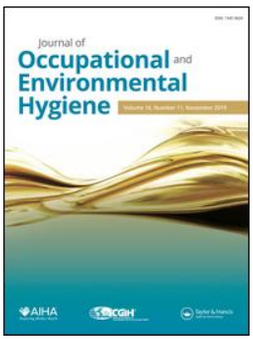

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REVIEW

Exposure to lead, mercury, styrene, and toluene and hearing impairment: Evaluation of dose-response relationships, regulations, and controls

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ABSTRACT

The risk of hearing loss from exposure to ototoxic chemicals is not reflected in occupational exposure limits and most jurisdictions. The aims of this research were to investigate dose-response relationships between exposure to lead, mercury, toluene, and styrene and hearing impairment based on current epidemiological evidence, conduct cross-jurisdictional comparisons, and investigate control measures for exposure to ototoxic chemicals. Ovid Medline and Ovid Embase databases were used to find relevant publications. A total of 86 epidemiological studies met the eligibility criteria for final evaluation. When significant associations between exposure and outcome were identified, exposure levels were evaluated to determine whether No Observed Adverse Effect Level (NOAEL) and Lowest Observed Adverse Effect Level (LOAEL) could be identified. Cross-jurisdictional comparisons included the U.K., U.S., Canada, and Australia occupational health and safety legislations. The majority of lead (75%), styrene (74%), and toluene (77%) studies showed significantly increased risks of hearing loss from exposure to these substances, although numerous studies on toluene (70%) and styrene (16%) compared auditory function between "solvent mixture" or "noise and solvent mixture" exposed groups and controls and not necessarily on groups exposed to a single agent. Based on five studies, blood lead ranges of 1–1.99 μg/dL to 2.148–2.822 μg/dL were identified as NOAELs while blood lead levels of 2 μg/dL up to 2.823–26.507 μg/dL were identified as LOAELs for hearing loss. Except for general duty clauses, the U.S., Canadian, and Australian jurisdictions have set no enforceable regulations specific to ototoxic chemical exposures. A biological exposure index of 2 μg/dL is recommended for prevention of hearing impairment from lead exposure. Based on Safe Work Australia, noise exposure limits may be reduced to 80 dB(A) for 8 hr. Other recommendations include performing audiometric testing and controlling exposure through all routes of entry.

KEYWORDS

Biological exposure index; blood lead level; ototoxic chemicals; pure tone audiometry

Introduction

Hearing loss is the fourth most prevalent disabling disease in the world (IHME 2017). The number of people with disabling hearing loss is estimated to be 466 million or 6.1% of the world's population. This number is expected to grow over the coming years and could rise to 630 million by 2030 and over 900 million in 2050, unless preventive actions are taken (WHO 2018).

Although loud noise has detrimental effects on auditory function, it is not the only source of work-related hearing impairment. Exposure to ototoxic chemicals can increase the risk of hearing loss with or without concurrent noise exposure (Fechter and Pouyatos 2005; Gagnaire and Langlais 2005). The European Agency for Safety and Health at Work classified several chemicals in five groups of substances as "confirmed" ototoxic substances including pharmaceuticals, solvents, asphyxiants, nitriles, and metals. The classification was based on a weight of evidence approach obtained from at least two well-documented animal studies or a single comprehensive and reliable animal study providing consistent and coherent evidence of ototoxic effects (Campo et al. 2009).

The mechanism of damage to hearing varies depending on the chemical substance. An acute or chronic neurotoxic effect of exposure to aromatic solvents such as toluene and styrene is central nervous system (CNS) depression (NIOSH 1987; Möller et al. 1990; Greenberg 1997) while chronic exposures affect the inner ear (Pryor et al. 1983; 1987) causing irreversible hearing impairment by poisoning cochlear hair cells and disorganizing their membranous structures (Johnson and Canlon 1994; Campo et al. 2001).

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Solvents may directly affect the cells of the organ of Corti forming chemically and biologically reactive intermediates including reactive oxygen species, which may trigger the death of these cells (Chen et al. 2007). While exposures to solvents such as styrene and solvent mixtures are associated with disorders in the central auditory pathway (Abbate et al. 1993; Morata et al. 1993; Greenberg 1997; Johnson et al. 2006), exposure to lead and mercury may affect both the cochlea (Rice and Gilbert 1992; Rice 1997) and the central auditory pathways (Discalzi et al. 1993; Otto and Fox 1993; Lasky, Maier, Snodgrass, Hecox, Laughlin 1995; Lasky, Maier, Snodgrass, Laughlin, Hecox 1995). Similar to aromatic solvents, the hearing-damaging effects of lead and mercury are caused by a neurotoxic mechanism (Discalzi et al. 1993; Counter and Buchanan 2002; Hwang et al. 2009). Lead exposure affects cognitive and central auditory nervous system function and peripheral nerve conduction (Araki et al. 1992). Blood lead levels are associated with adverse effects in conduction in the distal auditory nerve and are found to impair conduction in the auditory nerve and pathway in the lower brainstem (Bleecker et al. 2003). Dimethylmercury poisoning is shown to damage the auditory neural system (Musiek and Hanlon 1999) and exposure to methyl mercury chloride causes nerve conduction hypersensitivity in the brainstem (Wassick and Yonovitz 1985). Carbon monoxide and hydrogen cyanide deprive oxygen within the cochlea (Campo et al. 2013) impairing the cochlear function under extreme exposure conditions but have reversible auditory effects when exposure levels are low (Campo et al. 2009). Aminoglycosides penetrate the outer hair cells causing a reaction which generates the release of reactive oxygen species (ROS), resulting in death of cells (Rybak and Ramkumar 2007). Anti-neoplastic drugs cause loss of cochlear hair cells and cells of the spiral ganglion (Hamers et al. 2003). Exposure to nitriles is shown to cause cochlear hair cell losses and spiral ganglion cell losses in animal studies (Crofton et al. 1994; Soler-Martín et al. 2007).

In a recent study on the Australian workforce, more than 80% of workers who were exposed to noise above Occupational Exposure Limit (OEL) were also exposed to at least one ototoxic chemical (Lewkowski et al. 2019). In Europe in 2005, while 30% of workers reported being exposed to noise, about 45% were exposed to ototoxic chemicals (Parent-Thirion et al. 2007). The weighted prevalence of hazardous occupational noise exposure among U.S. workers was estimated to be 17.2% or 22.4 M workers out of the estimated 130 M based on a representative number of workers from the National Health and Nutrition Examination Survey (NHANES) data collected from 1999–2004 (Tak et al. 2009). Over 30 M U.S. workers are exposed to hazardous chemicals in their workplaces, some of which might be ototoxic and hazardous to hearing (OSHA 2004; NIOSH 2018).

The American Conference of Governmental Industrial Hygienists (ACGIH®), in its Threshold Limited Values and Biological Exposure Indices (TLVs® and BEIs) publication, has included a note entitled "Ototoxicant" under Definitions and Notations. The note explains that the designation "OTO" in the "Notations" column indicates the potential for a chemical to cause hearing impairment from exposure to the chemical alone or in interaction with noise of even below 85 dBA. The OTO notation is reserved for chemicals which adversely affect auditory capacity including permanent audiometric threshold shifts as well as difficulties in processing sounds based on animal studies or human experience. The note also states that "Some substances may act synergistically with noise, whereas others may potentiate noise effects. The OTO notation is intended to focus attention, not only on engineering controls, administrative controls and personal protective equipment needed to reduce airborne concentrations, but also on other means of preventing excessive combined exposures with noise to prevent hearing disorders. Specifically, affected employees may need to be enrolled in hearing conservation and medical surveillance programs to more closely monitor auditory capacity, even when noise exposures do not exceed the TLV for Audible Sound" (ACGIH 2019). Although employers are required to control risks of chemical exposures by the general duty clauses such as that contained in section 5(a)(1) of the U.S. OSH Act, however, in most jurisdictions, they are not explicitly required to control the risks of hearing loss arising from exposure to ototoxic chemicals. In addition, these risks are not reflected in occupational exposure limits. These issues have been linked to a lack of data on dose-response relationships and effects of exposure to ototoxic chemicals on hearing threshold shifts based on human epidemiological studies (Lawton et al. 2006; Hoet and Lison 2008; Vyskocil et al. 2008). The objectives of this research are: (1) to investigate dose-response relationships between exposure to two heavy metals (lead and mercury) and two solvents (toluene and styrene) and hearing impairment. The investigation will be based on current epidemiological evidence to support recognition of hearing impairment as an outcome of exposure to these substances and to determine whether occupational exposure

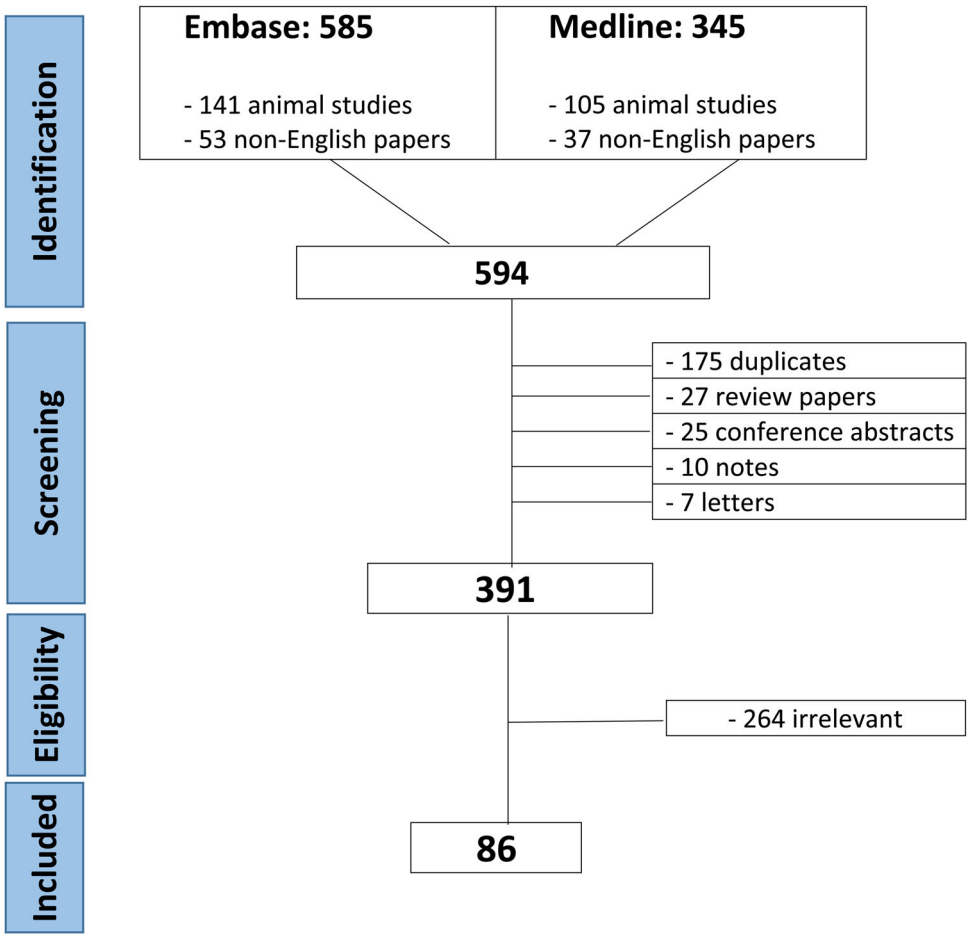

Figure 1. Summary of search strategy for selection of papers.

limits or biological exposure indices may be established for the selected substances; (2) to conduct cross-jurisdictional comparisons on regulations and guidelines on ototoxicity; and (3) to investigate control measures for prevention of hearing loss from ototoxic exposures.

Multi-chemical exposures including exposures to solvents and some heavy metals are ubiquitous. Due to the widespread use of solvents and possibility for exposure through multiple routes, almost all humans are exposed to solvent mixtures on a daily basis (Bonventre 2014). In its 1987 intelligence bulletin, NIOSH estimated that 9.8 million workers are exposed to organic solvents (NIOSH 1987). Toluene and styrene were chosen from the group of solvents as they are reported as the most extensively used aromatic solvents in industry (Meek and Chan 1994). Lead is the most prevalent heavy metal contaminant (Di Maio 2010) with over 1,600,000 U.S. workers and approximately 277,000 Canadians exposed to it in their workplaces (CAREX Canada 2016; Musick 2017).

Methods

Ovid Medline and Ovid Embase databases were used to find relevant publications. *Lead*, *Mercury*, *Toluene*, and *Styrene* were used as MeSH terms and keywords. *Hearing Impairment* was exploded and used as keyword as well as *Ototoxicity or Hearing or Deaf** which were used as keywords. Time parameters were not considered in the search. The scope of search was narrowed to epidemiological studies and animal studies were excluded. In the next step, only papers in English were selected. The search resulted in 391 papers from Ovid Embase and 203 papers from Ovid Medline, including both occupational and non-occupational exposures. There were 175 duplicate studies, 27 review papers, 25 conference abstracts, 10 notes, and 7 letters, which were excluded. Studies were eligible for inclusion if they measured exposure to one of the four substances of interest and hearing loss or auditory functions as the health outcome. The abstracts of the remaining 351 papers were reviewed to determine whether they met the inclusion criteria and 264 papers were excluded, leaving a final 86 papers for evaluation (Figure 1).

Table 1. Summary of literature review.

	Lead	Mercury	Styrene	Toluene
Number of studies	33	9	19	26
Study design				
Cross-sectional	29	8	15	18
Retrospective	1		2	3
Case study	1	1		
Case control	1		1	
Prospective				3
Retrospective case control			1	2
Cross-sectional and prospective	1			
Exposure assessments				
Blood	29	4	2	2
Airborne	5		14	23
Nail	1	1		
Hair	1	3		
Mandelic acid (MA)			5	
Noise	5		15	9
Other cases	1 (bone)	1 (poisoned)	2 (other metabolites)	1 (BMA) 2 (hippuric acid)
Auditory function*				
PTA	27	6	18	20
Bone conduction	1		3	4
BAER	5	4		3
DPOAE	3	3	4	1
TEOAE	1		4	1
ASR	1	1		
Other tests	1 (SPM-HKC)	1 (tuning fork) 1 (CEOAE) 1 (neurobehavioral evaluation system	4	1 (VEMP) 4 (HINT, ART, DD, FS, PPS, RGD)
Significant association	24	5	12	4
Concurrent association (along with other agents)	1 (toluene)		2 (noise & solvents) 1 (noise & chemicals)	6 (noise & solvents) 1 (noise & metals) 9 (solvents) 2 (noise)
No association	8	4	5	6

*PTA: Pure Tone Audiometry; BAER: Brainstem Auditory Evoked Response; DPOAE: Distortion Product Otoacoustic Emissions; TEOAE: Transient Evoked Otoacoustic Emissions; ASR: Automatic Speech Recognition; CEOAE: lick-evoked otoacoustic emissions; VEMP: vestibular evoked myogenic potential; ART: Acoustic Reflex Threshold; HINT: Hearing In Noise Test; DD: dichotic digit, FS: filtered speech, PPS: pitch pattern sequence, and RGD: random gap detection.

Research was reviewed to find if there were any relationships between exposure to substances of interest and hearing impairment. When significant associations were identified, exposure levels were evaluated to determine whether concentrations associated with increased risk of hearing loss could be identified including the No Observed Adverse Effect Level (NOAEL) and/or the Lowest Observed Adverse Effect Level (LOAEL). NOAEL is the highest exposure level at which there are no statistically significant increases in the frequency or severity of adverse effects between the exposed group and its appropriate control. LOAEL is the lowest exposure level at which there are statistically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control (Lewis et al. 2002).

When evaluating studies which used multiple regression analysis, if odds ratios were found to be above 1 and the 95% CI did not span 1, it was concluded that the increased odds of outcome from exposure reaches statistical significance (Szumilas 2010).

Cross-jurisdictional comparisons of U.K., Canada, Australia, and U.S. occupational health and safety legislations were conducted. Jurisdictions were selected from top four industrialized, high-income countries with developed occupational health and safety legislation systems where legislation was available in English. The online portal of International Labor Organization (ILO 2014) was used to identify and access legislation. The websites of regulatory organizations were also searched for any relevant guidelines. The keywords used for search in the regulations and guidelines were "ototoxicity" and "hearing loss." The aim was to find how non-auditory hearing loss is handled by jurisdictions as a workplace exposure and identify recommended or required control measures.

Results

A summary of the literature review is provided in Table 1. Details on exposure and outcome assessment techniques, number and age of participants, study designs and main findings of each study are provided

Table 2. Summary of research on exposures to lead (N = 30) and lead and mercury (N = 2). One more study on lead is listed under Table 4.

Reference	Exposure	Outcome	No. of Participants	Age	Study Design	Main Findings
(Xu et al. 2020)	Blood Lead Level (BLL): 3.61–7.40; mean: 5.29 μg/dL (exposed); 2.98–4.77; mean: 3.63 μg/dL (unexposed)	PTA: 0.25–8 kHz	116	3–7	Cross-sectional	BLL in exposed group increased odds of HL (OR 1.40, 95% CI: 1.06, 1.84) compared with reference group.
(Huh et al. 2018)	BLL: 0.515–26.507 μg/dL	PTA: 0.5–6 kHz	2,387	19–85	Cross-sectional	Q3 of BLL (2.248–2.723 μg/dL) increased odds of HL at 4 kHz (OR 1.72, 95 CI: 1.06–2.80).
(Cai et al. 2019)	BLL cut off value: 5 μg/dL (high vs. low)	Sensory Processing Measure SPM-HKC	574	3–6	Cross-sectional	BLL > 5 μg/dL is associated with higher scores for hearing system.
(Liu et al. 2018)	BLL (median), exposed: 4.94 ± 0.20, non-exposed: 3.85 ± 1.81 μg/dL	PTA: 0.25–8 kHz (except for 3 & 6 kHz)	234	3–7	Cross-sectional	BLL of exposed group increased odds of HL (OR 1.24 (95% CI: 1.029, 1.486)).
(Al-khfajy et al. 2018)	BLL: study group: 23.14 ± 1.76 μg/dL; control group: 21.20 ± 2.08 μg/dL	PTA: 0.5–8 kHz	51	13–75	Cross-sectional	BLL of patients with hearing impairment is significantly elevated compared to control group.
(Kang et al. 2018)	BLL of males: 1.56–4.22 μg/dL; females: 1.12–3.03 μg/dL	PTA: low frequency: 0.5–2 kHz; high frequency: 3–6 kHz	6,409	20 or older	Cross-sectional	Q4 of male BLL (4.22 ± 0.08 μg/dL) increased odds of high frequency HL (OR 1.629, (1.161–2.287). Q4 of female BLL (3.03 ± 0.03 μg/dL) increased odds of high frequency HL (OR 1.502, 1.027–2.196).
(Choi and Park 2017)	BLL: 0.3–26.5 μg/dL; Blood Hg: 0.3–60.6 μg/dL	PTA (high frequency): 3–6 kHz; (speech frequency: 0.5–4 kHz (excluding 3 kHz)	5,515 879	20–87 12–19	Cross-sectional	Q4 of BLL (2.823 − 26.507 μg/dL) increased odds for high frequency HL (OR 1.70, 1.25, 2.31). No association between blood Hg and HL.
(Huh et al. 2016)	BLL: GM = 2.08 (95% CI: 2.05, 2.11 μg/dL)	PTA: 2–4 kHz	7,596	10–87	Cross-sectional	Each 1 μg/dL increase in BLL increased odds of HL 1.43 times (OR 1.43, 1.03, 2.00). Q4 of BLL (2.278–2.919 μg/dL) increased odds of HL (OR 1.41, 1.04, 1.92).
(Pawlas et al. 2015)	BLL: median of 36.0 μg/L and 55.0 μg/L among 2 groups	PTA: 0.5–8 kHz excluding 3 kHz, TOAE: 1–5 kHz	483	4–13	Cross-sectional	Significant correlation between BLL and PTA (rS= 0.12; P < 0.01) and between BLL and TOAE (rS= −0.24 ; P < 0.001)
(Alvarenga et al. 2015)	BLL: ≥10 g/dL (eligibility criteria); mean: 12.2 g/dL	PTA: 0.5–4 kHz, TEOAE: 1.5–5 kHz	130	18 months–14 years	Cross-sectional	No association between BLL and auditory function.
(Choi et al. 2012)	BLL: 1.54 μg/dL (GM); noise: exposed vs. unexposed	PTA: 0.5–8 kHz	3,698	20–69	Cross-sectional	No association between BLL and HL.
(Abdel Rasoul et al. 2012)	BLL: 6.72 ± 4.3 μg/dL (mean ± SD); environmental Pb: 73–80.0 ppm; area noise: 55.0 ± 17.14 dB	PTA: 0.25—8 kHz	190	Not provided	Cross-sectional	BLL is associated with hearing threshold. BLL ≥10 μg/dL is associated with 18.8 ± 9.42 while BLL < 10 μg/dL is associated with 15.63 ± 7.89 threshold shift in hearing (p = 0.03).
(Shargorodsky et al. 2011)	BLL: median Q1: 0.47 μg/dL, Q4: 1.57 μg/dL and blood	PTA: 0.5–8 kHz HL: > 15 dBA	3,389	12–19	Cross-sectional	BLL ≥ 2 μg/dL increased odds of high frequency (3–8 kHz) HL (OR, 2.22;

(*Continued*)

Table 2. Continued.

Reference	Exposure	Outcome	No. of Participants	Age	Study Design	Main Findings
	Hg: median Q1: 0.20 μg/dL, Q4: 1.28 μg/dL					95% CI, 1.39–3.56). No association between HgB & HL.
(Galal et al. 2011)	BLL; exposed group: 52.5 μg/dl + 21.5 non-exposed: 18.2 μg/dl + 5.9 Area noise	PTA: 0.25–8 kHz HL: >15 dB	111	20–60	Cross-sectional	A significant positive correlation was found between BLL and HL at 0.5–2 kHz (r = 0.7), 4 kHz (r = 0.63), 6 kHz (r = 0.67), and 8 kHz (r = 0.69).
(Counter et al. 2011)	BLL: 4.0–83.7 μg/dL	ASR: 0.5–2 kHHz; broadband noise (0.125–4 kHz)	117	2–18	Cross-sectional	No association between ASR decay/adaptation (ASRD) and BLL for any of the stimulus activators.
(Buchanan et al. 2011)	BLL: 4.2–94.3 μg/dl	DPOAE: 1.187–7.625 kHz	53	6–16	Cross-sectional	No significant correlation between BLL and hearing sensitivity for 6 pure-tone test frequencies from 1–8 kHz.
(Park et al. 2010)	Bone lead levels in tibia (22.5 ± 14.2 μg/g) and patella (32.5 ± 20.4 μg/g)	PTA: 0.25–8 kHz	448	21–80	Cross-sectional and prospective	An IQR increment in patella lead (21 μg/g) was associated with a 48% (OR = 1.48, 95% CI, 1.14, 1.91) higher odds of HL in air conduction PTA.
(Counter et al. 2009)	BLL: 4–128 μg/dl	PTA; ABR; otoscopy, tympanometry and otoacoustic emissions measurements.	3	14, 16, 19	Case study	There were significant neurocognitive deficits, with demonstrated severe and chronic Pb intoxication that cannot be attributed to neurosensory hearing loss.
(Hwang et al. 2009)	BLL: 55.9 ± 33.9 μg/dl (mean ± SD); area noise: 62.2 ± 0.5 dB (office) to 85.5 ± 8.6 dB (furnace area)	PTA: 0.5–8 kHz	412	36.0 ± 6.5	Cross-sectional	BLL > 7 μg/dL was significantly associated with hearing loss at 3–8 kHz (ORs from 3.06–6.26 ($p < 0.05$-$p < 0.005$). There was no interaction between BLL and noise exposure on hearing loss level.
(Chuang et al. 2007)	BLL: 106.62 μg/dl (GM), selenium, manganese, and arsenic	PTA: 0.5–6 kHz	294	39.4 ± 9.8	Case control	The net effect of Pb is 7.11 dB when increasing 1 μg/L (ppb or 0.1 μg/dL) logarithmic transformed lead level.
(Counter and Buchanan 2002)	BLL: 11.2–80.0 μg/dL	PTA: 0.25–8 kHz Bone conduction, BAER	30	17–55	Cross-sectional	There was no statistically significant relationship between BLL and pure-tone threshold at any frequency.
(Wu et al. 2000)	BLL: (mean): 56.9 μg/dl, ambient lead: 0.190 ± 0.331 mg/m^3, noise: 86 dBA	PTA: 0.5–8 kHz excluding 3 kHz	339	mean: ∼37	Cross-sectional	There is a significant correlation between a high, long-term Pb exposure index (i.e., duration of employment & ambient Pb levels) and decreased hearing ability.
(Szanto et al. 1999)	BLL of adults: 15–40 μg/dl; BLL of children: 20 and 70 μg/dl; BLL of reference groups: <15 μg/dl	PTA	147 152	20–50 7–12	Cross-sectional	There was a statistically significant decrease of the hearing threshold to 6 and 8 kHz in the exposed, as compared to the non-exposed women.
(Osman et al. 1999)	BLL: 19–281 μg/L	PTA: 0.5–8 kHz BAEP	155	4–14	Cross-sectional	BLL had a significant ($P < 0.001$) impact on hearing thresholds even at BLL <10 μg/dL.

(Buchanan 1999)	BLL of children: 33.4–118.2 μg/dl, BLL of adults: 19.2–55.7 μg/dl	DPOAE	14 5	5–14 17–51	Cross-sectional	No consistent correlation of DPOAEs with BLL was found.
(Farahat et al. 1997)	Maximum respirable Pb: 23.7 $\mu g/m^3$; BLL: 36.94 ± 4.36 μg/dL (mean ± SD); noise: up to 50 dBA,	PTA: 0.25–8 kHz	90	20–40	Cross-sectional	Significant association between hearing thresholds and BLL at 8000 Hz.
(Forst et al. 1997)	BLL: 1–18 μg/dl	PTA: 0.5–6 kHz	183	19–65	Cross-sectional	A statistically significant correlation between BLL and elevated hearing threshold at 4 kHz (P = 0.03); but not in other frequencies.
(Counter, Buchanan, et al. 1997)	BLL: 6.2–128.2 μg/dL (exposed group)	PTA: 0.25–8 kHz; ABR	107	4 months–15 years	Cross-sectional	No relation between BLL and auditory thresholds, neural transmission times or normal wave latencies.
(Schwartz and Otto 1991)	BLL: 5–18 μg/dL (mean in each study group)	PTA: 0.5–4 kHz	3,545	6–19	Cross-sectional	Pb was associated with an increased risk of hearing thresholds at 0.5–4 kHz. The relationships appeared to continue when BLL < 10 μg/dl. An increase of BLL, from 6 μg/dl to 18 μg/dl, was associated with a 2-dB loss in hearing at all frequencies.
(Schwartz and Otto 1987)	BLL: <1 to + 45 μg/dL	PTA: 0.5–4 kHz excluding 3 kHz	4,519	4–19	Cross-sectional	BLL is associated with increased hearing thresholds at 0.5–4 kHz (p < .0001).
(Counter, Vahter, et al. 1997)	BLL: 9.9–110 μg/dl (exposed), 3.9–12.0 μg/dl (unexposed); Hg (blood): 0.04-0.58 μg/dL	PTA: 0.5–8 kHz; ABR	82	4–15	Cross-sectional	Blood Hg and BLL were not associated with auditory function.
(Saunders et al. 2013)	Hg= 0.31 μg/g & Pb = 3.93 μg/g (in nails) - median	PTA: 0.5–4 kHz; DPOAE	89	9–78	Cross-sectional	PB is associated with DPOAE at 3&4 kHz but no relationship between Hg & HL.

in Tables 2–5. In some papers, exposure to more than one substance of interest was studied. These studies were grouped with either of the other substance(s).

Lead

Thirty-three epidemiological studies on the effects of exposure to lead on hearing impairment were eligible for final review including 29 cross-sectional studies. Blood Lead Level (BLL; N = 29) and Pure Tone Audiometry (PTA; N = 27) were the most frequently used assessment techniques for measuring exposure and outcome, respectively. Exposure to noise was evaluated and compared among high to low noise exposed groups or adjusted as a potential confounder in nineteen studies. Five of these studies measured personal or environmental noise levels while other studies primarily used self-reported noise exposure status. Fourteen studies did not evaluate potential effects of co-exposures to noise on hearing loss. Approximately 75% of studies (N = 25) provided evidence of statistically significant increased odds of hearing loss or a significant association between exposure to Pb and increased hearing thresholds (Schwartz and Otto 1987; 1991; Farahat et al. 1997; Forst et al. 1997; Osman et al. 1999; Szanto et al. 1999; Wu et al. 2000; Chuang et al. 2007; Counter et al. 2009; Hwang et al. 2009; Park et al. 2010; Galal et al. 2011; Shargorodsky et al. 2011; Abdel Rasoul et al. 2012; Saunders et al. 2013; Huh et al. 2016; Choi and Park 2017; Al-khfajy et al. 2018; Kang et al. 2018; Liu et al. 2018; Schaal et al. 2018; Cai et al. 2019; Xu et al. 2020). Among these studies, six papers identified a concentration or a quartile of BLL, that was associated with increased odds of hearing loss compared with the reference group (Hwang et al. 2009; Shargorodsky et al. 2011; Huh et al. 2016; Choi and Park 2017; Huh et al. 2018; Kang et al. 2018). One study found each 1 µg/dL increase in BLL increased odds of hearing loss 1.43 times (OR 1.43, 95% CI 1.03, 2.00) (Huh et al. 2016). Eight studies found no significant association between exposure to lead and hearing loss (Counter, Buchanan, et al. 1997; Counter, Vahter, et al. 1997; Buchanan 1999; Counter and Buchanan 2002; Buchanan et al. 2011; Counter et al. 2011; Choi et al. 2012; Alvarenga et al. 2015). Table 6 details the blood lead levels (in µg/dL), odds ratios, and frequencies for hearing impairment. It also includes blood lead concentrations identified as NOAEL or LOAEL based on the significance level of odds ratios. This information is also illustrated in Figure 2.

Based on five studies, blood lead ranges between 1–1.99 µg/dL (Shargorodsky et al. 2011) up to 2.148–2.822 µg/dL (Choi and Park 2017) were identified as NOAELs. Blood lead levels between 2 µg/dL (Shargorodsky et al. 2011) up to a range of 2.823–26.507 µg/dL (Choi and Park 2017) were identified as LOAEL. The LOAEL at 2 µg/dL was associated with an increased odds of hearing loss of 2.22 (95% CI 1.39–3.56) (Shargorodsky et al. 2011) while a blood lead range of 2.823–26.507 µg/dL was associated with an increased odds of hearing loss of 1.70 (95% CI 1.25–2.31) (Choi and Park 2017). The other study which could be used for deriving NOAEL and LOAEL values, used relatively higher BLLs as reference including a BLL of less than 4 µg/dL and BLL between 4 and 7 µg/dL. There were no significant associations between exposure and hearing loss at these levels. However, significant increased odds of hearing loss were observed at 3, 4, 6, and 8 kHz at concentration ≥7 µg/dL (Hwang et al. 2009). Other research comparing exposed to non-exposed groups or using cut off values for BLL found varying levels of BLL to be significantly associated with hearing loss including a median BLL of 4.94 ± 0.20 µg/dL (Liu et al. 2018), BLL between 3.61 and 7.40 µg/dL (Xu et al. 2020), BLL ≥5 µg/dL (Cai et al. 2019), and a BLL ≥10 µg/dl (Schwartz and Otto 1991).

Mercury

Nine studies on mercury were eligible for final review including eight cross-sectional studies and a case study. Blood mercury levels (N = 6) and PTA (N = 9) were the primary methods used to assess exposure and hearing impairment, respectively. One study adjusted for the effect of self-reported noise exposure status on the potential relationship between hearing test results and mercury levels. None of the other eight studies on mercury evaluated effects of co-exposures to noise on hearing loss. Four studies found no significant association between mercury exposure and hearing loss (Dutra et al. 2012; Maruyama et al. 2012; Saunders et al. 2013; Orlando et al. 2014). One study showed a significant correlation between blood Hg levels and hearing thresholds at 3 kHz in the right ear in children, but not adults (Counter et al. 1998). Similarly, another study showed Automatic Speech Recognition (ASR) thresholds in children exposed to an average HgB of 15.6 µg/L (range: 2.0–89 µg/L) increased significantly with HgB level but found no significant associations between HgB and hearing loss among adults (Counter et al. 2012). Other studies

showed an increased latency of peak III of the Brainstem Auditory Evoked Response (BAER) potentials at 40 Hz when Hg exposure exceeded 10 µg/g (Murata et al. 1999) and abnormal Auditory Brainstem Response (ABR) and inability to understand speech in case study of methylmercury poisoning (Musiek and Hanlon 1999).

Toluene

Twenty-six papers including 18 cross-sectional studies evaluated the effects of toluene exposure on hearing impairment. Twenty-three studies evaluated the auditory effects of co-exposures to toluene and noise. Twenty-two papers measured personal or environmental noise exposures or obtained data from previous noise assessments. In six studies, noise exposure was only used as a criterion for inclusion or exclusion of study participants while one study did not address the impact of exposure to noise and the outcome. Four studies showed a positive relationship between exposure to toluene and hearing impairment (Abbate et al. 1993; Morata, Fiorini, et al. 1997; Hsu et al. 2015; Staudt et al. 2019). One of these studies showed an increased odds of hearing loss (OR 1.76, 95% CI 1.00–2.98) for each microgram of hippuric acid per gram of creatinine and an increased odds of 4.4 (95% CI 2.50–7.45) for hearing loss for 2.5 µg/g creatinine of hippuric acid (Morata, Fiorini, et al. 1997). Sixteen other studies found significant differences in hearing thresholds among "solvent mixture", "noise and solvent mixture", "metals, solvents and noise", or "toluene and noise" exposed groups compared with controls, where toluene was one of the solvents comprising the solvent mixtures (Morata et al. 1993; Morata, Engel, et al. 1997; Sułkowski et al. 2002; Sliwińska-Kowalska et al. 2003; De Barba et al. 2005; Prasher et al. 2005; Sliwinska-Kowalska et al. 2005; Chang et al. 2006; Fuente and McPherson 2007; Rabinowitz et al. 2008; Fuente et al. 2009; Mohammadi et al. 2010; Metwally et al. 2012; Juárez-Pérez et al. 2014; Unlu et al. 2014; Schaal et al. 2018). Four studies found no association between toluene exposure and hearing loss (Morioka et al. 1999; Schäper et al. 2003; 2008; Pudrith and Dudley 2019) and two studies found no additional risk for hearing impairment among those exposed to noise and solvents or solvents only, where toluene was among the solvents (Hughes and Hunting 2013; Loukzadeh et al. 2014).

Styrene

Nineteen papers including 15 cross-sectional papers were eligible for final review on relationship between exposure to styrene and auditory function. Sixteen studies on styrene measured personal or environmental noise exposures or employed data from previous noise exposure assessments. Three of these studies used exposure levels only to screen study participants for eligibility while the remaining 13 papers evaluated the auditory effects of co-exposures to styrene and noise. Two other studies evaluated self-reported noise exposures for eligibility of participants and one study did not address the effect of noise exposure on hearing. About 63% of studies (N = 12) demonstrated a significant increased hearing loss from exposure to styrene (Muijser et al. 1988; Morioka et al. 1999; Morata et al. 2002; Sliwińska-Kowalska et al. 2003; Sliwinska-Kowalska et al. 2005; Johnson et al. 2006; Triebig et al. 2009; Zamyslowska-Szmytke et al. 2009; Morata et al. 2011; Sisto et al. 2013; Pudrith and Dudley 2019; Sliwinska-Kowalska et al. 2020) including increased odds of 3.9-fold (95% CI 2.4–6.2) (Sliwinska-Kowalska et al. 2005) and 5.2-fold (95% CI = 2.9–8.9) (Śliwińska-Kowalska et al. 2003) for hearing loss. One study showed that the odds ratio for hearing loss was 2.44 (95% CI, 1.01–5.89) for each millimole of mandelic acid per gram of creatinine in urine (Morata et al. 2002). Two other research found a positive relationship between exposure to a mixture of solvents including styrene and hearing impairment or reduced amplitudes of otoacoustic emissions (Sułkowski et al. 2002; Botelho et al. 2009). In five other studies no significant associations were found between exposure to styrene and hearing impairment (Sass-Kortsak 1995; Morioka et al. 2000; Hoffmann et al. 2006; Staudt et al. 2019) or exposure to solvent mixtures and hearing loss where styrene was one of the substances among the solvent mixture (Hughes and Hunting 2013).

Exposure to the four substances studied primarily affected hearing at medium to high frequency range. Lead exposure affected hearing thresholds predominantly in 3,000, 4,000, and 6,000 Hz frequencies (Hwang et al. 2009; Shargorodsky et al. 2011; Huh et al. 2016; Choi and Park 2017; Huh et al. 2018; Kang et al. 2018). Studies on styrene and toluene also showed exposure primarily affected hearing thresholds at medium to high range frequencies of 3–8 kHz (Muijser et al. 1988; Morata et al. 2002; Johnson et al. 2006; Triebig et al. 2009; Sisto et al. 2013) for styrene and 2–6 kHz for exposure to toluene concurrent with other solvent exposures (Prasher et al. 2005; Fuente

Table 3. Summary of research on exposures to mercury (N = 7). Two more studies on mercury are listed under Table 2.

Reference	Exposure	Outcome	No. of Participants	Age	Study Design	Main Findings
(Orlando et al. 2014)	Hg in hair: 6.89 ppm (mean)	PTA: 0.5–8 kHz, excluding 3 & 6 kHz; ABR DPOAE: 1-6 kHz CEOAE: 1-4 kHz	517	18.1–20.6	Cross-sectional	No association between MeHg exposure and HL.
(Maruyama et al. 2012)	Hg in hair > 100 μg/g	Tuning fork of 512 Hz and a ticking watch; phonation; etc.	103	31–63	Cross-sectional	Prevalence odds ratios of hearing impairment and mercury content in hair were not significant.
(Counter et al. 2012)	Hg (blood): 2.0–89 μg/L (children); 2.0–32 μg/L (adults)	PTA: 0.25–8 kHz, ASRT, ASRD	22 29	6–17 19–83	Cross-sectional	The ASR thresholds in children increased significantly with HgB level (rho = 0.433; p = 0.008). No significant associations between HgB and HL based on PTA.
(Dutra et al. 2012)	Hg in umbilical cord: 14.63 μg/L (median)	PTA: 0.25–8 kHz	90	8–10	Cross-sectional	No significant differences between groups in hearing thresholds.
(Musiek and Hanlon 1999)	Dimethylmercury poisoning	PTA, DPOAE, ABR	1	48	Case study	The patient showed inability to understand speech, yet relatively good hearing sensitivity for pure tones. DPOAE showed minimal deficits in each ear. The ABR was abnormal, indicating neural and/or central involvement.
(Murata et al. 1999)	Hg (in hair) children: 0.4 to 26.0 μg/g; Maternal: 1.1 to 54.4 μg/g	BAER, Neuro-behavioral Evaluation System	149	Not provided	Cross-sectional	The mean (+/-SD) latency of peak III of the BAE potentials at 40 Hz was increased by 0.128+/-0.047 ms when maternal hair-mercury levels exceeded 10 μg/g.
(Counter et al. 1998)	Hg (blood): 17.5 μg/L (mean)	PTA: 0.5–8 kHz	109	Not available	Cross-sectional	Correlation coefficients showed a significant relationship between B-Hg level and hearing level in children at 3 kHz in the right ear, and at no frequency for adults.

Table 4. Summary of research on exposures to toluene (N = 18), toluene and styrene (N = 7), and toluene and lead (N = 1).

Reference	Exposure	Outcome	No. of Participants	Age	Study Design	Main Findings
(Hsu et al. 2015)	Toluene: 100 – 350 ppm	PTA: 0.5–3 kHz, oVEMP, cVEMP,	18 exposed 18 non-exposed	61 ± 9 55 ± 7	Cross-sectional	50% of exposed ears had abnormal PTA average (>25 dB).
(Loukzadeh et al. 2014)	Toluene: 79.8 or 4.97 ppm, other solvents; noise: <75 dBA	PTA: 0.5–8 kHz	99	Not provided	Cross-sectional	No association between solvents exposure and HL.
(Juárez-Pérez et al. 2014)	Toluene: 1.1 – 495.9 ppm; other solvents; noise: 59.89–84.88 dBA	PTA: 0.125–16 kHz; bone conduction: 0.25–4 kHz; BAEP	161	22–64	Cross-sectional	Significant difference in 0.125–8 kHz PTA results between solvent exposed vs. unexposed R2 = 33% and 38%, ($p < 0.001$).
(Unlu et al. 2014)	Toluene: 26–36 mg/m^3 and other solvents; noise: 78–87 dBA	PTA: 0.5–8 kHz	588	19–63	Retrospective case control	HL was increased in solvent and noise exposed workers in 2–8 kHz range.
(Metwally et al. 2012)	Toluene: 142–182 mg/m^3, other solvents; noise: 69–87 dBa	PTA: 0.5–8 kHz	222	35–53	Retrospective case control	Higher prevalence of sensory neural hearing impairment (43%) in noise and solvents exposed group compared to noise only exposed group (24.3%).
(Mohammadi et al. 2010)	Toluene: 19–31 mg/m^3 and 3 other solvents; noise: 75–88 dBA	PTA: 0.5–8 kHz	411	~ 33 ± 6	Cross-sectional	Workers exposed to both solvents and noise had significantly increased odds of HL compared to only noise exposed (OR, 4.13; 95% CI, 2.59–6.58).
(Fuente et al. 2009)	Toluene: 0.001–131 ppm and methyl ethyl ketone; noise: 74–84 dBA	PTA: 0.5– 8 kHz and 12–16 kHz; dichotic digits test	110	21–56	Cross-sectional	Solvent exposure is significantly associated with PTA ($\beta = 0.285$, $P = 0.011$).
(Fuente and McPherson 2007)	Toluene: 25.72 mg/m^3 and other solvents; noise: only participants exposed to noise below 85 dBA were included	PTA: 0.25–8 kHz; HINT, DD, FS, PPS, RGD	100	18–55	Cross-sectional	Significant differences were noted for hearing thresholds at 1, 2, 3 and 6 kHz for the right ear ($p < 0.05$), and at 1, 2 and 3 kHz for the left ear ($p < 0.01$) between exposed vs. non-exposed groups.
(Schäper et al. 2008)	Toluene: 45 ± 17 vs. 10 ± 7 ppm (high vs. low exposed); noise: 82 ± 7	PTA: 0.125–12 kHz	333	38.1 ± 9.8	Prospective	Toluene exposure had no significant effect on hearing thresholds.
(Rabinowitz et al. 2008)	Toluene: 4.0 ± 5.9 ppm, xylene, and/or methyl ethyl ketone; noise: <82 and >88 dBa	PTA: 3–6 kHz	1319	<35	Prospective	Solvent exposure (OR = 1.87, CI 95% = 1.22–2.89, p = 0.004) was a risk factor for high frequency HL.
(Chang et al. 2006)	Toluene: 33, 107.6, and 164.6 ppm; noise: 67.9–90.1 dBA	PTA: 0.5–6 kHz	176	40.0 ± 9.7	Cross-sectional	The OR for HL for all toluene-noise exposed workers was 7.7 and 4.2 times greater than that for the noise-only group. The risk of HL at the exposure of 200–530 year ppm was highest among other toluene cumulative exposures (OR = 55.6; 95% CI, 9.7–317).

(*Continued*)

Table 4. Continued.

Reference	Exposure	Outcome	No. of Participants	Age	Study Design	Main Findings
(Prasher et al. 2005)	Toluene, benzene, n-hexane, xylenes, naphthalene, etc. all exposures were estimated. Personal noise exposure: 59.6 – 97.9 dBA	PTA: 0.5–8 kHz TOAE, ABR, ART, OKN and other tests	379	~47.4 ± 7.5	Cross-sectional	For solvents and noise group, significant differences were observed at 1, 4 & 6 kHz, but not at 0.5, 2, 3 & 8 kHz.
(De Barba et al. 2005)	Toluene: 0.05 ppm; benzene, xylene, butadiene; area noise: 68.2–91.8	PTA: 0.5–8 kHz; bone conduction: 0.5–4 kHz	172	25–57	Cross-sectional	Despite the low exposures to solvents and a moderate exposure to noise, 45.3% of workers had HL and 29.6% had STS.
(Schäper et al. 2003)	Toluene: 25.7 ± 20.1 ppm (printing) 3.2 ± 3.1 ppm (end process); noise: 81.1 ± 3.5 dBA (printing)	PTA: 0.125–12 kHz	333	24–56	Prospective	Toluene exposure and all interactions of the stratification factors did not show significant effects on the auditory thresholds.
(Morata, Fiorini, et al. 1997)	Toluene: 0.14 to 919 mg/m^3, Hippuric acid: <0.5 to >5.5 g/g creatinine, ethyl acetate, ethanol; noise: <80 to >91 dBA	PTA: 0.5–8 kHz; bone conduction: 0.5–4 kHz	124	21–58	Cross-sectional	The OR for HL was 1.76 for each gram of hippuric acid per gram of creatinine (95% CI 1.00–2.98). The OR for HL is 4.4 (95% CI 2.50–7.45) for 2.5 μg/g creatinine of hippuric acid (the biological index exposure (BEI)).
(Morata, Engel, et al. 1997)	Toluene: 11 ppm (aromatics plant), 13.2 ppm (maintenance); other aromatics; average noise: 87, 88 dBA	PTA: 0.5–8 kHz	438	Mean: ~40–44	Cross-sectional	The OR for HL were 2.4 times greater for groups from aromatics (95% CI 1.0–5.7), and 3 times greater for the maintenance group (95% CI 1.3–6.9).
(Morata et al. 1993)	Toluene: 10–70 ppm, xylene, benzene, methyl ethyl ketone and other chemicals; noise: 88–97 dBA	PTA: 0.5–8 kHz	190	Mean: 32–36	Cross-sectional	The adjusted relative risk estimates were 11 times greater (95% CI 4.1–28.9) for the noise and toluene group, and 5 times greater (95% CI 1.4–17.5) for the solvent-mixture group.
(Abbate et al. 1993)	Toluene: 97 ppm (exposed), hippuric acid: 2.7 g/l (average)	PTA: 0.25–8 kHz BAEP	40	30–40	Cross-sectional	Exposure to toluene is able to induce a statistically significant alteration in the electric responses with both 11 and 90 stimuli repetitions.
(Pudrith and Dudley 2019)	Toluene: (BMA); styrene (PHEMA): Q2: 0.495 ng/mL, Q3: 0.857 ng/mL, Q4: 1.69 ng/mL and MA	PTA: 4–8 kHz	849	20–69	Retrospective	PHEMA of 1.69 ng/mL (Q4 median) was associated with a HL mean of 2.49 dB. No significant association between BMA metabolite and HL.
(Staudt et al. 2019)	Toluene: 0.17 (ng/mL); and styrene 0.04 (ng/mL) - median (IQR) of PTA assessed) (blood levels)	PTA: 0.5–8 kHz (HL: >15 dB)	1,085–2,471	20–59	Cross-sectional	Toluene increased odds of high-frequency HL (OR 1.27, 95% CI 1.06–1.52). No association between styrene and HL.
(Schaal et al. 2018)	Toluene: 25 ppm, Pb: 0.03 mg/m^3 (exceedance fraction), noise	PTA: 0.5–6 kHz	1,266	24–75	Retrospective	The hearing threshold of high metals/ solvents/ noise group changed 2.1 dB more than reference group.

(Hughes and Hunting 2013)	Toluene & styrene (levels not provided); noise > 85 dB (exposed groups)	PTA: 2–4 kHz (HL: >10 dB)	503	25–>55	Retrospective	No additional risk was found for hearing loss among those exposed to noise and solvents or solvents only.
(Sliwinska-Kowalska et al. 2005)	Toluene: 54.4 ± 70.3 mg/m^3, styrene: 61.8 ± 51.9 mg/m^3, xylene, n-hexane; noise: 64–100 dBA	PTA: 1–8 kHz	1,117	20–66	Cross-sectional	OR of HL was 3.9 (95% CI 2.4–6.2) in case of styrene and 5.3 (95% CI 2.6–10.9) in case of n-hexane and toluene exposure.
(Sliwinska-Kowalska et al. 2003)	Toluene: 224.9 mg/m^3, styrene: 0.2–198.4 mg/m^3 ; acetone, dichloromethane and noise: 73.2 ± 5.3 (non-exposed); 89.2 ± 3.1 (styrene and noise)	PTA: 1–8 kHz; bone conduction: 1–4 kHz	513	20–60	Cross-sectional	In the styrene-only group, the OR of HL was 5.2-fold (95% CI = 2.9–8.9) greater than in the unexposed controls. In cases of styrene and toluene or styrene and noise groups, the OR increased up to the respective values of 13.1 (95% CI = 4.5–37.7) and 10.9 (95% CI = 4.9–24.2). In the subgroup coexposed to styrene, toluene, and noise, the odds ratio of hearing loss was as high as 21.5 (95% CI = 5.1–90.1).
(Sułkowski et al. 2002)	Toluene (blood): (0.95—56.27 μg/dm^3); styrene (MA): (0.1—3.0 mg/h) – mixture of solvents; noise: 60–75 dBA	PTA, ART, OAE, TEOAE, DPOAE	101	22–58	Cross-sectional	The solvent mixture-induced HL was a sensorineural high frequency (above 1 kHz) loss of various degrees with significantly reduced amplitudes of otoacoustic emissions.
(Morioka et al. 1999)	Toluene: 0.8–98.8 ppm, styrene: 0.1–91.6 ppm, acetone, methanol – MA: ≥0.3 to > 1 g/l, hippuric acid; noise: 53.0–95.0 dBA.	PTA: 0.5–8 kHz excluding 3 & 6 kHz; upper limit of hearing: 0.5–25 kHz	115	36.3 ± 12.6 (mean ± SD)	Cross-sectional	A significant correlation between individual percentiles of the upper limit of hearing and airborne styrene levels. No relationship between toluene exposure and HL.

Table 5. Summary of research on exposures to styrene (N = 12). Seven more studies on styrene are listed under Table 4.

Reference	Exposure	Outcome	No. of Participants	Age	Study Design	Main Findings
(Sisto et al. 2013)	Styrene: 4.9 – 150 mg/m^3; noise (mean): 87.7 & 83 dBA	PTA: 0.5–8 kHz; TEOAEs: 0.5–5 kHz; DPOAEs: 1–6.4 kHz	28	28–47 24–46	Cross-sectional	Hearing of workers exposed to styrene & noise and styrene only was different for frequencies ≥ 1.6 kHz and 2.5 to 5 kHz, respectively.
(Morata et al. 2011)	Styrene: 309 mg/m^3; noise: 70–84 dBA	PTA: 0.25–8 kHz	1,620	18–72	Cross-sectional	The audiometric thresholds of styrene-exposed workers were significantly poorer than those in published standards.
(Triebig et al. 2009)	Styrene (blood): 53.9 ± 68.6 to 108 ± 109 μg/dl; MA; PGA; MA + PGA; CEI MA + PGA; LWAE MA + PGA; area noise: 70–96 dBA	PTA: 0.125–16 kHz TEOAE: 1–4 Khz & 1.4, 2, 2.8, 4, 5.7, and 8 khZ	248	~37.9 ± 11	Cross-sectional	Elevated odds ratio for HL at 3–6 kHz among group exposed to styrene > 30 ppm for more than 10–26 years. There is no dose-response relationship between threshold and exposure data.
(Zamyslowska-Szmytke et al. 2009)	Styrene: 38 8 ± 24 mg/m^3; noise: 79 ± 3 dBA	PTA: 0.125–8 kHz; gaps-in-noise, frequency pattern test and duration pattern test	59	24–64	Case control	Styrene-exposed subjects exhibited significantly worse frequency and duration pattern tests and hearing thresholds than non-exposed subjects at 0.5, 1, 2, 4, 6, and 8 kHz for the right ear, and at 0.25, 0.5, 1, 2, 4, 6, and 8 kHz for the left ear.
(Botelho et al. 2009)	Styrene, acetone, resin, cobalt (exposures not provided); noise: 80.5–99.5 dBHL	PTA: 0.5–8 kHz; bone conduction: 0.5–4 kHz	155	18–50	Retrospective case control	Significantly higher rate of HL in noise and chemical exposed group (18.3%).
(Johnson et al. 2006)	Styrene: 0.2 – 96 mg/m^3; noise: 69–116 dBA	PTA: 3–8 kHz DPOAE, CRA, speech, etc.	313	21–65	Cross-sectional	There were poorer thresholds in styrene-exposed groups for the worst ear at 4 and 8 kHz and for both ears at 6 kHz.
(Hoffmann et al. 2006)	Styrene: MA ± PGA: 656 ± 639 mg/g creatinine	PTA: 0.25–8 kHz; TEOAE	32	41 ± 8	Cross-sectional	Chronic styrene exposures are not associated with a significant hearing dysfunction.
(Morata et al. 2002)	Styrene: 0.2–96 mg/m^3, MA: 0.9 (mmol/g creatinine); noise: 79–89 dBA	PTA: 1–8 kHz	313	20–64	Cross-sectional	The OR for HL was 2.44 for each millimole of mandelic acid per gram of creatinine in urine (95% CI, 1.01–5.89).
(Morioka et al. 2000)	Styrene: 2.9–28.9 ppm, methanol and methyl acetate; noise: 58-92 dBA	PTA: 0.5–8 kHz, excluding 3 & 6 kHz	54	20–68	Cross-sectional	The correlation between hearing and styrene concentrations was not significant ($p > 0.1$).
(Sass-Kortsak et al. 1995)	Styrene: 73.5 mg/m^3 (mean); noise: 87.2 dBA (mean)	PTA	299	Mean: 36.6	Cross-sectional	No evidence for a chronic styrene-induced effect on hearing acuity.
(Muijser et al. 1988)	Styrene: up to 150 mg/m^3 (area) and up to 700 mg/m^3 (personal); noise: 70–104 dBA	PTA: 0.25–16 kHz	153	19–55	Cross-sectional	Significant difference on hearing thresholds at high frequencies between the least exposed and the most exposed workers.
(Sliwinska-Kowalska et al. 2020)	Styrene: 1.6 – 147.9 mg/m^3, acetone, dichloromethane; mean lifetime noise exposure: 74–85 dBA	PTA: 1–16 kHz; bone conduction: 1–4 kHz DPOAEs, ABR	279	20–58	Cross-sectional	Significance was observed for control/styrene contrast (CI 2.660, 8.8831). Styrene-exposed workers present hearing thresholds around 5.9 and 4.8 dB higher than control-group in the right and left ear, respectively.

Table 6. Odds ratio of hearing loss by lead exposure.

Reference	NOAEL / LOAEL	Blood lead level (μg/dL) / Quartile#	Hearing loss frequency (kHz)	Odds ratio (95% CI) – Gender
(Huh et al. 2018)	NOAEL	1.780–2.248 / Q2	4 (right ear)	1.33 (0.81–2.17)
	LOAEL	2.248–2.723 / Q3	4 (right ear)	1.72 (1.06–2.80)
	–	2.723–3.396 / Q4	4 (right ear)	1.77 (1.08–2.88)
	–	3.396–26.507 / Q5	4 (right ear)	1.65 (1.02–2.68)
(Kang et al. 2018)	NOAEL	1.56 ± 0.01 Q1	3, 4, & 6	Reference
	LOAEL	2.22 ± 0.01 / Q2	3, 4, & 6	1.368 (1.006–1.859) - males
	–	2.82 ± 0.01 / Q3	3, 4, & 6	1.402 (1.005–1.955) - males
	–	4.22 ± 0.08 / Q4	3, 4, & 6	1.629 (1.161–2.287) - males
	NOAEL	2.11 ± 0.01 / Q3	3, 4, & 6	1.009 (0.695–1.464) - females
	LOAEL	3.03 ± 0.03 / Q4	3, 4, & 6	1.502 (1.027–2.196) - females
(Choi and Park 2017)	NOAEL	2.148–2.822 / Q3	3, 4, & 6	1.35 (1.00, 1.81)
	LOAEL	2.823–26.507 / Q4	3, 4, & 6	1.70 (1.25, 2.31)
(Huh et al. 2016)	NOAEL	1.798–2.277 / Q3	2, 3, & 4	1.31 (0.97, 1.77)
	LOAEL	2.278–2.919 / Q4	2, 3, & 4	1.41 (1.04, 1.92)
	–	2.920–26.507	2, 3, & 4	1.52 (1.11, 2.10)
(Shargorodsky et al. 2011)	NOAEL	1–1.99	3, 4, 6, & 8	1.20 (0.80–1.80)
	LOAEL	≥2	3, 4, 6, & 8	2.22 (1.39–3.56)
(Hwang et al. 2009)	NOAEL	4–7	3, 4, 6, & 8	2.11 (0.94–4.77) (for 6 kHz)
	LOAEL	≥7	3, 4, 6, & 8	3.06 (1.27–7.39) (for 6 kHz)

and McPherson 2007; Unlu et al. 2014; Staudt et al. 2019).

Cross-jurisdictional comparisons

A summary of cross-jurisdictional comparisons in terms of enforceable regulations, information provided on ototoxic chemicals and control measures is provided in Table 7.

Canada

None of the Canadian jurisdictions have set enforceable regulations on ototoxic chemicals. WorkSafeBC has published a systematic review evaluating the potential (causal) ototoxicity of styrene exposure (WorkSafeBC 2016). The review concludes: "At present, there is no evidence to support a causal association between exposure to styrene and ototoxicity" and that it is not possible to develop a TLV to styrene exposure indicative of the potential to cause hearing loss (WorkSafeBC 2016).

United States

The Occupational Safety and Health Administration (OSHA) of the U.S. has not established regulations specific to ototoxic chemical exposures, however, it has provided a Safety and Health Information Bulletin, entitled "Preventing Hearing Loss Caused by Chemical (Ototoxicity) and Noise Exposure" (OSHA-NIOSH 2018). General information on ototoxic properties of chemicals are provided including potential additive or synergistic effects, current limited research, classifications, and examples of ototoxic chemicals and type of industries likely to have exposure. The OSHA Technical Manual (Section III: Chapter 5) also provides a summary of research findings particularly on solvents exposure and hearing loss (OSHA 1990).

United Kingdom

The *Control of Noise at Work Regulations 2005* by the Health and Safety Executive of U.K. sets out that "An employer who carries out work which is liable to expose any employees to noise at or above a lower exposure action value shall make a suitable and sufficient assessment of the risk from that noise to the health and safety of those employees, and the risk assessment shall identify the measures which need to be taken to meet the requirements of these Regulations." The regulation also sets out that "The risk assessment shall include consideration of… as far as is practicable, any effects on the health and safety of employees resulting from the interaction between noise and the use of ototoxic substances at work…." In section 5(3) of the guidance, several measures are recommended for management of exposure to ototoxic chemicals. The guidance sets out that "studies have suggested that some chemicals, particularly solvents, can act in combination with noise to cause further damage to hearing than the noise or chemical exposures alone. Where there are likely to be such mixed exposures in your workplace, you should note this within your risk assessment and monitor developments on these issues."

Australia

The "Managing Noise and Preventing Hearing Loss at Work Code of Practice" established by Safe Work Australia outlines hearing loss risks from exposure to

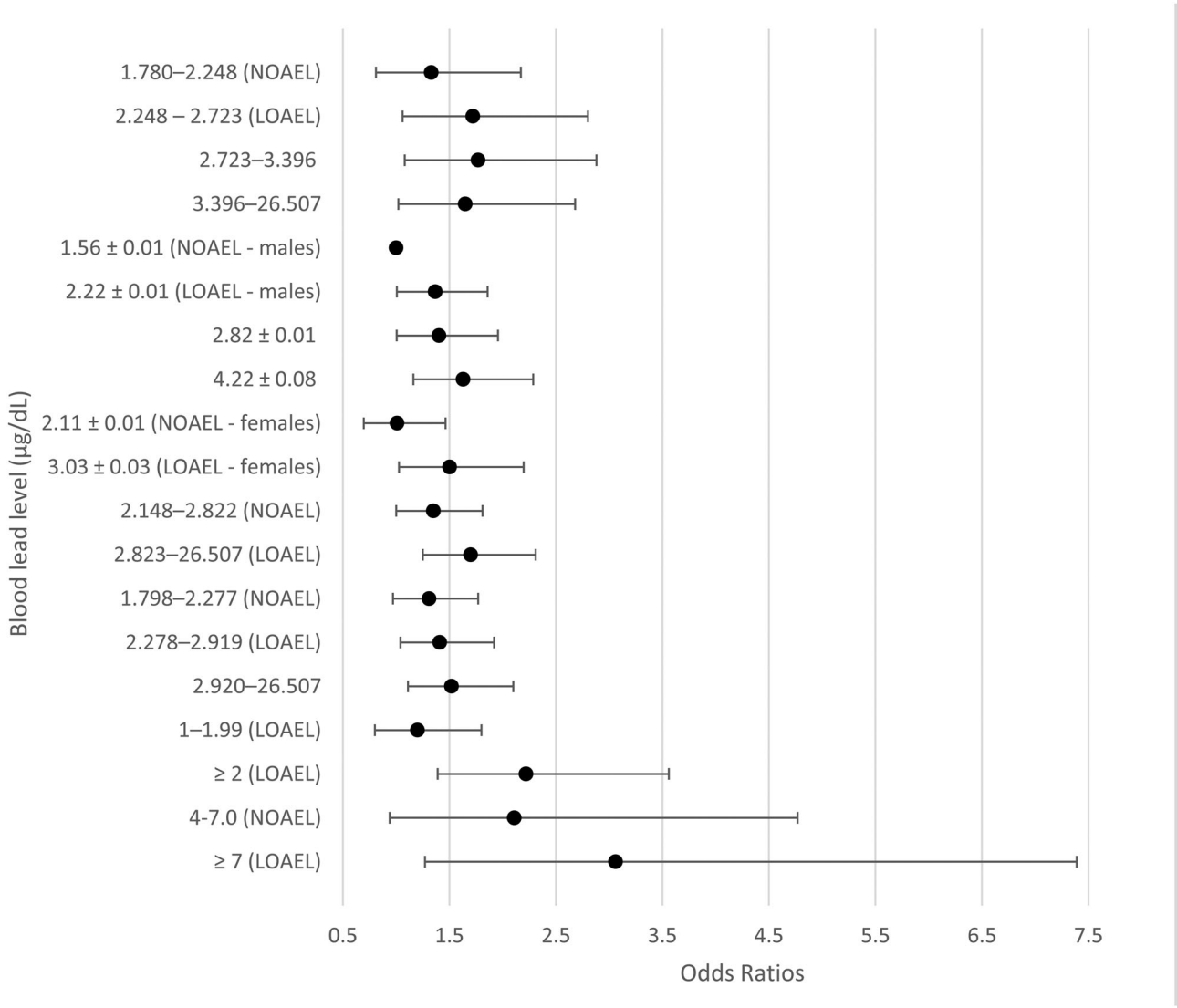

Figure 2. Forest plot of odds ratios for hearing impairment associated with blood lead levels and identified NOAELs and LOAELs (Huh et al. 2018, Huh et al. 2016, Hwang et al. 2009, Shargorodsky et al. 2011, Choi and Park 2017, Kang et al. 2018).

ototoxicants, mechanism of damage, a list of ototoxicants, and recommendations for control. The code of practice states that "exposure standards for chemicals and noise do not take account of the increased risk to hearing caused by ototoxic substances."

Control measures

Preventive and control measures suggested by OSHA include reviewing SDSs, substitution, isolation and enclosures, use of ventilation, use of chemical-protective equipment to prevent absorption through the skin, wearing hearing protection, and using audiometric testing to control exposures to ototoxic chemicals. The guideline section of *Control of Noise at Work Regulation 2005* established by the Health and Safety Executive advocates three precautions when the use of chemicals or vibrating equipment might increase the risk of hearing damage to any of the employees. These recommendations include: (a) consider whether you can limit their exposure by reducing the time spent on particular tasks; (b) monitor the health surveillance results of those workers; and (c) increase the frequency of health surveillance for those workers. The "Managing Noise and Preventing Hearing Loss at Work Code of Practice" by Safe Work Australia suggests monitoring hearing with regular audiometric testing for workers exposed to ototoxic substances in the following circumstances:

- where the airborne exposure is greater than 50% of the workplace exposure standard for the substance (without regard to respiratory protection worn), regardless of the noise level and

Table 7. Summary of cross-jurisdictional comparisons in relation to exposure to ototoxic chemicals.

Country	Regulatory Agency – Regulation / Report / Code of Practice	Regulation*	Information*	Control Measures*
Canada	WorkSafeBC – Evidence-Based Practice Group - Styrene Exposure and Its Potential Effect on Hearing, Vision and Lung Function	–	✓	–
United States	Occupational Safety and Health Administration (OSHA) – Safety and Health Information Bulletin -Preventing Hearing Loss Caused by Chemical (Ototoxicity) and Noise Exposure	–	✓	✓
United Kingdom	Health and Safety Executive (HSE) – *The Control of Noise at Work Regulations 2005*	✓	–	✓
Australia	Safe Work Australia - Managing Noise and Preventing Hearing Loss at Work Code of Practice 2015	–	✓	✓

*__Regulation:__ Legally enforceable regulation(s) on exposure to ototoxic chemicals; __Information:__ Information provided on ototoxic chemicals e.g., substances identified as ototoxicants and industries more likely to have exposure to ototoxicants, effects on hearing, etc.; __Control Measures:__ Control measures specified for prevention and/or management of exposure to ototoxic chemicals.

- ototoxic substances at any level and noise with $L_{Aeq,8h}$ greater than 80 dB(A) or $L_{C,peak}$ greater than 135 dB(C).

The Australian code of practice also states that "until revised standards are established, the daily noise exposure of workers exposed to any of the substances listed in Table A1 of the code be reduced to 80 dB(A) or below. They should also undergo audiometric testing and be given information on ototoxic substances."

Discussion

Approximately, 75% of current epidemiological evidence (N = 25) regarding auditory effects induced by lead exposure consistently demonstrated that lead is ototoxic to humans. Based on five studies, the highest blood lead levels which were associated with no significant increases in hearing thresholds between the exposed groups and controls (NOAELs) ranged from 1–1.99 μg/dL (Shargorodsky et al. 2011) up to 2.148–2.822 μg/dL (Choi and Park 2017). On the other hand, the lowest blood lead levels at which significant increases in hearing thresholds between the exposed population and controls (LOAELs) were identified was 2 μg/dL (Shargorodsky et al. 2011) up to 2.823–26.507 μg/dL (Choi and Park 2017). The ACGIH recommends a Biological Exposure Index (BEI) of 200 μg/L (20 μg/dL) for lead in blood (ACGIH 2019), which according to findings of this research, would not protect workers from hearing threshold shifts. Based on the NOAEL and LOAELs identified, a BEI of 2 μg/dL is recommended for prevention of hearing impairment from lead exposure.

The ACGIH in its documentation for Audible Sound recommends performing annual audiometric testing for workers exposed to more than 20% of the TLV for potentially ototoxic chemicals (ACGIH 2018). This indicates that the current TLVs may not be protective against hearing impairment from exposure to ototoxic chemicals and aligns with the recommended BEI for lead exposure in this research, which is well below the current BEI for blood lead.

Similar to the findings of this study, in a review of 38 lead-based ototoxicity studies, Carlson and Neitzel concluded that the epidemiological evidence from 24 human studies provided stronger support compared with data from the 14 animal studies (Carlson and Neitzel 2018). The authors stated that NIOSH has lowered their definition of an elevated BLL in adults to 5 μg/dL in 2018 (NIOSH 2017) and recommended amending the medical provisions of 29 CFR § 1910.1025 to require a hearing examination to assess the possible influence of Pb on auditory outcomes and assist in investigating the relationship between lead exposure and hearing loss (Carlson and Neitzel 2018).

While four studies showed reduced auditory function from mercury exposure, evidence was not sufficient to determine the exposure level below which hearing thresholds were not affected. About 70% of studies on toluene and styrene demonstrated that exposure to these substances are associated with increased hearing thresholds. However, 70% of studies on toluene (N = 18) and 16% of studies on styrene (N = 3) compared hearing loss among groups of participants exposed to "solvent mixture" or "noise and solvent mixture", and not necessarily on groups exposed to a single agent. Nevertheless, there is sufficient evidence to support the ototoxicity of

toluene and styrene and preventive measures need to be taken to protect workers from hearing impairment. The NOAEL and LOAEL for hearing loss from styrene and toluene exposure could not be identified based on current research available. However, two studies showed each microgram of hippuric acid per gram of creatinine (toluene urinary metabolite) and each millimole of mandelic acid per gram of creatinine (styrene urinary metabolite) are associated with increased odds of hearing impairment of 1.76 (Morata, Fiorini, et al. 1997) and 2.44 (Morata et al. 2002), respectively. The ACGIH has recently incorporated the OTO notation for Styrene in its 2020 TLVs and BEIs publication (ACGIH 2020) and recommends a maximum concentration of 400 mg/g creatinine for mandelic acid plus phenylglyoxylic acid in urine at the end of work shift as one of the BEIs for styrene, however, it has not established a BEI for hippuric acid (ACGIH 2019). The molecular weight of mandelic acid is 152.15 g/mol or 152.15 mg/mmol, the concentration linked with increased risk of hearing loss based on one of the above studies by Morata et al. (2002), which is lower than the ACGIH recommended BEI for mandelic acid plus phenylglyoxylic acid. Although evidence based on current studies may not be sufficient to propose BEIs, in light of these findings, new research should be undertaken to further evaluate dose-response relationships and propose biological exposure indices to protect against hearing impairment effects of exposure to styrene and toluene.

The above findings are in congruence with the results of research conducted by the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG) entitled "Occupational exposure to chemicals and hearing impairment" (Johnson and Morata 2010). The research evaluated experimental animal studies to identify NOAELs and LOAELs for auditory effects from exposure to chemicals as well as epidemiological evidence to generate or test relevant hypotheses. Epidemiological research supported findings of animal studies that toluene, styrene, and lead are ototoxic. Human evidence also showed that exposure to 10–50 ppm of toluene, 3.5–22 ppm of styrene, blood lead concentrations of 28–57 µg/dl and blood mercury levels close to the biological exposure limits are associated with auditory effects while interaction with noise was either not clear or not studied.

Limitations

Cross-sectional design was predominantly used in studies on substances of interest including 85% of studies on lead (N = 21), 89% of studies on mercury (N = 8), 69% of research on toluene (N = 15), and 79% of styrene research (N = 19). These studies are associated with limitations for sampling without regard to exposure or outcome or establishing cause–effect relationships. Some studies used more than 1000 participants including 27% of studies on lead (N = 9), 15% of studies on toluene (N = 4) and 16% of studies on styrene (N = 3). The studies used to derive NOAELs and LOAELs for hearing loss based on BLL recruited between 2,387 (Huh et al. 2018) and 7,596 (Huh et al. 2016) participants. In contrast, the number of study participants in 48% of studies on lead (N = 16), 46% of studies on toluene (N = 12), 42% of studies on styrene (N = 8), and 89% of studies on mercury (N = 8) was less than 200. These studies might be associated with a lower power for statistical analysis. Blood lead level was the main method used for assessment of exposure to lead in about 87% of studies (N = 29). The half-life of lead in adult human blood is estimated to be between 28 days (Griffin et al. 1976) and 36 days (Rabinowitz et al. 1976). Thus, it reflects recent lead exposures but is not indicative of chronic, cumulative lead exposures. Lead may be stored for long periods in mineralizing tissue such as teeth and bones (ASTDR 2017). Therefore; bone lead level is a more reliable marker of cumulative lead exposure (Spivey 2007). Lead stored in bones may be released into the bloodstream and contribute significantly to an individual's current BLL (ASTDR 2017) which is another limitation arising from grouping studies with different patterns and levels of exposure. Studies on workers may be associated with healthy worker selection bias and therefore associated with limitations for general populations.

Four of the six studies which were used for deriving NOAEL and LOAEL values for BLL used the same study population from The Korea National Health and Nutrition Examination Survey, KNHANES from 2010–2013 (Saunders et al. 2013; Huh et al. 2016; Choi and Park 2017; Kang et al. 2018). However, the study conducted on U.S. adolescents where NHANES cohort from 2005–2008 was used (Shargorodsky et al. 2011) also found blood lead levels within similar ranges ($\geq$2 µg/dL) affect hearing impairment. Moreover, such data are comprehensive and nationally representative, drawn from a large and diverse sample of participants.

Uncertainty factor is used to allow for uncertainties in extrapolation from a small group of individuals to a large population, including possibly undetected effects on particularly sensitive members of the population, inter-individual differences, synergistic effects

of multiple exposures, the seriousness of the observed effects, and the adequacy of existing data (WHO 1994). However, in this research uncertainty factors were not considered for proposing BEI values. Otherwise, lower values might have been obtained. Auditory function is affected by many factors including human lifestyle differences, e.g., smoking, recreational activities, use of ototoxicant drugs or toxic substance history, middle ear diseases, physical trauma, genetic variations, and other confounding factors, all of which may not have been adjusted in some of the studies.

Cross-jurisdictional comparisons

The cross-jurisdictional comparisons showed that standards have not currently been developed to take account of increased risk of hearing impairment from exposure to ototoxic chemicals. The Health and Safety Executive regulation requiring that the effects of interaction between noise and use of ototoxic substances on the health and safety of workers be considered during risk assessment of noise exposure may be incorporated by other regulatory agencies as a requirement during evaluation of risks of noise exposure. As evidence shows, exposure to some chemicals affects auditory functions even when noise exposures are below occupational limits. The recommendation of the Code of Practice on Managing Noise established by the Australian Government to lower noise exposure limits to LAeq of 80 dBA for 8 hr for workers at risk may be adopted to prevent and control hearing loss risks. Other measures may include performing audiometric testing based on OSHA and Safe Work Australia recommendations or monitoring and increasing the frequency of health surveillance according to the Health and Safety Executive guideline, which are in line with the recommendations of the ACGIH to prevent hearing disorders (ACGIH 2019). Further precautions may need to be taken in case of exposure to impulse noise per OSHA recommendations as it is associated with particular risk for hearing loss.

Conclusion

The majority of studies on lead, styrene, and toluene showed significantly increased risks of hearing loss from exposure to these substances. Although 70% of studies on toluene and 16% of studies on styrene compared auditory function between "solvent mixture" or "noise and solvent mixture" exposed groups and controls, and not necessarily on groups exposed to a single agent. Therefore, the exclusive effect of toluene or styrene exposure on hearing could not be determined based on these studies. Based on 5 studies on lead, blood lead ranges up to 2.148–2.822 μg/dL were identified as NOAELs. Further research is needed to establish dose-response relationships between exposure to toluene and styrene and hearing loss. With a view to limitations on the current level of knowledge on exposure levels to ototoxic chemicals associated with hearing thresholds, consideration should be given to adopting the precautionary principle. The increased risk of hearing loss from exposure to lead, styrene, and toluene should be taken into consideration during assessment of noise exposures. Enforceable regulations specific to ototoxic chemical exposures should be established for prevention of hearing loss.

Recommendations

A BEI of 2 μg/dL blood lead level is recommended for protection against ototoxic effects of exposure to lead. Regulations that can be established may include requirements to evaluate the effects of exposure to ototoxic chemicals during noise exposure risk assessments, performing audiometric testing for exposed workers regardless of level of noise exposure and controlling exposures to ototoxic chemicals through all routes of entry. While other jurisdictions do not make a recommendation to lower noise exposure limits, based on the "Managing Noise and Preventing Hearing Loss at Work Code of Practice" by Safe Work Australia, the noise exposure of workers exposed to ototoxic substances may be reduced to 80 dB(A) or below, during an 8-hr shift.

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