2008-12-14

Ototoxic effects of industrial chemicals**

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

A. Vyskocil[1]*, G. Truchon[2], T. Leroux[3], F. Lemay[2], M. Gendron[3], F. Gagnon[1], S. Botez[2], N. El Majidi[1], S.Lim[1], C. Émond[1], C. Viau[1]

Introduction

There is accumulating epidemiological evidence that exposure to some solvents, metals, asphyxiants and other substances in humans is associated with an increased risk of hearing loss. This project was undertaken to develop a toxicological database allowing the identification of possible ototoxic substances present in the work environment. Critical toxicological data were compiled for chemical substances included in the Quebec Occupational Health Regulation.

Methods

The data were evaluated only for realistic exposure concentrations up to the short-term exposure limit or ceiling value or five times the 8-h time weighted average exposure limit value(TWAEV) for human data and up to 100 times the 8-h TWAEV or ceiling value for animal studies.

Using a systematic weight of evidence approach, the information from both human and animal studies was examined.

At first, information from each source was given a weight of evidence qualifier for ototoxicity: strong, medium, weak, absent or "no study found". We took into consideration the following parameters: studied specie, number of subjects, exposure way, characteristics of control groups, exposure levels, audiometric and statistical tests, dose/effect relation. Table 1 shows how this information was combined to yield an overall assessment of the ototoxic potential of a given substance. Human data were generally given more weight in the overall assessment. When no human studies were available, which is different from the absence of evidence from the available human studies, the overall assessment was deemed the same as that from animal studies.

We built a weight of evidence table that allowed us to combine the information from both human and animal studies on ototoxicity of chemicals. Table 1 shows how the information from both types of studies were combined to yield an overall assessment and corollary conclusion about the ototoxicity of the investigated chemicals.

Human data were generally given more weight in the overall assessment. When no human studies were available, or when good quality human studies showed absence of evidence of an ototoxic effect, the overall assessment was one degree lower than that resulting from the animal studies. For example, a "strong" evidence from animal studies combined with an "absence" of evidence from the available human studies yielded a "medium" evidence overall.

Regarding the final conclusion about the ototoxic potential of chemical substances, all substances bearing a "strong evidence" of ototoxicity overall are considered "ototoxic". Those with "medium evidence" overall are rated "possibly ototoxic". We consider the ototoxic potential of those with only "weak evidence" as "non conclusive". Finally, those for which there is absence of evidence overall bear the mention "no evidence".

* Corresponding author : adolf.vyskocil@UMontreal.CA
** Production of this document was supported by the IRSST (Grant 099-542)

[1] Groupe de recherche interdisciplinaire en santé- Département de santé environnementale et santé au travail, Université de Montréal
[2] Institut de recherche Robert-Sauvé en santé et en sécurité du travail (IRSST)
[3] École d'orthophonie et d'audiologie, Université de Montréal

Table 1. Weight of evidence approach for the assessment of ototoxicity of various industrial chemicals

Strength of evidence about ototoxicity in assessed studies			Conclusion about ototoxicity
Human	**Animal**	**Overall**	
S	S	S	O
S	M	S	O
S	W	S	O
S	A	S	O
S	X	S	O
M	S	S	O
M	M	M	PO
M	W	M	PO
M	A	M	PO
M	X	M	PO
W	S	M	PO
W	M	W	NC
W	W	W	NC
W	A	W	NC
W	X	W	NC
A	S	M	PO
A	M	W	NC
A	W	W	NC
A	A	A	NE
A	X	A	NE
X	S	M	PO
X	M	W	NC
X	W	W	NC
X	A	A	NE

Indication of ototoxicity:

S = strong; M = medium; W = weak; A = absent; X = no study found

General conclusion about ototoxicity:

O = ototoxic substance; PO = possibly ototoxic substance; NC = non conclusive; NE = no evidence

---

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

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

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 animal studies: **Strong** From human studies: **Absent** Overall: **Medium**

ANALYSIS OF ANIMAL STUDIES

Six studies on rats of different strains were identified. An ototoxic effect was observed in 4 inhalation and 1 oral studies. Three studies from the same laboratory showed the ototoxic effect depending on the duration of exposure. One study compared the ototoxicity of 3 xylene isomers (Gagnaire 2001). 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.

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.

CONCLUSION

Only one human study was identified showing no ototoxic effect after a short-term exposure. In rats xylene affects the auditory function. Given the current evidence from animal studies, we recommend considering xylenes as possibly ototoxic agents. Further studies with sufficient data on the exposure of workers to xylene isomers are necessary to make a definitive conclusion.

Xylène (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 :

Remarks : Exposure to a mixture of xylene isomers without details on its composition

Tests

Test type • Effects reported	Precisions 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

Action mechanism

Authors' conclusion

Mid-frequency hearing loss at 1800 ppm in rats

Our conclusion

Ototoxic effect at 1800 ppm in rats

Xylène (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 :

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

Tests

Test type • Effects reported	Precisions 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

Action mechanism

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-Xylène []

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 :

Remarks :

Tests

Test type • Effects reported	Precisions on test • 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

Action mechanism

Authors' conclusion

Ototoxic effect of p-xylene in rats

Our conclusion

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

Xylène (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 :

Remarks : Mixture of 10% of ortho-, 80% of meta- and 10% of para- xylene use

Tests

Test type • Effects reported	Precisions 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

Action mechanism

Authors' conclusion

LOAEL of 800 ppm for ototoxic effect in rats

Our conclusion

LOAEL of 800 ppm for ototoxic effect in rats

Xylène (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 :

Remarks : Mixture of 10% of ortho-, 80% of meta- and 10% of para- xylene use

Tests

Test type • Effects reported	Precisions 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

Action mechanism

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

Xylène (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 :

Remarks : Mixture of 10% of ortho-, 80% of meta- and 10% of para- xylene use

Tests

Test type • Effects reported	Precisions 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

Action mechanism

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-Xylène []

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 :

Remarks : Subjects either sedentary or exercised at 100 W for 10 minutes at the beginning of each session

Tests

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

Action mechanism

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

BIBLIOGRAPHY

Crofton 1994 Crofton, K.M., et al. (1994) Solvent-induced ototoxicity in rats: an atypical selective mid-frequency hearing deficit. Hear Res. 80(1): 25-30.

Gagnaire 2001 Gagnaire, F., et al. (2001) Ototoxicity in rats exposed to ortho-, meta- and para-xylene vapours for 13 weeks. Pharmacol Toxicol. 89(1): 6-14.

Gagnaire 2005 Gagnaire, F., et al. (2005) Relative ototoxicity of 21 aromatic solvents. Arch Toxicol. 79(6): 346-54.

Pryor 1987 Pryor, G.T., et al. (1987) Hearing loss in rats caused by inhalation of mixed xylenes and styrene. J Appl Toxicol. 7(1): 55-61.

Seppalainen 1989 Seppalainen, A.M., et al. (1989) Changes induced by short-term xylene exposure in human evoked potentials. Int Arch Occup Environ Health. 61(7): 443-9.