Chemical Substances and Biological Agents

Studies and Research Projects

REPORT **R-747**

Effect of Chemical Substances on Hearing

Interactions with Noise

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LIST OF ABBREVIATIONS

ACGIH: American Conference of Governmental Industrial Hygienists

OHC: Outer hair cells

dB: Decibel (relative sound pressure unit)

dB(A): A-weighted decibel (corresponds to the sound pressure weighted in relation to the sensitivity of the human ear, less sensitive at low frequencies and more sensitive at high frequencies)

IRSST: Institut de recherche Robert-Sauvé en santé et en sécurité du travail

LOAEL: Lowest Observed Adverse Effect Level (minimum dose with observed adverse effect)

NOAEL: No Observed Adverse Effect Level (dose without observed adverse effect)

C: Ceiling exposure [limit] value in Québec

RROHS: Regulation respecting occupational health and safety

STEV: Short-term exposure [limit] value in Québec

TWAEV: 8-h time-weighted average exposure [limit] value in Québec

SUMMARY

Today, no one would consider challenging the idea that noise exposure causes deafness. In fact, hearing losses caused by industrial noise represent one of the main occupational diseases in Québec and in many industrialized countries. It is slightly more surprising to learn that exposure to certain industrial chemicals may lead to hearing loss. These substances are said to be ototoxic. The ear, like other body organs, is irrigated by the blood. Toxic substances circulating in the body are therefore likely to affect this organ as much as other organs.

In the first phase of this project, the scientific literature was carefully scrutinized. This examination revealed that more than one hundred chemicals have been considered as potential ototoxic agents by various authors. A systematic analysis grid of the existing data was used to scrutinize this information and a reliability rating was assigned to the various studies. By proceeding in this way, it was concluded that ethylbenzene, styrene, toluene, trichloroethylene and lead are ototoxic. Furthermore, carbon disulfide, *n*-hexane and xylene were considered as possibly ototoxic at concentrations that can be found in the workplace.

The next logical step consisted of examining the combined effect of noise and chemical exposure on auditory function. This is the goal of this report. The same systematic analysis grid as the one used in the first phase was applied to the human and animal data found in the scientific literature. By proceeding this way, it was noted that only some fifty studies characterize exposure to noise and chemicals with sufficient precision and reliability. In addition, the definitions given by the studies' authors for "high" or "low" noise exposure vary from one study to the next. The result is that it is very difficult to combine all of the data to arrive at unequivocal conclusions.

From all of the scientific literature consulted, or approximately 150 articles, there were only two cases of interaction with noise: toluene and noise interact synergically, and carbon monoxide possibly potentiates the effect of noise. This does not rule out that other substances may exacerbate noise-induced hearing losses. As expressed in legal language, one could say that these substances cannot really be accused of having such an effect beyond all reasonable doubt. All that remained was to declare them innocent, while waiting for other studies to provide a different possible clarification. The authors of this report strongly recommend that workplace preventionists remain alert for any new information about this potential problem.

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1. INTRODUCTION

Occupational hearing loss is mainly attributed to workers' exposure to noise. However, certain chemicals can also have impacts on hearing, either by disrupting the function of the cochlea, or by affecting the central auditory system, or even by potentiating the effects of noise. In fact, the presence of an ototoxic agent in the internal ear could make it more vulnerable to noise assault than an ear exposed solely to noise.[1] In the scientific literature, more than 100 substances present in workplaces have been identified as being potentially ototoxic.[2] These substances include solvents, with the primary ones being toluene, styrene, xylene, carbon disulfide and trichloroethylene; asphyxiants, namely carbon monoxide and hydrogen cyanide; metals such as lead and mercury; as well as pesticides such as paraquat and organophosphates.[3] Several of these substances are prevalent in workplaces. Since more than 400,000 workers in Québec are exposed to noise levels in the order of 85 dB(A)-8h,[4] occupational health preventionists' concern about this issue remains important.

In the first phase of the project, dealing with the ototoxicity of chemicals (*Report R-604*),[5] we evaluated the effects of chemicals alone on hearing. From a review of human and animal studies, we concluded that ethylbenzene, styrene, toluene, trichloroethylene and lead are ototoxic, and that carbon disulfide, n-hexane and xylene are possibly ototoxic at conceivable concentrations in the workplace (see Table 1). For the first phase of the project and on the IRSST's recommendation, we decided to focus on the abundant scientific literature addressing the effect of chemicals on hearing, which excluded studies that analyzed the combined effect of noise exposure. To obtain a more complete picture of the situation, this study takes into account the noise factor. In the framework of this project, the analysis of epidemiological studies revealed that in numerous workplaces, workers' exposure to potentially ototoxic substances is often combined with noise exposure. Also, the addition of information on the interaction of the substances with noise was recommended to us during the presentation of the Phase 1 results at international conferences (EUROTOX 2007, 2008 International Congress of Toxicology 2007, Society Of Toxicology 2008) and was required by the reviewers of the paper "A weight of evidence approach for the assessment of the ototoxic potential of industrial chemicals" submitted to an international journal.

This study allowed us to identify the substances most likely to cause interactions with noise, while taking into account the standards of the Québec Regulation respecting occupational health and safety (RROHS).[6] It also provides occupational health and safety professionals with a critical analysis of the scientific literature available up to now on the problem of ototoxicity and on the interaction of noise and chemicals. When a substance causes an increase in the toxicity of another, without itself producing the toxic effect considered, it is generally called *potentiation*. Substances that mutually increase the toxicity of either one are called *synergic*.

Readers who want more information on the physiology of the ear and on possible mechanisms of ototoxicity can consult a recent report by the European Agency for Safety and Health at Work[7] and our previous report on ototoxicity.[5]

2. OBJECTIVES

The objectives of this research project were:

- To document the interactions in the auditory system between the chemicals appearing on the RROHS list and noise.
- To identify the chemicals presenting a risk of interaction with noise for workers, based on the standards in effect in Québec.
- To combine the results of phases 1 and 2, to build a single database.

3. METHOD

A literature review was done using articles identified in Phase 1 of the project in the Medline, Toxline and Chemical Abstracts bibliographical databases for the period from 1970 to 2005. This review was completed by the articles identified in an update of the bibliographical search covering the years 2005, 2006 and 2007.

The inclusion criteria for the published studies, being part of an approach used previously by our research group for projects on toxicological interactions,[8] were the following:

a) For human studies, the exposure concentrations for the reported substances should not exceed the STEV, the ceiling value, or 5 times the TWAEV as mentioned in the RROHS.

b) For animal experiments, the concentrations (or equivalent doses) reported should not exceed 100 times the TWAEV or 100 times the ceiling value.

The methodology of each retained study was considered: species studied, number of individuals, route, duration and levels of exposure, tests used to evaluate auditory function, etc. Noise/substance interactions were documented and, when available, information on the action mechanisms was collected.

The variables taken into consideration in examining the potential interactions were the concentration of the chemicals in the air inhaled by the workers or animals, and the sound pressure expressed in dB. Regarding measurement of the effect, the results of the following tests were used: behavioural hearing tests (e.g., conditioned behavioural audiometry in animals or pure-tone audiometry in humans), physiological tests and electrophysiological tests (e.g., otoacoustic emissions, electrocochleography, auditory brainstem response). In animals, the results of histological examinations were taken into consideration.

A weight-of-evidence approach was used to identify the substances presenting a risk of interaction with noise in workers. It had already been used in the first phase of the project on ototoxicity.[5]

For a given substance, a qualifier of the weight of evidence was assigned to all of the studies carried out on humans. Similarly, such a qualifier was assigned to the animal experiments. The possible qualifiers are: “strong”, “medium”, “weak”, “none”, and “no study found.”

Note that the weight-of-evidence value “none” must not be considered as evidence that a substance does not interact with noise. Since the number of studies on interactions between chemicals and noise is low, it seems prudent at this stage of knowledge to retain the term “no evidence” of interaction, rather than suggesting that evidence of a lack of interaction exists by an indication “no interaction.” Table 2 is a synthesis of how this information was combined to arrive at an overall evaluation of the potential of interaction of a substance and noise. Human data received greater weight than animal data in the overall evaluation because the evidence provided by human studies is more significant than that provided by animal experiments.

When no human study is available, the overall weight of evidence is lower than that resulting from animal studies. For example, the lack of evidence of an interaction based on human studies

combined with a “strong” weight of evidence from animal experiments resulted in a “medium” overall weight of evidence.

Regarding the final conclusion about the interaction of substances with noise, all those whose weight of evidence is “strong” are considered as substances with “evidence of interaction.” Those whose overall weight of evidence is “medium” are considered as substances with “possible interaction.” When the weight of evidence is “weak,” we consider it “inconclusive.” Finally, for substances whose weight of evidence is “none,” we assign the mention “no evidence” of interaction.

The data from the studies was organized into a database, which is an adaptation of the database developed in Phase 1 of this project in order to take noise into account. The database was also used to disseminate the results by the production of individual data sheets, in PDF format, on the substances, in French and in English. The data sheets contain both the information on ototoxicity obtained in the first phase and the new information on the interactions with noise. The HTML document serving as an index for the substance data sheets produced in Phase 1 was completely revised. These data can be used to update the portion on the auditory system in the database on toxicological interactions, developed in a project on chemical interactions,[8] by completing the list of substances that can affect the cochlea and the central auditory system.

4. RESULTS

A selection of the publications taking into consideration (a) the substances listed in the Québec RROHS, and (b) realistic exposure concentrations, led us to the evaluation of 224 experiments (in 150 publications), 51 of which (taken from 44 publications) studied the effect of exposure to a substance combined with exposure to noise.

In this report, we use the term "experiment" to describe an experiment done on animals or a study carried out on humans: one article can report more than one experiment.

Table 3 presents the summary of the conclusions regarding interactions between 11 industrial chemicals and noise. For 7 substances, the evaluation is based on only one experiment. At the other extreme, the evaluation of carbon monoxide is based on 18 experiments.

Analysis of the considered studies identified a few points. First, for measuring the effect, a large variety of tests were used. They were pure-tone audiometry, reflex modification audiometry, distortion product otoacoustic emissions, transient evoked otoacoustic emissions, multisensory conditioned avoidance response, electrocochleography, and even auditory brainstem responses. Various approaches were used to evaluate exposure to chemicals, and for lead, toluene and styrene, exposure was evaluated by biological monitoring.

Of all of the chemicals studied, a conclusion about the nature of the interaction could be established for only two substances. Toluene was identified as a substance interacting with noise ("evidence of interaction"); the animal and human studies suggest that the combined exposure to toluene and noise produces additive or synergic damage. Carbon monoxide was identified as a substance that possibly potentiates the effect of noise on hearing ("possible interaction"). For 7 substances, the lack of toxicological data does not allow a conclusion ("inconclusive"). The mention "no evidence" of interaction with noise was given to 2 substances.

Figure 1 presents the structure of the database developed using Microsoft Access. Each cell represents a table, with the names of the columns (fields) also given. While the database is bilingual, for simplification we did not present the names of the columns in French. Figure 1 also includes a brief description of the main tables. The relationships between the tables are indicated by arrows. For example, the permissible exposure values in the '`regulatedSubstance`' table, which reflects the Québec regulations on the use of toxic substances in the workplace, originate from the '`regulatedSubstance_OEL`' table.

The substance data sheets, in French and in English, are accessible on the Université de Montréal Web site (http://www.dsest.umontreal.ca/recherche_rayonnement/autres_contributions.html) as well as on the IRSST Web site (http://www.irsst.qc.ca).

In Appendix 1, the reader will find an abridged version of the data sheets presenting the evaluation of the interactions between noise and chemicals.

5. DISCUSSION AND CONCLUSION

Recent studies suggest that several substances present in the industrial environment can interact with noise synergically or by potentiating noise-induced hearing loss. However, in the majority of cases where synergy or potentiation were proposed, it cannot be clearly decided whether there is interaction or not, due to a lack of toxicological data.

The weakness or lack of data on noise and chemical exposure in several studies was a main difficulty in arriving at a conclusion. In an occupational environment, since the workers are usually exposed to mixtures of substances, it is not easy to evaluate the effects associated with exposure to a specific chemical. In addition, from one study to the next, different thresholds are used to distinguish the groups exposed to noise from those that are not.

Extrapolation of the results of animal studies to humans must be done with care. The metabolism of chemicals and the range of audible frequencies are different in animals and humans. However, the models describing the pharmacokinetic mechanisms and toxicological mechanisms suggest that cellular processes are similar in humans and animals, at least for some substances, mainly ethyl benzene.[9] Several studies have demonstrated differences in sensitivity to the ototoxicity of solvents in guinea pigs, chinchillas and rats, with rats showing greater sensitivity.[10-14]

The very large majority of the studies were carried out on rats. The audible frequency range for this species is between 5 and 80 kHz, with a maximum sensitivity around 8 kHz, while in humans, the value of these parameters ranges from 0.02 to 20 kHz and from 0.25 to 8 kHz respectively.[15,16] Despite this difference, in the two species, the effects on hearing are in the outer hair cells (OHCs) located at the base of the cochlea, the region responsible for high frequency sound detection.[17]

In summary, the studies on animals as well as those on humans indicate that at realistic exposure concentrations for workplaces, toluene is a substance that interacts synergically with noise, and carbon monoxide possibly potentiates the effect of noise. As for the other substances, the data from the studies currently available are insufficient to make a precise statement about their possible interaction with noise.

Recently, Hoet et al.[18] proposed a “noise notation” analogous to the “skin notation” established for exposure to chemicals. Since an increasing number of substances seem to present an ototoxic potential and this is one of the major occupational health problems, the implementation of such a noise notation should be considered. It could be added to the permissible exposure values for ototoxic substances and would serve as a warning for medical monitoring of the auditory function of exposed workers. Based on the results of our literature review, we support this proposal.

The ototoxic risk and the combined risk should be included in the monitoring programs of the Québec public health network, which should be able to detect early the hearing problems attributable to exposure to chemicals and to combined exposure with noise.

Table 1. Summary of the Phase 1 results on ototoxicity[5]

INDUSTRIAL SUBSTANCE [CAS]	PEV[a]		WEIGHT OF EVIDENCE			CONCLUSION ABOUT OTOTOXICITY
	RROHS TWAEV (STEV)	**ACGIH** TWA (STEL)	Human studies	Animal studies	Overall	
Acrylonitrile [107-13-1]	2	2	X	W	W	NC
n-Butyl alcohol [71-36-3]	P50	20	W	A	W	NC
p-tert-Butyltoluene [98-51-1]	1	1	X	A	A	NE
Carbon disulfide [75-15-0]	4 (12)	1	W	W	W	NC
Carbon monoxide [630-08-0]	35 (200)	25	X	A	A	NE
Cyanides (as CN)	C10	C 5 mg/m^3	X	W	W	NC
Enflurane [13838-16-9]	75	75	X	A	A	NE
Ethyl alcohol [64-17-5]	1000	1000	X	A	A	NE
Ethyl benzene [100-41-4]	100 (125)	100 (125)	X	S	M	PO
n-Heptane [142-82-5]	400 (500)	400 (500)	X	W	W	NC
Hexachlorobenzene [118-74-1]	0.025 mg/m^3	0.002 mg/m^3	X	A	A	NE
n-Hexane [110-54-3]	50	50	W	S	M	PO[b]
Hydrogen cyanide (as CN) [74-90-8]	C10	C 4.7	X	A	A	NE
Lead and inorganic compounds (as Pb)	0.05 mg/m^3	0.05 mg/m^3	S	X	S	O
Mercury, Alkyl compounds (as Hg)	0.01 mg/m^3	0.01 (0.03) mg/m^3	W	X	W	NC
Mercury, inorganic compounds	0.025 mg/m^3	0.025 mg/m^3	W	A	W	NC
Mercury, mercury vapor (as Hg)	0.025 mg/m^3	0.025 mg/m^3	W	X	W	NC
Methyl chloroform [71-55-6]	350 (450)	350 (450)	X	A	A	NE
α-Methyl styrene [98-83-9]	50 (100)	50 (100)	X	W	W	NC

Methylene chloride [75-09-2]	50	50	X	A	A	NE
Parathion [56-38-2]	0.1 mg/m^3	0.05 mg/m^3	X	W	W	NC
Perchloroethylene [127-18-4]	25 (100)	25 (100)	A	A	A	NE
Styrene (monomer) [100-42-5]	50 (100)	20 (40)	M	S	S	O
Tin, organic compounds (as Sn)	0.1 (0.2) mg/m^3	0.1 (0.2) mg/m^3	X	W	W	NC
Toluene [108-88-3]	50	50	M	S	S	O
Trichloroethylene [79-01-6]	50 (200)	50 (100)	M	S	S	O[b]
Xylenes (o-,m-,p-isomers)	100 (150)	100 (150)	A	S	M	PO

[a] ppm; [b] neurotoxic/ototoxic effect

PEV = Permissible exposure value; TWAEV = 8-h time weighted average exposure value in Québec; STEV = Short-term exposure value in Québec; C = Ceiling value; TWA = Time Weighted Average; STEL = Short Term Exposure Limit; RROHS = Regulation respecting occupational health and safety; ACGIH = American Conference of Governmental Industrial Hygienists

Indication of ototoxicity: S = strong; M = medium; W = weak; A = absent; X = no study found

Conclusion about ototoxicity: O = ototoxic substance; PO = possibly ototoxic substance; NC = inconclusive; NE = no evidence

Table 2. Estimation of the interaction between noise and the various industrial chemicals based on the weight of evidence

Indication of interaction in the studies analyzed			Conclusion about interaction
Human	**Animal**	**Overall**	
S	S	S	I
S	M	S	I
S	W	S	I
S	A	S	I
S	X	S	I
M	S	S	I
M	M	M	PI
M	W	M	PI
M	A	M	PI
M	X	M	PI
W	S	M	PI
W	M	W	NC
W	W	W	NC
W	A	W	NC
W	X	W	NC
A	S	M	PI
A	M	W	NC
A	W	W	NC
A	A	A	NE
A	X	A	NE
X	S	M	PI
X	M	W	NC
X	W	W	NC
X	A	A	NE

Indication of interaction: S = strong; M = medium; W = weak; A = absent; X = no study found

Conclusion about interaction: I = evidence of interaction; PI = possible interaction; NC = inconclusive; NE = no evidence

Table 3. Summary of the conclusions about interaction between chemicals and noise

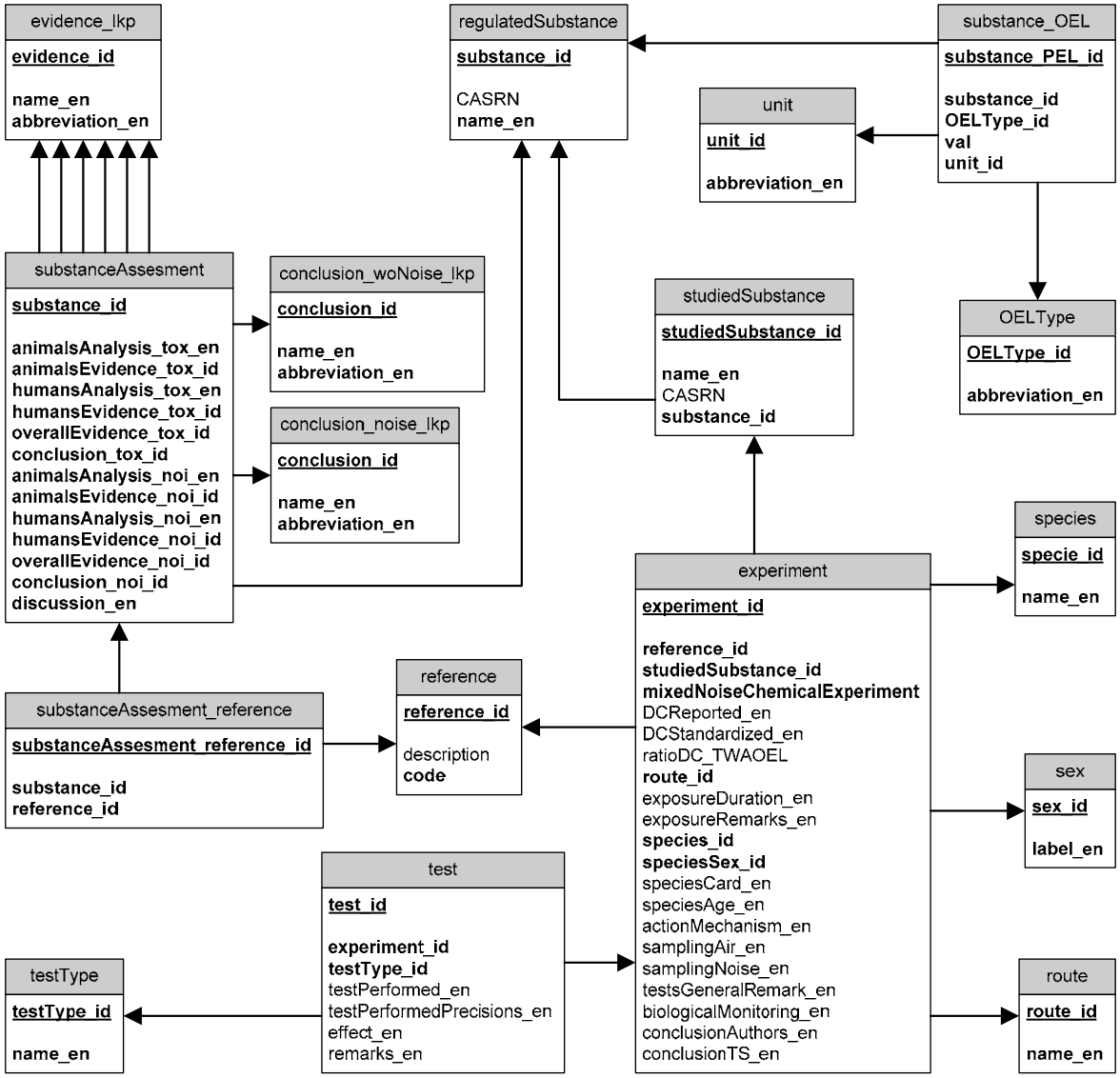
SUBSTANCE [CAS]	PEV[a]		REFERENCES		WEIGHT OF EVIDENCE			CONCLUSION
	RROHS TWAEV (STEV)	**ACGIH** TWA (STEL)	Human studies	Animal studies	Human studies	Animal studies	Overall	
Acrylonitrile [107-13-1]	2	2		19-22	X	M	W	NC
Carbon disulfide [75-15-0]	4 (12)	1	23		W	X	W	NC
Carbon monoxide [630-08-0]	35 (200)	25		24-35	X	S	M	PI
Ethyl benzene [100-41-4]	100 (125)	100 (125)		37	X	W	W	NC
Hydrogen cyanide (as CN) [74-90-8]	P10	C 4.7		36	X	W	W	NC
Lead and inorganic compounds (as Pb)	0.05 mg/m^3	0.05 mg/m^3	40		A	X	A	NE
Nicotine [54-11-5]	0.5 mg/m^3	0.5 mg/m^3		39	X	A	A	NE
Styrene (monomer) [100-42-5]	50 (100)	20 (40)	41-46	10, 47-49	W	M	W	NC
Toluene [108-88-3]	50	50	50-53	11, 12, 54-58	S	M	S	I
Trichloroethylene [79-01-6]	50 (200)	50 (100)		59	X	W	W	NC
Welding fumes (not otherwise classified)	5 mg/m3			38	X	W	W	NC

[a] ppm

PEV = Permissible exposure value; TWAEV = 8-h time weighted average exposure value in Québec; STEV = Short-term exposure value in Québec; C = Ceiling value; TWA = Time Weighted Average; STEL = Short Term Exposure Limit; RROHS = Regulation respecting occupational health and safety; ACGIH = American Conference of Governmental Industrial Hygienists

Indication of interaction: S = strong; M = medium; W = weak; A = absent; X = no study found

Conclusion about interaction: I = evidence of interaction; PI = possible interaction; NC = inconclusive; NE = no evidence



experiment experiments – one article can result in more than one experiment. This table is the main component of the data sheets.

test auditory function measuring tests.

reference bibliographical references to the articles. The references are the source of the information contained in an **experiment** and some – of a more general nature – are used to support the toxicologist's judgement (**substanceAssesment**).

studiedSubstance specific substances subject of the experiments' studies.

regulatedSubstance regulated substances in Québec according to the RROHS, a substance (studiedSubstance) must, to be considered, be associated with a regulated substance.

substances_OEL Limit exposure values in the workplace in Québec according to the RROHS.

substanceAssesment judgements about the weight of evidence of the documentation used and about the ototoxicity of the regulated substances.

Figure 1. Diagram of the database

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APPENDIX 1 – SUMMARY DATA SHEETS

Otoxicity of industrial substances alone or in the presence of noise**

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Introduction

There is increasing epidemiological evidence that exposure to certain solvents, metals, asphyxiants and other substances is associated in humans with a risk of hearing loss. However, the interaction of chemicals and noise has received little attention. This project was undertaken to develop a toxicological database, from the primary literature, allowing the identification of ototoxic substances and substances that interact with noise in the work environment. Critical toxicological data have been compiled for chemical substances included in the Québec *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-hr time-weighted average exposure value (TWAEV) for humans, or 100 times the 8-hr TWAEV or the ceiling value for animal studies. The following parameters were taken into account: the number of studies and, for each study, the species studied, the number of subjects or animals, the exposure route, the characteristics of the control groups, the exposure levels, the audiometric and statistical tests used, the dose-effect relationship and, when available, the action mechanisms.

The information obtained from animal and human studies was examined by using a systematic weight-of-evidence approach. First, for each substance, the weight of evidence of the human and animal studies relating to ototoxicity and the interaction with noise was determined by using one of the following qualifiers: “strong,” “medium,” “weak,” “none” and “no study found.” Note that the “none” weight-of-evidence qualifier should not be considered as proof that a substance is not ototoxic or that it does not interact with noise.

Table 1 indicates how, for each substance, this information was combined to arrive at an overall evaluation of the potential for ototoxicity and interaction with noise. Human data were generally given greater weight than animal data in the overall evaluation. For example, “strong” evidence from animal studies combined with a lack of evidence from human studies gave “medium” overall evidence.

Regarding the final conclusion about the ototoxicity of substances or their interaction with noise, substances whose overall evidence is “strong” are considered to be “ototoxic” or to have “evidence of interaction.” Those whose overall value is “medium” are “possibly ototoxic” or to have a “possible interaction.” When the overall evidence is “weak,” we determined them to be “inconclusive.” Finally for those substances whose evidence is “none,” we assigned the mention “no evidence” of ototoxicity or of an interaction with noise.

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Table 1. Estimation of the ototoxicity of industrial chemicals and their interaction with noise based on the weight of evidence of the studies

Weight of evidence of the studies			Conclusion about ototoxicity	Conclusion about interaction with noise
Human studies	Animal studies	Overall		
S	S	S	O	EI
S	M	S	O	EI
S	W	S	O	EI
S	N	S	O	EI
S	X	S	O	EI
M	S	S	O	EI
M	M	M	PO	PI
M	W	M	PO	PI
M	N	M	PO	PI
M	X	M	PO	PI
W	S	M	PO	PI
W	M	W	PO	PI
W	W	W	IC	IC
W	N	W	IC	IC
W	X	W	IC	IC
N	S	M	PO	PI
N	M	W	IC	IC
N	W	W	IC	IC
N	N	N	IC	IC
N	X	N	NE	NE
X	S	M	PO	PI
X	M	W	IC	IC
X	W	W	IC	IC
X	N	N	NE	NE
X	X	X	X	X

Indication of ototoxicity or interaction with noise:
S = strong, M = medium, W = weak, N = none, X = no study found

Conclusion about ototoxicity:
O=ototoxic substance, PO=possibly ototoxic substance, IC=inconclusive, NE=no evidence, X=no documentation
Conclusion about interaction with noise
EI=evidence of interaction, PI= possible interaction, IC=inconclusive, NE=no evidence, X=no documentation

Abbreviations

TWAEV: 8-hr time-weighted average exposure [limit] value in Québec
D-TWAEV: Calculated Inhaled dose for pulmonary ventilation of 10 m^3/d and a body weight of 70 kg
CEILING: Ceiling exposure [limit] value in Québec
D-CEILING: Calculated inhaled dose for pulmonary ventilation of 10 m^3/d and a body weight of 70 kg
STEV: Short-term exposure [limit] value in Québec
C/D reported: Reported concentration or dose
CSU/DSU: Reported concentration expressed in mg/m^3 or reported dose expressed in mg/kg/d
Ratio: For the concentration: CSU/TWAEV or CSU/CEILING; and for the 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

Acrylonitrile

Québec permissible exposure values: TWAEV: 4.3 mg/m³ (2 ppm)

Conclusion about ototoxicity **Inconclusive**	Strength of evidence Human studies: **No study found** Animal studies: **Weak** Overall: **Weak**
Conclusion about interaction with noise **Inconclusive**	Strength of evidence Human studies: **No study found** Animal studies: **Medium** Overall: **Weak**

Ototoxicity - ANALYSIS OF HUMAN STUDIES

No study was identified.

Ototoxicity - ANALYSIS OF ANIMAL STUDIES

Four studies by the same laboratory were identified. In these studies, acrylonitrile was administered to rats subcutaneously at a high dose of 50 mg/kg/d for 1 to 5 days. A temporary elevation in the auditory threshold was observed after a single administration of acrylonitrile. However, no hearing loss or hair cell loss was observed 4 weeks after repeated exposures of up to 5 days.

Interaction with noise - ANALYSIS OF HUMAN STUDIES

No study was identified.

Interaction with noise - ANALYSIS OF ANIMAL STUDIES

Four studies by the same laboratory were identified. In these studies, acrylonitrile was administered subcutaneously to rats at a high dose of 50 mg/kg/d for a period of 1 to 5 days. Acrylonitrile potentiates permanent noise-induced hearing loss particularly for high frequencies and when acrylonitrile and noise were administered repeatedly. Outer hair cells are the main target of toxicity.

Discussion

No study was performed on humans. Acrylonitrile potentiated permanent noise-induced hearing losses in rats. However, the acrylonitrile exposure route and dose were different from those experienced by workers. Chronic animal and human studies are necessary to arrive at a definitive conclusion. Without additional studies, it is impossible to draw any conclusion about the ototoxicity of acrylonitrile or its interaction with noise.

Carbon disulfide

Québec permissible exposure values: TWAEV: 12 mg/m³ (4 ppm). STEV: 36 mg/m³ (12 ppm)

Conclusion about ototoxicity **Inconclusive**	Strength of evidence Human studies: **Weak** Animal studies: **Weak** Overall: **Weak**
Conclusion about interaction with noise **Inconclusive**	Strength of evidence Human studies: **Weak** Animal studies: **No study found** Overall: **Weak**

Ototoxicity - ANALYSIS OF HUMAN STUDIES

A single study was identified using the auditory brainstem response test. In workers, an ototoxic effect was observed after chronic exposure, but it appears that this effect is reversible. However, no data relating to noise exposure were reported.

Ototoxicity - ANALYSIS OF ANIMAL STUDIES

Two rat studies were identified that used the auditory brainstem response test. In the first study on Wistar rats, transiently delayed parameters were observed in the group exposed to 200 ppm for 15 weeks. In the second study, no ototoxic effect was reported in Long-Evans rats exposed to 400 ppm for 11 weeks. However, in this latter study, the exposure was interrupted for 17 days after 6.5 weeks of exposure.

Interaction with noise - ANALYSIS OF HUMAN STUDIES

A single study was identified using pure-tone audiometry. Potentiation of noise-induced hearing loss by carbon disulfide (CS_2) was observed. However, the group exposed to CS_2 and noise was older and its duration of employment was twice as long as that of the control group or the noise-exposed group. No group was exposed only to CS_2 in this study. As a result, no meaningful conclusion regarding an interaction between noise and CS_2 can be drawn from this study.

Interaction with noise - ANALYSIS OF ANIMAL STUDIES

No study was identified.

Discussion

Studies on workers and animals regarding the ototoxic effect of carbon disulfide as well as human studies on its interaction with noise are inconclusive. Other animal and human studies are necessary to draw a conclusion about the ototoxicity of carbon disulfide or its interaction with noise.

Carbon monoxide

Québec permissible exposure values: TWAEV: 40 mg/m³ (35 ppm). STEV: 230 mg/m³ (200 ppm)

Conclusion about ototoxicity **No evidence**	Strength of evidence Human studies: **No study found** Animal studies: **None** Overall: **None**
Conclusion about interaction with noise **Possible interaction**	Strength of evidence Human studies: **No study found** Animal studies: **Strong** Overall: **Medium**

Ototoxicity - ANALYSIS OF HUMAN STUDIES

No study was identified.

Ototoxicity - ANALYSIS OF ANIMAL STUDIES

There are 10 rat studies that showed that carbon monoxide exposure by inhalation is not ototoxic for rats. All these studies but one were conducted in the same laboratory. The rats were exposed to carbon monoxide concentrations up to 1500 ppm for intermittent exposure durations varying between 3.5 hours and 13 weeks. The authors used electrocochleography, auditory brainstem response tests, reflex modification audiometry, and optical microscopy.

Interaction with noise - ANALYSIS OF HUMAN STUDIES

No study was identified.

Interaction with noise - ANALYSIS OF ANIMAL STUDIES

Eighteen rat studies were evaluated. All the studies were carried out in the same laboratory. Long-Evans rats were exposed to up to 1500 ppm carbon monoxide (CO) and the noise intensity varied between 95 and 115 dB. The noise level used was designed to induce hearing impairment. It is therefore impossible to draw a conclusion about lower noise levels. The duration of the intermittent exposures varied between 4.5 hours and 13 days. The authors used electrocochleography, reflex modification audiometry, distortion product otoacoustic emissions (DPOAE), compound action potentials and optical microscopy. Potentiation of noise-induced hearing loss by CO was observed in all the studies. The proposed mechanism is the generation of reactive oxygen species that cause oxidative stress, which damages the cochlea (Pouyatos 2008). Auditory threshold shifts were observed at all frequencies, but the greatest effects were seen at the highest test frequencies. The outer hair cells proved to be particularly vulnerable (Fechter 1988). Potentiation does not increase with an increasing noise level (Rao 2000a) or exposure duration (Fechter 2000a, Fechter 2000b). A LOAEL of 500 ppm was observed for this potentiation in rats (Fechter 1989, Chen 1999a, Fechter 2000a, Fechter 2000b).

Discussion

No human study was identified. No ototoxic effect of carbon monoxide alone was observed in the 10 animal studies on rats. However, potentiation of noise-induced hearing loss by carbon monoxide was found in 18 rat studies. Other studies with sufficient data on workers' carbon monoxide exposure are necessary to reach a definitive conclusion about interaction with noise. Without human studies, we cannot draw a conclusion about the ototoxicity of carbon monoxide. However, from the results of the animal studies, carbon monoxide should be considered a possible potentiator of noise-induced hearing loss.

Hydrogen cyanide (expressed as CN)

Québec permissible exposure values: Ceiling: 11 mg/m³ (10 ppm)

Conclusion about ototoxicity **No evidence**	Strength of evidence Human studies: **No study found** Animal studies: **None** Overall: **None**
Conclusion about interaction with noise **Inconclusive**	Strength of evidence Human studies: **No study found** Animal studies: **Weak** Overall: **Weak**

Ototoxicity - ANALYSIS OF HUMAN STUDIES

No study was identified.

Ototoxicity - ANALYSIS OF ANIMAL STUDIES

One inhalation study on rats was identified. Using pure-tone audiometry and histology, no ototoxic effect was observed after a single exposure to concentrations up to 50 ppm for 3.5 hours.

Interaction with noise - ANALYSIS OF HUMAN STUDIES

No study was identified.

Interaction with noise - ANALYSIS OF ANIMAL STUDIES

One study reported potentiation of noise-induced hearing loss by hydrogen cyanide in rats after a combined exposure, measured using electrocochleography and optical microscopy.

Discussion

No human study was identified. The only animal study showed no ototoxic effect from hydrogen cyanide inhalation. The same study showed potentiation of noise-induced hearing loss by hydrogen cyanide. Without additional studies, it is impossible to draw any conclusion about the ototoxicity of hydrogen cyanide or its interaction with noise.

Ethyl benzene

Québec permissible exposure values: TWAEV: 434 mg/m³ (100 ppm). STEV: 543 mg/m³ (125 ppm)

Conclusion about ototoxicity **Possibly ototoxic substance**	Strength of evidence Human studies: **No study found** Animal studies: **Strong** Overall: **Medium**
Conclusion about interaction with noise **Inconclusive**	Strength of evidence Human studies: **No study found** Animal studies: **Weak** Overall: **Weak**

Ototoxicity - ANALYSIS OF HUMAN STUDIES

No study was identified.

Ototoxicity - ANALYSIS OF ANIMAL STUDIES

Seven studies were identified, six on rats from two different strains, and one on guinea pigs. Five of these studies were carried out in the same laboratory. An ototoxic effect was reported in five studies following inhalation exposure, and in one study following oral exposure. Susceptibility to ethyl benzene is species dependent. With guinea pigs, ethyl benzene exposure did not damage the auditory system, while with rats, this exposure induced a permanent loss of hair cells in the cochlea (Cappaert 2002). An important characteristic of ethyl benzene is a higher susceptibility of outer hair cells (OHCs) compared to inner hair cells. This effect is dose-dependent, and higher ethyl benzene concentrations induce a higher hair cell mortality. Mid-frequency hearing loss was most often reported. In the rat, morphological examination determined a corresponding loss of OHCs in the mid-frequency region of the cochlea. Hair cell losses are not directly related to hearing threshold shifts in the rat (Cappaert 2001).

No chronic studies were identified. With rats, there is no ethyl benzene hearing loss for subacute exposure up to concentrations of approximately 300 ppm (Cappaert 2000) or for subchronic exposure to concentrations of 200 ppm (Gagnaire 2007). Above 300 ppm, ethyl benzene exposure induces threshold shifts directly related to the concentration (Cappaert 2000, Gagnaire 2007). The loss of OHCs is a more sensitive evaluation parameter than auditory threshold. OHC losses were observed at an ethyl benzene concentration of 200 ppm (Gagnaire 2007).

Interaction with noise - ANALYSIS OF HUMAN STUDIES

No study was identified.

Interaction with noise - ANALYSIS OF ANIMAL STUDIES

One subacute study in rats was identified. The combined exposure to 105 dB SPL noise and to 300 or 400 ppm ethyl benzene caused a greater outer hair cell loss than the sum of the losses induced by noise or ethyl benzene alone, which indicates cosynergy.

Discussion

No human study was identified. However, in rats, ethyl benzene affects auditory function mainly in the cochlear mid-frequency range, and combined exposure with noise showed a synergic effect in one study. Given the current evidence from animal studies, we recommend that ethyl benzene be considered as a possibly ototoxic agent. Other studies with sufficient data on worker exposure to ethyl benzene are necessary to draw a definitive conclusion about its ototoxicity and or any conclusion about its interaction with noise.

Welding fumes (not otherwise classified)

Québec permissible exposure values: TWAEV: 5 mg/m³

Conclusion about ototoxicity **Inconclusive**	Strength of evidence Human studies: **No study found** Animal studies: **Weak** Overall: **Weak**
Conclusion about interaction with noise **Inconclusive**	Strength of evidence Human studies: **No study found** Animal studies: **Weak** Overall: **Weak**

Ototoxicity - ANALYSIS OF HUMAN STUDIES

No study was identified.

Ototoxicity - ANALYSIS OF ANIMAL STUDIES

One rabbit study was identified (Mirzaee 2007). The animals were exposed to 157 mg/m³ welding fumes by inhalation for 12 days. Exposure to welding fumes caused a reduction in amplitude in the distortion product otoacoustic emissions (DPOAE) test at high frequencies.

Interaction with noise - ANALYSIS OF HUMAN STUDIES

No study was identified.

Interaction with noise - ANALYSIS OF ANIMAL STUDIES

One rabbit study was identified (Mirzaee 2007). The animals were exposed to 157 mg/m³ welding fumes by inhalation and to 110 dB SPL noise simultaneously for 12 days. Exposure to welding fumes caused an amplitude reduction in distortion product otoacoustic emissions (DPOAE) at high frequencies. It also potentiated the noise-related loss of outer hair cell function.

Discussion

No human study was identified. In one rabbit study, welding fumes caused high-frequency hearing loss and potentiated the noise-induced loss of outer hair cell function. Other animal and human studies are necessary to draw a definitive conclusion about the ototoxicity of welding fumes or their interaction with noise.

Nicotine

Québec permissible exposure values: TWAEV: 0.5 mg/m³

Conclusion about ototoxicity **No evidence**	Strength of evidence Human studies: **No study found** Animal studies: **None** Overall: **None**
Conclusion about interaction with noise **No evidence**	Strength of evidence Human studies: **No study found** Animal studies: **None** Overall: **None**

Ototoxicity - ANALYSIS OF HUMAN STUDIES

No study was identified.

Ototoxicity - ANALYSIS OF ANIMAL STUDIES

Only one guinea pig study was identified. Using electrocochleography and optical microscopy, no ototoxic effect was observed after 20 days of intravenous exposure to nicotine concentrations up to 20 mg/kg/d.

Interaction with noise - ANALYSIS OF HUMAN STUDIES

No study was identified.

Interaction with noise - ANALYSIS OF ANIMAL STUDIES

Only one guinea pig study was identified. Using electrocochleography and optical microscopy, no ototoxic interaction with noise was observed after 20 days of intravenous nicotine exposure at doses as high as 20 mg/kg/d.

Discussion

No human study was identified. In guinea pigs, no ototoxic effect or interaction with noise were detected. However, the nicotine exposure route and dose were different from those for humans. In summary, there is no evidence of ototoxicity for nicotine or of its interaction with noise.

Lead and its inorganic compounds (expressed as Pb)

Québec permissible exposure values: TWAEV: 0.05 mg/m³

Conclusion about ototoxicity **Ototoxic substance**	Strength of evidence Human studies: **Strong** Animal studies: **No study found** Overall: **Strong**
Conclusion about interaction with noise **No evidence**	Strength of evidence Human studies: **None** Animal studies: **No study found** Overall: **None**

Ototoxicity - ANALYSIS OF HUMAN STUDIES

Twelve studies were identified, eleven on workers and one on humans accidentally exposed to lead. Pure-tone audiometry and auditory brainstem response (ABR) tests were used. Eight studies demonstrated the ototoxicity of Pb (Discalzi 1992; Discalzi 1993; Farahat 1997; Forst 1997; Bleecker 2003; Holdstein 1986; Murata 1993; Hirata 1993). For one of these studies, the blood lead concentration (PbB) ranged between 10 and 180 mg/L (Forst 1997). Two of the eight studies showed a correlation between auditory thresholds and PbB (Farahat 1997; Forst 1997), and one study showed a correlation between the ABR responses and PbB (Bleecker 2003). Conversely, four of the twelve studies reported no ototoxic effect associated with lead (Murata 1995; Lille 1988; Counter 2002; Yokoyama 2002), while one study carried out on workers reported a mean PbB concentration of 1000 mg/L (Lille 1988). Unfortunately, noise levels were reported in only one well-conducted study (Farahat 1997) in which the noise levels ranged from 40 to 50 dB.

Ototoxicity - ANALYSIS OF ANIMAL STUDIES

No study was identified.

Interaction with noise - ANALYSIS OF HUMAN STUDIES

One study on workers was identified (Wu 2000). A significant correlation was found between the high long-term lead exposure index (defined by duration of employment and by ambient lead concentration) and the reduction in hearing ability. However, such a correlation between short-term lead exposure (defined by blood lead concentration) and hearing ability was not significant. Neither the noise exposure level alone, nor the simultaneous exposure to noise and lead over the short or long term were correlated with reduced hearing ability.

Interaction with noise - ANALYSIS OF ANIMAL STUDIES

No study was identified.

Discussion

There is convincing evidence of lead-induced hearing loss in workers. Correlation between these two parameters has been demonstrated. No animal study with a realistic lead exposure was identified. Given the current evidence from human studies, we recommend considering lead as an ototoxic agent. There is no evidence of interaction after combined exposure to lead and noise in the industrial population in one study. Other studies are necessary to draw a definitive conclusion about interaction with noise.

Styrene (monomer)

Québec permissible exposure values: TWAEV: 213 mg/m³ (50 ppm). STEV: 426 mg/m³ (100 ppm)

Conclusion about ototoxicity **Ototoxic substance**	Strength of evidence Human studies: **Medium** Animal studies: **Strong** Overall: **Strong**
Conclusion about interaction with noise **Inconclusive**	Strength of evidence Human studies: **Weak** Animal studies: **Medium** Overall: **Weak**

Ototoxicity - ANALYSIS OF HUMAN STUDIES

Recently, Lawton et al. (Lawton 2006) reviewed a number of workplace studies on exposure and the relationship between inhaled styrene and hearing loss. Our conclusions agree with theirs. We have added a few recent studies. In twelve studies, the differences in auditory thresholds were used to classify workers in exposed and unexposed groups. Of the twelve studies, four observed no evidence of an effect of styrene on auditory thresholds (Möller 1990, Sass-Kortsak 1995, Calabrese 1996, Hoffman 2006). Two studies were limited to styrene effects in the high frequency region (Muijser 1988, Morioka 1999), and in one of them, the workers were exposed to other solvents as well (Morioka 1999). However, six studies report styrene-induced hearing losses (Sliwinska-Kowalska 2003, Morata 2002, Sliwinska-Kowalska 2005, Morioka 1999, Mascagni 2007, Triebig 2008). Only the study by Morioka (1999) found a dose-response relationship.

Ototoxicity - ANALYSIS OF ANIMAL STUDIES

Many experimental animal studies have shown that styrene exposure by inhalation had an ototoxic effect. Susceptibility to solvents is species dependent. Guinea pigs are less susceptible than rats to styrene's ototoxic effect (Lataye 2003, Fechter 1993). Styrene induces permanent auditory system damage mainly in rats. In rats, styrene exposure damages the cochlear hair cells, and the spiral ganglia are damaged as well. An important characteristic of styrene is a higher susceptibility of the outer hair cells (OHCs) compared to the inner hair cells (Lataye 2003). This effect seems to be dose-related. One study suggested that Dieters cells are more vulnerable to styrene toxicity and that cell death due to this substance occurs mainly by apoptosis (Chen 2007). While subacute styrene exposure does not seem to damage hair cells, these cells are damaged by long-term exposure. For chronic exposure, higher styrene concentrations cause higher hair cell mortality. Mid-frequency hearing loss is most often reported. In the rat, morphological examination showed a corresponding loss of OHCs in the mid-frequency region of the cochlea (Yano 1992). Hair cell death is not directly linked to auditory threshold shifts in the rat.

In the rat, no styrene induced hearing loss was induced by chronic exposure up to a concentration of approximately 600 ppm. Above 600 ppm, exposure induces permanent threshold shifts directly linked to styrene concentration.

Interaction with noise - ANALYSIS OF HUMAN STUDIES

Six studies evaluated workers exposed to noise and styrene. Two studies found no interaction between styrene and noise. However, due to confounding factors, it was concluded that the data were insufficient to evaluate the combined effects of noise and styrene exposure on hearing

(Morata 2002, Sass-Kortsak 1995). In one study (Muijser 1988), the control group was exposed to a much higher level of noise than the group exposed to styrene, precluding the evaluation of the interaction between noise and styrene. Three studies by the same laboratory showed additive or infra-additive effects (Sliwinska-Kowalska 2001, Sliwinska-Kowalska 2003, Sliwinska-Kowalska 2005). No dose-response relationship between styrene exposure and hearing thresholds was observed, and only one English abstract was available for the 2001 study.

Interaction with noise - ANALYSIS OF ANIMAL STUDIES

Four animal studies were evaluated. Susceptibility to solvents is species dependent. The auditory system of the guinea pig is not damaged by styrene as much as that of the rat. One study on guinea pigs exposed simultaneously to 500 or to 1200 ppm styrene and to 95 dB(A) noise for 7 hours provided no evidence of interaction between the two agents (Fechter 1993). Three rat studies demonstrated an ototoxic interaction between styrene and noise. Potentiation of styrene-induced hearing loss by noise was observed in one study after exposure to 400 ppm styrene (Lataye 2005) and cosynergy occurred in two studies after simultaneous exposure to 300 ppm styrene and to 100 dB noise (Lataye 2000, Mäkitie 2003).

Discussion

While ototoxic effects were reported in workers, other human studies are necessary to complete the evidence of ototoxicity. In rats, styrene clearly affects auditory function mainly in the mid-frequency range of the cochlea. In workers, there is weak evidence of an ototoxic interaction with noise. In rats, a synergic interaction was found in two studies, as well as potentiation of noise-induced hearing losses in another study. Other studies are necessary to draw a conclusion about the interaction with noise. Taking into account the results of the human studies and the evidence provided by the animal studies, we recommend that styrene be considered an ototoxic agent.

Toluene

Québec permissible exposure values: TWAEV: 188 mg/m ³ (50 ppm)

Conclusion about ototoxicity **Ototoxic substance**	Strength of evidence Human studies: **Medium** Animal studies: **Strong** Overall: **Strong**
Conclusion about interaction with noise **Evidence of interaction**	Strength of evidence Human studies: **Strong** Animal studies: **Medium** Overall: **Strong**

Ototoxicity - ANALYSIS OF HUMAN STUDIES

The data on toluene's effects on human hearing originate mainly from case reports of acute toluene poisoning. In the studies that focused on the voluntary inhalation of toluene, severe hearing loss in the central auditory pathways was reported (Morata 1994, Ryback 1992).

One study on workers with normal hearing ability (evaluated by pure-tone audiometry) and exposed to 97 ppm of toluene for 12-14 years showed a change in auditory brainstem evoked responses. This test demonstrated auditory nervous system modification before the appearance of clinical signs due to chronic toluene exposure (Abbate 1993). A change in auditory brainstem evoked responses was also observed in another study carried out on workers, but data on noise exposure were not reported (Vrca 1997, Vrca 1996).

Ototoxicity - ANALYSIS OF ANIMAL STUDIES

Thirty-five studies on rats were identified. In thirty-one studies, the rats were exposed to toluene by inhalation; in two studies, the exposure was orally, and in one study, the rats received toluene intravenously. The inhaled concentrations were 600 ppm (Lataye 2003) or more, and the exposure duration varied between 30 minutes (Witter 1980) and 23 weeks (Pryor 1985). Hearing losses were measured by behavioural methods and confirmed by electrophysiological tests. Most often, permanent high frequency hearing loss was reported. Factors such as concentrations and duration of exposure seem to affect the loss of hearing sensitivity in rats. The daily concentration is far more significant than the total duration of the exposure (Pryor 1984b). Also, toluene, rather than its metabolites, seems to be responsible for the ototoxic effects (Campo 2008, Waniusiow 2008). However, toluene's ototoxicity was also observed in a quiet environment during a study on rats orally exposed to toluene, which excludes noise caused by the inhalation system as a possible causal factor for the ototoxic effect (Sullivan 1989). The LOAEL for the ototoxicity of toluene in rats is between 700 and 1500 ppm.

In rats, the evidence suggests that toluene exposure causes permanent damage to the outer hair cells (OHCs) of the cochlea. In several rat studies, no changes in the latencies of the auditory brainstem responses was noted (Campo 2008, Johnson 1988, Nylén 1994a, Rebert 1983b), suggesting that damage is localized in the cochlea and not in the central auditory pathways (Johnson 1995). The effect on OHCs has been confirmed by morphological examinations of the cochlea, showing a loss of OHCs, mainly in the third row (Johnson 1994b, Pryor 1984a, Sullivan 1989). The examinations show that cochlear toxicity is in the frequencies from 16 to 29 kHz and from 4 to 5 kHz. Inner hair cells seem to be preserved (Campo 1997). Hair cell loss seems to be progressive and continues even after exposure ends (Johnson 1994b). Also, the results from the

intravenous study suggest that toluene exposure might change the response of protective acoustic reflexes (Lataye 2007).
Three inhalation studies on guinea pigs were identified. In two studies, toluene concentrations of 600 and 1000 ppm induced no effect (Lataye 2003, Campo 1993) while in the third study, an ototoxic effect was observed with a LOAEL of 250 ppm. One inhalation study on chinchillas exposed to 1000 ppm showed no toluene-related ototoxicity.

Interaction with noise - ANALYSIS OF HUMAN STUDIES

Four studies on workers were identified, two of which used the data from the same experiment (Schaper 2003, Schaper 2008). In a well-conducted study on plant workers (Morata 1993), simultaneous exposure to toluene (100 to 365 ppm) and noise (88-98 dB(A)) significantly increased the predicted probability of developing hearing loss compared to a group of workers exposed to comparable noise levels. The acoustic reflex measurements suggested that the hearing losses found in the group exposed to the two agents might be due to lesions in the central auditory system.
Another well-conducted study identified hearing impairment from simultaneous exposure to toluene (33-165 ppm) and 85 dB noise in workers (Chang 2006). However, no hearing impairment was observed in the study in which workers were simultaneously exposed to up to 45 ppm toluene and 82 dB noise, indicating that the threshold for developing hearing loss due to toluene exposure could be above 50 ppm (Schaper 2003, Schaper 2008).

Interaction with noise - ANALYSIS OF ANIMAL STUDIES

Six rat studies were identified. Toluene interaction with noise, producing additive or synergic cochlear damage, was suggested in five studies. The reduction in hearing sensitivity of rats exposed to toluene followed by noise was greater than the sum of the effects of toluene and noise alone (synergic effect) (Lataye 1997, Brandt-Lassen 2000). When exposures were in the reverse order (namely noise followed by toluene exposure), the loss in sensitivity was greater than the individual loss caused by toluene or noise, but did not exceed the sum of the two losses (Johnson 1990). Also, one study showed a greater effect of impact noise than wide-band noise during simultaneous co-exposure to 500 to 1500 ppm toluene (Lund 2008). However, the value of the results of these studies is limited with respect to occupational exposure, because the daily exposures were long (10-16 h/d), the exposure durations were short (2-4 weeks), and the noise and toluene exposure was not simultaneous in three of the studies (Johnson 1988, Johnson 1990, Lataye 1997). The results of the single study in which the daily exposures as well as the exposure durations were more representative (6 h/d, 90 days for rats exposed to 100 to 500 ppm toluene) were negative and the authors found a hearing protective effect for exposures to low concentrations of toluene (Lund 2008). One study on guinea pigs (Campo 1993) and one study on chinchillas (Davis 2002) were negative.

Discussion

While certain ototoxic effects have been reported for workers, other human studies are necessary to arrive at a final conclusion. However, a series of animal studies clearly revealed ototoxic effects in relation to high toluene concentrations. In rats, toluene affects auditory function mainly in the mid-frequency range of the cochlea. There is convincing evidence of an ototoxic interaction after combined exposure to toluene and noise in workers and rats. Taking into account the results of the human studies and the evidence provided by the animal studies, we recommend that toluene be considered an ototoxic agent that can also interact synergically with noise to cause more severe hearing losses.

Trichloroethylene

Québec permissible exposure values: TWAEV: 269 mg/m³ (50 ppm). STEV: 1070 mg/m³ (200 ppm)

Conclusion about ototoxicity **Ototoxic substance**	Strength of evidence Human studies: **Medium** Animal studies: **Strong** Overall: **Strong**
Conclusion about interaction with noise **Inconclusive**	Strength of evidence Human studies: **No study found** Animal studies: **Weak** Overall: **Weak**

Ototoxicity - ANALYSIS OF HUMAN STUDIES

In case studies, hearing losses were reported for workers in relation to trichloroethylene exposure (Gist 1995). In one epidemiological study of 40 exposed workers, 26 had bilateral sensorineural hearing loss (Szulc-Kuberska 1976). Workers with long-term exposure to solvents, including trichloroethylene, were reported to have abnormally distorted speech audiometry results (Odkvist 1987). This suggests damage to the central auditory system that cannot be attributed to noise. The exposure concentrations, like the noise levels, were not precisely reported in any of these studies.

Ototoxicity - ANALYSIS OF ANIMAL STUDIES

In rats, the results of 7 studies demonstrate that trichloroethylene inhalation had an ototoxic effect. Permanent hearing loss was limited to the mid and high frequencies (4 to 20 kHz) and the greatest hearing loss was observed at 16 kHz. In rats, ototoxicity seems to be a high-concentration effect, as shown by the results to the auditory brain stem response measurements and reflex audiometry tests. Following 13-week exposure to trichloroethylene, the LOAEL for the ototoxic effect was 2500 ppm (Crofton 1997), and the NOAEL was 800 ppm (Albee 2006). Morphological examination showed spiral ganglion damage in the cochlea (sign of a neurotoxic effect) of rats exposed to trichloroethylene (Fechter 1998).

Interaction with noise - ANALYSIS OF HUMAN STUDIES

No study was identified.

Interaction with noise - ANALYSIS OF ANIMAL STUDIES

One rat study was identified (Muijser 2000). The authors report a supra-additive ototoxic interaction between trichloroethylene and low-frequency noise after a combined exposure to 95 dB noise and 3000 ppm trichloroethylene for 3 weeks.

Discussion

While effects were reported in workers, other human studies are necessary to complete the evidence of ototoxicity. In the rat, trichloroethylene clearly affects auditory function mainly in the mid-frequency range of the cochlea. No human study on the ototoxic interaction between trichloroethylene and noise was identified. In one rat study, evidence of supra-additive interaction at low frequencies was found. Other studies are necessary to draw a conclusion about the interaction with noise. Taking into account results of the human studies and evidence supplied by the animal studies, we recommend that trichloroethylene be considered an ototoxic agent.