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PROMOTION OF NOISE-INDUCED HEARING LOSS BY CHEMICAL CONTAMINANTS

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Recent studies have underscored the ability of a wide range of chemical agents to potentate noise-induced hearing loss. Given the ubiquitous nature of noise exposure particularly in many work settings, the high rate of noise-induced hearing loss, the limited degree to which auditory function can recover following damage to the inner ear, and the disparate chemical structures that appear capable of impairing hearing, this issue appears to have great public health significance. A compendium of chemicals known to potentiate noise induced hearing loss is presented along with a hypothesis that might explain at least one basis for potentiation of noise-induced hearing loss by certain chemical toxicants. The use of benchmark dose analysis to undertake a risk assessment for promotion of noise-induced hearing loss by both carbon monoxide and hydrogen cyanide is described.

Complex exposures to multiple chemical and physical agents have the potential to produce several different sorts of interaction with regard to health outcomes. The nature of interactions among multiple agents can, indeed, be included in a discussion of fundamental principles of toxicology (Eaton & Klaassen, 1996). Interactions include additive effects in which the combined effects of exposure represent the sum of exposure to the individual agents. Considerably more problematic, however, are synergistic or potentiation interactions. These are "super-additive" interactions that often involve one agent that by itself has no adverse health effect on the measure of interest, but that is capable of promoting the adverse effects of the second agent (Eaton & Klaassen, 1996). The problem of synergism among toxic agents is a difficult real-world problem faced both in risk assessment and in standard setting, in industrial and ambient environmental settings. In the case of complex chemical mixtures, prediction of interaction can often be made based upon analogies of chemical structure, overlap in metabolic pathways, or suspected target of

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toxicity (Hodgson & Levi, 1997). For example, the interaction of two chemical agents that share a metabolic pathway is predictable based on what is known about fundamental enzyme kinetics. Chemicals metabolized via the same metabolic pathway may yield inhibition of metabolism of one agent by the other or may produce enzyme induction yielding increased rates of metabolism (Goldstein et al., 1974). These clues are largely absent for studying interaction between chemical and physical agents. In addition, there is a very real practical difficulty: Different professionals frequently study physical stressors and chemical agents, and there is typically a different "language" in terms of both units of measurement (dose) and expertise when dealing with such agents. Progress in identifying chemical agents that potentiate noise-induced hearing loss is hampered too because of a tendency to attribute hearing loss in noisy environments to the noise alone (Morata et al., 2002). Despite such difficulties, there has been significant progress made in the past two decades establishing that potentiation of noise-induced hearing loss by chemicals can occur, that it may represent an important public health problem (Bahadori & Bohne, 1993), and that we are approaching a point in time when prediction of interactions between noise and chemicals is becoming somewhat easier.

Noise-induced hearing loss (NIHL) is the most common occupational disease in the United States (NIOSH, 1996b). Nearly 30 million U.S. workers are exposed to potentially hazardous noise levels in the workplace (Franks et al., 1996). Consequently, the Occupational Safety and Health Administration (OSHA) has adopted a permissible exposure level (PEL) that is designed to prevent NIHL in the Hearing Conservation Amendment (OSHA, 1981) to the U.S. Occupational Safety and Health Act of 1970 (PL 91-596). Nevertheless, NIHL remains a critical occupational concern in the United States and around the world (NIOSH, 1996). Noise is estimated to be a significant contributor to hearing loss in roughly 30% of Americans with hearing loss, despite the adoption of exposure standards. The reasons for this epidemic of occupational hearing loss are many. They include substantial individual differences in susceptibility to noise (NIOSH, 1996b), difficulty in quantifying and controlling noise exposure of particular individuals in the workplace (dosimetry) (NIOSH, 1996b), the uncertainty involved in the trade-off between duration of noise exposure and noise intensity that is reflected in the different guidelines recommended by NIOSH and those adopted by OSHA (NIOSH, 1996b), and, probably, the understudied phenomenon of potentiation of NIHL by coexposure to particular chemical ototoxicants (Fechter, 1989). This article focuses on the last of these issues.

Auditory system injury can result from exposure to a wide variety of drug and chemical exposures as well as from the physical agent, noise. In addition, a number of chemical toxicants that do not themselves produce permanent hearing loss can potentiate NIHL. Laboratory animal studies as well as occupational epidemiology studies have identified such chemicals. Table 1 provides a summary of the range of chemical agents that have been shown to be ototoxic by themselves. Several useful literature reviews have been published previously

TABLE 1. Chemical Agents Known to Produce Auditory System Impairment

Organic solvents	
Toluene	Johnson et al. (1988), Morata et al. (1997b)
Styrene	Crofton et al. (1994), Muijser et al. (1988)
Ethylbenzene	Cappaert et al. (2000, 2002)
Xylene	Crofton et al. (1994)
Trichloroethylene	Crofton and Zhao (1997), Fechter et al. (1998)
Metals	
Mercury (perinatal exposure)	Rice and Gilbert (1992), Wu et al. (1985)
Lead (perinatal exposure)	Schwartz and Otto (1987)
Trimethyltin	Fechter et al. (1986, 1992)
Asphyxiants	
Carbon monoxide	Fechter et al. (1987), Shahbaz et al. (2003)
Hydrogen cyanide	Tawackoli et al. (2001)
Endocrine (thyroid) disruptors	
Aroclor 1254 (perinatal exposure)	Goldey et al. (1995), Crofton et al. (2000), Lasky et al. (2002)
Acrylonitrile	Fechter et al. (2003)

that focus primarily on ototoxic drugs (Rybak, 1995; Henley & Rybak, 1995). Organic solvents (e.g., Crofton et al., 1994; Campo et al., 1997; Johnson et al., 1988; Crofton & Zhao, 1994; Fechter et al., 1998; Morata et al., 1993, 1994, 1997a, 1997b), metals (e.g., Rice & Gilbert, 1992; Wu et al., 1985; Schwartz & Otto, 1987; Fechter et al., 1992), and chemical asphyxiants (Young et al., 1987; Fechter et al., 1988; Fechter, 1989; Chen & Fechter, 1999; Chen et al., 1999) can all have ototoxic effects. Table 2 provides a list of agents that interact with noise exposure in either an additive or synergistic fashion. Simultaneous and even successive exposure to certain of these agents in combination with noise can greatly increase susceptibility to NIHL (Johnson et al., 1988, 1990; Fechter et al., 1988, 2002; Johnson, 1993; Lataye & Campo, 1997; Morata et al., 1993; Chen & Fechter, 1999; Chen et al., 1999). It appears that solvents generally have an additive effect to noise in producing hearing loss. Asphyxiants, by contrast, appear capable of true synergistic effects on NIHL. While in most instances the mechanisms responsible for chemical ototoxicity

TABLE 2. Agents That Can Promote Noise-Induced Hearing Loss

Organic solvents		
Toluene	+	Johnson et al. (1988), Lataye and Campo (1997), Morata et al. (1993), Morata et al. (1997b)
Ethylbenzene	+	Cappaert et al. (2000)
Styrene	+	Lataye et al. (2000)
Asphyxiants		
Carbon monoxide	×	Chen et al. (1999), Young et al. (1987)
Hydrogen cyanide	×	Fechter et al. (2002)
Hypoxic hypoxia	×	Chen (2002)

have not been elucidated, there are sufficient data relating oxygen delivery and cochlear function to begin to focus on the process by which chemical asphyxiants and noise interact to permanently disrupt hearing at least in a laboratory animal model. Specifically, evidence showing that intense noise can initiate reactive oxygen species (e.g., Seidman et al., 1993; Yamane et al., 1995; Yamasoba et al., 1999; Lautermann et al., 1997, Henderson et al., 1999) and evidence that both carbon monoxide and hydrogen cyanide may further contribute to oxidative stress (Fechter et al., 1997, 2002) suggest that attention be paid to other chemical agents which may promote reactive oxygen species generation. Recent evidence with respect to the potentiation of noise induced hearing loss by acrylonitrile (Fechter et al., in press) give increased weight to this suggestion. These findings open the bigger question of whether or not oxidative stress may be a basis by which several chemical agents promote NIHL.

CHEMICAL ASPHYXIANTS AND PROMOTION OF NIHL

Chemical asphyxiants are among the most common chemicals to which workers are exposed. Cyanides are used in the extraction of low-grade ores, in electroplating, and as chemical intermediates (U.S. Department of Health and Human Services, 1995). Some of the occupations in which cyanides are used intentionally include steel production, electroplating, mining, metal leaching operations, metal cleaning, and analytical chemistry. Cyanides are used in the manufacture of synthetic fibers such as nylon, plastics, dyes, and pigments. In addition to the inadvertent exposure to cyanide as a combustion product, this toxicant is also a significant breakdown product of acrylonitrile— a compound used in manmade fibers, and in certain plastics. The OSHA PEL for HCN is 5 ppm as an 8-h time-weighted average.

Carbon monoxide exposure is ubiquitous, as it is the major combustion-related pollutant in air (U.S. EPA, 1991). All workers whose employment involves vehicles using internal combustion engines have potential exposure to carbon monoxide. These include car, bus, and truck drivers, toll takers, mechanics, garage attendants, and police officers. NIOSH (1972) estimated that nearly 1 million workers are exposed to significant levels of CO in their workplaces. NIOSH has recently reiterated the risk that CO poses in the workplace (NIOSH, 1996). Carbon monoxide is a leading cause of inhalation injuries in the workplace (Henneberger et al., 2000; Valent et al., 2002). It is a prominent factor in ongoing health hazard evaluations conducted by NIOSH (www2.cdc.gov/hhe/hhesearch.html search term=carbon monoxide).

In addition to being a major air pollutant and a waste gas generated by incomplete combustion, CO exposure may occur among acetylene workers, steel and coke oven workers, and pulp and paper workers, among others (U.S. EPA, 1991). Carbon monoxide is also produced as a metabolic by-product of the paint stripper methylene chloride. The OSHA 8-h time-weighted PEL for CO is 50 ppm with an instantaneous ceiling of 200 ppm.

The ACGIH time-weighted threshold limit value (TLV) is 25 ppm. The NIOSH recommended exposure level is 35 ppm averaged over 8 h with a 200-ppm ceiling.

While exposure standards for noise are of primary importance in protecting against NIHL, it is important to evaluate complex exposures, that include chemicals for their potential to injure the ear. The data presented here focus on an approach to risk assessment for combined exposure to noise and the chemical asphyxiants CO and HCN.

Figure 1 presents data on the relationship between carbon monoxide concentration and potentiation of noise induced hearing loss. In this experiment, rats were exposed to carbon monoxide concentrations of 300–1500 ppm for 8 h in combination with octave band noise. Comparison groups received either 1200 ppm carbon monoxide for 8 h but with no noise or no experimental treatment. Four weeks following these treatments, auditory thresholds were assessed at a range of tone frequencies between 2 and 40 kHz. This range covers a broad spectrum of the rat's auditory range. Auditory thresholds were measured by recording the tone intensity needed to produce a compound action potential recorded from the round window of the cochlea. The compound action potential represents synchronous neuronal activity generated at the spiral ganglion cell. The abscissa shows the specific test frequencies used, while the ordinate shows the sound level required to obtain a just noticeable compound action potential. The control rats show auditory thresholds that

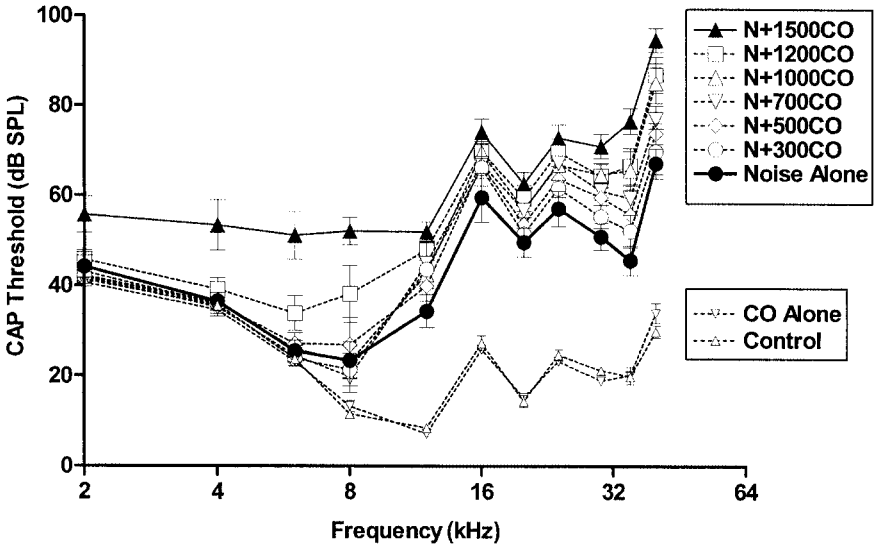

FIGURE 1. Effect of carbon monoxide exposure dose on potentiation of noise-induced hearing loss assessed 4 wk following exposure. Carbon monoxide levels of 500 ppm and higher produced a significant elevation in noise-induced hearing loss.

approach 0 dB SPL in the most sensitive frequency range (12–16 kHz). Auditory thresholds are less sensitive at low and high frequencies, although thresholds are readily measurable at all frequencies tested. It is clear from this figure that CO exposure by itself has no persisting effects on compound action potential sensitivity; thresholds for the rats receiving CO alone are comparable to control rats. However, as CO concentration increases for rats receiving combined exposure of CO + noise, there is an orderly increase in the extent of auditory threshold impairment relative to the rats receiving noise by itself. Statistically significant elevations in NIHL are observed with CO exposures of 500 ppm and higher. This study also provides both a "no-observed-adverse-effect level" (NOAEL) and a "lowest-observed-adverse-effect level" (LOAEL). A benchmark concentration analysis suggests that much lower CO concentrations are able to potentiate NIHL in rats. The question of how much lower the concentration of CO need be to yield potentiation of NIHL is dependent in part on selection of criteria for determining what the benchmark effect should be.

Developing a Benchmark Dose Analysis for Potentiation of NIHL

While agencies and scientists differ with regard to the precise manner in which risk determinations are made (Ohanian et al., 1997), the basis for such assessments are laboratory investigations that characterize the relationship between exposure dose and toxic effect as well as clinical and epidemiological findings, where they exist. By making use of the entire dose-response curve rather than selecting a specific point on that function (e.g., the LOAEL or NOAEL) as the basis for standard setting, a more confident risk assessment may be obtained. This is performed through the process known as "benchmarking," in which a function is fitted to dose-response data in order to predict the concentration of a chemical having a specified effect (Slikker et al., 1996; Crump, 2002; Gaylor & Gold, 1995), such as, in the current instance, the elevation of auditory threshold by a specified amount. Many definitions of "effect" can be used to determine a benchmark dose or benchmark concentration (Glowa & MacPhail, 1995; MacPhail & Glowa, 1999; Slikker & Gaylor, 1995). In general, such definitions take into account the variability in the data obtained from the control group relative to the outcome scores obtained from toxicant-treated subjects. Subsequently, confidence intervals can be established for the BMD such that a lower bound to the BMD (BMDL) can be defined.

Two different criteria of effect have been selected in this study: a 5-dB elevation in threshold above the effect of noise alone and a value that is 10% above the mean effect of noise alone. Selection of these criteria can be justified in terms of the biological relevance of a 5-dB elevation in auditory threshold above an already elevated threshold resulting from noise alone and to the variability in auditory threshold resulting from noise alone. Clearly, other definitions might also be utilized. Crofton and Zhao (1997), for instance, used a 15-dB threshold shift as the basis for benchmark concentration estimates for

the ototoxic effects of the solvent trichloroethylene. The rationale they cited for this definition was the judgment that a threshold loss of 15 dB would correspond to a clinically significant hearing loss in humans. This definition was rejected in the current work since our focus is on *potentiation* of a threshold shift that already represented a significant departure from normal auditory acuity. In addition, the methods for assessing hearing in the current study resulted in very small standard errors, permitting the reliable identification of a threshold shift as small as 5 dB.

To undertake such a BMD analysis based on the data shown in Figure 1, the average potentiation of noise induced hearing loss was calculated between 12 and 40 kHz for groups of rats exposed to the different levels of CO. That is, elevation of auditory threshold *above that observed for noise-only subjects* was averaged for each subject in each CO + noise exposure group. These averages are plotted in Figures 2 and 3. These two figures, then, provide a means of determining both a benchmark dose and a lower bound to the benchmark dose.

One potential weakness in our determination of a benchmark concentration for CO reflects the fact that the noise exposure conditions selected in the CO dose-response study are not optimal for producing potentiation by CO. If a shorter duration noise were used (e.g., 100 dB OBN for 2 h rather than 8 h) the extent of potentiation produced by all CO concentrations might have been more apparent. The potentiation of NIHL observed following a 2-h

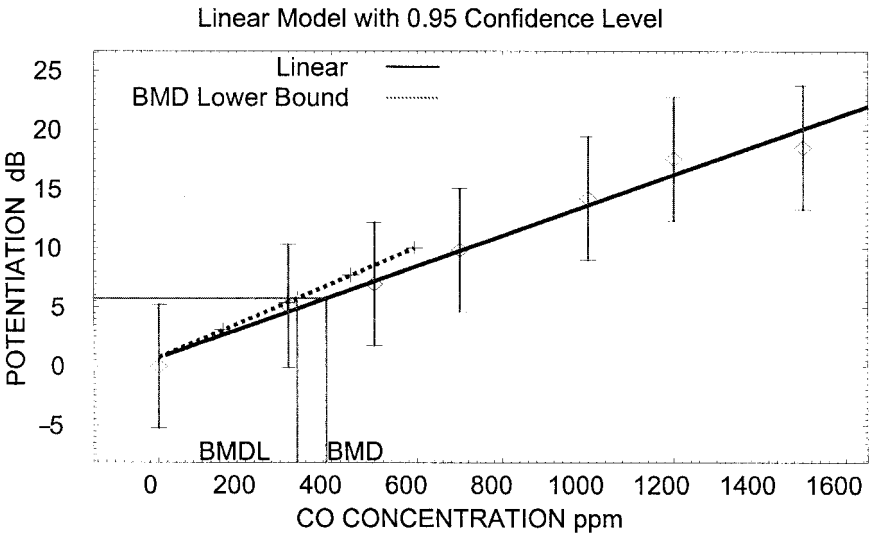

FIGURE 2. Benchmark dose analysis documenting a linear relationship between carbon monoxide concentration and potentiation of noise induced hearing loss. The benchmark dose (BMD) and the lower bound to the benchmark dose (BMDL) is plotted based on a benchmark response of 5 dB excess loss in auditory threshold. Data are adapted from Fechter et al. (2000).

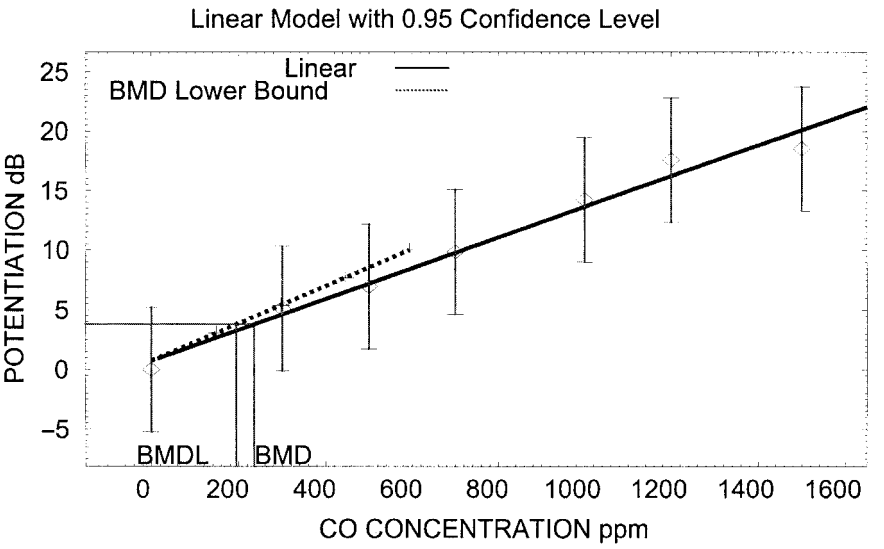

FIGURE 3. Benchmark dose analysis documenting a linear relationship between carbon monoxide concentration and potentiation of noise-induced hearing loss. The benchmark dose (BMD) and the lower bound to the benchmark dose (BMDL) are plotted based on a benchmark response of 10% excess loss in auditory threshold above the effect of noise alone. Data are adapted from Fechter et al. (2000).

noise exposure exceeds that seen with 8 h of noise exposure (Fechter et al., 2000). Thus, the current estimated benchmark may not, in fact, represent the most sensitive combination of noise and carbon monoxide for estimating a threshold of effect.

Determining a Reference Concentration From the BMDL

Once a benchmark concentration is identified, a reference concentration is obtained by modifying the benchmark dose by safety factors. The safety factors applied are intended to account for uncertainties related to interspecies extrapolation, extrapolation from acute studies to chronic exposure, limitations in numbers of subjects tested, and having limited data concerning low-dose effects and, specifically, having a good estimate of the NOAEL (Faustman & Omenn, 1996). Once these safety factors or applied to the benchmark, the resulting reference dose (RfD) or reference concentration (RfC) can be used as a reasonable estimate of a safe exposure level. This is an especially difficult yet necessary aspect of risk assessment. It recognizes uncertainty in the relationship between the study sample and the human population with which we are actually concerned. There is an ongoing debate about the size of the safety factor that should be used to account for differences in species sensitivity, chronicity of exposures, and increased sensitivity of particular groups within

the population such as the elderly or very young. In the current study, development of a safety factor is important in trying to extrapolate the results obtained from a small sample of rats (eight subjects per exposure condition) to a large human population and from a single acute exposure to repeated daily exposures or chronic exposures. It is fairly common to adopt safety factors of 1/2 to 1 log step to account for each factor relevant to the toxicant and study population although this is not a universal practice. Based on our data, we predict a lower bound to the benchmark dose of CO for potentiation of NIHL of 195–320 ppm. Adjustment of this benchmark by 1 log unit (a factor of 10) would place the reference concentration within the permissible range of human workplace exposure. In the current study, the relevant safety factors that should be considered in setting a RfC include interspecies extrapolation, a small sample size, and chronicity of exposure. Because of extensive dose-response study, both a NOAEL and a LOAEL concentration of CO that promotes NIHL are known. Of the safety factor to be applied, there is no basis for determining whether or not humans and rats differ in terms of sensitivity to CO and noise. There is concern that group sizes as small as eight subjects per group may impede the identification of auditory impairment relative to control subjects. Moreover, the experimental results obtained when a limited number of daily repeated exposures are employed suggest increased risk of potentiation with repeated exposures to CO and noise (Fechter et al., 2000). Thus employing safety factors as small as 3 for the factors of species, chronicity of exposure, and small group size would yield RfC values of 22–36 ppm. For comparative purposes, the U.S. EPA 8-h standard for CO is 9 ppm, the ACGIH threshold limit value is 25 ppm, and the OSHA permissible exposure limit is 50 ppm.

ESTIMATING CYANIDE LEVELS THAT PROMOTE NOISE INDUCED HEARING LOSS

Potentiation of NIHL has also been observed for hydrogen cyanide. Statistically significant promotion of noise induced hearing loss was observed when noise was combined with 30 ppm HCN. HCN at 10 ppm did not produce significant potentiation or pronounced outer hair cell loss (see Figure 4). For the purposes of traditional risk assessment, then, both a LOEL and a NOEL have been identified by this study. However, using a benchmark dose defined as the lower bound to the 95% confidence interval about the benchmark concentration that potentiates NIHL falls between 2 and 16 ppm HCN (see Figure 5). If these values are subjected to an 8-h TWA in line with OSHA protocols, then the lower bound to the 95% confidence interval for benchmark dose would be 0.5 and 4 ppm. For comparative purposes, the current PEL for cyanide provided by OSHA is 10 ppm, based on an 8-h TWA with a STEL value also set at 10 ppm.

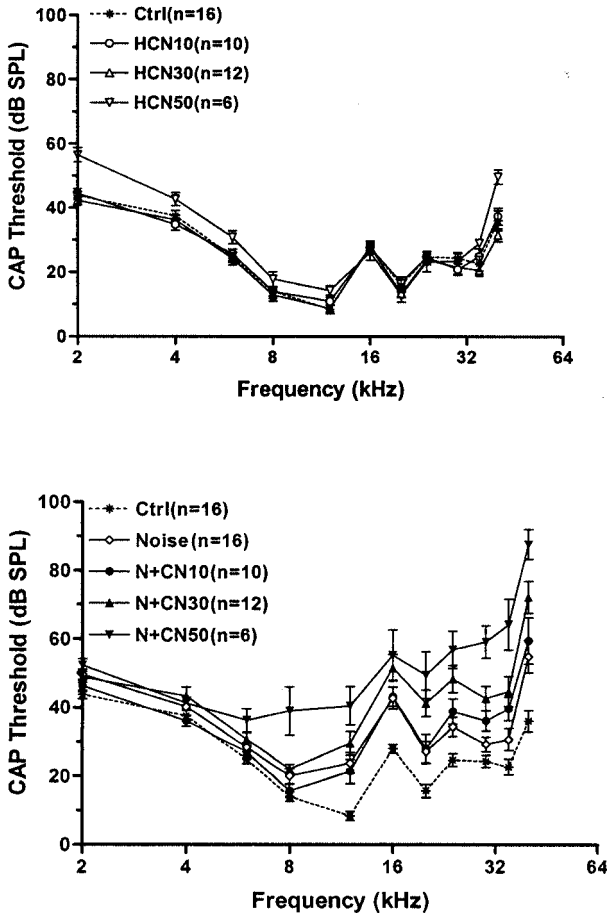

FIGURE 4. Effect of hydrogen cyanide exposure dose alone (A) or in combination with noise (B) on auditory function assessed 4 wk following exposure. Hydrogen cyanide by itself disrupted auditory function only slightly at concentrations of 50 ppm. However, hydrogen cyanide levels of 30 ppm and higher produced a significant elevation in noise-induced hearing loss. Data are adapted from Fechter et al. (2002).

This article has attempted to point out the difficulties inherent in identifying chemical contaminants capable of potentiating the damaging effects of noise on hearing. Once such chemical contaminants are identified experimentally, a process of benchmarking can be used to estimate a dose of agent that produces a specified impairment. Several different definitions of such a benchmark of effect have been proposed in this work. Finally, the next step in risk assessment, identification of a reference concentration, can be used as an initial approach to risk estimation when it is determined that chemical agents promote noise induced hearing loss.

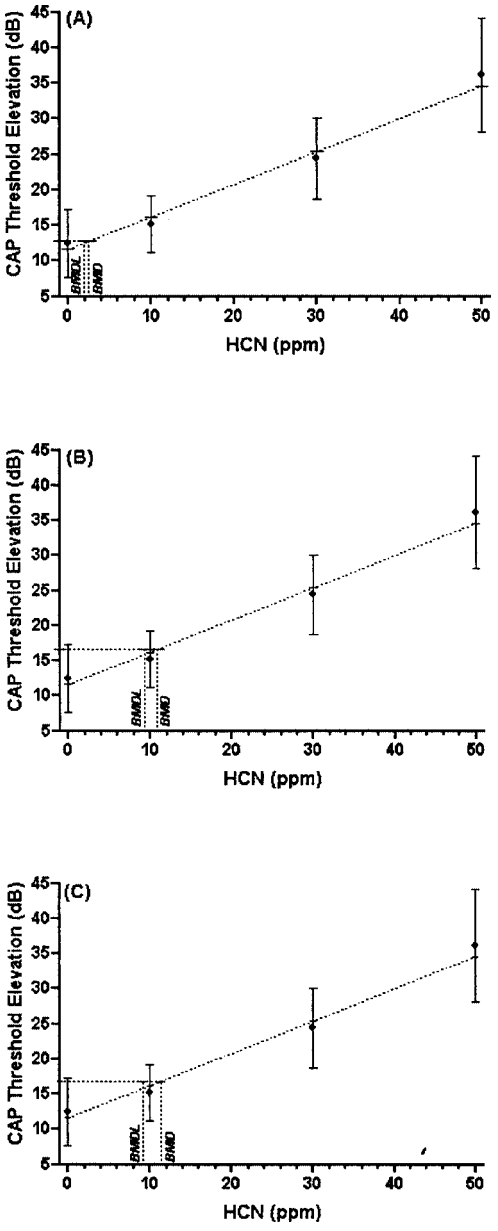

FIGURE 5. Benchmark dose analysis documenting a linear relationship between hydrogen cyanide concentration and potentiation of noise induced hearing loss. The benchmark dose (BMD) and the lower bound to the benchmark dose (BMDL) are plotted based on three different benchmark responses: (A) 10% excess loss in auditory threshold above the effect of noise alone, (B) 5 dB excess loss in auditory threshold above the effect of noise alone, and (C) 1 standard deviation (SD) elevation above the effect of noise alone. Data are adapted from Fechter et al. (2002).

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