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

Tin, Organic compounds (as Sn)

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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

Tin, Organic compounds (as Sn)

Quebec's Occupational exposure limits: TWAEV: 0,1 mg/m³. STEV: 0,2 mg/m³

Conclusion about ototoxicity **Non conclusive**	Strength of evidence From human studies: **No study found** From animal studies: **Weak** Overall: **Weak**
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

Four animal studies were identified using the same single dose of trimethyl tin chloride administered by i.p. route. No ototoxic effect was found in one rat study (Young 1986). Three studies from the same laboratory, performed on guinea pigs, found a persistent ototoxic effect at high frequencies (Clerici 1991,Fechter 1990, Fechter 1992).

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. Ototoxic effect was observed after a single exposure in 3 studies in guinea pigs. In the absence of other studies, it is not possible to draw any conclusion regarding the ototoxicity of organic tin compounds. No human or animal study on ototoxic interaction between organic tin compounds and noise was identified.

Tin (Chlorure de triméthylétain)

Tin, Organic compounds (as Sn)
• TWAEV : 0,1 mg/m³ D-TWAEV : 0,0143 mg/kg/d

Population

Species : Guinea pig # : 5 Sex : Males

Age :

Exposure

Route : Intraperitoneal
Duration : Single dose
C/D reported : 2 mg/kg
CSU/DSU : 1.18 mg Sn/kg
Ratio : 83
ASM :
BM :
NSM :
NL :
Remarks :

Tests

Test type • Effects reported	Details on test • Remarks
Electrocochleography (Compound action potential : CAP)	at 2, 4, 6, 8, 12, 16, 20, 24, 30, 35 and 40 kHz Pure tones for MC, Tone bursts for CAP
• Marked elevation of electrophysiologic thresholds across the frequency range tested (up to 36 dB at 24 kHz. No effect on cochlear microphonic potential	• Test performed before injection and 30 and 60 minutes after injection

Mechanism of action

Authors' conclusion

Acute toxic action on the auditory system

Our conclusion

Acute ototoxic effect of the single dose of 2 mg/kg in guinea pigs

Tin (Chlorure de triméthylétain)

Tin, Organic compounds (as Sn)
• TWAEV : 0,1 mg/m³ D-TWAEV : 0,0143 mg/kg/d

Population

Species : Guinea pig # : 3 - 6 Sex : Not reported
Age :

Exposure

Route : Intraperitoneal
Duration : Single dose
C/D reported : 2 mg/kg
CSU/DSU : 1.18 mg Sn/kg
Ratio : 83
ASM :
BM :
NSM :
NL :
Remarks :

Tests

Test type • Effects reported	Details on test • Remarks
Auditory brainstem responses	Tone pips of 6, 12 and 24 kHz
• - High frequency auditory impairment which tended to improve within the first 2 weeks after exposure. - No alteration at 6 or 12 kHz	• Test performed before exposure and 3 days, 7 days and than weekly over a 6- week period
Light and electron microscopy	
• Outer hair cell loss (50-100 %) in the basal turn of cochlea and vascular pathology in the cochlea	• Histology performed 6 weeks after injection

Mechanism of action

Authors' conclusion

High frequency auditory impairment along with cochlear injury in guinea pigs. Persistent outer hair cell loss

Our conclusion

Persistent ototoxic effect after the single dose of 2 mg/kg in guinea pigs

Tin (Chlorure de triméthylétain)

Tin, Organic compounds (as Sn)
• TWAEV : 0,1 mg/m³ D-TWAEV : 0,0143 mg/kg/d

Population

Species : Guinea pig # : 5 Sex : Males
Age :

Exposure

Route : Intraperitoneal
Duration : Single dose
C/D reported : 2 mg/kg
CSU/DSU : 1.18 mg Sn/kg
Ratio : 83
ASM :
BM :
NSM :
NL :
Remarks :

Tests

Test type • Effects reported	Details on test • Remarks
Electrocochleography (Compound action potential : CAP)	at 2, 4, 6, 8, 12, 20, 24, 30, 35 and 40 kHz
• - Marked elevation of acoustic thresholds across the frequency range tested. - Recovery observed 24 and 48 hours after injection mainly in middle and low frequencies. - Reduction of cochlear microphonic amplitude. - No changes in endocochlear potential	• Test performed 6, 24 and 48 hours after administration of tin
Light and electron microscopy	
• Impairment of outer hair cells but not inner hair cells	• Test performed 24 and 48 hours after injection

Mechanism of action

Outer hair cells are targets responsible for hearing loss

Authors' conclusion

Acute toxic action on the auditory system

Our conclusion

Acute ototoxic effect of the single dose of 2 mg/kg in guinea pigs

Tin (Chlorure de triméthylétain)

Tin, Organic compounds (as Sn)
• TWAEV : 0,1 mg/m³ D-TWAEV : 0,0143 mg/kg/d

Population

Species : Rat Long Evans # : 4 Sex : Males
Age : 90 days

Exposure

Route : Intraperitoneal
Duration : Single dose
C/D reported : 2, 4 and 6 mg/kg
CSU/DSU : 1.19 – 3.56 mg Sn/kg
Ratio : 83 - 249
ASM :
BM :
NSM :
NL :
Remarks :

Tests

Test type	Details on test
• Effects reported	• Remarks
Reflex modification audiometry	
• No effect	• Test performed 1 week after the end of exposure

Mechanism of action

Authors' conclusion

No ototoxic effect at 2 mg/kg in rats after a single dose

Our conclusion

No ototoxic effect at 2 mg/kg in rats after a single dose

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