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

n-Hexane

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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

n-Hexane

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

Conclusion about ototoxicity	Strength of evidence
Possibly ototoxic substance	From human studies: **Weak** From animal studies: **Strong** Overall: **Medium**
Conclusion about interaction with noise	Strength of evidence
No documentation	From human studies: **No study found** From animal studies: **No study found** Overall: **No study found**

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

Ototoxicity - 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.

Interaction with noise - Analysis of human studies

No study was identified.

Interaction with noise - Analysis of animal studies

No study was identified.

Discussion

Although certain effects were reported in workers, other human studies are necessary to come to a definitive conclusion. 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. No human or animal study on ototoxic interaction between n-hexane and noise was identified.

n-Hexane

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 :
NSM : NR
NL : NR
Remarks : Exposed subjects were workers with a polyneuropathy

Tests

Test type • Effects reported	Details 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

Mechanism of action

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

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 :

NSM : NR

NL : NR

Remarks : Exposed subjects were workers with a polyneuropathy

Tests

Test type • Effects reported	Details 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

Mechanism of action

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

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 :

NSM :

NL :

Remarks :

Tests

Test type • Effects reported	Details on test • Remarks
Auditory brainstem responses	Clicks of 40-50 dB SL
• - 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	• Test performed each week from the 4 week of exposure until fifth week after the end of exposure

Mechanism of action

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

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 :

NSM :

NL : NR

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	Details 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 60-70 dB SL

Mechanism of action

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

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 :
NSM :
NL :
Remarks :

Tests

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

Mechanism of action

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

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 :
NSM :
NL :
Remarks :

Tests

Test type • Effects reported	Details 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

Mechanism of action

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

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 :
NSM :
NL :
Remarks :

Tests

Test type • Effects reported	Details 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

Mechanism of action

Authors' conclusion

Neurotoxic effect at 2000 ppm in young rats

Our conclusion

Ototoxic effect at 2000 ppm in young rats

n-Hexane

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 :
NSM :
NL :
Remarks :

Tests

Test type • Effects reported	Details 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

Mechanism of action

Authors' conclusion

Neurotoxic effect at 4000 ppm in young rats

Our conclusion

Probable ototoxic effect at 4000 ppm in young rats

n-Hexane

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 :
NSM :
NL :
Remarks :

Tests

Test type • Effects reported	Details on test • Remarks
Auditory brainstem responses • - 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	Clicks of 35, 45, and 65 dB SL • Test performed before exposure, on the second day after the last exposure of each week and for 14 weeks after the end of exposure

Mechanism of action

Authors' conclusion

Neurotoxic effect at 1000 ppm in rats

Our conclusion

Ototoxic effect at 1000 ppm in rats

n-Hexane

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 :

NSM :

NL :

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

Tests

Test type • Effects reported	Details 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

Mechanism of action

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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