The weight of evidence approach in the assessment of hearing impairment induced by noise and ototoxic chemicals

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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 (Miller 1985; Ryback 1992; Morata et al. 1994; Johnson & Nylen 1995; Franks & Morata 1996; Cary et al. 1997; Campo 2004; Fechter 2004; Campo et al. 2009; Johnson & Morata 2010). Data from animal studies suggest ototoxicity of some substances at relatively high concentrations. However, detailed exposure-effect relationships have not yet been identified. Therefore it is difficult to draw any conclusion regarding the effects that might or might not be observed at concentrations relevant for the occupational setting (Cary et al. 1997; Prasher 2002).

This project was undertaken 1) to assess the available data on ototoxicity of chemical substances and consider their relevance to the occupational setting and 2) to organize this information into a structured database indicating potential ototoxicity of industrial chemicals alone or in combination with noise exposure.

METHODS

Critical toxicological data were compiled for 695 chemical substances included in the Quebec regulation (Regulation Respecting Occupational Health and Safety - RROHS). Information was taken from primary references available in TOXLINE (U.S. National Library of Medicine, National Institutes of Health) database up to July 2009. For each study the following parameters were taken into account: 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. The data were evaluated only for chemical exposure concentrations up to the short-term exposure limit (STEV) or ceiling value (CV) or five times the 8-h time weighted average exposure value (TWAEV) for human data. In the RROHS, STEV is defined as the maximum concentration to which workers can be exposed for a period of 15 minutes; TWAEV represents the average concentration of a given chemical to which workers can be exposed for normal 8-h workdays, 5 days a week. For animal studies, the limit was set at 100 times the 8-h TWA OEL (occupational exposure level) or ceiling value. Concerning the noise exposure, a level of 75 dBA during 8 h was considered as a NOAEL (No Observed Adverse Effect Level) and subjects were considered "without noise exposure" (ISO-1999 1990).

We built a weight of evidence table (Table 1) 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. 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. 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.

RESULTS

In total, 224 experiments (in 150 articles), of which 51 (in 44 articles) evaluate simultaneous exposure to noise and a chemical) covering 29 substances were assessed using a weight of evidence approach. The information was organized to create a data sheet for each study (available in both French and English). These datasheets can be accessed at the following address:

http://www.dsest.umontreal.ca/recherche_rayonnement/ototoxicity_en.html

Table 2 presents a summary of conclusions about ototoxic effects of industrial chemicals without a concomitant exposure to noise. Among 29 substances, 7 were identified as ototoxic or potentially ototoxic. For ten substances (acrylonitrile, n-butyl alcohol, carbon disulfide, cyanides, n-heptane, mercury (vapors, alkyl compounds and inorganic compounds), alpha-methyl styrene, parathion, trimethyl tin and welding fumes), the lack of toxicological data did not allow a definitive conclusion to be reached. Eleven substances (p-tert-butyltoluene, carbone monoxide, enflurane, hexachlorobenzene, hydrogen cyanide, methyl chloroform, methylene chloride, nicotine, perchloroethylene and ethyl alcohol) were considered as non-ototoxic.

For nine substances, the assessment was based on only one study, thus limiting the reliability of the toxicological assessment. On the other extreme, the assessment of toluene was based on 36 studies.

Table 3 gives a summary of conclusions about interactions of industrial chemicals with noise. Relevant data for eleven substances were found. Toluene is identified as an ototoxic agent that can also interact with noise to induce more severe hearing losses. Carbon monoxide is considered as a possible potentiator of noise-induced hearing loss. For seven substances, the lack of toxicological data did not allow a definitive conclusion to be reached and for two substances there is no evidence of interaction with noise. For seven substances, the assessment was based on only one study, thus limiting the reliability of the toxicological assessment. On the other extreme, the assessment of carbon monoxide was based on 18 studies.

Table 1: Weight of evidence approach for the assessment of ototoxicity and interaction with noise of industrial chemicals

Weight of evidence of studies			Conclusion	
Human studies	**Animal studies**	**Overall**	**Ototoxicity**	**Interaction with noise**
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

Table 2: Summary of conclusions about ototoxic effects of industrial chemicals

Industrial chemical	Occupational exposure level*		Weight of evidence			Conclusion ototoxicity
	Quebec TWAEV (STEV)	ACGIH TWA (STEL)	Human studies	Animal studies	Overall	
Ototoxic						
Lead	0.05 mg/m^3	0.05 mg/m^3	S	X	S	O
Styrene	50 (100)	20 (40)	M	S	S	O
Toluene	50	50	M	S	S	O
Trichloroethylene	50 (200)	50 (100)	M	S	S	O**
Possibly ototoxic						
Ethylbenzene	100 (125)	100 (125)	X	S	M	PO
n-Hexane	50	50	W	S	M	PO**
Xylene	100 (150)	100 (150)	A	S	M	PO

* in ppm; **ototoxic and neurotoxic effects on the auditory system; (see Table 1 for abbreviations)

Table 3: Summary of conclusions about interactions of industrial chemicals with noise

Industrial chemical	Occupational exposure level*		Weight of evidence			Conclusion interaction
	Quebec TWAEV (STEV)	ACGIH TWA (STEL)	Human studies	Animal studies	Overall	
Interaction with noise						
Toluene	50	50	S	M	S	I
Possible interaction with noise						
Carbon monoxide	35 (200)	25	X	S	M	PI
Non conclusive						
Acrylonitrile	2	2	X	M	W	NC
Carbon disulfide	4 (12)	1	W	X	W	NC
Ethyl benzene	100 (125)	100 (125)	X	W	W	NC
Hydrogen cyanide and cyanide salts	10	4.7 mg/m^3	X	W	W	NC
Styrene	50 (100)	20 (40)	W	M	W	NC
Trichloroethylene	50 (200)	50 (100)	X	W	W	NC
Welding fumes	5 mg/m^3		X	W	W	NC
No evidence						
Lead	0.05 mg/m^3	0.05 mg/m^3	A	X	A	NE
Nicotine	0.5 mg/m^3	0.5 mg/m^3	X	A	A	NE

* in ppm; (see Table 1 for abbreviations)

The analysis also showed that a wide variety of tests are used to identify adverse effects on hearing: pure-tone audiometry, reflex modification audiometry, distorsion product otoacoustic emissions, transiently evoked otoacoustic emissions, multisensory conditioned avoidance response task, electrocochleography and auditory evoked brainstem responses. Exposure to industrial chemicals was also documented with different approaches and, in the cases of lead, toluene and styrene, biological monitoring has been used.

CONCLUSIONS

For the large majority of substances, epidemiology studies looking at a toxicological dimension are rare. In many studies, absence of detailed data about noise exposure and the exposure to all chemical contaminants is a common problem. This is the most important barrier to reach an appropriate conclusion about ototoxicity (or absence of). The evaluation of the effect of exposure to a single substance is particularly challenging because workers are usually exposed to a cocktail of various chemicals. In addition, there is a long list of confounding factors that need to be addressed: physical contaminants: noise, vibrations, ototoxic medications, including diuretics and salicylates, noise exposure during leisure activities and individual factors (age, gender, tobacco, alcohol, drugs and genetics).

For the majority of cases where potential ototoxicity was previously highlighted, there is a paucity of toxicological data in the primary literature. Human and animal studies indicate that lead, styrene, toluene and trichloroethylene are ototoxic and ethyl benzene, n-hexane and xylene are possibly ototoxic at concentrations that are relevant to the occupational setting. Toluene and possibly carbon monoxide appear to exacerbate noise-induced hearing impairment. Toluene interacts with noise to induce more severe hearing losses than noise alone.

FUNDING

This study was supported by the Institut de recherche Robert-Sauvé en santé et en sécurité du travail, Montréal, Canada [099-549; 099-745].

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Perceived quality of the living environment and noise

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INTRODUCTION

In those regions of the world where primary living conditions are good and basic needs are easily fulfilled, the perceived quality of the local living environment is of growing concern. Traffic has an important impact on this perceived quality of the local living environment and as such also on the mental well-being of the population (Guite et al., 2006). Traffic influences the life of people in different ways: on the one hand, traffic is inevitable to guarantee accessibility to various types of functions, on the other hand, traffic noise, traffic emissions, road safety, etc. threaten health and well-being. Assessing this complex interplay requires a set of indicators (Botteldooren and Lercher, 2006) and suitable aggregation models (Botteldooren et al., 2006). It was previously noted that environmental sound plays an important role (Botteldooren et al., 2011) in the perceived quality of the living environment both in a positive and a negative way and therefore several of these indicators may be related to environmental sound.

Existing models tend to evaluate traffic liveability at specific dwelling locations on the basis of the characteristics of the nearest street (road width, bicycle facilities, etc.) and its traffic (e.g. traffic flow, traffic speed). The living environment is however not limited to the house and garden. Subjective assessment of the sonic environment may include the wider neighbourhood (Klaboe et al., 2005) or relax the adverse effect at home (Gidlof-Gunnarsson, A. and Ohrstrom, E. 2007). The effect of exposure during trips is even more pronounced for air quality where it was shown that in some cases the majority of exposure to air pollution and in particular to fine and ultrafine particles occurred while away from home (Int Panis et al., 2010). A model capable of quantifying the quality of the living environment should therefore not only take into account the dwelling but also the routes giving access to the dwelling and the nearby public space. For some aspects it may even be required to include an assessment of usual destinations such as the work environment.

Based on the above observations a model was designed by first unravelling the constituents of quality of life and then focussing on the factors that might be influenced by traffic – the result is sometimes referred to as traffic liveability. Then a methodology is proposed that has as a main focus to achieve a better quantification of exposure to different types of traffic impacts by including not only the exposure at the home address, but also the impacts during activities at other locations and the impacts during trips.

In this paper the proposed model is briefly described, before presenting some of the first results for the case-study of Ghent.