2008-12-14

Ototoxic effects of industrial chemicals**

Toluene

A. Vyskocil[1]*, G. Truchon[2], T. Leroux[3], F. Lemay[2], M. Gendron[3], F. Gagnon[1], S. Botez[2], N. El Majidi[1], S.Lim[1], C. Émond[1], C. Viau[1]

Introduction

There is accumulating epidemiological evidence that exposure to some solvents, metals, asphyxiants and other substances in humans is associated with an increased risk of hearing loss. This project was undertaken to develop a toxicological database allowing the identification of possible ototoxic substances present in the work environment. Critical toxicological data were compiled for chemical substances included in the Quebec Occupational Health Regulation.

Methods

The data were evaluated only for realistic exposure concentrations up to the short-term exposure limit or ceiling value or five times the 8-h time weighted average exposure limit value(TWAEV) for human data and up to 100 times the 8-h TWAEV or ceiling value for animal studies.

Using a systematic weight of evidence approach, the information from both human and animal studies was examined.

At first, information from each source was given a weight of evidence qualifier for ototoxicity: strong, medium, weak, absent or "no study found". We took into consideration the following parameters: studied specie, number of subjects, exposure way, characteristics of control groups, exposure levels, audiometric and statistical tests, dose/effect relation. Table 1 shows how this information was combined to yield an overall assessment of the ototoxic potential of a given substance. Human data were generally given more weight in the overall assessment. When no human studies were available, which is different from the absence of evidence from the available human studies, the overall assessment was deemed the same as that from animal studies.

We built a weight of evidence table that allowed us to combine the information from both human and animal studies on ototoxicity of chemicals. Table 1 shows how the information from both types of studies were combined to yield an overall assessment and corollary conclusion about the ototoxicity of the investigated chemicals.

Human data were generally given more weight in the overall assessment. When no human studies were available, or when good quality human studies showed absence of evidence of an ototoxic effect, the overall assessment was one degree lower than that resulting from the animal studies. For example, a "strong" evidence from animal studies combined with an "absence" of evidence from the available human studies yielded a "medium" evidence overall.

Regarding the final conclusion about the ototoxic potential of chemical substances, all substances bearing a "strong evidence" of ototoxicity overall are considered "ototoxic". Those with "medium evidence" overall are rated "possibly ototoxic". We consider the ototoxic potential of those with only "weak evidence" as "non conclusive". Finally, those for which there is absence of evidence overall bear the mention "no evidence".

* Corresponding author : adolf.vyskocil@UMontreal.CA
** Production of this document was supported by the IRSST (Grant 099-542)

[1] Groupe de recherche interdisciplinaire en santé- Département de santé environnementale et santé au travail, Université de Montréal
[2] Institut de recherche Robert-Sauvé en santé et en sécurité du travail (IRSST)
[3] École d'orthophonie et d'audiologie, Université de Montréal

Table 1. Weight of evidence approach for the assessment of ototoxicity of various industrial chemicals

Strength of evidence about ototoxicity in assessed studies			Conclusion about ototoxicity
Human	**Animal**	**Overall**	
S	S	S	O
S	M	S	O
S	W	S	O
S	A	S	O
S	X	S	O
M	S	S	O
M	M	M	PO
M	W	M	PO
M	A	M	PO
M	X	M	PO
W	S	M	PO
W	M	W	NC
W	W	W	NC
W	A	W	NC
W	X	W	NC
A	S	M	PO
A	M	W	NC
A	W	W	NC
A	A	A	NE
A	X	A	NE
X	S	M	PO
X	M	W	NC
X	W	W	NC
X	A	A	NE

Indication of ototoxicity:

S = strong; M = medium; W = weak; A = absent; X = no study found

General conclusion about ototoxicity:

O = ototoxic substance; PO = possibly ototoxic substance; NC = non conclusive; NE = no evidence

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Abbreviations

TWAEV : 8 h time weighed average exposure [limit] value in Quebec

D-TWAEV : Calculated inhaled dose for pulmonary ventilation of 10 m^3/d and body weight of 70 kg

Ceiling : Ceiling exposure [limit] value in Quebec

D-Ceiling : Calculated inhaled dose for pulmonary ventilation of 10 m^3/d and body weight of 70 kg

STEV : Short term exposure [limit] value in Quebec

C/D reported : Reported concentration or reported dose

CSU/DSU : Reported concentration expressed in standard units of mg/m^3 or reported dose expressed in standard units of mg/kg/d

Ratio : For concentrations CSU/TWAEV or CSU/Ceiling and for doses DSU/ D-TWAEV or DSU/D-Ceiling

ASM : Air sampling method

BM : Biological monitoring results

Toluene

Occupational exposure limits: TWAEV: 188 mg/m³ (50 ppm)

Conclusion about ototoxicity	Strength of evidence
Ototoxic substance	From animal studies: **Strong** From human studies: **Medium** Overall: **Strong**

ANALYSIS OF ANIMAL STUDIES

Twenty-seven inhalation and 3 oral studies on rats were identified. Rats were exposed to 600 ppm (Lataye 2003) and more and exposure duration varied between 30 minutes (Witter 1980) and 23 weeks (Pryor 1985). Hearing losses were measured by behavioural methods and confirmed by electrophysiologic testing. The permanent high-frequency hearing loss is most often reported. Factors such as concentrations and duration of exposure influence the loss of auditory sensitivity in rats. The daily concentration is far more important than the total length of exposure (Pryor 1984b). The noise levels were not always reported. However, the ototoxicity of toluene has been demonstrated in a quiet environment by oral administration, which excludes noise from the inhalation system as a causative factor for this effect (Sullivan 1989). A LOAEL for ototoxicity of toluene in rats is 700 – 1000 ppm.

In rats, evidence suggests that toluene exposure causes a permanent damage to the outer hair cells (OHC) of the cochlea. No changes in the latencies of the auditory brainstem responses have been noted in several studies of toluene-exposed rats (Jonhson 1988, Nylén 1994a, Rebert 1983b) suggesting that the damage is localised in the cochlea and not within the central auditory pathways (Johnson 1995). The effect on the OHCs has been confirmed by morphologic examinations of cochlea showing loss of OHCs, predominantly in the third row (Johnson 1994b, Pryor 1984a, Sullivan 1989). The examinations show that cochlear toxicity is localised in the middle (16-29 kHz) and mid-low (4-5kHz) frequency region of the cochlea. Inner hair cells seem to be preserved (Campo 1997). The hair cell loss is progressive and continues even after the end of exposure (Johnson 1994b).

Three inhalation studies on guinea pigs were identified. Two studies on guinea pigs exposed to 600 and 1000 ppm were negative (Lataye 2003, Campo 1993) and one study showed an ototoxic effect with a LOAEL of 250 ppm. One inhalation study on chinchillas exposed to 1000 ppm was negative.

ANALYSIS OF HUMAN STUDIES

Data on toluene effects on human hearing originate mainly from case reports on toluene abusers. In the studies that focused on the voluntary inhalation of toluene, dramatic hearing loss originating from the central auditory pathways has been reported (Morata 1994, Ryback 1992).

One study on workers with normal hearing ability (assessed by pure tone audiometry), exposed to 97 ppm toluene for 12-14 years showed an alteration in the auditory brainstem evoked responses. This test demonstrated auditory nervous system modification before the occurrence of clinical signs due to chronic exposure to toluene (Abbate 1993). An alteration in the auditory brainstem evoked responses were observed also in another study on workers, however there was a lack of information on the noise exposure (Vrca 1997, Vrca 1996).

CONCLUSION

Although certain effects were reported in workers, other human studies are necessary to come to a final decision. However, a series of animal studies clearly highlighted ototoxic effects in relation to high concentrations of toluene. In the rat, toluene affects the auditive function mainly in the range of the mid frequencies of the cochlea. We recommend, by taking account of the results of the human studies and the evidence brought by the animal studies, to regard toluene as an ototoxic agent.

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Worker # : 40 Sex : Males

Age : 30 - 40 years

Exposure

Route : Inhalation

Duration : 12 - 14 years

C/D reported : 97 ppm

CSU/DSU :

Ratio :

ASM :

BM : Average urinary excretion of hippuric acid of less 2.7 g/L

Remarks : Controls are workers not professionally exposed to toluene and with urinay excretion of hippuric acid < 1.6 g/L.
The subjects chosen are rotogravure workers exposed to < 80 dB and with auditory thresholds loss < 20 dB nHL

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Clicks 80 dB nHL
• - Responses of the exposed workers were statistically different from those of the control group for all the waves and each of the repetitions - Statistically significant difference between the exposed subjects and the controls for each latency interval between the waves	• Test performed after 16 hours of acoustic pause

Action mechanism

Authors' conclusion

Chronic toluene exposure causes significant alterations of the brainstem auditory evoked potentials. These altarations were visible for all the waves and all the waves intervals studied

Our conclusion

Brainstem auditory pathway altered in workers exposed for 97 ppm toluene

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Guinea pig # : 5 - 9 Sex : Females
Age : 4 months

Exposure

Route : Inhalation
Duration : 6 h/d for 14 d
C/D reported : 1000 ppm
CSU/DSU :
Ratio : 20
ASM :
BM :
Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Electrocochleography	Tone bursts at 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24 and 32 kHz
• Temporary and permanent hearing losses in toluene group not different from the control	• Test performed before exposure, after the last day of exposure and 3 weeks after the end of exposure
Electron microscopy	
• Losses not different from the control group	• Test performed 3 - 4 weeks after the end of exposure

Action mechanism

Authors' conclusion

No evidence of an ototoxic effect of moderate doses of toluene on the cochlea of the adult guinea pig

Our conclusion

No ototoxic effect of toluene at 1000 ppm in cochlea of the adult guinea pig exposed for 14 days

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Rat Long Evans # : 5 - 24 Sex : Males
Age : 7 months

Exposure

Route : Inhalation
Duration : 6 h/d; 5 d/w; 4 w
C/D reported : 1000, 1200, 1500, 1750 and 2000 ppm
CSU/DSU :
Ratio : 20 - 40
ASM :
BM :
Remarks : Background noise: 66 dB SPL

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Inferior colliculus Clicks at 2, 4, 6, 8, 10, 12, 16, 20, 24 and 32 kHz
• - Only three toluene concentratons (1500, 1750 and 2000 ppm) produce significant auditory threshold shift - Maximal amplitude shifts are 4 dB, 14 dB and 23 dB - No significant shift at 32 kHz, indicating no high frequency hearing loss - No effect were found at frequencies below 6 kHz, which indicates that the low frequncy regions were also spared	• Test performed prior to the exposure, 24 - 32 hours and 6 weeks after the end of exposure
Light microscopy	Cytocochleograms
• - Most significant losses at the third row of outer hair cells (OHC) (OHC3>OHC2>OHC1). - Two peaks of OHC at 4 kHz and 20 kHz - Outer hair cells losses at 1750 and 2000 ppm are equivalent - Small amount of hair cell loss (1%) in control group	• Test performed 7 - 8 weeks after the end of exposure
Electron microscopy	
• - 2000 ppm : the third row of the outer hair cells has been completely destroyed. - Inner hair cells do not seem to be injured	• Test performed 7 - 8 weeks after the end of exposure

Action mechanism

Authors' conclusion

Concentration of at least 1500 ppm is necessary to obtain significative hearing loss

Our conclusion

LOAEL of 1500 ppm for toluene ototoxic effect in rats exposed for 4 weeks

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Rat Long Evans # : 8 - 16 Sex : Males
Age : adults

Exposure

Route : Inhalation
Duration : 6 h/d; 5 d/w; 4 w
C/D reported : 1750 ppm
CSU/DSU :
Ratio : 35
ASM :
BM :
Remarks : Background noise: < 66 dB SPL

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Inferior colliculus Clicks at 2 - 32 kHz
• Permanent hearing threshold shift is significantly greater at 12, 16 and 20 kHz in comparison with the control group	• Test was performed before and 6 weeks after the end of exposure
Light microscopy	
• - The most significant losses at the third row of outer hair cells (OHC) and OHC3>OHC2>OHC1 - Two peaks of OHC loss at 4 kHz and 20 kHz - Inner hair cells seem to be relatively well preserved	• Test performed at 6 - 7 weeks after the end of exposure
Electron microscopy	
• Missing hair cells located at OHC3 and more rarely at OHC2	• Test performed at 6 - 7 weeks after the end of exposure

Action mechanism

Authors' conclusion

Toluene induced toxicity alters the auditory function by causing an outer hair cells loss from the third to the first row. Inner hair cells seem to be preserved

Our conclusion

Ototoxic effect at 1700 ppm in rats exposed for 5 weeks

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Rat Long Evans # : 7 - 8 Sex : Males

Age : 60 days

Exposure

Route : Inhalation

Duration : 8 h/d; 5 d

C/D reported : 2500 ppm

CSU/DSU :

Ratio : 50

ASM :

BM :

Remarks : Background noise: 30 dB

Tests

Test type • Effects reported	Precisions on test • Remarks
Reflex modification audiometry	at 0.5 - 40 kHz
• Hearing loss at 8, 16 and 24 kHz	• Test performed 5 to 8 weeks after the end of exposure

Action mechanism

Authors' conclusion

Mid-frequency hearing loss at 2500 ppm in rats

Our conclusion

Ototoxic effect at 2500 ppm in rats

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Chinchilla # : 4 - 6 Sex : Not reported
Age : adults

Exposure

Route : Inhalation
Duration : 8 and 12 h/d; 5 d
C/D reported : 2000 ppm
CSU/DSU :
Ratio : 40
ASM :
BM :
Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Tone bursts at 0.5, 1, 2, 4, 8 and 16 kHz
• No significant effect due to toluene alone	• Test performed 30 days after the end of exposure

Action mechanism

Authors' conclusion

No ototoxicity effect of toluene in chinchillas

Our conclusion

No ototoxicity effect of toluene at 2000 ppm in chinchillas

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Rat # : 6 Sex : Males

Age : 9 weeks

Exposure

Route : Gavage

Duration : 5 d/w; 2 w

C/D reported : 8.47 mmol/kg/d

CSU/DSU : 780 mg/kg/d

Ratio : 29

ASM :

BM :

Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Light and electron microscopy	Cytocochleogram
• 90, 50 and 25 % losses in the third, second and first rows of outer hair cells for frequencies from 10 to 25 kHz	• Histology performed 10 days after the end of exposure

Action mechanism

Authors' conclusion

Ototoxic effect of toluene in rats

Our conclusion

Ototoxic effect of toluene after exposure by oral way in rats

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Rat Sprague Dawley # : 9 - 10 Sex : Males

Age : 5 weeks

Exposure

Route : Inhalation

Duration : 16 h/d; 7 d/w; 2 w

C/D reported : 1000 ppm

CSU/DSU :

Ratio : 20

ASM :

BM :

Remarks : Background noise: 40 dB SPL

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Pulsed pure sons at 1.6, 3.15, 6.3, 12.5 and 20.0 kHz
• Hearing threshold was higher than in the controls for all the frequencies	• Test perfomed 1-3 weeks after the end of exposure to toluene

Action mechanism

Toluene causes a structural damage to the stereocilia and hair cell membranes that decreases their resistance against ensuing mechanical stress

Authors' conclusion

Exposure to toluene alone causes a considerable and long lasting decrease in the auditory sensitivity in rats

Our conclusion

Ototoxic effect of toluene at 1000 ppm in rats exposed for 2 weeks

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Rat Sprague Dawley # : 9 - 12 Sex : Males

Age : 4 weeks

Exposure

Route : Inhalation

Duration : 16 h/d; 10 d

C/D reported : 1000 ppm

CSU/DSU :

Ratio : 20

ASM :

BM :

Remarks : Background noise: < 50 dB SPL

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	at 1.6, 3.15, 6.3, 12.5 and 20.0 kHz
• - 2 to 5 days after exposure : a loss of auditory sensitivity (23 dB) was seen at 12.5 kHz - 4 months after exposure : no recovery of the auditory sensitivity	• Test performed 2 - 5 days and 4 months after the end of exposure

Action mechanism

Toluene change the fluidity of the cellular membranes of the brain

Authors' conclusion

Exposure to toluene alone causes a considerable (20 dB) and permanent loss of auditory sensitivity. The loss was mainly in the high frequencies (12.5 kHz)

Our conclusion

Ototoxic effect at 1000 ppm in rats

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Rat Sprague Dawley # : 2 - 16 Sex : Males
Age : adults

Exposure

Route : Inhalation
Duration : 16 h/d; 8 d
C/D reported : 1400 ppm
CSU/DSU :
Ratio : 28
ASM :
BM :
Remarks : Background noise: 50 dBA

Tests

Test type • Effects reported	Precisions on test • Remarks
Distortion product otoacoustic emissions (DPOAE)	at 3, 4, 5, 6.3, 8, 9, 11.4, 14.3 and 17.9 kHz L1 = 30 to 80 dB L1 = L2 + 10 ratio f2/f1 = 1.225
• - No difference in the amplitude after the third day of exposure - After the fifth day of exposure, the amplitude of the DPOAE was depressed by 5 or 10 dB for the frequencies between 6.3 and 14.3 kHz, out of these frequencies there was no difference - Amplitudes measured after 4 days post exposure were lowered at all frequencies and, except at 17.9 kHz, few emissions could be obtained below stimulus level of 60 dB - Areas under DPOAE curve were decreased in the mid frequency range during the exposure and a more severe damage is seen post exposure	• Test performed before, after the third and the fifth day of toluene exposure and also 4 days after the end of the exposure
Auditory brainstem responses	at 1.6, 3.15, 6.3, 12.5 and 20 kHz (post exposure only)
• - Auditory thresholds measured for frequency of 12.5 kHz on the third day of exposure showed a shift of 10 dB - After 5 days of exposure, rats showed higher threshold elevated by 20 dB - Four days after exposure, the thresholds were further elevated by 20 dB - Auditory threshold responses measured for all frequencies 4 days after exposure were higher in exposed group, with an average loss of 20-40 dB	• Test performed before, after the third and the fifth day of toluene exposure and also 4 days after the end of the exposure

Action mechanism

Authors' conclusion

Toluene exposure causes lowered DPOAE amplitudes and an elevation in the auditory thresholds. The decrease of the DPOAE amplitude was prominent in the mid frequencies

Our conclusion

Ototoxic effect at 1400 ppm in rats for 8 days

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Rat Sprague Dawley # : 2 - 4 Sex : Males

Age : adults

Exposure

Route : Inhalation

Duration : 16 h/d; 8 d

C/D reported : 1400 ppm

CSU/DSU :

Ratio : 28

ASM :

BM :

Remarks : Background noise: < 50 dBA

Tests

Test type • Effects reported	Precisions on test • Remarks
Light microscopy	
• After 3 days of exposure : total hair cell loss did not exceed 0.5 % which correspond to the normal loss After 5 days of exposure : loss in the third (5-10%) and in the second (3%) row of outer hair cells (OHC). No loss found in the first row of OHC or in the inner hair cells (IHC) 4 days after the end of exposure : OHC loss in all 3 rows (OHC3: 85 - 100%, OHC2: 10 - 65%, OHC1: 5 - 60%) but no loss in the IHC 6 weeks after the end of exposure : loss of OHC (50-100% for all the rows) and loss in the IHC	• Histology performed after 3 and 5 days of exposure and 4 days and 6 weeks after the end of exposure
Electron microscopy	
• - After 3 days of exposure : OHC and IHC had normal appearance. - After 5 days of exposure : loss of OHC can be observed in the third row. - Four days after exposure: a total or almost total loss of the third and the second row OHC - Six weeks after exposure : large areas with a total loss of OHC were found and scattered loss of IHC was noted	• Histology performed after 3 and 5 days of exposure and 4 days and 6 weeks after the end of exposure
Distortion product otoacoustic emissions (DPOAE)	9 frequencies between 3.0 and 17.9 kHz L1 = 30 to 80 dB L1 = L2+10 dB Ratio f2/f1 = 1.225
• - After 5 days of toluene exposure : DPOAE threshold shift of 10 to 20 dB in the middle frequencies - Four days after the end of exposure : DPOAE maximal threshold shift raised to 40-50 dB between 5 and 14 kHz - Six weeks after the end of exposure : the DPOAE threshold shift increased to 50 to 60 dB	• Test performed after 3 and 5 days of exposure and 4 days and 6 weeks after the end of exposure
Auditory brainstem responses	9 frequencies between 3.0 and 17.9 kHz
• Four 4 days after the end of exposure : substantial threshold shift (30 dB) in the middle frequencies	• Test performed after 3 and 5 days of exposure and 4 days and 6 weeks after the end of exposure

Action mechanism

Authors' conclusion

In rats a loss of outer hair cells can occur already after 5 days of toluene exposure. The third row in the mid frequency region is affected first and the inner hair cells become damaged as the exposure and also the post exposure period

progresses

Our conclusion

Ototoxic effect at 1400 ppm in rats

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Rat Sprague Dawley # : 8 - 12 Sex : Males

Age : 21 days

Exposure

Route : Inhalation

Duration : 16 h/d; 5 d/w; 2 w

C/D reported : 1000 ppm

CSU/DSU :

Ratio : 20

ASM :

BM :

Remarks : Background noise: 40 dB SPL

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Pulsed pure tones (100 dB SPL) at 1.6, 3.15, 6.3, 12.5 and 20 kHz
• Hearing thresholds were higher than in the control group at all frequencies. One month after the exposure a slight improvement in threshold (5-10 dB) was observed at all frequencies tested, except at 3.15 kHz. Six months after the exposure, there was an improvement of another 5 dB. The latency of ABR after the solvent exposure was slightly increased and after 1 and 6 month, the latency was similar to the control	• Test performed 2 at 5 days, 1 and 6 monthsafter the end of exposure

Action mechanism

Authors' conclusion

Toluene exposure caused a considerable decrease in the auditory sensitivity of rats, particularly at high frequencies

Our conclusion

Ototoxic effect of toluene at 1000 ppm in rats exposed for 2 weeks

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Rat Long Evans # : 21 - 24 Sex : Males

Age : adults

Exposure

Route : Inhalation

Duration : 6 h/d; 5 d/w; 4 w

C/D reported : 2000 ppm

CSU/DSU :

Ratio : 40

ASM :

BM :

Remarks : Background noise: 66 dB SPL

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Clicks at 2, 4, 6, 8, 10, 12, 16, 20, 24 and 32 kHz
• - Auditory threshold shift values obtained at 2, 4, 6 and 32 kHz are lower than 5 dB SPL, indicating that low and high frequency regions were spared. - Shift peak amplitude at 16 kHz (23 dB SPL) - Statistically significant difference between the threshold shifts of the toluene group and control group at all frequencies except at 4 and 16 kHz - No difference between permanent and temporary auditory threshold shift for all frequencies except at 4 and 6 kHz, indicating the irreversibility of the loss	• Test performed before exposure, the day after the end of exposure and 6 weeks after the end of exposure
Light microscopy	
• - Largest loss at the third row of outer hair cells (OCH3>OHC2>OCH1). - Inner hair cells appear to be well preserved. - Two peaks of losses observed: One at around 18-20 kHz and the other one at 4-5 kHz. 18-20 kHz : OHC3 = 73%, OHC2 = 42%, OHC1 = 25% 4-5 kHz: OHC3 = 87%, OH2 = 59%, OHC1 = 30 % - Frequencies above 30 kHz are relatively well preserved	• Histology performed 7 - 8 weeks after the end of exposure
Electron microscopy	
• The third row of outer hair cells has completely disappeared. Inner hair cells don't seem to be injured	• Histology performed 7 - 8 weeks after the end of exposure

Action mechanism

Authors' conclusion

Toluene exposure can cause a permanent elevation of the auditory thresholds in rats. No recovery of the auditory thresholds

Our conclusion

Ototoxic effect of toluene at 2000 ppm in rats exposed for 4 weeks

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Rat Long Evans # : 5 - 8 Sex : Males

Age : 5 months

Exposure

Route : Inhalation

Duration : 6 h/d; 5 d/w; 4 w

C/D reported : 1750 ppm

CSU/DSU :

Ratio : 35

ASM :

BM :

Remarks : Background noise: 66 dB SPL

Tests

Test type • Effects reported	Precisions on test • Remarks
Electrocochleography	Tone bursts at 2, 3, 4, 5, 6, 8, 10, 16, 20 and 32 kHz
• The greatest permanent threshold (20 dB) obtained at 16 kHz and a significant threshold (12 dB) is also obtained at 3-4 kHz	• Test performed 6 weeks after the end of exposure
Light microscopy	
• - Control group : small amount of hair cell loss (< 1%) - Exposed group : The largest loss, about 90 %, appeared at the third row of outer hair cells. The second row was less damaged (30-35 %) than the third group but more than the first group (20 %) - The inner hair cells seem to be relatively well preserved - Outer hair cells losses appeared from 20 to 4 kHz	• Test performed at 6 - 7 weeks after the end of exposure
Electron microscopy	
• The largest loss of outer hair cells at the third row and more rarely at the second row	• Histology performed at 6 - 7 weeks after the end of exposure

Action mechanism

Authors' conclusion

Significant hearing deficit in the 3 - 4 kHz and 16 kHz regions caused by toluene exposure

Our conclusion

Ototoxic effect at 1750 ppm in rats

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Rat Long Evans # : 5 - 6 Sex : Males
Age : 10 weeks

Exposure

Route : Inhalation
Duration : 6 h/d; 5 d
C/D reported : 600 ppm
CSU/DSU :
Ratio : 12
ASM :
BM :
Remarks : Background noise: 66 dB SPL

Tests

Test type • Effects reported	Precisions on test • Remarks
Distortion product otoacoustic emissions (DPOAE)	at 2, 3, 4, 5, 6, 8, 10, 12 and 16 kHz L1 = 10 to 60 dB L1 = L2 Ratio f1/f2 = 1.20
• No effect	• Test performed 1 week before exposure and 20 minutes, 2 and 4 weeks after the end of exposure
Light and electron microscopy	
• Control and toluene group revealed a small loss of the hair cells along the organ of Corti (1%)	• Histology performed 4 weeks after the end of exposure

Action mechanism

Authors' conclusion

No ototoxic effect at 600 ppm in rats

Our conclusion

No ototoxic effect at 600 ppm in rats

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Guinea pig # : 5 - 6 Sex : Males
Age : 7 weeks

Exposure

Route : Inhalation
Duration : 6 h/d; 5 d
C/D reported : 600 ppm
CSU/DSU :
Ratio : 12
ASM :
BM :
Remarks : Background noise: 66 dB SPL

Tests

Test type • Effects reported	Precisions on test • Remarks
Distortion product otoacoustic emissions (DPOAE)	at 2, 3, 4, 5, 6, 8, 10, 12 and 16 kHz L1 = 10 to 60 dB L1 = L2 Ratio f2/f1 = 1.20
• No effect	• Test performed 20 minutes, 2 and 4 weeks after the end of exposure
Light and electron microscopy	
• Control and toluene group revealed a small loss of the hair cell along the organ of Corti (1%)	• Histology performed 4 weeks after the end of exposure

Action mechanism

Authors' conclusion

No ototoxic effect at 600 ppm in guinea pigs

Our conclusion

No ototoxic effect at 600 ppm in guinea pigs exposed for 5 days

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Rat Long Evans # : 5 - 8 Sex : Males

Age : 4 months

Exposure

Route : Inhalation

Duration : 6 h/d; 5 d/w; 4 w

C/D reported : 1000, 1250, 1500, 1750 and 2000 ppm

CSU/DSU :

Ratio : 20 - 40

ASM :

BM :

Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Inferior colliculus potential Clicks at 2, 4, 6, 8, 10, 12, 16, 20, 24 and 32 kHz
• - Auditory threshold shifts increase significantly as a function of the concentration of toluene - 23 dB shift with 2000 ppm at 16 kHz - 14 dB shift with 1750 ppm at 16-20 kHz - 4 dB shift with 1500 ppm at 20 kHz - Statistically, the toluene ototoxic effect started at 1360 ppm	• Test performed before exposure and 6 weeks after the end of exposure
Light microscopy	
• - The most significant loss in the third row (OHC3>OHC2>OHC1). - Two peaks of OHC losses around 4 and 20 kHz	• Histology performed 2 to 3 months after the end of exposure
Electron microscopy	
• The third row (20 kHz) was damaged more than either of the others rows	• Histology performed 2 to 3 months after the end of exposure

Action mechanism

Cochlea, and more speciafically the one, seem to be the preferential target of toluene

Authors' conclusion

Toluene exposure can cause permanent hearing losses in the rats.

Our conclusion

LOAEL of 1500 ppm for ototoxicity in rats exposed for 4 weeks

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Guinea pig # : 4 - 8 Sex : Males
Age : 60 days

Exposure

Route : Inhalation
Duration : 8 h/d; 5 d/w; 1 and 4 w
C/D reported : 250, 500 and 1000 ppm
CSU/DSU :
Ratio : 5 - 20
ASM :
BM :
Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Distortion product otoacoustic emissions (DPOAE)	at 6, 8, 12, 16, 20 and 24 kHz L1 = 50 to 80 dB SPL L2 = L1-10 Ratio f2/f1 = 1.28
• - 250 ppm : hearing loss of 5-10 dB at all frequencies - 500 ppm : hearing loss of 15 dB at all frequencies - 1000 ppm : hearing loss equivalent to that found for 500 ppm - Exposure to 500 ppm for 4 weeks resulted in greater hearing loss than that seen after 1 week Although the hearing loss increased as exposures continued from 1 to 4 weeks of exposure, a permanent hearing loss was not observed	• Test performed immediately after exposure for 1 and 4 weeks and 3 days after the end of each exposure
Light microscopy	Succinate dehydrogenase (SDH) activity
• Toluene preferentially impairs hair cells metabolic activity in regions of the cochlea corresponding to frequencies above 8 kHz. But at 40 kHz, SDH activity returns to that of the control	• Histology performed immediately after exposure for 1 and 4 weeks and 3 days after the end of each exposure

Action mechanism

Authors' conclusion

Low toluene concentrations of 250 ppm are able to produce auditory dysfunction. A permanent auditory deficit could not be generated after 4 weeks of exposure

Our conclusion

LOAEL of 250 ppm for ototoxic effect in guinea pigs but no permanent hearing loss

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Rat Sprague Dawley # : 15 - 18 Sex : Males

Age : adults

Exposure

Route : Inhalation

Duration : 21 h/d; 7 d/w; 4 w

C/D reported : 1000 ppm

CSU/DSU :

Ratio : 20

ASM :

BM :

Remarks : Bakground level between 76 and 78 dB SPL

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	at 1.6, 3.15, 6.3, 12.5 and 20 kHz
• - Two days after exposure, shorter N1 and P1 latencies were found in the toluene group compared with the control group. - Three months after exposure N1P1 and N1P2 amplitudes in the toluene group were smaller than in the control group. - One year after, a loss of auditory sensitivity in the exposed group was recorded	• Test performed 2 days, 3 months and 12 months after the end of exposure

Action mechanism

Toluene induced auditory loss is probably of cochlear origin

Authors' conclusion

Three months after toluene exposure, a loss of sensitivity was observed in rats, as well as lower amplitudes compared to the control

Our conclusion

Ototoxic effect at 1000 ppm in rats exposed for 28 days

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Rat Long Evans # : 9 Sex : Males

Age : 4 - 6 months

Exposure

Route : Inhalation

Duration : 21 h/d; 7 d/w; 8 w

C/D reported : 1000 ppm

CSU/DSU :

Ratio : 20

ASM :

BM :

Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	at 1.6, 3.15, 6.3, 12.5 and 20.0 kHz
• Hearing loss at all studied frequencies	• Test performed 1 week after the end of exposure

Action mechanism

Toxicity induced by toluene is probably caused by unmetabolised toluene and not a metabolite

Authors' conclusion

Toluene alone induced the loss of auditory sensitivity which the largest at mid frequency 12.5 kHz

Our conclusion

Ototoxic effect at 1000 ppm in rats exposed for 8 weeks

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Rat Fisher 344 # : 13 - 14 Sex : Males

Age : 21 days

Exposure

Route : Inhalation

Duration : 14 h/d; 7 d/w; 14 w

C/D reported : 900 or 1400 ppm

CSU/DSU :

Ratio : 18 - 28

ASM :

BM :

Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Multisensory conditionned avoidance response task	at 4 kHz
• - On the first day of acquisition of the conditioned avoidance response, all exposed groups performed significantly more poorly than controls. - On the second day, rats exposed to 1400 ppm performed significantly more poorly than the others. - After the end of the 3rd day, average performance for all the groups was above 80 %. - On the fouth day, rats exposed to 1400 ppm showed a slight impairment compared to controls and the other exposed rats	• Test performed during the 8th week
Intensity discrimation	at 4 kHz
• Control group and exposed to 900 ppm maintained a high percentage of successful avoidances over 11 test sessions whereas the group exposed to 1400 ppm performed about 20 to 30 % less	• Test performed on the 12th to the 14th weeks of exposure
Auditory brainstem responses	Clicks
• - No substancial effects on the latencies of ABR. - Amplitude of the 5th component was decreased at 1400 ppm, this effect disapeared rapidly after the end of exposure	• Test performed from the 6th week of exposure to the 6th week after the end of exposure
Light microscopy	
• No damage of the peripheal nerve caused by exposure to toluene	• Histology performed 14 weeks after the end of exposure
Cortical auditory evoked potentials	Tone pips at 8 kHz
• No substancial effect on the latencies of auditory evoked response	• Test performed from the 6th week of exposure to the 6th week after the end of exposure

Action mechanism

Authors' conclusion

Effects on conditioned avoidance response acquisition represent persisting cognitive deficits caused by exposure to toluene. The apparent cognitive deficits seen in the present experiment were caused by acute pharmacological effects of toluene

Our conclusion

Persistent cognitive deficits caused by exposure to 1400 ppm toluene

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Rat Fisher 344 # : 8 Sex : Males

Age : 23 days

Exposure

Route : Inhalation

Duration : 14 h/d; 7 d/w; 5 w

C/D reported : 1200 - 1400 ppm

CSU/DSU :

Ratio : 24 - 28

ASM :

BM :

Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Multisensory conditionned avoidance response task	Tone at 20 kHz
• - Control group performed better than the toluene exposed rats - Two months after the end of exposure, there was marked impairment still evident of toluene exposed rats' perfomance	• Test performed on the 5th week of exposure, 1 week, 3 week and two months after the end of exposure
Reflex modification audiometry	Tone at 4, 8, 12, 16 and 20 kHz
• Hearing loss in the toluene exposed rats increased from 2 dB (at 4 kHz) to 30 dB (at 16 and 20 kHz)	• Test performed 2.5 months after the end of exposure
Intensity discrimation	at 4 kHz
• No difference between control and toluene exposed rats in their abilities to learn the 4 kHz tone intensity	• Test performed 4 weeks after the end of exposure

Action mechanism

Authors' conclusion

Toluene exposure caused a very pronounced and apparently irreversible high frequency hearing loss

Our conclusion

Ototoxic effect at 1200 ppm in young rats exposed for 5 weeks

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Rat Fisher 344 # : 8 Sex : Males

Age : 25 and 60 days

Exposure

Route : Inhalation

Duration : 14 h/d; 7 d/w; 5 w

C/D reported : 1200 ppm

CSU/DSU :

Ratio : 24

ASM :

BM :

Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Multisensory conditionned avoidance response task	at 4 and 20 kHz
• - No significant effects of toluene on perfomance at 4 kHz. - Impaired performance after toluene exposure at 20 kHz	• Test performed 8 jours after the end of exposure
Reflex modification audiometry	Tone at 4, 8, 12 and 16 kHz
• - No differences among groups at 4 and 8 kHz. - Markedly impaired performance at higher frequencies	• Test performed on the 2th and the 3th weeks after the last exposure and repeated 3 months later
Auditory brainstem responses	Tone pips at 4, 8 and 16 kHz
• - Significant hearing loss at all three frequencies tested and increased in magnitude with increasing frequency - 3 months after exposure, the first ABR component integrated latency at 16 kHz were clearly steeper in the toluene-exposed rats	• Test performed during the 4th and the 5th weeks and 3 months after the end of exposure
Light microscopy	
• Inner and outer hair cell loss or damage in the basal turn of the cochlea	• Histology performed 3 months after end of exposure

Action mechanism

Authors' conclusion

Toluene causes an irreversible high frequency hearing loss. Conditioned avoidance response data shows an acquisition deficit. Electrophysiological data confirms a sensory deficit. The high frequency hearing loss observed behaviourally and electrophysiologically is associated with hair cell damage

Our conclusion

Ototoxic effect at 1200 ppm in rats

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Rat Fisher 344 # : 5 Sex : Males

Age : 23 or 35 days

Exposure

Route : Inhalation

Duration : 14 h/d; 7 d/w; 16 w - see remarks

C/D reported : 0, 400, 700 and 1000 ppm

CSU/DSU :

Ratio : 2 - 14

ASM :

BM :

Remarks : After 16 weeks, the concentrations were changed to 0, 850, 1000 and 1000 ppm, respectively, for an additionnal 5 weeks

Tests

Test type • Effects reported	Precisions on test • Remarks
Multisensory conditionned avoidance response task	Tone at 4, 8, 12, 16 and 20 kHz
• - 1000 ppm toluene : decrease in performance after 2 weeks of exposure. - 400 and 700 ppm : slightly impaired performance during the first 2 or 3 weeks of exposure but performance comparable to that in controls from the 4th through the 16th weeks of exposure. - After increasing the concentration to 850 and 1000 ppm at the 16th week, performance declined rapidly from the 18th to 19th week	• Test performed weekly or biweekly after the exposure started
Reflex modification audiometry	Tone at 4, 8, 12, 16 or 20 kHz
• - No differences among groups at 4 or 8 kHz - Rats exposed to 1000 ppm toluene for 21 weeks were markedly impaired at 12 kHz and above - Rats initially exposed to 700 ppm were not impaired at 12 kHz, but were moderately impaired at 16 and 20 kHz - Rats initially exposed to 400 ppm were affected at 12 kHz and above	• Test performed 2 weeks after the end of exposure
Auditory brainstem responses	Tone pips at 4, 8 and 16 kHz
• - Hearing thresholds at 16 kHz were elevated after 2 weeks in the rats exposed to 1000 ppm toluene - Lower concentrations of toluene did not cause any clear changes overthe first 3 weeks of exposure at 16 kHz - Three weeks after the end of exposure, thresholds were elevated in all toluene exposed rats relative to controls - No differences among groups at 4 and 8 kHz	• Test performed weekly during exposure and 3 weeks after the end of exposure

Action mechanism

Authors' conclusion

Threshold concentration of toluene causing hearing loss is between 700 and 1000 ppm in rats

Our conclusion

LOAEL of 700 - 1000 ppm for ototoxicity in rats exposed for 16 weeks

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Rat Fisher 344 # : 5 - 12 Sex : Males

Age : 35 days

Exposure

Route : Inhalation

Duration : 14 h/d; 8 h/d; 4 h/d; 16 d - see remarks

C/D reported : 1000, 2000 and 4000 ppm

CSU/DSU :

Ratio : 20 - 80

ASM :

BM :

Remarks : 1000 ppm for 14 h/d; 2000 ppm for 8 h/d; 4000 ppm for 30 minutes each hour for 8 hours each day
On the fourth day, the toluene concentration was reduced to 1500 and 3000 ppm

Tests

Test type • Effects reported	Precisions on test • Remarks
Multisensory conditionned avoidance response task	Pure tone at 4 and 20 kHz
• Performance by the 3 groups was markedly impaired in all the tests. This effect was moderate after 7 daily exposures and was marked after 14 daily exposures. No recovery was evident 3 months after the last exposure	• Test performed after 7 and 14 days of exposure and 5 days and 3 months after the end of exposure
Reflex modification audiometry	Tone at 4, 8, 12, 16 and 20 kHz
• - All toluene exposed groups had markedly impaired hearing thresholds at 12 and 20 kHz - No differences among the three toluene-exposed groups at any frequency tested	• Test performed 2 weeks after the end of exposure
Auditory brainstem responses	Tone pips at 4, 8 and 16 kHz
• - Thresholds were elevated in all toluene exposed groups. - Increase in threshold at 4 kHz in the group exposed to 1000 ppm toluene for 14 hours each days. - Thresholds at 8 and 16 kHz were moderately to markedly elevated in all the groups. - No differences among the toluene exposed groups in thresholds at any frequency tested	• Test performed 2 weeks after the end of exposure

Action mechanism

Authors' conclusion

Total time-weighted daily exposure concentration is the important variable, regardless of how the exposure is distributed over the day

Our conclusion

Ototoxic effect at 1000 ppm in rats

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Rat Fisher 344 # : 12 Sex : Males

Age : 35 days

Exposure

Route : Inhalation

Duration : 4 - 8 h/d; 6 d/w; 15 w - see remarks

C/D reported : 1500 and 3000 ppm

CSU/DSU :

Ratio : 30 - 60

ASM :

BM :

Remarks : 1500 ppm for 8 h/d; 3000 ppm for 30 minutes each hour for a total of 4 hours exposure each day - which was increased for 6 h/d on week 9; 3000 ppm for 30 minutes each hour for total of 8 hours exposure each day

Tests

Test type • Effects reported	Precisions on test • Remarks
Multisensory conditionned avoidance response task	at 20 kHz
• - No difference among groups after 2 weeks of exposure. - Marked impairment in 3000 ppm - 8h and 1500 ppm - 8 h toluene exposed rats after 16 days of exposure. - 3000 ppm - 6 h toluene exposed rats were not affected. - Last 6 weeks of exposure, groups performed more poorly than controls. However, only 1500 ppm - 8 h differed consistently from controls.	• Test performed on the 14th and 16th days of exposure and weekly intervals there after
Auditory brainstem responses	Tone pips at 4, 8 and 16 kHz
• - No differences among groups at 4 kHz. - Only 1500 ppm - 8h exposed group had elevated thresholds at 8 kHz. - All toluene exposed groups had elevated thresholds at 16 kHz, with 3000 ppm - 6 h exposed rats affected less	• Test performed 4 weeks after the end of exposure
Reflex modification audiometry	Tone at 4, 8, 12, 16 and 20 kHz
• - No differences among groups at 4 and 8 kHz. - 12 kHz and above, 1500 ppm and 3000 ppm for 8 h toluene exposed rats were markedly impaired and 3000 ppm - 4 h toluene exposed rats were only moderately impaired	• Test performed 2 weeks after the end of exposure

Action mechanism

Authors' conclusion

Ototoxic effect of toluene had progressed after sufficient number of exposure and may have been triggered by few (from 7 to 14 days) days of exposure

Our conclusion

Ototoxic effect of toluene at 1500 ppm in young rats exposed for 8 hours

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Rat Fisher 344 # : 7 - 8 Sex : Males

Age : 23 days

Exposure

Route : Inhalation

Duration : 8 - 14 h/d; 3 d - see remarks

C/D reported : 1500, 2000 and 4000 ppm

CSU/DSU :

Ratio : 30 - 80

ASM :

BM :

Remarks : 1500 ppm for 14 h/d; 2000 ppm for 8 h/d; 4000 ppm for 30 minute each hour for a total of 8 h/d exposure

Tests

Test type • Effects reported	Precisions on test • Remarks
Multisensory conditionned avoidance response task	Tone at 4 and 20 kHz
• - No difference among groups performance at 4 kHz. - Markedly impaired exposed groups performance at 20 kHz, intermittenly (4000 ppm - 8 h) toluene exposed group was less impaired than groups exposed continuously (1500 ppm - 14 h and 2000 ppm - 8 h)	• Test performed 22 days after the end of exposure
Reflex modification audiometry	Tone at 4, 8, 12, 16 and 20 kHz
• - Response threshold elevations in all exposed groups at 12 kHz and above. - Intermittenly (4000 ppm - 8 h) toluene exposed group was less impaired than groups exposed continuously (1500 ppm - 14 h and 2000 ppm - 8 h)	• Test performed 5 weeks after the end of exposure
Auditory brainstem responses	Tone pips at 4, 8 and 16 kHz
• - No difference among exposed groups at 4 kHz - Threshold elevation of all exposed groups at 8 and 16 kHz, intermittenly (4000 ppm - 8 h) toluene exposed group was less impaired at 8 kHz than groups exposed continuously (1500 ppm - 14 h and 2000 ppm - 8 h) - Effect on component amplitudes was greatest at 16 kHz and less depressed in intermittenly (4000 ppm - 8 h) toluene exposed group than groups exposed continuously (1500 ppm - 14 h and 2000 ppm - 8 h)	• Test performed 5 weeks after the end of exposure

Action mechanism

Authors' conclusion

3 days toluene exposure can cause hearing loss at sufficient concentration and duration

Our conclusion

Ototoxic effect of toluene at 1500 in young rats exposed for 3 days

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Rat Fisher 344 # : 3 - 6 Sex : Males

Age : 23 days

Exposure

Route : Inhalation

Duration : 4 - 8 h/d; 1 - 3 d - see remarks

C/D reported : 2000 and 4000 ppm

CSU/DSU :

Ratio : 40 - 80

ASM :

BM :

Remarks : 4000 ppm for 4 h; 2000 ppm for 8 h; 2000 ppm for 8 h/d for 3 days

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Tone pips at 16 kHz
• - No difference among group 1 week after exposure - Only rats expose to 2000 ppm during 3 days had elevated threshold compared to controls 3 and 5 weeks after exposure	• 1, 3 and 5 weeks after the end of exposure
Multisensory conditionned avoidance response task	Tone at 4 and 20 kHz
• - No difference among groups at 4 kHz. - Only rat expose to 2000 ppm during 3 days performed more poorly than controls at 20 kHz	• Test performed 6 weeks after the end of exposure

Action mechanism

Authors' conclusion

As little as 3 days of toluene exposure could cause permanent high frequencies loss and there is a period of time for ototoxic effect to become functionnally manifest

Our conclusion

Ototoxic effect of toluene at 2000 ppm in young rats exposed for 3 days

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Rat Fisher 344 # : 8 - 9 Sex : Males

Age : 23 days

Exposure

Route : Inhalation

Duration : 4 - 8 h/d; 1 - 3 d - see remarks

C/D reported : 2000 and 4000 ppm

CSU/DSU :

Ratio : 40 - 80

ASM :

BM :

Remarks : 4000 ppm for 4 h; 2000 ppm for 8 h; 2000 ppm for 8 h/d for 3 days

Tests

Test type • Effects reported	Precisions on test • Remarks
Multisensory conditionned avoidance response task	Tone at 4 and 20 kHz
• - No difference among groups at 4 kHz. - Impaired performance in group exposed to 2000 ppm during 3 days at 20 kHz	• Test performed from 30 to 35 days after the end of exposure
Reflex modification audiometry	Tone at 4, 8, 12, 16 and 20 kHz
• Impaired response threshold only in rats exposed to 2000 ppm during 3 days at 12 kHz and above	• Test performed 6 weeks after the end of exposure

Action mechanism

Authors' conclusion

LOAEL for toluene ototoxic effect may be 3 days exposure to 2000 ppm for 8 h/d

Our conclusion

Ototoxic effect of toluene at 2000 ppm in rats exposed for 3 days

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Rat Fisher 344 # : 12 Sex : Males

Age : 23 days

Exposure

Route : Inhalation

Duration : 8 h/d; 7 d/w; 2 w

C/D reported : 2000 ppm

CSU/DSU :

Ratio : 40

ASM :

BM :

Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Multisensory conditionned avoidance response task	Pure tone at 4 and 20 kHz
• Rats exposed to toluene perfomed the test more poorly at 20 kHz (high intensity) than control group	• NR
Reflex modification audiometry	Tone at 4, 8, 12, 16 and 20 kHz
• - No differences among groups at 4 and 8 kHz. - Clear indication of hearing loss caused by exposure to toluene was seen at 12 and 20 kHz.	• NR

Action mechanism

Authors' conclusion

Hearing loss caused by exposure to toluene at hight frequencies

Our conclusion

Ototoxic effect at 2000 ppm in young rats exposed for 2 weeks

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Rat Fisher 344 # : 7 - 10 Sex : Males

Age : 40 days

Exposure

Route : Inhalation

Duration : 8 h/d; 7 d

C/D reported : 2000 ppm

CSU/DSU :

Ratio : 40

ASM :

BM :

Remarks : The concentration of toluene was 1500 ppm on the first day and then increased to 2000 ppm

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Tone pips at 16 kHz
• Hearing deficit in toluene exposed rats	• Test performed 1 week after the end of exposure

Action mechanism

Toluene and not one of its metabolites is responsible for an ototoxic effect in rats

Authors' conclusion

Hearing deficit in toluene exposed rats

Our conclusion

Ototoxic effect at 2000 ppm in rats exposed 7 days

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Rat Fisher 344 # : 12 Sex : Males

Age : 33 days

Exposure

Route : Inhalation

Duration : 8 h/d; 7 d/w; 11 w - see remarks

C/D reported : 2000 - 2600 ppm

CSU/DSU :

Ratio : 40 - 52

ASM :

BM :

Remarks : Rats exposed to 2000 ppm until the 6th week when the concentration increased to 2600 ppm for the rest of the 11 weeks

Tests

Test type • Effects reported	Precisions on test • Remarks
Multisensory conditionned avoidance response task	Tone at 4 and 20 kHz
• - No differences among groups at 4 kHz. - Performance impaired in rats exposed to toluene at 20 kHz	• Test performed 2 weeks after the end of exposure
Reflex modification audiometry	Tone at 4, 8, 12, 16 and 20 kHz
• Toluene caused a decrease in auditory sensitivity at all frequencies above 4 kHz	• Test performed 4 weeks after the end of exposure

Action mechanism

Authors' conclusion

No conclusion about ototoxicity

Our conclusion

Ototoxic effect at 2600 ppm in young rats

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Rat Fisher 344 # : 8 - 10 Sex : Males

Age : 30 days

Exposure

Route : Inhalation

Duration : 8 h/d; 4 h/d; 2 h/d; 7 d/w; 23 w - see remarks

C/D reported : 2200, 4400 and 8800 ppm

CSU/DSU :

Ratio : 44 - 176

ASM :

BM :

Remarks : Rats exposed to 2200 ppm for 8 h/d; rats exposed to 4400 ppm for 30 minutes each hour for 8 h/d; rats exposed to 8800 ppm for 15 minutes each hour for 8 hours each day

Tests

Test type • Effects reported	Precisions on test • Remarks
Multisensory conditionned avoidance response task	Tone at 4 and 20 kHz
• No significant differences among groups at any time during the test at 4 kHz Impaiment performance at 20 kHz	• Test performed 2 weeks after the end of exposure
Reflex modification audiometry	Tone at 4, 8 and 16 kHz
• Impairments at 8 and 16 kHz were highly significant	• Test performed 2 weeks after the end of exposure

Action mechanism

Authors' conclusion

No conclusion about ototoxicity

Our conclusion

Ototoxic effect at 2200 ppm in young rats

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Rat Fisher 344 # : 12 Sex : Males

Age : 23 days

Exposure

Route : Inhalation

Duration : 14 h/d; 7 d/w; 9 w

C/D reported : 1200 ppm

CSU/DSU :

Ratio : 24

ASM :

BM :

Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Tone pips at 4, 8 and 16 kHz
• - Effects are most pronounced at mid to high frequencies, and were clearest with the 16 kHz stimulus - Amplitudes were signfiicantly smaller than in control group	• Test performed 2 weeks after the end of exposure
Multisensory conditionned avoidance response task	Tone at 4 and 16 kHz
• Slight impairment at 4 kHz progressing to a marked impairment at 16 kHz	• Test performed 12 weeks after the end of exposure

Action mechanism

Authors' conclusion

No conclusion about ototoxicity

Our conclusion

Ototoxic effect at 1200 ppm in rats exposed for 9 weeks

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Rat Fisher 344 # : 12 - 20 Sex : Males

Age : 23 days

Exposure

Route : Inhalation

Duration : 14 h/d; 7 d/w; 5 w

C/D reported : 1200 ppm

CSU/DSU :

Ratio : 24

ASM :

BM :

Remarks : Background noise: 60 to 80 dB

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Tone pips at 8, 12 and 16 kHz Clicks at 16 kHz
• - Latencies of the component I in the toluene-exposed rats were normal at the highest intensities of the stimulus but prolonged at lower intensities - The amplitude of the third component increased as the intensity of the stimulus increased - Hearing thresholds were elevated by about 15-25 dB in treated rats	• Test performed 2.5 months after the end of exposure

Action mechanism

Authors' conclusion

Loss of auditory sensitivity

Our conclusion

Ototoxic effect at 1200 ppm in young rats

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Rat Fisher 344 # : NR Sex : Males

Age : NR

Exposure

Route : Inhalation

Duration : 30 minutes

C/D reported : 500, 2000, 5000 and 8000 ppm

CSU/DSU :

Ratio : 10 - 160

ASM :

BM :

Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Clicks at 1.5 - 20 kHz Tone pips at 16 kHz
• - 500 and 2000 ppm : little effect on auditory brainstem responses (ABR) and on the amplitudes of ABR component. - 5000 and 8000 ppm : increases in the latencies of all but one components and in amplitudes also. For each exposure the toluene-induced increase in latency was greatest 5 minutes after cessation of exposure and declined thereafter	• Test performed before, during and 5, 30 and 120 minutes after the end of exposure

Action mechanism

Authors' conclusion

Toluene exposure does make effects on evoked potentials, those effects were evident few minutes after the beginning of exposure, increasing, and then decreasing with continued exposure.

Our conclusion

LOAEL of 5000 ppm for the effect ototoxic of toluene after a short exposure (30 minutes)

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Rat Sprague Dawley # : 6 - 8 Sex : Males

Age : NR

Exposure

Route : Gavage

Duration : 49 d

C/D reported : 1.0 mL/kg (body weight)

CSU/DSU : 867 mg/kg/d

Ratio : 32

ASM :

BM :

Remarks : Background noise: < 60 dB SPL

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Tone bursts at 0.5, 1, 2, 4, 8, 16 and 32 kHz
• Hearing losses observed in toluene-exposed rats were significantly different from the control group. In this range of responses, the lesion appears to begin in the middle and upper base turn and progress towards the apical region. The rats, which had the greatest hair cell loss, also exhibited the greatest threshold elevations. The greatest threshold elevations, up to 60 dB, occurred in the midfrequency regions, typically at 2-8 KHz	• Test performed before and after the end of exposure
Light microscopy	
• Loss of outer hair cells were observed in toluene-treated rats and were significantly different from controls. The toluene exposure induced lesion of the third row but did not affect the inner hair cell	• Histology performed immediately after the end of exposure

Action mechanism

Authors' conclusion

Selective outer hair cell loss was observed in the middle and upper basal turns of the cochlea of all toluene-treated rats. ABR threshold elevations in the midfrequency regions of the cochlea, typically 2-8 kHz, in toluene treated rats

Our conclusion

Ototoxic effect in rats treated orally to 867 mg/kg

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Worker # : 49 Sex : Not reported

Age : 42.3 years (mean)

Exposure

Route : Inhalation

Duration : 21.4 years (mean)

C/D reported : NR

CSU/DSU :

Ratio :

ASM :

BM : Blood toluene = 0.036 mg/L(before shift); Urine hippuric acid = 0.426 g/g creatinine (before shift) + 0.485 g/g creatinine (after shift)

Remarks : - Toluene in blood were measured on Wednesday before shift.
- Hippuric acid in urine were measured on Wednesday before and after shift.
- Ortho-creosol in urine is also measured on Wednesday before (0.211 g/g creatinine) and after (0.276 g/g creatinine) shift

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Clicks
• Prolongation of latency and diminution of amplitude of all brainstem components.	• Test performed after weekend before shift

Action mechanism

Authors' conclusion

Brainstem components change during chronic exposure to low concentrations of toluene

Our conclusion

Auditory function altered and possible ototoxic effect of toluene in workers, however there is no sufficient evaluation of noise exposure

Toluene [108-88-3]

Toluene
• TWAEV : 50 ppm | 188 mg/m³ D-TWAEV : 27 mg/kg/d

Population

Species : Worker # : 49 Sex : Not reported

Age : 42.3 years (mean)

Exposure

Route : Inhalation

Duration : 21.4 years (mean)

C/D reported : 40 - 60 ppm

CSU/DSU :

Ratio : 0.8 - 1.2

ASM :

BM : Blood toluene = 0.036 mg/L(before shift); Urine hippuric acid = 0.426 g/g creatinine (before shift) + 0.485 g/g creatinine (after shift)

Remarks : - Toluene in blood were measured on Wednesday before shift
- Hippuric acid in urine were measured on Wednesday before and after shift
- Exposure to toluene was estimated according to the hippuric acid concentration

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Clicks
• - With the exception of P2 wave, there was an increase in the latencies of all waves as well as in the interpeak latency (IPL) P3-P4. whereas IPL P4-P5 deceased with the length of exposure - No correlation between the amplitudes of examined waves and length of exposure	• Test performed after weekend before shift

Action mechanism

Authors' conclusion

Brainstem components change during chronic exposure to low concentrations of toluene

Our conclusion

Auditory function altered and possible ototoxic effect of toluene in workers, however there is no sufficient evaluation of noise exposure

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