2010-11-23

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

Carbon monoxide

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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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** Production of this document was supported by the IRSST (Grants 99-542 and 99-745)

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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

Carbon monoxide

Quebec's Occupational exposure limits: TWAEV: 40 mg/m³ (35 ppm). STEV: 230 mg/m³ (200 ppm)

Conclusion about ototoxicity	Strength of evidence
No evidence	From human studies: **No study found** From animal studies: **Absent** Overall: **Absent**
Conclusion about interaction with noise	Strength of evidence
Possible interaction	From human studies: **No study found** From animal studies: **Strong** Overall: **Medium**

Ototoxicity - Analysis of human studies

No study was identified.

Ototoxicity - Analysis of animal studies

There are 10 studies demonstrating that carbon monoxide by inhalation is not ototoxic in rats. All but one studies were performed in the same laboratory. Rats were exposed up to 1500 ppm carbon monoxide and the duration of intermittent exposures varied between 3.5 hours and 13 weeks. The authors used electrocochleography, auditory brainstem responses tests, reflex modification audiometry and light microscopy.

Interaction with noise - Analysis of human studies

No study was identified.

Interaction with noise - Analysis of animal studies

Eighteen rat studies were evaluated. All studies were performed in the same laboratory. Long Evans rats were exposed up to 1500 ppm CO and noise intensity varied between 95 and 115 dB. The level of noise employed was designed to induce auditory impairment, so it is not possible to draw any conclusion regarding lower noise levels. The duration of intermittent exposures varied between 4.5 hours and 13 days. The authors used electrocochleography, reflex modification audiometry, distortion product otoacoustic emissions (DPOAE), compound action potentials and light microscopy. A potentiation of noise-induced hearing loss by CO was found in all studies. The proposed mechanism is the generation of reactive oxygen species that cause oxydative stress which damages the cochlea (Pouyatos 2008). The threshold shifts were observed at all frequencies, but greatest effects were seen at the highest test frequencies. Outer hair cells were found to be particularly vulnerable (Fechter 1988). The potentiation does not increase with increasing noise level (Rao 2000a) or duration (Fechter 2000a, Fechter 2000b). A LOAEL of 500 ppm for this potentiation was observed in rats (Fechter 1989, Chen 1999, Fechter 2000a, Fechter 2000b).

Discussion

No human study was identified. No ototoxic effect of carbon monoxide alone was observed in 10 studies in rats. However, a potentiation of noise-induced hearing loss by carbon monoxide was found in 18 studies in rats. Further studies with sufficient data on the carbon monoxide exposure of workers are necessary to make a definitive conclusion. In the absence of human studies, it is not possible to draw any conclusion regarding the ototoxicity of carbon monoxide. However, the actual data suggest that carbon monoxide should be considered as a possible potentiator of noise-induced hearing loss.

Carbon monoxide

Carbon monoxide
• TWAEV : 35 ppm | 40 mg/m³ D-TWAEV : 5,7 mg/kg/d

Population

Species : Rat Long Evans # : 4 - 7 Sex : Not reported
Age : 2 months

Exposure

Route : Inhalation
Duration : CO : 1.5 h + 8 h; Noise : 8 h - see remarks
C/D reported : 1200 ppm
CSU/DSU :
Ratio : 34.2
ASM :
BM :
NSM :
NL : 100 dB and 115 dB ; Octave band noise at 1.2-2.4 kHz; 2.4-4.8 kHz; 4.8-9.6 kHz and 9.6-19.2 kHz
Remarks : Background noise : 40 dB(A)
Noise exposure began 1.5 hours after the beginning of the exposure to carbon monoxide

Tests

Test type • Effects reported	Details on test • Remarks
Electrocochleography (Compound action potential : CAP)	Pure tone at 2, 4, 6, 8, 12, 16, 20, 24, 30, 35 and 40 kHz Continuous pure tone for CM eliciting and tone burst for CAP eliciting
• - Exposure to the high frequencies (9.6-19.2 kHz) at 100 dB or low frequencies (2.4-4.8 kHz) at 115 dB noise + CO induced a greater elevation of the compound action potential (CAP) threshold and cochlear microphonic (CM) iso-amplitude curve than exposure to noise alone - Exposure to CO + noise at high frequency (9.6-19.2 kHz) induced much greater elevation of CAP, especially at high and mid frequency region, than exposure to CO + noise at lower frequencies - CM and CAP threshold were not affected by carbon monoxide exposure alone	• Test performed 4 weeks after the end of exposure (1 to 2 weeks in some cases)

Mechanism of action

Potentiation may be due to the reduction of the cell's ability to repair noise induced damage by carbon monoxide

Authors' conclusion

Carbon monoxide potentiates significantly the vulnerability of the auditory system at any noise frequency

Our conclusion

Carbon monoxide potentiates significantly the vulnerability of the auditory system at any noise frequency

Carbon monoxide

Carbon monoxide
• TWAEV : 35 ppm | 40 mg/m³ D-TWAEV : 5,7 mg/kg/d

Population

Species : Rat Long Evans # : 4 - 7 Sex : Not reported
Age : 2 months

Exposure

Route : Inhalation
Duration : CO : 1.5 h + 8 h; Noise : 8 h - see remarks
C/D reported : 300, 500, 700, 1200 and 1500 ppm
CSU/DSU :
Ratio : 8.6 - 42.9
ASM :
BM :
NSM :
NL : 100 dB ; Octave band noise at 9.6-19.2 kHz
Remarks : Background noise : 40 dB(A)
Noise exposure began 1.5 hours after the beginning of the exposure to carbon monoxide

Tests

Test type • Effects reported	Details on test • Remarks
Electrocochleography (Compound action potential : CAP)	Pure tone at 2, 4, 6, 8, 12, 16, 20, 24, 30, 35 and 40 kHz Continuous pur tone for CM eliciting and tone bursts for CAP eliciting
• Elevation of auditory threshold and the CM amplitude curve was greater after the combined exposure to noise and carbon monoxide than the noise alone if the concentration was 500 ppm and more	• Test performed 4 weeks after the end of exposure (1 to 2 weeks in some cases)

Mechanism of action

Potentiation may be due to the reduction of the cell's ability to repair noise induced damage by carbon monoxide

Authors' conclusion

Presence of carbon monoxide increases significantly the vulnerability of the auditory system

Our conclusion

LOAEL of potentiation is of 500 ppm in the rats

Carbon monoxide

Carbon monoxide
• TWAEV : 35 ppm | 40 mg/m³ D-TWAEV : 5,7 mg/kg/d

Population

Species : Rat Long Evans # : 4 - 7 Sex : Not reported
Age : 2 months

Exposure

Route : Inhalation
Duration : CO : 1.5 h + 8 h; Noise : 8 h - see remarks
C/D reported : 1200 ppm
CSU/DSU :
Ratio : 34.2
ASM :
BM :
NSM :
NL : 100 dB ; Octave band noise at 9.6-19.2 kHz
Remarks : Background noise : 40 dB(A)
Noise exposure began 1.5 hours after the beginning of the exposure to carbon monoxide

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 Continuous tone for CM eliciting and tone bursts for CAP eliciting
• - Hearing loss induced by noise alone partially recovered - No recovery of hearing loss caused by the combined exposure to CO + noise	• Test performed 1, 2 and 4 weeks after the end of exposure

Mechanism of action

Potentiation may be due to the reduction of the cell's ability to repair noise induced damage by carbon monoxide

Authors' conclusion

Presence of carbon monoxide increases significantly the vulnerability of the auditory system

Our conclusion

Hearing loss induced by noise alone gradually recovered (partially), but the hearing loss caused by the combined exposure did not

Carbon monoxide

Carbon monoxide
• TWAEV : 35 ppm | 40 mg/m³ D-TWAEV : 5,7 mg/kg/d

Population

Species : Rat Long Evans # : 4 - 7 Sex : Not reported
Age : 2 months

Exposure

Route : Inhalation
Duration : 9.5 h
C/D reported : 1200 ppm
CSU/DSU :
Ratio : 34.2
ASM :
BM :
NSM :
NL :
Remarks : Background noise : 40 dB(A)

Tests

Test type • Effects reported	Details on test • Remarks
Electrocochleography (Compound action potential : CAP)	Tone at 2, 4, 6, 8, 12, 16, 20, 24, 30, 35 and 40 kHz Continuous tone for CM eliciting and tone bursts for CAP eliciting
• Cochlear microphonic (CM) and compound action potential (CAP) threshold results were not affected by carbon monoxide exposure alone	• Test performed 4 weeks after the end of exposure

Mechanism of action

Authors' conclusion

The cochlear microphonic and compound action potential threshold results were not affected by carbon monoxide exposure alone

Our conclusion

Carbon monoxide alone doies not produce permanent auditory effects in rats expoxure to 1200 ppm

Carbon monoxide

Carbon monoxide
• TWAEV : 35 ppm | 40 mg/m³ D-TWAEV : 5,7 mg/kg/d

Population

Species : Rat Long Evans # : 4 - 6 Sex : Not reported
Age : 2 months

Exposure

Route : Inhalation
Duration : CO : 1.5 + 3 - 5 h according to the exposure cycle to noise; Noise : 2 h - see remarks
C/D reported : 1200 ppm
CSU/DSU :
Ratio : 34.2
ASM :
BM :
NSM :
NL : 100 dB SPL ; Octave band noise with a center frequency of 13.6 kHz
Remarks : For combined exposure, 90 minutes of carbon monoxide exposure preceded noise onset
Intermittent noise with a 67 % noise duty cycle (1 hour noise - 1 hour silence - 1 hour noise), 50 % noise duty cycle (40 minutes noise -1 hour silence - 40 minutes noise - 1 hour silence - 40 minutes noise) and 40 % noise duty cycle (30 minutes noise - 1 hour silence - 30 minutes noise - 1 hour silence - 30 minutes noise - 1hour silence - 30 minutes noise)

Tests

Test type • Effects reported	Details on test • Remarks
Electrocochleography (Compound action potential : CAP)	Pure tones for CM eliciting and tone bursts for CAP eliciting at 2, 4, 6, 8, 12, 16, 20, 24, 30, 35 and 40 kHz
• - Permanent hearing loss resulting from octave band noise alone was less severe as the proportion of silence periods increased - Carbon monoxide alone did not cause threshold elevation of the compound action potential (CAP) - Differing from the noise alone, rest period between noise phases can not protect the ear from noised-induced damage in the presence of carbon monoxide - Cochlear microphonic (CM) iso-amplitude curves revealed similar results to those seen by using the CAP threshold	• Test performed 4 weeks after the end of exposure
Light microscopy	
• - Animals exposed to the 40% noise alone duty cycle did not show outer hair cell (OHC) loss - OHC loss in the high frequency region of rats exposed to noise + carbon monoxide	• Histology performed 4 weeks after the end of exposure

Mechanism of action

Authors' conclusion

CAP threshold elevation after the combined exposure to noise and carbon monoxide was higher than that after the noise alone

Our conclusion

Potentiation of the intermittent noise induced hearing loss by exposure to 1200 ppm carbon monoxide in rats

Carbon monoxide

Carbon monoxide
• TWAEV : 35 ppm | 40 mg/m³ D-TWAEV : 5,7 mg/kg/d

Population

Species : Rat Long Evans # : 4 - 6 Sex : Not reported
Age : 2 months

Exposure

Route : Inhalation
Duration : 4.5 - 6.5 h
C/D reported : 1200 ppm
CSU/DSU :
Ratio : 34.2
ASM :
BM :
NSM :
NL :
Remarks :

Tests

Test type • Effects reported	Details on test • Remarks
Electrocochleography (Compound action potential : CAP)	Pure tones for CM eliciting and tone bursts for CAP eliciting at 2, 4, 6, 8, 12, 16, 20, 24, 30, 35 and 40 kHz
• Carbon monoxide alone did not cause threshold elevations of the compound action potential (CAP)	• Test performed 4 weeks after the end of exposure

Mechanism of action

Authors' conclusion

Carbon monoxide alone did not cause threshold elevation of the compound action potential at 1200 ppm in rats

Our conclusion

Carbon monoxide alone did not cause threshold elevation of the compound action potential at 1200 ppm in rats

Carbon monoxide

Carbon monoxide
• TWAEV : 35 ppm | 40 mg/m³ D-TWAEV : 5,7 mg/kg/d

Population

Species : Rat Long Evans # : 2 - 6 Sex : Not reported
Age : 2 months

Exposure

Route : Inhalation
Duration : CO : 1.5 h + 2 h; Noise : 2 h - see remarks
C/D reported : 1200 ppm
CSU/DSU :
Ratio : 34.2
ASM :
BM :
NSM :
NL : 100 dB SPL ; Octave band noise centered at 13.6 kHz
Remarks : For combined exposure, 90 minutes of carbon monoxide exposure preceded noise onset

Tests

Test type • Effects reported	Details on test • Remarks
Electrocochleography (Compound action potential : CAP)	Tone burst at 2, 4, 6, 8, 12, 16, 20, 24, 30, 35 and 40 kHz
• - Noise alone : compound action potential (CAP) threshold elevation - Noise + carbon monoxide : more severe CAP threshold elevation	• Test performed 4 weeks after the end of exposure
Light microscopy	
• - Noise alone : decreased succinate deshydrogenase (SDH) activity in the inner hair cells. - Noise alone : no or little hair cell loss. - Noise + carbon monoxide : more severe decrease of SDH activity in the inner hair cells. - Noise + carbon monoxide : outer hair cells loss	• Histology performed 4 weeks after the end of exposure

Mechanism of action

Authors' conclusion

Across all the test frequencies, neither the hair cell loss nor the succinate deshydrogenase reduction alone had good correlation to the reduction of the auditory sensitivity

Our conclusion

Potentiation of the noise effect on the auditory system by 1200 ppm carbon monoxide in rats

Carbon monoxide

Carbon monoxide
• TWAEV : 35 ppm | 40 mg/m³ D-TWAEV : 5,7 mg/kg/d

Population

Species : Rat Long Evans # : 3 - 6 Sex : Not reported
Age : 2 months

Exposure

Route : Inhalation
Duration : CO : 1.5 h + 2 h; Noise : 2 h - see remarks
C/D reported : 1200 ppm
CSU/DSU :
Ratio : 34.2
ASM :
BM :
NSM :
NL : 100 dB SPL ; Octave band noise with a center frequency of 13.6 kHz
Remarks : Background noise : 50 dB(A)
For combined exposure, 90 minutes of carbon monoxide exposure preceded noise onset

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
• - Carbon monoxide exposure alone did not cause elevation of the compound action potential (CAP) threshold - Group exposed to noise with saline injection had higher CAP threshold comparing to the control group (saline only) - Saline + noise + carbon monoxide group has significantly higher CAP threshold than the saline + noise group	• Test performed 4 weeks after the end of exposure
Light microscopy	
• Outer hair cells losses, at the basal portion of the cochlea, of noise + carbon monoxide exposed rats at high frequencies were significantly different from the control.	• Histology performed 4 weeks after the end of exposure

Mechanism of action

Authors' conclusion

Combined exposure to noise and carbon monoxide induces greater auditory threshold elevation than exposure to noise alone

Our conclusion

Carbon monoxide alone does not produce permanent auditory effects. There is potentiation of noise-induced auditory loss by carbon monoxide

Carbon monoxide

Carbon monoxide
• TWAEV : 35 ppm | 40 mg/m³ D-TWAEV : 5,7 mg/kg/d

Population

Species : Rat Long Evans # : 3 - 6 Sex : Not reported
Age : 2 months

Exposure

Route : Inhalation
Duration : 3.5 h
C/D reported : 1200 ppm
CSU/DSU :
Ratio : 34.2
ASM :
BM :
NSM :
NL :
Remarks : Background noise : 50 dB(A)

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
• Carbon monoxide exposure alone did not cause elevation of the compound action potential threshold	• Test performed 4 weeks after the end of exposure

Mechanism of action

Authors' conclusion

Carbon monoxide exposure alone did not cause elevation of the compound action potential threshold

Our conclusion

Carbon monoxide alone does not produce permanent auditory effects at 1200 ppm in rats

Carbon monoxide

Carbon monoxide
• TWAEV : 35 ppm | 40 mg/m³ D-TWAEV : 5,7 mg/kg/d

Population

Species : Rat Long Evans # : 2 - 4 Sex : Males
Age : NR

Exposure

Route : Inhalation
Duration : CO : 1.5 h + 2 h; Noise : 2 h - see remarks
C/D reported : 1200 ppm
CSU/DSU :
Ratio : 34.2
ASM :
BM :
NSM :
NL : 105 dB(A)
Remarks : Background noise : 40 - 50 dB(A)
For combined exposure, 90 minutes of carbon monoxide exposure preceded noise onset

Tests

Test type • Effects reported	Details on test • Remarks
Reflex modification audiometry	Tone pips between 2.5 - 40 kHz
• - CO alone : any shift in auditory thresholds - Noise alone : minimal thresholds shifts - CO and noise : significant loss of auditory sensitivity after exposure. The most severe disruption in thresholdat the highest test frequency (10 and 40 kHz) - No evidence of recovery of auditory sensitivity among the CO + noise exposed subjects tested between 6-8 weeks after exposure	• Test performed 2 - 8 weeks after the end of exposure
Light microscopy	
• - CO alone : No loss of hair cells - Noise alone :hair cell loss in the extreme basal portion of the organ of Corti - Noise + CO : greater loss of inner and outer hair cells than noise alone	• Histology performed 6 - 8 weeks after the end of exposure

Mechanism of action

Hypoxia and hyperoxia may play an important role under conditions of noise exposure, reinforcing the noise induced damage result

Authors' conclusion

Noise and carbon monoxide did not produce any detectable threshold shift when given individully but when given simultaneous, they are able to produce profound autitory dysfunction.
Potentiation of noise induced injury by hypoxia.
Vulnerability of thresholds for high frequency tones

Our conclusion

Potentiation of noise induced hearing loss by carbon monoxide in rats

Carbon monoxide

Carbon monoxide
• TWAEV : 35 ppm | 40 mg/m³ D-TWAEV : 5,7 mg/kg/d

Population

Species : Rat Long Evans # : 2 - 4 Sex : Males
Age : NR

Exposure

Route : Inhalation
Duration : 3.5 h
C/D reported : 1200 ppm
CSU/DSU :
Ratio : 34.2
ASM :
BM :
NSM :
NL :
Remarks : Background noise : 40 - 50 dB(A)

Tests

Test type • Effects reported	Details on test • Remarks
Reflex modification audiometry	Tone pips between 2.5 - 40 kHz
• - Carbon monoxide alone did not show any shift in auditory thresholds - Noise alone showed minimal thresholds shifts	• Test performed 2 - 8 weeks after the end of exposure
Light microscopy	
• Exposure to carbon monoxide alone did not produce a loss of hair cells	• Histology performed 6 - 8 weeks after the end of exposure

Mechanism of action

Authors' conclusion

Carbon monoxide did not produce any detectable threshold shift

Our conclusion

Carbon monoxide alone does not produce permanent auditory effects at 1200 ppm in rats

Carbon monoxide

Carbon monoxide
• TWAEV : 35 ppm | 40 mg/m³ D-TWAEV : 5,7 mg/kg/d

Population

Species : Rat Long Evans # : 4 - 5 Sex : Males

Age : NR

Exposure

Route : Inhalation

Duration : CO : 1.5 h + 2 h; Noise : 2 h

C/D reported : 250, 500 and 1200 ppm

CSU/DSU :

Ratio : 7.1 - 34.2

ASM :

BM :

NSM :

NL : 105 dB(A)

Remarks : For combined exposure, 90 minutes of carbone monoxide exposure preceded noise exposure onset

Tests

Test type • Effects reported	Details on test • Remarks
Reflex modification audiometry • - No hearing loss after exposure to noise only. - Subjects exposed to 250 ppm carbon monoxide + noise did not show a loss in auditory sensitivity. - Significant loss of auditory sensitivity following combined exposure to noise and 500 or 1200 ppm carbon monoxide	Pure tone at 10 kHz and 40 kHz • Test performed one week after the end of exposure

Mechanism of action

Authors' conclusion

Potentiation of noise induced hearing loss in rats by exposure to 500 ppm carbon monoxide

Our conclusion

LOAEL of potentiation of ototoxic effect is 500 ppm in rats

Carbon monoxide

Carbon monoxide
• TWAEV : 35 ppm | 40 mg/m³ D-TWAEV : 5,7 mg/kg/d

Population

Species : Rat Long Evans # : 6 Sex : Males

Age : 2 - 3 months

Exposure

Route : Inhalation

Duration : CO : 1.5 h + 8 h; Noise : 8 h - see remarks

C/D reported : 300, 500, 700, 1200 and 1500 ppm

CSU/DSU :

Ratio : 8.6 - 42.9

ASM :

BM :

NSM :

NL : 100 dB SPL ; Octave band with a center frequency of 13.6 kHz

Remarks : Background noise : < 50 dB(A)
For combined exposure, 90 minutes of carbon monoxide exposure preceded noise onset

Tests

Test type • Effects reported	Details on test • Remarks
Electrocochleography (Compound action potential : CAP)	Tone burst at 2, 4, 6, 8, 12, 16, 20, 24, 30, 35 and 40 kHz
• - Compound action potential (CAP) threshold elevation progressively higher as carbon monoxide concentration increases at high (24, 30, 35 kHz) and middle (12, 16, 20 kHz) frequencies. - Elevation of CAP threshold induced by exposure to 500 ppm carbon monoxide and greater is significantly different from the group exposed to the noise only	• Test performed 4 weeks after the end of exposure

Mechanism of action

Authors' conclusion

Linear increase in potentiation observed when carbon monoxide concentrations are increased in presence of noise. A statistically significant loss of sensitivity is observed with carbon monoxide exposure of 500 ppm and higher

Our conclusion

LOAEL of 500 ppm for potentiation of ototoxic effect

Carbon monoxide

Carbon monoxide
• TWAEV : 35 ppm | 40 mg/m³ D-TWAEV : 5,7 mg/kg/d

Population

Species : Rat Long Evans # : 6 Sex : Males

Age : 2 - 3 months

Exposure

Route : Inhalation

Duration : CO : 1.5 h + 2 - 4 h; Noise : 2 - 4 h

C/D reported : 1200 ppm

CSU/DSU :

Ratio : 34.2

ASM :

BM :

NSM :

NL : 95 and 100 dB SPL ; Octave band noise with a centered frequency at 13.6 kHz

Remarks : Background noise : < 50 dB(A)
Exposure to noise level of 95 and 100 dB for 2 hours or 100 dB for 4 hours
For combined exposure, 90 minutes of carbon monoxide exposure preceded noise onset

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
• - At 100 dB SPL for 2 hours, a clear potentiation of noise induced hearing loss by carbon monoxide was present at high frequencies, ranging up to 20 dB beyond the effect of noise alone - Increasing the duration to 4 hours do not yield any increase in potentiation	• Test performed 4 weeks after the end of exposure

Mechanism of action

Authors' conclusion

Potentiation of noise induced hearing loss by carbon monoxide does not increase with increasing severity of noise exposure. Permanent threshold shifts from noise alone increase as noise exposure becomes more severe, but there is no added potentiation effect added due to carbon monoxide when noise exposurel exceeds 100 dB for 2 hours

Our conclusion

Potentiation of noise induced hearing loss by carbon monoxide does not increase with increasing duration of noise exposure

Carbon monoxide

Carbon monoxide
• TWAEV : 35 ppm | 40 mg/m³ D-TWAEV : 5,7 mg/kg/d

Population

Species : Rat Long Evans # : 6 Sex : Males

Age : 2 - 3 months

Exposure

Route : Inhalation

Duration : CO : 1.5 h + 3, 4 and 5 h depending of the noise duty cycles - Noise : 2 h - see remarks

C/D reported : 1200 ppm

CSU/DSU :

Ratio : 34.2

ASM :

BM :

NSM :

NL : 100 dB SPL ; Octave band noise with frequency centre at 13.6 kHz

Remarks : Background noise : < 50 dB(A)
For combined exposure, 90 minutes of carbon monoxide exposure preceded noise onset
2 hours of noise exposure with rest periods fom 60 to 240 minutes (2 cycles of 60 minutes noise + 60 minutes rest; 3 cycles of 40 minutes noise + 60 minutes rest; 4 cycles of 30 minutes noise + 60 minutes rest)

Tests

Test type • Effects reported	Details on test • Remarks
Electrocochleography (Compound action potential : CAP)	Tone burst at 2, 4, 6, 8, 12, 16, 20, 24, 30, 35 and 40 kHz
• - Auditory threshold impairment increased for subjects receiving noise alone as the number and the duration of rest periods decreased - Loss in threshold observed for exposure to carbon monoxide + noise remained relatively stable for all the noise duty cycles - No evidence that carbon monoxide exposure alone can produce permanent threshold shifts	• Test performed 4 weeks after the end of exposure

Mechanism of action

Authors' conclusion

Loss of hearing threshold observed for exposure to carbon monoxide + noise remained relatively stable for different duration of rest periods

Our conclusion

Loss of hearing threshold observed for exposure to carbon monoxide + noise remained relatively stable for different duration of rest periods

Carbon monoxide

Carbon monoxide
• TWAEV : 35 ppm | 40 mg/m³ D-TWAEV : 5,7 mg/kg/d

Population

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

Exposure

Route : Inhalation
Duration : 4.5 - 6.5 h
C/D reported : 1200 ppm
CSU/DSU :
Ratio : 34.2
ASM :
BM :
NSM :
NL :
Remarks : Background noise : 50 dB(A)

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
• No evidence that carbon monoxide exposure alone can produce permanent hearing threshold shifts	• Test performed 4 weeks after the end of exposure

Mechanism of action

Authors' conclusion

No evidence that carbon monoxide exposure alone can produce permanent hearing threshold shifts in rats

Our conclusion

No evidence that carbon monoxide exposure alone to 1200 ppm can produce permanent hearing threshold shifts in rats

Carbon monoxide

Carbon monoxide
• TWAEV : 35 ppm | 40 mg/m³ D-TWAEV : 5,7 mg/kg/d

Population

Species : Rat Long Evans # : 8 Sex : Males

Age : 2 - 3 months

Exposure

Route : Inhalation

Duration : CO : 1.5 h + 8 h; Noise : 8 h - see remarks

C/D reported : 300, 500, 700, 1200 and 1500 ppm

CSU/DSU :

Ratio : 8.6 - 42.6

ASM :

BM :

NSM :

NL : 100 dB SPL ; Octave band noise centered at 13.6 kHz

Remarks : Background noise : < 50 dB(A)
Noise exposure began 1.5 hours after the beginning of the exposure to carbon monoxide

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
• - 1200 ppm carbon monoxide by itself does not alter auditory function. - Potentiation is very limited at 300 ppm, it becomes more apparent at 500 pm with an increase in the CAP thresholds above the noise exposed group of approximatively 5-10 dB, and is quite distinct for exposure of 700 ppm and more. - Potentiation at 1500 ppm is 30 dB above the effect of noise alone	• Test performed 4 weeks after the end of exposure

Mechanism of action

Authors' conclusion

Potentiation of noise induced hearing loss by carbon monoxide increses linearly as carbon monoxide concentration increases between 500 and 1500 ppm. The NOAEL is 300 ppm and the LOAEL is 500 ppm

Our conclusion

Potentiation of noise induced hearing loss by carbon monoxide. The NOAEL is 300 ppm and the LOAEL is 500 ppm

Carbon monoxide

Carbon monoxide
• TWAEV : 35 ppm | 40 mg/m³ D-TWAEV : 5,7 mg/kg/d

Population

Species : Rat Long Evans # : 6 Sex : Males

Age : 2 - 3 months

Exposure

Route : Inhalation

Duration : CO : 1.5 h + 2 h to 4 h; Noise : 2 h to 4 h

C/D reported : 1200 ppm

CSU/DSU :

Ratio : 34.2

ASM :

BM :

NSM :

NL : 95 and 100 dB SPL ; Octave band noise centered at 13.6 kHz

Remarks : Background noise : < 50 dB(A)
Noise exposure began 1.5 hours after the beginning of the exposure to carbon monoxide

Tests

Test type • Effects reported	Details on test • Remarks
Electrocochleography (Compound action potential : CAP)	Tone burst at 2, 4, 6, 8, 12, 16, 20, 24, 30, 35 and 40 kHz
• - At 100 dB SPL for 2 hours, a clear potentiation of noise induced hearing loss by carbon monoxide was present at high frequencies, ranging up to 30 dB beyond the effect of noise alone - Increasing the duration to 4 hours do not yield any increase in potentiation	• Test performed 4 weeks after the end of exposure

Mechanism of action

Authors' conclusion

Relationship between noise exposure level and potentiation of noise induced hearing loss by carbon monoxide shows nonlinear pattern. The greatest potentiation was observed at moderate noise exposures : 2 hours at 100 dB SPL.

Our conclusion

Potentiation of noise induced hearing loss by carbon monoxide does not grow with increasing duration of noise exposure

Carbon monoxide

Carbon monoxide
• TWAEV : 35 ppm | 40 mg/m³ D-TWAEV : 5,7 mg/kg/d

Population

Species : Rat Long Evans # : 4 Sex : Males

Age : 2 - 3 months

Exposure

Route : Inhalation

Duration : CO : 1.5 h/d + 2 h/d; Noise : 2 h/d; 5 d

C/D reported : 1200 ppm

CSU/DSU :

Ratio : 34.2

ASM :

BM :

NSM :

NL : 95 dB SPL ; Octave band noise centered at 13.6 kHz

Remarks : Background noise : < 50 dB(A)
Noise exposure began 1.5 hours after the beginning of the exposure to carbon monoxide

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
• - Repeated exposure to carbon monoxide alone has no effect on CAP threshold - CAP threshold observed in the noise + carbon monoxide treated rats was approximatively 5 dB above the threshold seen in noise treated rats at frequencies at or below 8 kHz. Above 8 kHz, potentiation ranged from 10 to 15 dB above noise exposed subjects	• Test performed 4 weeks after the end of exposure

Mechanism of action

Authors' conclusion

Potentiation of noise induced hearing loss during repeated exposures to 95 dB SPL noise by 1200 ppm carbon monoxide

Our conclusion

Potentiation of noise induced hearing loss during repeated exposures to 95 dB SPL noise by 1200 ppm carbon monoxide

Carbon monoxide

Carbon monoxide
• TWAEV : 35 ppm | 40 mg/m³ D-TWAEV : 5,7 mg/kg/d

Population

Species : Rat Long Evans # : 8 Sex : Males
Age : 2 - 3 months

Exposure

Route : Inhalation
Duration : 9.5 h
C/D reported : 300, 500, 700, 1200 and 1500 ppm
CSU/DSU :
Ratio : 8.6 - 42.6
ASM :
BM :
NSM :
NL :
Remarks : Background noise : < 50 dB(A)

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
• 1200 ppm carbon monoxide by itself does not alter auditory function	• Test performed 4 weeks after the end of exposure

Mechanism of action

Authors' conclusion

1200 ppm carbon monoxide by itself does not alter auditory function

Our conclusion

Carbon monoxide alone does not produce permanent auditory effects at 1200 ppm in rats

Carbon monoxide

Carbon monoxide
• TWAEV : 35 ppm | 40 mg/m³ D-TWAEV : 5,7 mg/kg/d

Population

Species : Rat Long Evans # : 4 Sex : Males
Age : 2 - 3 months

Exposure

Route : Inhalation
Duration : 3.5 h/d; 5 d
C/D reported : 1200 ppm
CSU/DSU :
Ratio : 34.2
ASM :
BM :
NSM :
NL :
Remarks : Background noise : < 50 dB

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
• Repeated exposure to carbon monoxide alone has no effect on auditory threshold	• Test performed 4 weeks after the end of exposure

Mechanism of action

Authors' conclusion

Repeated exposure to carbon monoxide alone has no effect on auditory threshold

Our conclusion

Carbon monoxide alone does not produce permanent auditory effects at 1200 ppm in rats

Carbon monoxide

Carbon monoxide
• TWAEV : 35 ppm | 40 mg/m³ D-TWAEV : 5,7 mg/kg/d

Population

Species : Rat Fisher 344 # : 12 Sex : Males and females

Age : 16 weeks

Exposure

Route : Inhalation

Duration : 6 h/d; 5 d/w; 13 weeks

C/D reported : 135 ppm

CSU/DSU :

Ratio : 3.9

ASM :

BM :

NSM :

NL :

Remarks :

Tests

Test type • Effects reported	Details on test • Remarks
Auditory brainstem responses • No effect	Clicks • Test perfomed 65 or more hours after the end of exposure
Auditory brainstem responses • No effect	Tone pips at 10 and 30 kHz • Test perfomed 65 or more hours after the end of exposure

Mechanism of action

Authors' conclusion

No evidence of persistent central nervous system alteration after subchronic exposure in rats

Our conclusion

No effects in rats 135 ppm carbon monoxide for 13 weeks

Carbon monoxide

Carbon monoxide
• TWAEV : 35 ppm | 40 mg/m³ D-TWAEV : 5,7 mg/kg/d

Population

Species : Rat Long Evans # : C = 8; E1 = 10; E2 = 12 Sex : Males
Age : 7-8 weeks

Exposure

Route : Inhalation
Duration : CO : 3.5 h/d, 2 d; Noise : 2 h/d; 2 d
C/D reported : E1 = 0 ppm; E2 = 800 ppm
CSU/DSU :
Ratio : 22.9
ASM :
BM :
NSM :
NL : 105 dB SPL ; Octave band noise centered at 8 kHz
Remarks : -Exposure to CO begun 1.5 h prior to noise exposure

Tests

Test type • Effects reported	Details on test • Remarks
Distortion product otoacoustic emissions (DPOAE)	From 2.9 to 56.3 kHz (geometric mean) L1 = 65 dB SPL L2 = 55 dB SPL Ratio f2/f1 = 1.25
• - At 1-hour postexposure, DPOAE amplitudes were profoundly reduced between 5.5 and 58.8 kHz (f2) for all groups - At 1 week postexposure, noise only group showed substantial recovery of DPOAE amplitudes at all frequencies that were impaired - At 1 and 4 weeks postexposure, CO + noise rats showed persistent reductions in DPOAE amplitudes that averaged 15 dB between 5.5 and 58.8 kHz(f2) and 30 dB from 8.0 to 20.0 kHz	• Test performed 1 week, 1 month and 4 month pst-exposure
Electrocochleography (Compound action potential : CAP)	Tone bursts at 2, 4, 6, 8, 12, 16, 20, 24, 30, 35 and 40 kHz
• - Animals that recieved noise alone had slightly elevated thresholds, compared with control subjects (<15 dB between 8.0 and 16.0 kHz) - CAP thresholds from the animals that recieved CO + noise were significantly increased by an average of 27 dB between 8.0 and 40.0 kHz compared to control subjects	• Test performed 4 weeks postexposure
Light microscopy	
• - Noise-alone animals displayed some damaged to the extreme base of the cochlea, corresponding to frequencies above 40.0 kHz - The cochleae from rats exposed to CO + noise exhibited damage extending over the basal third of the organ of Corti, corresponding to the 25.0 to 60.0 kHz range	• Test performed 4 weeks post-exposure

Mechanism of action

Reactive oxygen species generation that damage the cochlea

Authors' conclusion

Oxydative stress is probably the cause of noise-indused hearing loss potentiation by CO

Our conclusion

Oxydative stress is probably the cause of noise-indused hearing loss potentiation by CO

Carbon monoxide

Carbon monoxide
• TWAEV : 35 ppm | 40 mg/m³ D-TWAEV : 5,7 mg/kg/d

Population

Species : Rat Long Evans # : 6 Sex : Not reported
Age : NR

Exposure

Route : Inhalation
Duration : 1, 2 and 4 h depending of the noise level - see remarks
C/D reported : 1200 ppm
CSU/DSU :
Ratio : 34.2
ASM :
BM :
NSM :
NL : 95, 100 and 105 dB SPL
Remarks : Background noise : 50 dB(A)
Animals exposed to 95 dB SPL for 4 hours, 100 dB SPL for 2 hours and 105 dB SPL for 1 and 4 hours
For combined exposure, 90 minutes of carbon monoxide exposure preceded noise onset

Tests

Test type • Effects reported	Details on test • Remarks
Electrocochleography (Compound action potential : CAP)	Tone pips at 2, 4, 6, 8, 12, 16, 20, 24, 30, 35 and 40 kHz
• - Compound action potential (CAP) threshold in rats exposed to carbon monoxide (CO) is similar to that in control - No significant CAP threshold elevations in rats exposed to 95 dB noise + CO in comparison with rats exposed to noise only - CAP threshold of rats exposed to 100 dB and 105 dB noise + CO differed significantly from rats exposed to noise alone across all frequencies - Saturation effect for combined exposures may exist - Effect of combined exposure is dependent on noise and not on the duration of CO exposure	• Test performed 4 weeks after the end of exposure

Mechanism of action

Authors' conclusion

In general, hearing threshold elevations were greater following combined exposure to noise and carbon monoxide than noise alone. The potentiation does not increase with increasing noise severity

Our conclusion

In general, hearing threshold elevations were greater following combined exposure to noise and carbon monoxide than noise alone. The potentiation does not increase with increasing noise level

Carbon monoxide

Carbon monoxide
• TWAEV : 35 ppm | 40 mg/m³ D-TWAEV : 5,7 mg/kg/d

Population

Species : Rat Long Evans # : 6 Sex : Not reported
Age : NR

Exposure

Route : Inhalation
Duration : 5.5 h
C/D reported : 1200 ppm
CSU/DSU :
Ratio : 34.2
ASM :
BM :
NSM :
NL :
Remarks : Background noise : 50 dB(A)

Tests

Test type • Effects reported	Details on test • Remarks
Electrocochleography (Compound action potential : CAP)	Tone pips at 2, 4, 6, 8, 12, 16, 20, 24, 30, 35 and 40 kHz
• Compound action potential thresholds in rats exposed to carbon monoxide are similar to those in control group	• Test performed 4 weeks after the end of exposure

Mechanism of action

Authors' conclusion

Compound action potential thresholds in rats exposed to carbon monoxide are similar to those in rats exposed to air (control)

Our conclusion

Carbon monoxide alone does not produce permanent auditory effects at 1200 ppm in rats

Carbon monoxide

Carbon monoxide
• TWAEV : 35 ppm | 40 mg/m³ D-TWAEV : 5,7 mg/kg/d

Population

Species : Rat Long Evans # : 6 Sex : Males
Age : 6 - 8 weeks

Exposure

Route : Inhalation
Duration : CO : 1.5 h + 2 h; Noise : 2 h - see remarks
C/D reported : 1200 ppm
CSU/DSU :
Ratio : 34.2
ASM :
BM :
NSM :
NL : 100 dB SPL; Octave band with a center frequency of 13.6 kHz
Remarks : Background noise : 40 dB(A)
For combined exposure, 90 minutes of carbon monoxide exposure preceded noise onset

Tests

Test type • Effects reported	Details on test • Remarks
Electrocochleography (Compound action potential : CAP)	Tone burst elicited CAP and pure tones elicited CM at 2, 4, 6, 8, 12, 16, 20, 24, 30, 35 and 40 kHz
• - Noise + carbon monoxide demonstrate greater compound action potential (CAP) thresholds elevation (24 dB) than animals exposed to noise alone (9 dB). - Effects of noise + carbon monoxide and noise alone on cochlear microphonic (CM) are smaller than effects on CAP thresholds. - CM elevation due to noise alone was not significant	• Test performed 4 weeks after the end of exposure

Mechanism of action

Ototoxic effect due to noise and carbon monoxide exposure is mediated via free radicals, which are generated during carbon monoxide hypoxia or oxidative stress

Authors' conclusion

Potentiation of noise induced hearing loss by carbon monoxide exposure

Our conclusion

Potentiation of noise induced hearing loss by carbon monoxide exposure in rats exposed to 1200 ppm of carbon monoxide

Carbon monoxide

Carbon monoxide
• TWAEV : 35 ppm | 40 mg/m³ D-TWAEV : 5,7 mg/kg/d

Population

Species : Rat Long Evans # : 4 Sex : Males

Age : NR

Exposure

Route : Inhalation

Duration : CO : 1.5 h + 2 h; Noise : 2 h - see remarks

C/D reported : 1200 ppm

CSU/DSU :

Ratio : 34.2

ASM :

BM :

NSM :

NL : 110 dB(A) ; Broad band noise

Remarks : Background noise : 40 - 50 dB(A)
For combined exposure, 90 minutes of carbon monoxide exposure preceded noise onset

Tests

Test type • Effects reported	Details on test • Remarks
Reflex modification audiometry	Tone pips at 10 and 40 kHz
• - Performance of subjects exposed to carbon monoxide alone is quite similar to that of the control subjects - Subjects exposed only to noise show maximal impairment for 10 kHz stimuli - Subjects exposed to noise + carbon monoxide show greater auditory impairment, quantitatively and qualitatively. There was greater damage seen at 40 kHz than 10 kHz	• Test performed 1 and 3 weeks after the end of exposure

Mechanism of action

Noise induced hearing damage may not reflect direct mechanical trauma to the organ of Corti, but a disruption of normal cochlear metabolic process. Depressed cochlear blood flow or reduced oxygen delivery (hypoxia) cause reduction of oxidative metabolism which might cause cochlear dysfunctions

Authors' conclusion

Carbon monoxide alone does not produce permanent auditory effects. There is a potentiation of noise-induced auditory loss by carbon monoxide, especially at higher frequencies

Our conclusion

Carbon monoxide alone does not produce permanent auditory effects. There is a potentiation of noise-induced auditory loss by carbon monoxide

Carbon monoxide

Carbon monoxide
• TWAEV : 35 ppm | 40 mg/m³ D-TWAEV : 5,7 mg/kg/d

Population

Species : Rat Long Evans # : 4 Sex : Males
Age : NR

Exposure

Route : Inhalation
Duration : 3.5 h
C/D reported : 1200 ppm
CSU/DSU :
Ratio : 34.2
ASM :
BM :
NSM :
NL :
Remarks : Background noise : 40 - 50 dB(A)

Tests

Test type	Details on test
• Effects reported	• Remarks
Reflex modification audiometry	Tone pips at 10 and 40 kHz
• Performance of subjects exposed to carbon monoxide alone is quite similar to that of the control subjects	• Test performed 1 and 3 weeks after the end of exposure

Mechanism of action

Authors' conclusion

Carbon monoxide alone does not produce permanent auditory effects

Our conclusion

Carbon monoxide alone does not produce permanent auditory effects at 1200 ppm in rats

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