

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

Carbon disulfide

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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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** Production of this document was supported by the IRSST (Grants 99-542 and 99-745)

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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 m³/d and body weight of 70 kg

Ceiling : Ceiling exposure [limit] value in Quebec

D-Ceiling : Calculated inhaled dose for pulmonary ventilation of 10 m³/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/m³ 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

Carbon disulfide

Quebec's Occupational exposure limits: TWAEV: 12 mg/m³ (4 ppm). STEV: 36 mg/m³ (12 ppm)

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

Ototoxicity - Analysis of human studies

Only one study was identified using the auditory brainstem responses test. An ototoxic effect was observed after chronic exposure in workers. It seems that a recovery from this effect is possible. However, no data on exposure to noise were reported.

Ototoxicity - Analysis of animal studies

Two rat studies were identified using the auditory brainstem responses test. One study found a transient delay of the parameters in Wistar rats exposed to 200 ppm for 15 weeks. The second study did not find any ototoxic effect in Long-Evans rats exposed to 400 ppm for 11 weeks. However, in this study the exposure was interrupted for 17 days after 6.5 weeks of exposure.

Interaction with noise - Analysis of human studies

Only one study was identified using pure tone audiometry. A potentiation of noise induced hearing loss by CS₂ was observed. However, CS₂ + noise group was older and its duration of employment was twice higher than in noise or control groups. There was no CS₂ only exposed group in this study. Therefore no meaningful conclusion regarding an interaction between noise and CS₂ can be drawn from this study.

Interaction with noise - Analysis of animal studies

No study was identified.

Discussion

Human and animal studies on the ototoxic effect of carbon disulfide from occupational exposure as well as human studies on its interaction with noise are not conclusive. In the absence of other studies, it is not possible to draw any conclusion regarding the ototoxicity of carbon disulfide or its interaction with noise.

Carbon disulfide**Carbon di sul fi de**• TWAEV : 4 ppm | 12 mg/m³

D-TWAEV : 1,7 mg/kg/d

Population

Species : Worker

: E1 = 131; E2 = 105; C = 110

Sex : Males

Age : E1 = 48.3; E2 = 42.2; C = 42.0 years

Exposure

Route : Inhalation

Duration : E1 = 20.8; E2 = 12.1; C = 11.3 years

C/D reported : E1 = 1.6-20.1 ppm; E2 and C = 0 ppm

CSU/DSU :

Ratio : 0.4-5.1

ASM : Personal sampling and passive sampling with tubes-type diffusing samplers

BM :

NSM : Sound pressure level meter model B&K 2260

NL : E1 = 80-91; E2 = 83-90; C = 75-82 dB(A)

Remarks : Carbone disulfide exposure concentrations are average concentrations in different areas

Tests**Test type**

• Effects reported

Details on test

• Remarks

Pure tone audiometry

at 1, 2, 3, 4, 6, 1, and 0.5 kHz (ascending and then descending)

- Workers exposed to both CS₂ and noise had greater hearing impairment than did the noise-only exposure group at 0.5, 1 and 2 kHz (PTA)(Pure Tone Average). Both had similar hearing loss at 6 kHz
- Noise-only workers had a stronger effect at 4 kHz than at other frequencies
- CS₂ and noise workers had the most severe effects at 6 kHz and the least severe effect at 2 kHz

- Hearing tests conducted 16 h after the last work day.
- Both ears were tested

Mechanism of action**Authors' conclusion**

Significant ototraumatic dose-response interaction relationship between CS₂ and noise exposure. Higher risk of loss of hearing at speech frequencies when exposed to CS₂ levels higher than the permissible levels

Our conclusion

Potential of noise induced hearing loss by carbone disulfide. However, carbone disulfide and noise group was older and its duration of employment was twice higher than that in noise or control group. There was no carbone disulfide only exposed group in this study

Carbon disulfide**Carbon disulfide**• TWAEV : 4 ppm | 12 mg/m³

D-TWAEV : 1,7 mg/kg/d

Population

Species : Worker

: C = 39; E1 = 34; E2 = 24; E3 = 16

Sex : Males

Age : C = 46; E1 = 47; E2 = 44; E3 = 22.8 years

Exposure

Route : Inhalation

Duration : C = 0 year; E1 = 27.2 years; E2 = 4.39 years; E3 = 22.8 years

C/D reported : 3.3 – 8.2 ppm

CSU/DSU :

Ratio : 0.6 - 2.1

ASM :

BM :

NSM :

NL : NR

Remarks : C= group control ; E1 = group exposed > 240 months ; E2 = group exposed 24-84 months ;
 E3 = group exposed in the past for >120 months and not subjected to exposure for > 84 months
 Carbon disulfide exposure concentrations are average levels in 44 workers

Tests**Test type**

• Effects reported

Details on test

• Remarks

Auditory brainstem responses

Clicks of 126 dB SPL

• Latencies of components V, III-V IPL and I-V IPL significantly greater in groups E1 and E2 than in C group. No difference between groups E3 and C

Mechanism of action**Authors' conclusion**

Ototoxic effect after chronic exposure in workers. Recovery from this effect is possible

Our conclusion

Ototoxic effect after chronic exposure in workers. Recovery from this effect is possible

Carbon disulfide**Carbon di sul fi de**• TWAEV : 4 ppm | 12 mg/m³

D-TWAEV : 1,7 mg/kg/d

Population

Species : Rat Wistar

: 8 - 10

Sex : Females

Age : 11 weeks

Exposure

Route : Inhalation

Duration : 6 h/d; 5 d/w; 15 w

C/D reported : 200 and 800 ppm

CSU/DSU :

Ratio : 50 - 200

ASM :

BM :

NSM :

NL :

Remarks : Exposure to 800 ppm was not evaluated (dose ratio > 100)

Tests**Test type**

• Effects reported

Details on test

• Remarks

Auditory brainstem responses

- Latency of component I, interpeak latencies III-V and I-V at 96 dB were delayed significantly but transiently during the exposure period

Clicks of 61 and 96 dB SPL

- Test performed before exposure, every 3 weeks during the exposure period and 2 and 6 weeks after the end of exposure

Mechanism of action**Authors' conclusion**

The transient delay of the parameters in the group exposed to 200 ppm was considered to represent a slight conduction dysfunction

Our conclusion

LOAEL of 200 ppm for ototoxic effect in rats

Carbon disulfide**Carbon di sul fi de**• TWAEV : 4 ppm | 12 mg/m³

D-TWAEV : 1,7 mg/kg/d

Population

Species : Rat Long Evans

: 10

Sex : Females

Age :

Exposure

Route : Inhalation

Duration : 7 h/d; 7 d/w; 11 w

C/D reported : 400 ppm

CSU/DSU :

Ratio : 100

ASM :

BM :

NSM :

NL :

Remarks : Exposure interrupted for 17 days after 6.5 weeks of exposure

Tests**Test type**

• Effects reported

Details on test

• Remarks

Auditory brainstem responses

• No effect

Tone pips centered on 16 kHz

- Test performed before exposure, the first, fourth, seventh and eleventh weeks of exposure and 1 and 3 weeks after the end of exposure

Mechanism of action**Authors' conclusion**

No ototoxic effect after exposure to 400 ppm in rats

Our conclusion

No ototoxic effect after exposure to 400 ppm in rats

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