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

## Hexachlorobenzene

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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

# Hexachlorobenzene

Quebec's Occupational exposure limits: TWAEV: 0,025 mg/m³

| Conclusion about ototoxicity | Strength of evidence |
|---|---|
| **No evidence** | From human studies: **No study found**<br>From animal studies: **Absent**<br>Overall: **Absent** |
| Conclusion about interaction with noise | Strength of evidence |
| **No documentation** | From human studies: **No study found**<br>From animal studies: **No study found**<br>Overall: **No study found** |

## Ototoxicity - Analysis of human studies

No study was identified.

## Ototoxicity - Analysis of animal studies

Only one study on rats was identified. No ototoxic effect was observed using auditory nerve compound action potential test and histology after one month of oral exposure.

## 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. No ototoxic effect was observed after one month of oral exposure in rats. No human or animal study on ototoxic interaction between hexachlorobenzene and noise was identified. In summary, there is no evidence neither of ototoxicity of hexachlorobenzene nor of its interaction with noise.

## Hexachlorobenzene

**Hexachlorobenzene**
**• TWAEV : 0,025 mg/m³ D-TWAEV : 0,0036 mg/kg/d**

### Population

Species : Rat Sprague Dawley # : 5 - 7 Sex : Males
Age :

### Exposure

Route : Gavage
Duration : Once/d; 4 w
C/D reported : 0.16, 4 and 16 mg/kg/d
CSU/DSU :
Ratio : 45 - 4500
ASM :
BM :
NSM :
NL :
Remarks :

### Tests

Only a dose of 0.16 mg/kg evaluated as a ratio of other doses exceeded 100

| Test type<br>• Effects reported | Details on test<br>• Remarks |
|---|---|
| **Electrocochleography (Compound action potential : CAP)** | at 1, 2, 4, 8, 16 and 32 kHz |
| • No loss of acoustic sensitivity at a dose of 0.16 mg/kg | • Test performed after the end of each week's exposure |
| **Light and electron microscopy** | |
| • No cochlear hair cell loss or alteration of stereocilia | • Histology performed after the end of exposure |

### Mechanism of action

### Authors' conclusion

No ototoxic effect at 0.16 mg/kg/d in rats

### Our conclusion

No ototoxic effect at 0.16 mg/kg/d in rats

## BIBLIOGRAPHY

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