

# Ototoxicity of industrial chemicals alone or in combination with noise\* \*

## Toluene

A. Vyskocil<sup>1\*</sup>, T. Leroux<sup>3</sup>, G. Truchon<sup>2</sup>, F. Lemay<sup>1</sup>, F. Gagnon<sup>1</sup>, M. Gendron<sup>3</sup>, S. Botez<sup>1</sup>, N. El Majidi<sup>1</sup>, A. Boudjerida<sup>1</sup>, S. Lim<sup>1</sup>, C. Émond<sup>1</sup>, C. Viau<sup>1</sup>

### Introduction

There is increasing epidemiological evidence that exposure to some solvents, metals, asphyxiants and other substances is associated in humans with a risk of hearing loss. On the contrary, the interaction of chemicals and noise has received little attention. This project was undertaken to develop a database of toxicological data from the primary literature, allowing the identification of ototoxic substances and substances that interact with the noise present in the work environment. Critical toxicological data were compiled for chemical substances included in the Quebec regulation (Regulation Respecting Occupational Health and Safety).

### Methods

The data were evaluated only for realistic exposure concentrations up to:

- the short-term exposure limit value, or
- the ceiling value, or
- 5 times the 8-h time weighted average exposure limit value (TWAEV) for human data, or
- 100 times the 8-h TWAEV or the ceiling value for animal studies.

We took into consideration the number of studies and for each study the following parameters: studied species, number of subjects or animals, exposure route, characteristics of control groups, exposure levels, audiometric and statistical tests, dose/effect relationship and when available, mechanisms of action.

Using a systematic weight of evidence approach, the information from both human and animal studies was examined. At first, a weight of evidence qualifier was given for both the ototoxicity and the interaction with noise : "strong", "medium", "weak", "absent" or "no study found". Note that weight of evidence qualifier "absent" should not be regarded as evidence that a substance is not ototoxic or that it does not interact with noise.

We built a weight of evidence table (see Table 1) that allowed us to combine the information from both human and animal studies on ototoxicity of chemicals and their interaction with noise. Human data were given more weight in the overall assessment. 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 substances or their interaction with noise, a substance bearing an overall qualifier of "strong evidence" of ototoxicity or interaction with noise was considered as an "ototoxic substance" or as a substance for which there is an "evidence of interaction" with noise. Those with "medium evidence" overall were rated "possibly ototoxic" or "possible interaction". We considered the ototoxic potential of those with only "weak evidence" as "non conclusive". Finally, those for which there was absence of evidence bore the mention "no evidence" of ototoxicity or interaction with noise.

\* Corresponding author : [adolf.vyskocil@umontreal.ca](mailto:adolf.vyskocil@umontreal.ca)

\*\* Production of this document was supported by the IRSST (Grants 99-542 and 99-745)

<sup>1</sup> Institut de recherche en santé publique de l'Université de Montréal. Département de santé environnementale et de santé au travail, Université de Montréal.

<sup>2</sup> Institut de recherche Robert-Sauvé en santé et en sécurité du travail (IRSST), Montréal

<sup>3</sup> École d'orthophonie et d'audiologie, Université de Montréal

**Table 1**

Weight of evidence approach for the assessment of  
ototoxicity and interaction with noise  
of industrial chemicals

Weight of evidence of studies			Conclusion about ototoxicity	Conclusion about the interaction substance / noise
Human studies	Animal studies	Overall		
S	S	S	O	I
S	M	S	O	I
S	W	S	O	I
S	A	S	O	I
S	X	S	O	I
M	S	S	O	I
M	M	M	PO	PI
M	W	M	PO	PI
M	A	M	PO	PI
M	X	M	PO	PI
W	S	M	PO	PI
W	M	W	NC	NC
W	W	W	NC	NC
W	A	W	NC	NC
W	X	W	NC	NC
A	S	M	PO	PI
A	M	W	NC	NC
A	W	W	NC	NC
A	A	A	NE	NE
A	X	A	NE	NE
X	S	M	PO	PI
X	M	W	NC	NC
X	W	W	NC	NC
X	A	A	NE	NE
X	X	X	X	X

**Strength of evidence about ototoxicity or interaction substance / noise**

S = Strong, M = Medium, W = Weak, A = Absent, X = No study found

**Conclusion about ototoxicity**

O=Ototoxic substance, PO=Possibly ototoxic substance, NC=Non conclusive, NE=No evidence, X=No documentation

**Conclusion about the interaction substance / noise**

I=Evidence of interaction, PI=Possible interaction, NC=Non conclusive, NE=No evidence, X=No documentation

## Abbreviations

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

**D-TWAEV** : Calculated inhaled dose for pulmonary ventilation of 10 m<sup>3</sup>/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<sup>3</sup>/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<sup>3</sup> 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

**NSM**: Noise sampling method

**NL**: Noise levels

**SPL** : Sound pressure level

# Toluene

Quebec's Occupational exposure limits: TWAEV: 188 mg/m<sup>3</sup> (50 ppm)

Conclusion about ototoxicity <b>Ototoxic substance</b>	Strength of evidence From human studies: <b>Medium</b> From animal studies: <b>Strong</b> Overall: <b>Strong</b>
Conclusion about interaction with noise <b>Evidence of interaction</b>	Strength of evidence From human studies: <b>Strong</b> From animal studies: <b>Medium</b> Overall: <b>Strong</b>

## Ototoxicity - 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).

## Ototoxicity - Analysis of animal studies

Thirty-two inhalation, two oral and one intravenous studies in 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 mid-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). Moreover, toluene itself seems to be responsible for the ototoxic effect rather than its metabolites (Campo 2008, Waniusiow 2008). 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 – 1500 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 (Campo 2008, Johnson 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 OHC has been confirmed by morphologic examinations of cochlea showing loss of OHC, 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 (4-5 kHz) 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). Moreover, results from the intravenous study suggest that exposure to toluene might modify the response of protective acoustic reflexes (Lataye 2007).

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.

## Interaction with noise - Analysis of human studies

Four studies on workers were identified. Two of those used the same data (Schaper 2003, Schaper 2008). In a well done study (Morata 1993), simultaneous occupational exposure to 100-365 ppm toluene and 88-98 dBA noise was found to increase significantly the predicted probability of developing a hearing loss when compared with a group of workers exposed to matching doses of noise. Acoustic reflex measurements suggested that the hearing losses found in the group exposed to both agents might be due to lesions in the central auditory system.

Another well done study identified a hearing impairment from simultaneous exposure to 33-165 ppm toluene and 85 dB of noise in workers (Chang 2006). However, no hearing impairment was observed in the study in

which workers were simultaneously exposed up to 45 ppm toluene and 82 dB of noise, indicating that the threshold for developing a hearing loss due to toluene exposure might be above 50 ppm (Schaper 2003, Schaper 2008).

### Interaction with noise - Analysis of animal studies

Six studies in rats were identified. Interactions of toluene with noise producing additive or synergistic cochlear damage have been suggested in five studies. The decrease in auditory sensitivity of rats exposed to toluene followed by noise was greater than the sum of the effects of toluene and noise alone (synergistic effect) (Lataye 1997, Brandt-Lassen 2000). When exposures were carried out in reverse order (i.e., noise followed by toluene exposure), the loss of sensitivity was greater than the individual loss caused by toluene or noise, but did not exceed the summated loss (Johnson 1990). Also, one study found a greater effect of impact noise as compared to wide-band noise when exposed to 500 to 1500 ppm toluene simultaneously during 10 days (Lund 2008). However, the value of the results of these studies is limited with respect to occupational setting as the daily exposures were long (10-16 h/d), overall exposure periods were short (2-4 weeks) and exposure to noise and toluene was not simultaneous in three studies (Johnson 1988, Johnson 1990, Lataye 1997). The only study where daily and overall exposure periods were more representative (6 h/d, 90 days in rats exposed from 100 to 500 ppm), was negative and the authors found a protective effect on hearing of exposure to low levels of toluene (Lund 2008). One study on guinea pigs (Campo 1999) and one study on chinchillas (Davis 2002) were negative.

---

### Discussion

Although certain ototoxic effects were reported in workers, other human studies are necessary to come to a final conclusion. 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. There is a convincing evidence of the ototoxic interaction after combined exposure to toluene and noise in workers and in rats. 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 which can also interact with noise to induce more severe hearing losses.



**Toluene****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

D-TWAEV : 27 mg/kg/d

**Population**

Species : Rat Wistar

# : 12

Sex : Males

Age : 6 - 7 weeks

**Exposure**

Route : Inhalation

Duration : Toluene : 6 h/d; 10 d : noise : 2 h/d

C/D reported : E1 and E2 = 0 ppm ; E3 and E4 = 500 ppm ; E5 and E6 = 1000 ppm ; E7 and E8 = 1500 ppm ; E9 and E10 = 2000 ppm

CSU/DSU :

Ratio : 10 - 40

ASM :

BM :

NSM :

NL : 96 dB SPL, 4-20 kHz

Remarks : - Exposure to noise started after the end of toluene exposure  
 - E1, E3, E5, E7, E9 exposed to toluene  
 - E2, E4, E6, E8, E10 exposed to toluene + noise

**Tests****Test type**

• Effects reported

## Details on test

• Remarks

**Auditory brainstem responses**

• - Exposure toluene only. A) 500 and 1000 ppm : No effect B) 1500 and 2000 ppm : Mid-frequency threshold shift  
 - Exposure to toluene + noise. A) 500 ppm : Threshold shift equal to the hearing loss after exposure to noise only B) 1000, 1500 and 2000 ppm : Mid-frequency synergistic interaction

Pure tone at 4.0, 8.0, 12.5, 16.0, 20.0, 31.5 kHz

• Tests performed before exposure and 12 days after the end of exposure

**Mechanism of action****Authors' conclusion**

Synergistic interaction of toluene and noise at 1000 ppm and more

**Our conclusion**

LOAEL for synergistic interaction of toluene and noise is 1000 ppm

**Toluene****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

D-TWAEV : 27 mg/kg/d

**Population**

Species : Rat Wistar

# : 12

Sex : Males

Age : 6 - 7 weeks

**Exposure**

Route : Inhalation

Duration : 6 h/d; 10 d

C/D reported : C = 0 ppm ; E1 = 500 ppm ; E2 = 1000 ppm ; E3 = 1500 ppm ; E4 = 2000 ppm

CSU/DSU :

Ratio : 10 - 40

ASM :

BM :

NSM :

NL :

Remarks :

**Tests****Test type**

• Effects reported

## Details on test

• Remarks

**Auditory brainstem responses**

- 500 and 1000 ppm : No effect
- 1500 and 2000 ppm: Mid-frequency threshold shift

Pure tone at 4.0, 8.0, 12.5, 16.0, 20.0, 31.5 kHz

- Tests performed before exposure and 12 days after the end of exposure

**Mechanism of action****Authors' conclusion**

Ototoxic effect of toluene at 1500 ppm and more

**Our conclusion**

LOAEL for ototoxicity of toluene is 1500 ppm

**Toluene**

**Toluene**

• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

D-TWAEV : 27 mg/kg/d

**Population**

Species : Guinea pig

# : C(control) = 5 ; E1(toluene) = 8 ;  
E2(noise) = 5 ; E3 (toluene + noise) = 9

Sex : Females

Age : 4 months

**Exposure**

Route : Inhalation

Duration : Toluene : 6 h/d for 14 d; Noise : 8 h/d for 14 d; Noise + toluene - see remarks

C/D reported : 1000 ppm

CSU/DSU :

Ratio : 20

ASM :

BM :

NSM :

NL : 85 dB SPL ; 1/3 Octave band noise centered at 8 kHz

Remarks : Toluene + noise : The group was exposed to toluene followed by noise for 14 days

**Tests**

**Test type**

• Effects reported

Details on test

• Remarks

**Electrocochleography (Compound action potential : CAP)**

- - Toluene : Temporary and permanent hearing losses not different from the control.
- Noise : Significant temporary and permanent hearing losses in high frequencies. Compared to control
- Noise + toluene : Significant temporary and permanent hearing losses in high frequencies (region impaired wider than noise alone) compared to control but permanent losses not significant compared to toluene and noise exposed group

Tone burst at 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24 and 32 kHz

- Test performed before exposure, after the last day of exposure and 3 weeks after the end of exposure

**Electron microscopy**

- - Control group : Hair cell loss of 4% or less over the frequency range 2-32 kHz .
- Toluene, noise and noise + toluene groups : Hair cell loss of 5, 6 and 7% or less, respectively, over the frequency range 2-32 kHz
- Losses not different from the control group

- Test performed 3 - 4 weeks after the end of exposure

**Mechanism of action**

**Authors' conclusion**

No evidence of an ototoxic effect of moderate doses of toluene on the cochlea of the adult guinea pig. The combination of toluene and noise did not show more hearing loss than it would be expected from the noise exposure alone

**Our conclusion**

No ototoxicity effect at 1000 ppm toluene in guinea pigs. Exposure to toluene does not potentiate the damage induced by moderate noise exposure in this specie

**Toluene**

**Toluene**

• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL :

Remarks :

**Tests**

**Test type**

• Effects reported

Details on test

• Remarks

**Electrocochleography (Compound action potential : CAP)**

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

**Mechanism of action**

**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**

**Toluene**

• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL :

Remarks : Background noise : 66 dB SPL

**Tests**

**Test type**

• Effects reported

Details on test

• Remarks

**Auditory brainstem responses**

- - Only three toluene concentrations (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 frequency regions were also spared

Inferior colliculus  
Clicks at 2, 4, 6, 8, 10, 12, 16, 20, 24 and 32 kHz

- Test performed prior to the exposure, 24 - 32 hours and 6 weeks after the end of exposure

**Light microscopy**

- - 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

Cytocochleograms

- 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

**Mechanism of action**

**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**

**Toluene**

• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL :

Remarks : Background noise : < 66 dB SPL

**Tests**

**Test type**

• Effects reported

Details on test

• Remarks

**Auditory brainstem responses**

• Permanent hearing threshold shift is significantly greater at 12, 16 and 20 kHz in comparison with the control group

Inferior colliculus  
Clicks at 2 - 32 kHz

• 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

**Mechanism of action**

**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**

**Toluene**

• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

D-TWAEV : 27 mg/kg/d

**Population**

Species : Rat Long Evans

# : C = 8; E = 8

Sex : Males

Age : NR

**Exposure**

Route : Inhalation

Duration : 6 h/d; 5 d/w; 6 w - See remarks

C/D reported : 1750 and 2000 ppm

CSU/DSU :

Ratio : 35-40

ASM :

BM : Hippuric acid : 16.7±3.1 g/g creatinine ; Benzylmercapturic acid : 121.2±21.9 mg/g creatinine

NSM :

NL :

Remarks : 1750 ppm for the first 4 weeks, then 2000 ppm for the remaining 2 weeks

**Tests**

**Test type**

• Effects reported

Details on test

• Remarks

**Auditory brainstem responses**

- Best frequency sensitivity range around 8-12 kHz, no significant differences between control and exposed
- Rats exposed to toluene showed a clear loss in threshold sensitivity (14-15 dB) for tones between 12-20 kHz

Pure tones at 2, 4, 8, 12, 16, 20 and 32 kHz

- Performed before and 4 weeks after exposure

**Light microscopy**

- Largest losses in the third row of outer hair cells (OHC), the second row was less damaged, but more than the first one. Inner hair cells (IHC) were relatively well preserved
- Severe losses at a cochlear location corresponding to frequencies ranging from 2 to 25 kHz

- Performed 4 weeks post exposure

**Mechanism of action**

**Authors' conclusion**

Toluene is likely to be the compound responsible for the ototoxicity of the solvent

**Our conclusion**

Toluene is likely to be the compound responsible for the ototoxicity of the solvent

**Toluene****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

D-TWAEV : 27 mg/kg/d

**Population**

Species : Worker

# : 58 - 60

Sex : Males

Age : 40 years (mean)

**Exposure**

Route : Inhalation

Duration : 10 years and up

C/D reported : 33, 108 and 165 ppm (means)

CSU/DSU :

Ratio : 0.7 - 3.3

ASM : Environmental sampling with tubes filled with 100/50 mg activated charcoal with a flow rate of 20-200 mL/min

BM :

NSM :

NL : C = 70 dB; E1 = 85 dB; E2 = 84 dB

Remarks : C = control group ; E1 = noise only exposed group ; E2 = noise + toluene exposed group

**Tests****Test type**

• Effects reported

## Details on test

• Remarks

**Pure tone audiometry**

Pure tones at 0.5, 1, 2, 3, 4 and 6 kHz

- Poorer hearing thresholds observed at both low and high frequencies in the exposed groups, the maximal loss at 4 and 6 kHz.
- Noise + toluene : the prevalence of hearing loss of > 25 dB was 86% (without the exclusion of hearing loss at 0.5 kHz) and 67% (with the exclusion of hearing loss at 0.5 kHz); the estimated risk for hearing loss of > 25 dB was 10.9 times higher than that of noise only group
- Noise : the prevalence of hearing loss of > 25 dB was 45% (without the exclusion of hearing loss at 0.5 kHz) and 33% (with the exclusion of hearing loss at 0.5 kHz)
- Controls : the prevalence of hearing loss of > 25 dB was at 5 %

- Test performed 14 hour after the end of previous work day

**Mechanism of action****Authors' conclusion**

Strong effect of hearing impairment from simultaneous exposure to toluene and noise in humans. Magnitudes of ototoxic effect different for various tested pure tone frequencies among workers exposed to both agents, to noise only or to no of these agents

**Our conclusion**

Evidence of a strong ototoxic effect in simultaneous long exposure to 33 - 165 ppm (means) toluene and 84 dB(A) noise in humans

**Toluene****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL :

Remarks : Background noise : 30 dB

**Tests****Test type**

• Effects reported

## Details on test

• Remarks

**Reflex modification audiometry**

• Hearing loss at 8, 16 and 24 kHz

at 0.5 - 40 kHz

• Test performed 5 to 8 weeks after the end of exposure

**Mechanism of action****Authors' conclusion**

Mid-frequency hearing loss at 2500 ppm in rats

**Our conclusion**

Ototoxic effect at 2500 ppm in rats

**Toluene****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

D-TWAEV : 27 mg/kg/d

**Population**

Species : Chinchilla

# : 4 - 6

Sex : Not reported

Age : adults

**Exposure**

Route : Inhalation

Duration : 8-12 h/d; 5 d - see remarks

C/D reported : 2000 ppm

CSU/DSU :

Ratio : 40

ASM :

BM :

NSM :

NL : 97.5 dB(A)

Remarks : Background noise &lt; 60 dB(A)

Exposure 1 : Gr1 = 8 hours toluene; Gr2 = 8 hours noise ; Gr3 = 8 hours noise + toluene ; Gr4 = Control

Exposure 2 : Gr5 = 12 hours toluene + 8 hours noise\* ; Gr6 = 12 hours toluene

\* noise beginning 2 hours after the start and ending 2 hours before the end of toluene exposure

**Tests****Test type**

• Effects reported

## Details 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 or an interaction of toluene with noise.
- 12 hours toluene exposures show a slight elevation at 16 kHz when animals exposed only to toluene but when exposed to 12 hours of toluene and 8 hours of noise, the high frequency loss disappeared and only the low frequency effect was present

- Test performed 30 days after the end of exposure

**Mechanism of action****Authors' conclusion**

Exposure of toluene produced no measurable ototoxicity in chinchillas while noise effects were detected

**Our conclusion**

No ototoxic effect of toluene at 2000 ppm in chinchillas

**Toluene****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL :

Remarks :

**Tests****Test type**

• Effects reported

## Details on test

• Remarks

**Auditory brainstem responses**

• No significant effect due to toluene alone

Tone bursts at 0.5, 1, 2, 4, 8 and 16 kHz

• Test performed 30 days after the end of exposure

**Mechanism of action****Authors' conclusion**

No ototoxicity effect of toluene in chinchillas

**Our conclusion**

No ototoxicity effect of toluene at 2000 ppm in chinchillas

**Toluene****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL :

Remarks :

**Tests****Test type**

• Effects reported

## Details 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

**Mechanism of action****Authors' conclusion**

Ototoxic effect of toluene in rats

**Our conclusion**

Ototoxic effect of toluene after exposure by oral way in rats

**Toluene****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

D-TWAEV : 27 mg/kg/d

**Population**

Species : Rat Sprague Dawley

# : 8 - 12

Sex : Males

Age : 21 to 38 days

**Exposure**

Route : Inhalation

Duration : Toluene : 16 h/d; 5 d/w; 2 w: Noise : 10 h/d; 7 d/w; 4 w - see remarks

C/D reported : 1000 ppm

CSU/DSU :

Ratio : 20

ASM :

BM :

NSM :

NL : 105 dB SPL

Remarks : Background noise : 40 dB SPL

Group toluene + noise = exposure to toluene for 2 weeks followed by 4 weeks of noise exposure

**Tests****Test type**

• Effects reported

## Details on test

• Remarks

**Auditory brainstem responses**

- - Toluene alone : Higher hearing thresholds than in the control group at all frequencies
  - One month after the exposure, a slight improvement in threshold (5-10 dB) at all frequencies tested, except at 3.15 kHz
  - Improvement of another 5 dB six months after the exposure
  - Latency of ABR after the solvent exposure was slightly increased and after 1 and 6 month, the latency was similar to the control
  - Toluene + noise : Higher hearing thresholds than in the control group at all frequencies. The maximum observed at 12.5 and 20 kHz
  - 6 months after the combined exposure a slight recovery of the threshold recorded, but there was no change in the latency of the ABR. The threshold shift exceeded the summated loss caused by toluene alone and by noise alone, particularly at 3.5 and 6.3 kHz

at 1.6, 3.15, 6.3, 12.5 and 20 kHz

- Test performed 2 at 5 days, 1 and 6 months after the end of exposure

**Mechanism of action****Authors' conclusion**

Toluene alone and noise alone caused a considerable decrease in the auditory sensitivity of rats, particularly at high frequencies. The decrease in auditory sensitivity of rats exposed to toluene followed by noise was greater than the summated effects to toluene alone and noise alone

**Our conclusion**

Supraadditive effects at 1000 ppm toluene for 2 weeks followed by 105 dB SPL noise for 4 weeks in rats

**Toluene****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL :

Remarks : Background noise : 40 dB SPL

**Tests****Test type**

• Effects reported

## Details on test

• Remarks

**Auditory brainstem responses**

- 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

Pulsed pure tones (100 dB SPL) at 1.6, 3.15, 6.3, 12.5 and 20 kHz

- Test performed 2 at 5 days, 1 and 6 months after the end of exposure

**Mechanism of action****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****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

D-TWAEV : 27 mg/kg/d

**Population**

Species : Rat Sprague Dawley

# : 9 - 10

Sex : Males

Age : 5 weeks

**Exposure**

Route : Inhalation

Duration : Toluene : 16 h/d; 7 d/w; 2 w: Noise : 10 h/d; 7 d/w; 4 w - see remarks

C/D reported : 1000 ppm

CSU/DSU :

Ratio : 20

ASM :

BM :

NSM :

NL : 100 dB Leq (10h)

Remarks : Background noise : 40 dB SPL

In the first experiment, the exposure to noise for 4 weeks was immediately followed by the exposure to toluene for 2 weeks

In the second experiment, the exposure to noise for 4 weeks was followed by 4 weeks of rest and then 2 weeks of exposure to toluene

**Tests****Test type**

• Effects reported

## Details on test

• Remarks

**Auditory brainstem responses**

- Toluene : Hearing threshold higher in the exposed group for all the frequencies
- Noise followed immediately by toluene or Noise-Rest-Toluene : Threshold was higher than in the controls for all the frequencies. Sensitivity loss after both exposures was more severe than that recorded after toluene or noise alone at 6.0, 12.5 and 20.0 kHz. The loss did not exceed the summated effect of exposure to noise and toluene alone at all frequencies
- The loss of sensitivity after toluene followed by noise was greater than after the reversed sequence

Pure tones at 1.6, 3.15, 6.3, 12.5 and 20.0 kHz

- Test performed 1-3 weeks after the end of exposure to toluene and to toluene + noise or 3-5 weeks after the end of exposure to noise alone

**Mechanism of action**

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. The effect of sequential exposure to noise and toluene was a simple summation of the effects caused by the two agents alone.

**Our conclusion**

Additive effect in sequential exposure to toluene and noise in rats

**Toluene****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL :

Remarks : Background noise : 40 dB SPL

**Tests****Test type**

• Effects reported

## Details on test

• Remarks

**Auditory brainstem responses**

Pulsed pure tones 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 performed 1-3 weeks after the end of exposure to toluene

**Mechanism of action**

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****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL :

Remarks : Background noise : &lt; 50 dB SPL

**Tests****Test type**

• Effects reported

## Details 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

**Mechanism of action**

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****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL :

Remarks : Background noise : 50 dB(A)

**Tests****Test type**

• Effects reported

## Details 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

**Mechanism of action****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****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL :

Remarks : Background noise : &lt; 50 dB(A)

**Tests****Test type**

• Effects reported

## Details 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)**

- - 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

9 frequencies between 3.0 and 17.9 kHz  
 L1 = 30 to 80 dB  
 L1 = L2+10 dB  
 Ratio f2/f1 = 1.225

- Test performed after 3 and 5 days of exposure and 4 days and 6 weeks after the end of exposure

**Auditory brainstem responses**

- Four 4 days after the end of exposure : substantial threshold shift (30 dB) in the middle frequencies

9 frequencies between 3.0 and 17.9 kHz

- Test performed after 3 and 5 days of exposure and 4 days and 6 weeks after the end of exposure

**Mechanism of action**

---

#### 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****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL : 92 dB SPL ; Octave band noise centered at 8 kHz

Remarks : Background noise : 66 dB SPL

**Tests****Test type**

• Effects reported

## Details on test

• Remarks

**Auditory brainstem responses**

- Toluene : Auditory threshold shift values obtained at 2, 4, 6 and 32 kHz are lower than 5 dB, indicating that low and high frequency regions were spared
- Maximum threshold shift appears at 16 kHz. A statistically significant difference obtained between the threshold shifts of the toluene group and control group at all frequencies except at 4 kHz and 6 kHz
- No difference between permanent and temporary auditory threshold shift for all frequencies except for 4 and 6 kHz, indicating the irreversibility of the loss
- Noise : Permanent and temporary auditory threshold shift between 10 and 16 kHz, and also a large recovery
- Toluene + noise : The peak of the auditory threshold shift at 10-16 kHz. All the differences in threshold shifts between the exposed group and the control group are significant. The auditory deficit induced by the combined exposure exceeded the summated losses caused by toluene alone and by noise alone. A recovery observed between 4 and 10 kHz

## Inferior colliculus potential

clicks at 2, 4, 6, 8, 10, 12, 16, 20, 24 and 32 kHz

- Test performed before exposure, the day after the end of exposure and 6 weeks after the end of exposure

**Light microscopy**

- Toluene : 2 peaks of losses of outer hair cells (OHC) observed : 18-20 kHz (OHC3 = 73%, OHC2 = 42%, OHC1 = 25%) and 4-5 kHz (OHC3 = 87%, OHC2 = 59%, OHC1 = 30 %)
- Frequencies above 30 kHz are relatively well preserved
- Toluene + noise : 2 peaks of losses of OHC observed : 18-24 kHz (OHC3 = 98%, OHC2 = 86%, OHC1 = 60%) and 4-5 kHz (OHC3 = 89%, OHC2 = 74%, OHC1 = 41%)
- Control + noise: No losses significant
- All groups : Inner hair cells appear to be well preserved

- Histology performed 7 - 8 weeks after the end of exposure

**Electron microscopy**

- Toluene : The third row of OHC has completely disappeared. Inner hair cells don't seem to be injured
- Toluene + noise : Loss of outer hair cells is large even for the first row

- Histology performed 7 - 8 weeks after the end of exposure

**Mechanism of action**

#### Authors ' conclusion

Toluene exposure can cause a permanent elevation of the auditory thresholds in rats. There was no recovery of the auditory thresholds . Hearing loss induced by combined exposure exceeds the summated losses caused by toluene and noise itself

---

#### Our conclusion

Supradditive ototoxic effects in rats exposed to 2000 ppm toluene + 92 dB SPL noise for 4 weeks

**Toluene****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL :

Remarks : Background noise : 66 dB SPL

**Tests****Test type**

• Effects reported

## Details on test

• Remarks

**Auditory brainstem responses**

- 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

Clicks at 2, 4, 6, 8, 10, 12, 16, 20, 24 and 32 kHz

- 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%, OHC2 = 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

**Mechanism of action****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**

**Toluene**  
 • TWAEV : 50 ppm | 188 mg/m<sup>3</sup>                      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 :  
 NSM :  
 NL :  
 Remarks : Background noise : 66 dB SPL

<b>Tests</b>	
<b>Test type</b> • Effects reported	Details on test • Remarks
<p><b>Electrocochleography (Compound action potential : CAP)</b></p> <ul style="list-style-type: none"> <li>The greatest permanent threshold (20 dB) obtained at 16 kHz and a significant threshold (12 dB) is also obtained at 3-4 kHz</li> </ul>	<p>Tone bursts at 2, 3, 4, 5, 6, 8, 10, 16, 20 and 32 kHz</p> <ul style="list-style-type: none"> <li>Test performed 6 weeks after the end of exposure</li> </ul>
<p><b>Light microscopy</b></p> <ul style="list-style-type: none"> <li>- Control group : small amount of hair cell loss (&lt; 1%)</li> <li>- 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 %)</li> <li>- The inner hair cells seem to be relatively well preserved</li> <li>- Outer hair cells losses appeared from 20 to 4 kHz</li> </ul>	<ul style="list-style-type: none"> <li>Test performed at 6 - 7 weeks after the end of exposure</li> </ul>
<p><b>Electron microscopy</b></p> <ul style="list-style-type: none"> <li>The largest loss of outer hair cells at the third row and more rarely at the second row</li> </ul>	<ul style="list-style-type: none"> <li>Histology performed at 6 - 7 weeks after the end of exposure</li> </ul>

**Mechanism of action**

**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**

**Toluene**  
 • TWAEV : 50 ppm | 188 mg/m<sup>3</sup>                      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 :  
 NSM :  
 NL :  
 Remarks : Background noise : 66 dB SPL

**Tests**

<b>Test type</b> • Effects reported	Details on test • Remarks
<p><b>Distortion product otoacoustic emissions (DPOAE)</b></p> <ul style="list-style-type: none"> <li>• No effect</li> </ul>	<p>at 2, 3, 4, 5, 6, 8, 10, 12 and 16 kHz                      L1 = 10 to 60 dB                      L1 = L2                      Ratio f1/f2 = 1.20</p> <ul style="list-style-type: none"> <li>• Test performed 1 week before exposure and 20 minutes, 2 and 4 weeks after the end of exposure</li> </ul>
<p><b>Light and electron microscopy</b></p> <ul style="list-style-type: none"> <li>• Control and toluene group revealed a small loss of the hair cells along the organ of Corti (1%)</li> </ul>	<ul style="list-style-type: none"> <li>• Histology performed 4 weeks after the end of exposure</li> </ul>

**Mechanism of action**

**Authors' conclusion**

No ototoxic effect at 600 ppm in rats

**Our conclusion**

No ototoxic effect at 600 ppm in rats

**Toluene****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL :

Remarks : Background noise : 66 dB SPL

**Tests****Test type**

• Effects reported

## Details 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 f<sub>2</sub>/f<sub>1</sub> = 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

**Mechanism of action****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****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

D-TWAEV : 27 mg/kg/d

**Population**

Species : Rat Sprague Dawley

# : C = 12; E1 = 5; E2 = 5; E3 = 5

Sex : Not reported

Age : NR

**Exposure**

Route : Intravenous

Duration : Single dose

C/D reported : E1 = 58.4 µmol ; E2 = 116.2 µmol ; E3 = 229.5 µmol

CSU/DSU :

Ratio : 0.6-2.2

ASM :

BM :

NSM :

NL :

Remarks :

**Tests****Test type**

• Effects reported

## Details on test

• Remarks

**Electrocochleography (Compound action potential : CAP)**

2.6 s burts emitted every 12 s and centered around 4 kHz. Intensity ranging from 65 to 95 dB SPL

- An injection of 116.2 mM toluene dramatically increased the cochlear microphonic potential amplitude (~ 4 dB) in response to an 85-dB SPL noise
- The rise in CMP magnitude was intensity dependent at this concentration, suggesting that toluene could inhibit the auditory efferent system involved in the inner-ear or/and middle-ear acoustic reflexes

- Test performed in the left ear

**Mechanism of action**

Toluene mimics the effects of acetylcholine-receptors antagonists

**Authors' conclusion**

It is likely that toluene might modify the response of protective acoustic reflexes

**Our conclusion**

It is likely that toluene might modify the response of protective acoustic reflexes

**Toluene****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL :

Remarks :

**Tests****Test type**

• Effects reported

## Details on test

• Remarks

**Auditory brainstem responses**

- 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

## Inferior colliculus potential

Clicks at 2, 4, 6, 8, 10, 12, 16, 20, 24 and 32 kHz

- 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

**Mechanism of action**

Cochlea, and more specifically 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****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

D-TWAEV : 27 mg/kg/d

**Population**

Species : Rat Wistar

# : 5 groups of 12 rats

Sex : Males

Age : NR

**Exposure**

Route : Inhalation

Duration : 6 h/d; 5 d/w; 90 d; Noise : 4 h/d; 5 d/w; 90 d

C/D reported : C = 0 ppm ; E1 = 0 ppm ; E2 = 100 ppm ; E3 = 200 ppm ; E4 = 500 ppm

CSU/DSU :

Ratio : 2-10

ASM :

BM :

NSM :

NL : E1 to E4 : Wide-band noise, frequency range : 4-20 kHz, Leq (8 h) = 87 dB SPL

Remarks : - Background noise : 35 dB SPL, 2-48 kHz

**Tests****Test type**

• Effects reported

## Details on test

• Remarks

**Auditory brainstem responses**

at 4096, 8192, 12800 and 16384 Hz

- At 12 kHz, hearing thresholds increased in the group exposed to noise only (E1) and in the group exposed to 500 ppm toluene and to noise (E4)
- At 16 kHz, the hearing thresholds were significantly increased in the group exposed to 500 ppm toluene and noise (E4)

- Test performed before exposure and at 8 weeks after the end of exposure

**Distortion product otoacoustic emissions (DPOAE)**

at 4096, 8192, 12800 and 16384 Hz

L1=60 dB SPL

L2 = L1-10

Ratio f2/f1 = 1.23

- At f2 = 12800 Hz, the distortion products (DP) were significantly lower in the noise-exposed group (E1) and in the group exposed to 500 ppm toluene and noise (E4) compared to the control group
- At f2 = 16384 Hz, the DP differed from the control in the noise-exposed group (E1), and in the groups exposed to noise and 100 (E2) or 500 ppm toluene (E4), but not the 200 ppm (E3) group

- Test performed 8 weeks after the end of exposure

**Mechanism of action****Authors' conclusion**

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 (100 or 200 ppm), the hearing impairment seems to be less severe than in the group exposed only to noise

**Our conclusion**

Toluene does not seem to have additive or synergistic interactions with noise on hearing impairment and low level exposure to toluene could protect from noise-induced hearing impairment

## Toluene

### Toluene

• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

D-TWAEV : 27 mg/kg/d

#### Population

Species : Rat Wistar

# : 9 groups of 12 rats

Sex : Males

Age : NR

#### Exposure

Route : Inhalation

Duration : Toluene and noise : 6 h/d; 10 d

C/D reported : C = 1500 ppm ; E1 and E2 = 0 ppm ; E3 and E4 = 500 ppm ; E5 and E6 = 1000 ppm ; E7 and E8 = 1500 ppm

CSU/DSU :

Ratio : 10-30

ASM :

BM :

NSM :

NL : E1 to E8 : Wide-band noise, frequency range : 4-24 kHz, Leq (8 h) = 90 dB SPL

Remarks : - Background noise : 35 dB SPL, 2-48 kHz

- Simultaneous exposure to toluene and noise

- E1, E3, E5 and E7 were exposed to steady state wide-band noise (WBN)

- E2, E4, E6, E8 were exposed to impulse noise with a peak just above 130 dB SPL

#### Tests

##### Test type

• Effects reported

##### Details on test

• Remarks

##### Auditory brainstem responses

• Exposure to 1500 ppm toluene with no simultaneous noise exposure did not induce notable auditory impairment

at 16384 Hz

• Test performed before exposure and at 2 weeks after the end of exposure

##### Distortion product otoacoustic emissions (DPOAE)

• - At f<sub>2</sub> = 16384 Hz, all groups exposed to noise showed significantly different distortion products (DP) than before exposure  
 - When compared to the groups exposed to noise but not to toluene, no additive or synergistic interactions were found in groups exposed to noise and toluene at 500 or 1000 ppm  
 - A clear interaction was noted between the groups exposed to the steady state WBN and 1500 ppm toluene as well as impulse noise and 1500 ppm toluene when compared to groups exposed to noise only  
 - Exposure to impulse noise induced a considerably higher decrease in DP than did the steady state 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

at 4096, 8192, 12800 and 16384 Hz

L1=60 dB SPL

L2 = L1-10

Ratio f<sub>2</sub>/f<sub>1</sub> = 1.23

#### Mechanism of action

#### Authors' conclusion

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 steady state WBN-exposed groups, but the auditory impairment induced by impulse noise was considerably greater

#### Our conclusion

Impulse noise seems to have a greater impact on hearing impairment than does wide-band noise when exposed to toluene simultaneously

**Toluene****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL :

Remarks :

**Tests****Test type**

• Effects reported

## Details 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 f<sub>2</sub>/f<sub>1</sub> = 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**

- 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

Succinate dehydrogenase (SDH) activity

- Histology performed immediately after exposure for 1 and 4 weeks and 3 days after the end of each exposure

**Mechanism of action****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****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

D-TWAEV : 27 mg/kg/d

**Population**

Species : Worker

# : 51

Sex : Males

Age : 32.5 years (mean)

**Exposure**

Route : Inhalation

Duration : 8.1 years (8 - 13 years)

C/D reported : 75 - 365 ppm (means)

CSU/DSU :

Ratio : 1.5 - 7.3

ASM : Personal pumps with charcoal tubes, histological records

BM :

NSM : Historical records

NL : 88 - 98 dB(A)

Remarks : No hearing protectors were used

**Tests****Test type**

• Effects reported

## Details on test

• Remarks

**Pure tone audiometry**

Pure tones at 0.5, 1, 2, 3, 4, 6 and 8 kHz

- Prevalence of high-frequency loss in the group exposed to noise and toluene simultaneously was considerably higher (53%) than in other groups (noise only : 26% and controls : 8%)
- The adjusted relative risk estimated 4 time greater for the noise group and 11 time greater for noise + toluene group than for unexposed group

**Acoustic reflex**

Pure tones at 0.5, 1 and 2 kHz

- No absence or elevation of reflex among groups
  - Noise + toluene : percentage of abnormal acoustic reflex decay cases was significantly higher than other groups (noise only and controls)
  - Noise only : percentage of recruitment presence cases was significantly higher than other groups (noise + toluene and controls)
- 1) Absence or elevation of the threshold of the reflex
  - 2) Presence of recruitment (reflex triggered at low level)
  - 3) Presence of an abnormal acoustic reflex decay

**Mechanism of action**

Acoustic reflex measurements suggest that the site, as well as the mechanisms underlying the lesions in the group exposed to both agents, are probably different from those in the noise-only exposed group

**Authors' conclusion**

Hearing loss observed in the noise + toluene group was not only more prevalent, but also different from the hearing loss observed in the noise only exposed group

**Our conclusion**

Ototoxic effect more important after simultaneous exposure of toluene + noise to workers than after noise exposure

**Toluene****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL :

Remarks : Background level between 76 and 78 dB SPL

**Tests****Test type**

• Effects reported

## Details on test

• Remarks

**Auditory brainstem responses**

- 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

at 1.6, 3.15, 6.3, 12.5 and 20 kHz

- Test performed 2 days, 3 months and 12 months after the end of exposure

**Mechanism of action**

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****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL : 76 - 78 dB SPL

Remarks :

**Tests****Test type**

• Effects reported

## Details on test

• Remarks

**Auditory brainstem responses**

• Hearing loss at all studied frequencies

at 1.6, 3.15, 6.3, 12.5 and 20.0 kHz

• Test performed 1 week after the end of exposure

**Mechanism of action**

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****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL :

Remarks :

**Tests****Test type**

• Effects reported

## Details on test

• Remarks

**Multisensory conditioned 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 fourth 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 discrimination**

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 substantial effects on the latencies of ABR.
- Amplitude of the 5th component was decreased at 1400 ppm, this effect disappeared 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 peripheral 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 substantial 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

**Mechanism of action****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****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL :

Remarks :

**Tests****Test type**

• Effects reported

## Details on test

• Remarks

**Multisensory conditioned avoidance response task**

- 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' performance

Tone at 20 kHz

- Test performed on the 5th week of exposure, 1 week, 3 week and two months after the end of exposure

**Reflex modification audiometry**

- Hearing loss in the toluene exposed rats increased from 2 dB (at 4 kHz) to 30 dB (at 16 and 20 kHz)

Tone at 4, 8, 12, 16 and 20 kHz

- Test performed 2.5 months after the end of exposure

**Intensity discrimination**

- No difference between control and toluene exposed rats in their abilities to learn the 4 kHz tone intensity

at 4 kHz

- Test performed 4 weeks after the end of exposure

**Mechanism of action****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****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL :

Remarks :

**Tests****Test type**

• Effects reported

## Details on test

• Remarks

**Multisensory conditioned avoidance response task**

at 4 and 20 kHz

- No significant effects of toluene on performance 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

**Mechanism of action****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****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL :

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

**Tests****Test type**

• Effects reported

## Details on test

• Remarks

**Multisensory conditioned avoidance response task**

- 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

Tone at 4, 8, 12, 16 and 20 kHz

- Test performed weekly or biweekly after the exposure started

**Reflex modification audiometry**

- 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

Tone at 4, 8, 12, 16 or 20 kHz

- Test performed 2 weeks after the end of exposure

**Auditory brainstem responses**

- 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 over the 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

Tone pips at 4, 8 and 16 kHz

- Test performed weekly during exposure and 3 weeks after the end of exposure

**Mechanism of action****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****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL :

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

## Details on test

• Remarks

**Multisensory conditioned avoidance response task**

• 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

Pure tone at 4 and 20 kHz

• Test performed after 7 and 14 days of exposure and 5 days and 3 months after the end of exposure

**Reflex modification audiometry**

• - 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

Tone at 4, 8, 12, 16 and 20 kHz

• Test performed 2 weeks after the end of exposure

**Auditory brainstem responses**

• - 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

Tone pips at 4, 8 and 16 kHz

• Test performed 2 weeks after the end of exposure

**Mechanism of action****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****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL :

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

## Details on test

• Remarks

**Multisensory conditioned 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

**Mechanism of action****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****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL :

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

## Details on test

• Remarks

**Multisensory conditioned avoidance response task**

- No difference among groups performance at 4 kHz.
- Markedly impaired exposed groups performance at 20 kHz, intermittently (4000 ppm - 8 h) toluene exposed group was less impaired than groups exposed continuously (1500 ppm - 14 h and 2000 ppm - 8 h)

Tone at 4 and 20 kHz

- Test performed 22 days after the end of exposure

**Reflex modification audiometry**

- Response threshold elevations in all exposed groups at 12 kHz and above.
- Intermittently (4000 ppm - 8 h) toluene exposed group was less impaired than groups exposed continuously (1500 ppm - 14 h and 2000 ppm - 8 h)

Tone at 4, 8, 12, 16 and 20 kHz

- Test performed 5 weeks after the end of exposure

**Auditory brainstem responses**

- No difference among exposed groups at 4 kHz
- Threshold elevation of all exposed groups at 8 and 16 kHz, intermittently (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 intermittently (4000 ppm - 8 h) toluene exposed group than groups exposed continuously (1500 ppm - 14 h and 2000 ppm - 8 h)

Tone pips at 4, 8 and 16 kHz

- Test performed 5 weeks after the end of exposure

**Mechanism of action****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****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL :

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

**Tests****Test type**

• Effects reported

## Details on test

• Remarks

**Auditory brainstem responses**

- 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

Tone pips at 16 kHz

- 1, 3 and 5 weeks after the end of exposure

**Multisensory conditioned avoidance response task**

- No difference among groups at 4 kHz.
- Only rat expose to 2000 ppm during 3 days performed more poorly than controls at 20 kHz

Tone at 4 and 20 kHz

- Test performed 6 weeks after the end of exposure

**Mechanism of action****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 functionally manifest

**Our conclusion**

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

**Toluene****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL :

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

**Tests****Test type**

• Effects reported

## Details on test

• Remarks

**Multisensory conditioned avoidance response task**

- No difference among groups at 4 kHz.
- Impaired performance in group exposed to 2000 ppm during 3 days at 20 kHz

Tone at 4 and 20 kHz

- Test performed from 30 to 35 days after the end of exposure

**Reflex modification audiometry**

- Impaired response threshold only in rats exposed to 2000 ppm during 3 days at 12 kHz and above

Tone at 4, 8, 12, 16 and 20 kHz

- Test performed 6 weeks after the end of exposure

**Mechanism of action****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****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL :

Remarks :

**Tests****Test type**

• Effects reported

Details on test

• Remarks

**Multisensory conditioned avoidance response task**

Pure tones at 4-20 kHz

- Rats exposed to toluene performed the test more poorly at 20 kHz (high intensity) than control group

**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.

**Mechanism of action****Authors' conclusion**

Hearing loss caused by exposure to toluene at high frequencies

**Our conclusion**

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

**Toluene****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL :

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

**Tests****Test type**

• Effects reported

## Details on test

• Remarks

**Auditory brainstem responses**

• Hearing deficit in toluene exposed rats

Tone pips at 16 kHz

• Test performed 1 week after the end of exposure

**Mechanism of action**

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****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL :

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

## Details on test

• Remarks

**Multisensory conditioned avoidance response task**

- No differences among groups at 4 kHz.
- Performance impaired in rats exposed to toluene at 20 kHz

Tone at 4 and 20 kHz

- Test performed 2 weeks after the end of exposure

**Reflex modification audiometry**

- Toluene caused a decrease in auditory sensitivity at all frequencies above 4 kHz

Tone at 4, 8, 12, 16 and 20 kHz

- Test performed 4 weeks after the end of exposure

**Mechanism of action****Authors' conclusion**

No conclusion about ototoxicity

**Our conclusion**

Ototoxic effect at 2600 ppm in young rats

**Toluene****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL :

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

## Details on test

• Remarks

**Multisensory conditioned avoidance response task**

- No significant differences among groups at any time during the test at 4 kHz
- Impairment performance at 20 kHz

Tone at 4 and 20 kHz

- Test performed 2 weeks after the end of exposure

**Reflex modification audiometry**

- Impairments at 8 and 16 kHz were highly significant

Tone at 4, 8 and 16 kHz

- Test performed 2 weeks after the end of exposure

**Mechanism of action****Authors' conclusion**

No conclusion about ototoxicity

**Our conclusion**

Ototoxic effect at 2200 ppm in young rats

**Toluene****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL :

Remarks :

**Tests****Test type**

• Effects reported

## Details on test

• Remarks

**Auditory brainstem responses**

- Effects are most pronounced at mid to high frequencies, and were clearest with the 16 kHz stimulus
- Amplitudes were significantly smaller than in control group

Tone pips at 4, 8 and 16 kHz

- Test performed 2 weeks after the end of exposure

**Multisensory conditioned avoidance response task**

- Slight impairment at 4 kHz progressing to a marked impairment at 16 kHz

Tone at 4 and 16 kHz

- Test performed 12 weeks after the end of exposure

**Mechanism of action****Authors' conclusion**

No conclusion about ototoxicity

**Our conclusion**

Ototoxic effect at 1200 ppm in rats exposed for 9 weeks

**Toluene****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL :

Remarks : Background noise : 60 to 80 dB

**Tests****Test type**

• Effects reported

## Details 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

**Mechanism of action****Authors' conclusion**

Loss of auditory sensitivity

**Our conclusion**

Ototoxic effect at 1200 ppm in young rats

**Toluene****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL :

Remarks :

**Tests****Test type**

• Effects reported

## Details 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

**Mechanism of action****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****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

D-TWAEV : 27 mg/kg/d

**Population**

Species : Worker

# : 333

Sex : Males

Age : 38.1 years (mean)

**Exposure**

Route : Inhalation

Duration : 13.4 years (mean)

C/D reported : 10 or 45 ppm

CSU/DSU :

Ratio : 0.2 - 1

ASM : Active samplers, historic data

BM :

NSM :

NL : 82 dB(A) stationary sound meter + historic data

Remarks : Toluene and noise levels are mean lifetime weighted average exposures

**Tests**

- Same experiment as Schaper 2008
- Non exposure to noise before testing could be too short
- Pure tone audiometry was performed in different testing conditions (with or without sound proof booth) that can act upon the results

**Test type**

- Effects reported

## Details on test

- Remarks

**Pure tone audiometry**

Pure tone at 0.1, 0.3, 0.5, 0.8, 1, 1.5, 2, 3, 4, 6, 7 et 12 KHz

- Exposure to toluene and the combination of toluene + noise were not associated with significant changes in the auditory thresholds

- At least 3 hours of exposure-free time before examination

**Mechanism of action****Authors' conclusion**

Threshold level for developing a hearing loss due to toluene exposure might be above the actual limit, 50 ppm

**Our conclusion**

No ototoxic effect and no interaction with the noise at &lt; 50 ppm

**Toluene****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

D-TWAEV : 27 mg/kg/d

**Population**

Species : Worker

# : 333

Sex : Males

Age : 38.1 years (mean)

**Exposure**

Route : Inhalation

Duration : 13.4 years (mean)

C/D reported : 10 or 45 ppm

CSU/DSU :

Ratio : 0.2 - 1

ASM : Active samplers, historic data

BM :

NSM :

NL : 82 dB(A) stationary sound meter + historic data

Remarks : Toluene and noise levels are mean lifetime weighted average exposures

**Tests**

- Same experiment as Schaper 2003
- Non exposure to noise before testing could be too short
- Pure tone audiometry was performed in different testing conditions (with or without sound proof booth) that can act upon the results

**Test type**

- Effects reported

## Details on test

- Remarks

**Pure tone audiometry**

Pure tone at 0.1, 0.3, 0.5, 0.8, 1, 1.5, 2, 3, 4, 6, 7 et 12 KHz

- Exposure to toluene and the combination of toluene + noise were not associated with significant changes in the auditory thresholds
- At least 3 hours of exposure-free time before examination

**Mechanism of action****Authors' conclusion**

Threshold level for developing a hearing loss due to toluene exposure might be above the actual limit, 50 ppm

**Our conclusion**

No ototoxic effect and no interaction with the noise at &lt; 50 ppm

**Toluene****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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 :

NSM :

NL :

Remarks : Background noise : &lt; 60 dB SPL

**Tests****Test type**

• Effects reported

## Details on test

• Remarks

**Auditory brainstem responses**

• 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

Tone bursts at 0.5, 1, 2, 4, 8, 16 and 32 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

**Mechanism of action****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**

**Toluene**

• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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)

NSM :

NL : NR

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

Details on test

• Remarks

**Auditory brainstem responses**

• Prolongation of latency and diminution of amplitude of all brainstem components.

Clicks

• Test performed after weekend before shift

**Mechanism of action**

**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****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

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)

NSM :

NL :

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

Details 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 decreased with the length of exposure
- No correlation between the amplitudes of examined waves and length of exposure

- Test performed after weekend before shift

**Mechanism of action****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****Toluene**• TWAEV : 50 ppm | 188 mg/m<sup>3</sup>

D-TWAEV : 27 mg/kg/d

**Population**

Species : Rat Long Evans

# : C = 8; E = 8

Sex : Males

Age : NR

**Exposure**

Route : Inhalation

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

C/D reported : 1750 ppm

CSU/DSU :

Ratio : 35

ASM :

BM : Hippuric acid : C = ~1 g/g creatinine ; E = 11 ± 1.1 g/g creatinine ; Benzylmercapturic acids : C = 0 ; E = 137.1 ± 43.5 mg/g creatinine

NSM :

NL :

Remarks :

**Tests****Test type**

• Effects reported

## Details on test

• Remarks

**Auditory brainstem responses**

Pure tones at 2, 4, 8, 12, 16, 20 and 35 kHz

- Threshold shifts were statistically significant at all frequencies (maximal value of 7 dB at 16 kHz)

- Performed before and 4 weeks post exposure

**Light microscopy**

- - Largest losses in the third row of outer hair cells (OHC), the second row was less damaged, but more than the first one
- Severe losses located at frequencies ranging from 2 to 30 kHz. Two peaks were noticeable at 6 and 20 kHz
- Inner hair cells (IHC) and frequencies above 30 kHz were relatively well preserved

- Performed 4 weeks post exposure

**Mechanism of action****Authors' conclusion**

Toluene-induced hearing loss is not strongly mediated by the production of its cysteine S-conjugate metabolites. The parent molecule seems to be responsible for the ototoxicity process

**Our conclusion**

Toluene-induced hearing loss is not strongly mediated by the production of its cysteine S-conjugate metabolites. The parent molecule seems to be responsible for the ototoxicity process

## BIBLIOGRAPHY

- Abbate 1993** Abbate, C., et al. (1993) Neurotoxicity induced by exposure to toluene. An electrophysiologic study. *Int Arch Occup Environ Health*. 64(6): 389-92.
- Brandt-Lassen 2000** Brandt-Lassen, R., S. P. Lund, et al. (2000). "Rats exposed to Toluene and Noise may develop Loss of Auditory Sensitivity due to Synergistic Interaction." *Noise & Health* 3(9): 33-44.
- Campo 1993** Campo, P., et al. (1993) No interaction between noise and toluene on cochlea in the guinea pig. *Acta Acustica*. 1: 35-42.
- Campo 1997** Campo, P., et al. (1997) Toluene-induced hearing loss: a mid-frequency location of the cochlear lesions. *Neurotoxicol Teratol*. 19(2): 129-40.
- Campo 1998** Campo, P., et al. (1998) Combined effects of simultaneous exposure to toluene and ethanol on auditory function in rats. *Neurotoxicol Teratol*. 20(3): 321-32.
- Campo 2008** Campo, P., et al. (2008). Toluene-induced hearing loss in phenobarbital treated rats. *Neurotoxicol Teratol*, 30(1), 46-54.
- Chang 2006** Chang, S. J., C. J. Chen, et al. (2006). Hearing loss in workers exposed to toluene and noise. *Environ Health Perspect* 114(8): 1283-6.
- Crofton 1994** Crofton, K.M., et al. (1994) Solvent-induced ototoxicity in rats: an atypical selective mid-frequency hearing deficit. *Hear Res*. 80(1): 25-30.
- Davis 2002** Davis, R.R., et al. (2002) Susceptibility to the ototoxic properties of toluene is species specific. *Hear Res*. 166(1-2): 24-32.
- Gagnaire 2005** Gagnaire, F., et al. (2005) Relative ototoxicity of 21 aromatic solvents. *Arch Toxicol*. 79(6): 346-54.
- Johnson 1988** Johnson, A.C., et al. (1988) Effect of interaction between noise and toluene on auditory function in the rat. *Acta Otolaryngol*. 105(1-2): 56-63.
- Johnson 1990** Johnson, A.C., et al. (1990) Sequence of exposure to noise and toluene can determine loss of auditory sensitivity in the rat. *Acta Otolaryngol*. 109(1-2): 34-40.
- Johnson 1992** Johnson, A.C. (1992) Auditory sensitivity in rats exposed to toluene and/or acetyl salicylic acid. *Neuroreport*. 3(12): 1141-4.
- Johnson 1994a** Johnson, A.C., et al. (1994) Toluene exposure affects the functional activity of the outer hair cells. *Hear Res*. 72(1-2): 189-96.
- Johnson 1994b** Johnson, A.C., et al. (1994) Progressive hair cell loss induced by toluene exposure. *Hear Res*. 75(1-2): 201-8.
- Johnson 1995** Johnson, A. C. and P. R. Nysten (1995). Effects of industrial solvents on hearing. *Occup Med* 10(3): 623-40.
- Lataye 1997** Lataye, R., et al. (1997) Combined effects of a simultaneous exposure to noise and toluene on hearing function. *Neurotoxicol Teratol*. 19(5): 373-82.
- Lataye 1999** Lataye, R., et al. (1999) Toluene ototoxicity in rats: assessment of the frequency of hearing deficit by electrocochleography. *Neurotoxicol Teratol*. 21(3): 267-76.
- Lataye 2003** Lataye, R., et al. (2003) Solvent ototoxicity in the rat and guinea pig. *Neurotoxicol Teratol*. 25(1): 39-50.
- Lataye 2007** Lataye, R., et al. (2007). Increase in cochlear microphonic potential after toluene administration. *Hear Res*, 230(1-2), 34-42.
- Loquet 1999** Loquet, G., et al. (1999) Comparison of toluene-induced and styrene-induced hearing losses. *Neurotoxicol Teratol*. 21(6): 689-97.
- Lund 2008** Lund, S. P., et al. (2008). Hazards to hearing from combined exposure to toluene and noise in rats. *Int J Occup Med Environ Health*, 21(1), 47-57.
- McWilliams 2000** McWilliams, M.L., et al. (2000) Low-level toluene disrupts auditory function in guinea pigs. *Toxicol Appl Pharmacol*. 167(1): 18-29.
- Morata 1993** Morata, T.C., et al. (1993) Effects of occupational exposure to organic solvents and noise on hearing. *Scand J Work Environ Health*. 19(4): 245-54.
- Morata 1994** Morata, T. C., D. E. Dunn, et al. (1994). Occupational exposure to noise and ototoxic organic solvents. *Arch of Environ Health* 49(5): 359-365.
- Nylén 1994a** Nysten, P., et al. (1994) Function of the auditory and visual systems, and of peripheral nerve, in rats after long-term combined exposure to n-hexane and methylated benzene derivatives. I. Toluene. *Pharmacol Toxicol*. 74(2): 116-23.
- Nysten 1995** Nysten, P., et al. (1995) Function of the auditory system, the visual system, and peripheral nerve and long-term combined exposure to toluene and ethanol in rats. *Pharmacol Toxicol*. 76(2): 107-11.
- Pryor 1983a** Pryor, G.T., et al. (1983) Neurobehavioral effects of subchronic exposure of weanling rats to toluene or hexane. *Neurobehav Toxicol Teratol*. 5(1): 47-52.
- Pryor 1983b** Pryor, G.T., et al. (1983) Transient cognitive deficits and high-frequency hearing loss in weanling rats exposed to toluene. *Neurobehav Toxicol Teratol*. 5(1): 53-7.
- Pryor 1984a** Pryor, G.T., et al. (1984) Hearing loss in rats first exposed to toluene as weanlings or as young adults. *Neurobehav Toxicol Teratol*. 6(2): 111-9.

- Pryor 1984b** Pryor, G.T., et al. (1984) Factors affecting toluene-induced ototoxicity in rats. *Neurobehav Toxicol Teratol.* 6(3): 223-38.
- Pryor 1985** Pryor, G.T., et al. (1985) Interactions between toluene and alcohol. *Pharmacol Biochem Behav.* 23(3): 401-10.
- Pryor 1991a** Pryor, G., et al. (1991) The hearing loss associated with exposure to toluene is not caused by a metabolite. *Brain Res Bull.* 27(1): 109-13.
- Pryor 1991b** Pryor, G.T. (1991) A toluene-induced motor syndrome in rats resembling that seen in some human solvent abusers. *Neurotoxicol Teratol.* 13(4): 387-400.
- Pryor 1992** Pryor, G.T., et al. (1992) Interactive effects of toluene and hexane on behavior and neurophysiologic responses in Fischer-344 rats. *Neurotoxicol.* 13(1): 225-34.
- Rebert 1983b** Rebert, C.S., et al. (1983) Toluene-induced hearing loss in rats evidenced by the brainstem auditory-evoked response. *Neurobehav Toxicol Teratol.* 5(1): 59-62.
- Rebert 1989** Rebert, C.S., et al. (1989) Multimodal effects of acute exposure to toluene evidenced by sensory-evoked potentials from Fischer-344 rats. *Pharmacol Biochem Behav.* 32(3): 757-68.
- Ryback 1992** Ryback, L. P. (1992). Hearing: The effects of chemicals. *Otolaryngol. Head Neck Surg.* 106: 677-686.
- Schaper 2003** Schaper, M., et al. (2003) Occupational toluene exposure and auditory function: results from a follow-up study. *Ann Occup Hyg.* 47(6): 493-502.
- Schaper 2008** Schaper, M., A. Seeber, et al. (2008). "The effects of toluene plus noise on hearing thresholds: an evaluation based on repeated measurements in the German printing industry." *Int J Occup Med Environ Health* 21(3): 191-200.
- Sullivan 1988** Sullivan, M.J., et al. (1988) Ototoxicity of toluene in rats. *Neurotoxicol Teratol.* 10: 525-530.
- Vrca 1996** Vrca, A., et al. (1996) Brainstem auditory evoked potentials in individuals exposed to long-term low concentrations of toluene. *Am J Ind Med.* 30(1): 62-6.
- Vrca 1997** Vrca, A., et al. (1997) Brain stem evoked potentials and visual evoked potentials in relation to the length of occupational exposure to low levels of toluene. *Acta Med Croatica.* 51(4-5): 215-9.
- Waniusiow 2008** Waniusiow, D., et al. (2008). Toluene-induced hearing loss in acivicin-treated rats. *Neurotoxicol Teratol*, 30(3), 154-160.
- Witter 1980** Witter, H. L., R. C. Deka, et al. (1980). Effects of prestimulatory carbogen inhalation on noise-induced temporary threshold shifts in humans and chinchilla. *Am J Otol* 1(4): 227-32.