Ototoxic effects of styrene alone or in concert with other agents: A review

Thais C. Morata[1] and Pierre Campo[2]

[1] *National Institute for Occupational Safety and Health, Division of Applied Research and Technology, Cincinnati, USA*
tmorata@cdc.gov

[2] *Institut National de Recherche et de Sécurité, Laboratoire de Neurotoxicité, France*
campo@inrs.fr

Styrene is an organic solvent employed in many manufacturing industries, as well as in other economic sectors. Recently, evidence is beginning to accumulate on the hazardous effects that styrene exposures have on the auditory system. In rats, a well-suited metabolic animal model for these studies, aromatic solvents seem to affect the auditory sensitivity mainly in the cochlear mid-frequency range. Outer hair cells are the primary targets within the organ of Corti, although the spiral ganglions are not spared. Therefore, styrene must be considered as an ototoxic chemical agent that can be potentially neurotoxic. Finally, noise-styrene exposures can have synergistic effects on the auditory system. The findings reported in both human and animal studies indicate that exposures to styrene, or to styrene associated to noise, may dramatically impact occupational hearing conservation practices and legislation. Human and animal studies will be summarized in discussing the effects of styrene alone or in combination with noise and other chemicals. Gaps in scientific knowledge are highlighted to assist future research.

Keywords: Auditory system, organic solvents, noise, combined exposures, synergism, hearing loss prevention

Introduction

Styrene is an organic solvent widely used in the manufacturing of reinforced plastics, resins, synthetic rubbers, protective coatings, and insulating materials. The highest occupational exposures to styrene occur during the manufacturing of glass-reinforced polyester products, especially of large items such as boats that involve manual lay-up and spray-up operations. It is common for workers to be exposed to styrene in these operations (Miller et al., 1994), where noise overexposure is also frequent (Morata et al., 1994).

Styrene is one of the industrial chemicals proven to impair auditory structures and functions in the rat (Yano et al., 1992; Crofton et al., 1994; Loquet et al., 1999; Campo et al., 2001) and interact synergistically with noise (Lataye et al., 2000). The first section of this paper will be focused on styrene, and present its uses and the international limits for occupational exposure. The second section will discuss the ototoxic processes that may affect the auditory system and its functions. The final section will review evidence on the effects of single and combined exposures to styrene and other agents, and offer suggestions for further research.

Styrene

Physical Properties, Absorption, Distribution and Metabolism of Styrene

Styrene (C_8H_8 or $C_6H_5CH=CH_2$) is a member of the alkylbenzene family, aromatic hydrocarbons that consist of a single-benzene ring containing one or more aliphatic side-chains (Molecular weight= 104.15). It is a colorless to yellow, oily liquid, with a sweet sharp odor. Its odor threshold is 0.05 ppm in air. Styrene is a volatile liquid with a low vapor pressure (Vapor pressure at 20°C= 4.5 mmHg). A consequence of the

volatility of styrene is that a major route of exposure is through the respiratory system. Once vapors enter the lungs, they diffuse across respiratory membranes and enter the bloodstream. The partition coefficient "blood-air" is high: 40 in rats and 52 in humans (Ramsey and Anderson, 1984). Since the solubility of styrene in water and blood is low (solubility in water 320 mg/l; log (P)=2.95), the circulating blood rapidly comes to equilibrium with styrene vapor in the alveolar air. Pulmonary retention by humans at 4.6 to 46 ppm ranges from 69.5% to 72.1% (Wieczorek and Piotrowski, 1985), however total absorbed dose can be increased six fold with the increased respiratory rate of physical exertion (Engstrom et al., 1978). Liquid styrene is also rapidly absorbed through the skin (Limasset et al., 1999). A casual approach to its use almost assures skin contact with the solvent. The US EPA calculated a human skin permeability coefficient for styrene of 5.5×10^{-2} cm/hour (EPA, 1992). The absorption of styrene by skin is generally negligible compared to the uptake via the lungs, but frequent contact with styrene can lead to defatting of skin or skin irritation (Vanio, 1990). Oral exposure is less common and absorption appears to occur more slowly than through the respiratory tract (Kirk-Othmer, 1997). The main effects reported are symptoms involving the central nervous system and irritation of eye and throat mucosa (Vanio, 1990).

Over 90% of the styrene absorbed by humans is eliminated as urinary metabolites with only a small fraction accounted for as parent compound in expired air or urine (Ramsey and Andersen, 1984). Saturation of metabolism occurs at 200 ppm in humans (Sumner and Fennell, 1994), at 700 ppm in rats (Filser et al., 1993).

Styrene's Production, Uses and Sources of Exposure

Styrene is mainly obtained from crude oil or liquefied petroleum gas. The first step involves transforming crude oil or gas into styrene. Through a distillation process, crude oil is refined to produce naphtha, heating oil and gasoline. Then, the naphtha fraction is subsequently processed by steam cracking into ethylene, propylene, and a mixture of monocyclic compounds including benzene. At last, benzene is mixed with ethylbenzene. More than 90% of the styrene produced in the world is made by a dehydrogenation of ethylbenzene (Miller et al., 1994).

Styrene is a commercially-important intermediate chemical produced throughout the world in large quantities. The total worldwide production of styrene was approximately 16.5×10^6 tons in 1995 and it was projected to grow at a rate of more than 4% annually till the year 2005 (Kirk-Othmer, 1997). Many factors contribute to this growth, including that styrene is easy and safe to handle, it can be polymerized under a variety of conditions by common methods of plastics technology to a large number of polymers and copolymers of different properties and applications (Miller et al., 1994).

Numerous groups of individuals are exposed to styrene occupationally, especially in plants involved with the fabrication of reinforced plastics and composites, including boat producers. In addition, exposures to styrene may occur during the use of miscellaneous products such as floor waxes and polishes, paints, adhesives, metal cleaners, autobody fillers and varnishes. It was estimated by NIOSH (1988, 1990) and by INRS (1996) that approximately half a million American workers are exposed to styrene as a regular part of their jobs, whereas 30.000 French workers are exposed in France. Clearly, the manufacturing group has the greatest number of workers exposed to styrene. Displayed in Table 1 are the estimates (based on data from the American National Occupational Exposure Survey [NOES]) of total number of workers by economic sector and the percentage exposed for each major industry grouping, with individual industries listed within the manufacturing group.

In Table 1 it can be noted that up to 16% of the Services work force is estimated to be exposed to styrene. In the manufacturing sector, the industry that has the highest estimate of workers exposed to styrene is the chemical industry, with 15.6%, followed by the food industry, with 13.5%.

Table 1. Total number and percentages of workers exposed to styrene by economic sector, and by industry within the manufacturing group

Economic Sector	Exposed workers (N), in thousands	Percentage of workforce exposed
Agriculture, forestry & fisheries	0.1	0.02
Mining	0.5	0.09
Contract Construction	17.7	3.51
Manufacturing	263.6	0-15.60
Ordnance	1.5	0.08
Food	68.3	13.50
Tobacco	0.7	0.13
Textiles	0.9	0.17
Apparel	0.6	0.12
Lumber and wood	0	0
Furniture	1.5	0.29
Paper	5.5	1.09
Printing	0.7	1.27
Chemical	79.0	15.60
Petroleum	0.6	0.12
Rubber and plastic	40.1	7.95
Leather	0.6	0.12
Stone, clay and glass	14.3	2.83
Primary metals	1.3	0.26
Fabricated metals	8.5	1.68
Machines, non-electric	6.9	1.36
Electrical machines	12.7	2.51
Transportation equipment	11.0	2.19
Instruments	3.1	0.61
Miscellaneous manufacturing	5.8	1.15
Transportation, communication, gas, electric and sanitary services	9.0	1.78
Wholesale and retail trade	69.3	13.74
Finance, insurance, real estate	11.1	2.19
Services	131.7	16.11

Data from the National Occupational Exposure Survey (NIOSH, 1988, 1990).

Occupational Exposure Limits for Styrene

International occupational exposure limits for styrene vary from 20 to 100 ppm for time-weighted averages of exposure (AIHA, 1987; ACGIH, 1993; AS, 1993) and are primarily set to prevent neurotoxic effects. In the U.S., occupational exposure to styrene is regulated by Title 29 of the Code of Federal Regulations (OSHA, 1989); in France, styrene exposure is regulated by the Labour ministry. The permissible limit for an 8-hour time-weighted average is 100 ppm in the USA, while it is 50 ppm in France and 20 ppm in several European countries. Since the American Conference of Governmental Industrial Hygienists (ACGIH, 1998) and the National Institute for Occupational Safety and Health (NIOSH, 1983) have recommended an exposure limit of 20 ppm, OSHA officials are attempting to re-establish more stringent occupational exposure limits (NRR, 1993).

Styrene Effects on the Auditory System

Case reports suggesting organic solvent

ototoxicity were published since the 60's (Lehnhardt, 1965), but this ototoxicity was not clearly demonstrated until the late 80's. Styrene's ototoxicity has been studied more systematically in the past decade. Some of the questions raised by early reports that suggested an ototoxic property include:

1) are the auditory disorders a consequence of styrene's neurotoxicity, ototoxicity or both?

2) in case of ototoxicity, which structures in the auditory receptor are the most susceptible to damage by styrene exposures?

3) what are the effects of combined exposure to styrene and other ototraumatic agents?

4) what are the exposure conditions required to trigger these effects?

These issues and the questions that followed will be discussed next.

The narcotic and neurotoxic properties of styrene (Cherry and Gautrin, 1990; Murata et al., 1991) represent the main health hazards that are recognized in humans (ACGIH, 1993). These effects have been observed in the case of short-term exposures to high concentrations and/or long-term exposures to lower concentrations. The underlying neuropathological process induced by styrene is unknown, although volatile hydrocarbons like styrene are all highly lipophilic and are easily absorbed into the lipid-rich nervous system (Murata et al, 1991, Campo, 1999). Numerous studies were carried out with animals to understand the neuropathological process caused by styrene. They are summarized in Table 2.

The reviewed studies indicate that styrene exposure causes a permanent and progressive damage to the auditory system of the rat, and mainly of the rat. The auditory system of the guinea-pig, for instance, is not injured by styrene as much as that of the rat (Fetcher et al., 1993). Susceptibility to solvents is, therefore, species dependent. The metabolism of the aromatic solvents inherent to each species could be the origin of such a difference of susceptibility among species (Nakatsu et al., 1983). Unfortunately, solvent metabolism in human is similar to that of rat; the latter is, consequently, the best animal model for studying the ototoxic effects of solvents (Bond, 1989; Sumner et al., 1994).

In most of the experiments summarized in Table 2, animals were exposed to styrene by inhalation. Only Fechter (1993) used injections as a major route of exposure. This difference is not significant for studying the effects of aromatic solvents on the auditory system since the uptake of solvents by blood is so important that the solvents can reach the cochlea whatever the route of intoxication chosen, and finally contaminate the organ of Corti via the external sulcus (Campo et al., 1999).

To summarize the effects of styrene on animal's auditory system, several important characteristics deserve to be taken in consideration. First, styrene induced hearing loss is species dependent. If the rat is sensitive to styrene, guinea pig seems to ignore it. Unfortunately, styrene metabolism in human is closer to rat than that of guinea pig. Secondly, the mid-frequency hearing loss is the most often reported throughout the experiments mentioned in Table 2. In fact, based on several experiments, the apical turn of the cochlea could even be impaired. So, the tonotopicity of the trauma is different from that induced by aminoglycosides (high frequency) or by polyhalogenated aromatic hydrocarbons (low-frequency). The third characteristic is the higher susceptibility of outer hair cells compared to inner hair cells. The inner hair cells begin to be phagocyted when the quasi totality of the third and second rows of outer hair cells are already destroyed. A corollary of the outer hair cells susceptibility is the progression of the trauma from the third to the first row of hair cells within the organ of Corti. This feature is likely to be related to the intoxication route taken by the solvents to reach the organ of Corti.

Finally, the intoxication process could be efficient even after the end of the exposure. Since there is evidence that noise interacts with styrene (Lataye et al., 2000), noise levels should be measured and controlled in studies of the

Table 2. Animal experiments on the effects of single or combined exposure to styrene on the auditory system.

Agents & *animal model*	Exposure conditions	Auditory tests	References	Results	Authors' comments
Styrene(S)&Xylene(X) by inhalation *weanling rats*	**S**:800,1000,1200ppm,14h/d, 3w; **X**: 6w: mixture of 10%p,o and 80%m	ABR CAR BA	Pryor *et al.*, 1987	Both agents are ototoxic in the high-frequencies	**S** & **X** more potent ototoxicants than toluene
Styrene by inhalation *young rats*	800ppm, 14h/d, 5d/w 3w	ABR only at 4, 8, 16 and 30 kHz ME	Yano *et al.*, 1992	8-16 kHz HL and 30 kHz to a lesser extent $OHC_3>OHC_2>OHC_1$	Deficit restricted to mid-frequencies
Styrene by inhalation *adult rats*	**S**: 1000ppm, 6h/d, 5d/w, 1, 2, 3 and 4w	ABR ME	Campo *et al.*, 2001	16-20 kHz HL disorganization of the membranous structures	Deficit restricted to mid and mid-low frequencies
Styrene by inhalation *adult rats*	**S**: 750; 1000; 1500 ppm, 6h/d, 5d/w, 4w	ABR ME	Lataye *et al.*, 2001	12-16 kHz HL SGC from mid and basal turns are more sensitive than those from apical turn	2 intoxication routes within the cochlea
Noise (N) & Styrene by injection *adult guinea pigs*	**S**: 2 injections of 0.75ml each spaced 30 min apart **N**: 95dB(A) broadband noise	ECoG	Fechter, 1993	No difference btw exposed and control animals No potentiation with noise	Guinea pig not a good model for solvent experiments (metabolic differences?)
Styrene & (TCE) Trichloroethylene by inhalation *young rats*	8h/d,5d with the ratio **S/TCE**: (0/3000),(250/2250) (500/750),(1000/0)	ABR	Rebert *et al.*, 1993	16kHz HL induced by both **S** and **TCE**	Only 16 kHz was tested. Neither synergistic nor antagonistic effects
Toluene (T), Styrene Xylene & TCE by inhalation *adult rats*	**T**:2500ppm 8h/d, 5d; **S**: 1600ppm; **X**: 1800ppm; **TCE**: 3500ppm	RMA	Crofton *et al.*, 1994	8-16kHz HL, i.e., mid-freq. Loss	Deficit restricted to mid-frequencies
Noise & Styrene by inhalation *adult rats*	**S**:100,300,600ppm 12h/d, 5d/w, 4w **N**: 100-105dB	ABR ME	Mäkitie, 1997	Synergistic effects above the critical level (600ppm)	PhD thesis Univ. Helsinski. Results not published
Styrene & Toluene by inhalation *adult rats*	1750 ppm 6 consecutive h , 4h the following day	ABR ME	Campo *et al.*, 1999	**S** and **T** are present within the organ of Corti, not in the perilymph	At the same dose, a bigger amount of **S** compared to **T** reaches the organ of Corti.
Styrene &Toluene by inhalation *adult rats*	**T**: 1000- 2000ppm **S**: 500-1500ppm 6h/d, 5d/w for 4w	ABR ME	Loquet *et al.*, 1999	12-16-20-24kHz HL. Upper turn of the cochlea injured	**S** is 2.4 times more potent ototoxicant than **T**- Deficit restricted to mid/mid-low range
Noise & Styrene by inhalation *adult rats*	**S**: 750ppm 6h/d, 5d/w, 4w **N**: 97dB 8OBN	ABR	Lataye *et al.*, 2000	16-20kHz HL **S**: $OHC_3>OHC_2>OHC_1$ **N**:$OHC_1>OHC_2>OHC_3$	Synergistic effects, Deficit restricted to mid-frequencies
Styrene & Ethanol(E) by inhalation (S) or gavage (E) *adult rats*	**S**: 750ppm,6h/d, 5d/w, 4w **E**: 4g/Kg	ABR ME	Loquet *et al.*, 2000	16-20 kHz HL No (E) induced HL	Huge potentiation of the effects of **S** by **E** over a wide frequency range

Abbreviations used in Table 2: ppm= parts per million, h= hours, h/d= hours per day, d/w= days per week, ml= milliliter, g/Kg= grams per Kilogram , HL=hearing loss, CAR= conditioned avoidance response, TD= tone discrimination, ABR= auditory brainstem response, BA= behavioral audiometry, RMA= Reflex Modification Audiometry, ME= morphologic examination.

auditory system, to minimize its chance of being a confounder of the effects of the solvent. Similarly, ethanol consumption can potentiate the effects of styrene on the auditory system (Loquet et al., 2000). There are professional and extra-professional factors that could considerably aggravate the ototoxic effects of styrene. One can reasonably wonder about the pertinence of the limit values when people are exposed simultaneously to several factors.

Concentration and exposure time of styrene exposure were shown to influence the ototoxic effects in rats (Loquet et al., 2000; Campo et al., 2001). From the occupational point of view, what is still more insidious and worrisome is that the ototoxic effects continue to progress far beyond the cessation of the styrene exposure. In fact, an eventual interaction could take place even out of the workplace and therefore beyond preventionists' control.

Occupational Studies

In 1991, Bielski investigated the effects of combined exposure of noise and a mixture of solvents that included toluene, benzene, styrene, xylene and butyl acetate and found an increased prevalence of hearing disorders. Almost half of the workers reported hearing loss, which was documented by audiometric testing to be permanent hearing losses of 10 to 60 dB.

The majority of investigations on occupational hearing loss has relied on pure-tone audiometry and averaging thresholds as the means to assess noise effects on auditory function. To investigate the effects of chemical exposure, this traditional approach may not be always sufficient, or even adequate. Field studies conducted on styrene used this traditional approach and identified only minimal effects of the solvent on pure-tone thresholds (Muijser et al., 1988; Möller et al, 1990; Sass-Kortsak et al., 1995). Workers exposed to low levels of styrene did not appear to have increased hearing loss at high frequencies when compared to controls (Muijser et al., 1988). The comparison of the two extreme exposure groups, however, revealed a statistically significant difference in hearing thresholds at high frequencies. In another study, routine audiometric results of workers exposed to styrene in a plastic boat plant did not indicate hearing losses resulting from causes other than exposure to noise (Möller et al, 1990). Seven of eighteen workers, however, displayed abnormal results in central auditory system testing. Styrene and noise exposures, again, were meticulously assessed for 299 workers in the reinforced fibre industry (Sass-Kortsak et al., 1995). Noise levels were found to be in the range between 85 to 90 dB(A), while styrene levels were generally below 50 ppm. The association between noise exposure, based on the developed lifetime noise dose estimate, and hearing loss (assessed by averaging pure tone thresholds) was significant. That was not the case for styrene exposure. Styrene exposure approached significance for hearing loss only at some specific frequencies (4 and 6 kHz, left ear; Sass-Kortsak et al., 1995).

More recently, the effects of styrene were investigated in male workers exposed in factories that produced plastic buttons or bathtubs (Morioka et al., 1999, 2000). Medical examinations, audiological evaluations and exposure assessment to noise and solvents (in air and urine) were conducted in both investigations. In the 1999 study, workers whose noise exposures exceeded 85 dB(A) were excluded from the study population. Participants were exposed to a mixture of solvents containing mainly styrene and toluene. Of the 93 participants, only 6 were exposed to levels of styrene that exceeded the 50 ppm Japanese exposure limit, and 2 were exposed to toluene levels exceeding the Japanese limit of 50 ppm (Morioka et al., 1999). In the 2000 study, 48 study participants were divided in 3 subgroups by their exposure conditions: a control, unexposed group, a group exposed to low levels of styrene (2.9 to 28.9 ppm) and noise ranging from 69 to 76 dB(A), and group exposed to noise levels that ranged from 82 to 86 dB(A) (Morioka et al., 2000). No effects of the solvents were detected by conventional pure-tone audiometric testing. Although both noise levels and styrene concentration in air were within limits recommended by several international agencies, the high frequency hearing thresholds were

raised in workers exposed for 5 years or more. This effect was associated to styrene concentrations in air and mandelic acid concentrations in urine. No effects of other solvent exposure were detected.

The association of the biological determinant of styrene and auditory dysfunction was also observed in a cross sectional study conducted in Sweden, which aimed to investigate the effects of occupational exposure to low levels of styrene and noise (Johnson et al, 2000). The study protocol included a questionnaire, assessment of styrene and noise exposures, and an audiologic battery. The study population consisted of workers exposed to styrene and noise (n=150), noise alone (n=75) or unexposed controls (n=60). The questionnaire gathered information on work history, non-occupational solvent and noise exposure, and medical history. Exposure assessment included gathering data from interviews and company records, and site measurements of noise levels for different work tasks. Styrene measurements were conducted on all exposed workers by air samples and biological monitoring of mandelic acid in urine. About 60% of the participants in both groups exposed to noise (styrene/noise and noise alone) were exposed to noise levels above the Swedish threshold limit value (85 dBA/3 dB exchange rate) and the range of exposure was also similar in these groups (75-116 dB(A). Styrene exposures were low, averaging 3.5 ppm with a maximum level of 22 ppm, (8 h values, TLV (8h) in Sweden is 20 ppm). Hearing loss (> 25 dB at more than one frequency above 2 kHz) was observed in 47% of the workers exposed to styrene and noise, compared to 42% of the workers exposed to noise alone. Significantly higher mean audiometric thresholds ($p<0.05$) were observed in the styrene exposed workers at 2, 4 and 6 kHz, when compared to the noise only and the unexposed groups. From the numerous variables that were analyzed for their contribution to the development of hearing loss, age, noise exposure (past and current) and mandelic acid levels (the main biologic marker for styrene in urine), were the only variables that met the significance level criterion in the final multiple logistic regression model. The odds ratio estimates for hearing loss were 2.44 times greater for each mmol of mandelic acid per gram of creatinine (95% CI: 1.01-5.88), 1.18 times greater for each dB of current noise exposure (cumulative exposure index, 95% CI : 1.01-1.38), and 1.19 greater for each year of age (95% CI : 1.11-1.28). At the ACGIH recommended limit level (Biological Exposure Index, or BEI) of end-of-shift urine is 800 mg/g creatinine or 5.3 mmol/g of mandelic acid/creatinine, the odds ratio for hearing loss estimated in the present study is 12 (odds of 2.44 per mmol/g x 5.3 mmol/g of mandelic acid /gram of creatinine). Testing for interaction between noise and styrene exposure was not significant, suggesting an additive effect between the two agents. This observation is certainly dependent on the exposure levels of the studied populations.

As part of a large investigation conducted in Poland (N= 1366), which studied the auditory effects of several solvents and noise (Sliwińska-Kowalska et al. 1999), a group of styrene exposed workers (n= 171) was compared with groups of workers exposed to noise (n= 216) and other solvents, or unexposed (n=159). The study protocol included a questionnaire, assessment of styrene and noise exposures, and an audiologic test battery. The questionnaire, an adapted and translated version of the protocol used by Johnson et al., 2000, included questions on work history, non-occupational solvent and noise exposure, and medical history. Exposure assessment included gathering data from interviews and company records, and site measurements of noise levels for different work tasks. The participants from the styrene group were exposed to noise levels ranging from 78-86 dBA. Styrene average exposures (8 h values) ranged from 11 to 38 ppm with a maximum level of 120 ppm. Hearing loss (> 25 dB at more than one frequency above 2 kHz) was observed in 70% of the workers exposed to styrene and noise, compared to 16% of the unexposed workers. The prevalence of hearing loss among groups with exposure to other solvents in paint and lacquer, or furniture manufacturing industries ranged from 56 to 67%, while for the noise exposed group it was 20%. Significantly higher mean audiometric thresholds ($p<0.05$)

were observed in the styrene exposed workers at 2, 4 and 6 kHz, when compared to the noise only and the unexposed groups. When compared to the solvent exposed groups, mean thresholds were also significantly higher at the frequencies of 4 and 8 kHz. The odds ratio estimates for hearing loss were also the highest among all groups. The risk for developing a hearing loss was 12 times greater (95% CI: 5.7-19.2), when styrene exposed workers were compared to the unexposed group.

These observations constitute the strong evidence of the ototoxicity of styrene to date and the seriousness of the risk it represents. Evidence suggests that even when in combination with noise levels within recommended limits, styrene exposure may affect the auditory system. Both animal and human investigations have shown that the audiometric frequency range affected by this solvent is not limited to the range affected by noise. Nevertheless if careful analyses were not performed and attention had not been given to all the exposure conditions, the observed hearing disorders could have been erroneously attributed to noise.

Concluding Remarks

The studies reviewed provide clear indication that styrene affects auditory functions in rats, through different modes of exposure. The styrene concentrations used in animal experiments are higher than common occupational levels, but most important is the concentration used with regard to the recommended threshold limit values. A safety factor of 10 is considered as pertinent and representative compared to human exposures. In this case, the concentrations used in the reviewed investigations are not considered that high. Moreover, it is still common nowadays to observe high peak exposures in the work environment due to the misuse of solvents.

The sensitivity of the human auditory system to solvent exposure needs to be further explored, but several reports suggest effects of styrene exposure on the human auditory system, even at exposure levels within recommended limits (Sliwinska-Kowalska, 1999; Morioka, 1999, 2000; Johnson et al., 2000). These reports raise serious concerns. Current exposure limits for styrene (ranging from 20 to 50 ppm) may be adequate for preventing a series of health outcomes, but they do not seem adequate for preventing styrene-induced hearing loss. On the other hand, there is a possibility that peak, non-trivial exposures to styrene may be contributing considerably in causing the losses. Thus, a lowering of limit-normalized levels might not eliminate the risk. More research on styrene-induced hearing loss is needed to address the issue of adequacy of recommended limits.

The association between occupational exposure to solvents and hearing impairment is rarely assessed. Noise is often present in most occupational settings where solvent exposures occur and the hearing losses observed in these situations are often attributed to the noise exposure. In addition, by merely looking to a pure tone audiogram, one cannot determine the etiology of a hearing disorder. The audiometric configuration in cases of noise-induced hearing loss and ototoxicity can be identical. Complementary audiological tests may have to be performed to adequately assess the problem. Surveillance of noise-exposed workers may need to include those exposed to styrene and other organic solvents. The first step toward proposing a strategy for preventing chemical-induced hearing loss is to study further work site data that relates exposure conditions to hearing loss.

Even though several agencies now recommend that the hearing of workers exposed to potentially ototoxic chemicals be monitored (NIOSH, 1996, 1998; ACGIH, 1998, 1999, 2000, US Army, 1998), currently there are no regulations requiring that. Consequently, despite the large number of workers exposed to these chemicals in the presence of background noise, few will be required to have regular hearing tests because the noise exposure may not exceed the regulatory guidelines. Since there is evidence that exposure to these chemicals alone or in combination with noise can produce a hearing loss, it is very possible that current hearing loss prevention practices are not meeting the needs of

this population of workers. Some of the other issues raised by these findings include: the adequacy of pure tone audiometry testing in screening solvent-exposed workers; the appropriateness of the current threshold limits when certain hazards occur simultaneously in the work place; and finally, the role of hearing assessment as applied to the early identification of those most susceptible to neurotoxic disorders. These are some of the challenges to be addressed by studies of occupational hazards from combined exposure to chemicals and noise.

Correspondence Address

Thais C. Morata
National Institute for Occupational Safety and Health, Division of Applied Research and Technology, 4676 Columbia Parkway/ MS:C27
Cincinnati, Ohio 45226-1998, USA
E-mail: tmorata@cdc.gov

References

ACGIH, American Conference of Government Industrial Hygienists (1993). Threshold Limit Values and Biological Exposure Indices for 1992-1993, ACGIH, Cincinnati.

ACGIH, American Conference of Government Industrial Hygienists (1999). Threshold Limit Values and Biological Exposure Indices for 1998-1999, ACGIH, Cincinnati.

AIHA, American Industrial Hygiene Association, Cook, WA (Ed.), (1987). Occupational Exposure Limits - Worldwide, American Industrial Hygiene Association, ISBN#0-932627-27-7.

AS, Arbetarskyddsstyrelsen. Hygieniska grandsvarden. Arbetarskyddsstyrelsens forattningssamling; 9.

Bielski J. (1991). Health condition of workers exposed to synthetic varnishes and noise. Proceedings of the Fourth International Conference on the Combined Effects of Environmental Factors. Baltimore: The Johns Hopkins University, 1991:92-96.

Bond J. Review of the toxicology of styrene (1989). *Crit. Rev. Toxicol.* 19(3), 227-249.

Campo P., Loquet G., Blachère V., Roure M (1999). Toluene and styrene intoxication route in the rat cochlea. *Neurotox. Toxicol.* 21(4) : 427-434.

Campo P., Lataye R., Loquet G., Bonnet P. (2001) Styrene-induced hearing loss: a membrane insult. *Hear. Res.*, 154: 170-180.

Cherry N, Gautrin D (1990). Neurotoxic effects of styrene: further evidence. *Br. J. Ind. Med.* 47(1):29-37.

Crofton K.M., Lassiter T.L., Rebert C.S. (1994). Solvent-induced ototoxicity in rats: an atypical selective mid-frequency hearing deficit. *Hear. Res.* 80: 25-30.

Engstrom J, Astrand I, Wigaeus, E (1978). Exposure to styrene in a polymerization plant. Uptake in the organism and concentration in subcutaneous adipose tissue. *Scand. J. Work Environ. Health* 4 (Suppl. 2):84-91.

EPA, US Environmental Protection Agency (1992). Dermal Exposure Assessment. Principles and Applications. EPA/600/8-91/0110B. US EPA, Office of Research and Development, Washington, DC.

Fechter LD (1993). Effects of acute styrene and simultaneous noise exposure on auditory function in the guinea pig. *Neurotox. Teratol.* 15: 151-155.

Filser J, Schwegler U, Csanady G, Greim H, Kreuzer P, Kessler W (1993) Species-specific kinetics of styrene in rat and mouse. *Arch. Toxicol.* 67 : 517-530.

INRS (1999) Valeurs limites d'exposition professionnelle aux agents chimiques en France. CND 174: 59-77.

Johnson A-C, Morata T, Nylen P, Svensson E (2000). Hearing loss in workers exposed to styrene and/or noise: description of audiologic test battery and preliminary results. Abstracts of the Twenty-third Midwinter Research Meeting of the Association for Research in Otolaryngology. February 20-24, 2000, St Petersburg Beach, Florida, USA. Page 25.

Kirk R, Othmer D (1997). Kirk-Othmer Encyclopedia of Chemical Technology, Fourth Edition. John Wiley and Sons, New York, Vol. 22.

Lataye R., Campo P., Loquet G. (2000) Combined effects of noise and styrene exposure on hearing function in the rat. *Hear. Res.* 139: 86-96.

Lehnhardt E (1965). Die Berufsschaden des Ohres. *Arch. Ohren Nasen Kehlkopfheilk* 185:11-242.

Limasset JC., Simon P., Poirot P., Subra I., Grzebyk M. (1999) Estimation of the percutaneous absorption of styrene in an industrial situation. *Int. Arch. Occup. Environ. Health* 72 :46-51.

Loquet G., Campo P., Lataye R. (1999) Comparison of toluene-induced and styrene-induced hearing losses. *Neurotox. Teratol.* 6: 689-697.

Loquet G, Campo P., Lataye R. Cossec B. (2000) Combined effects of an exposure to styrene and ethanol on the auditory function in the rat. *Hear. Res.* 148 : 173-180.

Mäkitie A. (1997) The ototoxic effect of styrene and its interaction with noise. Published by the University of Helsinki, Finland, Thesis.

Miller R., Newhook R., Poole A. (1994) Styrene production, use, and human exposure. *Crit. Rev. Toxicol.* 24:1-10.

Möller C., Ödkvist LM., Larsby B., Tham R., Ledin T., Bergholtz L. (1990). Otoneurological findings in workers exposed to styrene. *Scand. J. Work Environ. Health* 16(3):189-94.

Möller C, Ödkvist LM, Thell J, Larsby B, Hydén D, Bergholtz LM, Tham R (1989). Otoneurological findings in psycho-organic syndrome caused by industrial solvent exposure. *Acta Otolaryngol* 107:5-12.

Morata TC, Dunn DE, Sieber WK (1994). Occupational exposure to noise and ototoxic organic solvents. *Arch. Environ. Health* 49 (5):359-65.

Morioka I, Kuroda M, Miyashita K, Takeda S (1999). Evaluation of organic solvent ototoxicity by the upper limit of hearing. *Arch. Environ. Health*;54 (5):341-6.

Morioka I, Miyai N, Yamamoto H, Miyashita K (2000). Evaluation of combined effect of organic solvents and noise by the upper limit of hearing. *Ind. Health* 38 (2):252-7.

Muijser H, Hoogendijk EMG, Hooiisma J (1988). The effects of occupational exposure to styrene on high frequency thresholds. *Toxicol.* 49 : 331-340.

Murata K, Araki S, Yokoyama K (1991). Assessment of the peripheral, central, and autonomic nervous system function in styrene workers. *Am. J. Ind. Med.* 20(6):775-84.

Nakatsu K, Hugenroth S, Sheng LS, Homing EC, Homing MG. (1983) Metabolism of styrene oxide in the rat and guinea pig. Drug. *Metabol. Dispos.* 11(5): 463-470.

NIOSH, National Institute for Occupational Safety and Health (1988, 1990). National Occupational Exposure Survey. DHHS (NIOSH) Publication #s 88-106, 89-102, 89-103. Washington, DC: US Department of Health and Human Services.

NIOSH, National Institute for Occupational Safety and Health (1983). Criteria for a Recommended Standard: Occupational Exposure to Styrene. DHHS (NIOSH) Publication No. 83-119. Washington, DC: US Department of Health and Human Services.

NRR, Noise Regulation Report (1993). Rizer S (Ed), Silver Spring: Business Publishers Inc., May 17.

OSHA, Occupational Safety and Health Administration (1989). Fed. Reg. 54:2462, Jan 19.

Pryor G.T., Rebert C.S., Howd R. (1987). Hearing loss in rats caused by inhalation of mixed xylenes and styrene. *J. Appl. Toxicol.* 7 : 55-61.

Ramsey JC, Andersen ME (1984). A physiologically based description of the inhalation pharmacokinetics of styrene in rats and humans. *Toxicol. Appl. Pharmacol.* 73:159-175.

Rebert C.S., Boyes W.K., Pryor G.T., Svensgaard D.J., Kassay K.M., Gordon G.R., Shinsky N. (1993). Combined effects of solvents on the rat's auditory system: styrene and trichloroethylene. *Int. J. Psychophysiol.* 14: 49-59.

Riihimaki V, Pfaffli P (1978). Percutaneous Absorption of Solvent Vapors in Man. *Scand. J. Work Environ. Health* 4:73-85.

Sass-Kortsak AM, Corey PN, Robertson JM (1995). An investigation of the association between exposure to styrene and hearing loss. *Ann. Epidemiol.* 5(1):15-24.

Sliwińska-Kowalska M, Zamysowska-Szmytke E, Kotyo P, Wesoowski W, Dudarewicz A, Fiszer M, Pawlaczyk-Luszczyńska M, Politański P, Bilski B (1999) Effects of occupational exposure to noise and organic solvents on hearing. Abstracts PAN 99 Conference. Ototoxicity, Noise, Chemicals and Hearing Loss. Zakopane, Poland, 20-23 March, 1999.

Sumner SJ., Fennell T. (1994) Review of the metabolic fate of styrene. *Crit Rev. Toxicol.* 24: 11-33.

Vanio H (1990). NordiskaExpertgruppen for Grandsvardesdokumentation;93. *Styren. Arbete och Halsa*; 49.

Wieczorek H, Piotrowski J (1985). Evaluation of low exposure to styrene. I. Absorption of Styrene vapors by inhalation under experimental conditions. *Int. Arch. Occup. Environ. Health* 4:324-329.

Yano B, Dittenber D, Albee R, Mattsson J (1992) Abnormal auditory brainstem responses and cochlear pathology in rats induced by an exaggerated styrene exposure regimen. *Toxicol. Pathol.* 20:1-6.