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

p-tert-Butyltoluene

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

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.

---

* Corresponding author : adolf.vyskocil@umontreal.ca
** Production of this document was supported by the IRSST (Grants 99-542 and 99-745)

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

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

p-tert-Butyltoluene

Quebec's Occupational exposure limits: TWAEV: 6,1 mg/m³ (1 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
No documentation	From human studies: **No study found** From animal studies: **No study found** Overall: **No study found**

Ototoxicity - Analysis of human studies

No study identified.

Ototoxicity - Analysis of animal studies

Two studies on two strains of rats exposed by inhalation were identified. No hearing loss has been found as shown by auditory brainstem responses measurements. Only minor neurofunctional changes were observed at high concentration of p-tert-butyltoluene. No morphologic examination was performed.

Interaction with noise - Analysis of human studies

No study identified.

Interaction with noise - Analysis of animal studies

No study identified.

Discussion

No human study was identified. Two animal studies showing no ototoxic effect were identified. No human or animal study on ototoxic interaction between p-tert-butyltoluene and noise was identified. In summary, there is neither evidence of ototoxicity of p-tert-butyltoluene nor of its interaction with noise.

p-tert-Butyltoluene

p-tert-Butyltoluene
• TWAEV : 1 ppm | 6,1 mg/m³ D-TWAEV : 0,87 mg/kg/d

Population

Species : Rat Long Evans # : 11 - 13 Sex : Males
Age : 3 months

Exposure

Route : Inhalation
Duration : 6 h/d; 7 d/w; 4 w
C/D reported : 20 and 40 ppm
CSU/DSU :
Ratio : 20 - 40
ASM :
BM :
NSM :
NL :
Remarks : LC50 = 165 ppm for 8 hours and 248 ppm for 4 hours in rat

Tests

Test type • Effects reported	Details on test • Remarks
Auditory brainstem responses • No shift in hearing threshold but amplitude of the first wave was increased at high stimulus levels (16 kHz; 95 dB)	Tone pips of 4, 8 and 16 kHz • Test performed 5 months after the end of exposure

Mechanism of action

Authors' conclusion

The effect on amplitude was interpreted as changes in stimulus attenuation due to loss of cochlear outer hair cells, however other interpretations are possible

Our conclusion

No adverse effect at 40 ppm in te rats

p-tert-Butyltoluene

p-tert-Butyltoluene
• TWAEV : 1 ppm | 6,1 mg/m³ D-TWAEV : 0,87 mg/kg/d

Population

Species : Rat Wistar # : 9 Sex : Males

Age :

Exposure

Route : Inhalation

Duration : 6 h

C/D reported : 50 and 150 ppm

CSU/DSU :

Ratio : 50

ASM :

BM :

NSM :

NL :

Remarks : LC50 = 165 ppm for 8 hours and 248 ppm for 4 hours in rat

Tests

Test type • Effects reported	Details on test • Remarks
Auditory brainstem responses	Clicks of 100 dB at 8 kHz
• - No effect on the amplitude. - Significant changes in the waveforms for at least 120 hours at 50 ppm and 288 hours at 150 ppm	• Test performed 2, 6, 24, 48, 120 and 288 hours after the end of exposure

Mechanism of action

Authors' conclusion

Minor neurofunctional changes

Our conclusion

No adverse effect at 150 ppm in the rats

BIBLIOGRAPHY

Lam 2000 Lam, H.R., et al. (2000) Four weeks' inhalation exposure of Long Evans rats to 4-tert-butyltoluene: effect on evoked potentials, behaviour, and brain neurochemistry. Pharmacol Toxicol. 87(1): 11-7.

Lund 1993 Lund, S.P., et al. (1993) Sensory-evoked potentials as indices of neurotoxicity in the rat: effect of 4-tert-butyltoluene. Int J Psychophysiol. 14(1): 41-8.