

Review

OTOTOXIC SUBSTANCES AT THE WORKPLACE: A BRIEF UPDATE*

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Ototoxic chemicals can impair the sense of hearing and balance. Lately, efforts have been intensified to compile evidence-based lists of workplace agents with ototoxic properties. This article gives a rough overview of the latest relevant publications, which confirm that toluene, styrene, and lead should receive particular attention as ototoxic substances at the workplace. Moreover, there is sufficient evidence that occupational exposure to trichloroethylene, mercury, carbon monoxide, and carbon disulfide can affect the ear. Based on the existing information, industrial hygienists should make sure that occupational health professionals and the workforce are made aware of the risks posed by ototoxic substances; support their replacement or new technical measures to reduce exposure; make these substances a part of regular screening, develop tools that can early diagnose chemically induced hearing impairment, and investigate further into the ototoxic properties of these substances. Further research should focus on quantifying the combined effects of ototoxic substances and noise.

KEY WORDS: *carbon disulfide, carbon monoxide, hearing impairment, evidence-based risk assessment, lead, mercury, styrene, toluene, trichloroethylene, xylene*

Noise is not the only potential cause of hearing loss from damage to the inner ear. Certain chemical substances can also have reversible or irreversible effects that impair the sense of hearing and balance. They can affect the structure and/or the function of the inner ear (auditory and vestibular apparatus) and the neural pathways from the inner ear to the auditory cortex in the brain.

The first reports on ototoxic effects concerned pharmaceuticals (1). Some 1000 years ago, the Persian philosopher and medical scholar Avicenna warned that the treatment with mercury vapour against head lice could deafen the host. In the 19th century, antimalarial

drugs chloroquine, quinine, and salicylates were found to temporarily damage the ear. Other examples with clinical relevance are the ototoxic side-effects of aminoglycoside antibiotics or the loop diuretic furosemide.

The European Physical Agents Directive (2) stipulates that “the employer shall give particular attention, when carrying out the risk assessment, to (...) any effects on workers’ health and safety resulting from interactions between noise and work-related ototoxic substances.”

This review focuses on common workplace substances that are assumed to have ototoxic effects. These have come to the fore only in the last few decades and mostly include organic solvents, several metals, and asphyxiants like carbon monoxide. It mostly summarises the findings of three recently

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published comprehensive literature reviews, one by the Canadian Institut de recherche Robert-Sauvé en santé et en sécurité du travail (IRSST) (3), one by the European Agency for Safety and Health at Work (4), and one jointly presented by the US National Institute for Occupational Safety and Health (NIOSH) and the Nordic Expert Group (5).

It also includes information from the latest articles (published between 2009 and 2011) indexed in PubMed and other biomedical research abstracts that have not been mentioned in the three reviews referred to above.

RESULTS

Canadian Institute IRSST is a private, non-profit agency in the province of Quebec. It published its report on ototoxic chemicals at the workplace in 2009, although it had presented the main results earlier at international conferences. In collaboration with Montreal University, searches were performed in the existing literature for evidence of ototoxic properties of all 695 chemicals listed in Quebec's occupational safety and health regulation. Promising scientific pointers were found for more than two dozen substances. The documents were evaluated only for exposure concentrations up to the domestic short-term exposure limit or ceiling value, which is five times the eight-hour time-weighted average (TWA) occupational exposure limit (OEL) for humans. In animal studies, concentrations of up to 100 times the TWA were taken into consideration. Each substance was classified as either "ototoxic", "possibly ototoxic", "non-conclusive", or "no evidence", according to the score combining human and animal data. Only lead (and its inorganic salts) and the organic chemicals toluene, styrene, and trichloroethylene were ranked as "ototoxic".

In an annex to the report, the authors presented *fiches toxicologiques* (toxicological cards) for 27 substances, making transparent the rationale behind the decisions by giving very brief statements on the evaluated human and animal data, followed by a short conclusion. The full report is available in French only; an English article in a scientific journal was published more than two years later (6).

The European Agency for Safety and Health at Work (EU-OSHA) is a so-called policy agency governed by the EU public law, with its own legal personality. It was established by the European Council in 1994. EU-OSHA commissioned an international team of authors to compile information on combined exposure to noise and ototoxic substances. Realising that little information was available on these combined effects, the authors proceeded to develop another classification scheme for ototoxic substances, that led to three categories: "confirmed", "suspected", and "questionable ototoxic substance". Their weight-of-evidence approach was based on the methodological quality, quantity (magnitude of effect, number of studies from different centres or research groups, and sample size), and consistency of results published by different laboratories.

As a rule, human data were given priority over animal data, but EU-OSHA criticised the poor quality of the majority of epidemiological studies. Indeed, a clear relationship between industrial chemicals and hearing impairment is not easy to assess in humans, given the complexity of workplace environments where noise and various chemicals may be present simultaneously. Most of the published epidemiological studies have a cross-sectional design and relate chronic effects to currently measured exposures.

As EU-OSHA used a qualitative weight-of-evidence approach and relied predominantly on animal experiments, the lists of substances classified as

Table 1 Classification of ototoxic substances by the Institut de recherche Robert-Sauvé (IRSST), the European Agency for Safety and Health at Work (EU-OSHA), and the Nordic Expert Group (NEG).

SUBSTANCE	IRSST (2009)	EU-OSHA (2009)	NEG (2010)
Toluene	ototoxic	confirmed	Category 1
Styrene	ototoxic	confirmed	Category 1
Trichloroethylene	ototoxic	confirmed	Category 3
Mercury	non-conclusive	confirmed	Category 1
Lead	ototoxic	confirmed	Category 1
Carbon disulfide	possibly ototoxic	confirmed	Category 1
Carbon monoxide	no evidence	confirmed	Category 1

ototoxic is much longer and includes all the chemicals identified by IRSST, plus several nitriles (acrylonitrile, 3-butenitrile, *cis*-2-pentenitrile, *cis*-crotonitrile, 3,3'-iminodipropionitrile), carbohydrates (*n*-hexane, *p*-xylene, ethylbenzene, *n*-propylbenzene, methylstyrenes), hydrogen cyanide and its salts, carbon monoxide, carbon disulfide, and compounds of mercury, germanium, and tin.

Most interestingly, only *p*-xylene, and not its *ortho*- or *meta*-isomers, seem to be ototoxic. This observation is also documented in IRSST's *fiche toxicologique* on xylene, although the Canadian authors consider "xylene (*o*-, *m*-, *p*-isomers)" as "possibly ototoxic" in the original version of their review. In the subsequent English journal article this ranking was limited to *p*-xylene alone (6).

The most comprehensive report was delivered by the Nordic Expert Group (NEG). This is a collaborative effort between the Nordic countries of Denmark, Sweden, Norway, and Finland to reach consensus and set up criteria documents on chemicals for occupational exposure limits. Their recent review on ototoxic substances was drawn up in cooperation with a Brazilian specialist, then working at the National Institute for Occupational Safety and Health (NIOSH) in the United States.

The Nordic Expert Group chose a quantitative approach, meticulously comparing the "no observed" or "lowest observed" effect levels with occupational exposure limits from various countries. Their criteria for the classification scheme with three categories are self-explanatory:

- Category 1: Human data indicate auditory effects below or near the existing OELs. There are also robust animal data supporting an effect on hearing resulting from exposure.
- Category 2: Human data are lacking, whereas animal data indicate an auditory effect below or near the existing OELs.
- Category 3: Human data are poor or lacking. Animal data indicate an auditory effect well above the existing OELs.

According to these criteria, toluene, styrene, carbon monoxide, carbon disulfide, lead and mercury were classified to Category 1, and *p*-xylene, ethylbenzene, and hydrogen cyanide to Category 2.

Publications issued since 2009 do not focus on particular substances, but rather on complex mixtures such as organic solvents (7, 8), on exposure to chemicals in a steel company (9), or even on the complex environment of military forces (10).

Remarkably, an increasing number of publications has covered combined exposure to noise and ototoxic chemicals (7-12).

DISCUSSION

As ototoxic substances are a heterogeneous group of chemicals that cause hearing impairment in various toxicological modes of action, risk identification and risk assessment present a challenge of their own. Several hundreds of chemical agents have been associated with ototoxic health effects, including diffuse classes like "solvents" or "pesticides". In this context, the effort of collecting, combining, evaluating and condensing the available scientific data may well contribute to a clearer understanding for non-experts.

Even though the three institutions IRSST, EU-OSHA, and NEG applied differing classification criteria, their key findings match quite well and yield a short list of workplace substances with sufficient scientific evidence of relevant ototoxic properties (Table 1). The seven substances compiled in this synoptic table rank the most ototoxic by at least two institutions. Three of them – toluene, styrene, and lead – are regarded by all three institutions as proven ototoxic substances of the highest category.

A few discrepancies are discernible in Table 1. In general, IRSST (3) tends to be more restrictive than the two other institutions. The most striking mismatch concerns carbon monoxide, which IRSST has ranked as "no evidence" while EU OSHA (4) and NEG (5) classify it as a proven ototoxic agent. The obvious reason is that carbon monoxide interacts synergistically with noise-induced hearing impairment, but apparently is not an ototoxic agent *per se*.

Trichloroethylene is a well-known disruptor of certain structures in the inner ear. Since these effects tend to occur only at high exposure concentrations, NEG has classified this halocarbon as Category 3 ototoxic substance in compliance with its own quantitative scheme (see above). With regard to mercury, it seems that IRSST has based its differing assessment on a smaller body of data.

An obvious step would be to call for the lowering of the established OELs on the grounds of the substances' ototoxic effects, but this should be undertaken prudently within the approved procedures. As a matter of course, every toxicological endpoint including ototoxicity has to be taken into account when

setting limit values. The point of departure for deriving OELs is usually the so-called “critical effect”, i.e. the most sensitive health effect caused by a substance. However, we are not aware of any workplace substance for which ototoxicity has been identified as the critical effect. Usually, ototoxicity seems to be a phenomenon of higher exposure concentrations. This observation is not necessarily in contradiction to the NEG statement that human data indicate auditory effects below or near the existing OELs for at least six chemicals. On the one hand, the reference lists in the NEG report reflect a wide range of OELs for a given substance, including relatively high limit values, for which newer information concerning various toxicological endpoints require urgent revision and lowering. On the other hand, most field studies lack a proper characterisation of historic exposure, thus hampering the use of these data for a sound OEL derivation.

Another regulatory problem is the interaction with noise, which has not been investigated in a satisfactory manner. This issue has recently been tackled systematically in another literature review by IRSST. In the English abstract of their French publication (13), the IRSST authors state: “The result is that it is very difficult to combine all of the data to arrive at solid conclusions. Of all the articles consulted, there are only two cases of interaction with noise: toluene and noise acting synergistically, and carbon monoxide possibly potentiating the effect of noise. This does not exclude the possibility that other chemical substances can worsen hearing losses due to noise.” Again, IRSST’s assessment seems to be rather conservative and refers to selected agents exclusively. There is further evidence, for instance, that a broad range of volatile lipophilic solvents can exacerbate noise-induced hearing impairment to a certain extent (4, 11).

CONCLUSIONS

All the substances listed in Table 1, namely toluene, styrene, lead, trichloroethylene, mercury, carbon monoxide, and carbon disulfide, deserve special attention with regard to their ototoxic properties when deciding on appropriate risk management measures in occupational settings.

Having examined the existing information, two specialised working groups of the German Social Accident Insurance (DGUV) have concluded that the

risk of hearing impairment may become high if the current German OELs for ototoxic substances are exceeded. These working groups have made the following recommendations (14), which may serve as a general guideline for industrial hygienists:

- Occupational health professionals and the workforce should be made aware of the risks posed by ototoxic substances. Employers and workers should be advised accordingly.
- Risk management measures aimed at reducing exposure to ototoxic substances should be encouraged.
- Ototoxicity should make part of occupational health-screening activities.
- Appropriate tools should be developed for early diagnosis of chemically induced hearing impairment.
- Suitable scientific investigations into ototoxic properties should be encouraged such as longitudinal epidemiological studies. Further research should focus on quantifying the combined effects of ototoxic substances and noise.

However, the European statistics on occupational diseases and their prevalent causes clearly indicate that ototoxic substances should not divert risk managers’ attention from the fundamental requirements in combating noise-induced hearing loss at the workplace that still has priority over chemically-induced hearing impairment.

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Sažetak

OTOTOKSIČNE TVARI NA RADNOM MJESTU: KRATAK UVID U STANJE

Ototoksične kemikalije mogu narušiti osjetilo sluha i ravnotežu. Nedavno su uloženi dodatni napor u izradu znanstveno utemeljenih popisa tvari koje su prisutne na radnom mjestu, a koje imaju ototoksična svojstva. Ovaj rad daje kratak uvid u najnovije publikacije objavljene na ovu temu. Usporedba navedenih publikacija potvrđuje da bi toluen, stiren i olovo trebalo razmatrati kao izrazito bitne ototoksične tvari koje postoje na radnom mjestu. Nadalje, postoje dovoljni dokazi koji potvrđuju da ototoksične tvari poput trikloretilena, žive, ugljikova monoksida i disulfida u radnom okruženju mogu oštetiti sluh. Temeljem postojećih informacija stručnjaci u području higijene rada trebali bi upozoravati stručnjake u području medicine rada i same radnike na rizike koje ototoksične tvari predstavljaju; poticati ih na zamjenu takvih tvari ili uvođenje novih mjera za smanjenje izlaganja; uključiti ototoksične tvari u redoviti program praćenja i osmisliti mjere za rano otkrivanje oštećenja sluha zbog izloženosti kemijskim tvarima; dodatno istražiti ototoksična svojstva ovih tvari. Buduća istraživanja trebala bi se usredotočiti na izračun ukupnih učinaka ototoksičnih tvari i buke.

KLJUČNE RIJEČI: *ksilen, olovo, oštećenje sluha, procjena rizika koja se temelji na znanstvenim činjenicama, stiren, toluen, trikloretilen, ugljikov disulfid, ugljikov monoksid, živa*

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