Occupational exposure to chemicals and hearing impairment - the need for a noise notation.

Ann-Christin Johnson

PhD

Karolinska Institutet

Dept. Clinical Science, intervention and technique

Section of Audiology

Aknowledgement

The work with the NEG-document

Chemicals and Hearing

have been preformed by me together with

Dr Thais Morata

National Institute for Occupational Health, USA

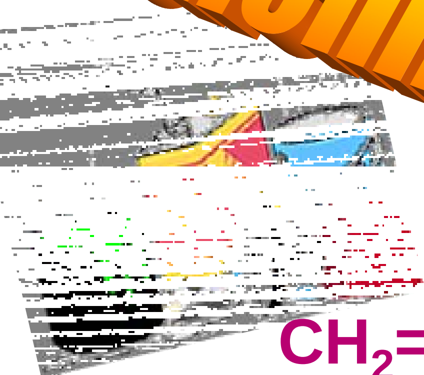
Without her this document would never have been done!

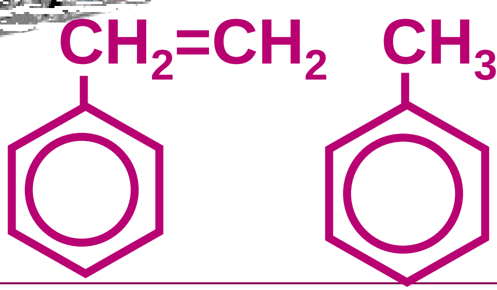
What causes hearing loss?

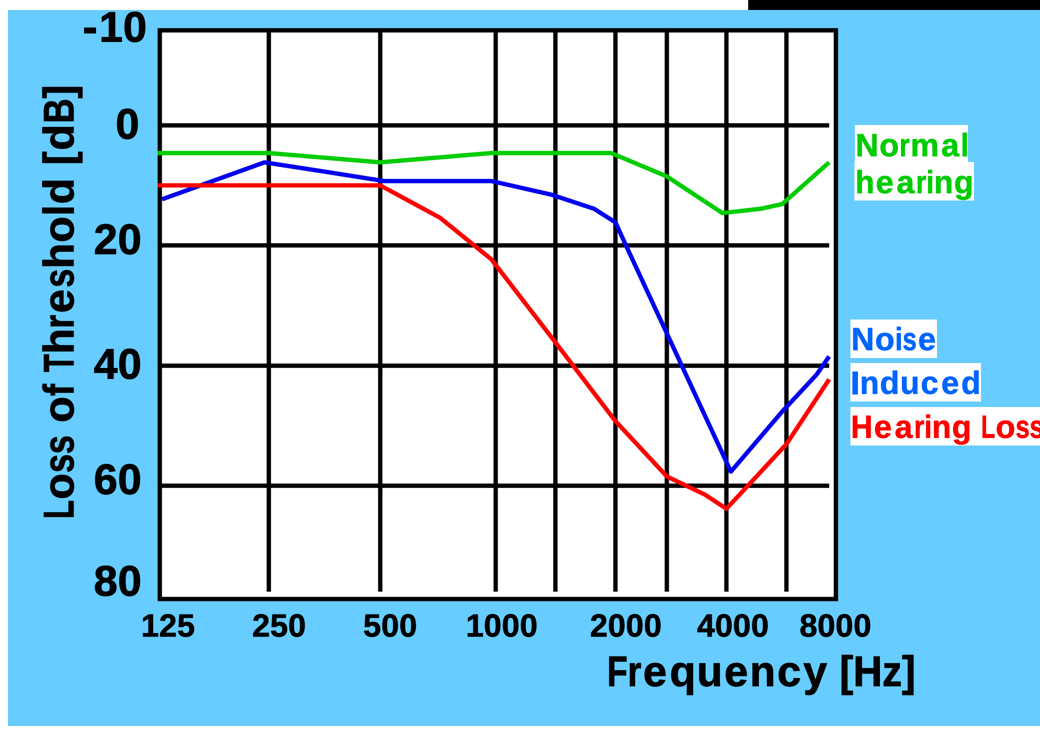
Drugs

Noise

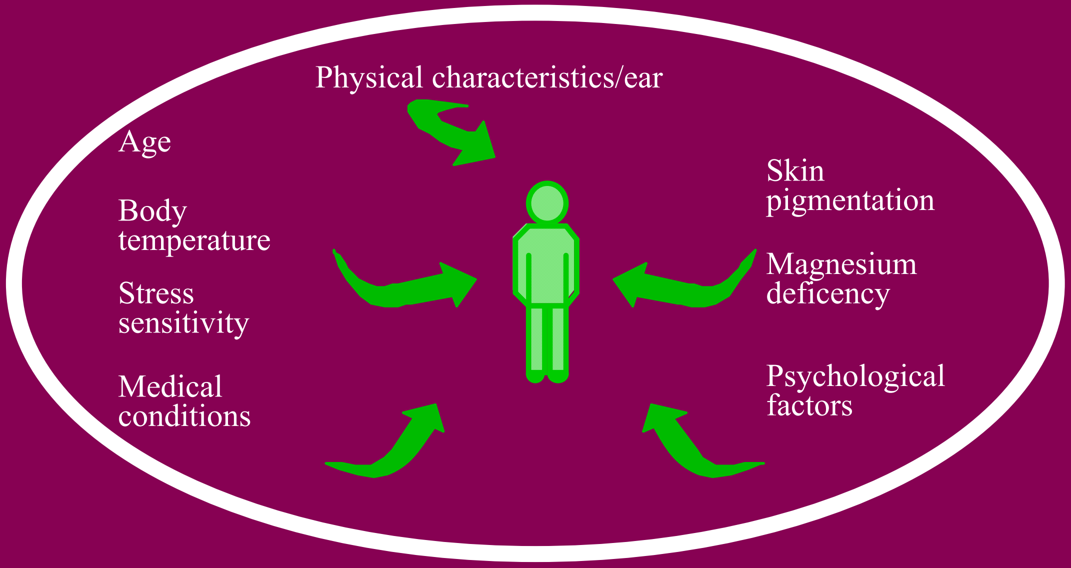
Chemicals





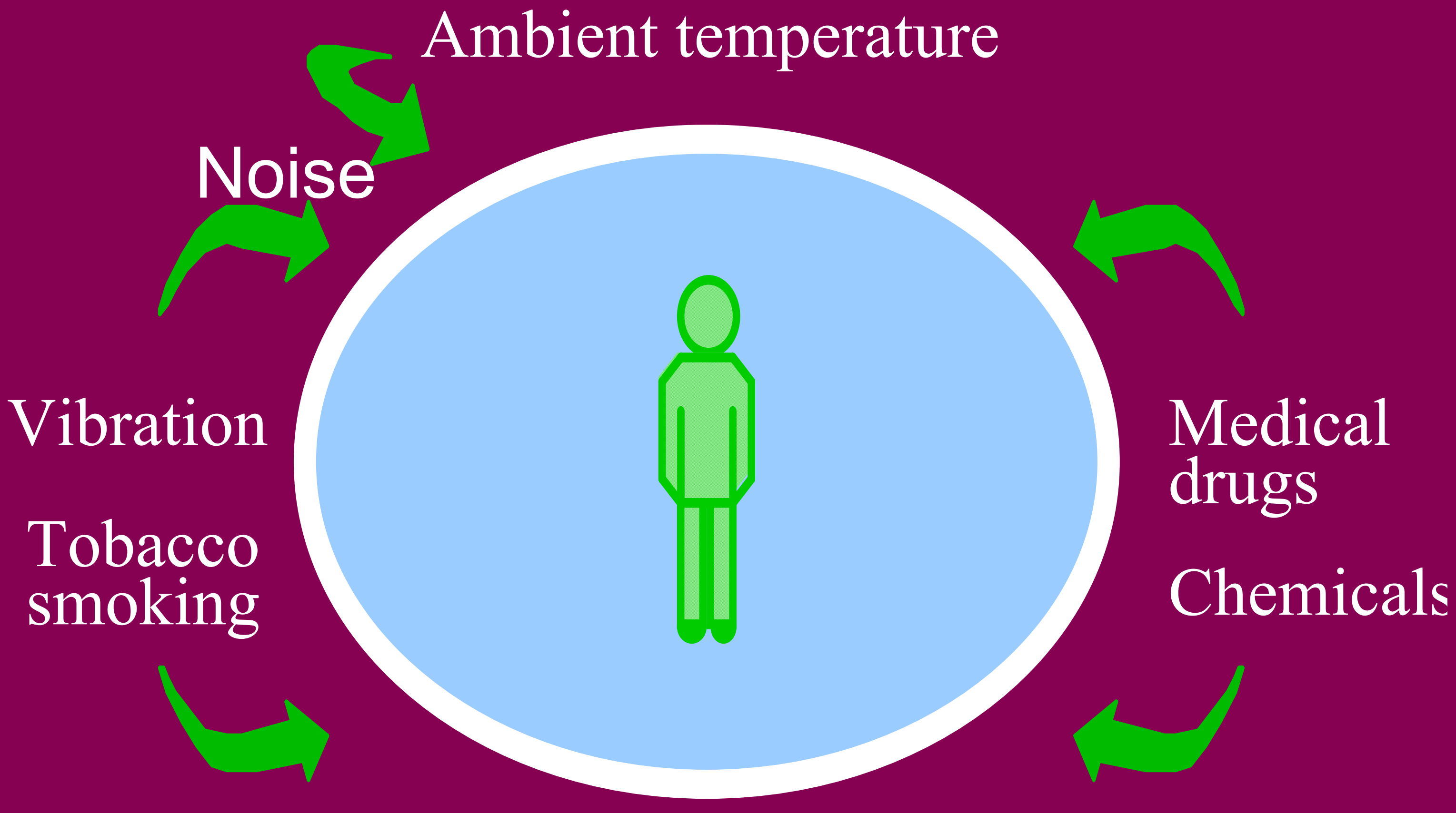


Risk factors for hearing loss
Endogenous



Risk factors for hearing loss

Exogenous



Definitions

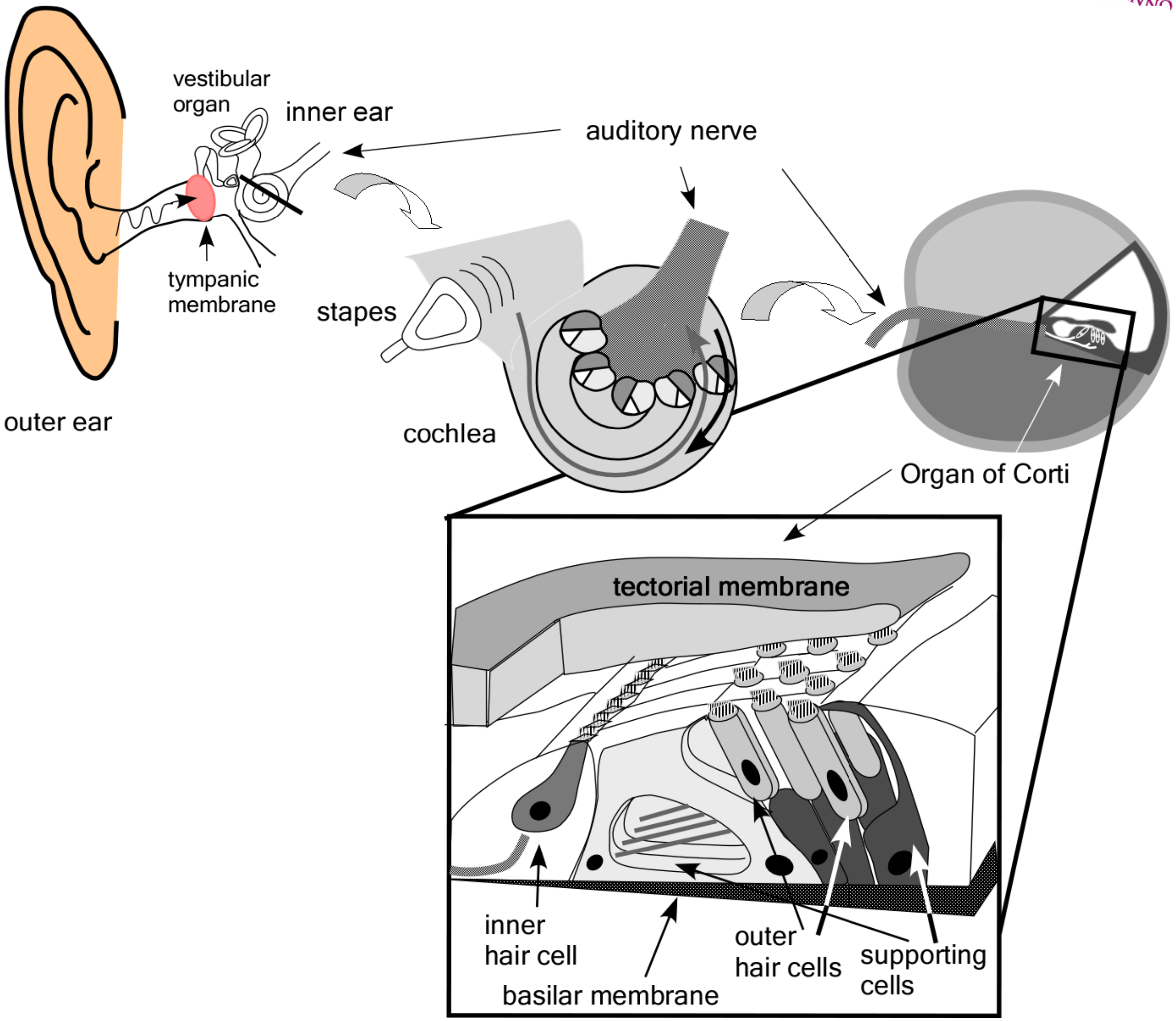
- Ototraumatic

  → any agent that has the potential to cause permanent hearing loss

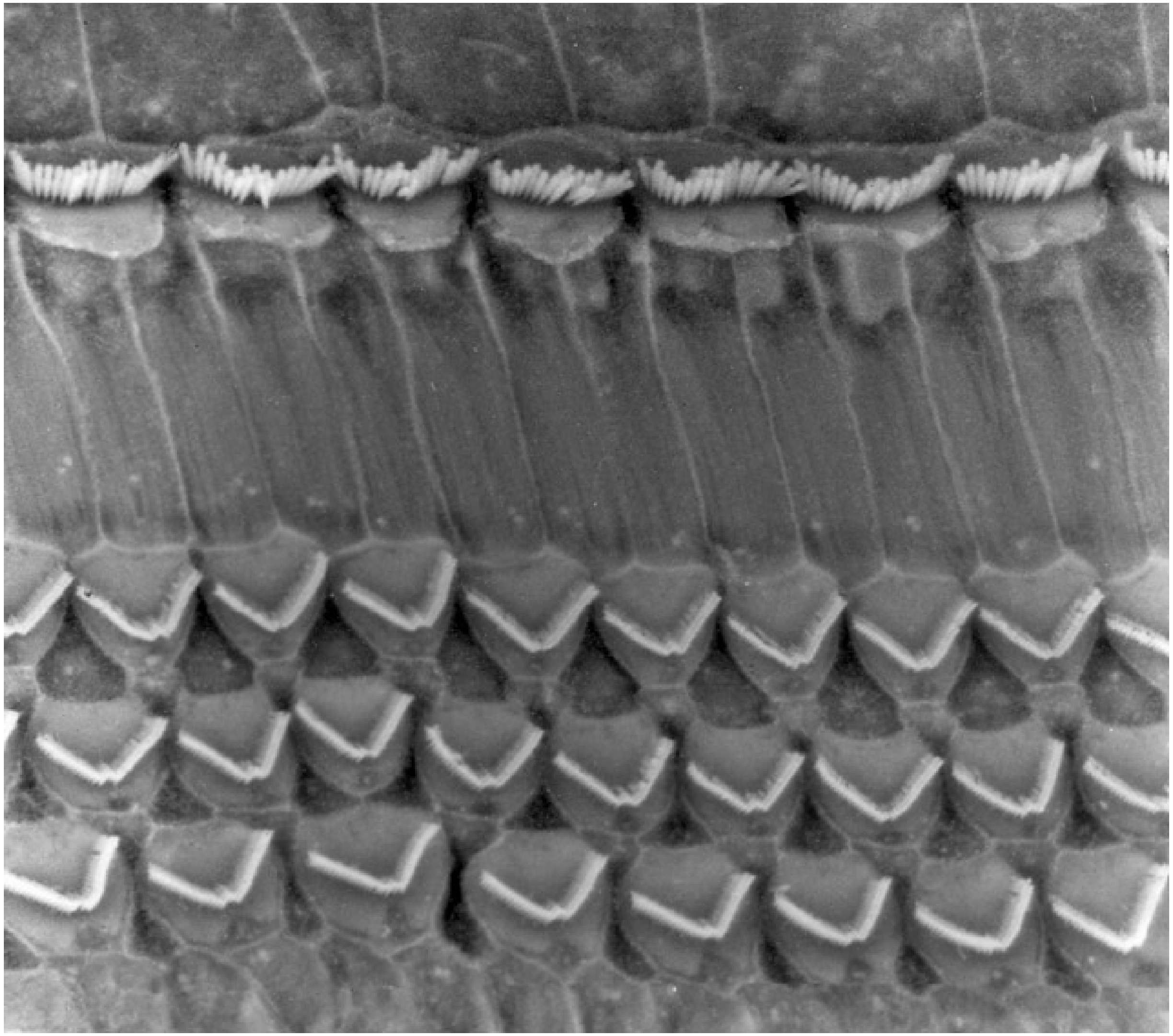
- Ototoxic

  → a substance that causes functional impairment or cellular damage in the inner ear (hearing or balance) or the VIII cranial nerve – the vestibulo-cochlear nerve

The inner ear



Normal cochlea



http://www.sickkids.ca/auditorysciencelab/images/haircells.jpg

Is this new? - Discovery of ototoxic substances

Therapeutic class	Ototoxicity recognized	Examples
Heavy metals	11th century	mercury
Antimalarial drugs	1843	quinine, chloroquine
Non-steroidal anti-infl ammatory drugs	1877	salicylate (aspirin), fenprofen, ibuprofen, indomethacin, naproxen, phenylbutazone, sulindac
Anthelmintics	late 19th century	oil of chenopodium (worm seed oil)
Arsenicals	early 20th century	atoxyl, salvarsan
Aminoglycosides	1945	streptomycin, amikacin, gentamicin, kanamycin, neomycin, netilmicin, paromomycin, tobramycin
Other antimicrobial agents	1960s	chloramphenicol, colistin, erythromycin, minocycline, polymyxin B, vancomycin
Loop diuretics	1960s	ethacrynic acid, bumetanide, furosemide
Industrial solvents and chemicals	1970s	toluene, organotins, carbon monoxide, potassium bromate
Topical disinfectants	1970s	chlorhexidine
Antineoplastic drugs	1970s	bleomycin, carboplatin, cisplatin, dichloro-methotrexate, nitrogen mustard, vinblastine, vincristine
Chelating agents	after 1980	deferoxamine

Schacht J, Hawkins JE. 2006 Sketches of otohistory. Part 11: Ototoxicity: drug-induced hearing loss. Audiol Neurootol. 2006;11(1):1-6.

Hearing loss from noise or chemicals

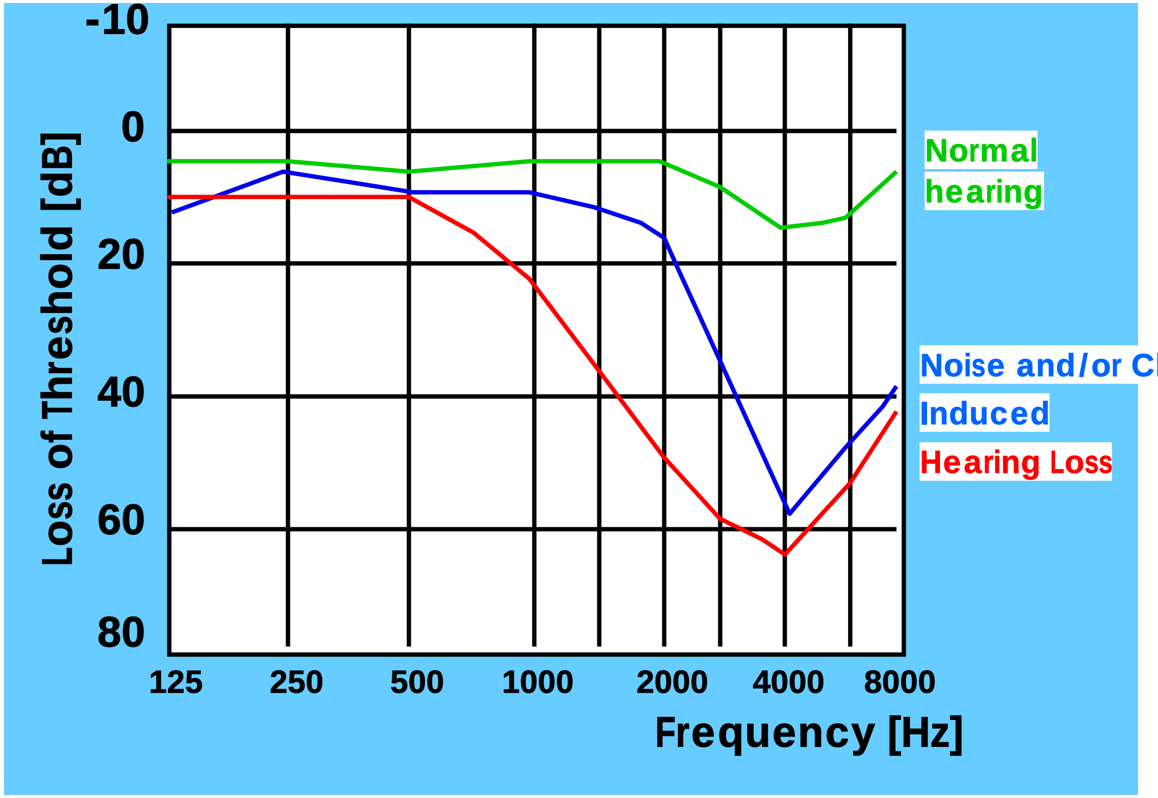
Similarities and differences

- Test methods in humans
  → Pure tone audiometry – The golden standard audiogram
  → Test for central effects on hearing – Speech tests

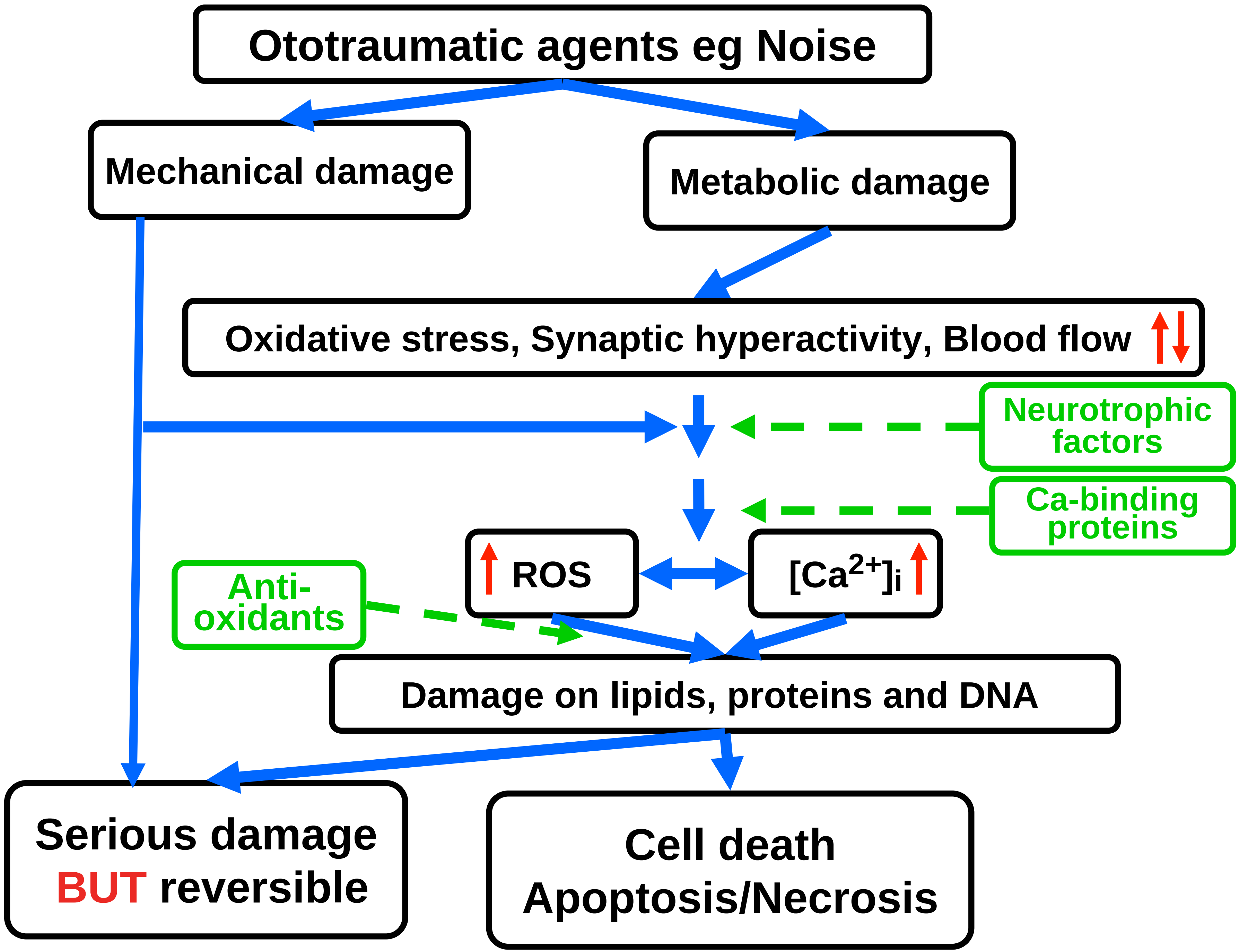
- Test methods in animals
  → Electrophysiology
  → Behavioral tests
  → Morphological examination – OHC-loss

- Mechanisms pathways

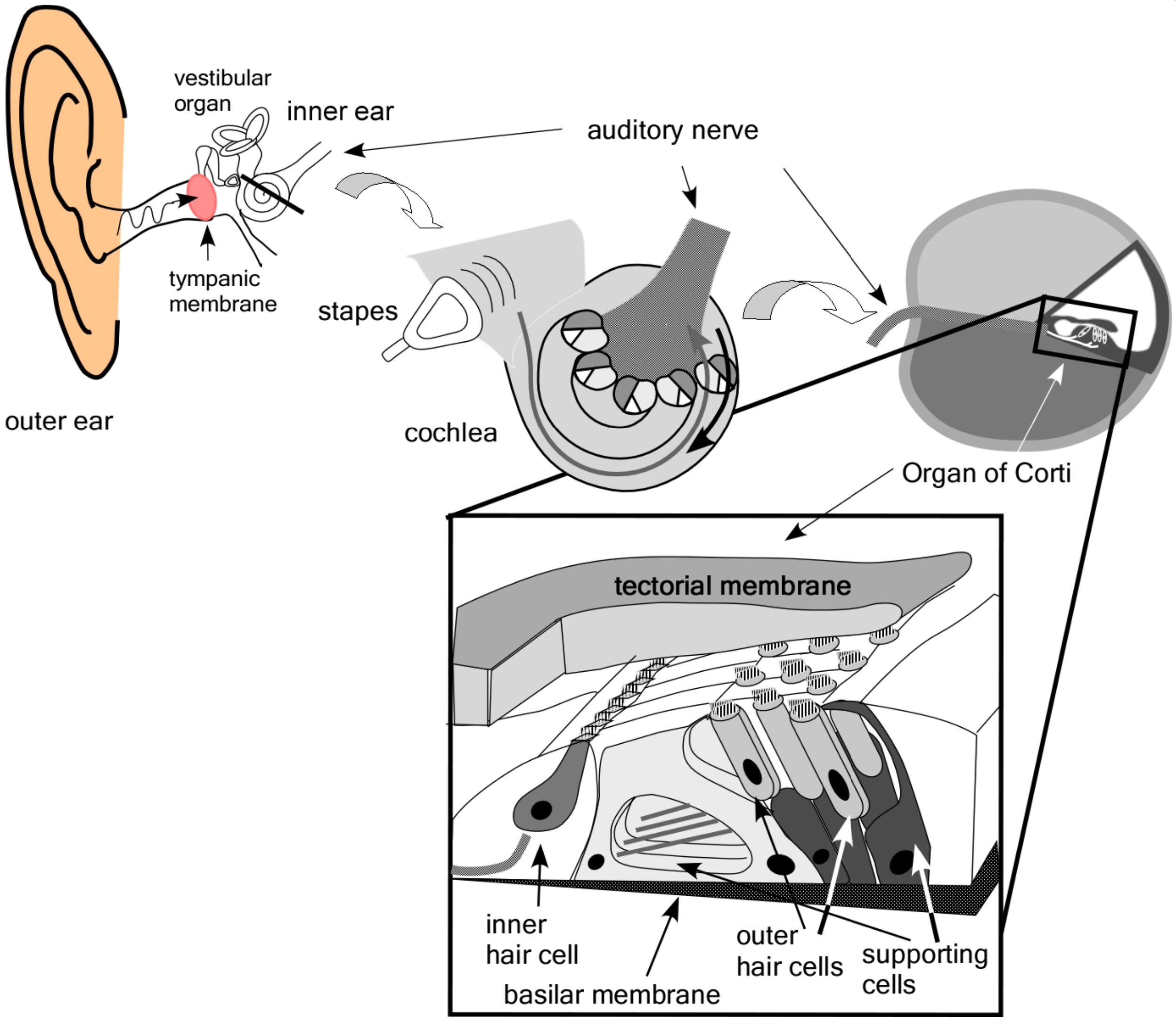
Hearing loss from noise or chemicals
- The audiogram



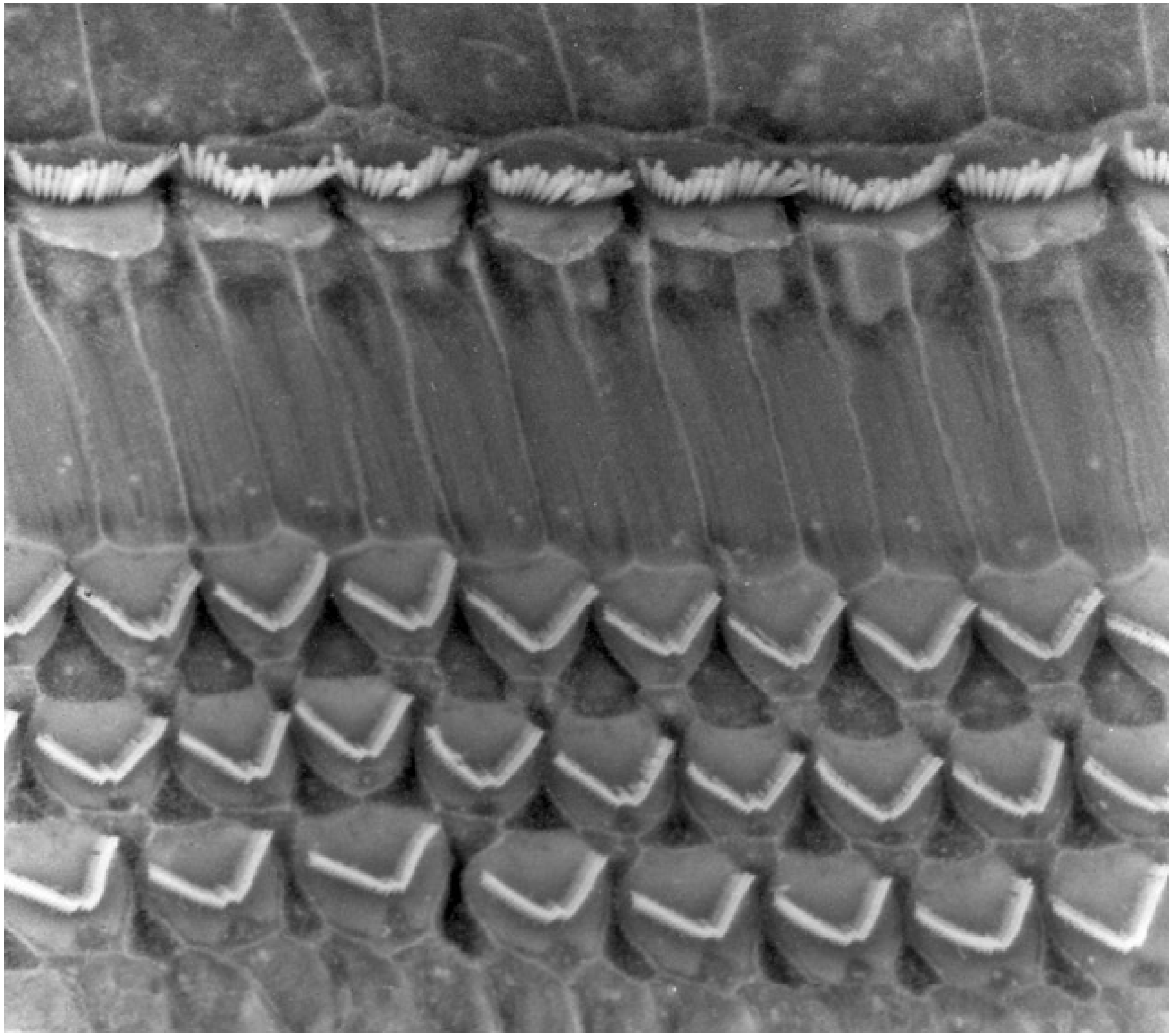
Return


Ototraumatic agents eg Noise
Mechanical damage
Metabolic damage
Oxidative stress, Synaptic hyperactivity, Blood flow
Neurotrophic factors
Ca-binding proteins
ROS
[Ca2+]i
Anti-oxidants
Damage on lipids, proteins and DNA
Serious damage BUT reversible
Cell death Apoptosis/Necrosis

The inner ear

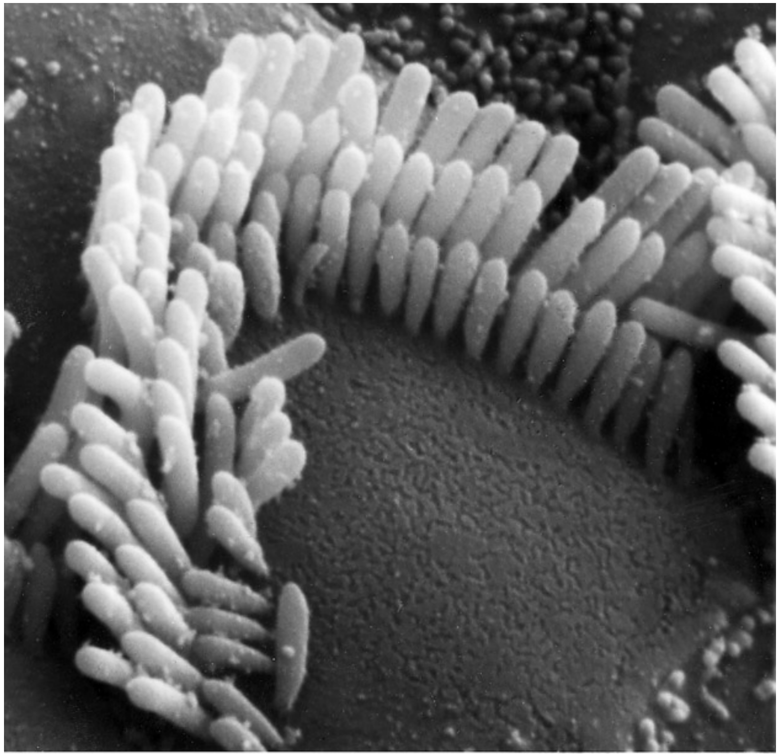


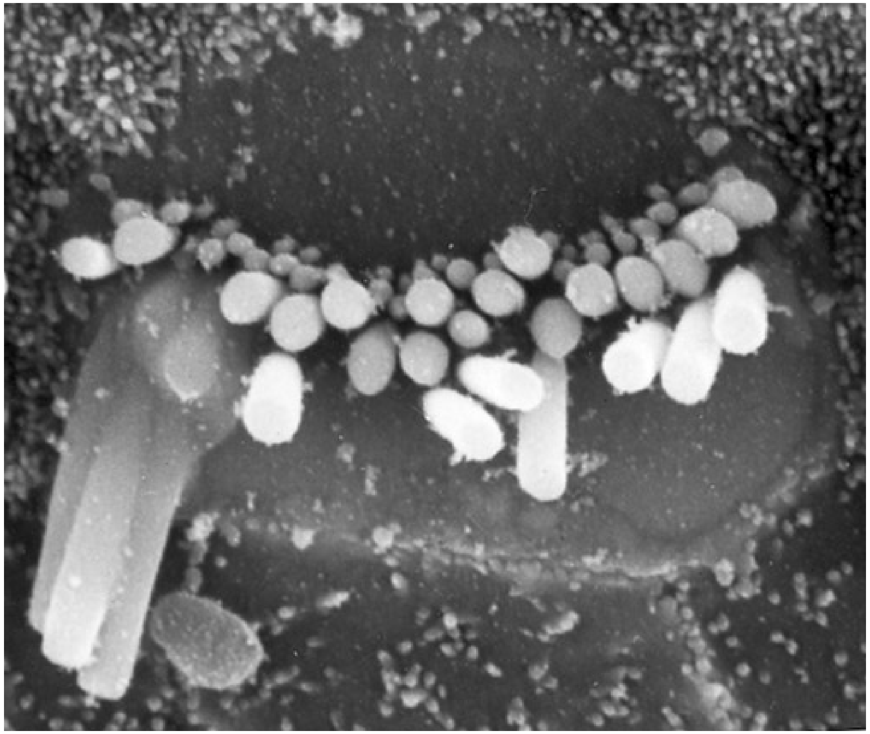
Normal cochlea



http://www.sickkids.ca/auditorysciencelab/images/haircells.jpg

Noise damage





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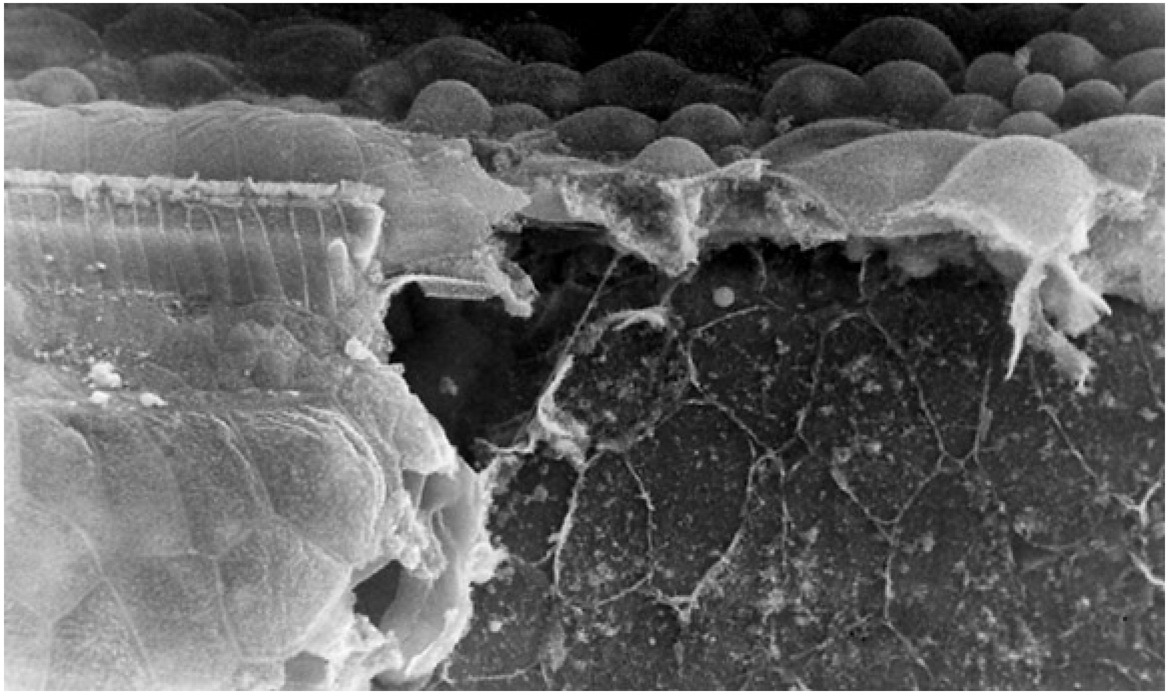
Noise damage

Impulse noise damage



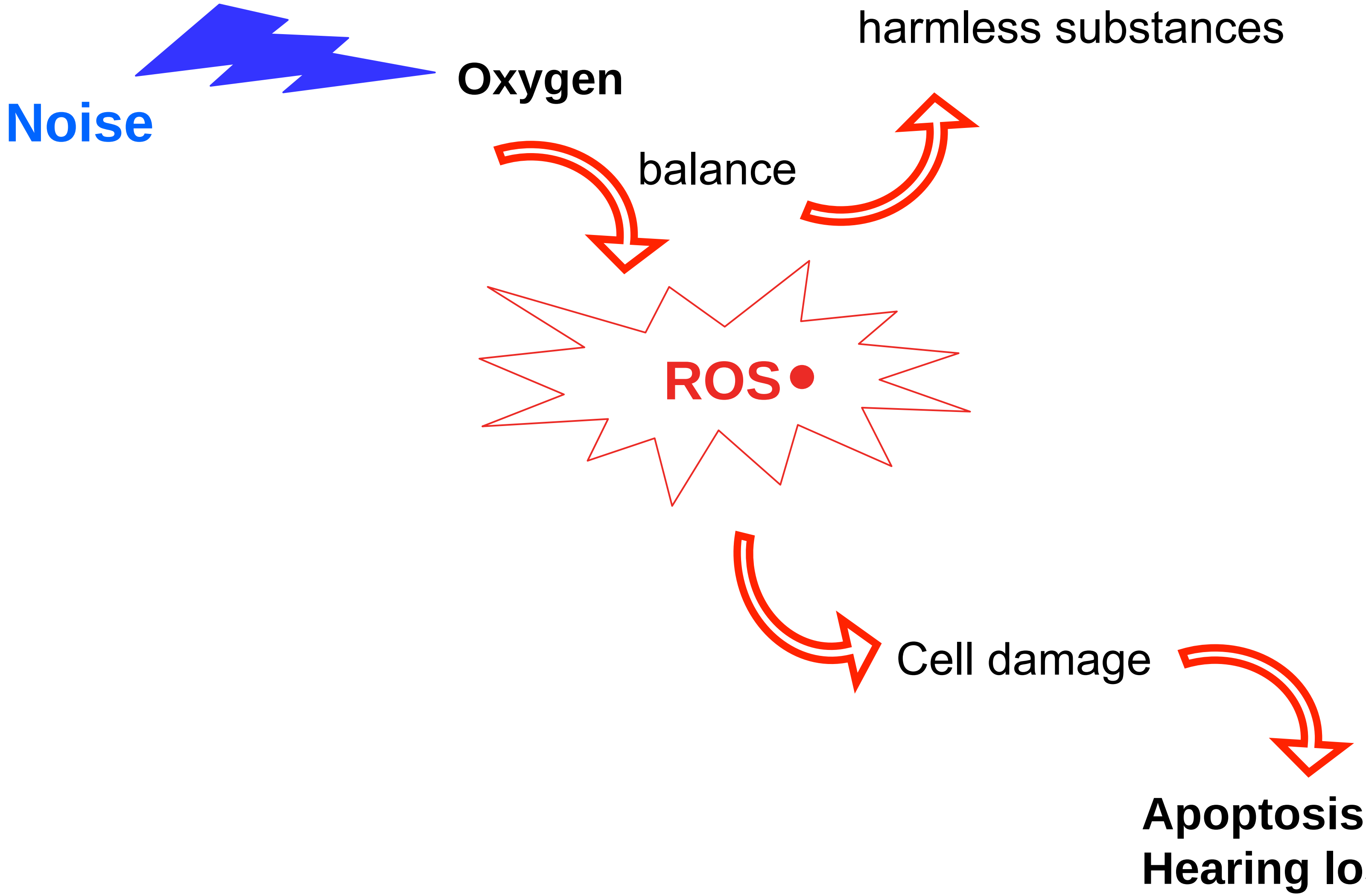
http://www.sickkids.ca/auditorysciencelab/images/haircells.jpg

You have all heard of anti-oxidants?

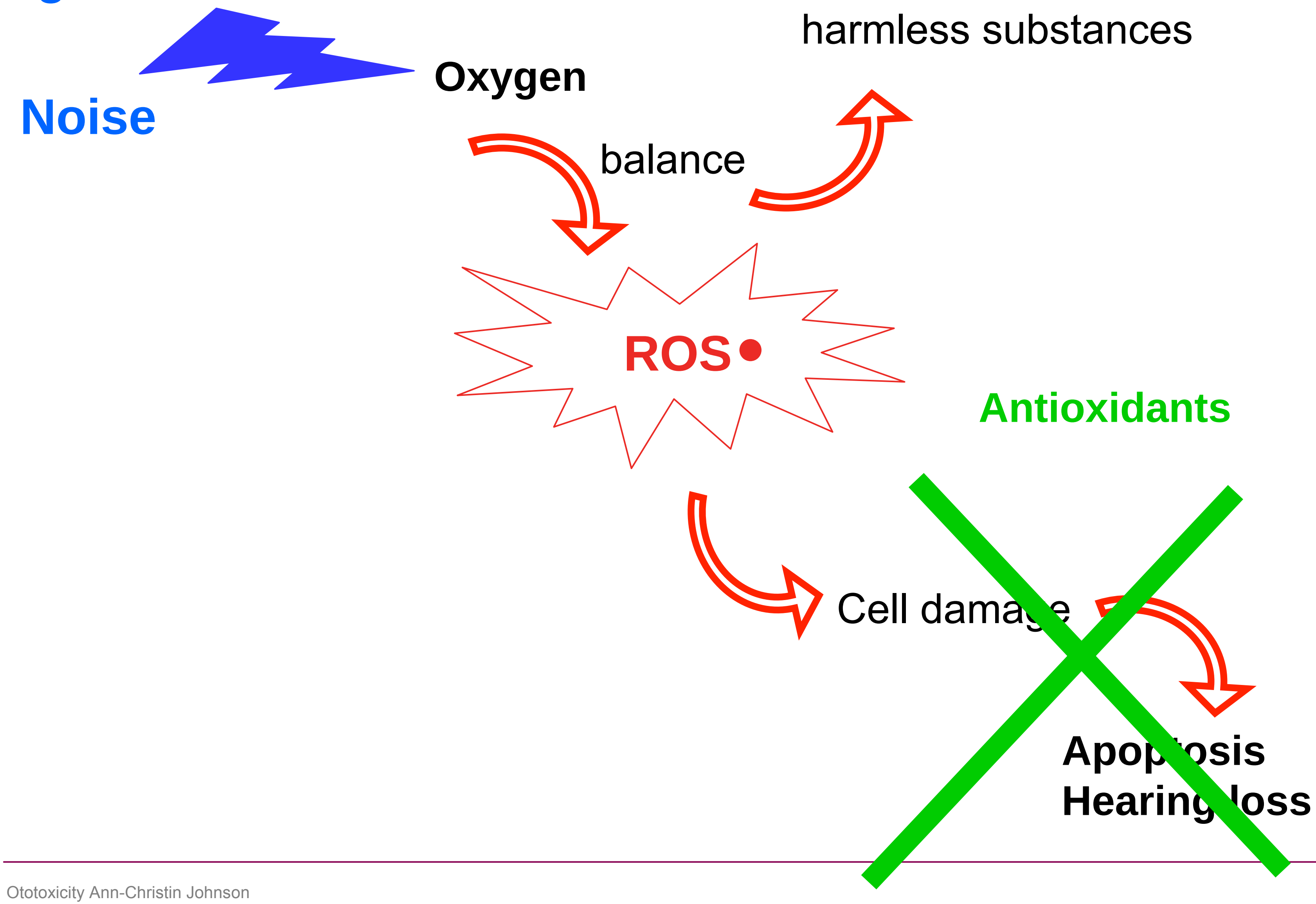
- Why are they good for you?
- What do they protect from?

Reactive Oxygen Species - ROS

Ototoxic agents



Ototoxic agents



Which chemicals are ototoxic?

- Drugs

- Solvents

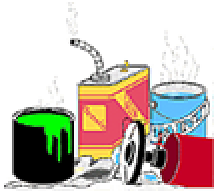
- Metals

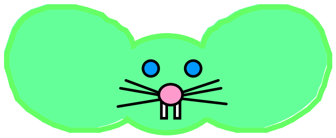
- Other chemicals
  - → Asphyxiants CO & HCN
  - → Pesticides
  - → PCBs

Drugs

- Anti-malarial drugs
- Antibiotics
- Anti-inflammatory drugs (non-steriodal)
- Anti-neoplastic agents
- Diuretics

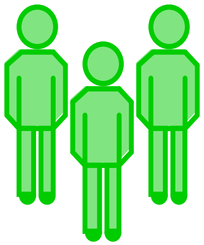
Solvents are ototoxic





Animal studies have shown:

- Ototoxic effects in rats, mice, chinchillas – also in guinea pigs
- Cochlear damage
- Noise not a necessary factor
- Interaction and potentiation with other ototraumatic agents

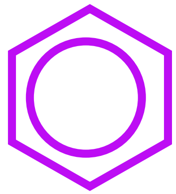


Human studies have shown

- Solvent abuse cause hearing damage
- Occupational exposure to toluene, styrene and mixtures cause hearing loss
- Interaction with noise
- Also at low noise levels

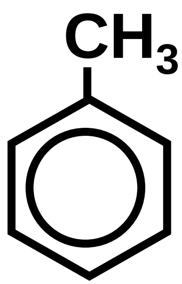
Ototoxic solvents

Benzene
NOT ototoxic

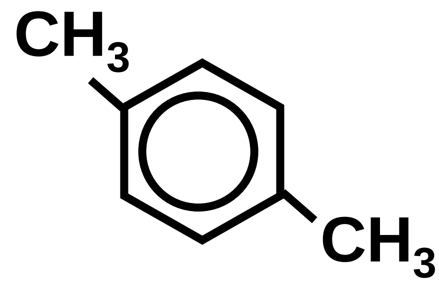


Triklorethylene $Cl_2C{=}CHCl$

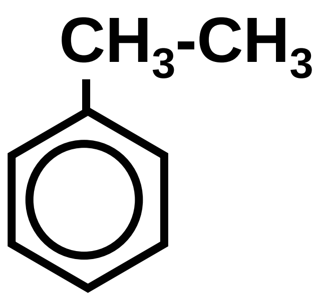
Toluene



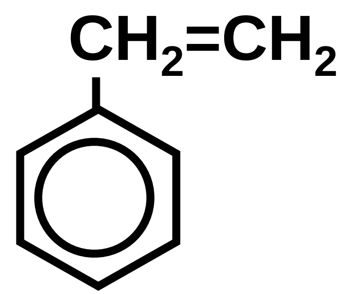
p-Xylene



Ethylbenzene



Styrene



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n-Hexane C_6H_{14}

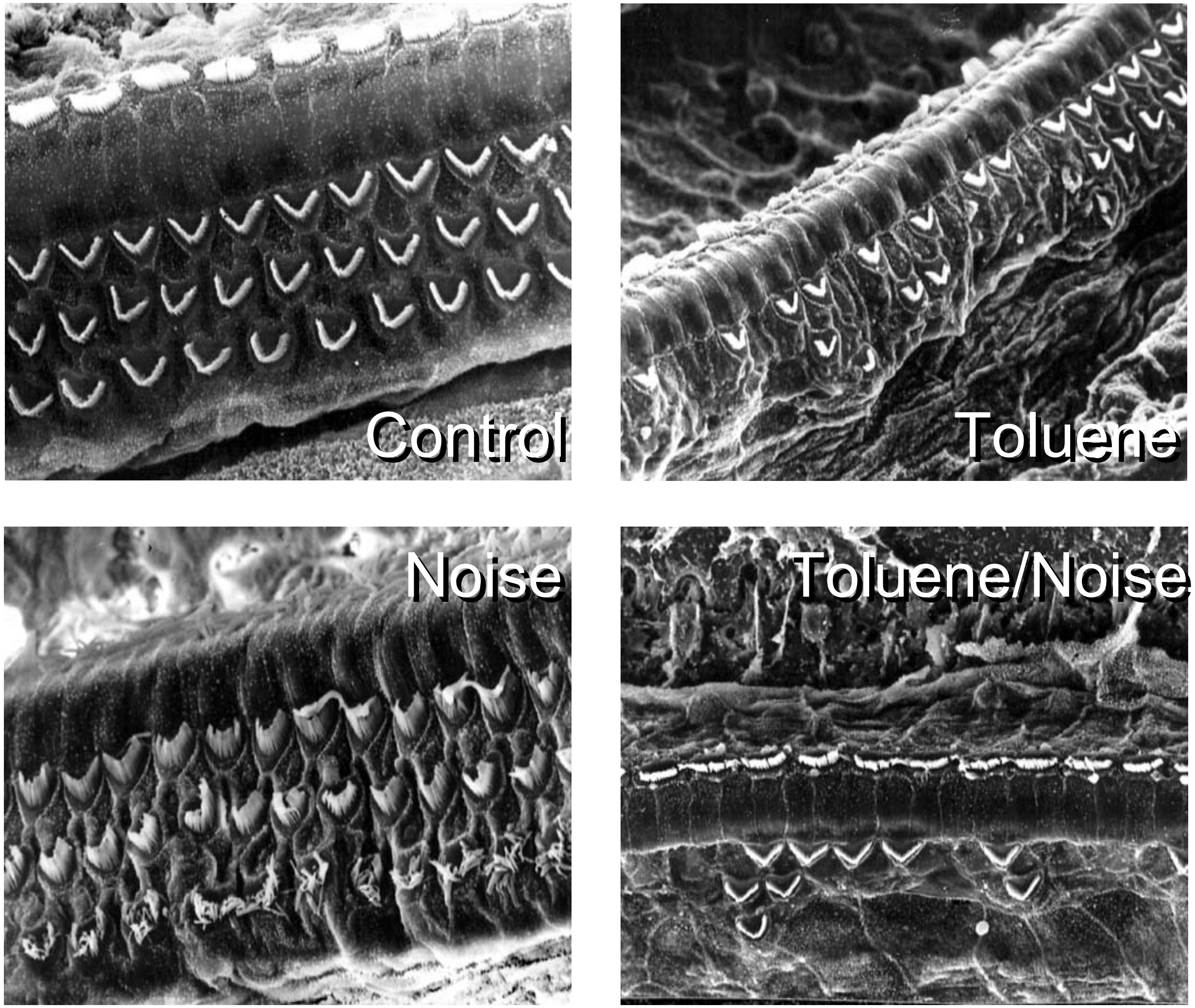
Carbon disulphide CS_2

Mixtures

Animal studies

NOAEL	LOAEL	Exposure duration	Reference
Styrene - only			
-	250 ppm – 500 ppm	Gavage or Inhalation 3 w – 4 w	Chen et al., 2007 ; Lataye et al., 2005
300	600	Inhalation 4 w	Mäkitie, et al 2002
-combined with noise (N)			
-	400 + 85 dB Leq8h	Inhalation and N 4 w	Lataye et al., 2005
300+ 100-105 dB SPL	600 + 100-105 dB SPL	Inhalation and N 4 w	Mäkitie et al., 2003
Toluene - only			
-	900 -1000	Inhalation14 h/d, 14 w or 6 h/d, 2-4 w	Pryor et al 1983a; Johnson et al 1988
700	1 000	Inhalation 14 h/d,16 w	Pryor et al 1984b
-combined with noise (N)			
500 + 87 dB Leq8h	-	Inhalation and N 90 d	Lund and Kristiansen 2008
500+90 dB Leq8h	1 000 + 90–100 dB Leq8h	Inhalation and N 10 d	Brandt-Lassen et al 2000
Xylene - only			
450 *p*-XYL	900 *p*-XYL	Inhalation 13 w	Gagnaire et al 2001
-combined with noise (N)			
No data			
Trichloroethylene - only			
-	2 000	Inhalation 3 w	Rebert et al 1991
800	2 500	Inhalation 13 w	Albee at al 2006
-combined with noise (N)			
-	3 000 + 95 dB SPL	Inhalation and N: 18 h/d, 3 w	Muijser et al 2000

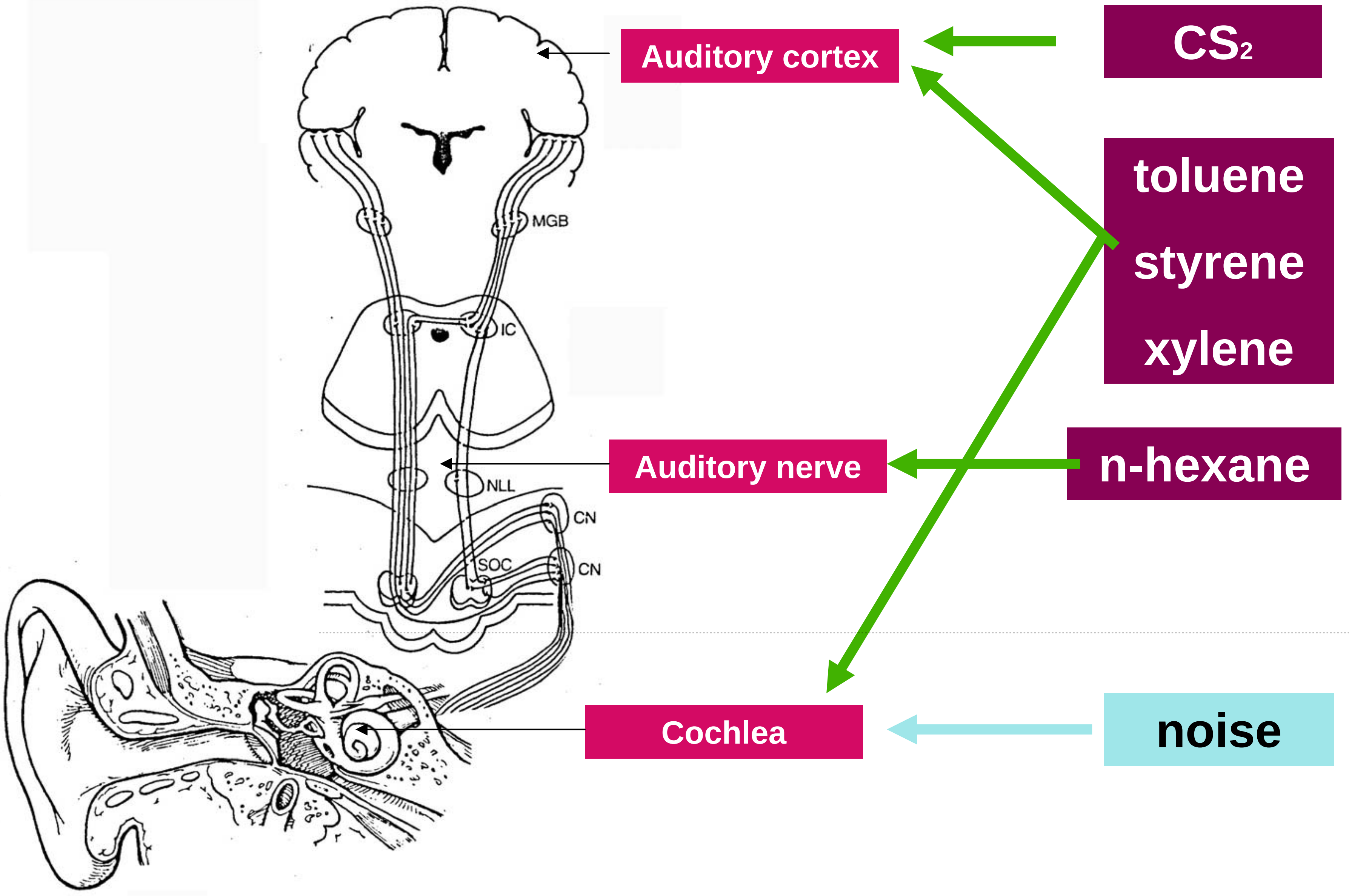
Toluene-Noise Interaction (rats)



Lataye and Campo, Neurotoxicol Teratol 1997; 19:373-382

Solvents - Possible Mechanisms

- Effect on isolated OHC
  - → Dose-response shortening of OHC, more pronounced in apical end of cochlea
  - → Free intracellular Ca^{2+} increased
- Intoxication Route via Organ of Corti
  - → Toluene/Styrene concentrations highest in stria vascularis
  - → Lower concentrations in supporting cells near to Organ of Corti
- Inhibit the auditory efferent system
  - → modifying the response of the protective acoustic reflexes
- ROS formation
  - → apoptotic cell death

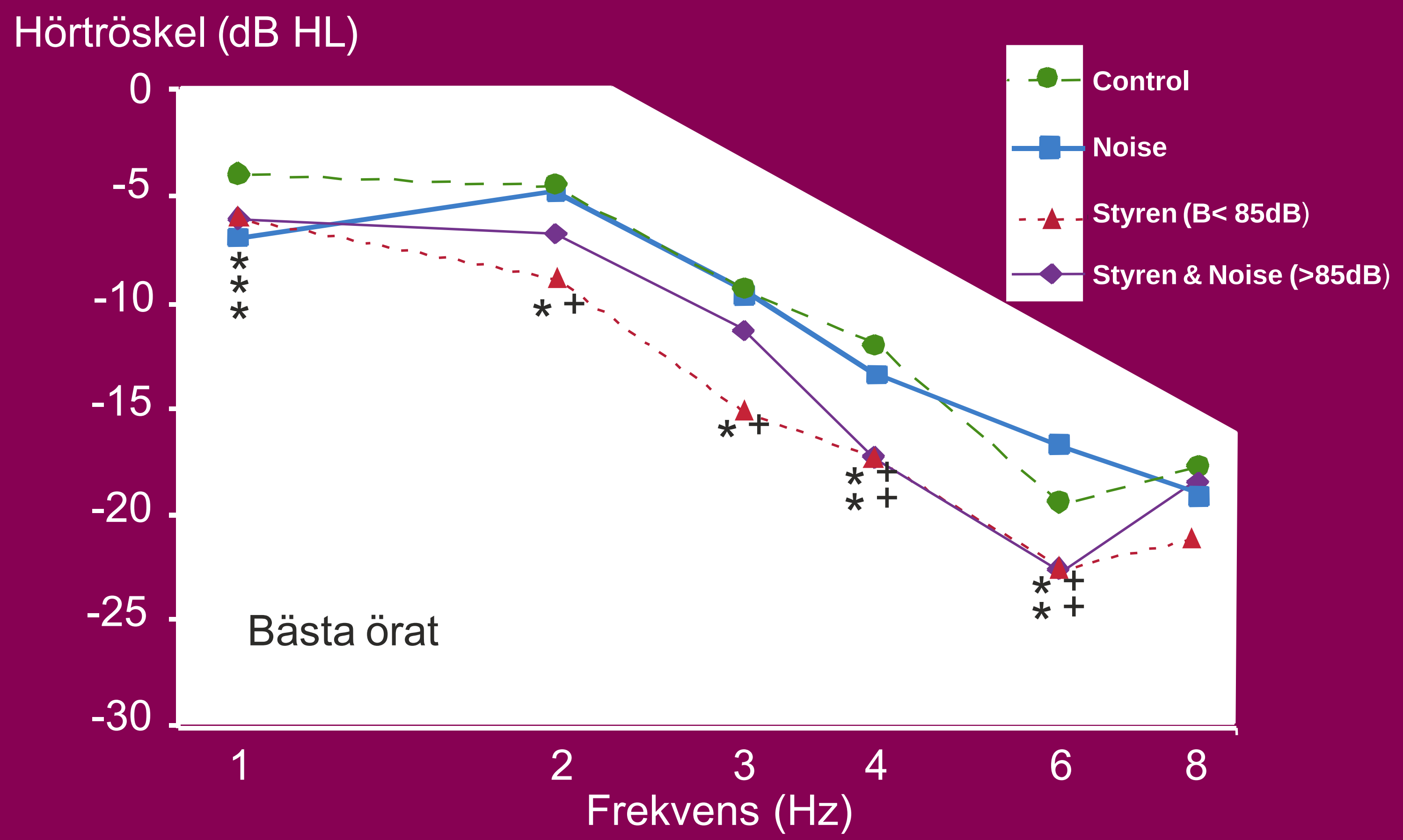


MGB
IC
NLL
CN
SOC
CN
Auditory cortex
Auditory nerve
Cochlea
CS2
toluene
styrene
xylene
n-hexane
noise

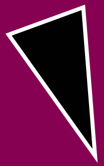
Human studies – Styrene OEL 20-100 ppm

Exposure levels S= Styrene, N= Noise	Styrene groups	Evidence of HL shown	References
S: Mean 3,5 ppm **N:** S+N mean 89 dBA	65, S 89, S and N; 81 controls	++	Morata *et al*, 2002, Johnson *et al*, 2007
S: Mean ca 5 ppm (biol. monit) **N:** 73 dB(A)	32 S 60 controls (agematched)	++	Mascagni et al, 2007
S: Mean 8 ppm **N:** < 85 dB	44, S; 49 S in mixt 33 controls	++	Morioka *et al*., 1999
S: Mean 11-38 ppm **N:** 70-93 dBA (>85 S+N)	220 S 70 S and N 157 controls	+++	Sliwinska-Kowalska et al, 2003
S: Mean ca 22 ppm (biol. monit) **N:** not given	16 S 16 controls	-	Hoffman *et al,* 2006
S: < 26 ppm. **N:** 80 to 89 dBA	170 dir exp 86 indir exp 43 controls	-	Sass-Kortsak *et al,* 1995
S: < 25 ppm. **N** not given	18 S Comp to reference pop.	+ ++ Bal	Möller *et al,* 1990
S: Mean < 30 ppm **N**: S + N =76 dBA	23 S and N 12 controls	++	Morioka *et al*, 2000
S: < 35 ppm. **N**:< 85 dBA	59 S 94 controls	+	Muijser *et al,* 1988
S: < 54 ppm **N** not given	20 S	- ++ Bal	Calabrese *et al*, 1996

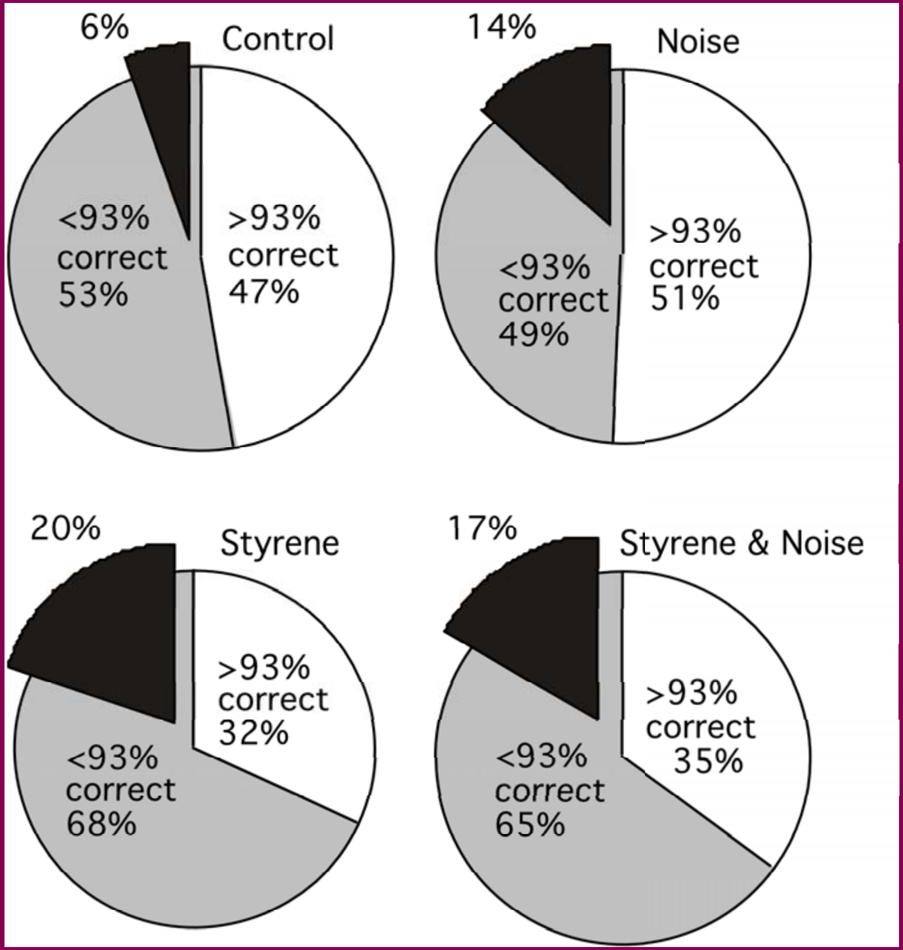
Results - Audiometry



Results - Interupted speech



= % with < 78% correct



Korsan - Bengtsson 1973

93% correct = mean of normal population

<78% correct = 93% - 3 STD abnormal result

Human studies on occupational exposure to Styrene

- 11 studies - 10 different groups of workers
- Different designs and out-come measures used
- Majority of studies showed effects on hearing
  - → PTA not the best indicator AND Central effects also present

- Styrene exposure levels in all studies were low
- Noise not a necessary factor
  - → BUT interactions with noise occur
- **Styrene IS** a risk factor for hearing loss

Conclusion **Effects seen at levels below 20 ppm (current exposure and low noise level at time of studies).**

Human studies – Toluene OEL 50-100 ppm

Exposure levels Current exposures T= Toluene, N= Noise	Toluene groups	Evidence of HL shown	References
T: low 3 ppm N 82 dBA **T:** high 26 ppm N 81 dBA	152 low T 181 high T	-	Schäper et al., 2003
T: 20 ppm **N:** Not given	49 TOL 59 controls	(+)	Vrca et al., 1996
T: ~ 97ppm **N:** Not given	40 T 40 controls	(+)	Abate et al., 1993
T + N 9-37 ppm 88-98 dBA **N** 88-98 dBA	50 T+N 50 N 40 controls	++ with N	Bernardi, 2000
T + N ≤50 ppm (in 109 workers; biol. monit.) 71-93 dBA	124 T (in mixture)+N	+ with N	Morata et al., 1997
Cumulative expo index **T + N** 176-2 265 year-ppm 79-87 dBA **N** 83-90 dBA	58 TOL+N 58 N 58 controls	++ with N	Chang et al., 2006
T + N 100-365 ppm 88-98 dBA **N** 88-98 dBA	50 N 51 T+N 50 controls	+++ with N	Morata et al., 1993

Human studies on occupational exposure to Toluene

- 7 studies
- Different designs and out-come measures used
- Majority of studies showed effects on hearing

  →PTA not the best indicator AND Central effects also present

- Toluene exposure levels in studies were moderate to high
- Noise was always present
- **Toluene IS** a risk factor for hearing loss at least with noise

***Conclusion* Effects seen at approximately 50-100 ppm (current exposure and low noise level at time of studies).**

Other solvents – with human studies

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- CS_2
  → Central auditory effects shown in rats [Hirata et al 1992; Rebert and Becker 1986]
    - NOAEL 200 ppm (5 w) or 400 ppm (11 w)
    - LOAEL 800 ppm
  → Central auditory effects and hearing loss shown in workers after chronic exposure [Hirata et al 1992; Kowalska et al.,2000; Chang et al.,2003]
    - Around 14 ppm current exposure
- Mixtures (Xylene often included)
  → In animal studies additive effects have been shown for solvent pairs in high doses
  → In humans many studies with solvent mixtures have shown HL at low current exposure levels
    - Due to differences in exposure content and levels evidence available is not sufficient for the identification of the NOAELs and LOAELs inhumans.

Metals

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Study finds Beethoven died of lead poisoning

By Rick Weiss
Washington Post

By focusing the most powerful X-ray beam in the Western Hemisphere on six of Ludwig van Beethoven's

which evidence now suggests occurred over many years. Among the possibilities are his liberal indulgence in wine consumed from lead cups or perhaps a lifetime of medical treatments, which in the 19th century

Metals

Was the Mad Hatter Deaf?

Fig. 2. 'Mad Hatter' from Lewis Carroll's *Alice's Adventures in Wonderland.* Illustration by John Tenniel. New York, Heritage Press, 1941, p 96.

Schacht J, Hawkins JE. 2006 Sketches of otohistory. Part 11: Ototoxicity: drug-induced hearing loss. Audiol Neurootol. 2006;11(1):1-6.

Metals

- Mercury
  → neurotoxicity and sensorineural hearing deficits
  → excitatory effects on central auditory structures
  → potassium channels may be targets

- Lead
  → dysfunction of the eighth cranial nerve in rats
  → cochlear effects were reported in studies with monkeys
  → central auditory effects in humans

- Organotins - trimethyltin
  → hair cell damage and vascular damage in the cochlea
  → disrupts function at the synapse between the inner hair cell and the Type 1 spiral ganglion cell

Metals – Animal studies

NOAEL	LOAEL	Exposure duration	Referenc-G
Lead (blood lead level)- only			
-	30 µg/dl	In diet: birth to 13 years of age	Rice 1997
35 µg/dl	55 µg/dl	In diet: prenatal to ~10 years of age	Lilienthal and Winneke, 1996
Mercury - only			
-	0.4 mg/kg bw $HgCl_2$	Gavage: daily in 12 weeks (rats)	Fazakas et al 2005
	10 µg/kg/d $HgCH_3Cl$	Orally: gestation to 4 y of age	Rice 1998
Trimethyltins - only			
	0.2 mg/kg bw	single i.p. injection Guinea pigs	Liu and Fechter, 1994
2 mg/kg bw	3 mg/kg bw	single i.p. injection Rats OHC-loss	Crofton et al.,1990

Metals – Human studies

- Lead
  - → NOAEL is not known
  - → Effects seen at blood lead concentrations of 12-64 µg/dl
    - Murata et al., 1993; Jacob, 2000; Wu et al., 2000
  - → No interaction between lead (57 µg/dl) and noise found
    - One study only (Wu et al., 2000)
  - → Auditory effects begin to appear at blood lead levels found in the general population
    - WesternEurope (37 µg/dl) and North America (17 µg/dl) (Sv Krit gruppen, 2005)
- Mercury
  - → Effects shown in central auditory tests at concentration in air of 0.008 mg/m_3 and mean blood mercury levels of 0.5 µg/l
    - (Moshe et al., 2002)
- Trimthyltins
  - → No human studies

Other chemicals

- **Asphyxiants**
- Interfere with cell “breathing”
- Not ototoxic alone
  BUT potentiates other ototoxic agents and Noise
  → Maybe by ROS formation

- Carbon monoxide – CO
  - Smoking

- Hydrogen cyanide
  → Other nitrils

Carbon monoxide – animal studies

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NOAEL	LOAEL	Exposure duration	Reference
Carbon monoxide - only			
1 500 ppm		Inhalation 3.5-9.5 h	Chen and Fechter 1999
-combined with noise (N)			
300 ppm + 95 or 100 dB	500 ppm + 95 or 100 dB	Inhalation 3.5-9.5 h, 5 d N 2 or 4 h, 5 d	Chen and Fechter 2000; Fechter et al 2000
300 ppm + 87 dB SPL Leq8h impulse noise	500 ppm + 87 dB SPL Leq8h impulse noise	Inhalation and N: 6 h/d, 10 d	Lund et al 2003
Hydrogen cyanide - only			
50 ppm		Inhalation: 3.5 h	Fechter et al 2002
-combined with noise (N)			
10 ppm + 100 dB	30 ppm + 100 dB	Inhalation: 3.5 h N: 2 h	Fechter et al 2002

Many stressors makes it worse –

Exposure to CO, noise AND Toluene caused even more HL than CO and noise alone (Lund,Kristiansen and Campo, 2008)

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Carbon monoxide

- Animal studies
  - →Interaction and synergism with noise shown
    - NOAEL without noise 1500 ppm
    - NOAEL with noise 300 ppm
    - LOAEL with noise 500 ppm
- Human studies
  - →Few studies of auditory effects
  - →Type of interaction between carbon monoxide and noise in human studies has not been established
  - →Lowest level is inconclusive,
    - One study suggested that effects occur at approximately 20 ppm without excessive noise exposure (Ahn et al., 2006)

Other chemicals

- Pesticides
  → Many different substances
  → Limited evidence because of the heterogenicity
  → No risk evaluation possible
- PCBs
  → Only investigated in animal studies
  → Some PCBs give auditory effects in the offspring after dosage during gestation
    - NOAEL: 0.25 µg/kg body weight/day (Crofton and Rice, 1999), or 1mg/kg (Powers et al., 2006) depending of PCB mixture
    - LOAEL:1 µg/kg body weight/day (Crofton and Rice, 1999), 1 mg/kg body weight/day (Herr et al, 1996) or 3 mg/kg (Powers et al., 2006) depending of PCB mixture

Is there evidence for the ototoxicity of chemicals in ocuupational settings?

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YES – I think there is!

- Strongest evidence for
  - → Styrene
  - → Toluene
  - → Mixtures of solvents
  - → Lead
  - → Carbon monoxide
- Dose - response relationship not possible from the human studies
  - → Meta analyzes needed
- Strong support from animal studies
  - → Increased risk with more exposure factors

Occupational exposure to chemicals

- **Ototoxic chemicals DO increase the risk for hearing loss**
- **OELs for chemicals do not account for ototoxicity**
- **New EU Noise directive**
  →Acknowledge ototoxic substances
- **Workers exposed to ototoxic chemicals should be included in Hearing Conservation Programs**

Information and knowledge important

- **Which chemicals are ototoxic?**
- **Acknowledge ototoxic substances – HOW??**
- **How do we get this message through?**
- **A need for a ”noise” or ”ototoxin” notation!**

Noise notation suggested by

Hoet P, Lison D. Ototoxicity of toluene and styrene: state of current knowledge. Crit Rev Toxicol.2008;38(2):127-70

Questions ?!
Discussion !