SOLVENT-INDUCED HEARING LOSS: MECHANISMS AND PREVENTION STRATEGY

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Abstract
While noise exposure is the most significant contributor to occupational hearing loss, evidence gained over the last 10 years, has pointed to organic solvents as additional contributors to occupational hearing disorders. Despite the implications of this finding, no significant measure has been undertaken to limit exposure to occupational solvents, or to occupational solvents and noise, within the European community. Guidelines for improving hearing protection of people exposed to solvents, or to solvents and noise, are addressed in the present article. Recently, it has been shown that the lowest-observed-adverse-effect level (LOAEL) of styrene was 300 ppm in active (working wheel) rats, and that the same amount of styrene-induced hearing loss (SIHL) can be obtained with styrene concentration difference of 200 ppm between active and sedentary (inactive) rats. Supported by a reasonable safety factor (SF) of 10, the authors proposed to decrease the French threshold limit value of styrene from 50 to 30 ppm (RfD = LOAEL/SF) to ensure a higher level of protection for human hearing. It is widely acknowledged that outer hair cells in the organ of Corti can be considered as the first target tissue of solvents, while little is known about the action of aromatic solvents on the auditory efferent system. In a recent experiment using both the cochlear microphonic and compound action potentials, the authors have shown that toluene can inhibit the action of the middle ear reflex by modifying the cholinergic receptors. It is likely that toluene affects the cholinergic receptors at the brainstem level. By its anticholinergic-like effect, toluene could allow higher acoustic energy penetration into the cochlea exposed to both noise and solvent. Based on this phenomenon, the authors recommend the use of hearing protection for the lower exposure action value: Lex,8h = 80 dB(A) in noisy environments polluted by solvents.

Key words: Toluene, Neurotoxicity, Ototoxicity, Auditory efferent system, Middle-ear acoustic reflex, Inner-ear acoustic reflex

INTRODUCTION
Despite massive efforts to eliminate hazardous noise sources in many factories, noise-induced hearing loss (NIHL) continues to be a significant health problem in France, but also throughout the world. Most research on the etiology of occupational hearing loss has focused on the damaging effects of noise on hearing. While noise exposure is undoubtedly the most significant contributor to occupational hearing loss, over the last 10 years several reports have pointed to organic or aromatic solvents as significant additional contributors to occupational hearing disorders. Both the human studies [1–3] and animal experiments have shown that toluene, styrene, xylene [4,5], and ethylbenzene [6] can provoke irreversible hearing loss, the cochlea being considered as a target organ for the solvents [7,8]. Despite the implications of this evidence, no significant measure has been undertaken to limit occupational solvent exposures, or occupational solvent and noise exposures, within the European or American community. The recent European legislation (Directive 2003/10/EC of 6 February 2003) did not bring striking changes to the establishment of permissible noise limits when workers are also exposed to noise and solvents.

We acknowledge that the concept of solvent-induced hearing loss (SIHL) has still not received adequate attention...
from the decision makers who enact sets of rules or procedural guidelines, still called standards. With this short review, we would like to draw the attention of those responsible for hearing conservation programs to the concept of ototoxicity.

Guidelines for improving the hearing protection of people exposed to solvents, or to solvents and noise, are rare. For this reason, some suggestions for improving the prevention strategy are addressed at the end of this brief and review.

The aims of this review are double. Firstly, to make the concept of SIHL as clear as that of NIHL in order to delineate and disseminate information on the risk encountered by workers exposed to solvents. Secondly, to propose scientific arguments based on studies performed with animal models in order to give policy makers a basis to examine permissible exposure limits, and thereby to facilitate future prevention strategies.

COCHLEOTOXICITY OF AROMATIC SOLVENTS

The notion of ototoxicants linked to chemical agents is important, especially when potential workplace exposures are concerned [1,2]. Aromatic solvents have been demonstrated to be ototoxicants, and some can even worsen the effects of noise in animals [9,10] and, what is more alarming, in humans [3].

Today, the different features of SIHL can be accurately characterized. Contrary to aminoglycosides, cisplatin, or most of the drugs, the infiltration of the solvents inside the cochlea is due to tissue contamination rather than to contamination of the inner ear fluids [11]. This is not really surprising since aromatic solvents are miscible in lipid-rich tissues, but are hardly water-soluble (see logP of organic solvents).

Conveyed by the whole blood, the aromatic solvents come from the stria vascularis, or from the spiral prominence, and diffuse through the lipid-rich membranes of the cubic cells constituting the outer sulcus before they impair the organ of Corti. Observations of disrupted membranes, as well as chemical analyses have revealed that aromatic solvents use the outer sulcus as the main intoxication route to reach the outer hair cells (OHCs) [8]. Actually, to be more accurate, we should specify that Hensen’s cells must be considered as the first supporting tissue impaired by the solvents, whereas the OHCs as the first sensorial tissue injured within the organ of Corti.

Because of the solvent progression through the organ of Corti from the vascular system, the third row of OHCs (the closest from the stria vascularis) is logically more vulnerable than the second row, which is itself more sensitive than the first row [8,12].

Despite the fact that significant progress has been made in defining the morphological aspects of solvent ototoxicity, and that several epidemiological surveys have confirmed the ototoxic potency in humans over the past 10 years, the molecular mechanisms underlying this kind of toxicity are not well known. Recently, the implication of reactive oxygen species, or free radicals, has been brought up in the general cochleotoxic process induced by solvents, but to the best of our knowledge, no data have been published yet.

What is the most likely scenario of the cochleotoxic process?

Firstly, an alteration of the supporting cells [8], like the Deiters and Hensen’s cells, which may affect the ionic K+ concentrations around OHCs by modifying the re-uptake of K+ from the corticolymph. Actually, the disturbances of these supporting cells could generate an excessive K+ build-up beneath the OHCs, which would cause their poisoning [13,14].

Secondly, the lipid peroxidation of the membranous structures follows, leading to serious disturbances of the cytoplasmic membrane of the OHCs.

Because such toxic responses are triggered by an exogenous agent, and because these responses are rapid, involve cellular injuries, cell swelling, and early loss of cytoplasmic membrane integrity, we contend that the general mechanism of the cochleotoxic process is rather a necrotic than an apoptotic phenomenon. Once the necrosis and then the apoptotic processes are triggered, Deiters’ cells, which are adjacent supporting cells, appear capable of phagocytizing and clearing cell debris within the sensitive epithelium. Therefore, Deiters’ cells are responsible for the cleaning and the sealing of the luminal surface to make phalangeal
NEUROTOXICITY OF AROMATIC SOLVENTS

Due to the lipid-rich content of the nervous tissue, the aromatic solvents can cause severe impairments to the central nervous system [16,17]. More recently, Bale et al. [18] showed with an in vitro experiment that the cholinergic and, more specifically, the nicotinic receptors were sensitive to toluene.

In a recent experiment, we confirmed their results with an in vivo experimental approach [19,20]. Besides, we showed that toluene, like most of the aromatic solvents, can mimic the effects of antagonists of the cholinergic receptors (AChRs) and thereby inhibit the action of both protective reflexes: the inner-ear and middle-ear acoustic reflexes. The anticholinergic-like effect of solvents are quite important to highlight because they can explain, at least partly, the synergistic effects of a simultaneous exposure to noise and solvents observed in animals [6,9,10] and human studies [3].

Indeed, the protective reflexes have their nervous center located in the brainstem [21–23]. By inhibiting the AChRs in the brainstem, the aromatic solvents might disturb the function of the efferent pathways and thereby the function of the acoustic reflexes. As a result, in the case of combined exposure to noise and solvents, a higher level of acoustic energy might penetrate into the imperfectly-protected cochlea. In other words, such a combined exposure would correspond to a noise-alone exposure with a higher acoustic energy.

In summary, in combined exposure to noise and solvent, the same acoustic energy would be more harmful for two main reasons:

1. The solvent would modify the membranous structures of the OHCs, making them more fragile and vulnerable.
2. The solvent would reduce the protective role played by the middle ear, allowing the penetration of more acoustic energy.

PREVENTION STRATEGIES BASED ON STUDIES CARRIED OUT WITH ANIMAL MODELS

An important issue, which is not adequately addressed in the occupational noise standards within the European communities, is the criteria for combined exposures. None of the current standards contains explicit requirements for this kind of exposure. Although noise is an undisputable risk factor, aromatic solvents also deserve to be considered as a potential risk factor for the development of significant hearing loss. In this respect, our challenge will be:

1. To persuade legislators to recognize and integrate aromatic solvents as identified work-related ototoxic substances.
2. To obtain adjustable noise/solvent standards depending on occupational exposure conditions.

In Europe, the recent directive (2003/10/EC of 6 February 2003) timidly recommended that employers pay attention to occupational noise monitoring in the case of co-exposure with work-related ototoxic substances, without mentioning them. In our opinion, this advice is hard to implement and far from being efficient to protect workers’ hearing against aromatic solvents or other ototoxic agents. Obviously, there is still a huge gap between the recognition of risk given to noise compared to that given to ototoxicants, like solvents, which are responsible for occupational hearing loss. This statement emphasizes the continuing need for research in this direction.

The concept of NIHL has been well described in animals and extensively studied in humans exposed to workplace noise. Due to health problems, and the social and economic costs of occupational deafness, the legislators promulgated exposure limits of exposure to protect workers against NIHL. As mentioned previously, the concept of SIHL is less clear than that of NIHL and we must admit that there are still questions raised throughout the scientific literature.

For instance, why is SIHL species-dependent? The hearing impairments provoked by aromatic solvents were observed in rats, but not in guinea pigs [24,25], nor in chinchillas [26]. A corollary of this statement is: Are humans sensitive to solvents, like rats?
We must find answers to these pertinent questions if we want to be more persuasive and establish aromatic solvents as an indisputable work-related ototoxic substance in the European hearing conservation program or, if this not possible, in several legislations within the European communities.

Several scientific responses can be easily brought to these questions.

The gas/blood partition coefficient, the uptake and the hepatic metabolism of solvents can explain the difference in susceptibility observed between animal species [26]. It is, of course, impossible to collect such information in humans, but the development of potent physiologically based pharmacokinetic models [27] demonstrated the utility of these models in predicting the kinetics of several aromatic solvents in humans and rats. Based on these studies, rat appears to be an excellent model for humans. Besides, non-invasive studies of urinary metabolites showed that human beings, like rats, detoxify the solvents using exactly the same process. Obviously, the rat metabolism seems to use the oxidative and the conjugation pathways to get rid of the solvent [28], whereas the guinea pig metabolism prioritizes the oxidative and the o-cresol routes [29]. There are almost no urinary mercapturic acids in the guinea pig, while the amounts of these metabolites are significant in humans [30]. In this respect, the metabolism of rats appears closer to that of humans. In summary, justifying the choice of the animal model yields the answer to the aforementioned questions.

In spite of these rational arguments, some researches remain skeptical about the ototoxic potency of solvents. Most of the time, these people will contest the data obtained with animals because of the high concentrations of solvent used in this kind of investigation.

Actually, by studying SIHL, we have to face the recurrent and traditional criticism formulated against experimental toxicology:

Are the experimental conditions realistic for humans?

Are data obtained with animals transferable to humans?

For investigators, it does not make sense to test real-world conditions which are often defined as realistic by detractors. For example, how could experiments replicate the life-long exposures to solvents encountered by workers? It would take forever, and an immoral number of animals would be needed to assess the phenomenon.

One conventional way to get round this problem is to determine the dose-effect relationships of toxicants and, then to use toxicological tools for evaluating what could happen in more realistic conditions.

Here, it is important to clearly enunciate certain fundamental concepts of toxicology in order to evaluate, from data obtained with animals, a reference dose which could be proposed, for instance, as a permissible time-weighted average (TWA in the USA or VME$_{8h}$ in France) for humans:

1. The notion of NOAEL (no-observed-adverse-effect level), or if this cannot be easily established the notion of LOAEL (lowest-observed-adverse-effect level) or the calculation of a benchmark dose [31].

2. The notion of safety factor (SF) which corresponds to the uncertainty. Usually, a safety factor of 10 is used for the presumed greater sensitivity in humans, another 10 for variability in sensitivity in humans, and another 10 when LOAEL is used instead of NOAEL.

These aforementioned concepts will help us define a reference dose (RID) as following: RID = NOAEL/SF or RID = LOAEL/SF.

Workers are exposed to numerous chemicals which are difficult to study individually. In a recent experiment, we have narrowed our investigations to styrene as a representative aromatic solvent, because of its wide use in many factories [32] and because workers are commonly exposed to styrene fumes in a working environment where noise pollution is also present [2].

We showed that a 300 ppm exposure to styrene (6 hours/day, 5 days/week, 4 weeks) was already ototoxic with “working” rats (see [33] for details). A cochleotoxic effect was clearly observed at the level of the third row of OHCs.

In an attempt to provide a strategy for revising the current VME$_{8h}$ of styrene in France, we decided to use the LAOEL rather than the NOAEL concept to establish a RID. The LAOEL concept seemed to be more difficult to discredit. Likewise, we chose the less severe safety factor: SF = 10. With a value as low as 10, nobody could reproach us to
overestimate the SF in order to excessively protect the workers. Presently, the styrene VME in France is 50 ppm. Based on our investigation, the reference dose was equal to 30 ppm [NAOEL \(= 300 / SF = 10\)]. Therefore, we proposed to decrease the French VME for styrene to ensure a higher level of protection for human hearing. I hope our strategy will pay off and that we will obtain a rapid decrease in the French VME for styrene. Of course, such a strategy could be used for other suspected chemicals. It becomes more difficult to deal with the occupational conditions of a co-exposure to noise and solvent, for instance. To simplify the problem, let us imagine that the French VME of styrene is brought down to 30 ppm. In that case, we must consider the standards: \(L_{ex_{8h}} = 85\) dB(A) (upper exposure action value) and \(VME = 30\) ppm, as two values which should not be transcended. Now, in the case of a co-exposure, these two values are not adequate anymore, because of the risk of synergy.

One simple way to reduce the risks encountered by people exposed to both noise and solvent (measured VME \(\geq 30\) ppm at the workplace) could be:

1. To bring down the VME to 30 ppm at workplace, if necessary, and,
2. To require hearing protectors from the lower exposure action value: \(L_{ex_{8h}} = 80\) dB(A).

We are aware that these propositions should be considered as the starting point for a more general and consensual debate. There is still room for constructive suggestions. We do hope that this short review will help people in their approach to make the solvent or noise standards evolve towards a safer work environment within the European communities.

REFERENCES

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