

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

Ethyl alcohol

A. Vyskocil^{1*}, T. Leroux³, G. Truchon², F. Lemay¹, F. Gagnon¹, M. Gendron³, S. Botez¹, N. El Majidi¹, A. Boudjerida¹, S. Lim¹, C. Émond¹, C. Viau¹

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 ototoxicity 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 m³/d and body weight of 70 kg

Ceiling : Ceiling exposure [limit] value in Quebec

D-Ceiling : Calculated inhaled dose for pulmonary ventilation of 10 m³/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/m³ 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

Ethyl alcohol

Quebec's Occupational exposure limits: TWAEV: 1880 mg/m³ (1000 ppm)

Conclusion about ototoxicity No evidence	Strength of evidence From human studies: No study found From animal studies: Absent Overall: Absent
Conclusion about interaction with noise No documentation	Strength of evidence From human studies: No study found From animal studies: No study found Overall: No study found

Ototoxicity - Analysis of human studies

No study was identified.

Ototoxicity - Analysis of animal studies

Three studies in rats were identified. No ototoxic effect was observed using auditory brainstem responses test or the multisensory conditioned avoidance response task after a subchronic exposure of ethyl alcohol (up to 8 % in drinking water during 2-8 weeks). Using auditory brainstem responses test, alcohol-addicted 22-month-old rats exposed from age of 3 months did not reveal any changes as compared with either 22-month-old or 3-month-old rats without exposure to ethyl alcohol.

Interaction with noise - Analysis of human studies

No study was identified.

Interaction with noise - Analysis of animal studies

No study was identified.

Discussion

No human study was identified. Three animal studies showed no ototoxic effect of ethyl alcohol. No human or animal study on ototoxic interaction between ethyl alcohol and noise was identified. In summary, there is neither evidence of ototoxicity of ethyl alcohol nor of its interaction with noise.

Ethyl alcohol**Ethyl alcohol**• TWAEV : 1000 ppm | 1880 mg/m³

D-TWAEV : 269 mg/kg/d

Population

Species : Rat Sprague Dawley

: E1 = 60; E2 = 5; E3 = 6

Sex : Not reported

Age : E1 = 3 months; E2 and E3 = 22 months

Exposure

Route : Oral

Duration : 19 months

C/D reported : E1 and E2 = 0 g/kg/d; E3 = 1-3 g/kg/d

CSU/DSU :

Ratio : 3.7-11.2

ASM :

BM :

NSM :

NL :

Remarks :

Tests**Test type**

• Effects reported

Details on test

• Remarks

Auditory brainstem responses

at 2, 4, 6, 8, 12, 16, 20 and 31.5 kHz
 Latency for wave 2 was determined at threshold level

- Significant differences between young and old normal rat at the best frequencies of 8-16 kHz
- No significant differences between aged alcohol-addicted rats and animals from the two other groups
- No significant differences in latencies between rats from both aged groups

Mechanism of action**Authors' conclusion**

The toxic effects of alcohol are exerted at higher levels than the brainstem

Our conclusion

The toxic effects of alcohol are exerted at higher levels than the brainstem

Ethyl alcohol**Ethyl alcohol**• TWAEV : 1000 ppm | 1880 mg/m³

D-TWAEV : 269 mg/kg/d

Population

Species : Rat DA-HAN

: 9

Sex : Males

Age : 6 months

Exposure

Route : Drinking water

Duration : 21 h/d; 7 d/w; 8 w

C/D reported : 8 % (v/v)

CSU/DSU : 6203 mg/kg/d

Ratio : 54

ASM :

BM :

NSM :

NL :

Remarks :

Tests**Test type**

• Effects reported

Details on test

• Remarks

Auditory brainstem responses

• No effect on auditory sensitivity

Clicks at 1.6, 3.15, 6.3, 12.5 and 20 kHz

• Test performed 1 week after the end of exposure

Mechanism of action**Authors' conclusion**

No effect ototoxic in the rats exposed to ethanol in drinking water (0.8%; v/v)

Our conclusion

No ototoxic effect in the rats exposed to ethanol in drinking water (0.8%; v/v)

Ethyl alcohol**Ethyl alcohol**• TWAEV : 1000 ppm | 1880 mg/m³

D-TWAEV : 269 mg/kg/d

Population

Species : Rat

: C = 10; E = 12

Sex : Males

Age : 23 days

Exposure

Route : Drinking water

Duration : 14 d

C/D reported : 6% v/v ad libidum

CSU/DSU :

Ratio :

ASM :

BM :

NSM :

NL :

Remarks :

Tests**Test type**

• Effects reported

Details on test

• Remarks

Multisensory conditioned avoidance response task

40.4 to 63.8 dB at 4 kHz
 37.6 to 61.6 dB at 8 kHz
 24.0 to 46.9 dB at 12 kHz
 20.5 to 43.5 dB at 20 kHz

• Alcohol consumption did not cause any changes in performance

Mechanism of action**Authors' conclusion**

Forced consumption of alcohol did not affect learning and/or performance of the multisensory CAR task, nor did it cause any hearing deficit

Our conclusion

Alcohol does not seem to be ototoxic to rats

BIBLIOGRAPHY

- Anniko 1989** Anniko, M., et al. (1989). Frequency-specific auditory brainstem response analysis of young normal, aged normal and aged alcohol-addicted rats. *ORL J Otorhinolaryngol Relat Spec*, 51(5), 285-289.
- Nylen 1995** Nylen, P., et al. (1995) Function of the auditory system, the visual system, and peripheral nerve and long-term combined exposure to toluene and ethanol in rats. *Pharmacol Toxicol*. 76(2): 107-11.
- Pryor 1985** Pryor, G.T., et al. (1985) Interactions between toluene and alcohol. *Pharmacol Biochem Behav*. 23(3): 401-10.