VISUAL SYSTEM MANIFESTATIONS DUE TO SYSTEMIC EXPOSURE TO MERCURY

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This article is a summary of the available literature on ocular symptoms due to systemic exposure to mercury. Mercury compounds are first described in terms of their different forms, industrial applications, mechanisms and routes of exposure, toxicity levels, and treatment methods. Eye symptoms are then characterized for organic and inorganic forms of mercury by using the form of various documented case studies of chronic and acute exposure to various mercury compounds.

Keywords: Mercury

INTRODUCTION

The adverse effects of mercury are so common that they have been anointed *mercurialism* (89). Mercury derivatives can either exist in inorganic forms (including inorganic salts and elemental form), and organic forms (102). One of mercury’s most common toxic forms is mercury vapor, which can be present in both organic and inorganic forms (38). Other highly toxic forms include fulminate of mercury [Hg (CNO)₂], an organic form, and mercury nitrate (inorganic) (89,102).

Organic mercury compounds are used as seed fungicides (e.g., ethylmercury), diuretics (e.g., chloromerodrin), sterilizing agents (e.g., phenylmercury), and topical antiseptics (e.g., thimerosal) (102). Inorganic mercury is used as a catalyst in industry (e.g., mercuric chloride), treatment of corneal ulcers (mercurous chloride), syphilis antidote (mercuric sulfide), and antiseptic for eye inflammation (mercuric oxide) (38). Combustion of fossil fuels contributes to almost one-third of all atmospheric mercury (72).

The use of mercury in production has caused one of the world’s largest industrial crises. The Minamata mine of Japan in the 1950s was a site where mercuric chloride was used as a catalyst for producing vinyl chloride and acetaldehyde. Large quantities of mercuric chloride were dispersed into the sewage, where it changed into an organic form and poisoned the fish that were later eaten by the natives and lead to Minamata disease, which resulted in about 700 poisonings and 70 fatalities (40,46,55,94,97). In a similar epidemic in Iraq, several hundred people ingested seeds

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treated with methylmercury, which was used as a preservative; many people were poisoned as a result (38,49).

Mercury is introduced into the body via inhalation (the quickest route to exposure, particularly with inorganic mercury), as well as ingestion (only 2.2% of the absorption rate of the lungs, e.g., methylmercury), or the gastrointestinal tract (mercury vapor) (38,72,75,76,89). After inhalation the mercuric ion is transferred to the blood and deposited to body tissues (mostly the kidneys) (89,94). If ingested, it changes into glutathione and cysteine, enters the blood, and eventually reaches the brain (20). Mercuric ions precipitate as protein forms, restraining cellular enzymes (75). Mercury is finally excreted directly by the blood within 2 to 3 days, or via the kidney and colon within 37 to 60 days (89). Methylmercury is excreted in the urine and feces as the inorganic form cysteine (89).

Although highly toxic, mercury is not considered carcinogetic, as designated A4 by American Conference of Governmental Industrial Hygienists (ACGIH) (5). Mercury compounds, due to their varying magnitude of toxicity within the same groups, have varying threshold limits. However, an approximate rule-of-thumb level is set as to not to exceed 0.1 mg/m³ of air (75). Table 1 lists the exposure limits as determined by ACGIH, National Institute for Occupational Safety and Health (NIOSH), and Occupational Safety and Health Administration (OSHA). Note that only ACGIH provides standard limits for inorganic mercury compounds (4,31).

The Biological Exposure Index (BEI) for inorganic mercury is 35 mg/g of creatinine in the urine (5). As for organic mercury, relationships exist between mercury levels in the urine and time-weighted air concentrations (38). Atkinson’s brownish reflection is used in detecting mercurialentis (60,89). The analysis of mercury levels in the hair has also been utilized (100). Topical antidotes for mercury exposure include mercuric oxide, sodium edetate (EDTA) (e.g., for mercuric chloride) (7), as well as hydraphogen (for treating blepharitis), mercuric sulfide (corneal opacities), and phenylmercuric salts (glaucoma) (38). Systemic medications include NAPA (N-acetyl-D-penicillamine) for chronic exposure, and BAL (British Anti-Lewisite) for acute exposure (56,72,76). Hemodialysis has been effective in removing mercury from the blood.

<table>
<thead>
<tr>
<th>Compound</th>
<th>OSHA: PEL⁴ (mg/m³)</th>
<th>NIOSH: REL⁴ (mg/m³)</th>
<th>ACGIH: TLV⁵ (mg/m³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkyl mercury (organic)</td>
<td>0.01, Ceiling limit: 0.04</td>
<td>0.01, IDLH⁴: 2</td>
<td>0.01, STEL⁵: 0.03</td>
</tr>
<tr>
<td>Aryl mercury (organic)</td>
<td>0.1</td>
<td>0.05, IDLH: 10</td>
<td>0.10</td>
</tr>
<tr>
<td>Inorganic mercury</td>
<td></td>
<td></td>
<td>0.025</td>
</tr>
<tr>
<td>Mercury vapor (inorganic)</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

⁴PEL: Permissible Exposure Limit set by OSHA (Occupational Safety and Health Administration).
⁵REL: Recommended Exposure Limit set by NIOSH (National Institute for Occupational Safety and Health).
⁶TLV: Threshold Limit Value set by ACGIH (American Conference of Governmental Industrial Hygienists).
⁷IDLH: Immediate Danger to Life and Health (NIOSH).
⁸STEL: Short-Term Exposure Limit (ACGIH).
OCULAR MANIFESTATIONS OF MERCURIALISM

Eye signs of mercurialism act chiefly on neural tissue, but visible ocular symptoms also do occur (e.g., on the cornea, sclera, and lens). In addition, signs are mainly chronic (e.g., photophobia and mercurialentis) (39, 61, 91); although, early symptoms from high exposure to mercury do occur, including eyelid tremors (58).

Mercury is known, in some instances, to cause partial or complete loss of vision (14, 75). In addition, severe constriction in peripheral visual fields is a symptom of organic mercury (ethyl- and methylmercury) poisoning in the blood, and is one of its earliest reported manifestations (30, 39, 61, 72, 85, 86, 89, 98, 102).

Organic Mercury

Methylmercury compounds, the most extensively covered organic mercurials (27), include dimethylmercury, as well as methylmercury hydroxide, -iodide, -nitrate, -phosphate, and -thioacetamide forms, most or all have some effect on vision and/or visual fields.

Methylmercury. Early in the twentieth century four cases of workers inhaling methylmercury vapor discharged from a fungicide plant were reported (42). Constriction of visual fields occurred in all of the workers, and it was localized in central visual areas in three cases. One patient, who was monitored for 15 years until his death, continued to have constricted visual fields, ataxia, and other symptoms. After death, the patient was found to have atrophy of the visual cortex (32).

Another case involves poisoning due to fungicides using a dimethyl compound of mercury; however, only the central nervous system was affected. Visual manifestations included immediate constriction of vision accompanied with tremor and ataxia (89).

A further incident occurred in the 1940s in which two workers were poisoned by spraying wood with a preservative containing methylmercury (3, 62). Bilateral concentric narrowing of visual fields occurred in both workers, causing them to develop total blindness, followed by death.

Methylmercury primarily causes neuro-ophthalmological effects, as experienced with Minamata disease (47, 48, 53, 57, 66, 68, 95), in Iraq (6, 81, 82), and in other epidemics (71, 74). Visual effects in these widespread instances include the degeneration of peripheral vision (a unique sign in all of these cases) while patients claim that their central vision is unharmed. The constriction developed over a period of 2 weeks, even after exposure to methylmercury ceased.

Other vision-related effects of methylmercury include the visually evoked response (VER) (47) and contrast sensitivity (68). In usual brightness conditions, VERs were degraded only when visual fields became constricted. However, in scotopic brightness the VERs decreased even when visual fields were normal (47). Contrast sensitivity also was reported to be impaired (68).

Other neuro-ophthalmological effects of methylmercury involve eye movements. Superficial ptosis, as well as uneven nystagmus occur infrequently (95). Methylmercury also causes degenerative effects on the occipital visual cortex and cerebellum (44, 47, 101). In some cases, it has caused the death of neurons and halted the increase of glial cells, in addition to a decrease in the nerve cells of the superior
colliculus. The optic nerve, optic chiasm, and optic radiations were all found unchanged in these studies.

Animal experiments with methylmercury, especially those conducted with monkeys, are of considerable importance (11,29,32,63,65,77,84,99). Macaque monkeys exhibit visual capabilities similar to those of man and demonstrate similar effects to methylmercury exposure. Tests also have been performed on cats (22) and swine (23,74), while less conclusively on rabbits (47) and rats (26,36).

Constriction of visual fields has been indicated in adult and baby monkeys, with reports similar to those of humans (64,77,78,99). Such adverse effects have been accounted for by the possibility of harm on the visual cortex. Adverse effects on peripheral visual fields have been accounted for by cortical magnification, the fact that there are fewer cells in the visual cortex responsive to a solid angle in the visual field as one moves to more peripheral locations (12,16,24,28,30,37,42,44,76,92).

Methylmercury also has an effect on the eye movement of animals. In all cases, the main disorder has been blindness, often associated with cerebral cortical disorders, while maintaining normal reaction to light. Low amounts of administered methylmercury have led to spontaneous, positional nystagmus, jerky pursuit, and abnormal saccadic eye movements (29,32).

Methylmercury also affects the lens and other eye tissues (38). A study was reported where fish, contaminated with methylmercury, were shown to have cataracts (50). This supports the fact that exposed people in the Minamata poisoning had a higher concentration of the toxic compound in their lenses than unexposed people. In another animal study, methylmercury was administered to rabbits subcutaneously over a 21-day period (25). It was found that most of the transported methylmercury collected in the rabbits' cornea, iris, retina, and lens. In another experiment, rats were given a one-time dosage of methylmercury, and its effects were monitored daily (50). After 7 days the chemical accumulated mostly in the lens. However, between 21 and 180 days the amount consistently decreased.

Other organic mercurials. Ethylmercury compounds include ethyl, and diethyl salts (38). Effects of these compounds on vision are similar to those of methylmercury, but only a few cases involving animals have been studied. In one, blindness occurred when diethyl mercury was applied subcutaneously to one dog and one cat. In another case, symptoms of blindness also appeared in one cat given doses of ethyl mercury sulfate, although the autopsy did not reveal much else about the eyes or brain. N-(Ethylmercuri)-p-toluensulfonanilide is another member of the ethylmercury family. It has been shown to cause constriction of the visual fields, degeneration of central vision, and optic atrophy (49).

Other organic mercurials inflicting adverse systemic eye effects include pCMB (p-chloromercuribenzoate), mercaptomerin, and mercuderamide. The pCMB has been shown to have an affect on the retina of rabbits after systemic administration. One report showed a quick decline in electroretinogram (ERG) readings (83). However, because other studies have not corroborated this evidence (69,88), pCMB has been labeled as only slightly toxic to the retina (38). When administered intramuscularly, mercaptomerin and mercuderamide cause a decrease in intraocular pressure, yet show no effect when applied topically to the eye (10).
Inorganic Mercury

Acute exposure to inorganic mercurials or their vapors may cause acute and chronic systemic eye toxicity in rare cases (38). Acute eye symptoms and acrodynia (painful extremities), a unique mercurial manifestation, have been treated in more than half of the documented cases (97). Chronic toxicity occurs by way of the skin and lungs gradually, in the case of chronic medications, and is cumulatively absorbed into the body.

Common eye signs of exposure to inorganic mercurials include opacities of the lens, "mercurialentis," and those of the cornea (38). Claims of damage to the optic nerve and retina are less well-established. Other effects include disturbances to the vision and the extraocular muscles (eyelid tremors). Severe eye signs include photophobia, which is one of the most prominent and acute symptoms, usually combined with conjunctivitis and eye irritation. This is sometimes accompanied with eye discharge, but seldom keratitis (97).

Mercurialentis. Mercurialentis is a unique systemic eye symptom of mercury poisoning that has been studied at length over the years (9,8,18,35,43,45,51,54,59, 73,79,80). It is described as the early formation of a mercury coating on the anterior lens surface due to acute exposure to inorganic mercury (75,89). When it occurs chronically, mercurialentis usually accumulates with time, appearing brownish with no gloss, and develops on the outer lens capsule (9,59). It is reported to have occurred mostly with dentists, thermometer-producers, and other industries that require dealing with mercury and mercury vapors.

Using a slit-lamp microscope, a "rose-brown" or "coffee-brown" tissue layer on the lens is observable (59). Some have observed lens lamination covering the entire exterior surface of the lens; others are confined to the subcapsular disc (59). The mercuric coating starts initially at the external lens as a dim grayish color and accumulates successively to the internal lens layers, eventually collecting mercury particulates in the lens (1). Similar techniques have shown that the interior lens layers exhibit discernible black and dark brown discoloration associated with mercurialentis (8,80).

Other ocular manifestations of inorganic mercury. Inorganic mercury also contributes to other opacities of the cornea, generally not accompanied by systemic signs. In one case, corneal discoloration was induced in animals by applying a systemic dosage on a daily basis (38). The opacity took a couple of years to appear. The effect produced is comparable to that experienced when mercuric oxide is applied topically. The blemish is composed of a circular rim around the external endothelium of the cornea, reaching 2 mm from the limbus.

There is controversy as to the effect of inorganic mercury on the optic nerve. There have been reported cases of eye and vision damage in the nineteenth century, including optic neuropathy (19,90). On the other hand, many scientists have argued that no direct or clear correlation has been generated between mercury poisoning, the optic nerve, and subsequent damage to vision. Furthermore, some suggest certain diseases, like syphilis, are accountable for apparent eye disorders, and not the direct cause of its treatment using inorganic mercury.

The effects of inorganic mercury on the retina have also caused some dispute, and when present are presumed rare occurrences (38). Changes in the ERG have
been recorded; in one instance the readings rose quickly, then were reduced significantly (13). This agrees with evidence showing that mercury hinders the action of rod phosphodiesterase (93).

In rare cases, inorganic mercury has been found to induce adverse outcomes on the extraocular muscles and eye movement. Tremor of eyelid muscles was reported in several circumstances, such as mercuryinduced hatter shakes, along with tremor of the fingers and tongue (76,89). This has occurred only with chronic exposures to inorganic mercury. Ptosis has also been noted due to mercurialism (2,21,38).

In further case studies, inorganic mercurials caused transient paralysis of the lateral conjugate eye movements (38), as well as paresis of the lateral rectus muscle (43). This latter case was associated with a brownish mercurialentis, as well as nystagmus. Workers handling mercury have shown eye signs including diplopia, accompanied by tremors and headache (13).

**Inorganic mercury and vision.** A study reported that in a series of 49 people exposed to mercury vapor in England in the 1950s, 12 people developed opacities of the lens (59). Visual field disorders were observed with Italian hatters exposed to inorganic mercury (38). Severe constriction of visual fields was noticed in many incidents, some contracted by as much as 20-40°. The constriction occurred concentrically in all cases. The progress of the patients was checked every year from 1948 to 1953, and nine cases showed increased constriction, three were constant, and in no case was there a notable recovery.

In another case, Polish environmental workers dealing with red mercury vapor experienced a reduction in visual fields (15). A further episode is found in former Czechoslovakia, where in 1964 three out of 127 workers handling mercury were found to have narrowing of their visual fields (54).

Rabbits exposed to a mercury concentration of 5 mg/m³ died within 3 to 8 months, after developing brain edema, including edema of the occipital lobes. Such effects help to account for visual field constriction with humans (38).

**Some inorganic mercurials.** Other inorganic compounds that induce systemic eye toxicity include mercuric chloride and mercuric iodide. In three children, mercuric chloride caused acute vision and ocular toxicity (87). Their symptoms included bilateral mydriasis, hyperemia of the optic nerve heads, increased pressure of the retinal veins, and reduced visual acuity. A man who took a tablet containing 0.5 g of mercuric chloride (38) had visual acuity, which decreased to 20/60 O.D. and 20/200 O.S. His retinal vessels were later found to contain white regions as well as bright, shiny spots in the central retina and around the optic disc.

Mercuric iodide has properties similar to mercuric chloride, both in local and systemic eye toxicity. An interesting experiment showed combined systemic-local eye toxicity due to mercuric iodide. Potassium iodide was applied systemically while mercuric chloride was applied topically to the conjunctiva. As a result, mercuric iodide was produced. It was found that eye symptoms involved a more severe eye irritation than normally produced with isolated systemic mercuric chloride (38).

**Metallic mercury.** The metallic form of inorganic mercury (Hg) is reported to cause various distinct ophthalmic toxicity signs. Several accounts state that acute systemic toxicity may occur before chronic eye signs for metallic mercury, but local
Table 2  Summary of the prominent ocular manifestations due to both acute and chronic mercurialism as classified for organic, inorganic, and metallic mercury

<table>
<thead>
<tr>
<th>Ocular symptoms</th>
<th>Organic mercury</th>
<th>Inorganic mercury</th>
<th>Metallic mercury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vision effects</td>
<td>constricted visual fields, degraded VER</td>
<td>corneal opacities</td>
<td>band keratopathy</td>
</tr>
<tr>
<td>Effect on cornea</td>
<td></td>
<td></td>
<td>bilateral keratopathy</td>
</tr>
<tr>
<td>Effect on lens</td>
<td></td>
<td>mercurialentis</td>
<td></td>
</tr>
</tbody>
</table>

signs are also known to exist (38). Mercury can, in some cases, remain as a metallic particle in the circulation, thus systemically reaching the eye in its administered form. Alternatively, it can also reach the eye having been chemically changed into a different compound.

Systemic eye signs involving mercury’s effect on the cornea were reported. In one incident, a band keratopathy was produced in people using mercury to remove hair from rabbit pelts (34,41). Bilateral keratopathy occurred in a different case with a man who had been producing thermometers for 20 years. This patient had no signs of mercurialentis (34), but the corneal opacity appeared calcified and unpredictably rough. A noticeable increase of intraocular pressure had to be treated with EDTA. After treatment, tonometry indicated a reduction in intraocular pressure; vision improved as well.

Separate cases are reported regarding the eye toxicity of metallic mercury vapor. Two cases are demonstrative of such chronic toxicity (73), where mercury vapor caused band keratopathy, as well as the appearance of shiny corneal particulates on the corneal stroma. Mercurialentis is actually the eye symptom that has been found to be associated most with the absorption of mercury vapor, via the aforementioned skin, lungs, or intestinal routes (38), and is very common at chronic or very low concentrations.

SUMMARY

A summary of the systemic ocular symptoms for the various mercury compounds discussed in this manuscript is shown in Table 2. As previously stated, most of the symptoms occur due to chronic poisoning, and are mostly neural involving either the visual or visual motor systems, as is the case with organic mercury. However, distinct physical symptoms are mostly documented with inorganic mercury. Mercurialentis is considered both a trademark of mercurialism, as well an early sign of exposure for inorganic mercury. Metallic mercury mainly targets the cornea, as is indicated by cases of keratopathy.

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Cutaneous and Ocular Toxicology
CONTENTS

155  Pretreatment of Human Epidermal Keratinocytes with D,L-Sulforaphane Protects Against Sulfur Mustard Cytotoxicity  
     Clark L. Gross, Eric W. Nealley, Mary T. Nipwoda, and William J. Smith

165  A Double-Blind, Vehicle-Controlled Clinical Study to Evaluate the Efficacy of MAS065D (XClair™), a Hyaluronic Acid-Based Formulation, in the Management of Radiation-Induced Dermatitis  
     G. Primavera, M. Carrera, P. Pinnaró, M. Messina, G. Arcangeli, and E. Berardesca

173  Visual System Manifestations due to Systemic Exposure to Mercury  
     Ahmed M. El-Sherbeeny, James V. Odom, and James E. Smith

185  Hydrocarbon-Based Weapons Maintenance Compounds Produce Evidence of Contact Hypersensitivity in Balb/C Mice  
     D. P. Arfsten, S. Azadi, L. F. Butterworth, and B. J. Meade

195  Gender: A Possible Determinant in Dosing of Dermatologic Drugs—an overview  
     Bobeck S. Modjtahedi, Sara P. Modjtahedi, and Howard I. Maibach

211  Percutaneous Absorption of Crotamiton in Man Following Single and Multiple Dosing  
     E. Dika, A. Tosti, M. Goldovsky, R. Wester, and H. I. Maibach

217  Prediction of Eye Irritation Potential of Surfactant-Based Rinse-Off Personal Care Formulations by the Bovine Corneal Opacity and Permeability (BCOP) Assay  
     Kathleen C. Cater and John W. Harbell