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

Xylene (o-,m-,p- isomers)

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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

Xylene (o-,m-,p- isomers)

Quebec's Occupational exposure limits: TWAEV: 434 mg/m³ (100 ppm). STEV: 651 mg/m³ (150 ppm)

Conclusion about ototoxicity	Strength of evidence
Possibly ototoxic substance	From human studies: **Absent** 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

One study on volunteers was identified (Seppalainen 1989). Auditory brainstem responses tests showed no ototoxic effect of 200 ppm meta-xylene inhaled for 3 hours.

Ototoxicity - Analysis of animal studies

Seven studies on rats of different strains were identified. An ototoxic effect was observed in fiveof six inhalation (Pryor 1987; Crofton 1994; Gagnaire 2001; Gagnaire 2005; Maguin 2006) and one oral (Gagnaire 2005) studies by four different tests. Three studies from the same laboratory showed the ototoxic effect depending on the duration of exposure. A LOAEL of 800 ppm was observed after 6 weeks of exposure (Pryor 1987). Two studies compared the ototoxicity of three xylene isomers in rats (Gagnaire 2001; Maguin 2006). No ototoxic effect was observed after a subchronic exposure up to 1800 ppm ortho- or meta-xylene but it was observed after exposure to 900 ppm para-xylene in one study and 1800 ppm in the other.

Interaction with noise - Analysis of human studies

No study was identified.

Interaction with noise - Analysis of animal studies

No study was identified.

Discussion

Only one human study was identified showing no ototoxic effect after a short-term exposure. In rats xylene affects the auditory function. Further studies with sufficient data on the exposure of workers to xylene isomers are necessary to make a definitive conclusion, however given the current evidence from animal studies, we recommend considering para-xylene and consequently mixtures of xylene isomers as possibly ototoxic. No human or animal study on ototoxic interaction between xylenes and noise was identified.

Xylene (isomers o,m,p)

Xylene (o-,m-,p- isomers)
• TWAEV : 100 ppm | 434 mg/m³ D-TWAEV : 62 mg/kg/d

Population

Species : Rat Long Evans # : 7 - 8 Sex : Males
Age : 60 days

Exposure

Route : Inhalation
Duration : 8 h/d; 5 d
C/D reported : 1800 ppm
CSU/DSU :
Ratio : 12
ASM :
BM :
NSM :
NL :
Remarks : Exposure to a mixture of xylene isomers without details on its composition

Tests

Test type • Effects reported	Details on test • Remarks
Reflex modification audiometry	at 0.5 - 40 kHz
• Hearing loss for 8 and 16 kHz	• Test performed 5 to 8 weeks after the end of exposure

Mechanism of action

Authors' conclusion

Mid-frequency hearing loss at 1800 ppm in rats

Our conclusion

Ototoxic effect at 1800 ppm in rats

Xylene (isomers o,m,p)

Xylene (o-,m-,p- isomers)
• TWAEV : 100 ppm | 434 mg/m³ D-TWAEV : 62 mg/kg/d

Population

Species : Rat Sprague Dawley # : 16 Sex : Males
Age : 13 weeks

Exposure

Route : Inhalation
Duration : 6 h/d; 6 d/w; 13 w
C/D reported : 450, 900 and 1800 ppm
CSU/DSU :
Ratio : 4.5 - 18
ASM :
BM :
NSM :
NL :
Remarks : Exposure to ortho-, meta- or para-xylene administred individually

Tests

Test type • Effects reported	Details on test • Remarks
Auditory brainstem responses	Clicks at 2, 4, 8 and 16 kHz
• orto-xylene : no effect. meta-xylene : no effect. para-xylene : 450 and 900 ppm : no effect. 1800 ppm : hearing loss of 35 - 42 dB at 2 -16 kHz. No recovery observed 8 weeks after the end of exposure	• Test performed before exposure, at the end of the 13th week of exposure and 8 weeks after the end of exposure
Light and electron microscopy	
• orto-xylene : no effect. meta-xylene : no effect. para-xylene : 450 ppm : no effect. 900 ppm : low outer hair cells losses in the first row. 1800 ppm : outer hair cells losses in the three rows	• Histology performed 8 weeks after the end of exposure

Mechanism of action

Authors' conclusion

NOAEL of 450 ppm for ototoxicity of para-xylene in rats. No ototoxicity of orto- and meta- xylene in rats exposed up to 1800 ppm

Our conclusion

NOAEL and LOAEL of 450 and 900 ppm, respectively for ototoxicity of para-xylene in rats. No ototoxicity of orto- and meta- xylene in rats exposed up to 1800 ppm

p-Xylene

Xylene (o-,m-,p- isomers)
• TWAEV : 100 ppm | 434 mg/m³ D-TWAEV : 62 mg/kg/d

Population

Species : Rat Long Evans # : 6 Sex : Males
Age : 9 weeks

Exposure

Route : Gavage
Duration : 5 d/w; 2 w
C/D reported : 8.47 mmol/kg/d
CSU/DSU : 2698 mg/kg/d
Ratio : 44
ASM :
BM :
NSM :
NL :
Remarks :

Tests

Test type	Details on test
• Effects reported	• Remarks
Light and electron microscopy	Cochleogram
• 90, 50 and 25 % losses in the third, second and first rows of outer hair cells, respectively at 10-25 kHz	• Histology performed 10 days after the end of exposure

Mechanism of action

Authors' conclusion

Ototoxic effect of p-xylene in rats

Our conclusion

Ototoxic effect of p-xylene after exposure by oral way in rats

Xylene (isomers o,m,p)

Xylene (o-,m-,p- isomers)
• TWAEV : 100 ppm | 434 mg/m³ D-TWAEV : 62 mg/kg/d

Population

Species : Rat Long Evans # : C = 8; E1 = 8; E2 = 8; E3 = 8 Sex : Males

Age : 9 weeks

Exposure

Route : Inhalation

Duration : 6 h/d; 5 d/w; 3 w

C/D reported : 1800 ppm (see remarks)

CSU/DSU :

Ratio : 18

ASM :

BM : Para-xylene : Methylhippuric acid : 33.16 g/g creatinine ; Methylbenzylmercapturic acid : 0.04 g/g ;
Ortho-xylene : Methylhippuric acid : 7.80 g/g creatinine ; Methylbenzylmercapturic acid : 6.22 g/g creatinine ;
Meta-xylene: Methylhippuric acid : 20.43 g/g creatinine ; Methylbenzylmercapturic acid : 0.025 g/g creatinine

NSM :

NL :

Remarks : Exposure to ortho-, meta- or para-xylene administred individually

Tests

Test type • Effects reported	Details on test • Remarks
Brainstem auditory evoked potentials	at 2, 4, 6, 8, 10, 12, 16, 20 and 32 kHz
• Ortho-xylene : No effects Meta-xylene : No effects Para-xylene : Significant permanent 39-dB threshold shifts in the p-xylene exposed group. - Main threshold shifts were located in a frequency range from 8 to 20 kHz, the midfrequency range in the rat	• Test performed prior to xylene exposure and 4 weeks after the end of the exposure
Light microscopy	
• Ortho-xylene : No effects Meta-xylene : No effects Para-xylene : Severe losses at the level of the three rows of OHCs, even though the third row is more damaged than the second row, which itself is more damaged than the first row	• Cochleae were dissected 4 weeks after the last exposure

Mechanism of action

Authors' conclusion

Para-Xylene can be considered a cochleotoxic solvent. No ototoxicity of orto- and meta-xylene

Our conclusion

Para-Xylene can be considered a cochleotoxic solvent in rats exposed to 1800 ppm. Ortho- and meta-xylene can not be considered cochleotoxic solvents in rats exposed to 1800 ppm

Xylene (isomers o,m,p)

Xylene (o-,m-,p- isomers)
• TWAEV : 100 ppm | 434 mg/m³ D-TWAEV : 62 mg/kg/d

Population

Species : Rat Fisher 344 # : 12 Sex : Males
Age : 23 d

Exposure

Route : Inhalation
Duration : 14 h/d; 6 w
C/D reported : 800, 1000 and 1200 ppm
CSU/DSU :
Ratio : 8 - 12
ASM :
BM :
NSM :
NL :
Remarks : Mixture of 10% of ortho-, 80% of meta- and 10% of para- xylene use

Tests

Test type • Effects reported	Details on test • Remarks
Pure tone audiometry	at 2, 4, 8, 12, 16 and 20 kHz
• Elevation of auditory thresholds at 12 and 20 kHz after exposure to 800 ppm, at 8 kHz and above after 1000 ppm and at all frequencies after 1200 ppm	• Test performed every 2 weeks during exposure and 2 weeks after the end of exposure
Auditory brainstem responses	Inferior colliculus Tone pips of 4, 8 and 16 kHz
• - 16 kHz : elevated thresholds in all exposed rats - 8 kHz : elevated thresholds in rats exposed to 1000 or 1200 ppm - 4 kHz : elevated thresholds in rats exposed to 1200 ppm	• Test performed 2 weeks after the end of exposure

Mechanism of action

Authors' conclusion

LOAEL of 800 ppm for ototoxic effect in rats

Our conclusion

LOAEL of 800 ppm for ototoxic effect in rats

Xylene (isomers o,m,p)

Xylene (o-,m-,p- isomers)
• TWAEV : 100 ppm | 434 mg/m³ D-TWAEV : 62 mg/kg/d

Population

Species : Rat Fisher 344 # : 12 Sex : Males
Age : 23 d

Exposure

Route : Inhalation
Duration : 8 h/d; 1 or 3 d
C/D reported : 1450 ppm
CSU/DSU :
Ratio : 15
ASM :
BM :
NSM :
NL :
Remarks : Mixture of 10% of ortho-, 80% of meta- and 10% of para- xylene use

Tests

Test type • Effects reported	Details on test • Remarks
Pure tone audiometry	at 2, 4, 8, 12, 16 and 20 kHz
• Hearing loss at the higher tone frequencies (12-20 kHz) in the rats exposed for 1 or 3 days	• Test performed 35 days after the end of exposure

Mechanism of action

Authors' conclusion

Ototoxic effect at 1450 ppm in rats after a short exposure

Our conclusion

Ototoxic effect at 1450 ppm in rats after a short exposure

Xylene (isomers o,m,p)

Xylene (o-,m-,p- isomers)
• TWAEV : 100 ppm | 434 mg/m³ **D-TWAEV : 62 mg/kg/d**

Population

Species : Rat Fisher 344 # : 12 Sex : Males
Age : 23 d

Exposure

Route : Inhalation
Duration : 4 h
C/D reported : 1700 ppm
CSU/DSU :
Ratio : 17
ASM :
BM :
NSM :
NL :
Remarks : Mixture of 10% of ortho-, 80% of meta- and 10% of para- xylene use

Tests

Test type • Effects reported	Details on test • Remarks
Pure tone audiometry	at 2, 4, 8, 12, 16 and 20 kHz
• No effect	• Test performed 35 days after the end of exposure

Mechanism of action

Authors' conclusion

No ototoxic effect after exposure to 1700 ppm during 4 hours in rats

Our conclusion

No ototoxic effect after exposure to 1700 ppm during 4 hours in rats

m-Xylene

Xylene (o-,m-,p- isomers)
• TWAEV : 100 ppm | 434 mg/m³ D-TWAEV : 62 mg/kg/d

Population

Species : Volunteer # : 9 Sex : Males
Age : 21 years

Exposure

Route : Inhalation
Duration : 3 h (morning) + 40 min pause + 40 min (afternoon)
C/D reported : 200 ppm or 135 - 400 ppm (peak of 400 ppm for 20 minutes at the beginning of each session)
CSU/DSU :
Ratio : 2 - 4
ASM :
BM :
NSM :
NL :
Remarks : Subjects either sedentary or exercised at 100 W for 10 minutes at the beginning of each session

Tests

Test type • Effects reported	Details on test • Remarks
Auditory brainstem responses	Clicks of 100 dB
• No effect	• Test performed before exposure and immediately after the morning and afternoon session

Mechanism of action

Authors' conclusion

No ototoxic effect at 200 ppm in human after a short-term exposure

Our conclusion

No ototoxic effect at 200 ppm in human after a short-term exposure

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