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<b>HESIS</b>	<b>MEDICAL GUIDELINES</b>
<p>850 Marina Bay Pkwy Building P, 3rd Floor Richmond, CA 94804</p> <p>(866) 282-5516</p>	<p>HAZARD EVALUATION SYSTEM AND INFORMATION SERVICE</p> <p><b>n-Hexane</b> (Revised July 2000)</p>

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n-Hexane is a petroleum distillate used as a solvent in vegetable oil extraction, and in cleaners, degreasers, glues, spray paints, paint thinners, coatings, silicones, and greases. These n-hexane-containing products are often used by workers in the food processing, printing, manufacturing, painting, and automotive repair industries as well as anywhere petroleum distillates are used.

Commercial or technical grade hexane (the form used in most products) contains varying amounts of n-hexane (20-80%) along with other related compounds, and should be treated as pure n-hexane. Pure n-hexane is used in laboratories. Both n-hexane and mixed hexanes are often referred to as "hexane" and sometimes as "petroleum distillate" and are listed on Material Safety Data Sheets (MSDSs) with the CAS # 110-54-3.

**Pharmacokinetics:**

n-Hexane can enter the body via inhalation, ingestion, and dermal absorption. Inhalation of n-hexane vapors or aerosols is the main route of occupational exposure. Dermal absorption is usually minor.

When n-hexane is inhaled, 10% is immediately eliminated unchanged through the lungs. The remaining portion is absorbed and metabolized by the liver microsomal monooxygenase system, ultimately forming the major metabolite, 2,5-hexanedione (2,5-HD). 2,5-HD reacts with the ε-amino groups of lysine in proteins, leading to the characteristic nerve damage.

2,5-HD is excreted in the urine and is not normally stored in the body; however, if exposure to n-hexane is prolonged or high, 2,5-HD can remain in the body and cause nerve damage. Since the urinary elimination half-life of 2,5-HD is 13–14 hours, 2,5-HD can accumulate in the body during the workweek if n-hexane products are used on a daily basis.

**Clinical Presentation:**

Symptoms of peripheral neuropathy develop after a few months to a year of repeated overexposure to n-hexane. Longer nerves and thicker fibers are more susceptible to toxin-induced neuropathy; thus the symptoms usually begin in the feet or legs. The first symptoms are sensory and consist of tingling, numbness, burning, or prickling sensations in the feet or toes. The symptoms are usually symmetric and graded distally, although symptoms may appear in one foot first or may be more pronounced in one foot. If overexposure to n-hexane continues, the dysesthesias spread in a centripetal, symmetrical manner. Ankle jerks are lost and weakness of dorsiflexion of the toes develops. Patients may have difficulty walking on their heels and may have a slapping gait. If the dysesthesias reach the upper shin, they begin to appear in the fingertips. When the dysesthesias reach the elbows and thighs, a tent-shaped area of hypesthesia may occur in the lower abdomen. With progression, this broadens with the apex extending rostrally toward the sternum. At this point, patients cannot stand, walk, or hold objects. If the neuropathy continues further, the patient may become paralyzed.

The severity of nerve damage is related to 2,5-HD concentrations in the body and prolonged usage. The extent of nerve damage may also depend on the history of exposure to other neurotoxic chemicals. Using acetone, methyl ethyl ketone (MEK), methyl isobutyl ketone, or lead acetate in combination with n-hexane can amplify the neurotoxic effects of n-hexane. MEK intensifies the metabolic processing of n-hexane, leading to a quicker, more pronounced initial motor weakness.

Some patients have also experienced CNS complaints such as

headache, dizziness, nausea, anorexia, giddiness, and/or drowsiness, and mucosal irritation with short-term overexposure. These symptoms are usually temporary and disappear within minutes to hours after removal from exposure. Health effects on other organ systems have not been noted in human studies.

**Diagnosis:***Symptom description*

Begin by asking the patient to describe the symptoms and how they initially appeared. Patients with peripheral neuropathy will usually describe a neuropathy that begins in the feet and spreads in a graded, symmetrical and centripetal fashion. Ask the patient how the disease progressed. Did the symptoms get worse over a few days or many years? Patients affected by n-hexane will describe disease progression over several weeks to a year. Symptoms that evolve over a period of more than five years usually suggest a genetic disorder.

*Occupational history*

- Description of all jobs held
- Work exposures
- Specific exposures to solvents, pesticides, and/or heavy metals (e. g. methyl n-butyl ketone, carbon disulfide, acrylamide, mercury, lead, and organophosphates)
- Clustering of symptoms in other workers

*Medical history*

The clinical presentation of n-hexane-associated neuropathy cannot usually be distinguished from other causes such as diabetes, renal failure, vitamin deficiency, or paraproteinemic neuropathy. Therefore, it is important to rule out these disorders. A complete medical history can aid in ruling out certain causes. Questions should be asked regarding the following:

- Viral illnesses such as polio
- Medications
- Occurrence of symptoms among family members
- Alcohol intake
- Pre-existing medical conditions or disorders such as diabetes

The following tests should also be considered to rule out other causes:

- Complete blood count
- Erythrocyte sedimentation rate
- Urinalysis

- Chest x-ray
- Postprandial blood glucose
- Serum and urine protein electrophoresis
- Vitamin B12
- Creatinine
- Thyroid-stimulating hormone

### *Diagnostic tests*

The somatosensory system can be examined by tests of primary sensation. The pinprick test can be used to determine the patient's sense of pain. A wisp of cotton can be used to determine the sense of touch (avoid touching hairy skin). A flask filled with warm water at about 35-36° C and cool water at

28-32° C can be used to determine the ability to distinguish thermal sensation. A tuning fork or vibrometer can be used to determine sense of vibration. Care should be taken in interpreting these results since these subjective tests are dependent on patient response. Therefore, it is best to have the patient close or cover their eyes. Also, patients should not be pressed to undergo this examination if they are fatigued. Test results are also dependent on the limb temperature, so be certain that the ambient temperature is controlled to maintain a limb temperature of 72° F.

Electrodiagnosis can determine the difference between axonal and demyelinating disorders, but cannot distinguish between toxic and nontoxic etiologies. Axonal degeneration usually shows a reduction in amplitude of evoked conduction action potentials with relative preservation of nerve conduction velocities. Demyelination shows a slowing of the nerve conduction velocity, dispersion of evoked compound action potentials, conduction block, and marked prolongation of distal latencies. n-Hexane neurotoxicity causes both axonal degeneration and demyelination and thus can present mixed electrodiagnostic findings. Nerve conduction tests usually show decreased motor and sensory nerve conduction velocities.

Nerve biopsies are useful for hexacarbon neuropathies since the results are distinctive. Results show axonal swellings with secondary retracted myelin sheaths filled with massive neurofilament accumulations that are tightly pressed together. Some unmyelinated axons have glycogen granule accumulations in the axonal lumen. The sural nerve at the ankle is the preferred site.

<b>Biological Monitoring:</b>	<p>As mentioned previously, 2,5-HD, the proximate neurotoxin, is excreted in the urine and can be measured by a specialty laboratory. However, 2,5-HD leaves the body quickly, so the testing must be performed within 2-3 days of n-hexane exposure. The best time for obtaining a urine sample would be at the end of the shift at the end of the workweek. Creatinine determination is important because the concentration of 2,5-HD depends on urine output.</p> <p>Previous studies determined that exposure to 50 ppm resulted in 4 mg/L 5 mg/L (adjusted for specific gravity) 2,5-HD. It should be noted that almost everyone is exposed to n-hexane and the general population has 2,5-HD urine levels of below 1 mg/L.</p>
<b>Treatment:</b>	<p>The patient should be removed from further exposure. There is no other useful treatment.</p>
<b>Prognosis:</b>	<p>If the patient is removed from further exposure, the prognosis is usually good. The patient may experience a worsening of symptoms within the first few weeks, but improves afterward. Recovery usually takes a few months to a few years depending on disease severity. Recovery in mild to moderate cases is usually complete. Severe cases take longer to recuperate and may not recover completely, possibly experiencing residual muscle atrophy, spasticity, muscle cramps and dyschromatopsia.</p> <p>If the patient continues to be exposed, the neuropathy worsens, ultimately developing into paralysis. Fortunately, death has not been reported in humans.</p>

### What you should do:

- Complete a Doctors First Report (DFR) of Occupational Illness.
- Get the MSDS of the solvent product(s) that the patient is using.
- Recommend that the patient inform their employer, if work-related, and provide documentation for medical removal.
- Contact HESIS at (866) 282-5516 if you have any questions.

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