

Ototoxic Risks from aromatic substances

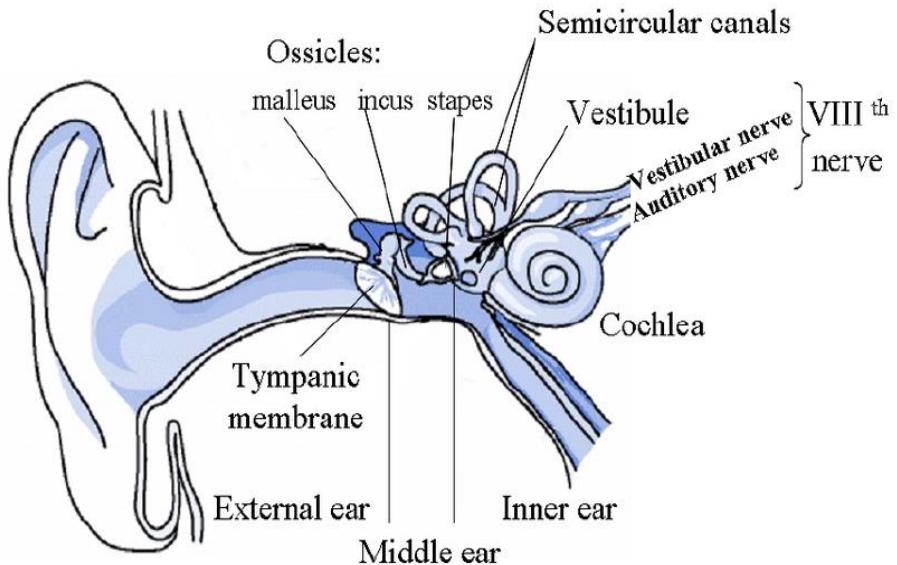
Wassim Maj

Marzhan Zhalilau

Romain Wacongne

Agenda

- Introduction
- Hazard Identification
- Background Information
- Risk Assessment
- Relevant Regulations
- Recommendations



- Aromatic compounds such as toluene, styrene, ethylbenzene, p-xylene, various methylstyrenes, allylbenzene and n-propylbenzene have a "good" level of evidence for ototoxicity.
- Cochlear hair cells is a target tissue for these solvents.
- Acute effect on the organ of Corti.
- Long-term exposure:
 - Disruption of K⁺ balance
 - Formation of reactive intermediates

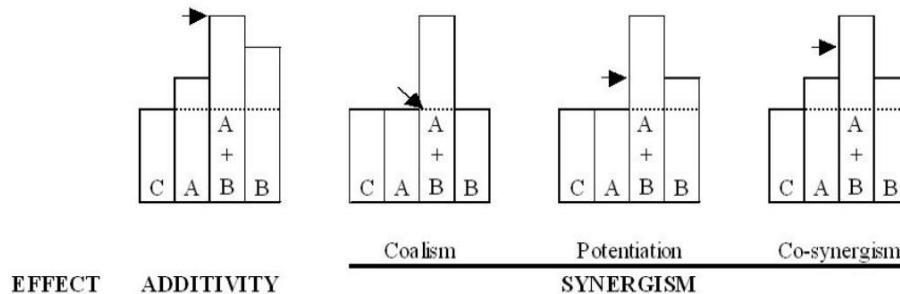
Background Information

- Sources of Ototoxic Aromatic Substances:

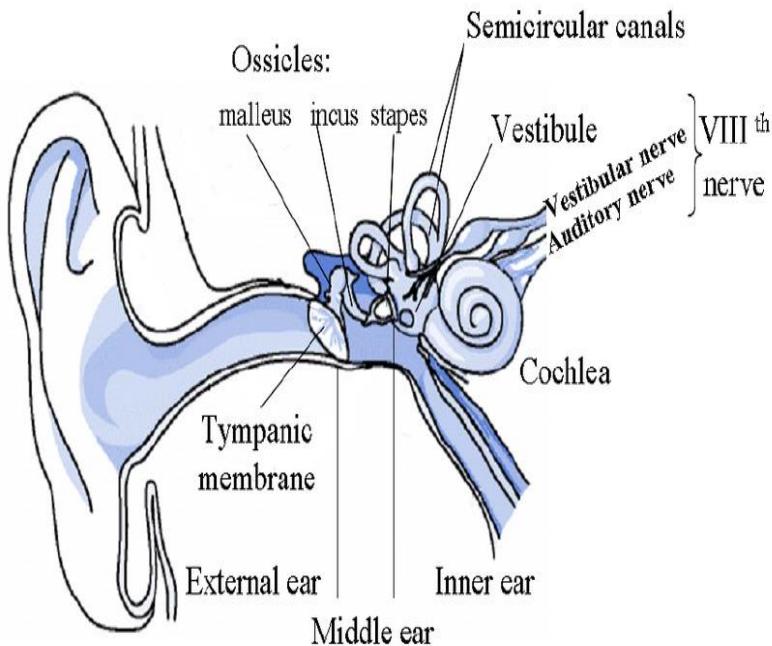
CHEMICAL AGENT	MAJOR USES
Toluene	Production of benzoic acid, benzaldehyde, explosives, dyes, and many other organic compounds; solvent for paints, lacquers, gums, resins; extracting agent; petrol and naphtha constituent; additive; fabric and paper coating, artificial leather and detergent manufacture. Toluene is often found together with other solvents.
Ethylbenzene	Almost exclusively used for the production of styrene. Only a small proportion is used as a solvent.
n-Propylbenzene	Textile dying, solvent for cellulose acetate.
Styrene	Manufacture of plastics, rubber articles, glass fibres; synthetic rubber; insulators; used as a chemical intermediate, particularly in the resin and plastics production, component in agricultural products and stabilising agent.
p-Xylene	Manufacture of resins, paints, varnishes, general solvent for adhesives; in aviation kerosene; protective coatings; synthesis of organic chemicals; solvent (e.g. for paints, coatings, adhesives and rubber); used in production of quartz crystal oscillators, perfumes, insect repellents, epoxy resins, pharmaceuticals, and in the leather industry. Used as a solvent in phenoxyalkanoic herbicides.

- Age, smoking, exposure to other types of chemicals.
- Aggravating factor: combined exposure with noise
- Solvents can reduce the protective role played by the middle-ear acoustic reflex.

Figure 6: Illustration of different outcomes after exposures to agents A and B. C = control (unexposed) group. Arrows indicate predicted effects. Dotted lines indicate control values (from Nylen, 1994).



Mechanisms of Ototoxicity



As defined before, ototoxic components can have some damage that could impair hearing, sound distortion, frequency resolution, temporal resolution and spatial resolution or both. These damages are resulted through different mechanisms:

- Blood-Labyrinth Barrier Permeability
- Cellular damage in hair cells
- Disruption of Ion Homeostasis
- Neurotoxicity
- Genetic Susceptibility
- Duration and dose of exposure

Data on illness/accidents

- "Research on ototoxicants and their interactions with noise is limited."
- As it is challenging to make the difference between the illness caused by noise exposure and by ototoxic exposure, collecting data becomes almost impossible.
- "Unfortunately, human inner ear tissue is generally inaccessible, making it difficult to study and to collect data."
- In a study it has been declared that:
 - 80% of Australian workers are exposed to noise and at least one ototoxic substance.
 - 30% of European workers reported being exposed to noise, about 45% were exposed to ototoxic chemicals.

Worldwide level for ototoxic exposure to medication

<i>Médicaments ototoxiques</i>	<i>Nombre de personnes exposées au médicament ototoxique (par an)</i>	<i>Nombre de cas de perte auditive associés (par an)</i>
Antibiotiques de type aminoglycosides (traitement de courte-durée)	118 676 000	19 641 000
Antibiotiques de type aminoglycosides pour le traitement de la tuberculose multi-résistante	135 000	55 000
Chimiothérapie avec sels de platine (cisplatine ou carboplatine)	1 022 000	441 000
Médicaments antipaludiques	133 736 000	12 276 000
Total	257 395 000	33 750 000

Example of collected data: Hot pressing working area

- The study result realized by the BGIA: Berufsgenossenschaftliches Institut für Arbeitsschutz.
- It was conducted on four of the most important aromatic substances.
- We can find three more different studies on other working areas such as prepreg, moulding and core-making in foundries, and surface coating, application with machines

Evaluations of the BGIA – MEGA hazardous substances database

Period of time: 1990 – 2007

Exposure level per shift

Ototoxic substance OEL	Number of measured values	Number of companies	Below detection limit: Number %	Below limit value (OEL) %	Concentration (mg/m ³)		
					50th percentile	90th percentile	95th percentile
Toluene 190 mg/m ³	20	11	11 55	100	ADL	3.4	4.1
Xylene 440 mg/m ³	13	8	7 53.8	100	ADL	2.92	30.21
Styrene 86 mg/m ³	298	43	23 7.7	75.5	51	136.8	179
Ethylbenzene 440 mg/m ³	4	3	1 25	100			

ADL: No percentile concentration is calculated because there are more values below the analytical detection limit (ADL) as represented by the percentage of this percentile OEL: Occupational Exposure Limit (Germany)

International Chemical Safety Cards (ICSCs)

- Jointly developed by **International Labour Organisation (ILO)**, **World Health Organisation (WHO)**, **United Nations Environment Programme (UNEP)**
- Consist of a series of standard sentences summarising health and safety information, collected, verified and peer-reviewed by internationally recognised scientists.
- Ototoxic properties (e.g., toluene, xylene) acknowledged when combined with noise exposure; other chemicals (e.g., styrene, ethylbenzene) lack this indication.

Regulation – International Organizations

TOLUENE Methylbenzene Toluol Phenylmethane CAS #: 108-88-3 UN #: 1294 EC Number: 203-625-9	ICSC: 0078 (November 2023)
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	ACUTE HAZARDS	PREVENTION	FIRE FIGHTING
FIRE & EXPLOSION	Highly flammable. Vapour/air mixtures are explosive. Risk of fire and explosion on contact with strong oxidants.	NO open flames, NO sparks and NO smoking. Closed system, ventilation, explosion-proof electrical equipment and lighting. Prevent build-up of electrostatic charges (e.g., by grounding). Do NOT use compressed air for filling, discharging, or handling. Use non-sparking handtools. NO contact with strong oxidizing agents.	Use foam, powder, carbon dioxide, water spray. In case of fire: keep drums, etc., cool by spraying with water.

AVOID ALL CONTACT!			
	SYMPTOMS	PREVENTION	FIRST AID
Inhalation	Sore throat. Cough. Dizziness. Drowsiness. Headache. Nausea. Unconsciousness.	Use ventilation, local exhaust or breathing protection.	Fresh air, rest. Refer immediately for medical attention.
Skin	Redness. Dry skin.	Protective gloves.	First rinse with plenty of water for at least 15 minutes, then remove contaminated clothes and rinse again. Rinse and then wash skin with water and soap. Refer for medical attention.
Eyes	Redness. Pain.	Wear safety goggles.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then refer for medical attention.
Ingestion	Aspiration hazard! Burning sensation. Abdominal pain. Vomiting. Further see Inhalation.	Do not eat, drink, or smoke during work.	Rinse mouth. Give nothing to drink. Do NOT induce vomiting. Refer immediately for medical attention. See Notes.

SPILLAGE DISPOSAL	CLASSIFICATION & LABELLING
Evacuate danger area! Consult an expert! Personal protection: chemical protection suit and self-contained breathing apparatus. Ventilation. Remove all ignition sources. Do NOT wash away into sewer. Do NOT let this chemical enter the environment. Collect leaking and spilled liquid in sealable containers as far as possible. Absorb remaining liquid in sand or inert absorbent. Then store and dispose of according to local regulations.	According to UN GHS Criteria  DANGER
STORAGE	Highly flammable liquid and vapour May be fatal if swallowed and enters airways Causes skin irritation May cause drowsiness or dizziness Suspected of damaging fertility or the unborn child May cause damage to nervous system through prolonged or repeated exposure Toxic to aquatic life with long lasting effects
PACKAGING	Transportation UN Classification

EU Directives:

- **Directive 98/24/EC:** Covers protection from chemical agents at work.
- In addition to occupational health and safety issues the EU chemical agent legislation regulates the internal market (<http://www.echa.europa.eu>)
- **Directive 2003/10/EC:** Sets minimum requirements for noise exposure at work.
 - Requires risk assessment for combined noise and ototoxic substances.
- **REACH Regulation:**
- Applies to the registration and risk assessment of chemicals, but limited to tonnages >10 tonnes/year.

IC Substance Infocard See a problem or have feedback?

[RSS](#)

Xylene

Regulatory process names 18 Translated names 22 IUPAC names 70 Trade names 10 Other identifiers 3

[BP](#) [OBL](#)

Substance identity

EC / List no.: 215-535-7

CAS no.: 1330-20-7

Mol. formula:

Cc1ccccc1

Hazard classification & labelling

Warning! According to the **harmonised classification and labelling** (CLP00) approved by the European Union, this substance is a flammable liquid and vapour, is harmful in contact with skin, is harmful if inhaled and causes skin irritation.

Additionally, the classification provided by companies to ECHA in **REACH registrations** identifies that this substance may be fatal if swallowed and enters airways, is a highly flammable liquid and vapour, causes serious eye irritation, may cause damage to organs through prolonged or repeated exposure, is harmful to aquatic life with long lasting effects and may cause respiratory irritation.

About this substance

This substance is registered under the REACH Regulation and is manufactured in and / or imported to the European Economic Area, at $\geq 1\,000$ to $< 10\,000$ tonnes per annum.

This substance is used by consumers, in articles, by professional workers (widespread uses), in formulation or re-packing, at industrial sites and in manufacturing.

Consumer Uses

This substance is used in the following products: lubricants and greases, anti-freeze products, biocides (e.g. disinfectants, pest control products), polishes and waxes and adhesives and sealants. Other release to the environment of this substance is likely to occur from: indoor use (e.g. machine wash liquids/detergents, automotive care products, paints and coating or adhesives, fragrances and air fresheners),

Important to know

- Substance included in the **Community Rolling Action Plan (CoRAP)**.

How to use it safely

- Precautionary measures** suggested by manufacturers and importers of this substance.
- Guidance on the safe use of the substance** provided by manufacturers and importers of this substance.

- **National Occupational Research Agenda (NORA)** (NIOSH, 1996)
Framework for innovative occupational safety research developed in the U.S
- **Priority areas:**
"Hearing Loss" & "Mixed Exposures" (focus on noise + ototoxic chemicals)
- **NIOSH Hearing Loss Research (HLR) Programme:**
 - Research on ototoxic chemical effects with/without noise
 - Engineering noise control and new hearing protection technologies
 - Partnerships with universities and health organizations

Preventing Exposure to Ototoxicants

1. Identify Ototoxicants

Review **Safety Data Sheets** for ototoxic substances

Train workers on hazards in clear, simple language (OSHA 29 CFR 1910.1200)

Investigate complaints of hearing loss (check SDS for ototoxic agents)

2. Control Exposure

Chemical Substitution: Replace with safer alternatives

Engineering Controls:

Isolation and enclosures

Ventilation to reduce airborne exposure

Administrative Controls:

Eliminate unnecessary noise/chemical tasks

Schedule noisy equipment away from workers

3. Personal Protective Equipment (PPE)

PPE Assessment: Follow OSHA standards (29 CFR 1910.132, 1910.134, 1910.138)

Protective Gear: Gloves, aprons for skin protection

Audiometric Testing:

Conduct testing even below action levels

Use hearing protection to prevent combined exposure effects (OSHA 29 CFR 1910.95)

Any Ototoxic Questions?



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