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Ototoxic effects of industrial chemicals**

Trichloroethylene

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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 an increased 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 ceiling value or five times the 8-h time weighted average exposure limit value(TWAEV) for human data and up to 100 times the 8-h TWAEV or 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 specie, number of subjects, exposure way, characteristics of control groups, exposure levels, audiometric and statistical tests, dose/effect relation. Table 1 shows how this information was combined to yield an overall assessment of the ototoxic potential of a given substance. Human data were generally given more weight in the overall assessment. When no human studies were available, which is different from the absence of evidence from the available human studies, the overall assessment was deemed the same as that from animal studies.

We built a weight of evidence table 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 were 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. When no human studies were available, or 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.

Regarding the final conclusion about the ototoxic potential of chemical substances, all substances bearing a "strong evidence" of ototoxicity overall are considered "ototoxic". Those with "medium evidence" overall are rated "possibly ototoxic". We consider the ototoxic potential of those with only "weak evidence" as "non conclusive". Finally, those for which there is absence of evidence overall bear the mention "no evidence".

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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

Trichloroethylene

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

Conclusion about ototoxicity	Strength of evidence
Ototoxic substance	From animal studies: **Strong** From human studies: **Medium** Overall: **Strong**

ANALYSIS OF ANIMAL STUDIES

There are 7 studies demonstrating that trichloroethylene 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 2400 ppm (Crofton 1997). Morphologic examination demonstrated that trichloroethylene damaged spiral ganglions in the cochleae of rats (Fechter 1998).

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.

CONCLUSION

Although certain effects were reported in workers, other human studies are necessary to come to a final decision. In the rat, trichloroethylene clearly affects the auditive function mainly in the range of mid frequencies of the cochlea. 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 [79-00-5]

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

Population

Species : Rat Fisher 344 # : NR Sex : Males

Age :

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 :

Remarks :

Tests

Only a summary of experience available

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Tone pips of 4, 8, 16 and 30 kHz
• 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	
Light microscopy	
• Focal loss of cochlear hair cells observed in the upper basal turn	

Action mechanism

Authors' conclusion

NOAEL of 800 ppm for ototoxic effect in rats

Our conclusion

NOAEL of 800 ppm for ototoxic effect in rats

Trichloroethylene [79-00-5]

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 :

Remarks :

Tests

Test type • Effects reported	Precisions 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

Action mechanism

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 [79-00-5]

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 :
Remarks :

Tests

Test type • Effects reported	Precisions 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

Action mechanism

Authors' conclusion

Mid-frequency hearing loss at 3500 ppm in rats

Our conclusion

Ototoxic effect at 3500 ppm in rats

Trichloroethylene [79-00-5]

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 :

Remarks :

Tests

Test type • Effects reported	Precisions 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

Action mechanism

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 [79-00-5]

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 :

Remarks :

Tests

Test type • Effects reported	Precisions 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	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

Action mechanism

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 [79-00-5]

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 :

Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Reflex modification audiometry	Tone pips at 5 and 20 or 5 and 35 kHz
• - 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	• 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)

Action mechanism

Authors' conclusion

Ototoxic effect at 3000 ppm in rats

Our conclusion

LOAEL at 3000 ppm for ototoxic effect in rats

Trichloroethylene [79-00-5]

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 :
Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Clicks of 60 dB at 400 Hz to 6 kHz Tone pips of 4, 8 and 16 kHz
• - 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	• Test performed after 1, 3, 6, 9 and 12 weeks of exposure and 1 and 3 weeks after the end of exposure

Action mechanism

Authors' conclusion

Predominantly high-frequency hearing loss

Our conclusion

Ototoxic effect at 3200 ppm in rats

Trichloroethylene [79-00-5]

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 :

Remarks :

Tests

Test type • Effects reported	Precisions 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

Action mechanism

Authors' conclusion

Predominantly high-frequency hearing loss

Our conclusion

Ototoxic effect at 2000 ppm in rats

Trichloroethylene [79-00-5]

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 :

Remarks :

Tests

Test type • Effects reported	Precisions 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

Action mechanism

Authors' conclusion

Predominantly high-frequency hearing loss

Our conclusion

Ototoxic effect at 3000 ppm in rats

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