

TOXICOLOGICAL HIGHLIGHT

Interaction between Noise and Asphyxiants: A Concern for Toxicology and Occupational Health

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The article highlighted in this issue is "Potentiation of Noise-Induced Hearing Loss by Low Concentrations of Hydrogen Cyanide in Rats" by Laurence D. Fechter, Guang-Di Chen, and David L. Johnson (pp. 131-138).

Occupational health, in its mission to identify and prevent work-related disorders, often relies on findings from toxicological studies. Many occupational issues, such as the exposure parameters and the mechanisms responsible for causing disorders, can only be addressed through toxicological experiments. In particular, more biological and toxicological research is needed to understand the toxicity of mixtures and the interaction between mixture components. Human data are characterized by great individual variability that arises mainly from differences in medical and exposure histories and in susceptibility. This variability makes it challenging to separate the effects of each agent, and to determine with precision the kind of interaction between agents.

In the past two decades a few research groups have studied a long neglected problem, the effects of certain environmental and occupational chemicals on the auditory system and their interaction with noise (Chen *et al.*, 1999; Fechter *et al.*, 1987; Lataye *et al.*, 2000; Liu and Fechter, 1995; Loquet *et al.*, 1999; Morata, 1989; Morata *et al.*, 1997). The results obtained have motivated these groups to continue pursuing this problem and have also attracted the attention of other groups (see <http://www.ami.dk/english/projekter/115.html>). Before the 1980s there was no research program that systematically focused on chemical-induced hearing loss, and only isolated studies reported such effects. This scenario started to change following reports from groups dedicated to investigations of the neurotoxic properties of chemicals (Pryor *et al.*, 1983).

It is natural to ask whether the ototoxicity of environmental and occupational chemicals is really an issue that merits further research. Reflection on this question raises other questions,

such as how could the scientific and public health community overlook an issue for so long that could have serious impact on the quality of life for such a large exposed population? Examination of the literature on noise and hearing conservation research leads one to realize that noise is often present in occupational settings where chemical exposures occur, the hearing disorders observed in these situations were often attributed to noise exposure alone, and little consideration was given to the possibility of involvement of other agents. Only workers who are exposed to noise levels above 85 dB (A) are required by the Hearing Conservation Amendment (48 CFR 9776, 8 March 1983) to the U.S. Occupational Safety and Health Act of 1970 to have their hearing tested periodically, by means of pure-tone air-conduction audiometry. Pure-tone audiometric thresholds only identify the magnitude of the hearing disorder, not the etiology. The audiometric configuration in cases of noise-induced hearing loss and ototoxicity can be identical. If careful analyses of these results were not performed and attention not given to all the exposure conditions, it is conceivable that the observed hearing disorders were erroneously attributed solely to noise. When chemicals are evaluated for their toxicity, only rudimentary auditory tests are used, yet we know that some chemical-induced auditory effects can only be detected by more sophisticated testing. All these factors could explain the paucity of research conducted until recently on ototoxic properties of chemicals present in the environment and in the workplace.

The strongest argument for research on the ototoxicity of industrial chemicals is still, unfortunately, the continuing high occurrence of work-related hearing loss in industrialized countries. NIOSH (Franks *et al.*, 1996) has estimated that approximately 30 million U.S. workers undergo significant workplace noise exposure; noise accounts for approximately 30% of all acquired hearing loss in the U.S. population. The findings made available by recent, more structured research efforts, indicate that environmental chemicals not only may have an effect on the auditory system, but also may interact synergistically with noise (Chen *et al.*, 1999; Lataye and Campo, 1997; Lataye *et al.*, 2000). These findings emphasize the continuing

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need for research as described in the highlighted article by Fechter, Chen and Johnson. Their report elegantly demonstrates how exposure to the chemical asphyxiant hydrogen cyanide can potentiate noise-induced hearing loss.

Previous publications by Fechter and colleagues regarding the interaction of another asphyxiant, carbon monoxide, and noise have been seminal to the current study and in motivating other researchers to include noise exposure in their experiments. Chen *et al.* (1999) and Rao and Fechter (2000a) indicated that under intermittent noise exposure with long quiet periods, carbon monoxide exposure could produce unexpectedly large, permanent threshold shifts. Surprisingly, the data did not validate the anticipated relationship between the percentage of time that noise is present (noise duty cycle) and increasing hearing loss. Instead, the mildest noise duty cycle produced maximal hearing loss when carbon monoxide was also present. Rao and Fechter (2000a) used the 5-dB time-intensity exchange rate to manipulate their noise exposures. Their observations raise the issue of the appropriateness of the time-intensity paradigm adopted by the Occupational Safety and Health Administration to determine noise permissible exposure levels when simultaneous exposure to noise and chemicals exist.

In the highlighted article, Fechter, Chen and Johnson demonstrate that hydrogen cyanide (HCN) exposure increases noise-induced hearing loss in a dose dependent manner. By itself, HCN had minimal auditory effects even at 50 ppm, the highest dose investigated. However, in combination with noise exposure, low concentrations of HCN potentiated noise-induced hearing loss. As in the studies on carbon monoxide, outer hair cell loss was noted along with the physiological impairment, which was measured using pure-tone compound action potential thresholds. Both the no-observed-effect level (NOEL) and the lowest-observed-effect level (LOEL) were obtained in their study. Exposure to noise and 10 ppm HCN did not produce significant potentiation or pronounced outer hair cell loss, while at the level of 30 ppm HCN, the potentiation of noise-induced hearing loss achieved statistical significance.

Observations on the ototoxic properties of three classes of chemicals (metals, organic solvents, and asphyxiants) have received criticism as being high-dose phenomena with little importance for low-level, real-world exposures. Fechter, Chen and Johnson's observations have shown that occupationally relevant exposure levels are potentially hazardous to the health of workers in ways not appreciated before the publication of their work. The authors did a series of calculations using a benchmark dose approach for risk assessment analysis, using software published by the U.S. EPA (BMDS version 1.3). Their calculations suggest that current permissible exposure limits for HCN are not conservative enough for the prevention of their auditory effects, as seems to be the case for carbon monoxide (Fechter *et al.*, 2000).

Fechter, Chen and Johnson examined the biological basis of

the interaction, searching for the mechanism underlying the observed effects. Based on parallel findings that have been obtained for noise and carbon monoxide (Rao and Fechter, 2000b), Fechter, Chen and Johnson suggest that hydrogen cyanide exposure potentiates noise-induced hearing loss through the generation of reactive oxygen species observed after combined exposures. Free radicals have been associated with cellular injury in different organ systems and are considered a basic mechanism of toxicity.

The comprehensive approach taken by Fechter and his colleagues in investigating the toxicity of asphyxiants (testing different exposure parameters and combinations of agents, attempting benchmark dose calculations, testing hypotheses for the inhibition of the observed effects) makes a major contribution toward a better understanding of the mechanisms involved in ototoxicity. It contributes substantially to the field of occupational health by addressing the risk posed by an industrial chemical used in the extraction of ores, in electroplating, and as a chemical intermediate, and that is also a common combustion product. It emphasizes that noise should not be viewed as the exclusive risk agent for work-related hearing loss and that its effects can be modified by other exposures.

Although mixed exposures are common in the work environment, not much is known about which agents may interact negatively to increase hazards to workers. The featured article brings this issue to the attention of the scientific community and policy makers, providing them with relevant scientific information upon which to make appropriate decisions in terms of public health policy. Ultimately, an increase in the awareness of the ototoxic potential of chemicals should contribute to the improvement of preventive efforts and help reduce the risk of work-related hearing loss.

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