

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

## n-Butyl alcohol

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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 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 m<sup>3</sup>/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<sup>3</sup>/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<sup>3</sup> 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

## n-Butyl alcohol

Quebec's Occupational exposure limits: Ceiling: 152 mg/m<sup>3</sup> (50 ppm)

Conclusion about ototoxicity <b>Non conclusive</b>	Strength of evidence From human studies: <b>Weak</b> From animal studies: <b>Absent</b> Overall: <b>Weak</b>
Conclusion about interaction with noise <b>No documentation</b>	Strength of evidence From human studies: <b>No study found</b> From animal studies: <b>No study found</b> Overall: <b>No study found</b>

### Ototoxicity - Analysis of human studies

Only one study was identified. Hearing loss was observed at workers exposed to 80 ppm for 3–11 years using pure tone audiometry test. According to the authors, "the noise was present but the analysis made reported that it was not intense".

### Ototoxicity - Analysis of animal studies

Only one study was identified. No permanent hearing loss was found in rats exposed to 4000 ppm for 5 days. Reflex modification audiometry test was performed 5 to 8 weeks after the end of exposure.

### Interaction with noise - Analysis of human studies

No study was identified.

### Interaction with noise - Analysis of animal studies

No study was identified.

## Discussion

One study reported hearing loss in workers. No ototoxic effect was observed in rats. In the absence of other studies, it is not possible to draw any conclusion regarding the ototoxicity of n-butyl alcohol. No human or animal study on ototoxic interaction between n-butyl alcohol and noise was identified.

**n-Butyl alcohol****n-Butyl alcohol**• Ceiling : 50 ppm | 152 mg/m<sup>3</sup>

D-CEILING : 22 mg/kg/d

**Population**

Species : Rat Long Evans

# : 10

Sex : Males

Age : 60 days

**Exposure**

Route : Inhalation

Duration : 6 h/d; 5 d

C/D reported : 4000 ppm

CSU/DSU :

Ratio : 80

ASM :

BM :

NSM :

NL :

Remarks :

**Tests****Test type**

• Effects reported

Details on test

• Remarks

**Reflex modification audiometry**

at 0.5 - 40 kHz

• No hearing loss

• Test performed 5 to 8 weeks after the end of exposure

**Mechanism of action****Authors' conclusion**

No hearing loss at 4000 ppm in rats

**Our conclusion**

No ototoxic effect at 4000 ppm in rats

**n-Butyl alcohol****n-Butyl alcohol**• Ceiling : 50 ppm | 152 mg/m<sup>3</sup>

D-CEILING : 22 mg/kg/d

**Population**

Species : Worker

# : E1 = 11; E2 = 47

Sex : Males

Age : 20 - 39 years

**Exposure**

Route : Inhalation

Duration : 3 - 11 years

C/D reported : 80 ppm

CSU/DSU :

Ratio : 1.6

ASM :

BM :

NSM :

NL : E1 = NR; E2 = 90-110 dB

Remarks : E1 = exposure to n-butyl alcohol only

E2 = exposure to noise only

**Tests****Test type**

• Effects reported

Details on test

• Remarks

**Pure tone audiometry**

at 0.125 - 8 kHz

- Group E1 : hearing loss with maximum of 39 dB between 3 and 4 kHz. Magnitude was in direct relationship to exposure time
- Group E2 : hearing loss with maximum of 55 dB between 3 and 4 kHz. Magnitude was in direct relationship to exposure times

**Mechanism of action****Authors' conclusion**

Hearing loss at 80 ppm in workers

**Our conclusion**

Hearing loss at 80 ppm in workers

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