Chemical Toxicity to the Special Senses: Vision, Hearing, Taste, and Smell

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Introduction

- 50% of neurotoxic chemicals may affect some aspect of SENSORY SYSTEM.
- Most sensitive to exposure related toxicity
- First reported following exposure.
- Exist in the absence of other organ toxicity
- Visual symptoms are the most frequently reported.
- Alteration in structure and function of the eye are often the criteria utilized for setting permissible exposure limits for chemicals in the USA
- Visual processing of information can have immediate, long term, delayed effects on mental, social and physical health and performance
- Auditory and visual impairments can lead to occupational injuries.
Overview

- Neuro-Ophthalmological Dysfunctions (Toxicology of the Visual System)
- Ototoxicity (Toxicology of the Auditory System)
- Gustatory Dysfunctions (Toxicology of the Sensory System of Taste)
- Olfactory Dysfunction (Toxicology of Sensory System of Smell)

Occupational Exposures

- Greater than 80,000 industrial chemicals in use today.
- Approx. 3,000 chemicals known toxic to the eye/visual system.
- Routes of exposure can vary depending on chemical form (i.e., fumes, liquids, solids).
  - Inhalation (e.g., fumes, gases) – Primary route of occupational exposures
  - Ingestion (e.g., liquids, dust)
  - Absorption (e.g., solvents)
- Onset of illness can be either by ACUTE or CHRONIC exposures
  - Chronic exposures are the most widely studied.
Visual System Anatomy

• Peripheral
  • External Layers of the Retina
    • Color Vision (cones)
    • Night vision (rods)
  • Central
    • Internal layers of the retina
    • Optic Nerve
    • Visual Pathways
    • Visual Cortex

Visual System Dysfunction

• Peripheral Visual System
  • Retinal pigmented epithelium (RPE)
    • photoreceptors have highest O2 consumption of any tissue in the human body
  • 75% of the retinal mitochondria in this area (vulnerable to toxicity)
  • High body affinity to bind PAH and metals including Pb, Hg

• Central Visual System Pathways
  • Optic nerve and Visual cortex
    • increased basal oxygen consumption increases with visual stimuli
Visual System Testing

• Color Vision Testing (dyschromatopsia)
• Electroretinogram (inner and outer layers)
• Visual Field Testing (Optic nerve dysfunction)
• Oculomotor Testing (Cranial nerve dysfunction)
• Contrast Sensitivity Testing (nonspecific threshold testing)
• Critical Flicker Fusion (non specific)
• **VISUAL SEARCH PERFORMANCE**
• Visual Evoked Potential Testing (central pathway dysfunction)

Vision Testing Methods

• **Color Vision Testing**
  • Farnsworth-Munsell 100 (FM-100) Hue Color Vision Test
  • Lanthony Desaturated D15 (LD15), or D15d most utilized.

• **Visual Evoked Potential (VEP)**
  • Initiated by brief visual stimuli, recorded by EEG signals.
  • Measures functional integrity of the visual pathways from retina via the optic nerves to the visual cortex of the brain.
Kollner’s Rule and Dyschromatopsia

• Dysfunction can be localized by the type of vision loss:
  • Toxicity to peripheral system (Retina) leads to Blue-Yellow (BY) deficits
  • Toxicity to central pathways leads to Red-Green (RG) deficits

• Type III: External retinal layers: BY loss; RARE INHERITED, ALTITUDE?
  • normal to moderate acuity loss. TRITAN
• Type II: Internal retinal layers: RG and BY loss ;
  • moderate to severe acuity loss. DEUTAN
• Type I: Internal retinal layers: RG loss:
  • moderate acuity loss. PROTAN

Toxins Associated with Vision Loss
Occupational Exposure to Styrene

Industrial solvent in the manufacturing of plastics; associated with alterations in color vision (Type III blue-yellow) in workers exposed to concentrations between 4-70 ppm for 5-17 years (Fox 2015).
Toxins Associated With Vision Loss
Occupational Exposure to Perchloroethylene and Trichloroethylene

33 dry cleaners (mean age 31) exposed to occupational levels of TCE

Results showed significantly lower contrast sensitivity ($p < 0.05$) and poorer color discrimination (BY) when compared to controls ($n = 35$).

High level deficits in perception of global form and motion were also recorded ($p < 0.0001$).

Toxins Associated With Vision Loss
Occupational Exposure to Carbon disulfide

Vast industrial uses (e.g., clothing, industrial solvent, pesticides)

Known for neurological and vascular dysfunction: retinal alterations (e.g., retrobulbar neuritis, pre-senile arteriosclerotic changes in the fundus, microaneurysms and small hemorrhages, delayed papillary filling, and irregularities in the caliber of retinal arterioles and veins).

Clinical studies describe severe loss of central vision (central scotoma), decreased sensitivity in peripheral visual fields (rod scotoma), optic atrophy, blurred vision, impaired color vision (BY), and papillary changes.
Toxins Associated With Vision Loss

Occupational exposure to **Lead (Pb) – inorganic**

Lead-acid battery manufacturing, welding, electronic manufacturing (lead solder), jewelry making, etc.

Decreases in critical flicker fusion have been recorded in workers with a mean blood lead level (BLL) of 35-47 ug/dL.

Peripheral and paracentral scotomas have also been seen in workers chronically exposed (>5 yrs) to moderate-levels of Pb or those acutely exposed to high-levels of Pb.

Many papers prior to 2000 documenting visual toxicity to lead using various method of assessment.

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**GENETICS AND ENVIRONMENT**

- Macular degeneration
  - Lead may accumulate in RPE layers and has been associated.
  - Herbicides in drinking water.

- Glaucoma and hair lead.

- Leber’s Optic Hereditary Neuropathy and organic solvents.
Ototoxicity: Auditory system anatomy

• Inner ear includes Cochlear hair cells
  • Converts of sound waves of different frequencies and amplitudes into electrical signals
  • Tonotopically organized with different sounds stimulating different areas of the organ which then stimulate different brain stem cell nuclei and different areas of auditory cortex
  • Conduction hearing deficit is the outer ear (on the way to the inner ear)
  • Sensory neural hearing loss is a change in the cochlea
  • Central hearing loss localizes to the acoustic nerve or auditory cortex
  • Outer hair cells affected first
  • Cochlear hearing loss is most common due to aging and noise

Noise induced hearing loss

• 10 years or more:
  • 8% of 85 db; 22% of 90 db; 38% of 95 db; 44% of 100 db
  • 20-25 db threshold shifts, and 10 db, high frequency loss is normal
  • Should not progress if noise ceases
  • Early detrimental exposure leads to worsened susceptibility to progression with age related hearing loss
  • Higher frequencies first affected than progress to lower frequencies
  • Combination with ototoxicity and aging
  • In 1940, occupational populations had higher prevalence of hearing loss without noise exposure in industry
**Audiology Testing Methods**
(Not sensitive to ototoxicity)

- **Pure-Tone Audiometry** (R/L ear hearing sensitivities)
- **High-Frequency Audiometry** (Frequencies: 10, 12.5, 14 and 16 kHz)
- **Immittance Audiometry** (physical volume, tympanometry, etc.)
- Behavioral and Reflex modification audiometry (animals, startle and warning thresholds)
- **Electrocochleography**
- **Central Auditory Processing Test** (electrophysiological and behavioral tests)

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**Toxins Associated with Hearing Loss**

**Occupational Exposure to Solvents (e.g., Styrene, Toluene, Trichloroethylene)**

Plastics (styrene), paint industry (toluene), dry cleaning industry (trichloroethylene).

*Synergistic relationship; exposures and to noise. Cochlear toxicity.*

Long-term exposure to Styrene ((OEL 20-100 ppm): demonstrated auditory effects in workers exposed to 30-50 ppm for at least 10 years with levels above 50 ppm in the past. In humans, the type of interaction taking place between noise and styrene exposure is not yet clear.

Ototoxic effects (BAER abnormalities) from Toluene (OEL 20-200 ppm): associated with current exposure levels of approximately 10-50 ppm. Historic toluene and/or noise exposure levels not well characterized and some with co-exposures. Exposed to higher concentrations in past and present could explain.
Toxins Associated with Hearing Loss
Occupational Exposure to Lead (Pb)

Used in gasoline as an antiknocking agent; jewelry industry, the automotive industry (e.g., lead-acid batteries), and in industrial paints. Inhalation of dust and fumes; ingestion in children.

Central auditory effects (BAER) found with current and life-time weighted average of 28-57 ug/dl of BLL.

- Workers with a mean BLL of 37 ug/dL as having significant increases in hearing thresholds compared to controls.
- Uncertain interaction with noise and lead.

Hearing loss and Toxicity

- TCE, CS2, Xylene, N hexane, Hg, CO, Pesticides associated with auditory effects in humans.
- Occupational studies (styrene, toluene, solvent mixtures and lead) indicate that much lower levels in industrial settings were associated with hearing deficits.
- Combinations of exposure with noise, other stressors such as physical activity during exposure contribute to lower exposure intensity and duration leading to ototoxicity.
Olfactory Toxicity and Anatomy

- Olfactory Dysfunction 1-5% from toxins.
- Exposures irritation and removal natural
- Chronic exposures, subthreshold dangerous with time; unnoticed gradual decrease of function.
- Age related loss secondary to accumulation of damage from low level non irritant exposures?
- Olfactory epithelium direct contact (10% of respired air flow)
  - Regenerative capacity
  - Immunological defense, antimicrobial agents, etc
  - Metabolizing potential detoxification (reactive oxygen scavenging) or increasing toxicity?
- Neurons with dendrites extending into Cribiform plate to contact directly with olfactory bulb in CNS.
- Gases and solvents may reach olf bulb via systemic circulation, Metals via receptors

Olfactory Dysfunction

- Types of olfactory dysfunction:
  - Psychophysical (detection sensitivity)
  - Electrophysiological (measured electrical changes following stimulus)
  - Psychophysiologicaal (assess odor-induced autonomic nervous system responses)
Olfactory Testing Method

- **UPSIT** (University of Pennsylvania Smell Identification Test)
  - Test consists of 4 different 10 page booklets with “scratch and sniff” strips
  - Scoring accounts for age and gender
  - Considered the gold standard of smell identification
  - Used in testing for a multiple of neurological diseases such as: Parkinson’s disease, Alzheimer’s, Huntington’s disease, brain tumors, and Multiple Sclerosis

Toxins Associated With Olfactory Dysfunction

**Highlights from the literature**

- **Cadmium**: Olfactory dysfunction noted even at ACGIH proposed levels.
- **Mercury**: UPSIT utilized in Minimata Bay survivors and found reduced ability to identify stimuli.
- **Manganese**: Excitability of neurons heralds toxicity, then function decreases. Increase in urine Mn associated with lower detection threshold; lower in iron alloy workers. Changes related to dopaminergic dysfunction at the level of receptor. Active transport through olfactory tract.
- **Populations in Italy with elevated environmental exposure to Mn had increased prevalence of PD and odor identification.**
Toxin Associated Olfactory Dysfunction

- **Lead:** No influence on Olfactory system in tetraethyl lead manufacturers using UPSIT.
- **Toluene:** Inhalation chamber study revealed increased thresholds that returned to normal. No permanent insult.
- **Paint solvent:** UPSIT testing revealed dose related decrement in non smoking paint manufacture workers suggesting protection.

Gustatory Toxicology: Anatomy of Taste

- **Saliva contains sodium, potassium, chloride and bicarbonate**
- **Salivary glands:** parotid, submandibular, sublingual and minor
  - Autonomic nervous system controlled
  - Alteration of components or volume will affect saltiness, sourness
  - Autoimmune disorders, medicines, systemic diseases
- **Oral mucosa**
  - Chemical burns, fungi, viruses, tobacco, gastric acid
- **Taste Bud Receptors**
  - Activated; reduced in number
  - Botox, tetrodotoxin, chemotherapeutics, tobacco
- **Central pathways**
  - Infection, inflammation: Botox, HZV, Bells palsy, GBS, poliomyelitis, MS
Gustatory Testing Methods

- **Taste strips** (taste infused strips)
  - Inexpensive and very simple to use
  - Administered and recorded in clinical or field setting
- **Electrogustometry** (measurement of taste threshold)
  - Clinical setting
  - Pass controlled anodal current through the tongue causing unique and distinct metallic taste (e.g., sensation experienced when placing 9-volt battery on the tongue)

Toxins Associated with Gustatory Dysfunction

Isodecanes used in manufacturing of paint, imaging toners and floor cleaners.

- 63-year-old woman: Smell and taste loss after a 3-year exposure. Initially welts on her tongue and lips, chest tightness, bitter taste 8 years prior.
- Gradual smell and taste loss, intraoral burning sensations, and periodic perioral dermatitis.
- No improvement occurred with cromolyn sodium, zinc chloride, or copper sulfate.
- Examination of the olfactory epithelium revealed a flat, yellow area with scarring. Sinus CT scan was normal.
- Olfactory testing: mild-to-moderate hyposmia.
- Suprathreshold taste testing: Depressed intensity ratings, poor taste identification, and no response to bitter stimuli.
- After topical anesthesia, taste responses were reduced to zero.
- Ineffective treatment.
**Toxins Associated with Gustatory Dysfunction**

**Acute ammonia exposure**

- A 31-year-old man presented with hypogeusia 4 months after biting down on an ammonia capsule hidden in a store-bought sandwich.
- He sustained an intraoral chemical burn injury, immediate-onset ageusia, and decreased sensitivity to oral stimuli.
- His medical history was significant for environmental allergies. He smoked <1 pack of cigarettes per day for <5 years.
- Examination and olfactory testing was normal.
- Suprathreshold taste was consistent with hypogeusia: identified stimuli of moderate and high concentration.

**Toxins Associated with Gustatory Dysfunction**

**Lead (Pb)**

- Workers complain of metallic tastes, coinciding with a specific metal.
- Brass pipe fitters and jewelry workers suffering from lead poisoning, frequently report a persistent, sweet, metallic taste.
- Because heavy metals are concentrated in saliva and their topical application on the tongue can diminish taste perception, a possible direct mechanism of action has been hypothesized.
Toxins Associated with Gustatory Dysfunction

Occupational exposure to Chromium (Cr)

- Metal plating, anti-corrosive agent, manufacture of stainless steel
- Increased taste thresholds noted in workers with chromium exposures using both chemical stimuli and electrical stimuli.

Toxins Associated with Gustatory Dysfunction

Organophosphate-based pesticides (e.g., DDT, Parathion)

- Workers with frequent exposure to pesticides have complaints of sustained metallic, bitter taste.
- Specific OP exposures associated with a garlic taste and odor.
- Experimental models, disruption of sensory nerve terminations, but they may also interfere with central neurotransmitters.
Toxins Associated with Gustatory Dysfunction

Solvents

Cross-sectional study of 264 workers exposed to organic solvents
Increase prevalence of smell and/or taste dysfunctions, similar to work related dizziness.
Disturbances in smell or taste were most often hyposmia, but hypogeusia and a persistent “glue” taste were reported.
Symptoms, however, were generally transitory, reversible, and likely due to concentration peaks rather than long-term exposures.

Solvent-induced sensory dysfunctions

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Reference</th>
<th>Neurotoxic Sensory Endpoint(s)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Vision</td>
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<tr>
<td>Ammonia</td>
<td>Prudhomme et al. 1998</td>
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<tr>
<td>Carbon disulfide</td>
<td>Fox D. 2015; Gobba 2003</td>
<td>C, P</td>
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<tr>
<td>Isodecanes</td>
<td>Smith et al. 2009</td>
<td></td>
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<tr>
<td>Methyl isobutyl ketone (MIBK)</td>
<td>Gagnon et al. 1994</td>
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<tr>
<td>n-Hexane</td>
<td>Gobba, 2003</td>
<td>P, C</td>
</tr>
<tr>
<td>Perchloroethylene (PCE)</td>
<td>Gobba and Cavalleri 2003</td>
<td>P, C</td>
</tr>
<tr>
<td>Styrene</td>
<td>Fox D. 2015; Kjell, ed. 2010</td>
<td>P</td>
</tr>
<tr>
<td>Toluene</td>
<td>Fox D. 2015; Kjell, ed. 2010; Mergler 1992</td>
<td>P, C</td>
</tr>
<tr>
<td>Trichloroethylene (TCE)</td>
<td>Barbosa et al. 2015; Gobba 2003</td>
<td>P, C</td>
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<tr>
<td>Xylene</td>
<td>Gobba 2003</td>
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# Heavy metal-induced sensory dysfunction

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<tbody>
<tr>
<td>Cadmium</td>
<td>Mascagni, 2003, Gobba 2003</td>
<td>Hearing, X, Taste</td>
</tr>
<tr>
<td>Chromium (Cr)</td>
<td>Reiter et al. 2006; Seeber et al. 1990, Gobba 2003</td>
<td>Vision, C or P, Hearing, X, Taste</td>
</tr>
<tr>
<td>Lead (Pb)</td>
<td>Fox D. 2015; Kjell, ed. 2010; Reiter et al. 2006; Bolla et al. 1995</td>
<td>Hearing, C, X, X, Taste</td>
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# Pesticide-induced sensory dysfunction

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<tr>
<td>DDT</td>
<td>Reiter et al. 2006</td>
<td>Vision, Hearing, X</td>
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<tr>
<td>OP-based pesticides</td>
<td>Reiter et al. 2006</td>
<td>Vision, Hearing, X</td>
</tr>
<tr>
<td>Parathion</td>
<td>Reiter et al. 2006</td>
<td>Vision, Hearing, X</td>
</tr>
<tr>
<td>Sulfuryl fluoride</td>
<td>Calvert et al. 1998</td>
<td>Vision, Hearing, X</td>
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References


References (cont’d)

References (cont’d)

- Prudhomme, JC, Shusterman DJ and Blanc PB. Acute-Onset Persistent Olfactory Deficit Resulting From Multiple Overexposures to Ammonia Vapor at Work JABFP Jan.-Feb.I998 Vol. II No.1

References

MOC Question ONE

• Which industries have NOT been studied regarding color vision toxicity?

• A. Dry cleaning  
• B. Airline workers  
• C. Boat builders  
• D. Tetraethyl Lead workers

MOC Question TWO

• Which of these sensory systems anatomical areas are considered part of the Central Nervous System?

• A. Olfactory Bulb  
• B. Cribiform Plate  
• C. Salivary Glands  
• D. External Retinal Layer
MOC Question THREE

• Which neurophysiological test is matched incorrectly?

• A. Critical Flicker Fusion: Vision
• B. UPSIT: Smell
• C. Electrogustography: Taste
• D. High Frequency Audiometry: Hearing
• E. None

Answers

• I. B
• II. A
• III. A-3, B-1, C-2, D-4