CME Article #2

Chemical Exposure as a Risk Factor for Hearing Loss

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Learning Objectives

- Discuss the interaction of noise and exposure to industrial chemicals in compromising auditory function.
- Present what is known about possible mechanisms of noise- and chemical-induced ototoxicity.
- Compare the merits of various test procedures that might help in assessing chemical-induced hearing loss.

Abstract

In 2002, the National Institute for Occupational Safety and Health and the National Hearing Conservation Association cosponsored the "Best Practices Workshop: Combined Effects of Chemicals and Noise on Hearing." This article summarizes the main results of the Workshop. Its goals were to review the knowledge of chemical ototoxicity and to stimulate participant discussion on how to address this risk. Speakers provided an overview of the effects of chemicals on the auditory system (http://www.cdc.gov/niosh/noise/noiseandchem/noiseandchem.html). Research priorities were discussed in concurrent working group sessions. The Workshop concluded with a panel of the groups' facilitators reporting on these sessions. The following key issues were identified: rationale and proposal of a list of priority chemicals; valid procedures for exposure (animal studies), exposure assessment, and audiological testing; need for mechanistic research and a Response Level; recommendations for preventive actions; and information dissemination. (J Occup Environ Med. *2003;45:676–682*)

Current Knowledge of the Ototoxicity of Industrial Chemicals

Occupational health research is generally characterized by the study of single agents, as if they occurred alone in the work environment. Exposure standards and recommendations are based on the evidence provided by such focused studies under the assumption that the health effects of exposure to two agents can be predicted by adding together the adverse effects resulting from exposures to each of the individual agents. A wealth of information has been generated by this single-agent approach and, as a result, many risks have been identified and controlled. Nevertheless, the limitations of this approach are revealed by recent investigations of mixed exposures. The idea to study exposures in relation to each other is not new but has very likely received only limited attention because of its complexity. Advances in research and statistical methods, however, have facilitated a recent increase in the number of scientific studies on combined/simultaneous exposures.

Research conducted over the last two decades has brought attention to the interaction between noise and chemicals in the workplace as a cause for hearing disorders. Since then, several research laboratories have become involved in investigating the ototoxic properties of agents, such as toluene, styrene, xylenes, ethyl benzene, *n*-hexane, trichloroethylene, stoddard solvent, carbon monoxide, hydrogen cyanide, lead, and mercury.

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On April 11 and 12, 2002, representatives from industry, government, labor, professional and trade organizations, and academia met in Cincinnati, Ohio, for the "Best Practices Workshop: Combined Effects of Chemicals and Noise on Hearing." The Workshop was cosponsored by the National Occupational Research Agenda (NORA), Hearing Loss Team of the National Institute for Occupational Safety and Health (NIOSH), and the National Hearing Conservation Association (NHCA). The goal of the conference was twofold: to review the current knowledge of chemical ototoxicity, alone or in combination with noise, and to stimulate participant discussion on how to address chemical exposures in hearing loss prevention efforts. Workshop registrants included speakers and representatives from academic, industrial, and governmental institutions, such as the French National Safety Institute for the Prevention of Occupational Accidents and Diseases (INRS); the Danish National Institute of Occupational Health; the Swedish National Institute for Working Life; both the Polish Nofer Institute of Occupational Medicine and the Institute of Occupational Medicine and Environmental Health; the US Environmental Protection Agency (EPA), NIOSH, and the NHCA.

Hearing Loss is one of the 21 NORA priority areas. The NORA Hearing Loss Team periodically sponsors best practices workshops, of which this was the third. Previous workshops have focused on the manufacturing and construction sectors. Future workshops will focus on small business, impulsive noise, and training programs for professionals in audiology and industrial hygiene. Members of the team come from industry, labor, academia, and government. The Hearing Loss Team membership is also professionally diverse, including audiologists, engineers, epidemiologists, industrial hygienists, and psychologists.

On the first day of the Workshop, invited speakers and posters provided an overview of the current state of the art on the effects of industrial chemicals on the auditory system (see http://www.cdc.gov/niosh/noise/noiseandchem/noiseandchem.html for abstracts and presentations). During the second day, the meeting research priorities and specific goals were discussed in four concurrent working group sessions. The Workshop concluded with a panel of the working groups' facilitators reporting on the discussions that had taken place in each group.

During the invited speaker plenary sessions and the poster session, reports from recent animal experiments confirmed earlier observations that chemicals, such as toluene, styrene, trichloroethylene, ethyl benzene, hydrogen cyanide, and carbon monoxide, interact synergistically with noise or potentiate its effects on the auditory system.[1–15] Moreover, if exposures to some of these chemicals occur in sufficiently high concentrations, hearing may be affected even in the absence of noise. The nature of the pathological changes in the cochlea that follow chemical exposure was also presented. Chemicals that were inhaled or absorbed through skin contact can reach the inner ear through the blood stream. These chemicals have been found in the inner ear fluids and have caused damage to some of the inner ear structures and functions. Although noise is particularly damaging to the cochlea, industrial chemicals tend to affect both the cochlear structures and the central auditory system.[16–18] This compound action may profoundly impact a worker's particular hearing loss because not only will the detection of sounds be impaired but also the discrimination of sounds may be affected (ie, not only will sounds be perceived as less loud but also as more distorted).

In the second session of the Workshop, presentations covered the following main topics: (1) noise and chemical exposures in manufacturing, construction, agriculture, and in the marine chemist profession; (2) findings from studies concerning the auditory effects of chemicals in manufacturing, construction, and US Air Force workers; (3) alternatives for testing the auditory system; and (4) recommended hearing loss prevention strategies for chemical-exposed workers proposed by the American Conference of Governmental Industrial Hygienists (ACGIH) and the US Army. In addition, one presentation described the position of *NoiseChem*, an European Commission research project, on the effects of exposure to noise and industrial chemicals on hearing and balance.[19] *NoiseChem*'s goal is to facilitate communication and collaboration between laboratories that are conducting research on the auditory effects of chemicals (http://europa.eu.int/comm/research/quality-of-life/ka4/ka4_noise_en.html).

Summary of the Main Results of the Working Group Meetings

The second day of the Workshop was reserved for the four concurrent working group meetings and elaboration of recommendations based on current knowledge. The objective of the working groups was to address the issues that face professionals working with populations exposed to chemicals and noise. The working groups also attempted to identify systematic approaches to research priorities that are most likely to yield a health gain for the worker. The working groups were divided into four topic areas: laboratory studies, human field studies, exposure assessments, and best practices. Each working group had a rapporteur and facilitator to guide and record the group discussion.

As a result of the working groups, key issues were identified based on the reports of each of the working group discussions. They are summarized in Table 1. The selection of these key issues was based on the time spent in their discussion, the

TABLE 1
Summary of the Main Results of the Working Groups Discussions on Research Needs and Best Practices for Hearing Loss Prevention

Identified Key Needs for Research and Best Practices
Mechanistic research
Priority chemicals
Rationale and consensus list
Exposure issues
Valid administration routes for animals studies
Methods for evaluating exposures of concern for workers and appropriate biomarkers
Methods for assessing the auditory effects
Identification of audiological test battery
Best Practices
Response level needed
Recommendation for what is the action to be taken, regarding inclusion criteria in HLPP, and appropriate components of such program
Information dissemination

HLPP, hearing-loss prevention program.

level of detail in which they were addressed, and the consensus reached in one or more groups. Details on key issues as discussed by each of the working groups follow in the next sections.

Mechanistic Research

There was a consensus across all working groups on the need for mechanistic research to answer questions on the auditory risk posed by industrial chemicals; however, the Laboratory Studies Working Group was the group that discussed this specific research need in more detail. Its participants argued that because of the enormous number of existing industrial chemicals and the thousands of new ones that are placed in the market every year, it is of crucial importance to understand the mechanisms by which chemicals affect the auditory system. Such an understanding could lead to a prediction of which chemicals to target by preventive efforts. This is very complex task, a challenge that was scrutinized by Fechter in 1995.[20] The working group brought up some of the issues involved in mechanistic research, including the following:

- Different species respond differently to the studied chemicals. Examining these differences could offer clues to the mechanism of ototoxicity.
- Toxic interactions among agents present the need to manipulate exposure parameters: doses, duty cycles, presentation order (sequential or simultaneous exposures).
- Physical or endogenous factors also should be taken into consideration: health status of the study participants (blood pressure, respiration etc.), genetics, and age.

List of Priority Chemicals: Rationale for Inclusion of Chemicals

All of the working groups agreed on the importance of identifying priority chemicals, not only for research purposes but also for establishing recommendations or identifying best practices for hearing loss prevention. The Laboratory Studies and the Human Field Studies Working Groups spent considerable time on the discussion of this issue. In both groups, consensus was reached that the magnitude of exposed populations is an important factor in assigning priority to a specific chemical. Although it is not clear exactly how many workers are exposed to noise and chemicals in the United States, useful estimates can be found in the literature for specific chemicals, and on the number of exposed workers or volume of chemicals purchased (commercial market) by industry category.[21–24]

A second criterion for the inclusion of a chemical in the research priority list was evidence of the chemical's ototoxicity, general toxicity, as well as nephro- or neurotoxicity. Currently, ototoxic properties have only been investigated for a very small number of industrial chemicals. When specific ototoxicity information is not available on the chemical under consideration, the investigator or occupational health professional should gather information on the agent's general toxicity, nephrotoxicity, and neurotoxicity (because most of the chemicals that were found to affect the auditory system are potentially neurotoxic and or nephrotoxic[25,26]), along with complaints from exposed populations. Information on whether a chemical produces reactive oxygen species could also help in the decision to examine that agent's ototoxicity. The generation of reactive oxygen species (free radicals) has been associated with cellular injury in different organ systems. It is considered a basic mechanism of toxicity, and is thought to be part of the mechanism underlying noise-induced hearing loss.[27] Glutathione is an important cellular antioxidant that limits cell damage by reactive oxygen species. Evidence is available to support the hypothesis that ototoxicity due to noise plus carbon monoxide or hydrogen cyanide exposure is mediated via free radicals.[28] For this reason, information on a certain chemical being associated with free radicals or glutathione depletion could also help in the decision to examine a chemical for potential ototoxicity.

Based on the criteria above, the Human Field Studies Working Group identified the following chemicals as having the highest priority for research and intervention:

- Solvents—toluene, styrene, xylene, *n*-hexane, ethyl benzene, white spirits/stoddard, carbon disulfide, fuels, perchloroethylene;
- Asphyxiants—carbon monoxide, hydrogen cyanide;

- Metals—lead, mercury;
- Pesticides/herbicides—Paraquat, organophosphates.

Exposure Issues

Methods for Administering Chemicals. The Laboratory Studies Working Group voiced the relevance of this methodologic issue to facilitate research progress. The group argued that the most common method for administering chemicals has been the inhalation route, but alternatives include dermal, injection through the round window, gavage, and in vitro (cellular, otocyst, organ culture, and cocultures). Because solvents themselves have been demonstrated to reach the organ of Corti[29] these alternative routes could prove useful in simplifying experiments. When the route of exposure is analyzed, a researcher should consider how the resulting biological concentration from a selected route correlates with relatively low-level, real-world exposures.

Methods for Evaluating Exposures of Concern. The Exposure Assessment, the Human Field Studies, and the Best Practices Working Groups indicated that it is necessary to identify adequate approaches for evaluating exposures to the chemicals of concern to further the knowledge on the ototoxicity of chemicals and to plan for appropriate preventive initiatives.

Based on the current knowledge in the area, the group formulated a series of recommendations that include the following:

- Start measurements with the task-based exposure assessments (TBEAM) approach, which can specify the time of exposure and its concurrency.
- Assume exposures are equal for all workers on task.
- Prioritize personal monitoring.
- Perform comprehensive measurements of noise, including both frequency and intensity of noise, and calculating kurtosis.
- Find biomarkers for type of cell damage in the ear.
- Evaluate personal protective equipment use.
- Examine the contribution of visual job analysis.
- Use exposure data to assign workers to hearing-loss prevention programs (HLPPs).
- Target workers who have held their jobs for a long period of time to be examined for biological effects.

Methods for Assessing Auditory Effects

Animal Studies. The Laboratory Studies Working Group briefly examined this issue but agreed there was value in developing an approach that discerns peripheral versus central symptoms when testing for auditory effects of chemicals in laboratory animals. The methods that have been used more frequently include auditory brainstem response, conditioned avoidance responses, behavioral audiometry, reflex modification of acoustic startle responses, distortion product otoacoustic emissions, and morphologic examinations. Other alternatives brought up by the group included masking level difference, gap detection, temporal integration, efferent testing, and contralateral suppression of distortion product otoacoustic emissions.

Human Studies. The Best Practices Working Group raised the issue of how the chemical effects should be assessed through audiological tests, which the Human Field Studies Working Group discussed quite extensively. The consensus was to use pure-tone audiometry (PTA) as a starting point when considering ways to test central auditory effects, since the effects of chronic exposure to industrial chemicals do not seem to be restricted to the cochlea.

If PTA is the only test performed, gathering information by means of a questionnaire on speech discrimination difficulties or other auditory problems that are inconsistent with thresholds can help in detecting some of the chemical effects on the auditory system. Comparing prevalence of hearing disorders between groups having different exposure conditions and calculating risk ratios may also allow for the detection of chemical effects.

A more robust approach involves auditory testing to assess more central portions of the auditory system, as a complement for the findings from PTA and a help in distinguishing between noise and chemical effects. The group agreed that a gold standard auditory test battery is not yet available.

Although ideal, a comprehensive audiological test battery in occupational studies may not be feasible because of both time and cost constraints. Screening workers to select those who should undergo further testing can also prove to be a fruitful approach. When selecting hearing tests, a researcher should consider administration time, ease of analysis, sensitivity and specificity, and the site of the auditory system evaluated. Ideally, one should use tests that evaluate the full extent of the system, from the cochlea to higher auditory centers.

Some of the tests the group suggested for examining chemical-exposed workers were as follows:

- Békésy audiometry or PTA, having a smaller step size than 5 dB.
- High-frequency audiometry.
- Sensitized pure tone tests (gap detection, duration pattern, and pitch pattern).
- Acoustic reflex tests (including thresholds and decay).
- Sensitized speech tests (interrupted speech, speech in noise).
- Otoacoustic emissions.
- Evoked potentials (auditory brainstem response, cortical potentials).

For a review of issues relevant to auditory testing for chemical exposures see Morata and Little[30]

Response Level and Action to Be Taken

Three of the working groups—Field Studies, Exposure Assessment, and Best Practices—agreed on the need for a *Response Level*, an action

level-like criterion, for inclusion in HLPPs. These groups also indicated that, given the evidence available, there is ground to make such a decision.

Response Level is the level or concentration at which remedial or protective actions should be performed in chronic exposure situations. In this specific case, it refers to the level of chemical exposure (alone or in combination with noise), at which employees should be enrolled in HLPPs. Currently, NIOSH recommends that HLPPs be implemented for all workers whose unprotected 8-hour time-weighted average (TWA) exposures (ie, exposures incurred when hearing protectors are not worn) equal or exceed 85 A-weighted decibels (dBA).[31]

The identification of a new Response Level based on chemical ototoxicity would be based on the available evidence on specific chemicals and mixtures. This expansion of the current recommendation to incorporate chemical exposures would consequently require also a revision of the recommended action to be taken. The groups agreed that novel strategies in hearing loss prevention are needed, but, first, these will involve answers to the following questions:

- What are the optimal intervals between periodic audiometric testing?
- Which criteria signal a need to review audiometric results and determine a probable etiology?
- What are the existing alternatives for exposure evaluation and control?
- What are the new training needs for exposed populations?

Information Dissemination

Three of the working groups—Field Studies, Exposure Assessment, and Best Practices—stressed the importance of disseminating information to educate industry, professional associations, unions and the public on the ototoxicity of chemicals, and the potential risks.

Additional Issues of the Laboratory Studies Working Group

The Laboratory Studies Working Group pointed out that the development of a human exposure database and longitudinal studies on exposed populations could assist in the formulation of hypotheses on the mechanisms underlying the observed ototoxicity. Moreover, the investigation of strategies for prophylaxis, such as conditioning and L-N-acetylcysteine administration, was identified as a research priority. The group pointed out a need for funding agencies to ensure representation by scientists having adequate expertise to examine the research proposals.

Finally, the group commented that the only hearing test required by the Organization for Economic Cooperation and Development for toxicity testing in the Functional Observational Battery is the qualitative assessment of the startle reflex following a 115 dB sound pressure level click. This test is not sensitive enough for the detection of chemically induced hearing loss,[32] which indicates a need for a revision of the guideline.

Additional Issues of the Human Field Studies Working Group

The Human Field Studies Working Group identified a number of research needs, including: (1) longitudinal studies on large populations exposed to chemicals; (2) dose–response studies; (3) chemical-specific site-of-lesion investigations on the combined effects of noise (including ultrasonic exposure) and chemicals; (4) development of standardized history questionnaire; (5) investigation of interactions between drugs and other factors that could modify the effect of the chemicals, ie, smoking; and (6) the potential association of exposure to industrial chemicals and the occurrence of tinnitus.

As a research strategy, the group participants agreed that, initially, it would be more advantageous to conduct research on single chemicals than on mixtures, which would contribute to mechanistic research. The group also noted some of the decisions that should be made in the early stages of designing a study, including the criteria for classification of hearing results and change from baseline hearing sensitivity and the criteria for assigning participants to a group based on their exposure.

Additional Issues of the Exposure Assessment Working Group

The Exposure Assessment Working Group agreed on the importance of identifying and itemizing already available databases of workers exposed to noise–chemical interactions. Unfortunately, the group also noted that limited data documenting combined exposures exist. Data often are stored separately for noise, chemical exposures, and hearing loss, which makes it difficult to connect exposure levels to health outcomes. The participants indicated that they perceived no sense of urgency for these records to be obtained and organized.

When possible, available data should be re-examined and combined with newly acquired data. Incentives could motivate industry and/or the military to provide data, or re-examine their data under the light of this new knowledge.

Additional Issues of the Best Practices Working Group

The group identified a series of questions that need to be answered so that HLPPs can be modified to meet the needs of workers exposed to chemical hazards. They include the following:

- Could a medical referral model be designed to guide occupational health personnel on the selection of appropriate audiological tests to

use on workers or the signals that indicate a need for further testing?
- Could hearing loss be considered an early indicator of the toxicity of certain chemicals?
- What would be the contribution of incorporating existing neurological tests in the periodical medical evaluation of workers exposed to ototoxic chemicals?
- Is the knowledge on the effects of antioxidant therapy likely to have an impact on preventive strategies?

Concluding Remarks

The Challenge of Mixed Exposures and Proposed Action

The Best Practices Workshop participants actively engaged in the discussions and provided excellent input to the four workgroups. Several issues emerged from almost all of the groups' discussions, and often there was agreement about research needs and priorities.

In summary, the strategies the participants envisioned that addressed the combined exposures of noise and chemicals included the following:

- Assessing potential interactions to allow for decision-making on strategic directions and priorities of mixed exposures research.
- Evaluating mechanisms of interaction to provide a rational basis for extrapolation of toxicological information across different mixtures, dose levels, exposure parameters, and routes.
- Conducting multidisciplinary epidemiologic investigations, which include careful mixed-exposure assessment, preferably collected by personal monitoring and biomarkers.
- Evaluating nonoccupational risk factors and individual variability in response to occupational environmental and organizational factors.
- Proposing a new Response Level criterion for inclusion of workers in HLPPs, which takes chemical exposure into consideration.
- Improving communication between scientists and partners about exposure and risks.

NIOSH, along with other international research agencies, has identified mixed noise and chemical exposures as a priority research area, which will impact future research planning and standard setting. During the interim, NIOSH advises workers, employers, and occupational health professionals to consider measures that will minimize exposures to ototoxic physical and chemical agents. NIOSH recommends involved industries to be alert to the work environment as a whole when evaluating the risks posed by a task or process. When hazard information on a specific combination of agents or exposures is not available, industry should seek information on the individual agents present (eg, common target organs) or the similar exposure combinations.

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