Evidence updates on risk factors for occupational noise-induced hearing loss (ONIHL)

Update 1: exposure to solvents with or without noise

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Executive summary

This update reviews recent evidence on occupational exposure to organic solvents, with or without noise, as a risk factor for hearing loss. It takes a pragmatic ‘best evidence’ approach and is a partial update of ACC’s 2010 epidemiological review of hearing loss risk factors.

The update concludes that evidence from systematic reviews/meta-analyses and to a lesser extent cohort studies published 2009-2018 indicates that occupational exposure to certain organic solvents, with or without noise, is a risk factor for hearing loss. These findings are in alignment with ACC’s 2010 review and with major international reviews.

Of the three main solvents discussed in this update, evidence of ototoxicity is strongest for styrene and toluene. It is weaker and more limited for xylene. There is evidence that styrene and particularly toluene have synergistic effects with noise.

No validated clinical tools or guidelines on assessing hearing loss associated with solvent exposure were identified. However, international agencies have released guidance on assessing and monitoring the hearing of people exposed to ototoxic solvents in the workplace.

1 Introduction

1.1 Background

It is widely accepted that occupational noise can damage workers' hearing. Since the 1990s, evidence has accumulated that hearing can also be affected by exposure to chemicals. Certain organic solvents, heavy metals and other substances commonly encountered in the workplace have been identified as ototoxic. In addition, some of these chemicals may interact with noise to exacerbate hearing loss. Changes in hearing thresholds from exposure to such agents appear to compound those produced by exposure to noise alone. This combined exposure is described as having a synergistic effect on hearing[1].

ACC is updating its 2011 publication *Assessment of occupational noise-induced hearing loss for ACC: a practical guide for otolaryngologists*[2]. The guide was informed by a set of evidence reviews summarising what was known at the time about various aspects of occupational noise-induced hearing loss (ONIHL). These included an epidemiological review of risk factors for ONIHL (Zhang, 2010)[3], which examined the role of age, genetics and exposure to agents other than noise, for example organic solvents and carbon monoxide.

Regarding solvent exposure, the epidemiological review drew the following conclusions:

- Exposure to solvents appeared to be a risk factor for hearing impairment
- Exposure to styrene at relatively low levels was associated with workplace hearing impairment at a low level of noise exposure
- Some studies found evidence of a potential synergistic effect from combined exposure to solvents (i.e. styrene and toluene) and noise; findings indicated that noise and solvent exposure combined may present a greater hearing loss risk than exposure to solvents or noise alone
- Some solvents were associated with hearing impairments at low (0.5, 1 and 2 kHz for toluene) or high (6-8 kHz for styrene) frequencies, which are not typically seen in working age people with noise-induced hearing loss.

The 2010 review found that much of the evidence on occupational solvent exposure came from studies with cross-sectional designs rather than more rigorous and meaningful cohort studies. No clinical tools or guidelines to assess hearing loss in association with occupational solvent exposure were identified.

1.2 Purpose

The Expert Advisory Group (EAG) overseeing the update of the 2011 guide has asked Research to examine recent evidence on risk factors for hearing loss. This evidence update focuses on exposure to organic solvents. The purpose is to identify and briefly review recent evidence on the following solvents, with or without noise, and comment on whether the evidence base has changed since the 2011 guide was released:

Table 1: list of organic solvents of interest (taken from the 2011 ACC guide, p. 26)

CHEMICALS IN THE WORKPLACE AFFECTING HEARING	
Organic solvents	Workplaces where these might be encountered
Toluene	Manufacture of chemicals, paint and lacquers, pharmaceuticals, rubber products, fibreglass products, food containers, carpet; oil refining, aircraft operation, boat building
Styrene	
Xylene	

Dimethylformamide	Manufacture of clothing and textiles
Dinitrobenzene	Dry cleaning Paint manufacture Manufacture of rubber items

Most of the evidence identified by the 2010 epidemiological review related to styrene or toluene.

2 Methods

2.1 Identifying the evidence

To identify published research studies in the clinical and broader scientific literature, the following databases and information sources were searched in March and April 2018:

- Embase on the Ovid platform
- Medline & Medline In-Process on the Ovid platform
- PubMed
- Science Direct
- Google Scholar

The search strategy is shown in the appendix. Studies were also sourced from members of the EAG.

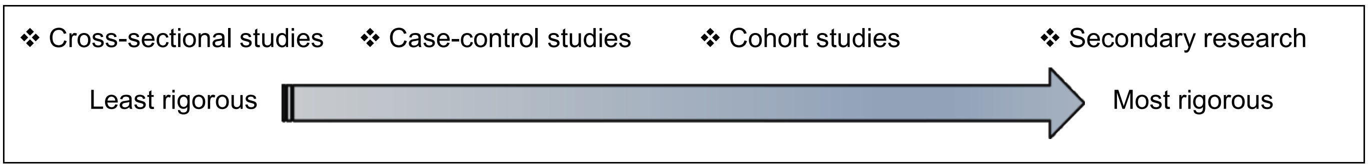
In addition, searches were carried out to identify any international post-2010 clinical tools or guidelines for assessing hearing loss associated with occupational solvent exposure.

2.2 Selecting the studies

For inclusion in this evidence update, studies were required to meet the following selection criteria:

- Study types:
  - primary epidemiological research investigating associations between hearing loss and workplace exposure to the solvents of interest with or without noise, e.g. observational studies with cohort (longitudinal), case-control or cross-sectional design
  - secondary research, e.g. meta-analyses or systematic reviews
  - published in English, 2009 (to pick up any studies missed by the 2010-2011 work) to March 2018
  - conference presentations and abstracts were included if they contained sufficient detail on methods, population and outcomes
- Study participants: working age adults exposed to the risk factors of interest
- Study outcomes: hearing loss diagnosed/assessed by accepted methods

For each exposure, a "best evidence" approach was taken, i.e. where a reasonable volume of higher quality research studies was available, less rigorously designed studies were excluded. The study design hierarchy was as follows:



2.3 Extracting the evidence

The findings are described in section 3. Evidence from research studies meeting the selection criteria was extracted in evidence tables in sections 3.1 and 3.2. Full critical appraisal and quality assessment were not carried out. Data extraction for primary studies (see section 3.2) was based on the evidence table format used in the 2010 epidemiological review.

3 Findings

Studies identified: the search identified 36 papers. The majority reported primary research such as cross-sectional or case-control studies (21 papers) or cohort studies (three papers). The primary studies were based in a range of countries including two involving Australian populations and three involving United States populations. Four secondary research studies were identified. The remaining papers were mainly narrative literature reviews, commentaries and other material useful for background information.

In addition to research studies published in clinical and scientific journals, several relevant reviews and guidance documents by international agencies were also identified. These are outlined in section 3.3.

Solvents included: the studies evaluated styrene, toluene, xylene, solvent mixtures and other substances such as jet fuel. No recent papers were found on ONIHL risk associated with dimethylformamide or dinitrobenzene. Earlier findings from animal studies described in the 1997 literature review by Cary et al[4] suggested that these two solvents may be ototoxic; however, this has not been confirmed by more recent evidence.

Best evidence approach: as a reasonable volume of secondary research and cohort studies was identified, this update focuses on evidence from these higher quality sources.

3.1 Secondary research

Hormozi et al (2017) carried out a systematic review and meta-analysis of hearing loss risk associated with exposure to organic solvent mixtures with and without noise[5]. The review included 15 studies. Xylene, toluene and styrene were among the main mixture components; the review did not assess risk associated with individual solvents. The analysis found evidence of increased risk of hearing loss, even at quite low solvent concentrations, and synergistic effects with noise. Adjusted odds ratio estimates of the strength of association between exposure and risk of developing hearing loss were 2.05 for solvent exposure alone and 2.95 for concurrent noise and solvent exposure. Even exposure to lower concentrations of solvent mixtures (i.e. below regulatory limits) appeared to be associated with increased risk of developing hearing loss (odds ratio 1.37). Examination of dose-response relationships found that risk increased with level and duration of solvent exposure and with the number of different solvents encountered.

Pleban et al (2017) conducted a systematic review of the effects of occupational styrene exposure on auditory function[6]. The review included 13 studies. Typically, sample sizes were small and studies reported no to mild associations between styrene exposure and auditory dysfunction. However, four studies investigating styrene combined with other organic solvent mixtures and noise found that such combined exposures may be more ototoxic than noise alone.

Vyskocil and colleagues developed an extensive toxicological database for the province of Quebec that identified potentially ototoxic workplace chemicals. In 2012 they published a "weight of evidence" review detailing their methods and findings[7]. The review combined information from human and animal studies, with human data given more weight in the overall assessment. It considered 224 human and animal studies covering 29 chemicals and is the largest review identified in this evidence update. Recommendations on the solvents of interest were as follows:

- Styrene: based on evidence from human and animal studies, styrene should be regarded as ototoxic. There is weak evidence of an ototoxic interaction with noise in workers, but further well designed studies are needed to draw firm conclusions.
- Toluene: based on evidence from human and animal studies, toluene should be regarded as an ototoxic agent that can interact with noise to induce more severe hearing loss than noise alone. There is convincing evidence of ototoxic interaction after combined exposure to toluene and noise in workers and in rats.
- Xylenes: evidence from animal studies suggests that the *p*-xylene (para-xylene) isomer, and consequently mixtures of xylene isomers, should be regarded as possibly ototoxic at concentrations typically encountered in the workplace. Further studies on the exposure of workers to xylene isomers are needed to draw definitive conclusions. No research was identified on interactions between xylene isomers and noise.

Warner et al (2015) carried out a literature review on the effects of combined exposure to noise and JP-8 jet fuel (or its aromatic solvent components including toluene and xylenes) on the central auditory nervous system[8]. The aim was to provide a better understanding of the risks faced by military aviation maintenance workers in the Australian Defence Force. The review had systematic search and study selection methods and presented a narrative summary of study findings, but did not attempt any statistical analysis. It included six primary studies with relatively small sample sizes. The review concluded that there is an association between aromatic solvents (including jet fuel) in combination with noise and central auditory dysfunction/hearing loss. However, as the evidence base is small and study designs and findings vary, the research provides only a partial understanding of the risks of combined exposure to noise and jet fuel or its components.

Table 2: summary of secondary research - systematic reviews/meta-analyses on styrene, toluene, xylene and solvent mixtures

Design & description	Selection criteria	Included studies & populations	Outcomes/assessment	Findings	Conclusions/ recommendations
Hormozi et al 2017[5] Systematic review and meta-analysis of hearing loss (HL) risk associated with work exposure to organic solvent mixtures* with or without concurrent noise exposure *main components were xylene, toluene & styrene; the analysis	Epidemiological studies that: • Calculated odds ratios/relative risk estimates for increased HL risk; or • Considered noise- & solvent-induced HL as outcome measures, using pure tone	15 studies were included: • 2 cohort and 13 cross-sectional studies • 7,530 participants in total (6% female) Settings: paint & lacquer, dockyard, oil, aviation, aluminum, automobile & petrochemical industries, also air force reserve	Included studies used pure tone audiometry or medical records to assess hearing The review: • Defined HL as an average hearing threshold >25dB in at least one ear (250-8,000 Hz) • Used a three-level exposure index to assess solvent exposure levels	Adjusted odds ratio estimates of associations between exposure (compared to a non-exposed reference group) and HL risk were as follows: • 2.05 for solvents only (95% CI 1.44 - 2.9) • 2.95 for solvents with concurrent noise (95% CI 2.1 - 4.17)	There is evidence of an increased risk of developing HL for workers exposed to organic solvents, even at quite low concentrations; the risk rises as level and duration of solvent exposure increases If exposure is accompanied by noise, it will exacerbate the extent of HL, i.e. there is evidence of a synergistic effect with noise

did not assess risk associated with individual solvents	audiometry to assess hearing levels	Exposures included: toluene (13 studies), xylene (13), styrene (3) Populations: Iran (2), Poland (4), USA (3), South America (2), Egypt (2), Denmark (1)	• Considered participants exposed to noise levels ≥85dB as noise-exposed All studies adjusted HL for confounding variables such as age and non-work noise	The meta-analysis showed significant associations between HL and level and duration of solvent exposure	
Pleban et al 2017[6] Systematic review of the effects of occupational exposure to styrene, styrene mixtures or styrene with noise, on auditory function	Peer-reviewed primary studies (any design) on adults in occupational settings: • Minimum sample size n=10 • Carried out in developed countries • Published 1990-2015 in English Military populations excluded	13 studies were included: • Two prospective cohort, nine case-control and two cross-sectional • Sample sizes ranged from 18 to 1,620 (4,854 participants in total) Settings included fibreglass manufacturing (6), boat building (3), plastic/ fibre-reinforced manufacturing (2), yacht shipyard/plastics factory (1) and paint and varnish industry (1) Studies examined exposure to: styrene only (4), styrene with noise (5) and styrene and/or other solvents with noise (4)	The review classified hazardous exposures as follows: • Styrene only, 15-600ppm • Styrene, 50-200ppm or 0-309mg/m^{3,} and noise, >69dBA • Styrene and/or other solvents, 0.2-450mg/m^3, and noise, >64dBA Across included studies, several assessment methods were used, including personal sampling, measures of hearing thresholds, transient evoked optoacoustic emissions and; otoneurological test batteries (2 main types) Pure tone audiometry was one of the primary hearing assessment methods	Study findings ranged from no to mild associations between styrene exposure and auditory dysfunction Four studies investigating styrene with other organic solvent mixtures and noise suggested such combined exposure may be more ototoxic than exposure to noise alone The review noted that: • Relatively small sample sizes may have contributed to the lack of association (6 of the 13 included studies had sample sizes ≤101) • Variability of hearing assessments used across different studies makes outcome comparison problematic	There is limited evidence on the effect of styrene on auditory function in humans However, findings suggest that chronic styrene-exposed individuals should be routinely evaluated with a comprehensive audiological test battery to detect early signs of auditory dysfunction Existing styrene exposure limits may be insufficient to prevent styrene-induced HL; further research is recommended in high risk workplaces (boat construction, fibreglass manufacturing) Measures to reduce exposure to noise should be considered at noise levels ≥85dBA
Vyskocil et al 2012[7] "Weight of evidence" review of ototoxic potential of 695 industrial chemicals listed by the Quebec OHS regulator	Human studies, all designs, on exposure & noise levels realistically encountered in the workplace[1] Animal studies[2]	224 studies covering 29 substances • 44 studies evaluated combined exposure to noise and chemicals Styrene alone: 31 studies (12 human, 19 animal); styrene plus noise: 10 studies (6 human, 4 animal) Toluene alone: 34 studies (3 human, 31 animal); toluene	Included studies used a wide variety of tests to assess HL, e.g. pure tone audiometry, electrocochleography The reviewers developed a system of "weight of evidence" qualifiers to rank the evidence from included studies	Of the 29 substances, 7 were identified as ototoxic or potentially ototoxic Styrene: should be regarded as ototoxic; further research is necessary to draw conclusions about interaction with noise Toluene: should be regarded as an ototoxic agent that can also interact with noise to induce more severe HL Xylenes: animal studies suggest	Evidence from human and animal studies suggests that: • Styrene & toluene are ototoxic (as are lead and trichloroethylene) • Toluene interacts with noise to induce more severe HL than noise alone • *p*-xylene is possibly ototoxic at concentrations encountered in occupational settings (ditto

[1] Criteria for human studies: 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 chemical exposure.
[2] Criteria for animal studies: up to 100 times the 8-h TWA OEL or CV for chemical exposure.

		plus noise: 11 studies (4 human, 7 animal) Xylene alone: 6 studies (1 human, 5 animal)		that *p*-xylene and consequently mixtures of xylene isomers are possibly ototoxic; no studies identified on interaction with noise	ethyl benzene & *n*-hexane)
Warner et al 2015[8] Literature review on the effects of noise & JP-8 jet fuel (or its aromatic solvent components) on the central auditory nervous system	Human studies published in English language, peer reviewed journals up to 2014	6 papers published 2005-2009 on work exposure to: • JP-4 jet fuel (1) • Solvent components inc. toluene & xylene (5) • Noise <85dBA (3) or >85dBA (3) Sample sizes ranged from 7 to379 (total 714 participants)	Included studies used a range of methods to assess hearing; 4 used pure tone audiometry The review summarised study findings, but did not attempt to statistically analyse or pool them	Results suggest there is an association between aromatic solvents, including jet fuel, in combination with noise and central auditory dysfunction/HL	The evidence base is small and available evaluative studies have differing designs and variable findings The evidence provides only a partial understanding of the effects of combined noise & jet fuel exposure on the central auditory nervous system in military aviation maintenance workers

3.2 Primary research

Hughes and Hunting (2013) conducted a retrospective cohort study on 503 US Air Force reserve personnel exposed to noise and/or organic solvents (toluene, xylene, styrene, benzene, and JP-8 jet fuel)[9]. Hearing loss was found to be significantly associated with age, duration of follow-up (mean 3.2 years) and noise exposure. Linear regression indicated that hearing decreased by 0.04 dB for every decibel increase in noise level, or by 0.4 dB for every 10 dB increase. Hearing worsened by 0.06 dB with every year increase in age at first study audiogram and by 0.25 dB for every year increase in follow-up time during the study period. Regarding solvent exposure, no associations were found and no interactions with noise were detected. Solvent exposure levels were low to moderate in this study.

The prospective cohort study by Marlenga et al (2012) examined associations between a range of occupational and recreational exposures and early stage hearing loss in 392 young workers in the American Midwest[10]. The primary hearing loss outcome was ∆HF (maximal change in hearing acuity at high frequencies). The study examined associations between ∆HF and different types of noise and chemical exposures (e.g. solvents, thinners, fuel vapours). Exposure histories were based on participants' self-reports. Over the 16-year study period, changes to hearing acuity exceeding 15 dB at high frequencies were observed in 42.8% of male and 27.7% of female participants. Analysis of risk factors in the male participants showed that hearing loss was more significantly associated with recreational noise exposure, particularly from gunshots and chainsaws, than with occupational noise exposure overall. There was a significant association with exposure to fuel vapours, but it is difficult to draw conclusions as the chemical exposures were not described in detail. The analysis did not distinguish between occupational and recreational chemical exposures.

A recent US retrospective cohort study by Schaal et al (2018) examined the effects of toluene, xylene, lead, cadmium and arsenic on hearing compared to noise alone[11]. Shipyard workers (n=1266) with at least five years' worth of audiograms were assigned to four groups according to the levels of noise and chemicals they had been exposed to over the 11-year study period. Statistical analysis showed that overall the (1) high metals/high solvents/high noise, (2) high metals/low solvents/high noise and

(3) high metals/high solvents/low noise groups exhibited hearing that was, on average, 3.3 dB worse than hearing in the (4) low metals/low solvents/high noise reference group across the 2000, 3000, and 4000 Hz range. Across the 500 to 6000 Hz frequencies, the (1) high metals/high solvents/high noise group recorded a hearing change 2.1 dB greater than the (4) low metals/low solvents/high noise reference group. The study concluded that simultaneous exposure to high levels of metals, solvents and noise damage hearing more than exposure to noise alone. The specific effects of solvents were not explored separately.

Table 3: summary of primary research - cohort studies on styrene, toluene, xylene and solvent mixtures

Study & design	Population	Study group(s)	Confounders controlled?	Results	Comments
Hughes & Hunting 2013[9] Retrospective cohort study on the effects of noise & solvent exposure on US Air Force Reserve personnel	Personnel exposed to noise with/without solvents (toluene, styrene, xylene, benzene, JP-8 jet fuel)	503 reserves (94.6% male) with available reference & annual audiograms grouped into 4 exposure profiles: noise (≥85dBA); solvents; noise + solvents; no exposure Participants were followed for a mean of 3.2 years 66% were aged ≥35 at the time of their 1st study audiogram	Age	HL risk factors determined using logistic & linear regression; stratified analysis used to assess interaction with exposures The incidence of HL was relatively low in this study HL was significantly associated with age at 1st study audiogram, length of follow up time & exposure to noise No additional risk was found for exposure to solvents, either with or without noise	Effects of noise exposure were relatively weak Use of hearing protection was not evaluated Solvent exposure levels were low (i.e. below established occupational exposure limits) Uncontrolled confounders & misclassification of employment status (full vs. part time) may have affected the results
Marlenga et al 2012[10] Prospective cohort study of associations between a range of occupational & recreational exposures and early stage HL in young workers	Young people taking part in a follow up to a randomised controlled trial of hearing conservation measures for US high school students	392 young people (68% male) exposed to a range of occupational & recreational exposures, e.g. noise, gun shots, ototoxic chemicals Participants were aged 12-16 when first evaluated and were followed up for 16 years Occupational noise exposures occurred in agricultural, construction & manufacturing settings Chemical exposures included fuels/fuel vapours and solvents/thinners	Smoking Use of hearing or chemical protection Gender	Primary outcome ΔHF = maximal hearing acuity change at high frequencies (3, 4 or 6kHz) from baseline to follow up Changes to hearing acuity exceeding 15dB at high frequencies were detected in 42.8% of men and 27.7% of women Risk factors for NIHL were analysed in men only Risk increased in association with higher exposure to noise & chemical exposures Strength of associations between exposures and ΔHF were expressed as odds ratios Statistically, the most significant exposures were gunshots (OR 3.05), chainsaws (OR 3.27) and fuel vapours (OR 2.41) Compare with all occupational noise OR 1.05 (not statistically significant)	Noise exposures were grouped and analysed as recreational or occupational, but chemical exposures were not Noise and chemical exposure histories were based on self-reports Generalisability may be limited to similar populations (young, US Midwest, commonly working in agricultural jobs)
Schaal et al 2018[11] Retrospective cohort	US shipyard workers exposed to different levels of solvents	1266 workers with ≥5 years of audiograms available over the	In line with NIOSH guidelines, audiograms were	Subjects averaged 9.6 audiograms each, covering 6.7- 8.2 years of the study period	Conclusion: simultaneous exposures to high concentrations of solvents,

study on effects of exposure to chemicals vs. noise alone on hearing	(toluene and/or xylene), heavy metals (lead, cadmium and/or arsenic) and noise	study period (2004-2015) Subjects were divided into 4 groups according to their level of exposure (high/low) to the agents of interest Exposures of interest classified as "high": • Noise ≥85dBA • Toluene ≥25ppm • Xylene ≥3ppm Mean age per group ranged from 47 to 51 years	not age adjusted Mean ages were comparable across the exposure groups	Mean hearing changes were calculated according to frequency & exposure group: • Mann-Whitney tests showed hearing in the 2000-4000Hz & 500-6000Hz range was significantly worse in the high metals/high solvents/high noise group (n=291) compared to the low metals/low solvents/high noise reference group (n=37) (p=0.014) • Compared to the reference group, hearing was on average 3.3dB worse in the other 3 groups over the 2000, 3000 and 4000Hz range Across the 500-6000Hz frequencies: • The high metals/high solvents/high noise group recorded a hearing change of 2.1dB higher than the reference group • The high metals/high solvents/low noise group & high metals/low solvents/high noise group both exhibited a 1.7dB higher hearing change than the reference group	heavy metals & noise appear to damage hearing more than exposure to noise alone Large & stable sample, but the reference group was small (n=37, 2.9% of total study group) Effects of solvents were not analysed separately

3.3 Other research

3.3.1 Reviews by international agencies

Two key publications were identified:

European Agency for Safety and Health at Work review on combined exposure to noise and ototoxic substances (Campo et al 2009)[12]

This 2009 literature review used a "weight of evidence" approach to classify potentially ototoxic substances and assess interactions with workplace noise. Evidence available at the time consisted mainly of animal studies plus some epidemiological studies on workers in various industries; human data was given more weight. The review recommended that styrene, toluene, *p*-xylene and several other industrial chemicals and pharmaceuticals should be classified as "confirmed ototoxic agents" and therefore be prioritized for risk reduction measures if present in the workplace. Conclusions on combined exposure were more guarded; however, the review noted that emerging evidence from cross-sectional studies suggested that solvents may exacerbate noise-induced hearing damage even where noise levels are below permissible limits.

Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals review (Johnson and Morata 2010)[13]

In 2010 the Nordic Expert Group on health risks from chemicals released a literature review on occupational chemical exposure and hearing impairment. It was undertaken as part of a collaborative effort to agree occupational exposure limits for Denmark, Sweden, Norway and Finland. The review categorized the solvents of interest to this update as follows:

- Styrene and toluene were classified as Category 1, i.e. *"Human data indicate auditory effects below or near the existing occupational exposure limits (OELs). There are also robust animal data supporting an effect on hearing resulting from exposure".* The lowest exposure levels associated with hearing loss were 3.5-22 ppm for styrene and 10-50 ppm for toluene. Interactions with noise were not clear in humans.
- Xylenes were classified as Category 2, i.e. *"Human data are lacking, whereas animal data indicate an auditory effect below or near the existing OELs"*. Animal studies found that *p*-xylene was ototoxic at high levels and that mixtures of xylene isomers and ethylbenzene were more ototoxic than ethylbenzene alone. No evidence was found on interactions with noise.
- Solvent mixtures were classified as Category 3, i.e. *"Human data are poor or lacking. Animal data indicate an auditory effect well above existing OELs".* However, several occupational studies have reported effects on the auditory system.

3.3.2 International guidance on assessment & monitoring

Currently there is insufficient data to develop reliable occupational exposure limits for most ototoxic substances. Standard audiometric tests, e.g. pure tone audiometry, cannot distinguish between hearing impairment caused by chemical exposure or by noise[14]. Some authors have proposed alternative tests and assessment tools that may allow better understanding and earlier detection of the effects of combined exposure[15], but further research is necessary to validate these methods.

Several international agencies have made recommendations on assessing and monitoring hearing in workers exposed to ototoxic substances with or without noise. Recommendations for Australasia and the US include:

WorkSafe New Zealand 2014 good practice guidelines on preventing noise induced hearing loss on farms[16]

The WorkSafe guidelines briefly explain that some workplace substances and prescription medicines are ototoxic. However, they do not identify or list substances of concern or make specific recommendations about testing or monitoring worker exposed to ototoxins. The guidelines simply recommend that employers:

- Eliminate or reduce exposure to solvents, pesticides or asphyxiants
- Follow doctors' instructions on noise exposure for any employees taking ototoxic drugs.

Safe Work Australia 2015 code of practice[17]

The code of practice recommends that hearing is monitored with regular audiometric testing where workers are exposed to:

- Listed ototoxic substances where airborne exposure levels (without regard to respiratory protection worn) are greater than 50% of the national exposure standard for the substance, regardless of noise levels

- Ototoxic substances at any level plus noise with $L_{Aeq,8h}$[3] greater than 80 dB(A) or $L_{C,peak}$[4] greater than 135 dB(C).

The code of practice lists three groups of ototoxic substances (solvents, heavy metals and asphyxiates and others) commonly encountered in the workplace. Listed solvents include styrene, toluene and xylene.

Australian Institute of Occupational Hygienists (AIOH) 2016 position paper[18]

The AIOH broadly supports Safe Work Australia's 2015 recommendations, but notes that it can be difficult to find specific information about ototoxicity, as this information is not generally provided in safety data sheets. Therefore, instead of listing *substances* of concern, the AIOH lists *at-risk occupations* and recommends that workers in these industries be included in annual audiometric testing programs.

US National Institute of Occupational Safety and Health (NIOSH) and Occupational Safety and Health Administration (OSHA) 2018 guidance[14]

A joint safety bulletin issued by NIOSH and OSHA in March 2018 presents a concise guide to preventing hearing loss caused by chemical and noise exposure. It warns that the synergistic effects of some ototoxic solvents may exacerbate noise-induced hearing loss even if noise levels are below permissible limits. The bulletin advises that, although OSHA standards only require audiometric testing at the noise action level (i.e. an 85 dB eight-hour time-weighted average), testing may identify early signs of hearing loss in workers exposed to ototoxic chemicals at lower levels of noise.

American College of Occupational and Environmental Medicine (ACOEM) 2012 guidance[19]

The ACOEM's guidance statement on occupational hearing loss recommends that exposure to ototoxic agents including styrene, toluene and *p*-xylene may act in synergy with noise and should be considered when evaluating sensorineural hearing loss.

4 Discussion

Overall, recent evidence from systematic reviews and cohort studies indicates that solvent exposure is a risk factor for hearing loss. This supports the findings of ACC's 2010 risk factor review[3] and of major international reviews[12, 13]. Of the three main solvents of interest, the evidence is strongest for styrene and toluene; it is weaker and more limited for the *p*-xylene isomer. There is evidence that styrene and especially toluene have synergistic effects with noise. Evidence that xylene exerts a synergistic effect is currently lacking.

No validated clinical tools to assess hearing impairment associated with solvent exposure were identified. However, some international agencies have released guidance on assessing and monitoring workers exposed to ototoxic solvents with or without noise.

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[3] $L_{Aeq,8h}$ is the eight-hour equivalent continuous A-weighted sound pressure level in decibels, determined in accordance with AS/NZS 1269.1. It relates to the total amount of noise energy a person is exposed to in the course of their working day. It takes account of both the noise level and the length of time the person is exposed to it. An unacceptable risk of hearing loss, without concurrent solvent exposure, occurs at LAeq,8h values above 85 dB(A).

[4] $L_{C,peak}$ is the C-weighted peak sound pressure level in decibels, determined in accordance with AS/NZS 1269.1. It usually relates to loud, sudden noises such as a gunshot or hammering. $L_{C,peak}$ values above 140 dB(C), without concurrent solvent exposure, can cause immediate damage to hearing.

The quality of the evidence

Because a "best evidence" approach was used, the update focused on systematic reviews and cohort studies. However, this limited the coverage of primary research, as relatively few cohort studies are available. The implications of excluding cross-sectional studies are discussed in section 5 below.

Assessment of exposure to a single organic solvent is difficult because workers tend to be exposed to mixtures of substances at varying compositions and concentrations over time[7]. Some studies included in the update examined a range of exposures and were not able to draw firm conclusions about individual solvents[10, 11]

the largest review identified in the update - Vyskocil et al 2012[7] - considered evidence from animal as well as human studies. The two international reviews also included findings from animal studies[12, 13]. Extrapolating the results of animal studies needs to be done with caution, as frequency ranges of hearing and metabolisation of chemicals is different in animals and humans. In addition, concentrations of solvents used in animal studies tend to be high.

Quantifying and characterizing hearing damage due to solvent exposure

Epidemiological studies have provided some evidence on the nature and degree of solvent-related hearing damage. Some studies included in ACC's 2010 review suggested that solvents were associated with hearing impairments at lower (toluene) and higher (styrene) frequencies than typically seen in workers with noise-induced hearing loss[3]. The literature review by Campo et al noted that several clinical and epidemiological studies on solvent exposure have provided evidence of "poor hearing thresholds beyond the traditional 4 kHz noise-related audiometric notch"[15].

Most of the studies included in this update have focused on estimating the strength of associations between exposure and hearing loss risk, in terms of odds ratios for example, rather than on quantifying solvent-related hearing damage. The cohort study by Schaal et al found that, across the 500 to 6000 Hz frequencies, workers exposed to high levels of metals, solvents and noise recorded a hearing change 2.1 dB higher than a reference group of workers with low chemical and high noise exposure[11]. However, the effects of solvents (toluene and xylene) were not examined separately. The cohort study by Hughes and Hunting found that that hearing decreased by 0.04 dB for every decibel increase in noise level, but detected no association between hearing loss and solvent exposure[9].

Other studies with cross-sectional designs have reported the following findings:

- A US study of noise-exposed construction apprentices (n=393) estimated that self-reported regular exposure to solvents (e.g. styrene, toluene) was associated with a 0.6 dB per year increase in hearing thresholds at 4 kHz[20].
- A Taiwanese study (n=174) found that elevated mean hearing thresholds of 25- 39 dB were more prevalent in workers exposed to toluene and noise than in those exposed to noise alone[21]. Average hearing loss peaked at 32.6 dB in workers with high exposure to toluene and the impact was greatest at lower frequencies.
- A large Korean cross-sectional study (n=30,072) found that adjusted hearing loss increments were significantly higher in workers exposed to organic solvents and occupational noise (4.43 dB, CI 3.43–5.42) than in those exposed to noise alone (2.06 dB, CI 1.75–2.37)[22].

Emerging areas of interest: solvent mixtures

ACC's 2010 epidemiological review found that exposure to solvent mixtures was a risk factor for hearing loss with potential interaction with noise exposure[3]. The Nordic Expert Group review, also published in 2010, noted that human data on solvent mixtures was limited; however, evidence of effects on the auditory system was emerging from occupational studies[13].

The update identified one systematic review/meta-analysis published in 2017 that examined the effects of combined exposure to noise and mixed organic solvents[5]. Interestingly, this review found that risk of hearing loss increased with the number of different solvents encountered, as well as with level and duration of exposures.

5 Limitations of the evidence update

The update took a "best evidence" approach and excluded cross-sectional and case-control studies from the evidence tables. The rationale is that, where a reasonable number of secondary studies are available, these incorporate and consolidate the findings of less rigorous primary studies, which can therefore be excluded. The "best evidence" approach focuses on higher quality research and is useful where there are time constraints. Given that most studies on the ototoxicity of workplace chemicals have been cross-sectional studies, taking this approach may have caused some evidence to be missed. However, although cross-sectional studies provide a snapshot of potential associations with risk factors at a point in time, they are less effective in investigating causal relationships over time than cohort studies.

Due to time constraints, the update did not carry out full critical appraisal of included studies. In addition, it focused solely on those solvents identified as ototoxic or potentially ototoxic in the 2011 ACC guide. It should be borne in mind that there is evidence to suggest that other solvents, for instance trichloroethylene[5], may be ototoxic[7, 12].

6 Conclusions

Overall, recent evidence from systematic reviews and cohort studies indicates that exposure to certain organic solvents, with or without noise, is a risk factor for hearing loss. This conclusion supports and builds upon the findings of ACC's 2010 epidemiological review of risk factors[3]. It also aligns with the findings of two major international reviews[12, 13].

Of the three main solvents of interest, evidence of ototoxicity is strongest for styrene and toluene. Evidence is weaker and more limited for xylene, i.e. the *p*-xylene isomer.

There is evidence that styrene and especially toluene have synergistic effects with noise. Evidence that xylene exerts synergistic effects is currently lacking.

This update identified no validated clinical tools to assess hearing impairment associated with solvent exposure. However, some international agencies have released guidance on assessing and monitoring hearing in workers exposed to ototoxic solvents with or without high levels of noise.

[5] An industrial cleaning and degreasing agent. Used in the dry-cleaning industry until it was largely replaced by tetrachloroethylene (also known as perchloroethylene or PERC) in the 1950s. Use for spot cleaning persisted up until the early 2000s.

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Appendix: search strategy

The following strategy was developed for the Medline database on the Ovid platform. The search terms and syntax were adapted for use in the other databases and web-based information sources:

1. Hearing Loss, Noise-Induced/
2. exp Hearing Loss/
3. Noise, Occupational/ or ototoxic$.mp.
4. *Occupational Diseases/
5. exp Occupational Exposure/
6. Occupational Injuries/
7. *Noise/
8. 3 or 4 or 5 or 6 or 7
9. 2 and 8
10. 1 or 9
11. limit 10 to (english language and humans and yr="2009 -Current")
12. Chemically-Induced Disorders/
13. ci.fs.
14. exp Toluene/
15. exp Styrenes/
16. exp Xylenes/
17. exp Dinitrobenzenes/ or exp Dimethylformamide/
18. exp Solvents/ or (toluene or styrene$ or xylene$ or dimethylformamide or dinitrobenzene$).mp
19. or/12-18
20. 11 and 19