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

Trichloroethylene

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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

Trichloroethylene

Quebec's Occupational exposure limits: TWAEV: 269 mg/m³ (50 ppm). STEV: 1070 mg/m³ (200 ppm)

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

Ototoxicity - Analysis of human studies

Hearing losses were reported in workers in association with exposure to trichloroethylene in case studies (Gist 1995). In a study of 40 exposed workers (Szulc-Kuberska 1976), 26 had bilateral sensorineural hearing loss. Workers with a long-term occupational exposure to solvents, including trichloroethylene, were reported to have abnormally distorted speech audiometry results (Odkvist 1987). This suggests a damage to the central auditory system which cannot be attributed to noise. However, the exposure concentrations and noise levels were not exactly reported, in all these studies.

Ototoxicity - Analysis of animal studies

There are 7 studies demonstrating that trichloroethylene exposure by inhalation is ototoxic in rats. Permanent hearing loss has been found to be restricted to the mid- to high-frequencies (4 to 20 kHz). The greatest reduction in hearing was observed at 16 kHz. The ototoxicity appears to be a high-concentration effect in rats as shown by auditory brain responses measurements or reflex modification audiometry. After 13-weeks exposure, the LOAEL for ototoxicity was 2500 ppm (Crofton 1997), and the NOAEL was 800 ppm (Albee 2006). Morphologic examination demonstrated that trichloroethylene damaged spiral ganglions (a sign of the neurotoxic effect) in the cochleae of rats (Fechter 1998).

Interaction with noise - Analysis of human studies

No study identified.

Interaction with noise - Analysis of animal studies

One study in rats was identified (Muijser 2000). A supraadditive ototoxic interaction between trichloroethylene and noise was found at low frequencies after a combined exposure to 95 dB SPL noise and to 3000 ppm trichloroethylene for 3 weeks.

Discussion

Although certain effects were reported in workers, other human studies are necessary to further support the current incomplete evidence. In the rat, trichloroethylene clearly affects the auditive function mainly in the range of mid frequencies of the cochlea. No human study on interaction between trichloroethylene and noise was found. In one study in rats, there was evidence of interaction at low frequencies. Further studies are necessary to draw any conclusion about interaction with noise. We recommend, by taking account of the results of the human studies and the evidence provided by the animal studies, to regard trichloroethylene as an ototoxic agent.

Trichloroethylene

Trichloroethylene
• TWAEV : 50 ppm | 269 mg/m³ D-TWAEV : 38 mg/kg/d

Population

Species : Rat Fisher 344 # : NR Sex : Males and females
Age : 14 weeks

Exposure

Route : Inhalation
Duration : 6 h/d; 5 d/w; 13 w
C/D reported : 250, 800 and 2500 ppm
CSU/DSU :
Ratio : 5 - 50
ASM :
BM :
NSM :
NL :
Remarks :

Tests

Test type • Effects reported	Details on test • Remarks
Auditory brainstem responses • Hearing loss observed only at 2500 ppm. Hearing threshold elevated by 4 dB at 4 and 8 kHz, 15 dB at 16 kHz and 8 dB at 30 kHz	Tone pips of 4, 8, 16 and 30 kHz
Light microscopy • Focal loss of cochlear hair cells observed in the upper basal turn	

Mechanism of action

Authors' conclusion

NOAEL of 800 ppm for ototoxic effect in rats

Our conclusion

NOAEL of 800 ppm for ototoxic effect in rats

Trichloroethylene

Trichloroethylene
• TWAEV : 50 ppm | 269 mg/m³ D-TWAEV : 38 mg/kg/d

Population

Species : Rat Long Evans # : 8 - 10 Sex : Males
Age : 60 days

Exposure

Route : Inhalation
Duration : 6 h/d; 5 d
C/D reported : 1000, 2000 and 4000 ppm
CSU/DSU :
Ratio : 20 - 80
ASM :
BM :
NSM :
NL :
Remarks :

Tests

Test type • Effects reported	Details on test • Remarks
Reflex modification audiometry	at 4, 8, 16, 24, 32 and 40 kHz
• - Hearing losses (22, 30 and 13 dB) at 8, 16 and 24 kHz tones following exposure to 4000 ppm. - No effect of exposure to 1000 or 2000 ppm	• Test performed 3 weeks after the end of exposure to 1000, 2000 and 4000 ppm
Reflex modification audiometry	at 0.5 - 40 kHz
• - Increase in thresholds began on day 4 of exposure and persisted up to 12 weeks post-exposure - 14 weeks, there were increased thresholds at 8 and 16 kHz	• Test performed prior to, 1 hour following each of 5 exposure days to 4000 ppm and 5 days, 1, 2, 4, 8 and 12 weeks post-exposure for frequency of 16 kHz. At 14 weeks, tests performed for 0.5, 1, 2, 4, 8, 16, 24, 32 and 40 kHz

Mechanism of action

Authors' conclusion

Persistent mid-frequency hearing loss at 4000 ppm in rats

Our conclusion

NOAEL of 2000 ppm for ototoxic effect in rats and ototoxic effect observed at 4000 ppm

Trichloroethylene

Trichloroethylene
• TWAEV : 50 ppm | 269 mg/m³ D-TWAEV : 38 mg/kg/d

Population

Species : Rat Long Evans # : 7 - 8 Sex : Males
Age : 60 days

Exposure

Route : Inhalation
Duration : 8 h/d; 5 d
C/D reported : 3500 ppm
CSU/DSU :
Ratio : 70
ASM :
BM :
NSM :
NL :
Remarks :

Tests

Test type • Effects reported	Details on test • Remarks
Reflex modification audiometry	at 0.5 - 40 kHz
• Hearing loss for 8 and 16 kHz	• Test performed 5 to 8 weeks after the end of exposure

Mechanism of action

Authors' conclusion

Mid-frequency hearing loss at 3500 ppm in rats

Our conclusion

Ototoxic effect at 3500 ppm in rats

Trichloroethylene

Trichloroethylene
• TWAEV : 50 ppm | 269 mg/m³ D-TWAEV : 38 mg/kg/d

Population

Species : Rat Long Evans # : 8 - 10 Sex : Males
Age : 60 days

Exposure

Route : Inhalation
Duration : 6 h/d; 5 d/w; 13 w
C/D reported : 800, 1600, 2400 and 3200 ppm
CSU/DSU :
Ratio : 16 - 64
ASM :
BM :
NSM :
NL :
Remarks :

Tests

Test type • Effects reported	Details on test • Remarks
Reflex modification audiometry • - Hearing losses of 21 and 35 dB following exposure to 2400 and 3200 ppm, respectively. - No effect of exposure to 800 or 1600 ppm	at 16 kHz • Test performed 3 to 5 weeks after the end of exposure

Mechanism of action

Authors' conclusion

Hearing loss LOAEL for a mid-frequency tone of 2400 ppm in rats

Our conclusion

LOAEL of 2400 ppm for ototoxic effect in rats

Trichloroethylene

Trichloroethylene
• TWAEV : 50 ppm | 269 mg/m³ D-TWAEV : 38 mg/kg/d

Population

Species : Rat Long Evans # : 3 - 10 Sex : Males
Age : 60 days

Exposure

Route : Inhalation
Duration : 6 h/d; 5 d
C/D reported : 4000 ppm
CSU/DSU :
Ratio : 80
ASM :
BM :
NSM :
NL :
Remarks :

Tests

Test type • Effects reported	Details on test • Remarks
Reflex modification audiometry	at 1, 4, 8, 16, 24, 32 and 40 kHz
• Hearing loss (25 dB) for 8 and 16 Hz tones	• Test performed 3 weeks after the end of exposure
Electrocochleography (Compound action potential : CAP)	at 2, 4, 8, 16, 32 and 40 kHz
• - Auditory threshold shifts elevated (20 dB) at 8 and 16 kHz. - Reduction of wave I amplitude at 16 kHz from 50 to 90 dB. 1 mV cochlear microphonic for 2-40 kHz tones not affected	• Test performed 5 to 7 weeks after the end of exposure
Light microscopy	Cochleogram
• Loss of spiral ganglion cells in the middle turn, but not in the basal turn of the cochlea	• Histology performed 11 weeks after the end of exposure

Mechanism of action

Data suggest that the loss in auditory function can be accounted for by cochlear impairment and that the spiral ganglion cell may be a prominent target of trichloroethylene

Authors' conclusion

Functional and structural damage to the cochlea at 4000 ppm in rats

Our conclusion

Ototoxic effect at 4000 ppm in rats

Trichloroethylene

Trichloroethylene
• TWAEV : 50 ppm | 269 mg/m³ D-TWAEV : 38 mg/kg/d

Population

Species : Rat Wistar
: 12
Sex : Not reported
Age : 11 weeks

Exposure

Route : Inhalation
Duration : 18 h/d; 5 d/w; 3 w
C/D reported : 1500 and 3000 ppm
CSU/DSU :
Ratio : 30 - 60
ASM :
BM :
NSM :
NL :
Remarks :

Tests

Test type • Effects reported	Details on test • Remarks
Reflex modification audiometry • - Hearing thresholds for 20 kHz but not 5 or 35 kHz tones increased by 25 dB at 3000 ppm. This effect persisted unchanged throughout the post-exposute period - No effect observed at 1500 ppm	Tone pips at 5 and 20 or 5 and 35 kHz • Test performed before exposure and at 1, 3 and 6 week after the end of exposure (5 and 20 kHz) or 5 weeks after the end of exposure (5 and 35 kHz)

Mechanism of action

Authors' conclusion

Ototoxic effect at 3000 ppm in rats

Our conclusion

LOAEL at 3000 ppm for ototoxic effect in rats

Trichloroethylene

Trichloroethylene
• TWAEV : 50 ppm | 269 mg/m³ D-TWAEV : 38 mg/kg/d

Population

Species : Rat Wag/Rij
Age : 11 weeks
: C = 8; E1 = 8; E2 = 8; E3 = 8
Sex : Not reported

Exposure

Route : Inhalation
Duration : 18 h/d; 5 d/w; 3 w
C/D reported : 3000 ppm
CSU/DSU :
Ratio : 60
ASM :
BM :
NSM :
NL : 95 dB(A) or 95.5 dB SPL ; White noise (1-30 kHz)
Remarks : Simultaneous exposure to trichloroethylene and noise

Tests

Test type • Effects reported	Details on test • Remarks
Reflex modification audiometry • - Exposure to TCE alone resulted in hearing loss at 4, 8, 16, and 20 kHz - Hearing loss due to exposure to noise alone occured at frequencies of 8, 16 and 20 kHz - Generally, combined exposure to TCE and noise resulted in larger auditory threshold changes than that produced by either TCE alone or noise alone. However, it was not larger than the algebraic sum of hearing loss due to exposure to TCE or noise alone at 8, 16 and 20 kHz - At 4 kHz, hearing loss due to combined exposure was significantly larger than the sum of that produced by TCE exposure alone or noise alone	at 4, 8, 16, 20, 24 and 32 kHz • Testing conducted at 2 and 3 weeks before exposure and at 1 and 2 weeks post-exposure

Mechanism of action

Authors' conclusion

Evidence of an interaction of combined exposure to TCE and noise at the lower edge of the range of frequencies affected

Our conclusion

Trichloroethylene might interact with noise to impair hearing at low frequencies

Trichloroethylene

Trichloroethylene
• TWAEV : 50 ppm | 269 mg/m³ D-TWAEV : 38 mg/kg/d

Population

Species : Rat Long Evans # : 6 - 10 Sex : Males
Age : 100 days

Exposure

Route : Inhalation
Duration : 12 h/d; 12 w
C/D reported : 1600 and 3200 ppm
CSU/DSU :
Ratio : 32 - 64
ASM :
BM :
NSM :
NL :
Remarks :

Tests

Test type • Effects reported	Details on test • Remarks
Auditory brainstem responses • - Decreased amplitude at 4-16 kHz through the third week of recovery phase in rats exposed to 3200 ppm - Increased latency of component 5 and the 3-5 and 1-5 inter-wave times after 9 weeks of exposure to 3200 ppm	Clicks of 60 dB at 400 Hz to 6 kHz Tone pips of 4, 8 and 16 kHz • Test performed after 1, 3, 6, 9 and 12 weeks of exposure and 1 and 3 weeks after the end of exposure

Mechanism of action

Authors' conclusion

Predominantly high-frequency hearing loss

Our conclusion

Ototoxic effect at 3200 ppm in rats

Trichloroethylene

Trichloroethylene
• TWAEV : 50 ppm | 269 mg/m³ D-TWAEV : 38 mg/kg/d

Population

Species : Rat Fisher 344 # : 4 - 10 Sex : Males
Age : 100 days

Exposure

Route : Inhalation
Duration : 12 h/d; 3 w
C/D reported : 2000 and 3200 ppm
CSU/DSU :
Ratio : 32 - 64
ASM :
BM :
NSM :
NL :
Remarks :

Tests

Test type • Effects reported	Details on test • Remarks
Auditory brainstem responses	Clicks of 60 dB Tone pips of 4, 8 and 16 kHz
• Decreased amplitude at 4-16 kHz in rats exposed to 2000 and 3200 ppm	• Test performed 1 week after the end of exposure

Mechanism of action

Authors' conclusion

Predominantly high-frequency hearing loss

Our conclusion

Ototoxic effect at 2000 ppm in rats

Trichloroethylene

Trichloroethylene
• TWAEV : 50 ppm | 269 mg/m³ D-TWAEV : 38 mg/kg/d

Population

Species : Rat Long Evans # : 9 Sex : Males
Age : 60 days

Exposure

Route : Inhalation
Duration : 18 h/d; 5 d
C/D reported : 3000 ppm
CSU/DSU :
Ratio : 60
ASM :
BM :
NSM :
NL :
Remarks :

Tests

Test type • Effects reported	Details on test • Remarks
Auditory brainstem responses • - Decreased amplitude. - Increased latency of component P1	Tone pips of 16 kHz • Test performed 10 days after the end of exposure

Mechanism of action

Authors' conclusion

Predominantly high-frequency hearing loss

Our conclusion

Ototoxic effect at 3000 ppm in rats

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