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Review

Occupational Co-Exposures to Noise and Chemicals—Review of Evidence and Regulatory Perspective †

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Abstract: The potential for harmful synergistic effects of workplace noise and chemical exposure is well-established. However, it is less conclusive whether such effects could still be seen if operators were complying with the relevant exposure standards for noise and/or chemicals. Bearing a regulatory perspective, this literature review explored whether any trends in the effects of combined exposure to noise and toxic chemicals could be established. A literature search was undertaken in seven databases, using key search terms on the combined effects of occupational noise and chemical exposures. A total of 1742 articles were identified, among which 82 were assessed in greater detail. Results in animals demonstrated a synergism of styrene, toluene and carbon disulfide when noise is delivered as a repeated 'impulse'. Other evidence suggested that noise, although at high levels, was responsible for systemic toxicity in organs other than hearing or nerves. Another significant observation was the early signs of hearing loss associated with mixed solvent exposures and noise, each below the respective occupational exposure limits (OELs). Based on these findings, we wondered whether current workplace exposure standards for noise give adequate protection against damage to hearing for workers exposed to chemicals like styrene or toluene. Additionally, they questioned whether compliance with airborne exposure standards and noise levels gave adequate protection for chemicals with a 'Skin' notation.

Keywords: combined exposures; combined effects; occupational noise; noise effects; toxic substances; chemicals; exposure standards

1. Introduction

Noise-induced hearing loss continues to be a major contributor to workplace harm. Anecdotal information from Return To Work South Australia (RTWSA) suggested over A$30 million was paid out in the first quarter of the 2023 financial year in claims related to occupationally-related hearing loss in South Australia. Furthermore, there is emerging evidence that noise also contributes to other forms of ill health or harm in the workplace, such as stress, elevated blood pressure (and associated co-morbidities), and poor communication, which trigger workplace accidents [1].

In 1997, a review [2] was published following concerns amongst some industries (such as printing) that the then workplace controls may not be adequately protecting against ill-health effects: The concern being the possibility of a potentiation of the adverse effects of noise together with exposure to various toxic chemicals encountered in workplaces. A similar concern was raised in a 2012 epidemiology survey, suggesting regulatory consideration of synergism [3]. In summary, at that time (1997) the amount of human and animal data available on the various chemicals implicated was limited, and there was no clear evidence of potentiation (additive or otherwise) at levels of noise and/or toxic chemicals

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where operators were complying with the relevant occupational exposure levels (OELs) for either. It is unclear whether such a trend still exists today and if it would bear regulatory implications for hazard assessments.

In Australia, regulatory workplace exposure standards (WES) are set by SafeWork Australia as maximum permissible limits that should not be exceeded to mitigate the risk of illness and disease from exposure to workplace hazards. Workplace exposure standards are often listed as an 8-h time-weighted average (TWA) to reflect average exposure levels over an eight-hour working day, for a five-day working week and sometimes, as a short-term exposure limit (STEL) to reflect the exposure level to a workplace hazard over a 15-min period. Under the Australian Work Health and Safety (WHS) Regulations, employers must comply with noise exposure limits of 85 dB(A) for an 8-h day and the peak exposure limit of 140 dB(C) [1]. Similarly, chemicals have designated WESs to ensure that exposures in the workplace do not result in ill health. Additionally, in recently agreed but not yet fully-implemented guidance, certain chemicals have also been identified with an 'Oto' label, advising that the chemical is potentially ototoxic, thus can be damaging to hearing function [1]. A list of such potentially ototoxic chemicals and their associated Australian WES is given in Table 1.

Table 1. List of 17 chemicals with potential ototoxicity concern identified by Cary et al. (1997) [2] and their respective Australian Workplace Exposure Standards (WES) and other advisory information [1].

Substance	Australian WES (8-h TWA †) January 2024	Australian WES (8-h TWA †) October 2024 ++	Other Advisory Information (January 2024)	Other Advisory Information (October 2024) ++
Acrylonitrile	2 ppm (4.3 mg/m^3)	No exposure limit	Carc 1B Sk, Sen	DSEN Sk Restricted carcinogen
Aluminium oxide	10 mg/m^3	10 mg/m^3		
Cadmium and compounds	0.01 mg/m^3	0.001 mg/m^3	Some compounds sensitising	Oto
Chromium VI compounds	0.05 mg/m^3	No exposure limit	Carc 1A Sen	DSEN Sk Restricted carcinogen
Carbon Disulfide	10 ppm (31 mg/m^3)	1 ppm (3.13 mg/m^3)	Sk	Oto Sk
Carbon Monoxide	30 ppm (34 mg/m^3)	20 ppm (23 mg/m^3)		Oto
Dimethyl formamide	10 ppm (30 mg/m^3)	5 ppm (15 mg/m^3)	Sk	Sk
1,3-Dinitrobenzene	0.15 ppm (1 mg/m^3)	0.15 ppm (1 mg/m^3)	Sk	Sk
Ethyl Benzene	100 ppm (434 mg/m^3)	20 ppm (87 mg/m^3)		Oto
Hydrogen Cyanide	10 ppm (11 mg/m^3) (peak limitation)	10 ppm (11 mg/m^3) (peak limitation)	Sk	Oto Sk
Lead (inorganic dusts and fumes)	0.05 mg/m^3	0.05 mg/m^3		Oto
Manganese, dust, and compounds	1 mg/m^3	0.1 mg/m^3		Oto
Silver	0.1 mg/m^3	0.1 mg/m^3		
Styrene, monomer	50 ppm (213 mg/m^3)	20 ppm (85 mg/m^3)		Oto
Toluene	50 ppm (191 mg/m^3)	20 ppm (75 mg/m^3)	Sk	Oto
Trichloroethylene	10 ppm (54 mg/m^3)	10 ppm (54 mg/m^3)	Carc 1B Sk	Oto
Xylene (o-, m- and p-isomers)	80 ppm (350 mg/m^3)	80 ppm (350 mg/m^3)		Oto

TWA †—Time-weighted average; Sk—Skin absorption; DSen—Dermal sensitizer; Oto—Ototoxicity; ++—Transition period—Values and advisory information published in October 2024 but do not come into force until 30 November 2026.

According to guidance by SafeWork Australia, hearing loss is more likely to occur if a worker is exposed to both noise and an ototoxic chemical than if exposed to just noise or just the chemical. However, the basis for having assigned 'Oto' labels to any of the chemicals identified in Table 1 is not clear. SafeWork Australia also recommends regular audiometric testing for workers who are exposed to ototoxic substances where (1) the airborne exposure is greater than 50% of the WES for the substance, regardless of the noise level, and (2) the airborne exposure to chemicals is at any level but noise levels are greater than 80 dB(A) or peak exposures greater than 135 dB(C). These are measures that recognise the potential for synergism between noise and chemical exposure, but it remains unclear how well this is regulated given that the principles are recommendations rather than regulatory prescriptions.

The purpose of this review was to review pertinent information on the synergism between noise and chemical exposures in the workplace, with an added regulatory perspective of their impact on health. To date, this has mainly

focused on hearing loss and, to a lesser degree, effects on other health outcomes such as blood pressure. We used the 1997 review by Cary et al. [2] as a foundation for substances of concern (Table 1) and surveyed original research articles for evidence from animal and human studies to identify new candidates. The review has been restricted to original research articles published in open literature and has looked at health outcomes rather than substance-specific mechanisms of toxicity. It has focused on occupational exposures to noise and chemicals only, and did not address other agents such as lifestyle factors or pharmaceutical use, and is written in the context of current Australian regulations regarding noise. The outcomes of this review will allow occupational hygiene scientists, practitioners and policymakers to identify further areas for research and potentially derive new risk reduction measures for workplaces.

2. Methods

2.1. Literature Review

A literature search was conducted in PubMed, Scopus, Embase, Science Direct, Web of Science, Google Scholar databases, and the Public Health Database. The search strategy was developed in consultation with a qualified University of Adelaide librarian. Search terms were "combined exposures", "combined effects", "occupational noise", "noise", "noise effects", "chemicals", "toxic substances" and specific chemicals such as "toluene", "solvents", "lead", "carbon monoxide", "pesticides", "silver, "aluminium oxide nanoparticles", "welding fume". Additionally, search was conducted for "mixed solvents", "mixed metals" and "mixed chemicals" exposures. Inclusion criteria were combined occupational exposures to noise and chemicals which exacerbated noise-induced adverse health outcomes. The review explored peer-reviewed experimental (animal and human) and qualitative studies, excluding studies that reported environmental exposures and those that were out of scope, i.e., not related to noise and/or chemical exposure, and did not discuss co-exposures, and if research was incomplete, with unclear description of methods and results. Articles were screened for eligibility from 1997 to 2024. Only studies published in English were considered. Two authors independently assessed the eligibility of the articles identified. Data extraction focused on the type of chemicals, species or strain, route of administration, substance dose and noise level investigated. The key findings for the related health outcomes were extracted. The adapted Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram below presents the flow chart of the identified and selected studies (Figure 1).

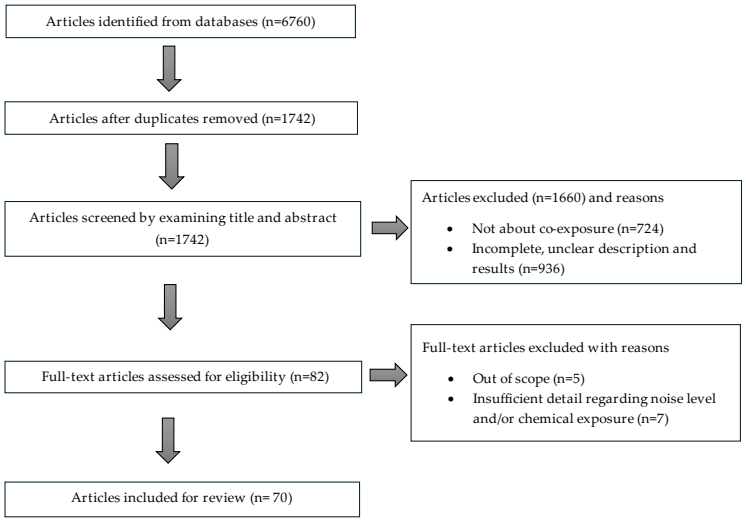

Figure 1. Flow diagram for the articles identified and selected for the review since 1997, adapted from the PRISMA chart.

2.2. Critical Analysis (Appraisal Tool)

A critical appraisal tool, adopting the "Ten Key Questions" approach, was used to assess the relevance and validity of the research articles identified [4]. Each question was assigned one mark if the answer was "yes" or a positive value. Based on the criteria, the quality of each paper was categorised as low (1–3 marks), medium (4–6 marks) or high (7–10 marks). An exemplar summary table of the results of this critical appraisal, as it was applied to Table 2, thus original research animal studies, is shown in Supplementary Information Table S1. All screened articles relevant to this section received high rankings, which denotes that the articles were relevant to identify and characterise health outcomes from co-exposures to noise and chemicals from animal studies. A similar approach was adopted to screen all articles discussed in this review.

Table 2. Summary of literature review of the health effects of co-exposure to noise and chemicals in animal studies.

Substance	Species/Strain	Route of Administration	Substance Dose	Noise Level	Primary Area of Investigation	Key Findings	Study
Acrylonitrile	5–6 rats (male Long-Evans)	Subcutaneous injection on each of 2 days	0, or 2 × 50 mg/kg	108 dB(A) at 2–40 kHz for 8 h	Compound action potential (CAP)	Acrylonitrile in combination with noise impaired the CAP by up to 20 dB, for up to 100 min post-exposure before returning to normal.	[5]
	5–16 rats (male Long-Evans)	Subcutaneous injection on each of the 5 days	0, or 50 mg/kg	105 dB(A) at 13.6 kHz for 4 h	Tissue glutathione levels Threshold shift	Acrylonitrile in combination with noise enhanced a threshold shift of up to 27 dB.	[5]
	6–11 rats (Long-Evans)	Subcutaneous injection on each of the 5 days	0 or 50 mg/kg	97 dB(A) at 8 kHz for 4 h	Distortion product otoacoustic emissions (DPOAE) CAP Threshold shift Histopathology	Noise-alone and Acrylonitrile-alone did not affect DPOAE or CAP. Combined exposure produced a threshold shift (up to 16 dB). Noise-alone and acrylonitrile-alone produced limited hair cell loss. Combined exposure resulted in substantial damage to the basal half of the organ of Corti, and outer hair cell loss.	[6]
Aluminium oxide nanoparticles (20–80 nm)	6 rats (male Wistar)	Intraperitoneal	0 or 30 mg/kg	95 dB 'white' noise at 20–20 kHz, 8 h/day for 2 weeks	DPOAE Histopathology	Synergism as determined by DPOAE, and hair loss seen histologically, was observed in all exposure groups and was enhanced by co-exposure to noise and aluminium oxide nanoparticles.	[7]
Cadmium and compounds	6–16 mice (CBA/CaJ)	Oral (drinking-water) for 12 weeks	0, 3, 11, 27 mg/L Cadmium chloride	102, 105, or 108 dB at 2–20 kHz for 2 h, once only	Blood biochemistry Histopathology	No adverse signs of toxicity were associated with Cd- or Cd + noise exposure.	[8]
	5 rats (male Wistar)	Intraperitoneal	0, 1, 2, 3 mg/kg Cadmium chloride	0 or 90 dB noise 4 h for 7 days	Blood biochemistry Histopathology	Some biochemistry parameters were elevated, and some of were decreased by co-exposure with noise.	[9]
Carbon disulfide	7–30 rats (female Long-Evans)	Inhalation, 6 h/day, 5 days/week for 4 weeks	0, 63, 250, 500 ppm	Equivalent to 106 dB(A) for 8 h at 0.5 to 2 kHz	DPOAE Blood biochemistry Urinalysis Histopathology	There were no histologically-observed changes. Noise alone caused decreases in DPOAE and this was potentiated when combined with 250 ppm and 500 ppm CS_2.	[10]
	7–16 rats (female Long-Evans)	Inhalation, 15 min/hour, 6 h/day for 5 days	250 ppm	Impulse for 7 ms equal to 84 dB, 8 h Continuous 90.2 dB (=89 dB, 8 h)	DPOAE Histopathology	Carbon disulfide only did not affect DPOAE. Impulse noise impaired DPOAE but was magnified by CS_2. Continuous noise plus CS_2 did not affect DPOAE as much as continuous noise alone. CS_2 and CS_2 in combination with continuous noise resulted in similar levels of hair loss. Impulse noise only did not affect cochleograms (hair loss) but in combination with CS_2 there was significant loss of outer hair cells.	[11]
	8–20 rats (female Long-Evans)	Inhalation, 6 h/day, 5 days/week for 4 weeks	250 ppm	Equivalent to 105 dB(A) for 8 h at 0.5, 1, 2 kHz	post-rotatory nystagmus (PRN) tests Histopathology	Co-exposure to CS_2 and noise was not associated with hair loss or morphological changes. Vestibular function, determined by PRN tests, was temporarily affected by CS_2 and enhanced by noise, although air-righting reflex and tail-lift reflex were unaffected.	[11]
	4–36 rats (female Long-Evans)	Inhalation 6 h/day, 5 days/week for 4 weeks	Continuous at 63 ppm, or intermittent at 250 ppm for 15 min, once or twice per day.	106 dB at 0.5–2 kHz	DPOAE PRN Histopathology	Continuous noise alone resulted in a decrease in DPOAE, although co-exposure with intermittent CS_2 resulted in a lesser reduction of DPOAE, and continuous 63 ppm CS_2 showed no differences in DPOAE. Vestibular function, as measured by PRN tests, was reduced on completion of CS_2 exposure, but showed significant recovery on completion of the 4-week post-recovery time. There were no clear histopathological differences seen.	[12]

Table 2. *Cont.*

Substance	Species/Strain	Route of Administration	Substance Dose	Noise Level	Primary Area of Investigation	Key Findings	Study
Carbon Monoxide	8 rats (Long-Evans, sex not stated)	Inhalation, single exposure	0, 300, 500, 700, 1200 or 1500 ppm	100 and 115 dB(A) at 1.2–19.2 kHz	CAP Cochlear microphonics (CM) Threshold shift	CO at 500 ppm or more had no effect on CAP or CM. However, at 500 ppm CO or more there was potentiation of the noise-induced effects on CAP and CM (up to 40 dB). Noise alone also produced a threshold shift in CAP and CM (up to 20 dB).	[13]
	6 rats	Inhalation, single exposure for 4.5–6.5 h	1200 ppm	100 dB(A) intermittent noise at 13.6 kHz of 30–60 min with interludes up to an hour to create a total noise exposure duration of 2 h	CAP Histopathology	Intermittent noise caused threshold shifts in CAP for each of the noise cycles but was more marked with longer durations of noise (up to 20 dB). CO alone did not affect CAP although histopathology did show outer hair cell loss. Combined exposure to noise and CO produced a potentiation of outer hair cell loss.	[14]
Carbon Monoxide	6 rats (Long-Evans)	Inhalation, Single exposure	1200 ppm	95 dB(A) for 4 h 100 dB(A) for 2 h 105 dB(A) for 1 h and 105 dB(A) for 4 h at 13.6 kHz	CAP Threshold shift	1200 ppm CO alone did not affect CAP thresholds, however, significant thresholds shifts were observed in combination with 100 dB(A) for 2 h or 105 dB(A) for 1 h (up to 49 dB). The degree of potentiation was similar despite the increased noise dose.	[15]
	5–8 rats (male Long-Evans) 8 rats (male Long-Evans)	Inhalation, single exposure for 8 h Inhalation, repeated exposure for 8 h, for 5 days	0, 300, 500, 700, 1200, or 1500 ppm 0 or 1200 ppm	95 dB(A) at 13.6 kHz for 2 h 95 or 100 dB(A) for 2 h, or 100 dB(A) for 4 h	CAP	1200 ppm CO did not affect hearing function, as determined by CAP. Single-exposure to noise at 95 dB(A) for 2 h was associated with limited hearing loss (up to 10 dB). Potentiation was observed at 300 ppm, the lowest CO concentration, although it was not statistically significant. However, there was evident dose-related hearing impairment at 500 ppm or more in combination with noise (95 dB(A) for 2 h)—up to 40 dB. In the single-exposure study the change in noise energy from 95 dB(A) to 100 dB(A) did not affect the degree of hearing impairment. In the repeated-exposure study, CO only did not affect hearing threshold. However, noise-only, and noise with 1200 ppm CO had an effect (up to 10 dB).	[16]
	6 guinea pigs (male Dunkin-Hartley)	Inhalation 6 h/day for 5 days	500 ppm	105 dB at 4 kHz	ABR threshold	In the combined exposure group, there was an enhancement of the reduction in ABR thresholds immediately post-exposure (up to 10 dB), with subsequent recovery after 1 or more weeks post-exposure.	[17]
Dimethyl formamide	No studies identified						
1,3-Dinitrobenzene	No studies identified						
Ethyl Benzene	8 rats (Wistar, sex not stated)	Inhalation 8 h/day for 5 days	0, 300 or 400 ppm	95 or 105 dB(A) at 50 Hz–50 kHz	DPOAE CAP Histopathology	EB alone, at 300 and 400 ppm resulted in outer hair cell loss. There were threshold shifts in DPOAE and CAP (of about 20 dB) with 105 dB(A) noise. Noise at 105 dB(A) in combination with 300 and 400 ppm EB resulted in a potentiation of outer hair cell loss that was greater than the sum of those losses seen by noise-only or EB only.	[18]
Hydrogen Cyanide	6–16 rats (male Long-Evans)	Inhalation Single-exposure	0, 10, 30 or 50 ppm for 3.5 h	100 dB(A) at 13.6 kHz for 2 h	CAP Histopathology	Noise exposure alone produced a reduction in CAP (about 10 dB), and outer hair cell loss (but no loss of inner hair cells). There was a potentiation of CAP impairment across all HCN-exposed groups, attaining statistical significance at 30 ppm or more (24–36 dB). Combined exposures also produced more outer hair cell loss. HCN alone did not produce any significant effects on CAP or hair cell loss.	[19]

Table 2. *Cont.*

Substance	Species/Strain	Route of Administration	Substance Dose	Noise Level	Primary Area of Investigation	Key Findings	Study
Lead	Mice (CBA/CaJ)	Oral (drinking-water) for 12 weeks	0, 4.8, 190, 550 mg/L lead acetate	102, 105 or 108 dB at 2–20 kHz for 2 h, once only	ABR Blood biochemistry Histopathology	No adverse signs of toxicity were associated with Pb- or Pb + noise exposure.	[20]
	6 mice (male C57BL/6)	Oral (drinking-water) for 28 days	0 or 2 mM lead acetate (approx. 66 mg/kg/day)	90 dB(A) at 2 2–20 kHz hours/day for 2 weeks (days 1–14 of the 28 days)	ABR Threshold shift	Lead exposure resulted in a marked threshold shift of up to 12 dB as determined by auditory brainstem response (ABR). In addition, noise levels alone also resulted in a significant threshold shift (up to 25 dB). Threshold shifts were further enhanced by co-exposure with noise (up to 30 dB).	[21]
	5 rats (male Wistar)	Oral gavage daily for 30 days	0 or 4 mg/kg aqueous lead acetate	105 dB(A) at 4 kHz 8 h/day	Histopathology	Testicular weights were reduced in lead-exposed and noise-exposed groups, with an exacerbation in animals co-exposed to noise and lead (around 30% decrease). Histologically, oedema, degeneration and necrotic cell debris were observed in lead-exposed and noise-exposed groups. For those exposed to noise + lead this had advanced to severe congestion, atrophy of seminiferous tubules, oedema and necrotic cell cell debris.	[22]
Manganese	6 rats (male Sprague-Dawley)	Oral (drinking-water) for 90 days	0 or 10 mg/L manganese (as manganese chloride)	90 dB(A) at 8–16 KHz for 8 h/day	DPOAE ABR CAP Histopathology	Manganese did not exacerbate the hearing loss caused by noise.	[23]
Silver nanoparticles (30–50 nm)	6 rats (male Wistar)	Intraperitoneal 5 days/week for 4 weeks	0, or 100 mg/kg	104 dB at around 8 kHz, 6 h/day	DPOAE Histopathology	Clinical signs of toxicity included reduced bodyweight gain in silver-exposed and noise-exposed animals, which was enhanced by co-exposure to noise + silver (around 30% reduction in bodyweight gain). DPOAE was affected by noise-only, and silver only, along with accompanying histological changes (damage to hair cells and degeneration of ganglion cells) which were enhanced when noise and silver were co-administered.	[24]
	6 rats (male Wistar)	Intraperitoneal 5 days/week for 4 weeks	0, 50, 100 mg/kg	104 dB noise at around 8 kHz, 6 h/day	Histopathology	Hepatic necrosis with an associated increase in liver weight was observed in animals exposed to silver at both exposure levels, and was enhanced by co-exposure to noise (around 30% increase).	[25]
Styrene	16 rats (male Long-Evans)	Inhalation	0 or 750 ppm	97 dB(A) at 8 kHz 6 h/day, 5 days/week for 4 weeks	Histopathology	Hearing loss and cytological damage (particularly of outer hair cells) was apparent in noise, styrene, and noise and styrene exposed groups and there was evidence of synergism of noise and styrene. The level of damage was greater than additive.	[26]
	5–12 rats (male Wistar)	Inhalation 12 h/day, 5 days/week for 4 weeks	0, 100, 300 or 600 ppm	100–105 dB(A) at 31.5 Hz–10 kHz	ABR Histopathology	There were no adverse effects observed at 100 and 300 ppm styrene only. In addition, ABR showed a synergistic action between noise and 600 ppm styrene (up to 27 dB). Also, for rats exposed to noise and 600 ppm styrene, cochleograms showed a more marked outer hair cell loss than noise-only, or styrene-only exposed animals.	[27]
	4 rats (male Long-Evans)	Inhalation 6 h per day, 5 days/week for 4 weeks	400 ppm	86 dB(A) at 8 kHz	Histopathology	Both noise and styrene exposure levels were set at a level anticipated to produce some ototoxicity. Cochleograms did not reveal any overt difference between the 'noise' and 'noise + styrene' groups. However, there was an increased loss of outer hair cells in the 'noise and styrene' group, indicative of hearing loss.	[28]

Table 2. *Cont.*

Substance	Species/Strain	Route of Administration	Substance Dose	Noise Level	Primary Area of Investigation	Key Findings	Study
Styrene	3–10 rats (male Long-Evans)	Oral gavage	0, 300, 400 or 800 mg/kg	100 dB(A) at 10–20 kHz continuously together with a 30 ms 'impact' noise of 110 dB(A) every second, 6 h/day, 5 days/week for 1 or 3 weeks	CAP Histopathology	Reduction in CAP was noticed at 300 and 400 mg/kg styrene administered for 3 weeks (<30 dB). Noise only produced a more noticeable shift in CAP (around 30 dB), and noise plus styrene produced a greater shift again (about 40 dB). Outer hair cell loss was observed in the 400 mg/kg styrene, noise only, and noise plus styrene groups. Combined exposure produced more severe hair cell loss. In the 7-day study, involving 800 mg/kg noise and styrene, noise alone did not produce loss of Deiters cells, although noise and styrene did exacerbate cell death.	[29]
	8–16 rats (male Brown-Norway)	Inhalation	300 ppm	86 dB(A) at 8 kHz 6 h/day, 5 days/week for 4 weeks, or impulses of noise of 112 dB(A) for 0.01 s every 15 s	DPOAE Histopathology	Exposure to 300 ppm styrene resulted in statistically significant changes in DPOAEs. Continuous noise and impulse noise caused permanent hearing loss as measured by DPOAE, although no histopathological changes were observable. Combined exposure of continuous noise and styrene appeared to produce a lesser degree of hearing damage that either alone. However, there was a potentiation of hearing loss with impulse noise and styrene.	[30]
	8 rats (male Brown-Norway)	Inhalation 6 h/day, 5 days/week for 4 weeks	600 ppm	Continuous at 85 dB(A) for 6 h Impulses of 7 ms equal to 80 dB(A), 8-h at 8 kHz	DPOAE	Styrene at 600 ppm did not affect DPOAE. Continuous noise, impulse noise alone and styrene alone each caused a similar change in DPOAE compared to controls. However, impulse noise plus styrene caused a potentiation of that impairment.	[31]
	15 rats (male Wistar)	oral gavage	400 mg/kg	98 dB(A) at 10 kHz for 60 min, 5 days/week for 3 weeks	DPOAE ABR Histopathology	A synergism of ototoxicity at already-ototoxic exposure levels of noise and styrene was reported (threshold shift of around 40 dB in the noise-only group, 30 dB in styrene only, and 45 dB in the noise + styrene group).	[32]
Styrene	6 rats (male Wistar)	Inhalation	0 or 750 ppm	100 dB(A) at 8 kHz 6 h/day for 6 days/week for 4 weeks	Histopathology	Lung pathology in controls and noise-exposed animals was essentially normal. Styrene-only resulted in epithelial hyperplasia, signs of fibrosis, and thickened alveolar septa, together with reduced alveolar space. Noise plus styrene caused more marked changes in alveolae, moderate to severe epithelial hyperplasia and aggregation of neutrophils in vessel walls.	[33]
Toluene	Rats (male Long-Evans)	Inhalation 6 h/day, 5 days/week, 4 weeks	0, 2000 ppm	92 dB(A) at 8 kHz	Threshold shift Histopathology	Threshold shifts and hair cell damage were observed with toluene alone, and noise alone (threshold shift up to 30 dB and 25 dB, respectively). The threshold shift was up to 40 dB in the group co-exposed to noise and toluene. Enhanced hair cell damage was observed with toluene and noise together.	[34]
	12 rats (male Wistar)	Inhalation 6 h/day for 10 days	0, 500, 1000, 1500 or 2000 ppm	96 dB(A) at 4–31.5 kHz for 2 h. Additional noise impulse of 105 dB(A) for 4 h on Day 71 amongst animals exposed to 1500 ppm toluene	Threshold shift	The noise level of 96 dB(A) was selected as the LOAEL for auditory effects based on a pilot study. Exposure to up to 1000 ppm toluene did not cause any change in auditory thresholds, although thresholds were elevated at 1500 and 2000 ppm (up to 45 dB). Rats exposed to 500 ppm toluene and noise showed threshold shifts similar to noise only. However, at 1000 ppm there was a slight elevation in auditory threshold (15 dB) and at 1500 and 2000 ppm there was a clear shift at most frequencies tested that was in excess of the sum of the individual parts (up to 45 dB).	[35]

Table 2. *Cont.*

Substance	Species/Strain	Route of Administration	Substance Dose	Noise Level	Primary Area of Investigation	Key Findings	Study
Toluene	6 rats (male and female Sprague-Dawley)	Inhalation 16 weeks, 3 days/week + 3 days/week totalling 104 h/week	40 ppm	80 dB(A) at 8 kHz	Functional observation battery Neurochemistry	No significant differences were seen in locomotor activity. Toluene alone decreased the rearing behaviour, but this was not impacted by noise. There was no potentiation of behavioural or neurochemical parameters (DOPA and 5-hydroxytryptamine).	[36]
	12 rats (male Wistar)	Inhalation 4 h/day, 5 days/week, 10 days. Inhalation 6 h/day, 5 days/week, 90 days	0, 500, 1000, or 1500 ppm 0, 100, 200 or 500 ppm	90 dB(A) at 4–20 kHz and impulses (at 130 dB(A)). 90 dB(A) for 4 h	ABR DPOAE	In the 10-day study, no additive effects or synergism were seen in the toluene and Wide-band noise, WBN-exposed groups at 1000 ppm or less. However, in animals exposed to WBN and 1500 ppm toluene, and the impulse noise + 1500 ppm toluene interaction was apparent. The effect was more marked with impulse noise. In the 90-day study, hearing impairment was evident in the noise, and the noise + 500 ppm toluene groups using the ABR and DPOAE methods. No synergism was apparent.	[37]
	6 rabbits (male New Zealand White)	Inhalation 8 h/day, 5 days/week, 90 days	0 or 1000 ppm	100 dB(A) at 70–80,000 kHz for 14 days	Haematology Blood biochemistry Histopathology	Noise-only resulted in some haematological changes, and biochemical changes reflective of impaired liver and kidney function and histologically-observed damage to kidneys, liver, heart, stomach and lungs as did toluene-only. However, effects were more marked amongst animals co-exposed to noise and toluene.	[38–41]
Trichloroethylene	8 rats (Wistar, sex not stated)	Inhalation 18 h/day, 5 days/week for 3 weeks	0 or 3000 ppm	95 dB(A), at 31.5 Hz to 31.5 kHz	Threshold shift	3000 ppm trichloroethylene (TCE) was reported to result in hearing loss. At 4 kHz there was an enhanced hearing loss of TCE plus noise when compared to noise alone, suggesting an interaction. There were no effects on hearing at 32 kHz, and at the other frequencies, hearing loss due to combined exposure was lower than TCE or noise alone.	[42]
Xylene	No studies identified.						

3. Results

Results across all databases yielded 6760 records. After removing duplicates, 1742 articles underwent title and abstract screening; subsequently, 82 articles were assessed for eligibility based on full-text screening. Of those, 70 articles met the inclusion criteria and were selected for final review (Figure 1). Results have been structured by chemical name, in alphabetical order; evidence from animal (Table 2) and where available, human studies (Table 3).

Out of the 17 substances reviewed, there were 3, namely dimethylformamide, 1,3-dintrobenzene, and xylenes, for which no new data had been published, and 8 which have been newly-identified as having potential synergism of toxicity with noise, namely acrylonitrile, aluminium oxide nanoparticles, ethylbenzene, hydrogen cyanide, manganese, silver nanoparticles, trichloroethylene, and welding fume.

Numerous animal studies have been conducted using a route of administration (intraperitoneal injection) that is not considered relevant to occupational settings and may have bypassed typical toxicokinetic involvement. This applies to work on acrylonitrile, aluminium oxide, cadmium, hydrogen cyanide and silver.

There have been too few studies published related to the possibility of enhanced toxicity due to solid being in nanoparticle form to be able to draw any conclusions about the influence of particle size.

Most studies either investigated hearing function or effects related to blood pressure but it was interesting to note a series of publications of a study in rabbits involving co-exposures to toluene and noise [38–41]. These studies showed that high levels of noise resulted in a broad spectrum of systemic effects in multiple organs. In addition, Masruri et al., 2022 [22] observed testicular damage in rats from high levels of noise.

No additional animal studies have been identified since 1997 for cadmium, dimethylformamide, 1-3-dinitrobenzene, or xylene.

Much published data came from epidemiological studies and almost all studies focused on potential hearing loss (although a small number have looked at other adverse health effects). Generally, the epidemiology studies were less clear on individual exposure to noise or personal exposure to chemicals, and many workplace studies involved potential exposure to multiple chemicals. Whilst this is typical of many work environments, it is difficult to identify a clear causative agent. From the nature of cross-sectional studies (which formed the backbone of most of the human data available) it is difficult to draw conclusions when conditions at the time of analyses could have been very different from historic conditions (i.e., much higher levels of noise or chemicals that may have contributed to changes and staff turn-over meaning that data are lost to study).

Table 3. Summary of literature review of the health effects of co-exposure to noise and chemicals in human studies.

Substance	Exposure Group	Noise Level (dB(A))	Substance Dose	Key Findings	Study
Acrylonitrile			No studies identified		
Aluminium oxide nanoparticles (20–80 nm)			No studies identified		
Cadmium and compounds			No studies identified		
Carbon Disulfide	Cross-sectional study of 131 male workers in a rayon-manufacturing plant	80–91 dB(A) (unclear if area or personal monitoring)	Banded into <14.6 ppm, or ≥14.6 ppm. Unclear if these were 8-h TWA values	Increased prevalence of hearing loss (68% compared to 24% in controls).	[43]
Carbon Monoxide	Analysis of 9396 audiograms collected between 1983 and 1996	No data	No data	Potentiation of noise-induced hearing loss due to carbon monoxide.	[44,45]
	Retrospective study of 80 workers at a steel foundry	87–93 dB(A)	200–700 ppm	Increased prevalence of hearing loss (23% compared to 7.5% in 'noise-only' group).	[46]
	Cross-sectional study of 30 fishermen	81.2–107 dB(A), 8-h TWA, area sampling	No data	Increased hearing loss associated with noise and CO.	[47]
Dimethyl formamide			No studies identified.		
1,3-Dinitrobenzene			No studies identified.		
Ethyl Benzene			No studies identified.		
Hydrogen Cyanide			No studies identified.		
Lead	Cross-sectional study of 339 lead battery workers from 2 factories	86 ± 5 dB(A)	Blood lead levels 56.9 ± 25 ug/dL Airborne lead levels were measured by area sampling	A statistically significant dose-related trend in the exacerbation of hearing impairment, using pure tone audiometry, in workers co-exposed to lead and noise (increased blood lead levels correlated with increased hearing loss but was not quantified). Noise levels alone, and airborne lead levels alone, did not correlate with hearing loss.	[48]
	Cross-sectional study of 412 steel plant workers	Banded: <80 dB(A), 80–85 dB(A), >85 dB(A).	Metals included manganese, copper, zinc, arsenic, cadmium and lead. Lead was taken to be the most significant element. Subjects were banded into 3 groups of BLL: ≤4 ug/dL, 4–7 ug/dL, ≥7 ug/dL.	Increased hearing loss was correlated with the highest BLLs, and also with the highest noise levels (Odds Ratio, OR 3.06–6.26). BLL below 10 ug/dL may enhance noise-induced hearing loss.	[49]
	Cross-sectional study of 105 workers in a lead-acid battery recycling plant	85 dB(A) ± 1 dB(A)	Mean blood lead levels 44 ± 15 ug/dL Personal monitoring of atmospheric lead showed levels ≤ 0.05 mg/m^3	Higher values of blood lead correlated with raised systolic and diastolic blood pressure although there was no correlation with noise levels (Odds Ratio 1.1).	[50]
Manganese			No studies identified.		
Silver nanoparticles (30–50 nm)			No studies identified.		

Table 3. *Cont.*

Substance	Exposure Group	Noise Level (dB(A))	Substance Dose	Key Findings	Study
Styrene	Cross-sectional study of 313 fibreglass workers	75–116 dB(A)	0.2–96 mg/m^3 (mean 16 mg/m^3)	An increased prevalence of high-frequency hearing loss was noted in the groups exposed to noise + styrene (48%), and those exposed to styrene alone (47%). These prevalences compared to 33% in non-exposed, and 42% in noise-only groups	[51]
	Cross-sectional study of 290 workers employed in boat-building and plastics manufacture	71–93 dB(A)	Exposures included a mixture of solvents but were stated to be mainly to styrene—0.2–198 mg/m^3	Results revealed increased hearing loss related to styrene (OR 3.9). Combined exposure to noise and styrene, appeared to be more ototoxic than noise alone (OR up to 10.9, compared to 3.4 in a noise-only group).	[52]
	Cross-sectional study of 15 workers in fiberglass manufacture	80.7–88 dB(A)	4.9–150 mg/m^3 (mean 50 mg/m^3)	Otoacoustic emissions were used to demonstrate an increased prevalence of hearing loss (about 10 dB) in workers exposed to noise and styrene.	[53]
Toluene	Cross-sectional study of 58 male workers	<70 to 90 dB(A) (area sampling)	Toluene measured from area sampling and presented as cumulative index.	Enhanced hearing loss amongst workers exposed to toluene and noise (86%, compared to 45% in noise-only controls).	[54]
	Longitudinal study of 33 workers in the printing industry	82 ± 7 dB(A)	45 ± 17 ppm	5 year study. No adverse effects were associated with toluene or toluene plus noise. Hearing loss was observed with high levels of noise (84 dB(A).	[55]
	333 male workers in the printing industry	No clear information		At exposure levels less than 50 ppm toluene there was no overt impairment of hearing function. Hearing loss was observed with high levels of noise.	[45,55]
Trichloroethylene	No studies identified.				
Xylene	No studies identified.				
‘Mixed Solvents’	Cross-sectional study of 701 male and female dockyard workers	70–85 dB(A) in the unexposed group and 85–100 dB(A) in the exposed groups	Mainly xylene and toluene, which are based on historical measurements. Other chemicals included ethyl benzene, ethyl acetate, butyl acetate, n-butanol, white spirit. Exposure levels were high and unclear if from personal monitoring.	Results suggested an additive effect of co-exposure to noise and the workplace chemicals (OR of hearing loss of about 3 in noise-only group, 5 for noise and solvents).	[56]
	Cross-sectional study of 1117 male and female workers in shipbuilding, yacht-building, plastic, shoe, paint and lacquer industries	Mean 79.3–89.9 dB(A) (range 64–100 dB). Exposure based on historic records and concurrent personal monitoring.	Exposure indices based on historic records.	Increased odds-ratios of developing hearing loss associated with mixed solvents (2.4), styrene (3.9), n-hexane and toluene (5.3). This was enhanced (OR >20) for workers co-exposed to noise, styrene + toluene, and n-hexane + toluene.	[57]

Table 3. *Cont.*

Substance	Exposure Group	Noise Level (dB(A))	Substance Dose	Key Findings	Study
‘Mixed Solvents’	Cross-sectional study of 542 male workers in the avionics industry	76.4 dB(A) to 91.6 dB(A) over 8-h (personal monitoring)	Including Methyl Ethyl Ketone (MEK), toluene, xylene, tetrachloroethylene, 1,2-dichloroethane, hexanone, dichloromethane, Methyl Isobutyl Ketone (MIBK), 2-butanol, 2-ethoxyethanol, ethyl benzene, n-hexane, acetone, ethyl acetate, benzene, ethanol, trichloroethylene, isobutanol, 1,4-dioxane.	Increased prevalence of hearing loss in workers exposed to a combination of noise and chemicals (55%, compared to 6% in unexposed controls, 17% in noise-only, and 28% in solvent-only groups).	[58]
	Cross-sectional study of 172 workers in the petrochemical industry	68.2 dB(A) to 91.8 dB(A), 8-h	Including benzene (<0.5 ppm), Toluene (0.05 ppm), Xylene (0.05 ppm), Butadiene <23 ppm), 8-h TWA	An increased percentage of workers with threshold shift at 3000 and 8000 Hz was reported (45% of workers had threshold shift).	[59]
	Cross-sectional study of 174 aircraft maintenance workers	84.9–115.9 dB(C) peak 59.6–97.9 dB(A) 8 h	No personal or static monitoring data	An increased prevalence of hearing loss, determined by pure-tone audiometry, DPOAEs, transient otoacoustic emissions was observed. Also, ABRs, acoustic reflex thresholds and nystagmus were adversely affected amongst aircraft maintenance workers—32% of solvent and noise exposed workers had abnormal ABR.	[60]
	Cross-sectional study of 59 workers at a synthetic leather manufacturing plant	72.8–82.2 dB(A), 8-h	5 ppm Dimethylformamide 1.6 ppm Toluene	An increased prevalence of hypertension was observed in groups exposed to noise-alone, and the solvents alone. OR of hypertension was 7.9 in solvent-exposed workers, 9.1 in noise-exposed workers and 13.5 in co-exposed.	[61]
	Cross-sectional study of 110 workers from a fabric reinforcing factory	74–84 dB(A)	Mainly toluene and methyl ethyl ketone, but several other solvents also present. No personal monitoring data.	Increased levels of solvent exposure and noise were associated with hearing impairment (median hearing scores for pure tone audiometry were 10, 17.5 and 20 for low, medium and high solvent-exposed groups).	[62]
	Cross-sectional study of 411 workers at a car manufacturing plant	75–88 dB(A) (static sampling)	Solvents included benzene, toluene, xylene, acetone and tetrachloroethylene, measured by static sampling.	An exacerbation of hearing loss amongst workers exposed to noise and solvents compared to noise alone was reported (24.1 dB in assembly workers, 25.7 dB in new paint shop, and 32.8 dB in the old paint shop).	[63]
	Retrospective case-control study of 222 workers exposed to noise only across various industries.	68–87 dB(A) (8 h) area sampling	Estimated from records, and included toluene, xylene, ethyl acetate, butanol, isopropranolol, ethanol and acetone.	Earlier hearing loss amongst workers exposed to noise and solvents (16 years in noise and solvent-exposed workers compared to 24.5 years in noise-only exposed workers).	[3]

Table 3. *Cont.*

Substance	Exposure Group	Noise Level (dB(A))	Substance Dose	Key Findings	Study
‘Mixed Solvents’	Retrospective study of 503 workers	Grouped <85, 85–94, >95 dB(A)	Toluene, styrene, xylene, benzene, JP-8 jet fuel	No association of combined effects of solvents and noise below the OELs of solvents. Relative Risks, RR were all around 1 for noise, solvents, or noise and solvents. Nor was there interaction above 85 dB(A) noise.	[64]
	Cross-sectional study of 502 male car-manufacturing workers	77–102 dB(A) 8-h, measured by static sampling.	Solvents included benzene, toluene, xylene, acetone and tetrachloroethylene—measured by static sampling.	Mean systolic and diastolic blood pressure were raised amongst workers exposed to noise, workers exposed to chemicals, and there was an increased effect in workers exposed to both. OR were 4.4 for controls, 9.4 for solvent-only, and 14.2 for noise and solvent groups.	[65]
	Retrospective case control study in 469 truck and bus plant workers	79–86.5 dB(A) 8-h, average 84–84.5 dB (area sampling)	Including benzene, toluene, xylene, acetone, tetrachloroethylene (area sampling)	Statistically significant exacerbation of hearing loss amongst workers exposed to noise and chemicals, measured by mean ranks of pure-tone audiometry ($p < 0.001$).	[66]
	Transversal retrospective cohort study of 198 workers	No clear data	‘aromatic hydrocarbons’, toluene, xylene, turpentine, oils, greases, lead chromates and molybdates	Co-exposure to noise and an environment of mixed chemicals reported to damage hearing (threshold shift)—16% of cases had hearing loss in noise-only group, 5% in noise and solvents group.	[67]
	Cross-sectional study of 25 male and female printing workers. A control group of 29 workers was also identified.	Based on historic data and by ‘walk-through’ measurements, and ranged from 57–83 dB(A), 8-h TWA.	Assessed by combining personal monitoring data, area sampling and historic data. Eight-hour TWA levels of ethylbenzene were below 78 ppm; 78 ppm for xylenes; 78 ppm for toluene; 50 ppm for n-hexane.	Individuals did not remark on noticeable hearing impairment, however co-exposure demonstrated temporary auditory effects such as reduced ABR, and early signs of permanent, high brainstem effects. There were threshold changes at 6000 Hz and 4000 Hz in pure-tone audiometry in the co-exposed group (16 dB compared to 12.75 dB in controls). Acoustic reflex at 2000 Hz, an indicator of auditory fatigue, was reduced although stated to be within normal range. Comparison of pre- and post-exposure acoustic reflex was different in the co-exposed group but not controls.	[68]
	Cross-sectional study of 1496 petrochemical workers	>80 dB(A) 8-h TWA Noise dose was presented as Combined Noise Exposure (CNE)—mean CNE was 93.3 dB(A) years.	Summary data only were presented but indicated levels of benzene up to 0.4 mg/m^3; toluene 0.233 mg/m^3; ethylbenzene 0.1 mg/m^3, xylene 0.2 mg/m^3; styrene 0.1 mg/m^3 (all <1 ppm, 8-h TWA)	Exposure to mixed solvents, together with a raised CNE was associated with increased hearing loss (OR 5.2).	[69]
	Cross-sectional study of 1160 petrochemical workers	71.4 to 87.8 dB(A)	Benzene, toluene, ethylbenzene, xylene, and styrene (BTEXS) were assessed by biological monitoring to various urinary metabolites	A combination of raised noise levels and urinary metabolites of BTEXS was not adversely associated with biomarkers of renal impairment.	[70]

Table 3. *Cont.*

Substance	Exposure Group	Noise Level (dB(A))	Substance Dose	Key Findings	Study
'Mixed Solvents'	Cross-sectional study of 176 printing press workers	No personal monitoring of noise.	No personal monitoring. Exposures stratified based on job-type or location	No evidence of interaction between noise and 'solvents', although there were poorer hearing thresholds in printing workers when compared to 'non-exposed' controls (up to 11 dB loss compared to controls).	[71]
Welding, Plasma arc-welding or plasma-cutting fume	A cross-sectional study of 16 male welders, with 8 noise-exposed airport workers as controls.	83.1 dB(A) in welders, 83.6 dB(A) in airport workers (8-h TWA)	1.41 ug/m^3 CrVI, 8-h TWA	Welders had an increased prevalence of Heart Rate Variation associated with exposure to noise and welding fume (attaining $p <$ 0.05 statistical significance in welders but not airport workers).	[72]
'Mixed metal' exposures	Cross-sectional study of 58 e-waste workers.	74.4–90 dB(A)	Blood samples were taken for quantification of various metals, such as arsenic, cadmium, lead, manganese, mercury, copper, iron, selenium and zinc.	60% workers had audiometric notches indicative of noise-induced hearing loss. Lead, mercury or cadmium were not associated with impaired hearing thresholds. Selenium and zinc were associated with better hearing.	[8]
Other mixed chemical exposures	Population survey of 30,072 Korean workers	No clear information	No clear information	Increased prevalence of noise-induced hearing loss in workers exposed to noise and chemicals in a variety of settings.	[73]
	Meta-analysis of Chinese workplaces	max or mean of 92.2–102.1 dB(A)	No clear information	Increased prevalence of noise-induced hearing loss in workers exposed to noise and chemicals in a variety of settings.	[74]
	Cross-sectional survey of 540 workers from a tyre factory	No clear information	No clear information	The presence of a 'Coles notch' was identified in noise and solvent exposed workers.	[75]
	Cross-sectional survey of 109 hairdressers, and 153 controls from other 'non-noisy' workplaces via their social media accounts	No clear information	No clear information	An increased prevalence of auditory complaints was reported amongst hairdressers.	[76]
	Cross-sectional survey of 66 workers at 2 palm oil mills	87.9–94.6 dB(A), 8-h TWA. The laboratory had a mean of 81.4 dB(A)	A risk-ranking method based on area monitoring and historic personal monitoring was used to qualitatively identify chemical exposures via all routes of exposure.	Some areas of these 2 plants presented an elevated risk of exposure to noise and ototoxic substances.	[77]
	Cross-sectional survey of 5815 workers by telephone	No clear information	No clear information		[78]
	Cross-sectional survey of 4970 workers survey by telephone	No clear information	No clear information		[79]
	Cross-sectional survey of 699 workers in an electronics factory	Static monitoring	Primarily to isopropanol and lead (around 28 ug/dL)	Reduced telomere length in peripheral blood samples was associated with noise.	[80]

Table 3. *Cont.*

Substance	Exposure Group	Noise Level (dB(A))	Substance Dose	Key Findings	Study
Other mixed chemical exposures	Meta-analysis of 15 studies	The mean noise levels in the majority of studies was often over 85 dB(A).	No clear information	Elevated risk of acquiring hearing loss for workers exposed to solvents and noise.	[81]
	Meta-analysis of 13 studies	No clear information	No clear information	Elevated risk of acquiring hearing loss for workers exposed to solvents and noise.	[82]
	Meta-analysis of 22 studies	The mean noise levels in the majority of studies was often over 85 dB(A).	No clear information	Workers exposed to noise and solvents had a higher prevalence of hearing loss than those exposed to solvents only.	[83]
'Epoxy adhesives'	Cross-sectional study of 182 stone workers	Estimated to be around 87 dB(A)	Classification was by walk-through assessment	A synergistic effect of epoxy resin exposure with noise was reported (prevalence of hearing loss was 42% in epoxy-exposed workers, compared to 21% in other stone workers)	[84]

One recent cross-sectional study of note involved 25 male and female printing workers studying early-onset and temporary hearing loss in workers co-exposed to noise and a mixture of solvents [68]. Individuals did not remark on noticeable hearing impairment, however co-exposure demonstrated temporary auditory effects such as reduced auditory brainstem response (ABR), and early signs of permanent, high brainstem effects. There were threshold changes at 6000 Hz and 4000 Hz in pure-tone audiometry in the co-exposed group. Acoustic reflex at 2000 Hz, an indicator of auditory fatigue, was reduced although stated to be within normal range. Comparison of pre- and post-exposure acoustic reflex was different in the co-exposed group but not controls.

The authors identify that it was not possible to identify the potential contribution of short-term peak exposures to solvents or noise. In addition, it was recognised that there may have been historic exceedances that could not be accounted for in the study design, and that the study size was relatively small. However, the study was noteworthy for providing evidence of hearing loss (either temporary or early-onset) when the combined levels of noise and chemical were each below most regulatory occupational exposure standards.

4. Discussion and Regulatory Perspectives

The available studies in rodents seemed to provide a good model for studying potential effects in humans, with rats offering hearing sensitivity that covers a broader span of noise frequencies than humans are sensitive to. At present, there are no species or strain-specific differences in rodents that would caution on the relevance of findings in any of the animal models used. Across the spectrum of animal studies conducted over the years, a variety of different methodologies for determining hearing loss have been used, although it is not possible to determine whether any one method is better than another.

In the case of noise administration, the same sort of 'uncertainty factors' and extrapolation that might be applied in respect of chemical exposure and toxicological response are not applied. Hence, the animal studies conducted using levels of noise clearly more than the typical occupational exposure limit (85 dB(A)) would be expected to result in harm, and it is unclear what may or may not have happened if those studies had utilised noise exposures at or lower than 85 dB(A).

The Australian 8-h TWA WES for styrene is 50 ppm (to be revised to 20 ppm, Table 1). When deriving OELs or standards based on the results of animal studies a 'safety factor', based on the No-Observed Adverse Effect Level or Lowest-Observed adverse Effect Level (NOAEL or LOAEL) is typically utilised. Animal studies have demonstrated some potentiation of ototoxicity at the LOAELs for noise and styrene but the study designs have been such that exposure levels to styrene are considerably greater than 20 ppm (around 300–400 ppm for repeated exposures). It is unclear, therefore, whether a combination of styrene at levels around the 8-h occupational exposure levels of 85 dB(A) and 20 ppm styrene may result in hearing impairment.

In humans, exposure to toluene levels below 50 ppm (8-h TWA, note that the Australian WES is set to be 20 ppm as shown in Table 1) did not result in overt impairment of hearing function. Hearing loss was observed with high levels of noise (not quantified). Animal studies showed synergism, and this was also noticed at a level of exposure of toluene that is not associated with overt otoxicity, 1000 ppm. However, the level of noise was set at the borderline of a level associated with hearing damage. As with styrene there is evidence of greater harm through noise when delivered as 'impulse', even though the overall sound energy was equivalent to a 'tolerable' level.

Carbon disulfide emerged as another chemical where synergism of hearing loss was observed in animals co-exposed to impulse noise at a 'tolerable' dose of sound energy (less than 85 dB(A) over 8 h). Synergism was not apparent with continuous noise. The exposure levels to CS_2 were considerably higher that the Australian WES of 10 ppm (8-h TWA, to become 1 ppm), so it remains unclear whether such synergism exists under conditions closer to that WES.

Certain substances, including acrylonitrile, CS_2, and hydrogen cyanide, have a 'Skin' notation to alert against the contribution made by the dermal route of exposure to overall body burden. It is known that in some situations, the dermal route can be a greater contributor to systemic toxicity than the inhalation route. In such cases, compliance with airborne exposure standards and noise levels may be inadequate. At present, Australia has proposed some recommendations for control measures, such as reduced noise levels or reduced airborne exposure limits, that reflect the possibility for synergism, but as these are not mandatory, it is expected that adherence to these recommendations would be low.

5. Conclusions

Overall, in 1997, human epidemiological studies were considered inadequate for assessing the combined effects of noise and chemicals on health. Since 1997, the evidence from epidemiology studies shows little change, many related to mixed exposure workplaces, or noisy environments where it was hard to be definitive about

associations. Few exceptions demonstrated potential early signs of hearing loss in workers co-exposed to low levels of noise, and a mixture of solvents, including toluene, ethylbenzene, xylenes, and n-hexane. Each component was lower than the respective occupational exposure standards. However, it was recognised that there may have been exceedances that could not be accounted for in the study design. Longitudinal studies would be more informative in determining hearing loss, or indeed some other chronic ill health outcomes. In animals, there was evidence of potentiation at ototoxic levels of noise and styrene. Of greater interest was the new observation of potentiation when noise was applied as a short-term peak exposure, one that equated to a noise energy level deemed 'compliant'. The most noteworthy finding to emerge has been from animal studies of styrene, toluene, and CS_2, showing synergism seen when noise is delivered as an 'impulse'. Under these study conditions, the noise levels did not exceed the instantaneous limit of 140 dB(C) nor the 85 dB(A) dose over 8 h, which poses the question whether current workplace exposure limits for noise give adequate protection against damage to hearing for workers exposed to styrene or toluene.

In summary, it remains unclear whether there is synergism between the toxic effects of certain chemicals and noise at levels of exposure at or below the regulatory standards for each, and further research is needed to address this gap in knowledge, particularly at levels around the corresponding substance and noise exposure standards. As can be seen, the available evidence on any given substance is variable in extent and quality. The magnitude of effect is frequently unclear, particularly when considering the potential harm at exposures at or below corresponding exposure limits. The mode of action of toxicity for any given substance is typically not well-understood and is expected to vary from substance to substance. There is also further emerging evidence that noise can cause harm to organs other than hearing or circulation, which have long been the focus of studies, and this too, would benefit from more work. In addition, the Australian Work Health and Safety regulations that are associated with noise make no reference to the importance of frequency—for individuals work-related hearing loss is very often limited to a particular frequency. The issue of how frequency impacts on organ damage has not been thoroughly investigated and warrants further research.

Supplementary Materials

The additional data and information can be downloaded at: https://media.sciltp.com/articles/others/250523115137549 8/WAH-907-SM.pdf.

Author Contributions

R.C.-C.: conceptualization, methodology, data curation, analysis and interpretation, writing—original draft preparation. L.T.N.: methodology curation and writing; C.R.: supervision; writing—reviewing and editing. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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