 4, 6, 8, 12, 16, 20, 24, 30, 35 and 40 kHz

• Test performed 4 weeks after the end of exposure

**Light microscopy**

• No effect

• Histology performed 4 weeks after the end of exposure

**Mechanism of action****Authors' conclusion**

No ototoxic effect after exposure to 10 - 50 ppm in rats

**Our conclusion**

No ototoxic effect after exposure to 10 - 50 ppm in rats

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**Exposure**

Route : Inhalation

Duration : 3.5 h

C/D reported : 10, 30 and 50 ppm

CSU/DSU :

Ratio : 1 - 5

ASM :

BM :

NSM :

NL : 100 dB lin during 2 hour ; Octave band noise centered at 13.6 kHz

Remarks :

**Tests****Test type**

• Effects reported

## Details on test

• Remarks

**Electrocochleography (Compound action potential : CAP)**

Tone burst at 2, 4, 6, 8, 12, 16, 20, 24, 30, 35 and 40 kHz (CAP)

- HCN alone : No significant effect
- Noise alone : Averaged elevation of auditory thresholds by 12 dB, between 12-40 kHz.
- No effect at 2-8 kHz
- HCN + noise : Cyanide dose-dependent auditory thresholds elevation that exceeds the noise exposure alone. Statistical significance at 30 ppm (elevation by 24 dB)

- Test performed 4 weeks after the end of exposure

**Light microscopy**

- HCN alone : No significant effect
- Noise alone : 5 % loss of outer hair cells at the base of cochlea (corresponding to > 20 kHz), but no inner hair cell loss
- HCN (10 and 30 ppm) + noise : More outer hair cells loss than at noise alone (6 and 9 %, respectively)

- Histology performed 4 weeks after the end of exposure

**Mechanism of action****Authors' conclusion**

Hydrogen cyanide exposure for 3.5 hours increases permanent noise-induced hearing loss in a dose-dependent manner

**Our conclusion**

LOAEL of 30 ppm for ototoxic effect in rats exposed for 3.5 hours. Potentialisation of noise caused hearing loss by hydrogen cyanide

## BIBLIOGRAPHY

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