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Ototoxic effects of industrial chemicals**

n-Hexane

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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

n-Hexane

Occupational exposure limits: TWAEV: 176 mg/m³ (50 ppm)

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

ANALYSIS OF ANIMAL STUDIES

Seven subacute and subchronic studies on rats of two different strains were identified. Five studies were performed in the same laboratory. A temporary ototoxic effect was suggested in young and adult rats using auditory brainstem responses test with a LOAEL of 500 ppm. However, no morphologic examination was performed.

ANALYSIS OF HUMAN STUDIES

Three studies on workers were identified. In two studies from the same laboratory (Chang 1987, Chang 1991), exposed subjects were workers with a polyneuropathy. The studies suggest an ototoxic effect of n-hexane (one of which suggests a permanent ototoxic effect), however exposure concentrations, noise levels, and duration of exposure were not reported. The third study (Huang 1989) on workers exposed for 5 – 30 years suggests an ototoxic effect of n-hexane, however workers were exposed to other solvents including benzene and C15-C19 hydrocarbons and exposure to noise was not reported.

CONCLUSION

Although certain effects were reported in workers, other human studies are necessary to come to a final decision. In the rat, exposure to n-hexane clearly affects the auditive function. We recommend, by taking account of the results of the human studies and the evidence brought by the animal studies, to consider n-hexane as a possibly ototoxic agent.

n-Hexane [110-54-3]

n-Hexane
• TWAEV : 50 ppm | 176 mg/m³ D-TWAEV : 25 mg/kg/d

Population

Species : Worker # : C = 25; E = 21 M + 1 F Sex : Males and females

Age : C = 32.8 years; E = 23.1 (17-34) years

Exposure

Route : Inhalation

Duration : NR

C/D reported : NR

CSU/DSU :

Ratio :

ASM : NR

BM :

Remarks : Exposed subjects were workers with a polyneuropathy

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses • No difference in wave I latency. The absolute wave III and V latencies and the I-III, III-V and I-V inter-peak latencies were prolonged	Clicks of 60 dB SL

Action mechanism

Authors' conclusion

Lack of difference of wave I latency suggests that the auditory nerve itself was not severely affected. Prolongation of inter-peak latencies should be interpreted as neurotoxic effects of n-hexane on the brainstem

Our conclusion

Study suggests ototoxic effect of n-hexane, however exposure concentrations were not reported

n-Hexane [110-54-3]

n-Hexane
• TWAEV : 50 ppm | 176 mg/m³ D-TWAEV : 25 mg/kg/d

Population

Species : Worker # : C = 50; E = 11 Sex : Males

Age : C = NR; E = 18 - 30 years

Exposure

Route : Inhalation

Duration : NR

C/D reported : NR

CSU/DSU :

Ratio :

ASM : NR

BM :

Remarks : Exposed subjects were workers with a polyneuropathy

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Clicks of 60 dB SL
• - No difference in wave I latency and in III-V inter-peak latency - Absolute wave III and V latencies and the I-III and I-V inter-peak latencies were prolonged	• Subjects followed up for 4 years after the end of exposure

Action mechanism

Authors' conclusion

Little improvement in the auditory brainstem responses 4 years after cessation of exposure

Our conclusion

Study suggests a permanent ototoxic effect of n-hexane, however exposure concentrations were not reported

n-Hexane [110-54-3]

n-Hexane
• TWAEV : 50 ppm | 176 mg/m³ D-TWAEV : 25 mg/kg/d

Population

Species : Rat Fisher 344 # : 5 Sex : Males

Age : E1 = 21 days; E2 = 80 days

Exposure

Route : Inhalation

Duration : 24 h/d; 6 d/w; 11 w

C/D reported : 1000 ppm

CSU/DSU :

Ratio : 20

ASM :

BM :

Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses • - Increased latency of the first component in young and adult rats. A complete recovery during recovery period - Increased latency between the I and V components with some recovery during recovery period in both groups	Clicks of 40-50 dB SL • Test performed each week from the 4 week of exposure until fifth week after the end of exposure

Action mechanism

Authors' conclusion

Comparable neurotoxic effect at 1000 ppm in young and old rats

Our conclusion

Temporary ototoxic effect at 1000 ppm in young and old rats

n-Hexane [110-54-3]

n-Hexane
• TWAEV : 50 ppm | 176 mg/m³ D-TWAEV : 25 mg/kg/d

Population

Species : Worker # : C = NR; E = 5 Sex : Males

Age : 17 - 26 years

Exposure

Route : Inhalation

Duration : 5 - 30 months

C/D reported : 55 ppm

CSU/DSU :

Ratio : 1.1

ASM : Gaz chromatography

BM :

Remarks : Two one hour air samples collected. Control data obtained form normal male subjects 20 to 29 years old. All exposed subjects had polyneuropathy

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Clicks of 60-70 dB SL
• No difference in wave I latency. The absolute wave III and V latencies and the I-III, III-V and I-V inter-peak latencies were prolonged	

Action mechanism

Authors' conclusion

Lack of difference of wave I latency suggests that the auditory nerve itself was not severely affected. Prolongation of inter-peak latencies should be interpreted as neurotoxic effects of n-hexane on the brainstem

Our conclusion

Study suggests ototoxic effect of n-hexane, however workers were exposed to other solvents including benzene and C15-C19 hydrocarbons

n-Hexane [110-54-3]

n-Hexane
• TWAEV : 50 ppm | 176 mg/m³ D-TWAEV : 25 mg/kg/d

Population

Species : Rat Sprague Dawley # : 22 Sex : Males

Age :

Exposure

Route : Inhalation

Duration : 21 h/d; 7 d/w; 28 d

C/D reported : 1000 ppm

CSU/DSU :

Ratio : 20

ASM :

BM :

Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Clicks at 40 dB SL
• - No effect on auditory sensitivity. - Prolonged latencies 2 days after the end of exposure. Return to normal 3 months after the end of exposure	• Test performed 2 days, 3 months and 12 months after the end of exposure

Action mechanism

The site of these alterations cannot be determined from the present data

Authors' conclusion

Temporary ototoxic effect at 1000 ppm in rats

Our conclusion

Temporary ototoxic effect at 1000 ppm in rats

n-Hexane [110-54-3]

n-Hexane
• TWAEV : 50 ppm | 176 mg/m³ D-TWAEV : 25 mg/kg/d

Population

Species : Rat Sprague Dawley # : 22 Sex : Males

Age :

Exposure

Route : Inhalation

Duration : 18 h/d; 7 d/w; 61 d

C/D reported : 1000 ppm

CSU/DSU :

Ratio : 20

ASM :

BM :

Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Clicks of 40 dB SL Frequencies 3,15, 6,3, 12,5, and 20,0 kHz
• - Slight loss of auditory sensitivity and prolonged latencies 2 days after the end of exposure - Return to normal 4 months after the end of exposure	• Test performed 2 days, 4 months and 10 months after the end of exposure

Action mechanism

The site of these alterations cannot be determined from the present data

Authors' conclusion

Temporary ototoxic effect at 1000 ppm in rats

Our conclusion

Temporary ototoxic effect at 1000 ppm in rats

n-Hexane [110-54-3]

n-Hexane
• TWAEV : 50 ppm | 176 mg/m³ D-TWAEV : 25 mg/kg/d

Population

Species : Rat Fisher 344 # : 11 - 12 Sex : Males

Age : 21 days

Exposure

Route : Inhalation

Duration : 14 h/d; 7 d/w; 14 w

C/D reported : 2000 ppm

CSU/DSU :

Ratio : 40

ASM :

BM :

Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Clicks of 60 dB SL
• - No effect on the latencies. - A decrease in the amplitude of the fifth component by the tenth week of exposure and throughout the recovery period	• Test performed each week from the sixth week of exposure until 6 weeks after the end of exposure
Intensity discrimation	4 kHz
• No effect	• Test performed 1, 4 and 6 weeks after the end of exposure

Action mechanism

Authors' conclusion

Neurotoxic effect at 2000 ppm in young rats

Our conclusion

Ototoxic effect at 2000 ppm in young rats

n-Hexane [110-54-3]

n-Hexane
• TWAEV : 50 ppm | 176 mg/m³ D-TWAEV : 25 mg/kg/d

Population

Species : Rat Fisher 344 # : 8 Sex : Males

Age : 23 days

Exposure

Route : Inhalation

Duration : 14 h/d; 7 d/w; 9 w

C/D reported : 4000 ppm

CSU/DSU :

Ratio : 80

ASM :

BM :

Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Tone pips of 4, 8 and 16 kHz
• Decreased amplitude at and above 65 dB at 16 kHz stimuli	• Test performed 2 weeks after the end of exposure
Multisensory conditionned avoidance response task	at 4 kHz
• No effect	• Test performed 12 weeks after the end of exposure

Action mechanism

Authors' conclusion

Neurotoxic effect at 4000 ppm in young rats

Our conclusion

Probable ototoxic effect at 4000 ppm in young rats

n-Hexane [110-54-3]

n-Hexane
• TWAEV : 50 ppm | 176 mg/m³ D-TWAEV : 25 mg/kg/d

Population

Species : Rat Fisher 344 # : C = 4; E = 6 Sex : Males

Age :

Exposure

Route : Inhalation

Duration : 24 h/d; 5 d/w; 11 w

C/D reported : 1000 ppm

CSU/DSU :

Ratio : 20

ASM :

BM :

Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Clicks of 35, 45, and 65 dB SL
• - Increased latency of the fifth component, with little effect on the first component - General decrease in the amplitude of most components. - Latency returned to normal within 5 weeks after termination of exposure, but amplitude not	• Test performed before exposure, on the second day after the last exposure of each week and for 14 weeks after the end of exposure

Action mechanism

Authors' conclusion

Neurotoxic effect at 1000 ppm in rats

Our conclusion

Ototoxic effect at 1000 ppm in rats

n-Hexane [110-54-3]

n-Hexane
• TWAEV : 50 ppm | 176 mg/m³ D-TWAEV : 25 mg/kg/d

Population

Species : Rat Fisher 344 # : 5 Sex : Males

Age : E1 = 21 days; E2 = 80 days

Exposure

Route : Inhalation

Duration : 24 h/d; 5 d/w; 11 w

C/D reported : 500, 1000 and 1500 ppm

CSU/DSU :

Ratio : 10 - 30

ASM :

BM :

Remarks : Only the latencies of waves I and V were measured

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Clicks of 40 dB SL
• - Prolonged latency of the fifth, but not the first component as a function of hexane concentration - Reversible effect	• Test performed each week of exposure until 6 weeks after the end of exposure
Cortical auditory evoked potentials	Tone bursts at 9 kHz, 50 dB SL
• - Prolonged latency of the P50 component as a function of hexane concentration - Effect reversible	• Test performed each week of exposure until 6 weeks after the end of exposure

Action mechanism

Results indicates an effect on central auditory tract conduction time

Authors' conclusion

Temporary ototoxic effect at 500 ppm in rats

Our conclusion

Temporary ototoxic effect at 500 ppm in rats

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