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

Acrylonitrile

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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

Acrylonitrile

Quebec's Occupational exposure limits: TWAEV: 4,3 mg/m³ (2 ppm)

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

Ototoxicity - Analysis of human studies

No study was identified.

Ototoxicity - Analysis of animal studies

Four studies from the same laboratory were identified. In these studies the acrylonitrile was administered subcutaneously to rats in a high dose of 50 mg/kg/d during 1 to 5 days. A transient elevated auditory threshold was found after single acrylonitrile administration. However, no permanent hearing or hair cell loss was observed 4 weeks after up to 5 days administration of acrylonitrile.

Interaction with noise - Analysis of human studies

No study was identified.

Interaction with noise - Analysis of animal studies

Four studies from the same laboratory were identified. In these studies the acrylonitrile was administered subcutaneously to rats at a high dose of 50 mg/kg/d during 1 to 5 days. Acrylonitrile potentiates permanent noise-induced hearing loss particularly for high frequency tones and particularly when acrylonitrile and noise were given on repeated occasions. Outer hair cells are the main target of toxicity.

Discussion

No studies were performed in humans. Acrylonitrile potentiated permanent noise-induced hearing losses in rats. However, the route and dose of acrylonitrile exposure were different from those experienced by workers. Chronic animal and human studies are necessary to make a definitive conclusion. In the absence of other studies, it is not possible to draw any conclusion regarding the ototoxicity of acrylonitrile or its interaction with noise.

Acrylonitrile

Acrylonitrile
• TWAEV : 2 ppm | 4,3 mg/m³ D-TWAEV : 0,61 mg/kg/d

Population

Species : Rat Long Evans # : 5 Sex : Males
Age : 2 - 3 months

Exposure

Route : Subcutaneous
Duration : Single dose
C/D reported : 50 mg/kg
CSU/DSU :
Ratio : 82
ASM :
BM :
NSM :
NL :
Remarks :

Tests

Test type • Effects reported	Details on test • Remarks
Electrocochleography (Compound action potential : CAP)	Pur tones at 2, 4, 6, 8, 12, 16, 20, 24, 30, 35 and 40 kHz (CAP)
• Elevated auditory threshold that reached a maximum 10-20 minutes and returned to control levels 75–100 minutes following injection. This transient loss in sensitivity is 10-20 dB at 8-40 kHz	• Test performed prior to exposure and then at 5 minutes interval over the next 100 minutes

Mechanism of action

Authors' conclusion

Acrylonitrile is acutely ototoxic at this elevated dose

Our conclusion

Acute ototoxic effect at elevated subcutaneous dose of 50 mg/kg/d

Acrylonitrile

Acrylonitrile
• TWAEV : 2 ppm | 4,3 mg/m³ D-TWAEV : 0,61 mg/kg/d

Population

Species : Rat Long Evans # : 6 Sex : Males
Age : 2 - 3 months

Exposure

Route : Subcutaneous
Duration : 2 d
C/D reported : 50 mg/kg/d
CSU/DSU :
Ratio : 82
ASM :
BM :
NSM :
NL :
Remarks : 2 injections of 50 mg/kg on two successive days with a 16 hours interval between injections

Tests

Test type • Effects reported	Details on test • Remarks
Electrocochleography (Compound action potential : CAP)	Pur tones at 2 - 40 kHz (CAP)
• Acrylonitrile by itself did not produce permanent threshold impairment 3 weeks following administration	• Test performed 3 weeks after the end of exposure

Mechanism of action

Authors' conclusion

No permanent hearing loss 3 weeks following administrations of 50 mg/kg/d acrylonitrile during 2 days

Our conclusion

No permanent hearing loss 3 weeks following administrations of 50 mg/kg/d acrylonitrile during 2 days

Acrylonitrile

Acrylonitrile
• TWAEV : 2 ppm | 4,3 mg/m³ D-TWAEV : 0,61 mg/kg/d

Population

Species : Rat Long Evans # : 6 Sex : Males

Age : 2 - 3 months

Exposure

Route : Subcutaneous

Duration : Acrylonitrile : 1 dose or 2 doses on 2 successive days; Noise : 8 h

C/D reported : 50 mg/kg/d

CSU/DSU :

Ratio : 82

ASM :

BM :

NSM :

NL : 108 dB ; Octave band noise centered at 13.6 kHz

Remarks : Noise followed immediately acrylonitrile administration (1 dose) or followed only the second acrylonitrile administration (2 doses)

Tests

Test type • Effects reported	Details on test • Remarks
Electrocochleography (Compound action potential : CAP)	Pure tones at 2, 4, 6, 8, 12, 16, 20, 24, 30, 35 and 40 kHz (CAP)
• - Acrylonitrile + noise increased auditory threshold impairment (27 dB at 12-40 kHz) relative to rats receiving noise only (<20 dB) - Acrylonitrile by itself did not produce permanent threshold impairment 3 weeks following administration	• Test performed 3 weeks following end of administration of acrylonitrile

Mechanism of action

Authors' conclusion

Acrylonitrile can potentiate noise-induced hearing loss damages particularly for high frequency tones

Our conclusion

Acrylonitrile potentiates damages related to noise-induced hearing loss. However, the route and dose of acrylonitrile exposure were different from that experienced by workers

Acrylonitrile

Acrylonitrile
• TWAEV : 2 ppm | 4,3 mg/m³ D-TWAEV : 0,61 mg/kg/d

Population

Species : Rat Long Evans # : 6 Sex : Males
Age : 3 - 4 months

Exposure

Route : Subcutaneous
Duration : 1 or 5 d
C/D reported : 50 mg/kg/d
CSU/DSU :
Ratio : 82
ASM :
BM :
NSM :
NL :
Remarks :

Tests

Test type • Effects reported	Details on test • Remarks
Electrocochleography (Compound action potential : CAP)	Tone bursts at 2, 4, 6, 8, 12, 16, 20, 24, 30, 35 and 40 kHz (CAP)
• No permanent threshold impairment	• Test performed 4 weeks after the end of exposure

Mechanism of action

Authors' conclusion

No permanent threshold impairment 4 weeks following administration

Our conclusion

No permanent hearing 4 weeks following administrations of 50 mg/kg/d acrylonitrile during 5 days

Acrylonitrile

Acrylonitrile
• TWAEV : 2 ppm | 4,3 mg/m³ D-TWAEV : 0,61 mg/kg/d

Population

Species : Rat Long Evans # : 5 - 8 Sex : Males
Age : 3 - 4 months

Exposure

Route : Subcutaneous
Duration : Acrylonitrile : dose or 1 dose/d for 5 d : Noise : 4 h/d; 1 or 5 d
C/D reported : 50 mg/kg/d
CSU/DSU :
Ratio : 82
ASM :
BM :
NSM :
NL : 105 dB ; Octave band noise centred at 13.6 kHz
Remarks : Noise exposure started 1 hour after acrylonitrile administration

Tests

Test type • Effects reported	Details on test • Remarks
Electrocochleography (Compound action potential : CAP)	Tone bursts at 2, 4, 6, 8, 12, 16, 20, 24, 30, 35 and 40 kHz (CAP)
• - After 1 exposure, acrylonitrile + noise increased auditory threshold impairment at 12-40 kHz by 20 dB above control values relative to rats receiving noise only (10 dB above control values). - Acrylonitrile by itself did not produce permanent threshold impairment	• Test performed 4 weeks after the end of exposure to acrylonitrile

Mechanism of action

Authors' conclusion

Acrylonitrile can enhance noise-induced hearing loss particularly for high frequency tones and particularly when acrylonitrile and noise were given on repeated occasions

Our conclusion

Acrylonitrile potentiates permanent noise-induced hearing loss. However, the route and dose of acrylonitrile exposure were different from that experienced by workers

Acrylonitrile

Acrylonitrile
• TWAEV : 2 ppm | 4,3 mg/m³ D-TWAEV : 0,61 mg/kg/d

Population

Species : Rat Long Evans # : 11 Sex : Males
Age :

Exposure

Route : Subcutaneous
Duration : 5 d
C/D reported : 50 mg/kg/d
CSU/DSU :
Ratio : 82
ASM :
BM :
NSM :
NL :
Remarks :

Tests

Test type • Effects reported	Details on test • Remarks
Electrocochleography (Compound action potential : CAP)	Pure tones at 2 - 40 kHz (CAP)
• No permanent threshold impairment	• Test performed 4 weeks following end of administration of acrylonitrile
Distortion product otoacoustic emissions (DPOAE)	at 4 - 32 kHz at 1 kHz steps. L2 = 65 dBSPL L1 = 55 dBSPL Ratio f2/f1 = 1.281
• No hearing loss	• Test performed before exposure, 1 day and 4 weeks after the end of exposure
Light microscopy	Cochleogram
• No permanent hair cell loss	• Histology performed 4 weeks after the end of exposure

Mechanism of action

Authors' conclusion

No permanent hearing or hair cell loss 4 weeks following administrations of 50 mg/kg/d acrylonitrile during 5 days

Our conclusion

No permanent hearing or hair cell loss 4 weeks following administrations of 50 mg/kg/d acrylonitrile during 5 days

Acrylonitrile

Acrylonitrile
• TWAEV : 2 ppm | 4,3 mg/m³ D-TWAEV : 0,61 mg/kg/d

Population

Species : Rat Long Evans # : 6 - 11 Sex : Males
Age : 2 - 3 months

Exposure

Route : Subcutaneous
Duration : Acrylonitrile : 1 dose/d for 5 d ; Noise : 4 h/d; 5 d
C/D reported : 50 mg/kg/d
CSU/DSU :
Ratio : 82
ASM :
BM :
NSM :
NL : 95 or 97 dB ; Octave band noise centered at 8 kHz
Remarks : Noise exposure started 30 minutes after acrylonitrile administration

Tests

Test type • Effects reported	Details on test • Remarks
Electrocochleography (Compound action potential : CAP)	Pure tones at 2 - 40 kHz (CAP)
• - No permanent threshold impairment after noise or acrylonitrile exposure. - Only reversible temporary threshold shift in noise exposed animals. - When given in combination, acrylonitrile + noise induced permanent threshold shifts (13-16 dB at 7-40 kHz)	• Test performed 4 weeks after the end of exposure to acrylonitrile
Distortion product otoacoustic emissions (DPOAE)	at 4 - 32 kHz at 1 kHz steps. L2 = 65 dBSPL L1 = 55 dBSPL Ratio f2/f1 = 1.281
• No permanent hearing loss after noise or acrylonitrile exposure. When given in combination, acrylonitrile + noise induced a decreased amplitudes (up to 25 dB at 19 kHz)	• Test performed before exposure, 1 day and 4 weeks after the end of exposure
Light microscopy	Cochleogram
• - Very limited outer hair cell loss after noise or acrylonitrile exposure. - When given in combination, acrylonitrile + noise induced outer hair cells loss (up to 20 % on the first row between 13 and 47 kHz)	• Histology performed 4 weeks after the end of exposure

Mechanism of action

Authors' conclusion

Acrylonitrile potentiates permanent noise-induced hearing loss particularly for high frequency tones and particularly when acrylonitrile and noise were given on repeated occasions. Outer hair cells are the main target of toxicity

Our conclusion

Acrylonitrile potentiates noise-induced hearing loss. However, the route and dose of acrylonitrile exposure were different from that experienced by workers

Acrylonitrile

Acrylonitrile
• TWAEV : 2 ppm | 4,3 mg/m³ D-TWAEV : 0,61 mg/kg/d

Population

Species : Rat Long Evans # : C = 7; E1 = 4; E2 = 12 Sex : Males
Age : 7-8 weeks

Exposure

Route : Subcutaneous
Duration : 5 d; Noise : 4 h/d; 5 d
C/D reported : C and E1 = 0; E2 = 50 mg/kg/d
CSU/DSU :
Ratio : 82
ASM :
BM :
NSM :
NL : C = 0; E1 and E2 = 97 dB SPL ; Octave band noise centered at 8kHz ; 4 h/d, 5 d
Remarks :

Tests

Test type • Effects reported	Details on test • Remarks
Distortion product otoacoustic emissions (DPOAE)	From 2.9 to 56.3 kHz L1 = L2 = 75 dB SPL Ratio f2/f1 = 1.25
• - DPOAE amplitudes were profoundly reduced between 7 and 55 kHz in animals exposed to ACN + noise - After the recovery period, 4 weeks post-exposure, the animals that recieved combined exposure showed little change in their DPOAE measurements - The permanent DPOAE amplitude drop was 22 dB in ACN + noise animals	• Test performed prior to exposure, 3 days post-exposure and 4 weeks after the last exposition
Electrocochleography (Compound action potential : CAP)	à 2, 4, 6, 8, 12, 16, 20, 24, 30, 35 and 40 kHz
• Hearing thresholds were significantly higher in animals exposed to ACN + noise than in controls	• Test performed 4 weeks post-exposure
Light microscopy	
• - Cochleae from subjects exposed to noise alone displayed very limited damage (less than 1,5% OHC loss) - Cochleae from rats exposed to ACN + noise exhibited substantial damage in the basal half of the organ of Corti. The mean OHC loss averaged 35% in the 3 OHC rows in the region corresponding to frequencies above 12 kHz and 42% above 25 kHz	• Cochleae dissected 4 weeks post-exposure

Mechanism of action

Authors' conclusion

Combined exposure to ACN and noise levels as low as 97 dB SPL for 4 h can induce auditory impairment and OHC loss. A true potentiation of noise-induced hearing loss occurs in the presence of ACN

Our conclusion

A true potentiation of noise-induced hearing loss occurs in the presence of ACN. However, the route and dose of acrylonitrile exposure were different from that experienced by workers

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