HAZARDS TO HEARING FROM COMBINED EXPOSURE TO TOLUENE AND NOISE IN RATS

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Abstract

Introduction: The main risk of hearing impairment from workplace exposure to organic solvents may stem from the potentiation of effects caused by concomitant noise exposure. The aim of the present study was to identify the main hazards from combined long-term, low-level exposure to noise and aromatic organic solvents, like toluene, in rats. Material and Methods: The rats were exposed to steady-state, wide-band noise (WBN) and 0 ppm, 100 ppm, 200 ppm and 500 ppm toluene for 90 days. Hearing was assessed using Auditory Brain Stem Responses (ABR) and Distortion Product Oto-Acoustic Emissions (DPOAE) eight weeks after exposure. The impact of noise composition on the interaction between solvent and noise exposure was investigated in rats exposed for 10 days either to 0 ppm, 500 ppm, 1000 ppm or 1500 ppm toluene and either WBN or impulse noise. ABR and DPOAE tests were performed before and two weeks after exposure. Results: Long-term exposure of rats to WBN and toluene at 500 ppm or less did not show any increase in hearing impairment, compared to the rats exposed to noise only. Synergistic interaction was demonstrated in short-term exposure to 1500 ppm toluene and both to WBN and impulse noise, but hearing impairment was much larger when following exposure to impulse noise. Conclusion: In combined exposure to low-levels of noise and toluene, even a long-term exposure did not reveal a potential hazard of hearing impairment. Synergistic interaction in combined short-term exposure to toluene and noise was noted both with respect to WBN and impulse noise, but the impulse noise was much more disruptive than WBN at the same level of noise exposure. The ototoxicity of organic solvents may primarily be a hazard also to human hearing due to the exacerbation of hearing loss by a possible co-exposure to especially harmful noise, such as impulse noise.

Key words:
Hearing, Wide Band Noise, Impulse noise, Interaction, Organic solvents, Toluene, Rat, ABR, DPOAE

INTRODUCTION

The possible ototoxic effect of toluene was first reported in rats by Pryor et al.[1], and subsequent studies demonstrated hearing loss in rats after exposure to toluene [2–11], styrene [8,12–18], xylene [8,9,12], ethyl benzene [19,20], trichloroethylene [8,9,21–24], chlorobenzene [9], and n-heptane [25]. The ototoxic potency of the different solvents varies significantly [9,14,26], but when rats were exposed to different combinations of organic solvents, the auditory impairment was additive with respect to the potency of the solvents under study [9]. In rats, the general auditory impairment from exposure to organic solvents is a mid-frequency hearing loss at 8–20 kHz following outer hair cell (OHC) loss in the middle and basal turns of the cochlea [3,6,8,10,11,13,23,27,28]. At lower exposure levels, there are only minor changes at frequencies close to 16 kHz, but as the exposure level increases, the changes spread upwards as well as downwards in the frequency domain [24]. However, a certain threshold level of toluene exposure has to be exceeded, before even a prolonged exposure can induce the signs of ototoxicity [4,7,23,29], and corresponding to the threshold concentration in exposure, there seems to be a threshold concentration of toluene in blood of 40–60 μg/ml, before any auditory impairment is evident. It further seems to be toluene itself rather than its metabolites that is responsible for OHC loss [7]. At present, the risk of human auditory impairment due to organic solvent exposure seems to be primarily a problem concerning the effect of combined exposure to solvents and...
noise. A large number of studies have examined the nature of the interaction between noise and organic solvents and its impact on hearing in animal experiments. A potentiation of the auditory impairment was found in rats exposed sequentially to toluene (1000 ppm 16 hours/day, 5 days/week for 2 weeks) and noise (100 dB L_{eq} 10 hours/day, 7 days/week for 4 weeks) when toluene exposure preceded noise exposure [5]. A reverse exposure order resulted only in an additive effect [30]. Synergistic interaction was demonstrated in rats after simultaneous exposure to 2000 ppm toluene and noise (92 dB SPL) for 6 hours a day, 5 days a week for 4 weeks [11], as well as to 1500 ppm toluene and noise (96 dB SPL), 6 hours/day for 10 days [31]. However, the synergistic interactions in both these studies were found only when the exposure to toluene, without concomitant noise exposure, caused considerable auditory impairment. A similar pattern of synergistic interaction has also been demonstrated in rats subjected to a combined exposure to ethyl benzene and noise [32] as well as styrene and noise [15,33].

Of particular interest are studies employing animal models of the possible interaction of low-level exposure to organic solvents and noise, where the exposure to each factor alone produces no effect. At present, no studies have shown synergistic effects of interaction in combined exposures to organic solvents and noise in animals, unless the levels of exposure were above, or at least very close to, the low adverse effects levels (LOAEL) of the organic solvent, without concomitant noise exposure. A possible reason for this is that the duration of combined exposures in these studies has been too short to provide data for evaluating the hazards from long-term exposure of humans in work environment [32]. However, some insights have been provided. The same degree of styrene-induced hearing loss can be obtained by a concentration approximately 200 ppm lower in active rats than in sedentary rats [34]. This finding demonstrates that the high exposure levels that are necessary to induce the ototoxic effects in rats are partially a consequence of the inactivity of the rats during exposure, which reduces the uptake of organic solvents. The susceptibility to the ototoxic properties of organic solvents is species-specific, and rats and mice appear to be very sensitive, while chinchillas and guinea pigs are not [35–38]. So far, the rat has been the preferred animal model for studying the risk from combined exposure to noise and organic solvents. Other factors have been considered as well in order to provide insight into the human risk of hearing impairment from the combination of the chemical, physical and intrinsic risk factors. Differences in the ototoxicity of styrene have been found between rats aged 14 and 21 weeks; the younger rats being most sensitive to styrene ototoxicity, possibly due to the age-related changes in the metabolic rate of styrene [39]. Ethanol has been found to potentiate the ototoxicity of styrene, either by inducing intrinsic changes in the cochlea, or by modifying styrene metabolism [40,41]. The present study has focused on the possible consequences of long-term combined exposure to noise and toluene, and on noise characteristics as an important factor accounting for the effects of interaction between the noise and the solvent.

MATERIALS AND METHODS

The animal welfare committee, appointed by the Danish Ministry of Justice, has granted ethical permission for the studies. All the procedures were carried out in compliance with the EC Directive 86/609/EEC and with the Danish law regulating experiments on animals.

Animals

Male Wistar rats (MOL:Wist Han) were purchased from a local breeder (M&B, Ltd.) and weighed 175–200 g on arrival. The rats were housed two by two in polypropylene cages (425×266×150 mm) with steam-cleaned pine-wood bedding (Lignocel S 8). Tap water and rodent chow (Altromin 1324) was accessible ad libitum. In the animal quarters, the temperature was maintained at 21±1°C and humidity at 55±10%. Lights were on from 7.00 p.m. to 7.00 a.m. To be exposed, the rats were transferred daily from their home cages to closed climate chambers and kept two by two in wire mesh cages without access to food and drinking water. In order to secure the most equal exposure of the individual rats, the cages within the chambers were rotated one position every day.
Toluene exposure
The exposures were performed in dedicated 1200 l inhalation chambers with walls made of stainless steel and glass. The chamber interior is divided into two compartments by a stainless steel plate with small holes, which imposes reduction of the main pressure of the system and secures a fairly laminar airflow through the chambers. The airflow is driven by a radial fan at the outlet, giving a slight negative pressure within the chambers, without a possible leakage of toluene to the surroundings. The air exchange rate was 12 per hour, air temperature 20±2°C and humidity 55±10% RH. During the exposure series, which was performed between 8.30 a.m. and 2.30 p.m. with the animals in their normal waking state, the rats were housed in wire mesh cages without access to food and water. Toluene (purity > 99.5% GC; CAS-No. [108-88-3]) was evaporated in the air inlet of each exposure chamber by individual HPLC-pumps feeding the toluene to the top of glass spirals, which were slightly heated by circulating water (36°C). Toluene concentration in the chamber was measured with an infrared gas cell spectrophotometer (Foxboro MIRAN-1A), automatically changing from chamber to chamber every 5 minutes. The system was calibrated directly in concentration units (ppm) and all exposure data were collected and stored on PC for later analysis. For the control of toluene concentration, the daily quantity of toluene supplied to each chamber was measured and checked against the toluene concentration in the chamber.

Noise exposure
Noise was generated by a PC with a 16-bit D/A-converter board, amplified by audio amplifiers (NAD 216), and delivered by dome tweeters (Vifa D26TG-05-06) located above each cage. The sound field was measured at various points at the floor level of the cages with a ½” condenser microphone (B&K4133) and a spectrum analyzer (HP35670A). The noise level in the exposure chambers was 35 dB SPL in the 2–48 kHz frequency range; the highest single frequency contribution being 25 dB at 4.8 kHz.

Exposure schedule
The 90-day study
This part of the study was performed to elucidate the consequences of long-term, low-level exposure both to toluene and noise. A 90-day exposure schedule was chosen in order to comply with the conditions specified in the OECD test guidelines for a subchronic inhalation toxicity study. Five groups of 12 rats were exposed to 0 ppm, 100 ppm, 200 ppm, or 500 ppm toluene for 6 hours/day, 5 days/week, and to steady-state 90 dB SPL, 4–20 kHz wide-band noise (WBN) for 4 hours/day, 5 days/week for 90 days, and one group was exposed neither to toluene nor noise. The mean and SEM of toluene concentrations for the groups at steady state, which was reached approximately 20 min. after switching on the dosage pumps, amounted to 102±1 ppm (SEM), 202±1 ppm, and 500±1 ppm toluene, respectively. The 90 dB SPL noise exposure for 4 hours/day corresponds to $L_{eq8hours} = 87$ dB SPL.

Toluene, WBN and impulse noise
This part of the study was to investigate the potential difference in the interaction between organic solvents and either wide-band noise (WBN) or impulse noise. Eight groups of 12 rats were exposed 6 hours/day for a period of 10 days to 0 ppm, 500 ppm, 1000 ppm, or 1500 ppm toluene and to 92 dB SPL noise, with a frequency range of 4–24 kHz, either as WBN or impulse noise. One group was exposed to 1500 ppm toluene without noise exposure. The mean and SEM of toluene concentrations were 491±15 ppm, 507±28 ppm, 1007±14 ppm, 1009±14 ppm, 1505±44 ppm, 1501±48 ppm, and 1505±15 ppm, respectively. The daily noise exposure started 2 hours later than the toluene exposure, and the exposure schedule and noise energy was the same for both types of noise exposure. The 6 hours of noise exposure corresponds to $L_{eq8hours} = 90.8$ dB SPL. The sound pressure level and frequency range of WBN within the pass band was quite uniform, and the level within the sound field varied less than ±1 dB between measuring points. The impulse noise was composed of sound impulses with a peak level just above 130 dB. The impulse noise had a somewhat less equal frequency distribution due to a higher energy level towards the lower frequencies, and its level varied up to ±1.5 dB between the measuring points within the sound field.
the level of primary tones fixed (L1 = 60 dB and L2 = 50 dB SPL). The DPOAE input/output curves (I/O curves) were assessed by measuring the amplitude of the CDP to varying levels of primary tones in 5-dB steps. The number of the time-averaged recordings for each point of I/O curve was based on running calculations of the signal-to-noise ratio, and the points on the final I/O-curve all have an S/N ratio above 3 dB. For statistical analysis, the data from the I/O curves were taken for a single point with the same levels of stimuli (L1 = 60 and L2 = 50 dB) as used in the assessment of the DP-gram.

In the 90-day study, the hearing thresholds (4096 Hz, 8192 Hz, 12 800 Hz, and 16 384 Hz) were tested before and 8 weeks after exposure, while DPOAE measurements were performed along with the testing of the hearing thresholds only after exposure. The auditory measurements were made with an Etymotic Research ER-10B+ low-noise microphone system coupled to ER-2 tube phones by standard front tubes [42]. All auditory measurements were performed randomly cage by cage, without any knowledge of the exposure status of the rats. Throughout the measurements, the rectal temperature of the rats was kept at 38.0±0.5°C.

Assessments of hearing
The assessment of hearing was based both on the determination of the hearing thresholds by the auditory brain stem response (ABR) and on the measurement of the distortion products otoacoustic emissions (DPOAE) by the same stimulus source (probe assembly), with the animals in anaesthesia (65 mg/kg pentobarbital sodium i.p.). The methods have been described previously [42–44]; therefore, only a brief overview of the measurements will be given.

The ABRs were recorded with a silver wire inserted subcutaneously at the back of the head as active electrode, a small roll of silver wire in the mouth as reference electrode and a stainless steel needle in the tail as ground electrode. The hearing thresholds were determined as the lowest stimulus level, where both the first wave and the first trough of the ABR could be clearly identified [42]. The only DPOAEs measured were the amplitude of cubic distortion product (CDP, i.e. 2f1-f2), having a fixed ratio of the primary tones (f1 and f2) of f2/f1 = 16/13 = 1.23, and with the level of f1 (L1) always higher by 10 dB than the level of f2 (L2 = L1 – 10 dB). The DP-grams across frequencies were obtained by measuring the CDP with the level of primary tones fixed (L1 = 60 db and L2 = 50 dB SPL). The DPOAE input/output curves (I/O curves) were assessed by measuring the amplitude of the CDP to varying levels of primary tones in 5-dB steps. The number of the time-averaged recordings for each point of I/O curve was based on running calculations of the signal-to-noise ratio, and the points on the final I/O-curve all have an S/N ratio above 3 dB. For statistical analysis, the data from the I/O curves were taken for a single point with the same levels of stimuli (L1 = 60 and L2 = 50 dB) as used in the assessment of the DP-gram.

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Figure 1. A. Hearing thresholds in groups of rats (group mean and SEM) exposed to 0 ppm, 100 ppm, 200 ppm or 500 ppm toluene and WBN for 90 days. Further, a control group exposed neither to noise nor toluene. The differences are greatest at 12 kHz, where the hearing thresholds are increased both in the group exposed only to noise and to noise and 500 ppm toluene. At 16 kHz, the hearing threshold is increased in the group exposed to 500 ppm toluene and noise. B. DP-grams for the same groups, where NF denotes the noise floor, computed as the average of 8 bins, 4 on either side of the CDP.
In the study on exposure to toluene, WBN and impulse noise, the auditory measurements were carried out with a custom-made system comprising a probe system, and using condenser microphones (B&K ½", type 4191) as stimulus transducers [43,44]. The hearing thresholds of all animals were measured at 16384 Hz before and 2 weeks after exposure along with DPOAE measurements. The rectal temperature of the rats was kept at 37.5±0.5°C.

Statistics
The comparison of exposure effects in different dosage groups was performed using the test of variance (ANOVA) for a single factor. Unless stated otherwise, the term statistically significant is used when the tested hypothesis is rejected at a 5% level.

RESULTS
The 90-day study
Figure 1A shows the hearing thresholds in the five groups of rats exposed to 0 ppm, 100 ppm, 200 ppm or 500 ppm toluene for 6 hours/day and to 90 dB SPL wide-band noise for 4 hours/day ($L_{eq,8hours} = 87$ dB SPL), 5 days/week for 90 days. The differences are greatest at 12 kHz.
where the hearing thresholds are increased both for the group exposed to noise (P < 0.05; F = 5.4) and to noise and 500 ppm toluene (P < 0.01; F = 9.3) when compared to the control group, while the increase in hearing thresholds is not statistically significant in the other two groups exposed to toluene and noise. At 16 kHz, the hearing threshold is significantly increased, compared to the controls, in the group exposed to 500 ppm toluene and noise (P < 0.05; F = 4.5).

The assessments of DPOAE (Figure 1 and Figure 2) show a fairly similar picture of hearing impairment in the exposed groups, where the CDP is reduced at f2 frequencies from 10 kHz upwards. At the different frequencies, the differences between the exposed groups and controls were analyzed at L2 = 50 dB. At f2 = 12 800 Hz, the difference was statistically significant in the noise-exposed group (P < 0.001; F = 28.5) and the group exposed to 500 ppm toluene and noise (P < 0.001; F = 18.5), but not in the other two groups exposed both to toluene and noise. At f2 = 16384 Hz, the CDP differed from the control in the noise-exposed group (P < 0.01; F = 11.3), and in the group exposed to noise and 500 ppm toluene (P < 0.01; F = 11.8) and to 100 ppm toluene (P < 0.05; F = 4.7), but was not significantly different in the 200 ppm toluene group. Overall, no additive or synergistic interactions were found between toluene and noise exposure with respect to their impact on hearing impairment, but it seems noteworthy that in the groups exposed to noise and low levels of toluene, i.e. 100 ppm and 200 ppm toluene, respectively, the hearing impairment seems to be less severe than in the group exposed only to noise.

**Toluene, WBN and impulse noise**

Figure 3 and Figure 4 show the DP-grams for all the nine groups of rats in this part of the study, when they were measured 14 days after the end of the exposure series. Figure 3 displays the differences in the effects of interaction between exposure to different levels of toluene and either WBN or impulse noise. In all the groups, the CDP determined after exposure differed from that before exposure. When the assessments were compared at f2 = 16 384 Hz, the differences were statistically significant for the groups exposed to WBN and 0 ppm toluene (P < 0.01; F = 9.5), 500 ppm toluene (P < 0.001; F = 15.2), 1000 ppm toluene (P < 0.01; F = 8.7) and 1500 ppm toluene (P < 0.001; F = 75.0), as well as impulse noise and 0 ppm toluene (P < 0.05; F = 6.2), 500 ppm toluene (P < 0.001; F = 19.6), 1000 ppm toluene (P < 0.001; F = 24.3), and 1500 ppm toluene (P < 0.001; F = 779). When compared to the groups exposed to noise but not to toluene, no additive or synergistic interactions were found either in the groups exposed to WBN and toluene at 500 ppm (P = 0.90; F = 0.02) or 1000 ppm (P = 0.37; F = 0.83), or the groups exposed to impulse noise and toluene at 500 ppm (P = 0.17; F = 2.0) and 1000 ppm (P = 0.75; F = 0.11). However, a clear interaction was noted between the groups exposed to WBN and 1500 ppm toluene (P < 0.001; F = 30.1) as well as impulse noise.
Figure 4. Comparison of the two sections demonstrates the effects of interaction between exposure to 1500 ppm toluene and either WBN or impulse noise. Left section shows the DP-grams (mean and 95% CI) for the groups exposed to WBN or impulse noise for 10 days and not exposed to toluene. Right section shows the DP-grams for the groups of rats (mean and 95% CI) exposed to 1500 ppm toluene only, 1500 ppm toluene and either WBN or impulse noise for 10 days. The DP-gram for the group marked as Control in these figures is the average of DP-grams for all the animals in the different groups, as measured before exposure to noise and toluene. NF denotes the noise floor, as in Fig. 1. Impulse noise is clearly more disruptive to hearing than WBN, and the effects of interaction seem to be proportional to the impairment induced by each type of noise without toluene exposure.

Figure 5. DPOAE I/O-curves at \( f_2 = 4096 \text{ Hz}, 8096 \text{ Hz}, 16384 \text{ Hz} \) and 32768 Hz for the same groups of rats, measured at the same time as the DP-grams in Fig. 3. The groups with open markings are exposed to noise only, while the groups with closed markings are simultaneously exposed to 1500 ppm toluene and either WBN or impulse noise. The DP-gram for the group marked as Control in these figures is the average of DP-grams for all the animals in the different groups, as measured before exposure to noise and toluene. The I/O-curves shown do not seem to supply more information on between-group differences other than what is equally clear from the DP-grams shown in Figure 3 and Figure 4.
and 1500 ppm toluene (P < 0.001; F = 61.0) when compared to the groups exposed to noise only. Figure 4 shows the main differences found between the two types of noise exposure. The left section shows the differences in hearing impairment between the different types of noise exposure without toluene exposure, while the right section shows respective findings for co-exposure to 1500 ppm toluene. Exposure to impulse noise induced a considerably higher decrease in CDP than did the WBN exposure, and the effects of interaction between toluene and noise exposure also seem to be proportionally greater for exposure to impulse noise at 1500 ppm toluene. Figure 5 presents the DPOAE I/O curves for all the groups, but the I/O-curves do not seem to supply any information on the differences between the groups, other than what is clear from the DP-grams shown in Figure 3 and Figure 4.

DISCUSSION

Toluene was the first aromatic organic solvent to be shown to be ototoxic to rats [1], and it is probably the one most investigated in laboratory animals. Toluene differs from styrene in that it exerts the ototoxicity by itself, while its main metabolites (hippuric and benzyl mercapturic acids) have little ototoxic potency [7,14,26]. The ototoxicity following toluene exposure without concomitant noise exposure has only been shown in rats after exposure to the concentrations considerably higher than the mandatory occupational exposure levels (OEL). This may be due in part to a very high metabolic rate of xenobiotic metabolism in rats as well as a tendency of the rats to reduce activity during exposure and thereby to sustain substantially higher levels of exposure with no effects [34]. However, as the synergistic interaction of combined exposure to organic solvents and noise has been shown for toluene as well as other organic solvents, the main risk of hearing impairment from workplace exposure to organic solvents may stem from the potentiation of the effects caused by concomitant noise exposure, which is rather frequent in combination with exposure to organic solvents.

The first objective of the present study was to investigate whether long-term, low-level exposure both to toluene and steady-state noise may cause auditory impairment in rats. This would imply that the generally used short-term exposure scheme of 5–14 days for testing the ototoxic potential of organic solvents like toluene seems to be inadequate to study the effects of interaction between the exposure to organic solvents and noise. As shown in Figures 3 and 4, no signs of synergistic or additive interactions were found in the 90-day subchronic exposures to 100 ppm, 200 ppm, and 500 ppm toluene. This supports the findings from other studies on toluene ototoxicity in rats, where hearing impairment occurred when a certain threshold of toluene exposure was exceeded [4,7,15,23,29,31]. However, contrary to what may have been expected, the exposure to 500 ppm toluene and noise was followed by the same changes in hearing thresholds and CDP loss as the exposure to noise only, while exposure to 100 ppm and 200 ppm toluene and noise was followed by a slightly lower decrease in auditory sensitivity than the exposure to noise alone. The same pattern can be seen in all the measurements of hearing in the mid-frequency region of 12–16 kHz, but it is most clearly shown in the input/output-curves (I/O-curves) at f2 = 12800 Hz and f2 = 16384 Hz. The differences between the groups are small (~5 dB) and the distribution of the outcome between the groups may have been coincidental. However, these results may also indicate that the mechanisms and effects of toluene exposure at low-level exposure may differ from the effects noted at higher exposure levels.

The mechanisms of toxicity of toluene and other aromatic organic solvents on the cochlea have not been clarified, but recently a possible explanation of the potentiation by aromatic organic solvents of the effects of noise exposure has appeared. It has been shown that toluene may act as an antagonist of the auditory medial efferent system, thereby augmenting the acoustic energy absorbed by the cochlea in response to the noise exposure [50]. As toluene at high levels of exposure is definitely ototoxic to rats, several mechanisms may be involved in the effects of interactions between toluene and noise exposure, which has been observed both in the studies on rats and in human studies [47,48]. The involvement of more than one mechanism...
may also help to explain the differences in hearing impairment from occupational exposure to toluene, which have been found in different reports [47,48,51]. These may be caused by the different levels of exposure, both with respect to organic solvent and noise exposure, which were subject to investigation.

The overall conclusion from the 90-day study is that even after a long-term combined exposure to ototoxic organic solvents, like toluene, and noise, no sign of synergistic or additive interactions was found below the LOAEL determined in short-term studies in rats [11,15,31]. In the second experiment, we wanted to further investigate the consequences of modifying the type of noise in combined exposure to toluene and noise. The level of the impulse noise exposure was set by the interval between noise impulses, each with a peak level of slightly more than 130 dB. The frequency distribution of the noise was fairly equal regarding WBN, but the impulse noise had a somewhat different frequency distribution due to the limitations of the loudspeakers used. The rats exposed to WBN had the main loss of sensitivity at 12–24 kHz, while the rats exposed to impulse noise had a hearing loss in the 4–24 kHz frequency band, although it was most pronounced at frequencies around 9 kHz, which is the frequency of the maximum amplification due to the formation of standing waves within the external ear canal in rats (see Figs. 3 and 4).

In general, the loss of auditory sensitivity detected in the rats from the groups exposed to impulse noise was more variable than what was seen in the WBN-exposed groups, but the auditory impairment induced by impulse noise was considerably greater (see Figs. 3–5). No effects of interaction were found in combined exposures to either type of noise and to toluene at exposure levels of 500 ppm or 1000 ppm. Also exposure to 1500 ppm toluene with no simultaneous noise exposure did not induce notable auditory impairment. These results are comparable to what has been observed in other studies of toluene and noise exposure in sedentary rats [11,15,31]. A combined exposure to 1500 ppm toluene and noise did not produce considerable auditory impairment, but a combined exposure involving impulse noise induced a far greater loss of auditory sensitivity over a broader range of frequencies than did the exposure to WBN.

The effects of toluene exposure can initially be seen in the rat in a narrow mid-frequency band, which broadens to include all the frequencies from 4 to 32 kHz [10,24]. In combined exposures to noise and organic solvents, synergistic effects of interaction are observed, depending on the level and frequency band of the concomitant noise exposure [11,15,31,32]. Impulse noise seems to have a potential to cause hearing impairment even at relatively low levels of noise exposure [52], and the possible effects of interaction between impulse noise and organic solvents may in fact significantly increase the risk of auditory impairment at very realistic scenarios of human exposure in work environment. If toluene may block the protective acoustic efferent reflexes from the medial olivo-cochlear bundle [50], there seems to be several ways by which toluene exposure may augment the risk of hearing loss from noise exposure.

REFERENCES