SYSTEMATIC REVIEW

Prevention and Management Intervention (PMI) of Occupational Ototoxic Exposure in Industrial Perspective Globally: A Systematic Review

Ainul Naqueah Zainal Abidin[1,2], Mohd Shukri Bin Mohd Aris[1], Ailin Razali[3], Norazura Ismail[4]

[1] Faculty of Health Sciences, Universiti Teknologi MARA, 42300 Bandar Puncak Alam, Selangor, Malaysia,
[2] Faculty of Occupational Safety and Health, University of Cyberjaya, 63000 Cyberjaya, Selangor, Malaysia,
[3] Faculty of Medicine, International Islamic University Malaysia, 25200 Kuantan, Pahang, Malaysia,
[4] Faculty of Industrial Sciences and Technology, University Malaysia Pahang, Lebuhraya Tun Razak, 26300 Kuantan, Pahang, Malaysia

ABSTRACT

Introduction: The World Health Organisation (WHO) has estimated an increasing number of occupational hearing loss. In Malaysia, there is high pervasiveness of hearing loss and hearing impairment among manufacturing workers. Ototoxicity Prevention and Management Intervention (PMI) is not yet established in the majority of countries, including Malaysia. This work aims to investigate the ototoxicity PMI from international guidelines and global reports. **Method:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flow diagram was adopted for item selection. Two large data sets were used: (1) published, peer-reviewed articles obtained through two search strategies (PubMed and Web of Science); and (2) grey literature. **Results**: Sixteen items were identified and were categorised into a triad of approaches; exposure-based, knowledge-based, and clinical-based approaches. **Conclusion**: The way forward rises from this study suggested that an effective ototoxicity PMI is needed in occupational settings where ototoxic chemical (ototoxicants) exposure occurs. Therefore, more efforts should be geared toward ototoxicity PMI especially in developing countries.
Malaysian Journal of Medicine and Health Sciences (2022) 18(SUPP15): 308-317. doi:10.47836/mjmhs18.s15.43

Keywords: Ototoxicity, Ototoxicants, Hearing loss, Occupational exposure, Industry

Corresponding Author:
Mohd Shukri Bin Mohd Aris, PhD
Email: myshukri@uitm.edu.my
Tel: +603-32584525

INTRODUCTION

Hearing loss is the world's fourth leading cause of disability, costing nearly 750 billion dollars yearly. The World Health Organisation (WHO) further estimated an increase occupational hearing loss, despite the successful enforcement of noise control in industries. More specifically, WHO has projected that nearly 2.5 billion individuals will suffer from hearing loss by 2050 (1). WHO (1) also stated that work-related ototoxic chemicals are one of the factors that lead to hearing loss. These chemicals are referred to as ototoxicants, characterised as "any substance, including drugs or industrial chemicals, that is toxic to the auditory system". This disease has become a universal concern but it is highly preventable.

As ototoxicants change the membrane structure of Corti, it may become more brittle and susceptible to noise (2). The immediate effect of ototoxicants on the cells of Corti is that it causes their membranous structures to be disrupted, resulting in an acute damage mechanism. Meanwhile, the chronic ototoxic consequences may be attributable to the development of chemically and physiologically reactive intermediates. The ototoxicants are damaging to both the peripheral and central auditory systems. Toluene, for example, has been found to increase inhibitory synaptic responses and block the middle-ear acoustic reflex as a central nervous system (CNS) depressant (cholinergic efferent system) (3).

According to the National Institute for Occupational Safety and Health (NIOSH) Bulletin (4), these ototoxicants could enter the body through inhalation of fumes, ingestion, and skin absorption. There are five classes of ototoxicants: [1] pharmaceuticals; [2] solvents (trichloroethylene, n-propylbenzene, toluene, carbon disulfide, methyl styrene, n-hexane, ethylbenzene, p-xylene, styrene); [3] asphyxiants (tobacco smoke, carbon monoxide, hydrogen cyanide and its salts); [4] nitriles (cis-crotononitrile; 3,3'-iminodipropionitrile;

cis-2-pentenenitrile; 3-butenenitrile; acrylonitrile); and [5] metal compounds (lead, organic tin compound, germanium dioxide, mercury compound). Some industries that utilise these potential ototoxicants are the utilities, agriculture, manufacturing, and mining sectors, where subsectors of the manufacturing industry could include machinery, petroleum, electrical equipment, fabricated metal, textiles and apparel, paper, chemical, furniture and related products, leather and allied products, transportation equipment (e.g., ship and boat building), appliance and component (e.g., batteries), and solar cell industries (4).

According to research conducted in the printing industry, the current limit of 50 ppm toluene was deemed insufficient causing the development of hearing damage from occupational exposure to toluene and noise (5). Juárez-Pérez et al. (6) discovered the possibility of concurrent ototoxicity and neurotoxicity conditions even in low solvent mixture concentrations and noise levels in the paint manufacturing industry. The authors also encouraged integrating brainstem auditory-evoked potentials (BAEP) investigation in the assessment evaluations. In Washington, Schaal et al. (7) conducted a study on shipyard workers. The authors concluded that simultaneous high-level exposures to metals, solvents, and noise appear to harm hearing more than noise alone. Therefore, exposure to metals, solvents, and noise should all be included in hearing conservation programs, not only noise exposure. According to Śliwinska-Kowalska et al. (8), the distortion product otoacoustic emissions (DPOAE) and auditory brainstem response (ABR) procedures in styrene-exposed, noise-exposed, and non-exposed participants signify the likelihood of styrene exposure linked to cochlear dysfunction in humans. Because of the variations in DPOAEs across groups, this study concluded that the method could be used in conjunction with pure-tone audiometry to monitor hearing in styrene-exposed employees.

Meanwhile, Mohd Aris et al. (9) have studied the accessible scientific literature on the negative consequences of ototoxicants, particularly on the impact of solvents on the auditory function of the workers in diverse workplace settings in Asia. Key findings of this study indicated that the ototoxic solvent's interaction with the noise might be synergistic and additive. In addition, the review discovered the significance of recognising the type of hearing loss and equipment that are essential for intensifying auditory reception in hearing loss. Researchers have recommended the adoption of a test with higher accuracy called the Otoacoustic Emission to complement pure tone audiometry. Hemmativaghef (10) performed a systematic review to establish the assessment of the dose-response relationships, controls, and regulations. This review focuses on lead, mercury, styrene, and toluene. This study concluded that the increased risk of hearing loss resulting from lead, styrene, and toluene exposure must be considered while establishing enforceable rules concerning ototoxicants exposures. Meanwhile, Nakhooda et al. (11) conducted another review to ascertain how combined exposure of solvents and noise affects auditory function. The findings indicated that when employees were exposed to both solvents and noise, their chances of developing hearing loss were substantially higher than those simply exposed to solvents. The study also recommended involvement in a Hearing Conservation Program (HCP) for those exposed to ototoxic solvents and noise simultaneously. All reviews found evidence of a substantial link between ototoxicants and hearing loss. Therefore, impactful action should be taken to avoid and control the risk of ototoxicity.

Further to the above, Sam et al. (12) reported a high prevalence of hearing loss and hearing impairment among manufacturing workers in Malaysia regardless of the successful enforcement of noise management in the industries. Malaysia lacks the legislation or guidelines to supervise ototoxicity, and local industrial working procedures conducted irrespective of possible adverse health effects of chemical substances on the auditory system. Legislation mandating the safe use of ototoxicants in the industry and managerial intervention or recommendations, should be established.

Therefore, the present systematic review aims to explore and provide an overview of ototoxicity prevention and management intervention (PMI) from international guidelines and studies reported across the globe. This review has gathered the existing ototoxicity PMI recommendations for policymakers to consider in developing the best ototoxicity PMI for the workplace.

METHODOLOGY

Data Sources

Two large data sets were used: [1] published, peer-reviewed publications (acquired via two search databases); and [2] grey literature. The Web of Science (WoS) and PubMed were accessed for articles within 21 years (2000–2021) using the following keywords: (solvent OR chemicals OR ototoxicant) AND hearing loss AND (interventions OR management OR protocol OR policy) NOT (patients OR clinical OR cisplatin OR neonates).

Quality Appraisal

One reviewer retrieved the study's features and entered them into the data extraction forms created especially for the review. A second reviewer assessed any inconsistencies, and decisions were reached via discussion. Several approaches were utilised to assure reliable, trustworthy data during the data collection and analysis phases, including confirming the legitimacy of the data source. The adoption of triangulation of different data sources and multiple data gathering methods has enhanced the reliability of the entire study.

This enhancement is achieved through triangulation by testing the validity through data convergence from various sources, all in a comprehensive search of ototoxicity management and intervention (grey, published). Subsequently, a backward and forward snowballing method was applied to guarantee full data coverage, and recognise any other relevant items (13). The relevant items were chosen via establishing a set of inclusion and exclusion criteria (Table I).

Table I: Inclusion and exclusion criteria

Criterion	Inclusion	Exclusion
Time	1st January 2000 onwards	31st December 1999 and below
Language setting	English	Non-English
Exposure setting	Occupational chemicals	Pharmaceutical drugs
Article type	Intervention study, Human study	Animal study, Environmental study, Clinical study, Systematic review study, Case study, Case series, Letter

RESULTS

Selection Process

The search was carried out according to the criteria set out in the Preferred Reporting Items for Systematic Reviews (PRISMA) 2020. A database search for human species and English language filters turned up 200 articles. Ten duplicate entries were deleted, and 160 were eliminated for other reasons. The inclusion and exclusion criteria were used to further filter the remaining 30 articles for further eligibility. Another 27 items were removed from the list because they did not fulfil all of the necessary criteria. The 27 items consisted of 16 non-intervention studies and 11 non-ototoxic studies. The remaining three selected articles were further screened using the snowballing approach to result in additional five articles. Snowballing is the process of identifying more articles utilising a paper's reference list or citations. On the other hand, snowballing may benefit from a systematic approach of looking at where publications are referred and cited, by looking at reference lists and citations (13). A total of eight published, peer-reviewed articles were eligible and included in this systematic review.

The search strategies were complemented with a comprehensive search of the 'grey' literature, i.e., publications not published in indexed peer-reviewed journals. According to Godin et al. (14) for large-scale review syntheses, grey literature is an essential source of information. Paez (15) reported that grey literature may reduce publication bias, increase the comprehensiveness and timeliness of reviews, and foster a balanced picture of the available evidence. A search on Google search engine was performed using the terms: 'chemical-induced hearing loss' OR 'ototoxicants' OR 'chemical' AND 'hearing loss'. The Google search was limited to the first 15 pages. During the selected published articles forward and backward snowballing process, the grey literature from the articles were extracted, reviewed, and analysed for the current study. After excluding two items due to language barriers, eight items from the grey literature were identified and selected from a directive, government report, and professional association. Therefore, 16 full-text items comprising of published articles (eight items) and grey literature (eight items) were selected for this systematic review. Fig. 1 summarises the items selection process.

Description of inclusion items

Data type

There were 16 selected full text items consisting of eight (n=8) published articles (16-23) and eight (n=8)

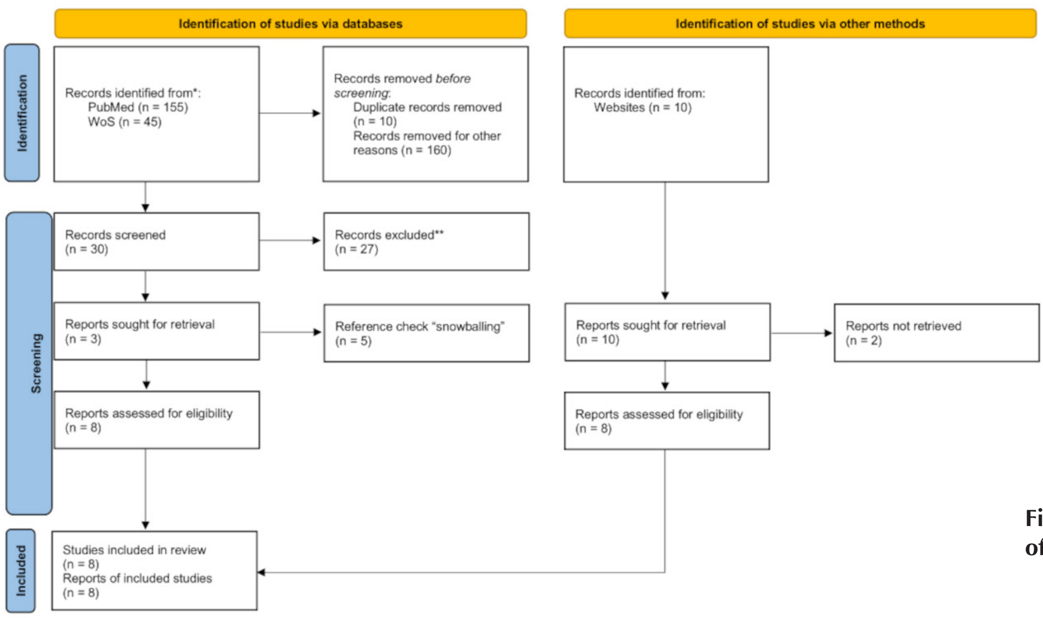

Figure 1: Flow Diagram of Selection Process

grey literature items from directives (24), professional association (4, 25-27), and government reports (28-30).

Country
The published articles were from France (16), United States (17), European countries (18), Nordic countries (Denmark, Sweden, Norway, Finland) (19), Australia & China (20), Germany (21), Canada & United States (22), and United States (23). The existing ototoxicity PMI from grey literature was mainly from developed countries including European countries (24), United States (4, 27, 29), Canada (25), Australia (26, 28), and Australia & New Zealand (30).

PMI Approach
In this review, 14 out of 16 (88%) selected items specifically focused on exposure risk reduction and control. The risk reduction and control approaches mentioned include [1] conducting risk assessment (4, 21-24), [2] wearing personal protective equipment (PPE) (4, 16, 17, 23), [3] reducing exposure limit of chemical exposure (17, 23, 27) and noise exposure (28), [4] audiometry monitoring (4, 17, 18, 20, 22-24, 26-30), and [5] adding a "Noise notation" to the Threshold Limit Values (TLV) (19, 27).

Additionally, 31% (n=5) of the selected items focused on stimulating and enhancing knowledge of the hazardous health effects of ototoxicants (4, 18, 25, 28, 30). Certain chemicals have been recognised and listed as ototoxic agents, and are associated with hearing loss (4, 25, 28, 30). NIOSH Bulletin (4) also suggested reviewing the Safety Data Sheet (SDS). Similarly, Śliwinska-Kowalska et al. (18) recommended a new R-phrase in labelling for ototoxic endpoints in the safety material. Furthermore, awareness among occupational physicians and decision-makers (18) as well as employers and employees (4) also need to be raised.

Of the selected items, 31% (n=5) suggested clinical assessments including the test battery approach (20), Otoacoustic Emissions (OAE) test (17, 22, 23), air conduction pure tone audiometry (without masking) (17, 30), assessment of the loss of communication skills (17, 22), middle-ear testing (22), extended high-frequency audiogram (17, 23), as well as electrophysiological and/or central auditory processing (CAP) screening tests (23). Table II and Table III provide a summary of the reviewed items that include reference, data type, countries, and PMI approach.

DISCUSSION

Exposure-based approach
A diverse approach to interventions was apparent in these 16 selected items. The exposure-based approach was the most commonly implemented and recommended type of ototoxicity intervention, whereby the focus was on exposure reduction and control to reduce the risk. Exposure elimination is the most effective and preferred primary preventive strategy in risk management. If removal is not achievable, exposure reduction is the second-best approach for primary prevention. Reduction refers to the diminution of the likelihood and severity of an undesirable risk event to be under acceptable threshold levels. Srinivas (31) reported that the risk reduction approach is applied if the resultant increase in cost is less than the potential loss generated by the risk being mitigated.

Another approach involves conducting a risk assessment for the combination of noise and ototoxic chemical exposure. European countries in the European Noise Directive indicated that the interactions of noise with other risks (ototoxicants) must be given special consideration by the employer by conducting a risk assessment (24). United States in NIOSH Bulletin (4) stated that when ototoxicants are discovered in the workplace, substituting a less toxic chemical for a hazardous chemical is a good approach to lower the risk of exposure. If removing ototoxicants from the workplace is not practicable, utilising engineering measures to restrict exposure to ototoxicants and noise, such as isolation and enclosures, may lower the likelihood of harmful health consequences. Regarding ototoxicants, ventilation is also a suggested control strategy (4). The bulletin also encouraged employers to examine and choose the necessary PPE in accordance with 29 CFR 1910.132, 29 CFR 1910.134, and 29 CFR 1910.138, which include general requirements, respiratory protection, and hand protection. Chemical-resistant gloves, long sleeves, aprons, and other appropriate clothing can help to reduce cutaneous exposure because most ototoxicants can enter the body through skin absorption.

The statement is in accordance with previous studies that suggested even though noise levels are below the legal limit, workers are still encouraged to wear hearing protection equipment while exposed to noise and ototoxicants concurrently (16-17, 23). Similarly, the Spanish transposition of the Noise Directive has clearly stated that ototoxicity could be prevented by controlling exposure using a suitable PPE while being exposed to the ototoxicants (32). Removing the source of risk via engineering controls, limited exposure time, and use of personal protective equipment is deemed the most effective means of avoiding hearing loss from noise or chemical exposure in the workplace (22). Previous studies also claimed that risk management strategies aimed at decreasing ototoxicants exposure should be encouraged and the personal protective equipment used by the workers exposed to ototoxicants need to be evaluated (11, 23).

The majority of the items suggested the implementation of audiometry monitoring for workers who were exposed to ototoxicants regardless of the noise level (4,

Table II: Summary of the included items from published literature

Reference	Country / Region	PMI Recommendation
Campo & Maguin (16)	France	1. Use of hearing protection for the lower exposure action value: Lex_{8h} = 80 dB(A) in noisy environments polluted by solvents.
Morata (17)	United States	2. Specify time of exposure. 3. Prioritise personal monitoring. 4. Evaluate personal protective equipment used. 5. Assign to hearing loss prevention program. 6. Target workers who work long period of time to examine biological effect. 7. Use pure-tone audiometry, high frequency audiometry, acoustic reflex test, speech test, otoacoustic emission, evoked potentials.
Śliwinska-Kowalska et al. (18)	Europe	1. Yearly audiograms. 2. A new R-phrase in labelling for ototoxic endpoints in the safety material. 3. Raise occupational physicians' and decision-makers' awareness.
Johnson & Morata (19)	Nordic countries (Denmark, Sweden, Norway, Finland)	1. A "Noise notation" to be added to the Threshold Limit Values (TLV) for certain chemicals that has a high probability of being ototoxic in an occupational setting.
Adrian Fuente and Bradley McPherson (20)	Australia & China	1. Routinely monitored employees who have been exposed to ototoxicants, regardless of noise level. 2. Enrolment in Hearing Conservation Programmes for employees who have been exposed to ototoxicants, regardless of noise level. 3. Test battery approach should be considered.
Nies (21)	Germany	1. Ototoxicity should make part of occupational health-screening activities. 2. Risk management measures aimed at reducing exposure.
Campo et al. (22)	Canada & United States	1. Conduct risk assessment and control. 2. Frequent medical monitoring for workers exposed to ototoxic substances, irrespective of the noise exposure level. 3. Use Distortion Product Otoacoustic Emissions (DPOAEs) test. 4. Assessment of the loss of communication skills, a middle-ear test (a quick measure of the stapedial reflex), and questionnaires on exposure to chemicals should be carried out for early detection of hearing loss.
Hammill et al. (23)	United States	1. Workplace hazard assessments. 2. Specific exposure durations and specific exposure levels for ototoxic substances, with and without concurrent noise exposure. 3. Remove the source of the hazardous exposures, engineering control. 4. Assessment of ventilation systems. 5. Wear PPE when exposed to noise and ototoxins, even when noise levels are below the regulated threshold. 6. Enrol in Hearing Conservation Program for ototoxicant-exposed workers. 7. OAE testing, extended high-frequency audiometry, electrophysiology, and/or central auditory processing (CAP) evaluations. 8. Perform electrophysiological and/or CAP screening tests despite normal pure-tone and OAE results.

17-18, 20, 22-24, 26-30). Furthermore, United States in U.S. Army (29), American Conference of Governmental Industrial Hygienists (ACGIH) (27), and NIOSH Bulletin (4) recommended annual audiometry monitoring. According to ACGIH (27), any exposure to ototoxicants that exceeds 50% of each chemical's individual occupational exposure limit, whether in conjunction with noise or alone, would result in participation in a hearing conservation program. Similar findings were also reported by other countries like Germany in German Social Accident Insurance (DGUV) (20), Spain in National Institute of Safety and Hygiene at Work (INSHT) (32), Australia in Australian-New Zealand Standard AS/NZS 1269.4.2014 (30), Safe Work Australia (28) and Australian Institute of Occupational Hygienist (AIOH) (26), who recommended that workers who have been exposed to chemicals (without using respiratory protection) should be subjected to frequent audiometric testing, regardless of the noise level. Moreover, past researches have reported the need to include audiometric monitoring in future regulations for exposed employees regardless of the level of noise exposure (10, 11, 20, 22). Additionally, a study from Śliwinska-Kowalska et al. (18) recommended that yearly audiograms should be suggested in chemical safety cards. Previous works have also revealed the necessity to include employees that have been exposed to ototoxicants in the HCP (9, 17, 20, 23). Nevertheless, the most significant enhancement for occupational safety and ototoxicity prevention would be the inclusion of personnel exposed to potentially ototoxicants in existing hearing conservation programmes despite whether they are subjected to noise or otherwise (23).

As recommended by Hoet & Lison (33), the Nordic Expert Group also stated that when a chemical is combined with noise exposure, a noise notation can be used to signify an elevated risk of hearing damage. A "Noise notation" was recommended to be added to the TLV for certain chemicals that are highly likely to be ototoxic in an occupational setting (19). Similarly, ACGIH added a new "OTO" note to its 2019 Threshold

Table III: Summary of the included items from grey literature

Reference	Data type	Country / Region	PMI Approach
EU Noise Directive 2003/10/EC (24)	Directive	European countries	1. Conduct a risk assessment for the combination of noise and ototoxic exposure. 2. Employers should pay attention to occupational noise monitoring in the case of co-exposure with work-related ototoxic substances.
CCOSH[1] (25)	Professional association	Canada	1. Listed benzene, xylene, ethylbenzene hydrogen cyanide, n-hexane, styrene, trichloroethylene, toluene associated with hearing loss.
Safe Work Australia (28)	Government report	Australia	1. Recognize solvent as ototoxic agents. 2. Reduce daily noise exposure to 80 dBA or below for workers exposed to solvents. 3. Regular annual audiometric testing for selected chemicals is at 50% or more of exposure standards, regardless of the noise level.
Army Hearing Program (29)	Government report	United States	1. Enrolment in the Army Hearing Program (AHP) for workers exposed to ototoxin exceeds 50 percent of the occupational exposure limit. 2. All noise-exposed and/or ototoxin-exposed DA Civilian personnel must receive annual and termination audiograms
AIOH[2], 2016 (26)	Professional association	Australia	1. Annual audiometric testing program
Hannah et al. (30)	Government report review	Australia & New Zealand	1. Audiometric test for workers exposed to known/suspected ototoxic chemicals. 2. Recognise organic solvents such as toluene, xylenes, styrene, and trichloroethylene as industrial ototoxicants. 3. Requirement for air conduction pure tone audiometry (without masking) (AS/NZS 1269.4.2014).
NIOSH Bulletin[3], (4)	Professional association	United States	1. Listed and recognized ototoxic chemicals 2. Conduct risk assessment 3. Review Safety Data Sheet 4. Provide information and training to workers 5. Replace with less toxic chemicals 6. If elimination is not possible, use engineering control or reduce exposure 7. Respiratory protection and hand protection equipment. 8. Audiometric test even to workers exposed below the noise action level and ototoxicants below the Permissible Exposure Limit.
ACGIH[4], Threshold Limit Values and Biological Exposure Indices, ACGIH Publication, Cincinnati (27)	Professional association	United States	1. Adopted a new “OTO” notation. 2. Periodic audiograms where exposure to toluene, lead, manganese, or n-butyl alcohol, carbon monoxide, styrene, toluene, or xylene occurs. 3. Established Permissible Exposure Limits for some organic solvents.

[1] Canadian Centre for Occupational Safety and Health
[2] Australian Institute of Occupational Hygienist
[3] National Institute for Occupational Safety and Health Bulletin
[4] Ameriacan Conference of Governmetal Industrial Hygienists

Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices to indicate a chemical’s propensity to induce hearing damage alone or in conjunction with noise. The OTO notation aims to illuminate the significance of diminishing exposure via engineering, administrative, and personal protective equipment (PPE) controls, apart from the consideration of assigning affected employees in the hearing conservation and medical surveillance programmes to regulate auditory capacity (27).

Meanwhile, Safe Work Australia (28) stated the need to reduce the daily noise exposure for workers concurrently exposed to ototoxic solvent to 80 dBA or below. ACGIH (27) in the United States has set an acceptable exposure limit for several organic solvents. Similarly, Nies (21) stated that Germany in DGUV also recommended that ototoxicants should have an exposure limit. As defined by the European Agency for Safety and Health at Work, scientists from France’s Institut National de la Research Scientifique (INRS) proposed reducing the styrene exposure limit from 50 to 30 ppm and implementing an eight-hour noise OEL of 80 dBA (32). Furthermore, a recent work by Mohd Aris et al. (9) suggested a lower permissible exposure limit for each noise and solvent than the current permissible limit. Correspondingly, Hemmativaghef (10) recommended reducing noise exposure of workers exposed to ototoxicants to 80 dB(A) or below in an 8-hour shift.

Knowledge-based Approach

The current review also revealed that providing sufficient education and information to the workers should be considered in developing an intervention (4, 18, 25, 28, 30). Workers must be aware of the dangers they face, the harm they may inflict, and the measures they can take to avoid these negative consequences.

Notably, United States in NIOSH Bulletin listed and grouped ototoxicants into five classes (4). The Australian and New Zealand standards (AS/NZS 1269.0:2005) have listed organic solvents such as toluene, xylenes, styrene, and trichloroethylene under occupational ototoxicants (30). Comparably, Australian government organisations, such as Safe Work Australia and the Department of Commerce, have recognised the aforementioned solvents as ototoxicants (28). Meanwhile, Canada reported hearing loss related to benzene, xylene, ethylbenzene hydrogen cyanide, n-hexane, styrene, trichloroethylene, and toluene (25). In European countries, EU-OSHA has classified solvents, including toluene, styrene, and p-xylene, among others, as agents with the high damaging potential to the hearing systems (32). In 2006, the European Parliament enacted the Noise Directive (2003/10/EC), unanimously approved by all EU member states (24). Employers need to assess the effect of noise and work-related ototoxicantson the health and safety of the workers under this regulation and in accordance with the abovementioned directive.

Other than recognising ototoxicants, United States in the NIOSH Bulletin also suggested the SDS to be reviewed (4). SDS is a document that contains basic information on a substance or chemical. It explains the material's characteristics and potential risks, as well as its proper usage and steps to take in case of emergencies. The SDS is a necessary first step in developing a comprehensive health and safety program for the substance (34). Moreover, the addition of new R-phrase for the labelling of ototoxic endpoints is recommended in the safety material for the described solvents. The R48 denotation describes the "danger of serious damage to health by prolonged exposure", which may be utilised similarly to toluene (18).

United States in NIOSH Bulletin (4) recommended the provision of information and training to workers. Similarly, scientific data should be disseminated to promote awareness among employees, employers, healthcare experts, and lawmakers (18). Germany in DGUV (32) also recommended the need to educate workers, public health professionals, and policy-makers on the ototoxicity risk. Additionally, DGUV has suggested public ototoxic risk communication. WHO (35) stated that advocacy efforts at the global, regional, and national levels should be pushed to encourage policymakers to prioritise hearing care funding allocation. It is also critical to improve public knowledge about hearing loss. By being informed of the risks involved, they will be empowered to protect their hearing. According to the Department of Occupational Safety and Health (DOSH) Malaysia, employees should get the skills and knowledge they need to do their jobs safely and without putting their health in danger through information, teaching, and training. It enables individuals to adhere to health and safety protocols, employ risk controls put in place for their protection, as well as understand the nature of the hazard, the risks connected with its usage, and why risk controls are used (36).

Clinical-Based Approach

Other than controlling the exposure and educating workers, some of the items suggested a more sensitive clinical assessment (17, 20, 22, 23, 30). According to (20), the test battery approach should be considered in the audiological procedure. Employees exposed to specific organic solvents may experience central auditory and/or vestibular dysfunction, according to human research. Hence, when creating their clinical test battery, physicians should take this information into account (23). Studies also suggested using the Distortion Product Otoacoustic Emissions (DPOAEs) test (22, 23). This was in agreement with a previous study by Sisto et al. (37) whereby the study found DPOAE to be a sensitive indicator of inner dysfunction linked to organic solvent exposure coming from the oxidative process. The study also confirmed DPOAE's high oxidative stress sensitivity.

Australia in Australian-New Zealand Standard stated the requirement for air conduction pure tone audiometry (without masking) (30). Additionally, Spain in Spanish transposition of the Noise Directive (32) proposed that audiometric control be expanded to include appropriate audiological tests such as OAE and high-frequency audiometry. OAEs postulate a delicate assessment of the outer hair cell integrity. As such, they can be applied to distinguish sensory and neural or central hearing issues, apart from detecting the early signs of cochlear injury. The diagnostic OAE testing aims to deliver fast, accurate, and non-invasive objective assessment of cochlear function. According to Hammil et al., (23) clinicians are also encouraged to do electrophysiological and/or central auditory processing (CAP) screening tests on people with a history of exposure to known neurotoxic drugs, particularly if the person has difficulty comprehending speech despite normal pure-tone and OAE findings.
Campo et al. (22) reported the necessity to conduct assessment of the loss of communication skills, a middle-ear test (a rapid assessment of the stapedial reflex), and questionnaires regarding chemical exposure. These tests are utilised to allow for early diagnosis and an accurate evaluation of the entire impact on employees' hearing. This set of tests might potentially be used to detect neurotoxicity early on. Apart from high frequency audiometry, speech test, and OAE, Morata (17) also suggested the use of acoustic reflex test and evoked potentials (auditory brainstem response and cortical potentials).

In this review, the recommendations amassed were encouraged by American Speech-Language-Hearing Association (ASHA) and the American Academy of Audiology (AAA). The aforementioned groups revealed that the baseline audiometry should comprise behavioural measures such as pure-tone audiometry (PTA) from 250 Hz to 8,000 Hz and high-frequency audiometry (HFA) from 9,000 Hz to 20,000 Hz, in addition to objective measures such as distortion product of otoacoustic emissions (DPOAEs) and tympanometry. Each measure of peripheral and/or central auditory function, apical versus basal cochlear turn, and subjective versus objective assessment is considered useful information in an ototoxicity monitoring programme (38).

Strengths and limitations of the study

This review's major strength is its thorough search for a large number of existing ototoxicity PMI studies including published articles and grey literature. However, only including items that were published in the English language is the limitation that should be considered. This may have prevented relevant articles in other languages from being included in the review.

CONCLUSION

This study has gathered the existing ototoxicity PMI for the policy-makers to consider in developing the best workplace ototoxicity PMI by using a triad approach; exposure-based, knowledge-based, and clinical-based approach. We acknowledge that developing countries have not paid enough attention to the ototoxicity PMI and that local industrial working procedures are carried out without awareness of the potential negative health effects of chemical agents on auditory systems. Hence, more efforts should be geared toward ototoxicity prevention and management particularly in developing countries. Despite the fact that some nations have taken initiatives to address hearing loss caused by ototoxicantsexposure, the ototoxicants exposure limits have yet to be revised by laws to account for the increased risk of hearing impairment. More epidemiological research should be done to investigate dose-response relationships between ototoxicants exposure levels and auditory outcomes in order to estimate the interactive effect and the involvement of other risk factors. Denial, especially when noise is the only risk factor for occupational hearing loss and policymakers do nothing to control ototoxic risk, can result in prolonged exposure and delayed treatment, further exacerbating the issues associated with hearing loss.

ACKNOWLEDGEMENT

UMP-IIUM-UiTM Sustainable Research Collaboration 2020 (600-RMC/SRC/5/3 (009/2020)) has granted fund for this research.

REFERENCES

1. World Health Organisation. Deafness and Hearing Loss [Internet]. 2021 April 1 [cited 2021 September 21]. Available from: https://www.who.int/news-room/fact-sheets/detail/deafness-and-hearing-loss
2. Hsu PC, Cheng PW, Young YH. Ototoxicity from organic solvents assessed by an inner ear test battery. J Vestib Res: Equilib Orientat. 2015;25(3–4):177–83. doi: 10.3233/ves-150559
3. Joong-Keun K and Jiho L. Occupational Hearing Loss. In: Wang T, editor. Hearing Loss - From Multidisciplinary Teamwork to Public Health [Internet]. London: IntechOpen; 2021 [cited 2022 January 20]. Available from: doi: 10.5772/intechopen.97109
4. Occupational Safety and Health Administration, & National Institute for Occupational Safety and Health. Preventing hearing loss caused by chemical (Ototoxicity) and noise exposure. Safety Health Inf. Bull. 2018;1–5.
5. Schaper M, Seeber A, Van Thriel C. The effects of toluene plus noise on hearing thresholds: An evaluation based on repeated measurements in the German printing industry. Int J Occup Med Environ Health. 2008;21(3):191–200. doi: 10.2478/v10001-008-0030-z
6. Juбrez-Pйrez C.A., Torres-Valenzuela A, Haro-Garcнa LC, Borja-Aburto VH, Aguilar-Madrid G. Ototoxicity effects of low exposure to solvent mixture among paint manufacturing workers. Int J Audiol. 2014;53(6):370–76. doi: 10.3109/14992027.2014.888597
7. Schaal NC, Slagley JM, Richburg CM, Zreiqat MM, Paschold HW. Chemical Induced Hearing Loss in Shipyard Workers. J Occup Environ Med. 2018;60(1):e55-e62. doi: 10.1097/jom.0000000000001186
8. Sliwinska-Kowalska M, Fuente A, Zamyslowska-Szmytke E. Cochlear dysfunction is associated with styrene exposure in humans. PLoS ONE 2020; 15(1):e0227978. doi:10.1371/journal.pone.0227978
9. Mohd Aris MS, Zainal Abidin AN, Razali A, Ismail N, Fuente A. Solvent-induced hearing loss from occupational exposure in Asia – A systematic review. Environ Behav Proc J. 2021;6(17):125–33. doi: 10.21834/ebpj.v6i17.2872
10. Hemmativaghef E. Exposure to lead, mercury, styrene, and toluene and hearing impairment: evaluation of dose-response relationships, regulations, and controls. J Occup Environ Hyg. 2020;17(11–12):574–597. doi: 10.1080/15459624.2020.1842428
11. Nakhooda F, Sartorius B, Govender SM. The effects of combined exposure of solvents and noise on auditory function – a systematic review and meta-analysis. S Afr J Commun Disord. 2019;66(1):e1–e11. doi: 10.4102/sajcd.v66i1.568
12. Sam WY, Anita AR, Hayati KS, Haslinda A, Lim CS. Prevalence of hearing loss and hearing impairment among small and medium enterprise workers in Selangor, Malaysia. Sains Malays. 2017;46(2):267–74. doi: 10.17576/jsm-2017-4602-11
13. Wohlin, C. Guidelines for snowballing in systematic literature studies and a replication in software engineering. New York, NY, USA: Association for Computing Machinery; 2014. doi: 10.1145/2601248.2601268
14. Godin K, Stapleton J, Kirkpatrick SI, Hanning RM, Leatherdale ST. Applying systematic review search methods to the grey literature: A case study

examining guidelines for school-based breakfast programs in Canada. Syst Rev. 2015;4(1):1–10. doi: 10.1186/s13643-015-0125-0
15. Paez A. Gray literature: An important resource in systematic reviews. J Evid Based Med. 2017;10(3):233–40. doi: 10.1111/jebm.12266
16. Campo P, Maguin K. Solvent-induced hearing loss: Mechanism and prevention strategy. Int J Occup Med Environ Health. 2007;20(3):265-70. doi: 10.2478/v10001-007-0031-3
17. Morata TC. Chemical exposure as a risk factor for hearing loss. J Occup Environ Med. 2003;45(7):676–82. doi: 10.1097/01.jom.0000071507.96740.70
18. Śliwinska-Kowalska M, Prasher D, Rodrigues CA, Zamysłowska-Szmytke E, Campo, P, Henderson D, et al. Ototoxicity of organic solvents - From scientific evidence to health policy. Int J Occup Med Environ Health. 2007;20(2):215–22. doi: 10.2478/v10001-007-0021-5
19. Johnson AC, Morata, TC. Occupational exposure to chemicals and hearing impairment. Arbete och Halsa. 2010; 44(4):1-177.
20. Fuente A, McPherson B. Occupational chemical-induced hearing loss. In: Naz S, editor Hearing Loss [Internet]. London: IntechOpen; 2012 [cited 2021 September 21]. Available from: doi: 10.5772/33852
21. Nies E. Ototoxic substances at the workplace: A brief update. Arh Hig Rada Toksikol. 2012;63(2):147–52. doi: 10.2478/10004-1254-63-2012-2199
22. Campo P, Morata, TC, & Hong OS. Chemical exposure and hearing loss. Dis Mon. 2013;59(4):119–38. doi: 10.1016/j.disamonth.2013.01.003
23. Hammill T L, McKenna E, Hecht Q, Buchanan K, & Pryor N. I'm wearing my hearing protection-Am I still at risk for hearing loss? Lurking ototoxins in the military environment. Military Medicine. 2019;184(Suppl 1):615–620. doi: 10.1093/milmed/usy329
24. European Parliament and the Council of the European Union. Directive 2003/10/EC on the minimum health and safety requirements regarding the exposure of workers to the risks arising from physical agents (noise) [Internet]. 2003 February 15 [cited 2021 September 21]. O J EU. 2003;42:38-44.
25. Canadian Centre for Occupational Health and Safety. Chemicals and noise – a hazardous combination. [Internet]. 2009 December 1 [cited 2021 September 21]. Available from: http://www.ccohs.ca/newsletters/hsreport/issues/2009/10/ezine.html#inthenews
26. AIOH Exposure Standards Committee. Occupational Noise And Its Potential For Health Issues. [Internet]. Australian Institute of Occupational Hygienist; 2012 November (reformatted May 2016) [cited 2021 September 21]. Available from: https://azslide.com/occupational-noise-and-its-potential-for-health-issues_5a6d685c1723dd60821e7b31.html
27. American Conference of Governmental Industrial Hygienists. Threshold Limit Values and Biological Exposure Indices for Chemical Agents [Internet]. ACGIH Publication, Cincinnati; 2019.
28. Safe Work Australia. Occupational noise-induced hearing loss in Australia: overcoming barriers to effective noise control and hearing loss prevention [Internet]. Safe Work Australia; 2010 [cited 2021 September 21]. Available from: https://www.safeworkaustralia.gov.au/system/files/documents/1702/occupational_noiseinduced_hearing_loss_australia_2010.pdf
29. Department of the Army. Medical Services: Army Hearing Program. Department of the Army Pamphlet 40–501. Washington, DC; 2015 January 8 [cited 2021 September 21]. https://armypubs.army.mil/epubs/DR_pubs/DR_a/pdf/web/p40_501.pdf
30. Hannah L, Page W, Mclaren S. A review of occupational noise in New Zealand. New Zealand Acoustics. 2016;29(1):4-26 [cited 2021 September 21]. Available from: https://www.acoustics.org.nz/sites/www.acoustics.org.nz/files/journal/pdfs/Hannah_L_NZA_2016.pdf
31. Srinivas K. Process of Risk Management, Perspectives on Risk, Assessment and Management Paradigms. In: In: Hessami A G, editor. Perspectives on Risk, Assessment and Management Paradigms [Internet]. London: IntechOpen; 2019 [cited 2021 September 21]. Available from: doi: 10.5772/intechopen.80804
32. European Agency for Safety and Health at Work. Combined exposure to noise and ototoxic substances, EU-OSHA European Agency for Safety and Health at Work, Luxembourg; 2009 [cited 2021 September 21]. Available from: https://osha.europa.eu/sites/default/files/Doss%20WRO-108%20-%20Combined%20exposure%20to%20noise%20and%20ototoxic.pdf
33. Hoet P, Lison D. Ototoxicity of toluene and styrene: State of current knowledge. Crit Rev Toxicol.. 2008;38(2):127–70. doi: 10.1080/10408440701845443
34. Rout Bk Sikdar Bk. Hazard identification, risk assessment, and control measures as an effective tool of occupational health assessment of hazardous process in an Iron Ore Pelletizing Industry. Indian J Occup Environ Med. 2017;21(2):56–76. doi: 10.4103/ijoem.IJOEM_19_16
35. World Helath Organization. Addressing The Rising Prevalence of Hearing Loss [Internet]. World Health Organization: Geneva, Switzerland; 2018 [cited 2021 September 21]. Available from: https://apps.who.int/iris/handle/10665/260336
36. Department of Occupational Safety and Health. Guidelines for Hazard Identification, Risk Assessment and Risk Control (HIRARC). 2008 [cited 2021 September 21]. Available from: https://www.dosh.gov.my/index.php/competent-person-form/

occupational-health/regulation/guidelines/hirarc-2/1846-01-guidelines-for-hazard-identification-risk-assessment-and-risk-control-hirarc-2008/file
37. Sisto R, Cerini L, Sanjust F, Carbonari D, Gherardi M, Gordiani A, et al. Distortion product otoacoustic emission sensitivity to different solvents in a population of industrial painters. Int J Audiol. 2020;59(6):443–54. doi: 10.1080/14992027.2019.1710776
38. Ganesan P, Schmiedge J, Manchaiah V, Swapna S, Dhandayutham S, Kothandaraman P. Ototoxicity: A challenge in diagnosis and treatment. J Audiol Otol. 2018;22(2):59–68. doi: 10.7874/jao.2017.00360