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What is This?
A weight of evidence approach for the assessment of the ototoxic potential of industrial chemicals

A Vyskocil1, G Truchon2, T Leroux3,4, F Lemay2, M Gendron3,4, F Gagnon1, N El Majidi1, A Boudjerida1, S Lim1, C Emond1 and C Viau1

Abstract
There is accumulating epidemiological evidence that exposure to some solvents, metals, asphyxiants and other substances in humans is associated with an increased risk of acquiring hearing loss. Furthermore, simultaneous and successive exposure to certain chemicals along with noise can increase the susceptibility to noise-induced hearing loss. There are no regulations that require hearing monitoring of workers who are employed at locations in which occupational exposure to potentially ototoxic chemicals occurs in the absence of noise exposure. This project was undertaken to develop a toxicological database allowing the identification of possible ototoxic substances present in the work environment alone or in combination with noise exposure. Critical toxicological data were compiled for chemical substances included in the Quebec occupational health regulation. The data were evaluated only for noise exposure levels that can be encountered in the workplace and for realistic exposure concentrations up to the short-term exposure limit or ceiling value (CV) or 5 times the 8-h time-weighted average occupational exposure limit (TWA OEL) for human data and up to 100 times the 8-h TWA OEL or CV for animal studies. In total, 224 studies (in 150 articles of which 44 evaluated the combined exposure to noise and a chemical) covering 29 substances were evaluated using a weight of evidence approach. For the majority of cases where potential ototoxicity was previously proposed, 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 p-xylene are possibly ototoxic at concentrations that are relevant to the occupational setting. Carbon monoxide appears to exacerbate noise-induced hearing dysfunction. Toluene interacts with noise to induce more severe hearing losses than the noise alone.

Keywords
Industrial chemicals, ototoxicity, interactions, noise, database

Introduction
Millions of workers in the world are exposed to industrial chemicals considered to be ototoxic, such as solvents, heavy metals and asphyxiants. A considerable number of these people work with industrial chemicals in a noisy environment, thereby enhancing the risk of auditory system injury (Cary et al., 1997; Franks and Morata, 1996; Prasher, 2002). The association between occupational exposure to ototoxic chemicals and hearing impairment is rarely evaluated and hearing losses observed in these situations are often attributed exclusively to noise exposure (Morata et al., 1994). The health criteria relating to these

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occupational exposures do not take into account the possibility of ototoxic effects of these contaminants (Franks and Morata, 1996).

Several useful literature reviews have been published previously that focus primarily on ototoxic drugs, organic solvents, metals and chemical asphyxiants (Cary et al., 1997; Campo, 2004; Campo et al., 2009; Fechter, 2004; Franks and Morata, 1996; Hoet et al., 2005; Johnson and Nylen, 1995; Miller, 1985; Morata et al., 1994; Ryback, 1992). Data from animal studies suggest ototoxicity of some substances at relatively high concentrations. However, detailed exposure–effect relationships have not yet been identified. So it is difficult to draw any conclusion regarding the effects that might or might not be observed at lower concentrations, which are of most relevance for the occupational setting (Cary et al., 1997; Prasher, 2002).

The objectives of this research project are as follows:

(a) To assess the available data on ototoxicity of chemical substances and consider their relevance to the occupational setting. The classes of compounds discussed in this review include organic solvents, asphyxiants and metals that are present in the occupational environment. Both human and animal investigations are summarized.

(b) To organize this information into a structured database indicating potential ototoxicity of industrial chemicals alone or in combination with noise exposure.

**Methods**

Data were collected among the 695 substances listed in the Québec Regulation Respecting Occupational Health and Safety ([RROHS] Gouvernement du Québec, 2001). Information was taken from primary references available in TOXLINE (US National Library of Medicine National Institutes of Health, 1965) database up to July 2009.

Since at massive doses most chemicals cause poly-systemic effects, the toxicity data were evaluated only for realistic exposure concentrations. Therefore, in humans, the upper limit was set at the short-term exposure value (STEV is the maximum concentration to which workers can be exposed for a period of 15 min) or at the ceiling value (CV); when no STEV is prescribed, it was established as 5 times the time-weighted average exposure value (TWAEV represents the average concentration of a given chemical to which workers can be exposed in a normal 8-h workdays, 5 days a week). This last factor was chosen because, according to the RROHS, ‘none of the excursions in exposure levels may exceed 5 times the TWAEV during any length of time whatsoever.’

Animal data were evaluated only for exposure concentrations up to 100 times the TWAEV or 100 times the CV (factor of 10 for extrapolation of the lowest observed adverse effect level [LOAEL] toward the no observed adverse effect level [NOAEL] and 10 for the differences between the species). In some cases, the ACGIH® TLV® Committee uses these uncertainty factors to establish the ‘threshold limit value’ (TLV) from animal data when there are no satisfactory human data available, and the Québec regulation is largely based on ACGIH recommendations.

Concerning the adverse hearing effect, the noise level of 75 dBA during 8 h was considered a NOAEL and subjects were considered ‘without noise exposure.’

In this article, we use the word ‘study’ to describe any single animal experiment or human study that examined the relationship between exposure to chemicals and ototoxic effects. There may be more than one study reported in any given article.

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.’ 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.

Note that the 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. Studies on ototoxicity of chemicals, and particularly those on their interaction with noise, remain relatively rare. Therefore, we considered more prudent, given our current knowledge, to adopt the mention ‘no evidence’ rather than ‘non-ototoxic’ or ‘no interaction,’ which would suggest that we have proof of absence of ototoxicity, or of lack of interaction 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 ‘ototoxic substance’ or 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 ‘nonconclusive.’ Finally, those for which there was absence of evidence overall bore the mention ‘no evidence’ of ototoxicity or interaction with noise.

A relational database was developed in Microsoft Access to record data about the effects of the industrial chemicals considered (see Figure 1). It contains about 15 tables, the main ones being ‘regulated substance,’ ‘study’ and ‘substance assessment.’ The database provides the toxicologist with a systematic framework to organize and analyze the available experimental data found in the literature. It further allows linking a regulated substance with the assessment of its ototoxicity.

**Results**

After filtering of the data to take into account (a) substances listed in the Québec Regulation and (b) realistic exposure concentrations, a total of 224 studies (from 150 articles of which 44 evaluate combined

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

<table>
<thead>
<tr>
<th>Weight of evidence of studies</th>
<th>Conclusion about ototoxicity</th>
<th>Conclusion about the interaction substance / noise</th>
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exposure to noise and a chemical) covering 29 substances were evaluated using a weight of evidence approach. The information was organized to create a separate data sheet in French and English for each study. These data sheets can be consulted at the following address:

Figure 1. Database schema.
Tables 2 and 3 give a summary of conclusions on ototoxic effects of evaluated industrial chemicals in the absence and presence of noise.

**Chemical substances evaluated for ototoxicity and interaction with noise**

**Acrylonitrile**

*Absence of noise.* No studies were found in humans. Four animal studies from the same laboratory were identified (Fechter et al., 2003, 2004; Pouyatos et al., 2005). In these studies, acrylonitrile was administered subcutaneously to rats in a high dose of 50 mg/kg/d for 1–5 days. Using an electrocochleography test, a transient elevated auditory threshold was found after a single acrylonitrile administration. However, no permanent hearing or hair cell loss was observed 4 weeks after up to 5-day repeated administration of acrylonitrile.

*Presence of noise.* No studies were found in humans. Four animal studies from the same laboratory were identified (Fechter et al., 2003, 2004; Pouyatos et al., 2005, 2007). In these studies, acrylonitrile was administered subcutaneously to rats in a high dose of 50 mg/kg/d for 1–5 days. Acrylonitrile potentiates permanent noise-induced hearing loss particularly for high-frequency tones and particularly when acrylonitrile and noise were given on repeated occasions. Outer hair cells (OHCs) are the main target of toxicity.

*Conclusion.* In the absence of other studies, it is not possible to draw any conclusion regarding the ototoxicity of acrylonitrile or of its interaction with noise.

**n-Butyl alcohol**

*Absence of noise.* Only one human and one animal studies were identified. In the human study (Velazquez et al., 1969), hearing loss was observed in workers exposed to 80 ppm for 3–11 years using pure tone audiometry test. However, no exact level of noise was reported. No permanent hearing loss was found in rats exposed to 4000 ppm for 5 days. Reflex modification audiometry test was performed 5–8 weeks after the end of exposure (Crofton et al., 1994).

*Presence of noise.* No study was identified.

*Conclusion.* In the absence of other studies, it is not possible to draw any conclusion regarding the ototoxicity of n-butyl alcohol. No study on interaction with noise was found.

**p-tert-Butyltoluene**

*Absence of noise.* No human study was identified. Two studies in two strains of rats exposed by inhalation were identified. No hearing loss was found as shown by auditory brainstem response (ABR) measurements after a single 6-h exposure (Lund and Simonsen, 1993) or 4 weeks of exposure (Lam et al., 2000). Only minor neurofunctional changes were observed. No morphologic examination was performed.

*Presence of noise.* No study was identified.

*Conclusion.* In summary, there is evidence neither of ototoxicity of p-tert-butyltoluene nor of its interaction with noise.

**Carbon disulphide**

*Absence of noise.* Only one human study was identified using the ABRs test (Hirata et al., 1992b). Prolonged latencies of several components were observed after chronic exposure in workers. It seems that recovery from this effect is possible. No data on exposure to noise were reported. Two rat studies were identified using the ABRs test. One study found a transient delay of the latency parameters in Wistar rats exposed to 200 ppm for 15 weeks (Hirata et al., 1992a). The second study did not find any ototoxic effect in Long-Evans rats exposed to 400 ppm for 11 weeks (Rebert and Becker, 1986). However, in this study exposure was interrupted for 17 days after 6.5 weeks of exposure.

*Presence of noise.* Only one human study was identified using pure tone audiometry (Chang et al., 2003). A potentiation of noise induced hearing loss by CS$_2$ was observed. However, CS$_2$ + noise group was older and its duration of employment was twice higher than in noise or control groups. There was no CS$_2$ only exposed group in this study. Therefore, no meaningful conclusion regarding an interaction between noise
and CS$_2$ can be drawn from this study. No animal study was identified.

**Conclusion.** Human and animal studies on the ototoxic effect of carbon disulphide from occupational exposure as well as human studies on its interaction with noise are not conclusive. In the absence of other studies, it is not possible to draw any conclusion regarding the ototoxicity of carbon disulphide or of its interaction with noise.

**Carbon monoxide**

**Absence of noise.** No human studies were identified. There are 10 studies demonstrating that CO by inhalation is not ototoxic in rats. All but one study were performed in the same laboratory. Rats were exposed up to 1500 ppm CO and the duration of intermittent exposures varied between 3.5 h and 13 weeks. The authors used electrocochleography, ABRs tests, reflex modification audiometry and light microscopy. 

**Presence of noise.** No human study was identified. No otoxic effect of CO alone was observed in 10 studies in rats. In the absence of human studies, it is not possible to draw any conclusion regarding the ototoxicity of CO. A potentiation of noise-induced hearing loss by CO was found in all studies. The threshold shifts were observed at all frequencies, but greatest effects were seen at the highest test frequencies. OHCs were found to be particularly vulnerable (Fechter et al., 1988). The potentiation does not increase with increasing noise level (Rao and Fechter, 2000a) or duration (Fechter, 2000a, b). A LOAEL of 500 ppm for this potentiation was observed in rats (Chen and Fechter, 1999; Fechter, 1989, 2000a, 2000b).

**Conclusion.** No human study was identified. No otoxic effect of CO alone was observed in 10 studies in rats. In the absence of human studies, it is not possible to draw any conclusion regarding the ototoxicity of CO. A potentiation of noise-induced hearing loss by CO in rats was found in 18 studies. The actual data suggest that CO should be considered a possible potentiator of noise-induced hearing loss. Further studies with sufficient data on the CO exposure of workers are necessary to make a definitive conclusion about CO interaction with noise.

**Cyanides**

**Absence of noise.** No human study was identified. Two studies from the same laboratory performed in rats were found. Using an electrocochleography test, a transient elevation of auditory threshold was observed after a single cyanide administration and a persistent elevation of auditory threshold was observed after three daily doses by the intraperitoneal (i.p.) route (Tawackoli et al., 2001).

**Presence of noise.** No study was identified.

**Conclusion.** No human study was identified. Two animal studies showed an otoxic effect of cyanides. However, the routes of exposure were different from those experienced by workers. In the absence of other studies, it is not possible to draw any conclusion regarding the ototoxicity of cyanides. No study on interaction with noise was found.

**Enflurane**

**Absence of noise.** No human study was identified. Only one study in rats was found using ABRs test. The results did not allow for any conclusion on an ototoxic effect after a short-term (50 min) inhalation exposure to a high concentration of 0.5% enflurane (Yeoman et al., 1980).

**Presence of noise.** No study was identified.

**Conclusion.** In summary, there is evidence neither of ototoxicity of enflurane nor of its interaction with noise.

**Ethyl alcohol**

**Absence of noise.** Three studies in rats were identified. No ototoxic effect was observed using ABRs test (Nylen et al., 1995) or the multisensory conditioned avoidance response task (Pryor et al., 1985) after a subchronic exposure to ethyl alcohol (up to 8% in drinking water during 2–8 weeks). Using ABRs test, alcohol-addicted 22-month-old rats exposed from age of 3 months did not reveal any changes as compared with either the 22-month-old or the 3-month-old rats without exposure to ethyl alcohol (Anniko et al., 1989).
Presence of noise. No study was identified.

Conclusion. Three animal studies showed no ototoxic effect of ethyl alcohol. In summary, there is evidence neither of ototoxicity of ethyl alcohol nor of its interaction with noise.

Ethyl benzene

Absence of noise. No human study was identified. Six studies in rats of two different strains (Cappaert et al., 1999, 2000, 2001, 2002; Gagnaire and Langlais, 2005; Gagnaire et al., 2007) and one study in guinea pigs (Cappaert et al., 2002) were identified. Five studies were performed in the same laboratory. An ototoxic effect was observed in five inhalation and one oral studies. Susceptibility to ethyl benzene is species dependent. Ethyl benzene causes a permanent damage to auditory system of the rats. The auditory system of the guinea pig is not injured by ethyl benzene (Cappaert et al., 2002). Ethyl benzene damages hair cells in the cochlea of rats. The important characteristic of ethyl benzene is higher susceptibility of OHCs compared to inner hair cells. The effect is dose-related. Higher ethyl benzene concentrations lead to greater hair cell mortality. The mid-frequency hearing loss is reported most often. Morphologic examination determined a corresponding loss of OHC in the mid-frequency region of the rat cochlea. Hair cell losses are not closely related to hearing threshold shifts in the rats (Cappaert et al., 2001).

No chronic studies were identified. There is no ethyl benzene-induced hearing loss for subacute exposure of rats up to about 300 ppm (Cappaert et al., 2000) or for subchronic exposure of rats to 200 ppm (Gagnaire et al., 2007). Concentrations greater than 300 ppm show threshold shifts directly related to ethyl benzene concentration (Cappaert et al., 2000; Gagnaire et al., 2007). Hair cells loss is a more sensitive end point than auditory threshold. The OHC losses were observed at 200 ppm (Gagnaire et al., 2007).

Presence of noise. No human study was identified. One subacute study in rats was identified. Combined exposure to 105 dB sound pressure level (SPL) noise and 300 or 400 ppm ethyl benzene caused greater OHCs loss than the sum of the losses induced by noise or ethyl benzene alone, which indicates a synergy (Cappaert et al., 2001).

Conclusion. No human study was identified. In rats ethyl benzene affects the auditory function mainly in the cochlear mid-frequency range and combined exposure with noise showed a synergy effect in one study. Given the current evidence from animal studies, we recommend considering the ethyl benzene as a possibly ototoxic agent. Further studies with sufficient data on the exposure of workers to ethyl benzene are necessary to make a definitive conclusion about ototoxicity or any conclusion about its interaction with noise.

n-Heptane

Absence of noise. No human study was identified. Only one study in rats was found (Simonsen and Lund, 1995). An ototoxic effect was observed using ABRs test after a 1-month inhalation exposure to 4000 ppm n-heptane.

Presence of noise. No study was identified.

Conclusion. In the absence of other studies, it is not possible to draw any conclusion regarding the ototoxicity of n-heptane. No study on interaction with noise was found.

Hexachlorobenzene

Absence of noise. No human study was identified. Only one study in rats was found (Hadjab et al., 2004). No ototoxic effect was observed using auditory nerve compound action potential test and histology after a 1-month oral exposure.

Presence of noise. No study was identified.

Conclusion. In summary, there is evidence neither of ototoxicity of hexachlorobenzene nor of its interaction with noise.

n-Hexane

Absence of noise. Three studies on workers were identified. In two studies from the same laboratory (Chang, 1987, 1991), exposed subjects were workers with a polyneuropathy. The studies suggest an ototoxic effect of n-hexane (one of which suggests a permanent ototoxic effect), however exposure concentrations, noise levels and duration of exposure were not reported. The third study (Huang and Chu, 1989) on workers exposed for 5–30 years suggests an ototoxic effect of n-hexane, however workers were exposed to other solvents including benzene and C15–C19 hydrocarbons and exposure to noise was not reported. Lack of difference in wave I latency suggests that the auditory nerve itself was not affected. Prolongation of
interpeak latencies should be interpreted as neurotoxic effect of $n$-hexane on the brainstem.

Seven subacute and subchronic studies in rats of two different strains were identified (Howd et al., 1983; Nylen et al., 1994; Pryor and Rebert, 1992; Pryor et al., 1983a; Rebert et al., 1982, 1983). Five studies were performed in the same laboratory. A temporary ototoxic effect was suggested in young and adult rats using ABRs test with a LOAEL of 500 ppm. However, no morphologic examination was performed.

**Presence of noise.** No study was identified.

**Conclusion.** Certain effects were reported in workers. In rats, exposure to $n$-hexane clearly affects the auditory function. We recommend, by taking into account the results of the human studies and the evidence brought by the animal studies to consider $n$-hexane as a possibly ototoxic agent. Other human studies are necessary to come to a definitive conclusion. No human or animal study on ototoxic interaction between $n$-hexane and noise was identified.

**Hydrogen cyanide**

**Absence of noise.** No human study was identified. One inhalation study in rats was found. No ototoxic effect was observed using pure tone audiometry and histology after a single exposure of up to 50 ppm for 3.5 h (Fechter et al., 2002).

**Presence of noise.** No human study was identified. In one study, a potentiation of noise-induced hearing loss by hydrogen cyanide was observed in rats after a combined exposure using electrocochleography and light microscopy (Fechter et al., 2002).

**Conclusion.** No human study was identified. Only one animal study showing no ototoxic effect of hydrogen cyanide inhalation was identified. The same study showed a potentiation of noise-induced hearing loss by hydrogen cyanide. In the absence of other studies, it is not possible to draw any conclusion regarding the ototoxicity of hydrogen cyanide or of its interaction with noise.

**Lead**

**Absence of noise.** Eleven studies in workers and one study in humans accidentally exposed to lead were identified. Pure tone audiometry and ABR tests were used. Eight studies demonstrated otoxicity (Bleecker et al., 2003; Discalzi et al., 1992, 1993; Farahat et al., 1997; Forst et al., 1997; Hirata and Kosaka, 1993; Holdstein et al., 1986; Murata et al., 1993), one of which was on workers with blood lead concentrations (PbB) ranging between 10 and 180 µg/L (Forst et al., 1997). Two of them found a correlation between hearing thresholds and PbB (Farahat et al., 1997; Forst et al., 1997) and one found a correlation between ABR responses and PbB (Bleecker et al., 2003). On the contrary, four studies did not demonstrate ototoxicity (Counter and Buchanan, 2002; Lille et al., 1988; Murata et al., 1995; Yokoyama et al., 2002), one of which was in workers with a mean PbB concentration of 1000 µg/L (Lille et al., 1988). Unfortunately, noise levels were reported only in one well-done study (Farahat et al., 1997) in which noise levels ranged between 40 and 50 dB. No animal studies were evaluated as the exposure concentrations exceeded more than 100 times the TWAEV.

**Presence of noise.** One study in workers was identified (Wu et al., 2000). A significant correlation was found between a high, long-term lead exposure index (defined by duration of employment and ambient lead concentration) and decreased hearing ability. In contrast, such a correlation between short-term lead exposure (defined by PbB level) and hearing ability was not significant. Neither noise exposure level alone nor the simultaneous noise and short- or long-term lead exposure was correlated significantly with decreased hearing ability.

**Conclusion.** There is convincing evidence of lead-induced hearing loss in workers. Correlation between exposure and hearing loss was demonstrated. No animal studies with realistic lead exposure were identified. Given the current evidence from human studies, we recommend considering lead as an ototoxic agent. In one study, there was no evidence of interaction with noise in the industrial population after combined exposure to lead. Further studies are necessary to draw any conclusion about interaction with noise.

**Mercury—alkyl compounds**

**Absence of noise.** Two studies on Japan inhabitants were identified (Mizukoshi et al., 1975, 1989). Their exposure was by ingestion. Ototoxic effect of organic mercury was reported using pure tone audiometry and Békésy’s audiometry. However, the levels of exposure were not reported and age was not taken into consideration. No animal study was identified.
Presence of noise. No study was identified.

Conclusion. In the absence of other studies, it is not possible to draw any conclusion regarding the otoxicity of alkyl mercury compounds. No study on interaction with noise was identified.

Mercury—inorganic compounds

Absence of noise. Two human studies using ABRs test were identified. One study showed that an ototoxic effect of inorganic mercury cannot be excluded. Reported mean urinary mercury concentration was 325 μg/g creatinine. The level of exposure to noise was not reported (Discalzi et al., 1993). The second study did not demonstrate any ototoxic effect. Reported mean urinary mercury concentration was 350 μg/g creatinine (Lille et al., 1988).

One study in rats was identified (Fazakas et al., 2005). Using cortical auditory evoked potentials test, no ototoxic effect was observed after subchronic oral exposure to mercuric chloride.

Presence of noise. No study was identified.

Conclusion. In the absence of other studies, it is not possible to draw any conclusion regarding the otoxicity of inorganic mercury. No study on interaction with noise was found.

Mercury—vapour

Absence of noise. Two studies in workers were identified. ABR tests showed that the ototoxic effect of mercury vapours cannot be excluded. Reported mean urinary mercury concentrations were 142–597 μg/g creatinine in one study (Chang et al., 1995) and a mean air mercury concentration was 0.008 mg/m3 in the second study (Moshe et al., 2002). The level of exposure to noise was not reported in these studies. No animal study was identified.

Presence of noise. No study was identified.

Conclusion. In the absence of other studies, it is not possible to draw any conclusion regarding the ototoxicity of mercury vapour. No study on interaction with noise was found.

Methyl chloroform

Absence of noise. No human study was identified. In one study (Mattsson et al., 1993), no ototoxic effect was observed using ABR test in rats subchronically exposed to methyl chloroform of up to 2500 ppm.

Presence of noise. No study was identified.

Conclusion. In summary, there is evidence neither of ototoxicity of methyl chloroform nor of its interaction with noise.

α-Methyl styrene

Absence of noise. No human study was identified. In one study (Gagnaire and Langlais, 2005), a loss of OHCs was observed in rats exposed by gavage for 2 weeks to α-methyl styrene.

Presence of noise. No study was identified.

Conclusion. In the absence of other studies, it is not possible to draw any conclusion regarding the ototoxicity of α-methyl styrene. No study on interaction with noise was found.

Methylene chloride. Absence of noise. No human study was identified. Only one study in rats was found. No ototoxic effect was observed using ABR test after chronic inhalation of up to 2000 ppm methylene chloride (Mattsson et al., 1990).

Presence of noise. No study was identified.

Conclusion. In summary, there is evidence neither of ototoxicity of methylene chloride nor of its interaction with noise.

Nicotine

Absence of noise. No human study was identified. Only one study in guinea pigs was identified (Bobbin and Gondra, 1976). No ototoxic effect was observed using electrocochleography and light microscopy after 20 days of intravenous exposure to up to 20 mg/kg/d of nicotine.

Presence of noise. No human study was identified. In the study conducted by Bobbin and Gondra (1976), no ototoxic interaction with noise was observed in guinea pigs, using electrocochleography and light microscopy, after 20 days of intravenous exposure to up to 20 mg/kg/d of nicotine.

Conclusion. No human study was identified. In guinea pigs, no ototoxic effect or interaction with noise were detected. However, the route and dose of nicotine exposure were different from those experienced by humans. In summary, there is evidence
neither of ototoxicity of nicotine nor of its interaction with noise.

**Parathion**

*Absence of noise.* No human study was identified. One study was reported in monkeys chronically exposed by oral route to parathion. A dysfunction of auditory system was observed using pure tone audiometry (Reischl et al., 1975).

*Presence of noise.* No study was identified.

**Conclusion.** In the absence of other studies, it is not possible to draw any conclusion regarding the ototoxicity of parathion. No study on interaction with noise was found.

**Perchloroethylene**

*Absence of noise.* Only one short-term human study and one subchronic animal study were identified. In volunteers exposed to perchloroethylene for 4 days for up to 50 ppm, no ototoxic effect was observed using ABR test (Altmann et al., 1990). In the rats exposed for 13 weeks for up to 800 ppm, no ototoxic effect was observed using ABR test (Mattsson et al., 1998).

*Presence of noise.* No study was identified.

**Conclusion.** In summary, there is evidence neither of ototoxicity of perchloroethylene nor of its interaction with noise.

**Styrene**

*Absence of noise.* Recently, Lawton et al. (2006) reviewed a number of occupational investigations of the exposure and relation between inhaled styrene and hearing loss. Our conclusions are in agreement with that of Lawton et al. We found several recent studies not reported in the article by Lawton et al. (2006). Twelve studies used threshold differences to differentiate between styrene-exposed and nonexposed workers. Of the 12 studies, 4 found no evidence to support the effect of styrene on the thresholds of hearing (Calabrese et al., 1996; Hoffmann et al., 2006; Moller et al., 1990; Sass-Kortsak et al., 1995). Two studies were limited to styrene effects in the very high-frequency region (Morioka et al., 1999; Muijser et al., 1988) and in one of the studies the workers were also exposed to other solvents (Morioka et al., 1999). In contrast, six studies reported styrene-induced hearing losses (Mascagni et al., 2007; Morata et al., 2002; Morioka et al., 1999; Sliwinska-Kowalska et al., 2003, 2005; Triebig et al., 2009). However, a dose–response relationship was only found in the study conducted by Morioka et al. (1999).

There are numerous studies demonstrating that inhalation of styrene is ototoxic in laboratory animals. Susceptibility to solvents is species dependent. Styrene causes a permanent damage to auditory system, mainly in rats. The auditory system of the guinea pig is not injured by styrene as much as that of rats (Fechter, 1993; Lataye et al., 2003). Styrene damages hair cells in the cochlea of rats, and the spiral ganglions are not spared. The important characteristic of styrene is its higher susceptibility to OHCs compared to inner hair cells (Lataye et al., 2003). The effect is dose related. One study suggested that Dieters cells are the most vulnerable target of styrene and that styrene-related cell death occurs primarily by apoptosis (Chen et al., 2007). Subacute styrene exposure seems not to damage the hair cells, but the long-term exposure does. For chronic exposure, higher styrene concentrations lead to greater hair cell mortality. Mid-frequency hearing loss is most often reported. Morphologic examination determined a corresponding loss of OHC in the mid-frequency region of the rat cochlea (Yano et al., 1992). Hair cell deaths are not closely related to hearing threshold shifts in rats. There is no styrene-induced hearing loss for chronic exposure of rats up to about 600 ppm. Concentrations greater than 600 ppm show threshold shifts directly related to styrene concentration.

*Presence of noise.* Six studies have investigated the workers exposed to both noise and styrene. Two studies found no interaction between styrene and noise. Due to confounding factors, however, it was concluded that the data were inadequate for assessing the combined effects of noise and chemical exposure on hearing (Morata et al., 2002; Sass-Kortsak et al., 1995). In one study (Muijser et al., 1988), the control group was exposed to much higher level of noise than the group exposed to styrene, precluding the evaluation of interaction between noise and styrene. Three studies from the same laboratory demonstrated additive or infra-additive effects (Sliwinska-Kowalska et al., 2001, 2003, 2005). No dose–response relationship between styrene exposure and hearing thresholds was found and only the abstract was available in English for the third study.
Four animal studies were evaluated. Susceptibility to solvents is species dependent. Exposure to styrene did not cause much damage to the auditory system in guinea pigs when compared to rats. A study in guinea pigs exposed simultaneously to 500 or 1200 ppm styrene and 95 dBA noise for 7 h showed no evidence of interaction between the 2 agents (Fechter, 1993). Three studies in rats demonstrated an ototoxic interaction between styrene and noise. The potentiation of styrene-induced hearing loss by noise was found in one study after exposure to 400 ppm styrene (Lataye et al., 2005) and synergism was observed in 2 studies after simultaneous exposure to 300–750 ppm styrene and 100 dB noise (Lataye et al., 2000; Makitie et al., 2003).

**Conclusion.** Although certain ototoxic effects were reported in workers, other human studies are necessary to further support the current incomplete evidence. In rats, styrene clearly affects the auditory function mainly in the range of the mid-frequencies of the cochlea. There is weak evidence of an ototoxic interaction with noise in workers. In rats, a synergistic interaction was found in two studies, as well as a potentiation of noise-induced hearing loss in another study. Further studies are necessary to draw a conclusion about interaction with noise. We recommend, by taking account the results of the human studies and the evidence from the animal studies to regard styrene as an ototoxic agent.

**Toluene**

**Absence of noise.** Data on toluene effects on human hearing originate mainly from case reports on toluene abusers. In the studies that focused on the voluntary inhalation of toluene, dramatic hearing loss originating from the central auditory pathways has been reported (Morata et al., 1994; Ryback, 1992). One study in workers with normal hearing ability (assessed by pure tone audiometry), exposed to 97 ppm toluene for 12–14 years, showed an alteration in the auditory brainstem–evoked responses. This test demonstrated modification in auditory nervous system before the occurrence of clinical signs due to chronic exposure to toluene (Abbate et al., 1993). An alteration in the auditory brainstem–evoked responses were also observed in another study on workers, however there was a lack of information on noise exposure (Vrca et al., 1996, 1997).

Thirty-seven inhalation, two oral and one intravenous studies in rats were identified. Rats were exposed to 600 ppm (Lataye et al., 2003) and more and exposure duration varied between 30 min (Witter et al., 1980) and 23 weeks (Pryor et al., 1985). Hearing losses were measured by behavioural methods and confirmed by electrophysiologic testing. Permanent mid-frequency hearing loss is reported most often. Factors such as concentrations and duration of exposure influence the loss of auditory sensitivity in rats. The daily concentration is far more important than the total length of exposure (Pryor et al., 1984b). Moreover, toluene itself seems to be responsible for the ototoxic effect rather than its metabolites (Campo et al., 2008; Waniaiow et al., 2008). The noise levels were not always reported. However, the ototoxicity of toluene has been demonstrated in a quiet environment by oral administration, which excludes noise from the inhalation system as a causative factor for this effect (Sullivan et al., 1988). A LOAEL for ototoxicity of toluene in rats is 700–1500 ppm.

In rats, evidence suggests that toluene exposure causes a permanent damage to the OHCs of the cochlea. No changes in the latencies of the ABRs have been noted in several studies in toluene-exposed rats (Campo et al., 2008; Johnson et al., 1988; Nylen et al., 1994; Rebert et al., 1983), suggesting that the damage is localized in the cochlea and not within the central auditory pathways (Johnson and Nylen, 1995). The effect on the OHC has been confirmed by morphologic examinations of cochlea showing loss of OHC, predominantly in the third row (Johnson and Canlon, 1994b; Pryor et al., 1984a; Sullivan et al., 1988). The examinations show that cochlear toxicity is localized in the middle (16–29 kHz) and mid-low (4–5 kHz) frequency regions of the cochlea. Inner hair cells seem to be preserved (Campo et al., 1997). The hair cell loss is progressive and continues even after the end of exposure (Johnson and Canlon, 1994a). Moreover, results from the intravenous study suggest that exposure to toluene might modify the response of protective acoustic reflexes (Lataye et al., 2007).

Three inhalation studies in guinea pigs were identified. Two studies in guinea pigs exposed to 600 and 1000 ppm were negative (Campo et al., 1993; Lataye et al., 2003) and one study showed an ototoxic effect with a LOAEL of 250 ppm. One inhalation study in chinchillas exposed to 1000 ppm was negative.

**Presence of noise.** Four studies in workers were identified. Two of those used the same data (Schaper et al., 2003, 2008). In a well done study (Morata et al., 1993), simultaneous occupational exposure to 100–365 ppm toluene and 88–98 dBA noise was found.
to significantly increase the predicted probability of developing a hearing loss when compared with a group of workers exposed to matching doses of noise. Acoustic reflex measurements suggested that the hearing losses found in the group exposed to both agents might be due to lesions in the central auditory system. Another study identified a hearing impairment in workers due to the simultaneous exposure to toluene of 33–165 ppm and 85 dB of noise (Chang et al., 2006). However, no hearing impairment was observed in the study in which workers were simultaneously exposed to toluene up to 45 ppm and 82 dB of noise, indicating that the threshold for developing a hearing loss due to toluene exposure might be above 50 ppm (Schaper et al., 2003, 2008).

Six studies in rats were identified. Interactions of toluene with noise producing additive or synergistic cochlear damage have been suggested in five studies. The decrease in auditory sensitivity of rats exposed to toluene followed by noise was greater than the sum of the effects of toluene and noise alone (synergistic effect; Brandt-Lassen et al., 2000; Lataye and Campo, 1997). When exposures were carried out in reverse order (i.e. noise followed by toluene exposure), the loss of sensitivity was greater than the individual loss caused by toluene or noise but did not exceed the summated loss (Johnson et al., 1990). Also, one study found a greater effect of impact noise as compared to wide-band noise as exposed simultaneously to 500–1500 ppm toluene during 10 days (Lund and Kristiansen, 2008). However, the value of the results of these studies is limited with respect to occupational setting as the daily exposures were long (10–16 h/d), overall exposure periods were short (2–4 weeks) and exposure to noise and toluene was not simultaneous in three studies (Johnson et al., 1988, 1990; Lataye and Campo, 1997). The only study where daily and overall exposure periods were more representative (6 h/d, 90 days in rats exposed from 100 to 500 ppm), was negative and the authors found a protective effect on hearing of exposure to low levels of toluene (Lund and Kristiansen, 2008). One study in guinea pigs (Campo et al., 1999) and one study in chinchillas (Davis et al., 2002) showed negative results.

**Conclusion.** Although certain ototoxic effects were reported in workers, other human studies are necessary to further support the current incomplete evidence. However, a series of animal studies clearly highlighted the ototoxic effects in relation to high concentrations of toluene. In rats, toluene affects the auditory function mainly in the mid-frequency range of the cochlea. There is convincing evidence of ototoxic interaction after combined exposure to toluene and noise in workers and in rats. We recommend, by taking into account the results of the human studies and the evidence brought by the animal studies, to regard toluene as an ototoxic agent that can also interact with noise to induce more severe hearing losses.

**Trichloroethylene**

**Absence of noise.** Hearing losses were reported in workers in association with exposure to trichloroethylene in case studies (Gist and Burg, 1995). Symmetrical bilateral eighth cranial nerve deafness, with subsequent recovery, was reported in a patient who had been overexposed to trichloroethylene (Tomasini and Sartorelli, 1971). In a study of 40 exposed workers (Szulc-Kuberska et al., 1976), 26 had bilateral sensorineural hearing loss. Workers with a long-term occupational exposure to solvents, including trichloroethylene, were reported to have abnormally distorted speech audiometry results (Odkvist et al., 1987). This suggests damage to the central auditory system, which cannot be attributed to noise. However, the exposure concentrations were not exactly reported in all these studies.

There are seven studies demonstrating that trichloroethylene exposure by inhalation is ototoxic in rats. Permanent hearing loss has been found to be restricted to the mid- to high-frequency range (4–20 kHz). The greatest reduction in hearing was observed at 16 kHz. The ototoxicity appears to be a high-concentration effect on rats as shown by auditory brain responses or reflex modification audiometry. After 13 weeks of exposure, the LOAEL for ototoxicity was 2500 ppm (Crofton and Zhao, 1997) and the NOAEL was 800 ppm (Albee et al., 2006). Morphologic examination demonstrated that trichloroethylene damaged the spiral ganglions (a sign of neurotoxic effect) in the cochlea of rats (Fechter et al., 1998).

**Presence of noise.** No human study was identified. In one study in rats (Muijser et al., 2000) a supraadditive ototoxic interaction between trichloroethylene and noise was found at low frequencies after a combined exposure to 95 dB SPL noise and to 3000 ppm trichloroethylene for 3 weeks.

**Conclusion.** Although certain ototoxic effects were reported in workers, other human studies are
necessary to further support the current incomplete evidence. In rats, trichloroethylene clearly affects the auditory function mainly in the mid-frequency range of the cochlea. No human study on the interaction between trichloroethylene and noise was found. In one study in rats, there was evidence of interaction at low frequencies. Further studies are necessary to draw any conclusion about interaction with noise. We recommend, by taking into account the results of the human studies and the evidence provided by the animal studies, to regard trichloroethylene as an ototoxic agent.

**Tin, organic compounds**

Absence of noise. No human study was identified. Four animal studies were identified using the same single dose of trimethyl tin chloride administered by i.p. route. One study in rats showed no ototoxic effect (Young and Fechter, 1986). Three studies from the same laboratory, performed on guinea pigs, found a persistent ototoxic effect at high frequencies (Clerici et al., 1991; Fechter and Carlisle, 1990; Fechter et al., 1992).

Presence of noise. No study with realistic exposure concentrations was identified.

Conclusion. In the absence of other studies, it is not possible to draw any conclusion regarding the ototoxicity of organic tin compounds. No study on interaction with noise was found.

**Welding fumes**

Absence of noise. No human study was identified. One study in rabbits was identified (Mirzaei et al., 2007). Animals were exposed to 157 mg/m³ welding fumes by inhalation during 12 days. Exposure to welding fumes caused an amplitude reduction in high-frequency DPOAE test.

Presence of noise. No human study was identified. One study in rabbits was identified. Animals were exposed to 157 mg/m³ welding fumes by inhalation and to 110 dB SPL noise simultaneously during 12 days. While exposure to welding fumes caused an amplitude reduction in high-frequency DPOAE, it also potentiated the noise-related decrease in OHCs function.

Conclusion. No human study was identified. In one rabbit study, welding fumes caused a high-frequency hearing loss and potentiated noise-induced OHC function decrease. In the absence of other studies, it is not possible to draw any conclusion regarding the ototoxicity of welding fumes or of their interaction with noise.

**Xylenes**

Absence of noise. One study on volunteers was identified (Seppäläinen et al., 1989). ABR tests showed no ototoxic effect when 200 ppm of m-xylene was inhaled for 3 h.

Seven studies were identified in rats of different strains. An ototoxic effect was observed in five of six inhalation studies (Crofton et al., 1994; Gagnaire and Langlais, 2005; Gagnaire et al., 2001; Maguin et al., 2006; Pryor et al., 1987) and one oral study (Gagnaire and Langlais, 2005) by four different tests. Three studies from the same laboratory showed the ototoxic effect depending on the duration of exposure. A LOAEL of 800 ppm was observed after 6 weeks of exposure (Pryor et al., 1987). Two studies compared the ototoxicity of three xylene isomers (Gagnaire et al., 2001; Maguin et al., 2006). No ototoxic effect was observed after a subchronic exposure of up to 1800 ppm o- or m-xylene, but it was observed after exposure to 900 ppm p-xylene in one study and 1800 ppm in the other.

Presence of noise. No study with realistic exposure concentration was identified.

Conclusion. Only one human study was identified showing no ototoxic effect after short-term exposure. In rats xylene affects the auditory function. Further studies with sufficient data on the exposure of workers to xylene isomers are necessary to make a definitive conclusion. Given the current evidence from animal studies, we recommend considering p-xylene and consequently a mixture of xylene isomers as possibly ototoxic. No human or animal study on ototoxic interaction between xylenes and noise was identified.

**Summary of results on the ototoxicity of substances**

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 10 substances, the lack of toxicological data did not allow for a definitive conclusion to be reached and
Table 2. Summary of conclusions about ototoxic effects of industrial chemicals

<table>
<thead>
<tr>
<th>Industrial chemical (CAS)</th>
<th>Quebec TWA EV (STEV)</th>
<th>ACGIH TWA (STEL)</th>
<th>Human studies</th>
<th>Animal studies</th>
<th>References</th>
<th>Weight of evidence</th>
<th>Conclusion about ototoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acrylonitrile (107-13-1)</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
<td>Fechter et al. (2003), (2004), Poyyatos et al. (2005)</td>
<td>X W W W NC</td>
<td></td>
</tr>
<tr>
<td>n-Butyl alcohol (71-36-3)</td>
<td>C50</td>
<td>20</td>
<td></td>
<td></td>
<td>Velazquez et al. (1969)</td>
<td>W A W W NC</td>
<td></td>
</tr>
<tr>
<td>p, p'-Terbutyltoluene (98-51-1)</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td>Lund and Simonsen (1993), Lam et al. (2000)</td>
<td>X A A A NE</td>
<td></td>
</tr>
<tr>
<td>Carbon disulphide (75-15-0)</td>
<td>4 (12)</td>
<td>1</td>
<td></td>
<td></td>
<td>Hirata et al. (1992a)</td>
<td>W W W W NC</td>
<td></td>
</tr>
<tr>
<td>Cyanides</td>
<td>C10</td>
<td>C5 mg/m³</td>
<td></td>
<td></td>
<td>Tawackoli et al. (2001)</td>
<td>X W W W NC</td>
<td></td>
</tr>
<tr>
<td>Enflurane (13838-16-9)</td>
<td>75</td>
<td>75</td>
<td></td>
<td></td>
<td>Yeoman et al. (1980)</td>
<td>X A A A NE</td>
<td></td>
</tr>
<tr>
<td>Ethyl alcohol (64-17-5)</td>
<td>1000</td>
<td>1000</td>
<td></td>
<td></td>
<td>Pryor et al. (1985), Amiko et al. (1989), Nylen et al. (1995)</td>
<td>X A A A AP</td>
<td></td>
</tr>
<tr>
<td>Ethyl benzene (100-41-6)</td>
<td>100 (125)</td>
<td>100 (125)</td>
<td></td>
<td></td>
<td>Cappaert et al. (1999), (2000), (2001), (2002), Gagnaire and Langlais (2005), Gagnaire et al. (2007)</td>
<td>X S M PO</td>
<td></td>
</tr>
<tr>
<td>n-Heptane (142-82-5)</td>
<td>400 (500)</td>
<td>400 (500)</td>
<td></td>
<td></td>
<td>Simonsen and Lund (1995)</td>
<td>X W W W NC</td>
<td></td>
</tr>
<tr>
<td>Hexachlorobenzene (118-74-1)</td>
<td>0.025 mg/m³</td>
<td>0.002 mg/m³</td>
<td></td>
<td></td>
<td>Rebert et al. (1982), (1983), Howd et al. (1983), Pryor et al. (1983a), Pryor and Rebert (1992), Nylen et al. (1994)</td>
<td>W S S M PO</td>
<td></td>
</tr>
<tr>
<td>n-Hexane (110-54-3)</td>
<td>50</td>
<td>50</td>
<td></td>
<td></td>
<td>Fechter et al. (2002)</td>
<td>X A A A NE</td>
<td></td>
</tr>
<tr>
<td>Hydrogen cyanide (74-90-8)</td>
<td>0.05 mg/m³</td>
<td>0.05 mg/m³</td>
<td></td>
<td></td>
<td>Holdstein et al. (1986), Lille et al. (1988), Discalzi et al. (1992), (1993), Hirata and Kosaka (1993), Murata et al. (1993), (1995), Farahat et al. (1997), Forst et al. (1997), Counter and Buchanan (2002), Yokoyama et al. (2002), Bleecker et al. (2003)</td>
<td>W X W W NC</td>
<td></td>
</tr>
<tr>
<td>Lead</td>
<td>C10</td>
<td>C4.7</td>
<td></td>
<td></td>
<td>Fazakas et al. (2005)</td>
<td>W A A A NE</td>
<td></td>
</tr>
<tr>
<td>Mercury—alkyl compounds</td>
<td>0.01 (0.03) mg/m³</td>
<td>0.01 (0.03) mg/m³</td>
<td></td>
<td></td>
<td>Mattsson et al. (1993)</td>
<td>X A A A NE</td>
<td></td>
</tr>
<tr>
<td>Mercury—inorganic compounds</td>
<td>0.025 mg/m³</td>
<td>0.025 mg/m³</td>
<td></td>
<td></td>
<td>Mattsson et al. (1990)</td>
<td>X A A A NE</td>
<td></td>
</tr>
<tr>
<td>Mercury—vapour</td>
<td>0.025 mg/m³</td>
<td>0.025 mg/m³</td>
<td></td>
<td></td>
<td>Mattsson et al. (2005)</td>
<td>X W W W NC</td>
<td></td>
</tr>
<tr>
<td>Methyl chloroform (71-55-6)</td>
<td>350 (450)</td>
<td>350 (450)</td>
<td></td>
<td></td>
<td>Bobbin and Gondra (1976)</td>
<td>X A A A NE</td>
<td></td>
</tr>
<tr>
<td>Methylene chloride (75-09-2)</td>
<td>50</td>
<td>50</td>
<td></td>
<td></td>
<td>Mattsson et al. (1993)</td>
<td>X A A A NE</td>
<td></td>
</tr>
<tr>
<td>n-Methyl styrene (98-83-9)</td>
<td>50 (100)</td>
<td>50 (100)</td>
<td></td>
<td></td>
<td>Mattsson et al. (1990)</td>
<td>X A A A NE</td>
<td></td>
</tr>
<tr>
<td>Nicotine (54-11-5)</td>
<td>0.5 mg/m³</td>
<td>0.5 mg/m³</td>
<td></td>
<td></td>
<td>Bobbin and Gondra (1976)</td>
<td>X A A A NE</td>
<td></td>
</tr>
<tr>
<td>Parathion (56-38-2)</td>
<td>0.1 mg/m³</td>
<td>0.05 mg/m³</td>
<td></td>
<td></td>
<td>Reischl et al. (1975)</td>
<td>X W W W NC</td>
<td></td>
</tr>
<tr>
<td>Perchloroethylene (127-18-4)</td>
<td>25 (100)</td>
<td>25 (100)</td>
<td></td>
<td></td>
<td>Mattsson et al. (1998)</td>
<td>A A A A NE</td>
<td></td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Industrial chemical (CAS)</th>
<th>Quebec TWAEV (STEV)</th>
<th>ACGIH TWA (STEL)</th>
<th>Human studies</th>
<th>Animal studies</th>
<th>Human studies</th>
<th>Animal studies</th>
<th>Overall</th>
<th>Conclusion about ototoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trimethyl tin</strong></td>
<td>0.1 (0.2) mg/m³</td>
<td>0.1 (0.2) mg/m³</td>
<td>Clerici et al. (1991), Fechter and Carlisle (1990); Fechter et al. (1992), Young and Fechter (1986)</td>
<td>X</td>
<td>W</td>
<td>W</td>
<td>NC</td>
<td></td>
</tr>
<tr>
<td><strong>Welding fumes</strong></td>
<td>5 mg/m³</td>
<td></td>
<td>Miresaei et al. (2007)</td>
<td>Crofton et al. (1994), Gagnaire et al. (2001), Gagnaire and Langlais (2005), Maguin et al. (2006), Pryor et al. (1987)</td>
<td>X</td>
<td>W</td>
<td>W</td>
<td>NC</td>
</tr>
<tr>
<td><strong>Xylenes</strong></td>
<td>100 (150)</td>
<td>100 (150)</td>
<td>Seppalainen et al. (1989)</td>
<td></td>
<td>A</td>
<td>S</td>
<td>M</td>
<td>PO</td>
</tr>
</tbody>
</table>


11 substances were considered as non-ototoxic. For nine substances, the assessment was based only on one study, thus limiting the reliability of the toxicological assessment. At the other extreme, the assessment of toluene was based on 36 studies.

Table 3 gives a summary of conclusions about the interactions of industrial chemicals with noise. Relevant data for 11 substances were found. Carbon monoxide is considered a possible potentiator of noise-induced hearing loss. Toluene is identified as an ototoxic agent that can also interact with noise to induce more severe hearing losses. For seven substances, the lack of toxicological data did not allow for a definitive conclusion to be reached and for two substances there is no evidence of interaction with noise.

### Discussion

Recent studies have shown that the occupationally relevant exposures to some industrial substances can be potentially ototoxic in workers. However, for the majority of cases where potential ototoxicity was identified, there is a lack of supporting toxicological data in the primary literature.

A wide variety of tests have been utilized, including pure-tone audiometry, immittance, reflex modification audiometry, reflex response audiometry, electrocochleography, auditory nerve compound action potential test and ABRs. Diverse approaches were used in the evaluation of chemical exposures. In many of the reported human investigations, the exposure history was evaluated through questionnaires combined with sparse exposure records. In the case of metals, exposure was evaluated through biological monitoring. For organic mercury, the exposure of population was not reported in the evaluated studies. In some cases, noise exposure was not even taken into account.

A lack of detailed noise and chemical exposure records in several studies constituted the main difficulty in reaching a conclusion from these reports. In workers, the assessment of exposure to a single chemical substance is particularly difficult because they are usually exposed to mixtures of chemicals and it is
difficult to identify workers with exposure to a specific compound only (Reischl et al., 1975).

Extrapolation of the results from animal studies to humans should be made with caution. The frequency range of hearing and the metabolism of chemicals are different between animals and humans. Studies have been performed mainly in rats, the auditory frequency range of which is from around 0.25 to 80 kHz, with a maximum sensitivity at around 8 kHz. The auditory range for young adult humans is around 20 Hz to 20 kHz, with the greatest sensitivity at around 1–4 kHz. Thus although extended to the ultrasonic range, the auditory range in rats overlaps with that of the human (Cary et al., 1997; Franks and Morata, 1996).

In summary, human and animal studies indicate that lead, styrene, toluene and trichloroethylene are ototoxic and ethyl benzene, n-hexane and p-xylene are possibly ototoxic at concentrations that are relevant to the occupational setting. Carbon monoxide appears to exacerbate noise-induced hearing dysfunction. Toluene interacts with noise to induce more severe hearing losses than the noise alone.

A recent workshop on the ototoxicity of organic solvents concluded that there is no consensus on the lowest occupational exposure limits for solvents in relation to their effect on the auditory organ but there is evidence that existing limited values might be inadequate (Sliwinska-Kowalska et al., 2007).

Hoet et al. (2005) proposed introducing a ‘Noise notation,’ in analogy with established ‘Skin notation.’ The ‘Noise notation’ could be added to OELs of certain ototoxic substances and would serve as an alert for targeted medical surveillance of the hearing function of exposed workers. The results of our review support this proposal.

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