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Ototoxic effects of industrial chemicals**

Styrene (monomer)

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Introduction

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

Methods

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

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

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

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

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

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

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

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

Indication of ototoxicity:

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

General conclusion about ototoxicity:

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

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Abbreviations

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

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

Ceiling : Ceiling exposure [limit] value in Quebec

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

STEV : Short term exposure [limit] value in Quebec

C/D reported : Reported concentration or reported dose

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

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

ASM : Air sampling method

BM : Biological monitoring results

Styrene (monomer)

Occupational exposure limits: TWAEV: 213 mg/m³ (50 ppm). STEV: 426 mg/m³ (100 ppm)

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

ANALYSIS OF ANIMAL STUDIES

There are numerous studies demonstrating that styrene by inhalation is ototoxic in laboratory animals. Susceptibility to solvents is species dependent. Styrene causes a permanent damage to auditory system mainly of the rat. The auditory system of the guinea-pig is not injured by styrene as much as that of the rat (Lataye 2003, Fechter 1993). Styrene damages hair cells in the cochleae of rats, although the spiral ganglions are not spared. The important characteristic of styrene is higher susceptibility of outer hair cells compared to inner hair cells (Lataye 2003). The effect is dose-related. Short-term styrene exposure seems not to damage the hair cells; long-term exposure does.. For chronic exposure, higher styrene concentrations lead to greater hair cell mortality. The mid-frequency hearing loss is most often reported. Morphologic examination determined a corresponding loss of OHC in the middle frequency region of the rat cochlea (Yano 1992). Hair cell deaths are not closely related to hearing threshold shifts in the rat.

There is no styrene induced hearing loss for chronic exposure of rats up to about 600 ppm. Concentrations greater than 600 ppm show threshold shifts directly related to styrene concentration.

ANALYSIS OF HUMAN STUDIES

Recently, Lawton et al. (Lawton 2006) reviewed a number of occupational investigations of the exposure and relation between inhaled styrene and hearing loss. Our conclusions are in agreement with theirs. Eight studies used threshold differences to differentiate between styrene exposed and non-exposed workers. Of the seven studies, three found no evidence to support an effect of styrene on the thresholds of hearing (Möller 1990,Sass-Kortskar 1995, Calabrese 1996). Two studies were limited to styrene effects in the very high frequency region (Muijser 1988, Morioka 1999) and in one of which the workers were exposed also to other solvents (Morioka 1999). In contrast, three studies report styrene-induced hearing losses (Slivinska 2003, Morata 2002, Sliwinska 2005). However, no dose-response relationship was found in these studies.

CONCLUSION

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

Styrene [100-42-5]

Styrene (monomer)
• TWAEV : 50 ppm | 213 mg/m³ D-TWAEV : 30 mg/kg/d

Population

Species : Worker # : 20 Sex : Not reported

Age : 32 (24-52) years

Exposure

Route : Inhalation

Duration : 7.6 (2 - 23) years

C/D reported : 14 – 416 mg/m³ (average over 8 h)

CSU/DSU :

Ratio : 0.06 - 2

ASM : Passive absorption badges 8 hours

BM : Mandelic acid + phenylglyoxylic acid : 81-943 mg/g creatinine

Remarks : Urine collected before the start of work on the next day

Tests

9 subjects also tested after a recovery period of 3 weeks without exposure. Results compared with reference values

Test type • Effects reported	Precisions on test • Remarks
Pure tone audiometry	
• No abnormalities	
Tympanometry	
• No abnormalities	
Acoustic reflex	
• No abnormalities	
Auditory brainstem responses	Clicks of 115 dB SPL
• No abnormalities	

Action mechanism

Authors' conclusion

Auditory system does not seem to be affected by the styrene at the exposure levels reported

Our conclusion

Auditory system does not seem to be affected by the styrene at the exposure levels reported

Styrene [100-42-5]

Styrene (monomer)
• TWAEV : 50 ppm | 213 mg/m³ D-TWAEV : 30 mg/kg/d

Population

Species : Rat Long Evans # : 12 - 16 Sex : Males

Age :

Exposure

Route : Inhalation

Duration : 6 h/d; 5 d/w; 1 to 4 w

C/D reported : 1000 ppm

CSU/DSU :

Ratio : 20

ASM :

BM :

Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Clicks at 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, and 32 kHz
• - Hearing loss of 35-40 dB at 16 kHz - Hearing loss of 20 dB at 4-5 kHz - No effect of the exposure duration	• Test performed immediately and 6 weeks after the end of exposure
Light and electron microscopy	Cochleogram
• - Outer hair cell loss observed throughout the entire range of damaged frequencies - Toxic process continued even after the end of exposure - Supporting cells are the first targets. Then, outer hair cells of the third row (OHC3) are disrupted followed successively by OHC2 and OHC1 from the middle (20 kHz) to the upper turn (4 kHz) of the cochlea	• Histology performed immediately and 6 weeks after the end of exposure

Action mechanism

Disorganization of the membranous structures could be the starting point for the cochlear injury induced by styrene

Authors' conclusion

Ototoxic effect at 1000 ppm in rats

Our conclusion

Ototoxic effect at 1000 ppm in rats

Styrene [100-42-5]

Styrene (monomer)
• TWAEV : 50 ppm | 213 mg/m³ D-TWAEV : 30 mg/kg/d

Population

Species : Rat Long Evans # : E1 = 13; E2 = 14 Sex : Males

Age : E1 = 3 months; E2 = 24 - 26 months

Exposure

Route : Inhalation

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

C/D reported : 700 ppm

CSU/DSU :

Ratio : 14

ASM :

BM :

Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Clicks at 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, and 32 kHz
• - Significant hearing loss in young rats only. Young animals showed threshold shifts only at high frequencies. - 15 dB hearing loss was located in the region of 16-20 kHz immediately after the end and 6 week after exposure	• Audiometry tests performed prior to styrene exposure, at the end of exposure and 6 weeks after exposure
Light and electron microscopy	
• - Aged rats had minimal outer hair cell loss. - Young rats showed significant outer hair cell loss, particularly in the third row	• Histology performed 6 weeks after the end of exposure

Action mechanism

Authors' conclusion

Ototoxic effect at 700 ppm in rats. There is an influence of age on styrene –induced threshold shift and hair cell loss in rats

Our conclusion

Ototoxic effect at 700 ppm in rats. There is an influence of age on styrene –induced threshold shift and hair cell loss in rats

Styrene [100-42-5]

Styrene (monomer)
• TWAEV : 50 ppm | 213 mg/m³ D-TWAEV : 30 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 : 1600 ppm

CSU/DSU :

Ratio : 32

ASM :

BM :

Remarks :

Tests

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

Action mechanism

Authors' conclusion

Mid-frequency hearing loss at 1600 ppm in rats

Our conclusion

Ototoxic effect at 1600 ppm in rats

Styrene [100-42-5]

Styrene (monomer)
• TWAEV : 50 ppm | 213 mg/m³ D-TWAEV : 30 mg/kg/d

Population

Species : Guinea pig # : 3 Sex : Males
Age :

Exposure

Route : Intraperitoneal
Duration : 2 doses
C/D reported : 1.5 mL
CSU/DSU : 2813 mg/kg/d
Ratio : 94
ASM :
BM :
Remarks : 2 injections of 0.75 mL each spaced 30 minutes apart

Tests

Test type • Effects reported	Precisions on test • Remarks
Electrocochleography	2 à 40 kHz, 11 frequency
• No adverse effects	• Test performed 30 minutes after the end of exposure

Action mechanism

Authors' conclusion

No ototoxic effect at the single dose of 2813 mg/kg/d in guinea pigs

Our conclusion

No ototoxic effect at the single dose of 2813 mg/kg/d in guinea pigs

Styrene [100-42-5]

Styrene (monomer)
• TWAEV : 50 ppm | 213 mg/m³ D-TWAEV : 30 mg/kg/d

Population

Species : Guinea pig # : 5 Sex : Males

Age :

Exposure

Route : Inhalation

Duration : 7 h

C/D reported : 500 ppm

CSU/DSU :

Ratio : 10

ASM :

BM :

Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Electrocochleography	2 à 40 kHz, 11 frequency
• No threshold shift	• Test performed 18 to 22 hours after the end of exposure

Action mechanism

Authors' conclusion

No ototoxic effect after exposure of 7 hours at 500 ppm in guinea pigs

Our conclusion

No ototoxic effect after 7 hour exposure to 500 ppm in guinea pigs

Styrene [100-42-5]

Styrene (monomer)
• TWAEV : 50 ppm | 213 mg/m³ D-TWAEV : 30 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 : 882 mg/kg/d

Ratio : 29

ASM :

BM :

Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Light and electron microscopy	Cochleogram
• - Almost complete loss in the three rows of outer hair cells in the medium and apical parts of the cochlea - About 50 % of the animals had losses in the basal part of the cochlea - Inner hair cell losses in some animals	• Histology performed 10 days after the end of exposure

Action mechanism

Authors' conclusion

High ototoxic effect of styrene in rats

Our conclusion

Ototoxic effect of styrene after exposure by oral way in rats

Styrene [100-42-5]

Styrene (monomer)
• TWAEV : 50 ppm | 213 mg/m³ D-TWAEV : 30 mg/kg/d

Population

Species : Worker # : C = 78; E = 89 Sex : Males and females

Age : C = 45 (26-62); E = 43 (21-62) years

Exposure

Route : Inhalation

Duration : C = 17 (1-39); E = 43(21-62) years

C/D reported : 16 (0.2 - 96) mg/m³

CSU/DSU :

Ratio : 0.08

ASM : Passive absorption badges

BM : Mandelic acid: 0.9 mmol/g creatinine

Remarks : Urine collected over 24h, beginning with the start of the work shift

Tests

Test type • Effects reported	Precisions on test • Remarks
Pure tone audiometry	at 1, 2, 3, 4, 6 and 8 kHz
• Higher threshold at 2-6 kHz	
Psycho-acoustical modulation transfer function	at 4 kHz
• No abnormalities	
Distortion product otoacoustic emissions (DPOAE)	
• No abnormalities	
Cortical auditory evoked potentials	
• A significant effect on the latency of the cortical evoked response	
Interrupted speech	
• A significant lower score	
Speech recognition in noise	
• Significant abnormalities	

Action mechanism

Authors' conclusion

Occupational exposure to styrene affects both the central and the peripheral auditory system even when the noise levels are low (mean of 16 mg/m³)

Our conclusion

Auditory system seems to be affected by the styrene at the low exposure concentrations

Styrene [100-42-5]

Styrene (monomer)
• TWAEV : 50 ppm | 213 mg/m³ D-TWAEV : 30 mg/kg/d

Population

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

Age :

Exposure

Route : Inhalation

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

C/D reported : 750 ppm

CSU/DSU :

Ratio : 15

ASM :

BM :

Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Clicks at 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, and 32 kHz
• - Hearing losses appeared between 16 and 20 kHz, with a peak of 13.5 dB at 20 kHz at the end of exposure - Six weeks after exposure, the recovery was significant from 2 to 20 kHz	• Audiometry tests performed prior to styrene exposure, the day following the end of exposure and 6 weeks after exposure
Light and electron microscopy	
• Outer hair cell losses were greatest in the third row, followed by the second and the first row. The largest losses located at the third row, 86 % at 20 kHz and 70 % at 4 kHz	• Histology performed 6 weeks after the end of exposure

Action mechanism

Exact mechanism of styrene toxicity is not understood, it is likely that styrene impairs preferentially the basal pole of outer hair cells and/or the supporting cells by tissue contamination. A possible route to reach the OHC is the lipid-rich content of the membranes of the different cells of the organ of Corti

Authors' conclusion

LOAEL of 750 ppm for ototoxic effect in rats

Our conclusion

LOAEL of 750 ppm for ototoxic effect in rats

Styrene [100-42-5]

Styrene (monomer)
• TWAEV : 50 ppm | 213 mg/m³ D-TWAEV : 30 mg/kg/d

Population

Species : Rat Long Evans # : 8 Sex : Males

Age :

Exposure

Route : Inhalation

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

C/D reported : 750, 1000 and 1500 ppm

CSU/DSU :

Ratio : 15 - 30

ASM :

BM :

Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Clicks at 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, and 32 kHz
• - 1500 ppm : hearing losses appeared in all frequencies with a peak of 54.3 dB at 12 kHz - 1000 ppm : hearing losses appeared in all frequencies with a peak of 34 dB at 12–16 kHz - 750 ppm : hearing losses appeared between 16 and 24 kHz, with a peak of 10 dB at 20 kHz	• Audiometry tests performed prior to styrene exposure and 6 weeks after the end of exposure
Light and electron microscopy	
• - Outer hair cell losses were greatest in the third row, followed by the second and the first row in all doses - Inner hair cell loss observed only at 1500 ppm, where up to 35 % of losses were observed in the high frequencies - Neurons of the spiral ganglion were injured with significant losses at 1000 and 1500 ppm in the median spiral ganglion	• Histology performed 6 weeks after the end of exposure

Action mechanism

Authors' conclusion

LOAEL of 750 ppm for ototoxic effect in rats

Our conclusion

LOAEL of 750 ppm for ototoxic effect in rats

Styrene [100-42-5]

Styrene (monomer)
• TWAEV : 50 ppm | 213 mg/m³ D-TWAEV : 30 mg/kg/d

Population

Species : Rat Long Evans # : 6 Sex : Males

Age :

Exposure

Route : Inhalation

Duration : 6 h/d; 5 d

C/D reported : 1000 ppm

CSU/DSU :

Ratio : 20

ASM :

BM :

Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Distortion product otoacoustic emissions (DPOAE)	at 2, 3, 4, 5, 6, 8, 10, 12 and 16 kHz L1 = 10 to 60 dB L1 = L2 Ratio f2/f1 = 1.20
• Amplitudes depressed at 2 and 4 weeks post-exposure	• Test performed 1 week before exposure, 20 minutes, 2 and 4 weeks after the end of exposure
Light and electron microscopy	
• - Outer hair cells of the third row (OHC3) were disrupted, followed successively by OHC2 and OHC1 - Inner hair cells were relatively well preserved	• Histology performed 4 weeks after the end of exposure

Action mechanism

Authors' conclusion

Ototoxic effect at 1000 ppm in rats

Our conclusion

Ototoxic effect at 1000 ppm in rats

Styrene [100-42-5]

Styrene (monomer)
• TWAEV : 50 ppm | 213 mg/m³ D-TWAEV : 30 mg/kg/d

Population

Species : Guinea pig # : 5 Sex : Males
Age :

Exposure

Route : Inhalation
Duration : 6 h/d; 5 d
C/D reported : 1000 ppm
CSU/DSU :
Ratio : 20
ASM :
BM :
Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Distortion product otoacoustic emissions (DPOAE)	at 2, 3, 4, 5, 6, 8, 10, 12 and 16 kHz L1 = 10 to 60 dB L1 = L2 Ratio f2/f1 = 1.20
• No changes in amplitude nor in otoacoustic emissions	• Test performed 1 week before exposure, 20 minutes, 2 and 4 weeks after the end of exposure
Light and electron microscopy	Cochleogram
• No permanent hair cell loss	• Histology performed 4 weeks after the end of exposure

Action mechanism

Authors' conclusion

No ototoxic effect at 1000 ppm in guinea pigs. Guinea pigs appear to be resistant to styrene ototoxic effect

Our conclusion

No ototoxic effect demonstrated at 1000 ppm in guinea pigs. Guinea pigs appear to be resistant to styrene ototoxic effect

Styrene [100-42-5]

Styrene (monomer)
• TWAEV : 50 ppm | 213 mg/m³ D-TWAEV : 30 mg/kg/d

Population

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

Age :

Exposure

Route : Inhalation

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

C/D reported : 700 ppm

CSU/DSU :

Ratio : 14

ASM :

BM :

Remarks : E1 = age of 3 months and weight of 345 g; E2 = age of 5 months and weight of 345 g; E3 = age of 5 months and weight of 312 g; E4 = age of 5 months and weight of 411 g

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Logons at 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, and 32 kHz
• - Hearing loss of 23.5 dB and 7.7 dB located in the region of 16 kHz in young (E1) and old (E2) rats, respectively. - Hearing loss of 7 dB obtained with the same age animals regardless of the body weight (groups E3 and E4)	• Audiometry tests performed prior to styrene exposure, at the end of exposure and 6 weeks after exposure
Light and electron microscopy	
• - In the region of 2 - 30 kHz, young and old animals showed 80.3 % outer hair cell (OHC) losses in the third row. In the second and the third row, the OHC losses were greater in the young rats than in old rats. - No large difference in OHC losses between E3 and E4 groups. The OHC losses were 58, 13 and 5 % for the third, the second and the first row, respectively, in the region of 2 - 27 kHz	• Histology performed 6 weeks after the end of exposure

Action mechanism

Authors' conclusion

Ototoxic effect at 700 ppm in rats. There is an influence of age on styrene –induced threshold shift and hair cell loss in rats. Young rats are more susceptible to styrene. Weight does not play a major role in styrene ototoxicity

Our conclusion

Ototoxic effect at 700 ppm in rats. There is an influence of age on styrene –induced threshold shift and hair cell loss in rats. Young rats are more susceptible to styrene. Weight does not play a major role in styrene ototoxicity

Styrene [100-42-5]

Styrene (monomer)
• TWAEV : 50 ppm | 213 mg/m³ D-TWAEV : 30 mg/kg/d

Population

Species : Rat Long Evans # : 4 - 8 Sex : Males

Age :

Exposure

Route : Inhalation

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

C/D reported : G1 (active rats): 300, 400, 500, 600 ppm; G2 (sedentary rats): 500, 650, 850, 1000 ppm

CSU/DSU :

Ratio : 6 - 20

ASM :

BM :

Remarks : Groups of active (using a running wheel) and sedentary rats exposed to styrene

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Logons at 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, and 32 kHz
• - Group G1 : 8 and 7 dB hearing loss at 2 and 3 kHz with 600 ppm styrene; 14 dB hearing loss at 16-20 kHz with 500 ppm styrene; 5 dB hearing loss at 16-20 kHz with 400 ppm styrene. - Group G2 : comparable effects as in G1 but at higher styrene concentrations. 9.7 dB hearing loss at 600 ppm with active rats and 802 ppm with sedentary rats	• Test performed before and 4 weeks after the end of exposure
Light microscopy	Cochleogram
• - In both groups, outer hair cell losses (OHC) observed throughout the entire range of damaged frequencies -The most significant losses located at the third row (OHC3) starting at 400 ppm with active rats and 650 ppm with non active rats, followed successively by OHC2 and OHC1	• Histology performed 4 weeks after the end of exposure

Action mechanism

Authors' conclusion

LOAEL of 400 ppm for ototoxic effect at in active rats and 650 ppm in sedentary rats

Our conclusion

LOAEL of 400 ppm for ototoxic effect at in active rats and 650 ppm in sedentary rats

Styrene [100-42-5]

Styrene (monomer)
• TWAEV : 50 ppm | 213 mg/m³ D-TWAEV : 30 mg/kg/d

Population

Species : Rat Long Evans # : 8 Sex : Males

Age :

Exposure

Route : Inhalation

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

C/D reported : 500, 650, 850, 1000 and 1500 ppm

CSU/DSU :

Ratio : 10 - 30

ASM :

BM :

Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Inferior colliculus Clicks at 2 - 32 kHz
• - Auditory threshold shifts increase as a function of the styrene concentration - At 850 ppm, the amplitude shift was large around 16-20 kHz (19 dB) but no hearing loss was found at higher and lower frequencies. - >1000 ppm : frequency independent hearing loss	• Test performed immediately and 6 weeks after the end of exposure
Light and electron microscopy	Cochleogram
• 650 ppm : outer hair cell losses along the organ of Corti. The outer hair cell losses most significant at the third row	• Histology performed immediately and 6 weeks after the end of exposure

Action mechanism

Authors' conclusion

LOAEL of 570 ppm for ototoxic effect in rats

Our conclusion

LOAEL of 570 ppm for ototoxic effect in rats

Styrene [100-42-5]

Styrene (monomer)
• TWAEV : 50 ppm | 213 mg/m³ D-TWAEV : 30 mg/kg/d

Population

Species : Rat Long Evans # : 5 - 11 Sex : Males

Age :

Exposure

Route : Inhalation

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

C/D reported : 750 ppm

CSU/DSU :

Ratio : 15

ASM :

BM :

Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Inferior colliculus Clicks from 2 to 32 kHz
• Hearing losses at 2,16 and 20 kHz (5, 7.1 and 9.2 dB, respectively)	• Audiometry tests performed prior to styrene exposure and 6 weeks after the end of exposure
Light microscopy	
• Outer hair cell (OHC) losses were greatest in the third row, followed by the second and the first row. The largest losses located at the third row, 86 % at 8 and 22 kHz	• Histology performed 6 weeks after the end of exposure

Action mechanism

Exact mechanism of styrene toxicity is not understood. A possible route to reach the outer hair cells is the lipid-rich content of the membranes of the different cells of the organ of Corti

Authors' conclusion

LOAEL of 750 ppm for ototoxic effect in rats

Our conclusion

LOAEL of 750 ppm for ototoxic effect in rats

Styrene [100-42-5]

Styrene (monomer)
• TWAEV : 50 ppm | 213 mg/m³ D-TWAEV : 30 mg/kg/d

Population

Species : Rat Wistar # : 7 - 12 Sex : Males

Age :

Exposure

Route : Inhalation

Duration : 12 h/d; 5 d/w; 4 w

C/D reported : 100, 300 and 600 ppm

CSU/DSU :

Ratio : 2 - 12

ASM :

BM : -

Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Inferior colliculus Clicks and tone bursts at 1.0, 2.0, 4.0 and 8.0 kHz
• 600 ppm : threshold shift of 3 dB at 8 kHz	• Test performed over 20 to 40 days after the end of exposure
Light and electron microscopy	Cochleogram
• 600 ppm : outer hair cell losses found in the third row of upper basal and middle coil	• Histology performed over 20 to 40 days after the end of exposure

Action mechanism

Authors' conclusion

LOAEL of 300 to 600 ppm for ototoxic effect in rats

Our conclusion

LOAEL of 300 to 600 ppm for ototoxic effect in rats

Styrene [100-42-5]

Styrene (monomer)
• TWAEV : 50 ppm | 213 mg/m³ D-TWAEV : 30 mg/kg/d

Population

Species : Worker # : C1 = 18; E = 18 Sex : Males

Age : C1 =39 (30 - 54); E = 40 (28 - 61) years

Exposure

Route : Inhalation

Duration : 10.8 (6 - 15) years

C/D reported : < 25-100 mg/m³ (average over 8 h)

CSU/DSU :

Ratio : 0.1 - 0.5

ASM : Passive absorption badges

BM :

Remarks :

Tests

Results compared with reference values or control groups

Test type • Effects reported	Precisions on test • Remarks
Pure tone audiometry • No abnormalities	Pure tones
Cortical auditory evoked potentials • Abnormal results in 6 subjects	Frequency glides at 50 Hz et 200 Hz

Action mechanism

Results suggest degradation in ability to discriminate frequeny changes

Authors' conclusion

At low doses, styrene causes central nervous system disturbances which can be apparent in special otoneurological tests

Our conclusion

At low doses, styrene causes central nervous system disturbances (at cortical-subcortical levels) which can be apparent in special otoneurological tests

Styrene [100-42-5]

Styrene (monomer)
• TWAEV : 50 ppm | 213 mg/m³ D-TWAEV : 30 mg/kg/d

Population

Species : Worker # : C = 81; E = 65 Sex : Males and females

Age : C = 45 (26 - 62) years; E = 43 (21 - 62) years

Exposure

Route : Inhalation

Duration : 7.6 (2 - 23) years

C/D reported : 16 (0.2-96) mg/m³ (average over 8 h + range)

CSU/DSU :

Ratio : 0.08

ASM : Passive absorption badges 7 hours

BM : Mandelic acid: 0.9 mmol/g creatinine

Remarks : Exposed workers employed for a minimum of 1 year. Cumulative lifetime exposure of 1303 mg.yr/m³
Urine samples collected over 24 h from the beginning of the workshift under study

Tests

Test type • Effects reported	Precisions on test • Remarks
Pure tone audiometry	at 1, 2, 3, 4, 6 and 8 kHz
• - Hearing losses at 2, 3, 4 and 6 kHz when compared with unexposed workers (> 25 dB HL) - No significant difference in prevalence of high-frequency hearing loss - Lack of dose-response relationship	

Action mechanism

Authors' conclusion

The study suggests ototoxic effect of styrene above 100 mg/m³ in workers

Our conclusion

No convincing ototoxic effect at this low concentration of styrene (average of 16 mg/m³) in the workers

Styrene [100-42-5]

Styrene (monomer)
• TWAEV : 50 ppm | 213 mg/m³ D-TWAEV : 30 mg/kg/d

Population

Species : Worker # : C = 88; E1 = 28; E2 = 31; E3 = 7 Sex : Males

Age : C = 35.3 years; E = 33.8 (19-55) years

Exposure

Route : Inhalation

Duration : 8.6 years (<1 month - 24 years)

C/D reported : mean (max): E1 = 61 (138) mg/m³; E2 = 138 (361) mg/m³; E3 = 452 (716) mg/m³

CSU/DSU :

Ratio : 0.3 - 3.4

ASM : Passive absorption badges during 3 days

BM :

Remarks : Control group exposed more to the noise than the group exposed to styrene; 3 groups of exposed workers + 1 control group

Tests

Test type • Effects reported	Precisions on test • Remarks
Pure tone audiometry	at 0.25, 0.5, 1, 2, 3, 4, 6 and 8 kHz
• No differences between the groups exposed and control	
Ultrahigh frequency audiometry	at 8, 10, 12, 14 and 16 kHz
• Difference between the groups E1 and E2 only at 8 KHz but not at 10-16 KHz	

Action mechanism

Authors' conclusion

The study suggests ototoxic effect of styrene for high frequency tones (>8kHz) in workers

Our conclusion

No evidence that low-level styrene exposure produce threshold shifts in the low or high freqencies

Styrene [100-42-5]

Styrene (monomer)
• TWAEV : 50 ppm | 213 mg/m³ D-TWAEV : 30 mg/kg/d

Population

Species : Rat Long Evans # : 9 - 15 Sex : Males

Age :

Exposure

Route : Inhalation

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

C/D reported : 650, 750 ppm

CSU/DSU :

Ratio : 13 - 15

ASM :

BM :

Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Clicks at 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, and 32 kHz
• 650 ppm : no hearing loss 750 ppm : hearing loss observed at 2-24 kHz, with a maximum of 27 dB at 16 kHz	• Test performed only 6 weeks after the end of exposure
Light microscopy	Cochleogram
• 650 ppm : outer hair cell loss observed mainly at low frequencies of 4-6 kHz 750 ppm : outer hair cell loss observed throughout the entire range of damaged frequencies. Outer hair cells of the third row (OHC3) are the most disrupted, followed successively by OHC2 and OHC1	• Histology performed only 6 weeks after the end of exposure

Action mechanism

Authors' conclusion

LOAEL of 650 ppm for ototoxic effect in rats

Our conclusion

LOAEL of 650 ppm for ototoxic effect in rats

Styrene [100-42-5]

Styrene (monomer)
• TWAEV : 50 ppm | 213 mg/m³ D-TWAEV : 30 mg/kg/d

Population

Species : Rat Long Evans # : 5 - 13 Sex : Males

Age :

Exposure

Route : Inhalation

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

C/D reported : 700 ppm

CSU/DSU :

Ratio : 14

ASM :

BM :

Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Clicks at 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, and 32 kHz
• - Hearing losses appeared between 10 and 24 kHz, with a peak of 14.6 dB at 20 kHz. - No significant recovery was measured six weeks after the end of exposure	• Audiometry tests performed prior to styrene exposure, at the end of exposure and 6 weeks after exposure
Light and electron microscopy	
• Outer hair cell losses were greatest in the third row, followed by the second and the first row in all doses. The largest losses located at the third row, 63 % at 2 to 32 kHz	• Histology performed 6 weeks after the end of exposure
Glutamate decarboxylase	Dosed in inferior colliculus
• No significant differences	

Action mechanism

Authors' conclusion

LOAEL of 700 ppm for ototoxic effect in rats

Our conclusion

LOAEL of 700 ppm for ototoxic effect in rats

Styrene [100-42-5]

Styrene (monomer)
• TWAEV : 50 ppm | 213 mg/m³ D-TWAEV : 30 mg/kg/d

Population

Species : Rat Fisher 344 # : 12 Sex : Males

Age :

Exposure

Route : Inhalation

Duration : 14 h/d; 3 w

C/D reported : 800, 1000 and 1200 ppm

CSU/DSU :

Ratio : 16 - 24

ASM :

BM :

Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Pure tone audiometry • Elevation of auditory thresholds at 12 kHz and above with 800 ppm, at 4 kHz and above with 1000 ppm and at all frequences with 1200 ppm	at 2, 4, 8, 12, 16 and 20 kHz
Auditory brainstem responses • All styrene exposed rats had elevated thresholds at all frequencies tested	Inferior colliculus Tone pips of 4,8 and 16 kHz

Action mechanism

Authors' conclusion

LOAEL of 800 ppm for ototoxic effect in rats

Our conclusion

LOAEL of 800 ppm for ototoxic effect in rats

Styrene [100-42-5]

Styrene (monomer)
• TWAEV : 50 ppm | 213 mg/m³ D-TWAEV : 30 mg/kg/d

Population

Species : Rat Long Evans # : 6 Sex : Males
Age : 60 days

Exposure

Route : Inhalation
Duration : 18 h/d; 5 d
C/D reported : 1000 ppm
CSU/DSU :
Ratio : 20
ASM :
BM :
Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Tone pips of 25 to 95 dB and 16 kHz
• Styrene exposed rats had decreased amplitude, indicative of hearing loss	• Test performed 10 days after the end of exposure

Action mechanism

Authors' conclusion

Ototoxic effect at 1000 ppm in rats

Our conclusion

Ototoxic effect at 1000 ppm in rats

Styrene [100-42-5]

Styrene (monomer)
• TWAEV : 50 ppm | 213 mg/m³ D-TWAEV : 30 mg/kg/d

Population

Species : Worker # : C = 43; E1 = 170; E2 = 86 Sex : Males

Age : C = 38 years; E1 = 36 years; E2 = 37 years

Exposure

Route : Inhalation

Duration : NR

C/D reported : E1 = 58.6 mg/m³; E2 = 12.8 mg/m³; C = 1.7 mg/m³ (geometric mean over 8 h)

CSU/DSU :

Ratio : 0 - 0.28

ASM : Personal air sampling pump during 1 shift

BM :

Remarks : Cumulative styrene lifetime exposure ranged from 0 to 53275 mg/m³ months

Tests

Test type • Effects reported	Precisions on test • Remarks
Pure tone audiometry	at 3, 4, 6 and 8 kHz
• Cumulative lifetime styrene exposure or time weight average exposure were not a significant factors for hearing loss	• Audiometry tests performed at the beginning and at the end of the workshift

Action mechanism

Authors' conclusion

No conclusive evidence for a chronic styrene-induced effect on hearing acuity

Our conclusion

No conclusive evidence for a chronic styrene-induced effect on hearing acuity

Styrene [100-42-5]

Styrene (monomer)
• TWAEV : 50 ppm | 213 mg/m³ D-TWAEV : 30 mg/kg/d

Population

Species : Worker # : E = 194; C = 157 Sex : Males and females

Age : C = 39.6 years; E = 33.8 years

Exposure

Route : Inhalation

Duration : At less 6 months

C/D reported : 60 ± 39.6 mg/m³

CSU/DSU :

Ratio : 0.3

ASM : Sampling pumps with glass tubes; during > 80 % of an 8 hour working shift

BM :

Remarks : - Styrene concentration is a mean value of individual worklife averaged concentration. Exposure varied between 3.6 and 308 mg/m³.
- Averaged noise exposure level over total time of employment.
- Exposed workers employed for a minimum of 6 months

Tests

Test type • Effects reported	Precisions on test • Remarks
Pure tone audiometry	at 1, 2, 3, 4, 6 and 8 kHz

- - 56.2 and 33.8 % of abnormal audiograms in styrene exposed and control group, respectively.
  - The odds ratio of hearing loss was 5.2- fold greater in exposed group
  - Significant increase in hearing threshold within the frequency range 2 to 8 kHz

Action mechanism

Authors' conclusion

Occupational exposure to styrene leads to a significant increase in the chance of developing sensorineural hearing loss

Our conclusion

No convincing ototoxic effect of styrene because the workers exposed to styrene were more exposed to the noise than the controls

Styrene [100-42-5]

Styrene (monomer)
• TWAEV : 50 ppm | 213 mg/m³ D-TWAEV : 30 mg/kg/d

Population

Species : Worker # : E = 290; C = 223 Sex : Males and females

Age : C = 40 years; E = 35 years

Exposure

Route : Inhalation

Duration : At less 6 months

C/D reported : 61.8 ± 51.9 mg/m³

CSU/DSU :

Ratio : 0.35

ASM : Sampling pumps with glass tubes; during > 80 % of an 8 hour working shift

BM :

Remarks : - Styrene concentration is a mean value of individual worklife averaged concentration. Exposure varied between 3.6 and 309 mg/m³.
- Averaged noise exposure level over total time of employment.
- Exposed workers employed for a minimum of 6 month.
E = styrene exposed workers; C = solvent non-exposed workers (including 66 workers exposed to noise only)

Tests

Test type • Effects reported	Precisions on test • Remarks
Pure tone audiometry	at 1, 2, 3, 4, 6 and 8 kHz Examination performed at least 16 h after last exposure to noise

- - Group exposed to styrene only : the odds ratio of hearing loss was 3.9 fold greater than in control group.
  - Significant increase in hearing threshold was found within the frequency range 1 to 8 kHz.
  - No dose-effect relationship between solvent exposure and hearing thresholds.

Action mechanism

Authors' conclusion

Exposure to styrene in humans is associated with a increased risk hearing loss.

Our conclusion

Exposure to styrene in humans is associated with a increased risk hearing loss.

Styrene [100-42-5]

Styrene (monomer)
• TWAEV : 50 ppm | 213 mg/m³ D-TWAEV : 30 mg/kg/d

Population

Species : Rat Fisher 344 # : 8 - 12 Sex : Males

Age :

Exposure

Route : Inhalation

Duration : 14 h/d; 5 d/w; 3 w

C/D reported : 800 ppm

CSU/DSU :

Ratio : 16

ASM :

BM :

Remarks :

Tests

Test type • Effects reported	Precisions on test • Remarks
Auditory brainstem responses	Tone pips of 75 dB at 4, 8, 16, and 30 kHz
• ABR were minimally affected at 4 kHz and moderately to severely affected at 8, 16 and 30 kHz	• Test performed 3 days after the end of exposure
Light and electron microscopy	Cochleogram
• - Outer hair cell loss observed in the upper basal and lower middle regions of the cochlea - Outer hair cells loss was least in the first row and greatest in the second and third rows	• Histology performed 3 days after the end of exposure

Action mechanism

Mechanism of styrene induced hair cell loss was not determined

Authors' conclusion

Ototoxic effect at 800 ppm in rats. Data document mid-frequency auditory dysfunction in rats with significant damage to the organ of Corti

Our conclusion

Ototoxic effect at 800 ppm in rats. Data document mid-frequency auditory dysfunction in rats with significant damage to the organ of Corti

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