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REVIEW

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Auditory and vestibular functions after single or combined exposure to toluene: a review

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Abstract Toluene is a widely used organic solvent, heavily employed in many manufacturing industries. Recently, evidence has begun to accumulate on the deleterious effect of toluene exposure has on the auditory and vestibular systems. Although little published information exists regarding these effects, the reported findings indicate a need for further investigation. The results of such investigations may dramatically affect occupational hearing conservation practices and legislation. Both human and animal studies will be summarized in discussing the effects of toluene alone or in combination with noise or other chemicals. Gaps in scientific knowledge are highlighted to assist future research.

Key words Balance · Hearing · Organic solvents · Ototoxicity · Toluene · Vestibulotoxicity

Introduction

The sensory function of the auditory and vestibular systems may be vulnerable to injury induced by a variety of physical, chemical and biological agents. Noise is a well known example of a physical agent that adversely impacts the auditory system. In addition, various classes of chemicals, and medicinal drugs in particular, have been proven to damage and impair auditory and vestibular structures and functions. The complications associated with medicinal drugs such as aminoglycosides, loop diuretics, salicylates, antitumor agents and quinine and its derivatives have been well publicized. Conversely, the ototoxic/vestibulotoxic effects of environmental and industrial chemicals have received comparatively little attention. In the early 1980s a class of chemical compounds called organic solvents was systematically studied following case reports linking substance abuse of these compounds with neurotoxic and/or ototoxic effects.

The first section of this paper will describe toluene, which has been the most frequently studied solvent regarding ototoxicity, and discuss its production, uses, and the international limits for occupational exposure. The second section will briefly introduce the auditory and vestibular systems, and discuss processes which may affect their function. The final section will review evidence on the effects of these systems of single and combined exposures to toluene and other agents, and offer suggestions for further research.

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Toluene

Physical properties, absorption, distribution and metabolism of toluene

Toluene ($C_6H_5CH_3$) is the common name for methylbenzene, the chemical formed when one hydrogen atom of the benzene molecule is replaced with a methyl group. Toluene is a noncorrosive, volatile and flammable liquid. The volatility of toluene makes inhalation the major route of exposure. In the lungs, toluene diffuses across respiratory membranes and enters the bloodstream. Since the solubility of toluene in water and blood is low, the circulating blood rapidly comes to equilibrium with toluene vapor in the alveolar air. In

human studies, the uptake of toluene has been estimated to be 40–60% of the total amount inhaled. Liquid toluene is also rapidly absorbed through the skin (Gerarde 1982; Fiserova-Bergerova 1985; WHO 1985; Andrews and Snyder 1991).

Following absorption, toluene is rapidly distributed, with the highest levels observed in adipose tissue followed by bone marrow, adrenal glands, kidneys, liver, brain and blood. Controlled studies on volunteers revealed that the higher the relative uptake of toluene, the lower the alveolar concentration of the solvent. The relationship between arterial blood and alveolar air concentration was linear and closely correlated. Thus, by measuring toluene concentration in alveolar air during or after exposure, it is possible to estimate the arterial blood concentration (Fiserova-Bergerova 1985; WHO 1985).

Part of the absorbed toluene (25–40%) is eliminated in exhaled breath, while 60–75% oxidized to benzoic acid, conjugated with glycine or glucuronic acid, and excreted as hippuric acid or benzoyl glucuronide in urine (WHO 1985). The excretion in urine was elevated within 30 min of the initiation of the inhalation exposure, indicating that the metabolism of toluene is rapid. The urinary hippuric acid levels have been reported to reach a steady-state level after 4 h of continuous exposure to a mean toluene concentration in air of 90 ppm (Gerarde 1982; WHO 1985).

The amount of hippuric acid excreted in a 24 h period by men exposed to toluene have been found to be proportional to the concentration of toluene in the air (Gerarde 1982; Inoue et al. 1993). The concentration of hippuric acid in urine is the currently recommended biochemical indicator for toluene exposures in the workplace (ACGIH 1993).

Toluene's production, uses and sources of exposure

Toluene is a commercially important intermediate chemical produced throughout the world in enormous quantities ($0.5–1 \times 10^7$ tons), primarily in the United States, Europe and Japan (Fishbein 1985; WHO 1985). Toluene is found in: (a) the production of other chemicals; (b) as a solvent carrier in paints, thinners, adhesives, inks, and pharmaceutical products; and (c) as an additive in cosmetic products. Toluene is also used to back-blend gasoline and is present in emissions from cars and other motor vehicles. The general population is exposed to toluene mainly through inhalation of vapor in ambient air, cigarette smoking, and, to a minor extent, by ingestion of food or water contaminated with toluene. A special group exposed to toluene includes individuals who intentionally inhale solvents mixtures containing toluene (e.g. "glue-sniffers") and those who are exposed to toluene accidentally (Arlien-Søborg et al. 1981). Numerous groups of individuals are exposed to toluene occupationally. The main routes of exposure are inhalation and dermal contact with toluene. Occupations in which exposure to toluene may occur include: aviation fuel blenders, benzene makers, chemical laboratory workers, coke oven workers, gasoline blenders, lacquer workers, paint and paint thinner makers, perfume makers, petrochemical workers, rubber cement makers, saccharin makers, solvent workers, toluene diisocyanate makers, vinyl toluene makers, painters and printers (WHO 1989; IARC 1985). Displayed in Table 1 are estimates [based on data from the National Occupational Exposure Survey (NOES)] of the total number of workers in the US by economic sector and the percentage exposed to toluene of workers in the US by economic sector and the % exposed to toluene for each major industry grouping.

Although occupational exposure to toluene is widespread, exclusive chemical exposure to toluene is rare. An exception is rotogravure printing, which provides an occupational setting with practically pure toluene exposure, that ranges as high as several hundred parts per million in air (Santodonato et al. 1985). Because of this characteristic, rotogravure printers have often been chosen to participate in studies that investigate effects of chronic toluene exposure.

Occupational exposure limits for toluene

International occupational exposure limits for toluene vary from 13 to 100 ppm for time-weighted averages of exposure (AIHA 1987; Swedish NBOSH 1990) and are primarily set to avoid neurotoxic effects. In the US, occupational exposure to toluene is regulated by Title 29 of the Code of Federal Regulations (OSHA 1989). Recently, the permissible limit for an 8 h time-weighted average was reinstituted to 200 ppm, after a federal court ruling that invalidated the Occupational Safety and Health Administration (OSHA) standards for 428 chemicals. Since the American Conference of Governmental Industrial Hygienists (ACGIH) and the National Institute for Occupational Safety and Health (NIOSH) have recommended exposure limits of 50 and 100 ppm respectively, OSHA officials are attempting to re-establish more stringent occupational exposure limits (Rizer 1993).

Toxic processes that may affect auditory and vestibular functions

The inner ear can be regarded, in functional terms, as if it were divided into two structures; the cochlea, subserving the sense of hearing, and the vestibular organs, subserving the sense of balance. These structures comprise a number of morphologically and physiologically distinct tissues. There is, however, an intimate relationship between the cochlea and vestibular system, in sharing certain fluids, and in the closely connected

Table 1 Total number of workers and percentages of workers exposed to toluene, in the USA, by economic sector and by industry within the manufacturing sector

Economic sector	Total number of workers (in thousands)	Part of work force exposed (%)
Agriculture, forestry, and fisheries	82	0.6
Mining	82	11
Contract construction	2535	7
Manufacturing	15241	8
Ordnance	33	8
Food	1402	2
Tobacco	80	1
Textile	232	4
Apparel	918	1
Lumber and wood	161	6
Furniture	295	18
Paper	571	12
Printing	1239	10
Chemical	996	18
Petroleum	195	9
Rubber and plastic	534	10
Leather	155	10
Stone, clay and glass	700	7
Primary metals	1347	3
Fabricated metals	1350	6
Machines, non-electric	1539	10
Electrical machines	1501	7
Transportation equipment	1224	14
Instruments	386	8
Miscellaneous manufacturing	384	11
Transportation, communication, gas, electric and sanitary services	3311	11
Wholesale and retail trade	9283	6
Finance, insurance, real estate	1946	7
Services	5803	8

Data from the National Occupational Exposure Survey (NIOSH 1988, 1989).

innervation, travelling together through the internal auditory meatus to the brainstem. Many diseases and lesions affect both senses. Despite this close relationship, some agents and diseases affect only the cochlea and certain virus and toxins affect only the vestibular portion without affecting hearing (Lock and Harpur 1992).

Ototoxicity is an example of a highly selective organ-directed toxicity. An ototoxic agent is usually defined as a drug or other chemical substance that causes functional impairment or cellular damage in the inner ear, especially upon the end organs and neurons of hearing, or balance, or the VIII cranial nerve. The mechanisms of action of ototoxic substances may involve the entire organ, specific cells within the organ, components of specific cells or individual biochemical paths. Drugs and other substances that alter hearing or equilibrium by acting primarily at the level of the brainstem or the central auditory pathways are considered to be neurotoxic and not strictly ototoxic (Hawkins 1976; Thomas 1985).

Ototoxicity has been known since the 19th century, when it was reported that certain drugs such as quinine and acetyl salicylic acid (ASA) can produce a temporary hearing loss as well as dizziness and tinnitus (Schwabach 1884). Drug ototoxicity was recognized as a problem in the 1940s, when permanent damage to the vestibular and cochlear organs was reported in several patients treated with the aminoglycoside antibiotic streptomycin, discovered as a cure for tuberculosis (Hinshaw and Feldman 1945).

Perhaps one of the most sinister aspects of ototoxins is that they may interact when administered simultaneously. It has become increasingly clear that the effects of many drugs or agents, when given concurrently, are not necessarily predicted on the basis of knowledge of their individual effects (Murad and Gilman 1985). In such instances, the damage incurred by agents acting together may exceed the simple summation of the damage each agent produces alone (Prosen and Stebbins 1980; Humes 1984). Since noise is the most common exogenous cause of hearing loss in humans, much interest has been focused on the combined exposure to noise and ototoxic agents (for review see, e.g. Boettcher et al. 1987, 1992).

Case reports suggesting organic solvent ototoxicity were published since the 1960s (Lehnhardt 1965), but this ototoxicity was not clearly demonstrated until the late 1980s. In a review paper that briefly discussed five occupational studies and four cases reports,

an ototraumatic interaction between noise and organic solvents was suggested and its biological plausibility discussed (Barregård and Axelsson 1984). It was observed that the incidence of sensorineural hearing loss was higher than expected in noise-exposed workers who were also exposed to solvents. Since organic solvents are known for their neurotoxic effects to both central and peripheral nervous systems, it was argued that solvents could injure the sensory cells and peripheral endings of the cochlea. It was hypothesized that, since solvent-related effects have been found in the brain, a more central action on auditory disorders could also be expected.

Toluene, the ototoxicity of which is the focus of the present review, has been the most frequently studied solvent. Some of the questions raised by early case reports that suggested an ototoxic property include: 1) are the reported auditory disorders consequences of toluene's neurotoxicity, ototoxicity (which structures in the auditory system are the most susceptible to damage by toluene exposure) or both? 2) what are the effects of combined exposure to toluene and other ototraumatic agents? 3) what are the exposure conditions necessary to trigger these effects? These issues and the questions that followed will be discussed in the next section.

Toluene and its effects on the auditory and vestibular systems

The narcotic and neurotoxic properties of toluene represent the main health hazards that are recognized in humans (for reviews on the general toxicity of toluene see IARC 1989; NTP 1990; Von Burg 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 toluene is unknown, although volatile hydrocarbons like toluene are all highly lipophilic and are easily absorbed into the lipid-rich nervous system (Cohr and Stokholm 1979; Benignus 1981). In a study of the regional central nervous system distribution of inhaled toluene in the rat and in humans, toluene was detected in all brain regions, with the highest concentrations in the brainstem, followed by the midbrain region and cerebellum. The initial uptake of toluene was significantly correlated with the total lipid content of each brain region (Gospe and Calaban 1988; Ameno et al. 1992).

Effects of toluene exposure on the vestibular system

The vestibular apparatus, lying adjacent to the cochlea in the inner ear, is the main receptor organ for the sense of balance. Intact postural equilibrium, does, however, also require intact vestibular pathways and nuclei together with visual and proprioceptive input, and cerebellar processing. Vestibular dysfunction can be perceived as vertigo and nausea, probably when the inadequate information from the vestibular apparatus conflicts with information from the additional sensory information mentioned above. Vestibular dysfunction can also induce alterations in gait, nystagmus and other oculomotor functions. The site of alterations in the centers responsible for the sense of balance can be difficult to determine due to the different modes of information and their complex integration and processing.

Disturbance of the sense of balance is considered an early manifestation of the neurotoxic action of industrial organic solvents (Wilson 1943; Stewart et al. 1968; Cohr and Stokholm 1979; Arlien-Søborg et al. 1981). The peripheral vestibular system has been of particular interest in this context (Ödkvist et al. 1983, 1987; Gyntelberg et al. 1986; Antti-Poika et al. 1989). Initial reports on the effects of toluene exposure on the auditory and vestibular systems were mainly from studies and case reports on toluene abusers and sniffers. This information is summarized in Table 2. Although no hypothesis on the underlying mechanisms for the outcomes listed in Table 2 were provided, an association between toluene abuse and the observed balance disorders was implicated. It should be noted that in the three reports where the hearing function was assessed (Ehyai and Freemon 1983; Fornazzari et al. 1983; Lazar et al. 1983), pronounced high frequency hearing impairments were also observed following toluene abuse. These positive findings, summarized in Table 2, contributed to the development of laboratory studies on myriad aspects of toluene neurotoxicity and/or ototoxicity.

Animal experiments

Electronystagmographic findings in rats acutely exposed to toluene demonstrated that the substance can cause dose-related vestibular disturbances, indicated by an enhanced rotatory response absent by positional nystagmus (Tham et al. 1982). The authors argued that the symptoms observed were elicited by stimulation of the central vestibulo-oculomotor pathways, possibly by blocking the inhibitory effect from the cerebellum (Ödkvist et al. 1979). This theory is in accordance with the findings of enhancement of induced vestibular nystagmus after cerebellar lesions (Fernadez and Fredrickson 1964). The biochemical mechanism by which toluene exerts this effect was suggested to be an incorporation of the solvent molecules into the nerve cell membrane with an effect on the ionic transfer (Tham et al. 1982).

Tests of the vestibulo- and opto-oculomotor system have been performed to investigate which pathways or nuclei are affected by toluene (Larsby et al. 1986). Nystagmographic findings in the rats acutely exposed

Table 2 Case reports on the effects of acute and chronic exposure to toluene on balance functions

Number of exposed	Exposure (years)	Effects/symptoms	Reference
1	2	Dizziness, mental confusion, cerebellar degeneration	Grabiski 1961
1	6	Ataxia, limb incoordination, permanent encephalopathy, tremor	Knox and Nelson 1966
2	10	Reversible ataxia. Severe persistent cerebellar syndrome	Boor and Hurtig 1977
1	13	Incoordination, ataxia, tremors, equilibrium disorder	Sasa et al. 1978
1	3	Severe gait ataxia, nystagmus, reduced vision	Keane 1978
1	6	Gait ataxia, nystagmus, incoordination, dysarthria	Malm and Lying-Tunell 1980
1	< 1	Cerebellar dysfunction, nystagmus, abnormal EEG, staggering gait	Takeuchi et al. 1981
6	accident	Spontaneous nystagmus, vestibular hyporeflexia, abnormal EEG	Biscaldi et al. 1981
24	3–6	Impairment of motor control, intellectual and memory capacity, hearing impairment	Fornazzari et al. 1983
4	3–10	Impairment of cognitive, cerebellar, brainstem and pyramidal tract function, central hearing disorder	Lazar et al. 1983
1	5	Wide-based reeling gait, truncal swaying, progressive visual impairment and dramatic hearing loss	Ehyai and Freemon 1983

to toluene were explained by the authors as being caused by a transient loss of cerebellar control of the vestibular and opto-oculomotor system. It was suggested that the vestibular and opto-oculomotor system may be an important tool for studying the action of solvents upon the nervous system. Recently, qualitative differences between four different solvents including toluene were found in post-stimulatory nystagmus duration and visual suppression at rotatory stimulation (Niklasson et al. 1993), which suggests that the alterations are to be found within the central vestibular system and that the mechanism at the site of action is specific rather than due to a general solvent effect (Tham et al. 1984). The long term effects of toluene inhalation on the vestibulo-oculomotor function of rats have also been investigated (Nylén et al. 1991). The results indicated that long term inhalation of toluene causes a long-lasting, possibly permanent, lesion within the vestibulo-cerebellum. No evidence that such exposure affects peripheral vestibular function was noted.

Toluene has recently been suggested to interfere with GABA transmission in the cerebellum, possibly by acting as a GABA agonist (Tham et al. 1990). This hypothesis was supported by increased extracellular levels within the cerebellum, found using microdialysis in toluene-exposed, freely-moving rats (Stengard et al. 1993).

Human exposure

Impaired visual suppression and increased saccade speed was seen in a group of 15 healthy volunteers acutely exposed to toluene (Hydén et al. 1983). Spontaneous vestibular abnormalities and vestibular hyporeflexia was observed in six female workers exposed to high levels of toluene by accident, 6 months after exposure the vestibular changes had improved (Biscaldi et al. 1981). Further case reports on toluenes effect on balance are shown in Table 2.

Dizziness, drunken feeling, lightheadedness, ringing in the ears and loss of hearing were some of the dose-related subjective symptoms reported by 193 nonsmoking and nondrinking toluene-exposed female workers, mostly in their 20s (Lee et al. 1988). Information about the workers was collected through a self administered questionnaire. The dose effect was assessed by dividing the workers into four exposure populations, 1–50 ppm, 51–100 ppm, 101–150 ppm and higher than 151 ppm. The prevalence of total complaints per person correlated significantly with the time-weighted average

Table 3 Animal experiments on the effects of single or combined exposure to toluene on the auditory system

Experimental animals	Toluene exposure	Other comparison groups/factors	Auditory tests	Results	Reference	Comment
Rats	900, 1200 or 1400 ppm, 14 h/d, 7 d/w, 5 w or 14 w, by inhalation	1. clean air	CAR TD ABR	Exposed groups had CAR impaired responses, elevated thresholds, latency-intensity functions of sensorineural HL	Pryor et al. 1983a, b; Rebert et al. 1983	Noise exposure reported (60–80 dBA) but not controlled for
Rats	1200 ppm, 14 h/d, 7 d/w, 5 w, by inhalation	1. clean air; 2. age (weanlings or young adults)	CAR BA ABR ME	Greater HL for weanlings, loss and/or damage to hair cells in cochlear basal turn	Pryor et al. 1984a	Noise exposure neither controlled for, nor reported
Rats	400 to 4000 ppm, varying schedules, all by inhalation	1. clean air	CAR BA ABR	Exposures below 1000 ppm and exposures to 4000 ppm/4h, had no effect. Exposures $\geqslant$ 1000 ppm/8–14 h/d caused HL	Pryor et al. 1984b	Noise exposure neither controlled for, nor reported
Rats	2000 ppm, 8 h/d, 7d/w, 2 w, by inhalation	1. clean air; 2. clean air + 6% ethanol in drinking solution; 3. ethanol + toluene.	CAR BA	Toluene caused HL, and forced consumption of alcohol increased severity of HL	Pryor et al. 1985	Noise exposure neither controlled for, nor reported. Alcohol alone did not have an effect
Rats	1.5 to 1.7 g/kg , 7 d, by subcutaneous administration	None	CAR	Exposure caused dose-related HL	Pryor and Howd 1986	Noise ruled out as a major factor in toluene-induced HL
Rats	1000 ppm, 16 h/d, 5 or 7 d/w, 2 w, by inhalation	1. clean air; 2. toluene; 3. noise (100 dB Leq, 10 h/d, 7d/w, 4w); 4. toluene followed by noise; 5. noise followed by toluene	ABR	Threshold elevations in all exposed groups, probable major cause was cochlear damage. Synergistic effect observed due to exposure to toluene followed by noise but not by reverse order	Johnson et al. 1988, 1990	Noise levels for non-noise groups reported (40 dBA), not expected to have any effect on hearing. No simultaneous exposure.
Rats	0.5 and 1 ml/kg for 21 d/each dose, by gavage	1. Controls received 1 ml of the vehicle, corn oil	ABR ME	Threshold elevations in mid-frequency regions, loss of cochlear hair cells	Sullivan et al. 1989	Noise exposure controlled (below 60 dBA)
Rats	1000 ppm, 16 h/d, 10 d, by inhalation	1. clean air; 2. acetyl salicylic acid (ASA, 200 mg/kg/d); 3. ASA + toluene	ABR	No hearing loss observed in ASA only group, but ASA potentiated the toluene -induced HL	Johnson, 1992	Noise levels reported (below 50 dBA)
Mice	1000 ppm, 12 h/d, 7 d, by inhalation	Mice of 2 genotypes (CBA/Ca, C57BL/6J) not exposed or exposed to toluene at 1 or 6 months old	ABR	Both strains exposed when one month old had mild HL. With increasing age, toluene had little effect on CBA mice, but accelerated age-related HL in C57 mice	Li et al. 1992	Noise levels reported (30–40 dBA). CBA mice HL starts late in life and C57 HL has an early onset
Rats	1200 ppm, 14 h/d, 7 d/w, 9w, by inhalation	1. clean air; 2. *n*-hexane (4000 ppm same schedule as toluene); 3. *n*-hexane + toluene	CAR ABR	A slight HL was observed in the n-hexane group. The group exposed to both chemicals had the poorer performance on auditory tests	Pryor and Rebert 1992	Noise exposure neither controlled for, nor reported

Table 3 continued

Experimental animals	Toluene exposure	Other comparison groups/factors	Auditory tests	Results	Reference	Comment
Rats	1000 ppm, 21 h/d, 7 d/w, 28 d, by inhalation	1. clean air; 2. *n*-hexane (1000 ppm, same schedule as toluene); 3 *n*-hexane + toluene	ABR	n-Hexane exposure had no effect, but when combined with toluene it caused an enhanced HL. The effect seemed to be specific to the cochlea	Nylén et al. 1994	Noise exposure reported (76–78 dB SPL)
Rats	1000 ppm, 21 h/d, 5 d/w, 8 w	1. clean air; 2. 5–8% ethanol in drinking water; 3. ethanol + toluene	ABR	HL only after exposures including toluene. Combined effects less severe than toluene effects	Nylén et al. 1995	Noise exposure reported (76–78 dB SPL)
Rats	1400 ppm, 16 h/d, 8 d, by inhalation	1. clean air	ABR DPOE ME	Parallel shift between ABR thresholds & DPOE amplitudes. Major cause was damage to outer hair cells (ME & DPOE)	Johnson and Canlon, 1994a, b	Noise levels reported (below 50 dBA)

ppm parts per million, *h/d* hours per day, *d/w* days per week, *g* or *mg/kg* grams or milligrams per kilogram, *ml* milliliter, *HL* hearing loss, *CAR* conditioned avoidance response, *TD* tone discrimination, *ABR* auditory brainstem response, *BA* behavioral audiometry, *DPOE* distortion product otoacoustic emission, *ME* morphological examination.

intensity of exposure to toluene for each individual. The prevalence of dizziness and drunken feeling symptoms showed a plateau in the exposure range below 100 ppm, followed by an abrupt increase at higher concentrations.

Altered vestibular function among male rotogravure printers, aging from 23 to 60 years (mean 42) and exposed to toluene at 100–110 ppm (mean duration 11.2 years), has been observed (Coscia et al. 1983). Vestibular function testing (electronystagmography with caloric testing) revealed alterations that could not be attributed to non-occupational factors in 15 of the 53 subjects examined. Eleven workers among the 15 who had a vestibular disorder also had a hearing impairment.

Effects of toluene on the auditory system

Animal experiments

A possible ototoxic effect of toluene was first reported by (Pryor et al. 1983a) in a study concerning neurobehavioral effects of toluene in rats. A series of experiments followed this first report. They are summarized in Table 3.

Conditioned avoidance response (CAR) task, together with auditory brainstem response (ABR), were the tests more frequently used to evaluate the effects of toluene during and after the exposures. Later experiments used cochlear morphologic examinations and/or distortion product otoacoustic emissions (DPOEs) to complement the information provided by ABR regarding lesion site.

The reviewed studies indicate that toluene exposure causes a permanent and progressive damage to the auditory system of the rat. In most of the experiments summarized in Table 3, animals were exposed to toluene by inhalation. The ototoxicity of toluene was also demonstrated following subcutaneous injections and oral administration (Pryor and Howd 1986; Sullivan et al. 1989), excluding noise from the inhalation system as a necessary causative factor for the effect. However, since there is evidence that noise interacts with toluene (Johnson et al. 1988, 1990; Morata et al. 1993), noise levels should be measured and controlled to minimize its chance of being a confounder.

Concentration, exposure time, and daily duration of toluene exposure were shown to influence the ototoxic effect in rats (Pryor et al. 1984b). The daily duration of exposure is important. Between 12000 and 16000 ppm h per day during 3 days was found to impair the auditory system, when measured 3 weeks after the end of exposures (Pryor et al. 1984b). Contrastingly, the total length of exposure is not decisive, since after long term exposure during 18 months to 6000 ppm h/day, no loss of auditory sensitivity was found (Nylén et al. 1987). Measurements of the toluene concentration in blood have shown that the ototoxic threshold concen-

tration for rats is between 40 and 60 μg/ml (Pryor et al. 1991).

Toluene exposure induced only a slight decrease in auditory sensitivity in mice (Li et al. 1992). The exposure was, however, less intense than in the rat experiments, since a severe toluene-induced auditory impairment would have prevented observation of the influence of the solvent on the age related hearing loss in the C57 mice. The fact that toluene exposure affects the auditory sensitivity also in mice is interesting, since all other animal studies of toluene ototoxicity have been made on rats. Toluene exposure thus affects the auditory sensitivity, at least in one other related animal species.

In some of the experiments summarized in Table 3, ABR thresholds were affected in frequencies ranging from 3.15 to 20 kHz. The ABR latency in toluene exposed rats (Johnson et al. 1988) was increased when measured 2–5 days after the end of the exposure. This effect was transient and had disappeared 1 month after the end of the exposure. No effect on the inter-peak interval was seen in this study, or in any of other investigations of toluene exposed rats (Rebert et al. 1983; Nylén et al. 1994). The unchanged inter-peak interval suggests that the damage is localized in the cochlea and not within central auditory pathways. Further evidence for a cochlear site of the damage are the diminished amplitudes of the DPOEs after exposure to toluene (Johnson and Canlon 1994a). Lowered amplitudes of the DPOEs have been seen after exposure to ototoxic substances known to interfere with the outer hair cells (Brown et al. 1989; McAlpine and Johnstone 1990). The DPOEs are believed to originate from the cochlea. A connection to outer hair cell (OHC) activity is supported by findings that stimulation of the cochlear efferent fibers in the olivocochlear bundle, making contact with the OHCs, causes changes in distortion products (Mountain 1980; Siegel and Kim 1982). The results of the DPOE measurements (Johnson and Canlon 1994a) thus indicate that toluene damages the OHCs. An effect on the OHCs was confirmed by morphologic examinations that revealed loss of hair cells seen after 5 days of toluene exposure (Pryor et al. 1984a; Sullivan et al. 1989; Johnson and Canlon 1994b). The areas showing loss of hair cells corresponded rather well with the frequency of the auditory impairment observed with the DPOE and ABR measurements (Johnson and Canlon 1994b). The most affected frequencies were found in the mid-frequency range of the cochlea, a phenomenon also observed in other studies of solvent ototoxicity (Jaspers et al. 1993; Crofton et al. 1994).

Several hypothesis may be proposed for the unknown mechanism for the damage to the OHCs (Johnson 1994). Indications of a disturbance of the cellular Ca^{2+} homeostasis have been seen by increased intracellular Ca^{2+} levels in synaptosomes exposed to toluene in vitro (Von Euler et al. 1990). Also, intracellular Ca-ATPase have been demonstrated immunohistochemically in the subsurface cisternal system of the OHCs especially in the middle and apical turns of the cochlea (Schulte 1993). If toluene affects the Ca^{2+} level in the OHCs, this distribution of the Ca-ATPase within the OHCs in the middle and apical parts of the cochlea may be one explanation for the higher vulnerability of the mid-frequency OHCs seen after toluene exposure.

Disturbed Ca^{2+} homeostasis, causing acute intoxication in the cell, has been proposed by Schulte (1993) to be a common factor contributing to OHC damages by different causes such as noise trauma, and sodium salicylate poisoning. This possibility of a common pathway for OHC damage is especially interesting in view of the interactions between toluene and noise, and toluene and other agents mentioned below.

Another possible mechanism is that toluene affects the stability of the membrane of the OHCs or their stereocilia, thereby causing cell damage. Toluene have been shown to increase the membrane fluidity in rat brain synaptosomes by altered phospholipid metabolism (Lebel and Schatz 1990; Von Euler et al. 1990). Decreased membrane stability may also make the OHCs more prone to the mechanical stress of ensuing noise exposure. The potentiation of the toluene ototoxicity by simultaneous administration of acetyl salicylic acid (Johnson 1992) may, at least partially, be explained by a joint action on the OHC membrane, since acetyl salicylic acid has been shown transiently to alter the membrane permeability of the OHCs (Stypulkowski 1990).

Influence of other factors on toluene ototoxicity

The experiments summarized in Table 3 demonstrated different interactions between toluene exposure and a myriad of agents or factors, including age, genotype, intake of ethanol or acetyl salicylic acid, exposure to *n*-hexane or noise. One of the salient effects was observed in the study of combined exposure to toluene and noise (Johnson et al. 1988). This combination caused a more severe loss of auditory sensitivity than toluene alone or noise alone. At some frequencies a potentiation was found when the toluene exposure preceded the noise exposure, while the reversed exposure order at most resulted in an additive effect. Variations in the extent of auditory impairment with the temporal sequence of exposure have also been shown after combined exposures to noise and other ototoxic drugs, as kanamycin and cisplatin (Marques et al. 1975; Ryan and Bone 1982; Boettcher et al. 1987, 1992; Laurell 1991). A synergistic loss of auditory sensitivity has also been found after combined exposure to toluene and other solvents such as *n*-hexane (Nylén et al. 1994) and to toluene and a non-prescription drug such as aspirin (Johnson 1992), whereas combined exposure to toluene and ethanol using different exposure protocols has

shown both enhancement (Pryor et al. 1985) and slight antagonism (Nylén et al. 1995)

Occupational studies

Workers in an electromechanical factory who had acute exposure to toluene vapors were studied audiometrically and with vestibular tests. The exposure was caused by toluene being inadvertently spread on a heated iron plate. Three of the six workers exposed had hearing losses recorded. In one of the cases, the audiogram reverted to normal 6 months after the exposure (Biscaldi et al. 1981).

In 1990, 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 a permanent hearing loss of 10–60 dB.

In 1989, Möller et al. conducted a study on auditory and vestibular functions of workers ($n = 9$) exposed to a mixture of unspecified alcohol, aromatic and industrial solvents. The findings after pure tone audiometry and speech discrimination test were essentially normal for age and noise exposure history, not indicating measurable cochlear damage due to solvent exposure. However, a significant abnormality was found in discrimination of interrupted speech and evoked cortical responses, tests that assess more central portions of the auditory pathways.

The effects of toluene on the auditory system was studied in a group of rotogravure printers through the use of brainstem auditory evoked responses (Abbate et al. 1993). Forty workers with normal hearing ability (assessed by pure tone audiometry), who had been exposed to an average of 97 ppm for 12–14 years, were selected to participate. Their results were compared with those from a group of workers of the same age but not occupationally exposed to solvents. The study indicated that exposure to toluene was able to induce a statistically significant alteration in the evoked responses, visible for all waves and all the intervals studied. The auditory brainstem evoked responses demonstrated auditory nervous system modifications before the occurrence of clinical signs due to chronic exposure to toluene.

In a cross-sectional study of the effects of occupational exposure to solvents and noise on hearing, workers from rotogravure printing and paint manufacturing industries (total $n = 190$) had their hearing function tested through pure tone audiometry, impedance audiometry and stapedius reflex testing (reflex threshold and decay; Morata et al. 1993). Workers who were exposed to noise (88–98 dBA) and toluene (100–365 ppm) were compared to groups of workers exposed solely to noise (88–97 dBA), exposed to a mixture of solvents in which toluene was the major component, and exposed to neither of these agents. The adjusted relative risk estimates for hearing loss were four times greater [95% confidence interval (95% CI) 1.4–12.2] for the noise group; 5 times greater (95% CI 1.4–17.5) for the solvent-mixture group, and 11 times greater (95% CI 4.1–28.9) for the noise and toluene group. The findings suggest that exposure to the solvents studied had a toxic effect on the auditory system and that an interaction between noise and toluene took place. Acoustic reflex findings indicated that the hearing losses observed in the noise plus toluene group were not only more prevalent, but also different from the hearing losses observed in the noise-exposed group with respect to probable lesion site. The results suggest a non-cochlear site of the lesion, since the percentage of workers with acoustic reflex decay was largest in the group exposed to noise and toluene. In addition, the decay was greatest after contra-lateral stimulation, suggesting involvement of the lower brainstem. A peripheral component of the observed hearing loss was, however, not excluded (Morata et al. 1993).

The relationship between occupational exposure to solvents and self-assessed hearing problems was investigated in a cross-sectional study with 3284 men aged 53–74 years (Jacobsen et al. 1993). Exposure to mixed solvents for 5 years or more resulted in an adjusted relative risk for hearing impairment of 1.4 (95% CI 1.1–1.9) in men without occupational exposure to noise. In men exposed to both solvents and noise the effect of the latter dominated and no additive effect was observed. A subsample of 51 men was examined using pure tone audiometry and 20 of 21 men who reported abnormal hearing also fulfilled an audiometric criterion for hearing impairment.

Discussion and concluding remarks

Balance disorders are commonly associated with occupational solvent exposure. This issue has been studied and otoneurological and audiological test batteries have been recommended for the clinical assessment of these cases (Ödkvist et al. 1992).

Vestibular function alterations have been found after exposure to toluene. In the 11 case reports (including sniffers) referred to in Table 2, symptoms such as different kinds of motor incoordinations (eight studies), cerebellar dysfunction (four studies), and nystagmus (four studies) are mentioned. These parameters were not included in any of the remaining studies. These fairly consistent findings strongly indicate that toluene affects the balance system, probably mainly cerebellar functions. This hypothesis is supported by experimental studies where functional cerebellar alterations in rats have been found both after acute and chronic exposure.

The recent findings of altered GABA transmission within the cerebellum of toluene-exposed rats seem to provide a plausible mechanism that might have contributed to the observed alterations in many of the above mentioned studies.

The reviewed studies provide clear indication that toluene affects auditory functions in rats and mice. Even if extrapolation of the results from animal studies to humans must be made with caution, several reports reviewed here suggest effects on hearing after toluene exposure in humans also, both in solvent abusers, with signs of hearing loss and abnormal ABR recordings (Ehyai and Freemon 1983; Fornazzari et al. 1983; Lazar et al. 1983), and reported hearing loss in workers exposed to toluene (Coscia et al. 1983; Morata et al. 1993; Bielski 1990).

The toluene concentrations used in animal experiments are higher than common occupational levels in, e.g. Europe and the USA. Solvent abusers are, however, often exposed to similar or even higher concentrations (Ehyai and Freemon 1983; Fornazzari et al. 1983) and only 15 years ago occupational exposures of the same order of magnitude were measured (Morata et al. 1993). Moreover, it is still common nowadays to observe high peak exposures in the work environment due to the misuse of solvents, e.g. to clean machinery or hands, mop floors, etc. (Morata 1990).

In experimental animals, there is strong evidence that toluene exposure produces cochlear lesions (Pryor et al. 1984a; Johnson et al. 1988; Sullivan et al. 1989; Johnson and Canlon 1994 a,b), indicating that ototoxicity is probably the process by which toluene affects the auditory system. Additional studies, however, have linked occupational exposures to a variety of solvents and disorders in the central auditory pathway (Ödkvist et al. 1982, 1987; Möller et al. 1989; Abbate et al. 1993; Morata et al. 1993). This suggests that solvents may play a role in both ototoxic and neurotoxic actions. In either case, the information provided by pure tone audiometry should be augmented by other tests, until further information on the effects of industrial chemicals on hearing is gathered.

Researchers in Sweden (Ödkvist et al. 1982, 1987; Möller et al. 1989) have used comprehensive audiological test batteries to investigate workers exposed to mixtures of solvents in different work settings. Although ideal, the use of an audiologic test battery in occupational studies may be prohibited by both time and cost constraints. In the face of these constraints, the use of immitance audiometry is suggested. Immitance testing has proven validity and reliability, as well as availability and ease of administration (< 5 min to administer) (Morata et al. 1993). Acoustic reflex measurements (part of the immitance battery) could be used both to identify those who are more susceptible to the development of hearing loss, and also to identify those who are more susceptible to neurotoxic effects of solvent exposure.

Distortion product otoacoustic emission (DPOE) has been used with experimental animals as a sensitive method to assess the effects of noise exposure and ototoxic actions of certain drugs and chemicals, including toluene. In the latter case, DPOE measurements have indicated that mainly the outer hair cells are adversely affected by toluene exposure.

Hitherto, this test has not yet been used in occupational studies. However, due to its reliability and the short time required for its application, it may be a viable complement to pure tone audiometry. Noise exposure, of course, would need to be taken into account.

An interaction between noise and solvent exposure in the work environment was indicated by the finding that the hearing loss in workers exposed to both agents was greater than that expected from the noise exposure alone (Barregård and Axelsson 1984; Bergström and Nyström 1986; Mehnert et al. 1992). Conversely, a report on a geriatric population ($n = 871$) with subgroups of workers with a history of industrial chemicals exposure failed to observe an interaction (Rosenhall et al. 1993). The fact that no detailed noise and solvent exposure records were available, together with the limited information that pure tone audiometry can offer, constitute the main difficulties in reaching a conclusion from these reports. Nevertheless, as described earlier, a recent epidemiologic study (Morata et al. 1993) specifically investigated the effect of an interaction between toluene and noise on hearing. The results demonstrated an increased (11 times) adjusted relative risk for hearing loss in the group exposed to noise and toluene compared to unexposed controls. Exposure to noise alone, or to a toluene containing solvent mixture, also increased the risk of hearing loss but only 4 or 5 times, respectively, suggesting an interactive effect in the combined exposure situation.

While laboratory animal studies generally support the ototoxicity of toluene, the research findings that toluene is ototraumatic whether presented alone or in combination with noise have far reaching implications for future research, and the methods used to assess occupational hearing deficit. The hearing test routinely performed (pure tone audiometry) to detect noise-induced hearing loss may be inadequate for identifying the disorders related with chemical exposure or a combined effect. Furthermore, the pure tone audiogram configuration of cases of noise-induced hearing loss or ototoxicity can be identical (both processes cause hearing losses in the middle or high frequencies). Complementary audiological tests may have to be performed in order to adequately assess the problem. Surveillance of noise-exposed workers may need to include those exposed to toluene 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 relate exposure conditions to hearing function.

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