# APPENDIX I

## GROUNDWATER LABORATORY ANALYTICAL REPORTS

# APPENDIX J

# STATE AND FEDERAL LISTED THREATENED AND ENDANGERED SPECIES

U.S. Fish & Wildlife Service

*North Florida Field Office*

# Manatee County Federally Listed Species

The following table lists those federally-listed species known to be present in the county.
Code Key: E = Endangered, T = Threatened, P = Proposed, C = Candidate, CH = Critical Habitat

| Category | Species Common Name | Species Scientific Name | Code |
|---|---|---|---|
| **Mammals** | West Indian (Florida) Manatee | *Trichechus manatus latirostris* | E/CH |
| **Birds** | Audubon's Crested Caracara | *Polyborus plancu audubonii* | T |
| | Bald Eagle | *Haliaeetus leucocephalus* | T |
| | Piping Plover | *Charadrius melodus* | T |
| | Florida Scrub-jay | *Aphelocoma coeruluscens* | T |
| | Wood Stork | *Mycteria americana* | E |
| | Red-cockaded Woodpecker | *Picoides borealis* | E |
| **Fish** | Gulf Sturgeon | *Acipenser oxyrhynchus desotoi* | T |
| **Reptiles** | Eastern Indigo Snake | *Dymarchon corais couperi* | T |
| | Green Sea Turtle | *Chelonia mydas* | E |
| | Leatherback Sea Turtle | *Dermochelys coriacea* | E |
| | Loggerhead Sea Turtle | *Caretta caretta* | T |
| **Amphibians** | None | | |
| **Mollusks** | None | | |
| **Crustaceans** | None | | |
| **Plants** | None | | |

*Last modified February 16, 2005*

# FNAI tracking list

## MANATEE COUNTY

93 Total Elements Found
**Last Updated: April 2005**

### Fish

EXPLANATION

| Scientific Name | Common Name | Global Rank | State Rank | Federal Status | State Status |
|---|---|---|---|---|---|
| *Microphis brachyurus* | Opossum Pipefish | G4G5 | S2 | SC | N |
| *Rivulus marmoratus* | Mangrove Rivulus | G3 | S3 | C | LS |

### Amphibians

EXPLANATION

| Scientific Name | Common Name | Global Rank | State Rank | Federal Status | State Status |
|---|---|---|---|---|---|
| *Rana capito* | Gopher Frog | G3 | S3 | N | LS |

### Reptiles

EXPLANATION

| Scientific Name | Common Name | Global Rank | State Rank | Federal Status | State Status |
|---|---|---|---|---|---|
| *Alligator mississippiensis* | American Alligator | G5 | S4 | SAT | LS |
| *Caretta caretta* | Loggerhead | G3 | S3 | LT | LT |
| *Chelonia mydas* | Green Turtle | G3 | S2 | LE,LT | LE |

| | | | | | |
|---|---|---|---|---|---|
| *Crotalus adamanteus* | Eastern Diamondback Rattlesnake | G4 | S3 | N | N |
| *Dermochelys coriacea* | Leatherback | G2 | S2 | LE | LE |
| *Drymarchon couperi* | Eastern Indigo Snake | G3 | S3 | LT | LT |
| *Gopherus polyphemus* | Gopher Tortoise | G3 | S3 | N | LS |
| *Lepidochelys kempii* | Kemp's Ridley | G1 | S1 | LE | LE |
| *Pseudemys concinna suwanniensis* | Suwannee Cooter | G5T3 | S3 | N | LS |

## Birds

EXPLANATION

| Scientific Name | Common Name | Global Rank | State Rank | Federal Status | State Status |
|---|---|---|---|---|---|
| *Accipiter cooperii* | Cooper's Hawk | G5 | S3 | N | N |
| *Aimophila aestivalis* | Bachman's Sparrow | G3 | S3 | N | N |
| *Ajaia ajaja* | Roseate Spoonbill | G5 | S2 | N | LS |
| *Aphelocoma coerulescens* | Florida Scrub-jay | G2 | S2 | LT | LT |
| *Aramus guarauna* | Limpkin | G5 | S3 | N | LS |
| *Ardea alba* | Great Egret | G5 | S4 | N | N |
| *Ardea herodias occidentalis* | Great White Heron | G5T2 | S2 | N | N |

| | | | | | |
|---|---|---|---|---|---|
| *Athene cunicularia floridana* | Florida Burrowing Owl | G4T3 | S3 | N | LS |
| *Buteo brachyurus* | Short-tailed Hawk | G4G5 | S1 | N | N |
| *Caracara cheriway* | Crested Caracara | G5 | S2 | LT | LT |
| *Charadrius alexandrinus* | Snowy Plover | G4 | S1 | N | LT |
| *Charadrius melodus* | Piping Plover | G3 | S2 | LT | LT |
| *Coccyzus minor* | Mangrove Cuckoo | G5 | S3 | N | N |
| *Dendroica discolor paludicola* | Florida Prairie Warbler | G5T3 | S3 | N | N |
| *Egretta caerulea* | Little Blue Heron | G5 | S4 | N | LS |
| *Egretta rufescens* | Reddish Egret | G4 | S2 | N | LS |
| *Egretta thula* | Snowy Egret | G5 | S3 | N | LS |
| *Egretta tricolor* | Tricolored Heron | G5 | S4 | N | LS |
| *Elanoides forficatus* | Swallow-tailed Kite | G5 | S2 | N | N |
| *Elanus leucurus* | White-tailed Kite | G5 | S1 | N | N |
| *Eudocimus albus* | White Ibis | G5 | S4 | N | LS |
| *Falco columbarius* | Merlin | G5 | S2 | N | N |
| *Falco peregrinus* | Peregrine Falcon | G4 | S2 | N | LE |

| | | | | | |
|---|---|---|---|---|---|
| *Falco sparverius paulus* | Southeastern American Kestrel | G5T4 | S3 | N | LT |
| *Fregata magnificens* | Magnificent Frigatebird | G5 | S1 | N | N |
| *Grus canadensis pratensis* | Florida Sandhill Crane | G5T2T3 | S2S3 | N | LT |
| *Haematopus palliatus* | American Oystercatcher | G5 | S2 | N | LS |
| *Haliaeetus leucocephalus* | Bald Eagle | G4 | S3 | LT,PDL | LT |
| *Ixobrychus exilis* | Least Bittern | G5 | S4 | N | N |
| *Laterallus jamaicensis* | Black Rail | G4 | S2 | N | N |
| *Mycteria americana* | Wood Stork | G4 | S2 | LE | LE |
| *Nyctanassa violacea* | Yellow-crowned Night-heron | G5 | S3 | N | N |
| *Nycticorax nycticorax* | Black-crowned Night-heron | G5 | S3 | N | N |
| *Pandion haliaetus* | Osprey | G5 | S3S4 | N | LS* |
| *Pelecanus occidentalis* | Brown Pelican | G4 | S3 | N | LS |
| *Picoides villosus* | Hairy Woodpecker | G5 | S3 | N | N |
| *Plegadis falcinellus* | Glossy Ibis | G5 | S3 | N | N |
| *Rallus longirostris scottii* | Florida Clapper Rail | G5T3? | S3? | N | N |

| | | | | | |
|---|---|---|---|---|---|
| *Rynchops niger* | Black Skimmer | G5 | S3 | N | LS |
| *Sterna antillarum* | Least Tern | G4 | S3 | N | LT |
| *Sterna caspia* | Caspian Tern | G5 | S2 | N | N |
| *Sterna maxima* | Royal Tern | G5 | S3 | N | N |
| *Sterna sandvicensis* | Sandwich Tern | G5 | S2 | N | N |
| *Vireo altiloquus* | Black-whiskered Vireo | G5 | S3 | N | N |

## Mammals

EXPLANATION

| Scientific Name | Common Name | Global Rank | State Rank | Federal Status | State Status |
|---|---|---|---|---|---|
| *Corynorhinus rafinesquii* | Rafinesque's Big-eared Bat | G3G4 | S2 | N | N |
| *Mustela frenata peninsulae* | Florida Long-tailed Weasel | G5T3 | S3 | N | N |
| *Neofiber alleni* | Round-tailed Muskrat | G3 | S3 | N | N |
| *Podomys floridanus* | Florida Mouse | G3 | S3 | N | LS |
| *Sciurus niger shermani* | Sherman's Fox Squirrel | G5T3 | S3 | N | LS |
| *Trichechus manatus* | Manatee | G2 | S2 | LE | LE |
| *Ursus americanus floridanus* | Florida Black Bear | G5T2 | S2 | N | LT* |

## Plants

EXPLANATION

| Scientific Name | Common Name | Global Rank | State Rank | Federal Status | State Status |
|---|---|---|---|---|---|
| *Acrostichum aureum* | Golden Leather Fern | G5 | S3 | N | LT |
| *Bonamia grandiflora* | Florida Bonamia | G3 | S3 | LT | LE |
| *Calopogon multiflorus* | Many-flowered Grass-pink | G2G3 | S2S3 | N | LE |
| *Chrysopsis floridana* | Florida Golden Aster | G1 | S1 | LE | LE |
| *Eragrostis pectinacea var. tracyi* | Sanibel Lovegrass | G5T1 | S1 | N | LE |
| *Glandularia tampensis* | Tampa Vervain | G2 | S2 | N | LE |
| *Gossypium hirsutum* | Wild Cotton | G4G5 | S3 | N | LE |
| *Gymnopogon chapmanianus* | Chapman's Skeletongrass | G3 | S3 | N | N |
| *Helianthus debilis ssp. vestitus* | Hairy Beach Sunflower | G5T2 | S2 | N | N |
| *Lechea cernua* | Nodding Pinweed | G3 | S3 | N | LT |
| *Pteroglossaspis ecristata* | Giant Orchid | G2G3 | S2 | N | LT |
| *Rhynchospora megaplumosa* | Large-plumed Beakrush | G2 | S2 | N | N |

## FNAI STATE RANK DEFINITIONS

**S1** = Critically imperiled in Florida because of extreme rarity (5 or fewer occurrences or less than 1000 individuals) or because of extreme vulnerability to extinction due to some natural or man-made factor.

**S2** = Imperiled in Florida because of rarity (6 to 20 occurrences or less than 3000 individuals) or because of vulnerability to extinction due to some natural or man-made factor.

**S3** = Either very rare and local in Florida (21-100 occurrences or less than 10,000 individuals) or found locally in a restricted range or vulnerable to extinction from other factors.

**S4** = Apparently secure in Florida (may be rare in parts of range).

**S5** = Demonstrably secure in Florida.

**SH** = Of historical occurrence in Florida, possibly extirpated, but may be rediscovered (e.g., ivory-billed woodpecker).

**SX** = Believed to be extirpated throughout Florida.

**SU** = Unrankable; due to a lack of information no rank or range can be assigned.

**SNA** = State ranking is not applicable because the element is not a suitable target for conservation (e.g. a hybrid species).

**SNR** = Element not yet ranked (temporary).

## STATE LEGAL STATUS

Provided by FNAI for information only.
For official definitions and lists of protected species, consult the relevant federal agency.

**Animals:** Definitions derived from "Florida's Endangered Species and Species of Special Concern, Official Lists" published by Florida Fish and Wildlife Conservation Commission, 1 August 1997, and subsequent updates.

**LE** Endangered: species, subspecies, or isolated population so few or depleted in number or so restricted in range that it is in imminent danger of extinction.
**LT** Threatened: species, subspecies, or isolated population facing a very high risk of extinction in the future.

**LS** Species of Special Concern is a species, subspecies, or isolated population which is facing a moderate risk of extinction in the future.
**PE** Proposed for listing as Endangered.
**PT** Proposed for listing as Threatened.
**PS** Proposed for listing as Species of Special Concern.
**N** Not currently listed, nor currently being considered for listing.

**Plants:** Definitions derived from Sections 581.011 and 581.185(2), Florida Statutes, and the Preservation of Native Flora of Florida Act, 5B-40.001. FNAI does not track all state-regulated plant species; for a complete list of state-regulated plant species, call Florida Division of Plant Industry, 352-372-3505 or see: **http://doacs.state.fl.us/~pi/5b-40.htm#.0055**.

**LE** Endangered: species of plants native to Florida that are in imminent danger of extinction within the state, the survival of which is unlikely if the causes of a decline in the number of plants continue; includes all species determined to be endangered or threatened pursuant to the U.S. Endangered Species Act.
**LT** Threatened: species native to the state that are in rapid decline in the number of plants within the state, but which have not so decreased in number as to cause them to be Endangered.
**PE** Proposed for listing as Endangered.
**PT** Proposed for listing as Threatened.
**N** Not currently listed, nor currently being considered for listing.

# APPENDIX K

# TOXICITY PROFILES AND CHEMICAL DATA SHEETS

**Toxicity Summary for COPPER**

Prepared by: Rosmarie A. Faust, Ph.D., Chemical Hazard Evaluation and Communication Group, Biomedical and Environmental Information Analysis Section, Health and Safety Research Division, *, Oak Ridge, Tennessee.

Prepared for: Oak Ridge Reservation Environmental Restoration Program.

*Managed by Martin Marietta Energy Systems, Inc., for the U.S. Department of Energy under Contract No. DE-AC05-84OR21400.

Copper occurs naturally in elemental form and as a component of many minerals. Because of its high electrical and thermal conductivity, it is widely used in the manufacture of electrical equipment. Common copper salts, such as the sulfate, carbonate, cyanide, oxide, and sulfide are used as fungicides, as components of ceramics and pyrotechnics, for electroplating, and for numerous other industrial applications (ACGIH, 1986). Copper can be absorbed by the oral, inhalation, and dermal routes of exposure. It is an essential nutrient that is normally present in a wide variety of tissues (ATSDR, 1990; U.S. EPA, 1987).

In humans, ingestion of gram quantities of copper salts may cause gastrointestinal, hepatic, and renal effects with symptoms such as severe abdominal pain, vomiting, diarrhea, hemolysis, hepatic necrosis, hematuria, proteinuria, hypotension, tachycardia, convulsions, coma, and death (U.S. AF, 1990). Gastrointestinal disturbances and liver toxicity have also resulted from long-term exposure to drinking water containing 2.2-7.8 mg Cu/L (Mueller-Hoecker et al., 1988; Spitalny et al., 1984). The chronic toxicity of copper has been characterized in patients with Wilson's disease, a genetic disorder causing copper accumulation in tissues. The clinical manifestations of Wilson's disease include cirrhosis of the liver, hemolytic anemia, neurologic abnormalities, and corneal opacities (Goyer, 1991; ATSDR, 1990; U.S. EPA, 1987). In animal studies, oral exposure to copper caused hepatic and renal accumulation of copper, liver and kidney necrosis at doses of >=100 mg/kg/day; and hematological effects at doses of 40 mg/kg/day (U.S. EPA, 1986; Haywood, 1985; 1980; Rana and Kumar, 1978; Gopinath et al., 1974; Kline et al., 1971).

Acute inhalation exposure to copper dust or fumes at concentrations of 0.075-0.12 mg Cu/$m^3$ may cause metal fume fever with symptoms such as cough, chills and muscle ache (U.S. AF, 1990). Among the reported effects in workers exposed to copper dust are gastrointestinal disturbances, headache, vertigo, drowsiness, and hepatomegaly (Suciu et al., 1981). Vineyard workers chronically exposed to Bordeaux mixture (copper sulfate and lime) exhibit degenerative changes of the lungs and liver. Dermal exposure to copper may cause contact dermatitis in some individuals (ATSDR, 1990).

Oral or intravenous administration of copper sulfate increased fetal mortality and developmental abnormalities in experimental animals (Lecyk, 1980; Ferm and Hanlon, 1974). Evidence also indicates that copper compounds are spermicidal (ATSDR, 1990; Battersby et al., 1982).

EPA established an action level of 1300 ug/L for drinking water (56 FR 26460, June 7, 1991).

No suitable bioassays or epidemiological studies are available to assess the carcinogenicity of copper. Therefore, EPA has placed copper in weight-of-evidence group D, not classifiable as to human carcinogenicity (IRIS 2005).

**REFERENCES**


ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Copper. In: Documentation of the Threshold Limit Values and Biological Exposure Indices, 5th ed. ACGIH, Cincinnati, OH, p. 146.

ATSDR (Agency for Toxic Substances and Disease Registry). 1990. Toxicological Profile for Copper. Prepared by Syracuse Research Corporation for ATSDR, U.S. Public Health Service under Contract 88-0608-2. ATSDR/TP-90-08.

Battersby, S., J.A. Chandler and M.S. Morton. 1982. Title not given. Fertil. Steril. 37: 230-235. (Cited in Aaseth and Norseth, 1986)

Ferm, V.H. and D.P. Hanlon. 1974. Toxicity of copper salts in hamster embryonic development. Biol. Reprod. 11: 97-101. (Cited in U.S. AF, 1990)

Gopinath, C., G.A. Hall and J.McC. Howell. 1974. Title not given. Res. Vet. Sci. 16: 57-69. (Cited in Aaseth and Norseth, 1986)

Goyer, R.A. 1991. Toxic effects of metals. In: M.O. Amdur, J. Doull and C.D. Klaasen, Eds., Casarett and Doull's Toxicology, 4th ed. Pergamon Press, New York, NY, p. 653-655.

Haywood, S. 1980. The effect of excess dietary copper on the liver and kidney of the male rat. J. Comp. Pathol. 90: 217-232.

Haywood, S. 1985. Copper toxicosis and tolerance in the rat. I. Changes in copper content of the liver and kidney. J. Pathol. 145: 149-158.

IRIS (Integrated Risk Information System), 2005. United States National Library of Medicine, National Institute of Health, Department of Health and Human Services 8600 Rockville Pike, Bethesda, MD 20894. http://toxnet.nlm.nih.gov

Kline, R.D., V.W. Hays and G.L. Cromwell. 1971. Effects of copper, molybdenum and sulfate on performance, hematology and copper stores of pigs and lambs. J. Animal Sci. 33: 771-779. (Cited in ATSDR, 1990)

Lecyk, M. 1980. Toxicity of cupric sulfate in mice embryonic development. Zool. Pol. 28: 101-105. (Cited in U.S. AF, 1990)

Mueller-Hoecker, J., U. Meyer, B. Wiebecke, et al. 1988. Copper storage disease of the liver and chronic dietary copper intoxication in two further German infants mimicking Indian childhood cirrhosis. Pathol. Red. Pract. 183: 39-45. (Cited in ATSDR, 1990)

Rana, S.V.S. and A. Kumar. 1978. Simultaneous effects of dietary molybdenum and copper on the accumulation of copper in the liver and kidney of copper poisoned rats. A histochemical study. Ind. Health 18: 9-17. (Cited in U.S. AF, 1990)

Spitalny, K.C., J. Brondum, R.L. Vogt, et al. 1984. Drinking-water-induced copper intoxication in a Vermont family. Pediatrics 74: 1103-1106.

Suciu, I., L. Prodan, V. Lazar, et al. 1981. Research on copper poisoning. Med. Lav. 72: 190-197. (Cited in ATSDR, 1990)

U.S. AF (U.S. Air Force). 1990. Copper. In: The Installation Program Toxicology Guide, Vol. 5. Wright-Patterson Air Force Base, Ohio, pp. 77(1-43).

U.S. EPA. 1986. 90-Day oral toxicity study of copper cyanide (CuCN) in Sprague-Dawley rats. Prepared by IIT Research Institute, Chicago, IL, for the Office of Solid Waste, Washington, DC.

U.S. EPA. 1987. Drinking Water Criteria Document for Copper. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Drinking Water, Washington, DC. ECAO-CIN-417.

**Toxicity Summary for LEAD**

December 1994

Prepared by Kowetha A. Davidson, Ph.D., Chemical Hazard Evaluation and Communication Program, Biomedical and Environmental Information Analysis Section, Health Sciences Research Division, *, Oak Ridge, Tennessee.

Prepared for OAK RIDGE RESERVATION ENVIRONMENTAL RESTORATION PROGRAM.

*Managed by Martin Marietta Energy Systems, Inc., for the U.S. Department of Energy under contract No. DE-AC05-84OR21400.

Lead occurs naturally as a sulfide in galena. It is a soft, bluish-white, silvery gray, malleable metal with a melting point of 327.5C. Elemental lead reacts with hot boiling acids and is attacked by pure water. The solubility of lead salts in water varies from insoluble to soluble depending on the type of salt (IARC, 1980; Goyer, 1988; Budavari et al., 1989).

Lead is a natural element that is persistent in water and soil. Most of the lead in environmental media is of anthropogenic sources. The mean concentration is 3.9 ug/L in surface water and 0.005 ug/L in sea water. River sediments contain about 20,000 ug/g and coastal sediments about 100,000 ug/g. Soil content varies with the location, ranging up to 30 ug/g in rural areas, 3000 ug/g in urban areas, and 20,000 ug/g near point sources. Human exposure occurs primarily through diet, air, drinking water, and ingestion of dirt and paint chips (EPA, 1989; ATSDR, 1993).

The efficiency of lead absorption depends on the route of exposure, age, and nutritional status. Adult humans absorb about 10-15% of ingested lead, whereas children may absorb up to 50%, depending on whether lead is in the diet, dirt, or paint chips. More than 90% of lead particles deposited in the respiratory tract are absorbed into systemic circulation. Inorganic lead is not efficiently absorbed through the skin; consequently, this route does not contribute considerably to the total body lead burden (EPA, 1986a).

Lead absorbed into the body is distributed to three major compartments: blood, soft tissue, and bone. The largest compartment is the bone, which contains about 95% of the total body lead burden in adults and about 73% in children. The half-life of bone lead is more than 20 years. The concentration of blood lead changes rapidly with exposure, and its half-life of only 25-28 days is considerably shorter than that of bone lead. Blood lead is in equilibrium with lead in bone and soft tissue. The soft tissues that take up lead are liver, kidneys, brain, and muscle. Lead is not metabolized in the body, but it may be conjugated with glutathione and excreted primarily in the urine (EPA, 1986a,c; ATSDR, 1993). Exposure to lead is evidenced by elevated blood lead levels.

The systemic toxic effects of lead in humans have been well-documented by the EPA (EPA, 1986a-e, 1989a, 1990) and ATSDR (1993), who extensively reviewed and evaluated data reported in the literature up to 1991. The evidence shows that lead is a multitargeted toxicant, causing effects in the gastrointestinal tract, hematopoietic system, cardiovascular system, central and peripheral nervous systems, kidneys, immune system, and reproductive system. Overt symptoms of subencephalopathic central nervous system (CNS) effects and peripheral nerve damage occur at blood lead levels of 40-60 ug/dL, and nonovert symptoms, such as peripheral nerve dysfunction, occur at levels of 30-50 ug/dL in adults; no clear threshold is evident. Cognitive and neuropsychological deficits are not usually the focus of studies in adults, but there is some evidence of neuropsychological impairment (Ehle and McKee, 1990) and cognitive deficits in lead workers with blood levels of 41-80 ug/dL (Stollery et al., 1991).

Although similar effects occur in adults and children, children are more sensitive to lead exposure than are adults. Irreversible brain damage occurs at blood lead levels greater than or equal to 100 ug/dL in adults and at 80-100 ug/dL in children; death can occur at the same blood levels in children. Children who survive these high levels of exposure suffer permanent severe mental retardation.

As discussed previously, neuropsychological impairment and cognitive (IQ) deficits are sensitive indicators of lead exposure; both neuropsychological impairment and IQ deficits have been the subject of cross-sectional and longitudinal studies in children. One of the early studies reported IQ score deficits of four points at blood lead levels of 30-50 ug/dL and one to two points at levels of 15-30 ug/dL among 75 black children of low socioeconomic status (Schroeder and Hawk, 1986).

Very detailed longitudinal studies have been conducted on children (starting at the time of birth) living in Port Pirie, Australia (Vimpani et al., 1985, 1989; McMichael et al., 1988; Wigg et al., 1988; Baghurst et al., 1992a,b), Cincinnati, Ohio (Dietrich et al., 1986, 1991, 1992, 1993), and Boston, Massachusetts (Bellinger et al., 1984, 1987, 1990, 1992; Stiles and Bellinger 1993). Various measures of cognitive performance have been assessed in these children. Studies of the Port Pirie children up to 7 years of age revealed IQ deficits in 2-year-old children of 1.6 points for each 10-ug/dL increase in blood lead, deficits of 7.2 points in 4-year-old children, and deficits of 4.4 to 5.3 points in 7-year-old children as blood lead increased from 10-30 ug/dL. No significant neurobehavioral deficits were noted for children, 5 years or younger, who lived in the Cincinnati, Ohio, area. In 6.5-year-old children, performance IQ was reduced by 7 points in children whose lifetime blood level exceeded 20 ug/dL.

Children living in the Boston, Massachusetts, area have been studied up to the age of 10 years. Cognitive performance scores were negatively correlated with blood lead in the younger children in the high lead group (greater than or equal to 10 ug/dL), and improvements were noted in some children at 57 months as their blood lead levels became lower. However, measures of IQ and academic performance in 10-year-old children showed a 5.8-point deficit in IQ and an 8.9-point deficit in academic performance as blood lead increased by 10 ug/dL within the range of 1-25 ug/dL. Because of the large database on subclinical neurotoxic effects of lead in children, only a few of the studies have been included. However, EPA (EPA, 1986a, 1990) concluded that there is no clear threshold for neurotoxic effects of lead in children.

In adults, the cardiovascular system is a very sensitive target for lead. Hypertension (elevated blood pressure) is linked to lead exposure in occupationally exposed subjects and in the general population. Three large population-based studies have been conducted to study the relationship between blood lead levels and high blood pressure. The British Regional Heart Study (BRHS) (Popcock et al., 1984), the NHANES II study (Harlan et al., 1985; Pirkle et al., 1985; Landis and Flegal, 1988; Schwartz, 1991; EPA, 1990), and Welsh Heart Programme (Ellwood et al., 1988a,b) comprise the major studies for the general population. The BRHS study showed that systolic pressure greater than 160 mm Hg and diastolic pressure greater than 100 mm Hg were associated with blood lead levels greater than 37 ug/dL (Popcock et al., 1984). An analysis of 9933 subjects in the NHANES study showed positive correlations between blood pressure and blood lead among 12-74-year-old males but not females (Harlan et al., 1985; Landis and Flegal et al., 1988), 40-59-year-old white males with blood levels ranging from 7-34 ug/dL (Pirkle et al., 1985), and males and females greater than 20 years old (Schwartz, 1991). In addition, left ventricular hypertrophy was also positively associated with blood lead (Schwartz, 1991). The Welsh study did not show an association among men and women with blood lead of 12.4 and 9.6 ug/dL, respectively (Ellwood et al., 1988a,b). Other smaller studies showed both positive and negative results. The EPA (EPA, 1990) concluded that increased blood pressure is positively correlated with blood lead levels in middle-aged men, possibly at concentrations as low as 7 ug/dL. In addition, the EPA estimated that systolic pressure is increased by 1.5-3.0 mm Hg in males and 1.0-2.0 mm Hg in females for every doubling of blood lead concentration.

The hematopoietic system is a target for lead as evidenced by frank anemia occurring at blood lead levels of 80 ug/dL in adults and 70 ug/dL in children. The anemia is due primarily to reduced heme synthesis, which is observed in adults having blood levels of 50 ug/dL and in children having blood levels of 40 ug/dL. Reduced heme synthesis is caused by inhibition of key enzymes involved in the synthesis of heme. Inhibition of erythrocyte -aminolevulinic acid dehydrase (ALAD) activity (catalyzes formation of porphobilinogen from -aminolevulinic acid) has been detected in adults and children having blood levels of less than 10 ug/dL. ALAD activity is the most sensitive measure of lead exposure, but erythrocyte zinc protoporphyrin is the most reliable indicator of lead exposure because it is a measure of the toxicologically active fraction of bone lead. The activity of another erythrocyte enzyme, pyrimidine-5-nucleotidase, is also inhibited by lead exposure. Inhibition has been observed at levels below 5 ug/dL; no clear threshold is evident.

Other organs or systems affected by exposure to lead are the kidneys, immune system, reproductive system, gastrointestinal tract, and liver. These effects usually occur at high blood levels, or the blood levels at which they occur have not been sufficiently documented.

The EPA has established a screening level of 400 ppm (ug/g) for lead in soil (EPA, 1994).

Inorganic lead and lead compounds have been evaluated for carcinogenicity by the EPA (IRIS 2005). The data from human studies are inadequate for evaluating the potential carcinogenicity of lead. Data from animal studies, however, are sufficient based on numerous studies showing that lead induces renal tumors in experimental animals. A few studies have shown evidence for induction of tumors at other sites (cerebral gliomas; testicular, adrenal, prostate, pituitary, and thyroid tumors).

**REFERENCES**

ATSDR (Agency for Toxic Substances and disease Registry). 1993. *Toxicological Profile for Lead*. Update. Prepared by Clement International Corporation under contract No. 205-88-0608 for ATSDR, U.S. Public Health Service, Atlanta, GA.

Baghurst, P.A.; Tong, S.-L.; McMichael, A.J.; et al. (1992a) Determinants of blood lead concentrations to age 5 years in a birth cohort study of children living in the lead smelting city of Port Pirie and surrounding areas. *Arch. Environ. Health*. 47:203-210.

Baghurst, P.A.; McMichael, A.J.; Wigg, N.R.; et al. (1992b) Environmental exposure to lead and children's intelligence at the age of seven years. The Port Pirie Cohort Study. *New Eng. J. Med*. 327:1279-1284.

Bellinger, D.C.; Needleman, H.L.; Leviton, A.; et al. (1984) Early sensory-motor development and prenatal exposure to lead. *Neurobehav. Toxicol. Teratol*. 6:387-402. (cited in EPA, 1986e)

Bellinger, D.; Leviton, A.; Waternaux, C.; (1987a) *Longitudinal analyses of prenatal and postnatal lead exposure and early cognitive development*. 316:1038-1043.

Bellinger, D.; Sloman, J.; Leviton, A.; et al. (1987b) Low-level lead exposure and child development: Assessment at age 5 of a cohort followed from birth. In: *Int. Conf.; Heavy Metals in the Environment, Vol. 1*, Sept, 1987, New Orleans, LA. CEP Consultants, Ltd.; Edinburgh, United Kingdom. pp. 49-53.

Bellinger, D.; Leviton, a.; Sloman, J. (1990) Antecedents and correlates of improved cognitive performance in children exposed *in utero* to low levels of lead. *Environ. Health Perspect*. 89:5-11.

Bellinger, D.C.; Stiles, K.M.; Needleman, H.L. (1992) Low-level lead exposure, intelligence and academic achievement: A long-term follow-up study. *Pediatrics*. 90:855-561. (abstract: BIOSIS/93/07320)

Budavari, S., Ed. 1989. *The Merck Index.* 11th ed. Merck and Co., Inc., Rahway, NJ.

Dietrich, K.N.; Krafft, K.M.;Bier, M.; et al. (1986) Early effects of fetal lead exposure: neurobehavioral findings at 6 months. *Inst. J. Biosoc. Res*. 8:151-168. (cited in EPA, 1990)

Dietrich, K.N.; Succop, P.A.; Berger, O.G.; Hammond, P.B.; Bornschein, R.L. (1991) Lead exposure and the cognitive development of urban preschool children: The Cincinnati lead study cohort at age 4 years. *Neurotoxicol. Teratol.* 13:203-212.

Dietrich, K.N.; Succop, P.A.; Berger, O.G.; Keith, R.W. (1992) Lead exposure and the central auditory processing abilities and cognitive development of urban children: the Cincinnati lead study cohort at age 5 years. *Neurotoxicol. Teratol*. 14:51-56.

Dietrich, K.N.; Succop, P.A.; Berger, O.G.; Hammond, P.B.; Bornschein, R.L. (1993) The developmental consequences of low to moderate prenatal and postnatal lead exposure: Intellectual attainment in the Cincinnati lead study cohort following school entry. *Neurotoxicol. Teratol.* 15:37-4.

Ehle, A.L.; McKee, D.C. (1990) Neuropsychological effect of lead in occupationally exposed workers: a critical review. *Crit. Rev. Toxicol.* 20:237-255.

Elwood, P.C.; Davey-Smith, G.; Oldham, P.D.; Toothill, C. (1988a) Two Welsh surveys of blood lead and blood pressure. *Environ. Health Perspect.* 78:119-121. (cited in EPA, 1990).

Ellwood, P.C. Yarnell, J.W.G.; Oldham, P.D.; et al. (1988b) Blood pressure and blood lead in surveys in Wales. *Am. J. Epidemiol.* 127:942-945. (cited in EPA, 1990)

Goyer, R.A. (1988) Lead. In: *Handbook on Toxicity of Inorganic Compounds*. H.G. Seiler and H. Sigel, eds. Marcel Dekker, Inc.: New York, pp. 359-382.

Harlan, W.R.; Landi, J.R.; Shcmouder, R.L.; Goldstein, N.G.; Harlan, L.C. (1985) Blood lead and blood pressure: relationship in the adolescent and adult US population. *J. Am. Med. Assoc.* 253:530-534. (cited in EPA, 1986e).

International Agency for Research on Cancer (IARC). 1980. *Lead and lead compounds, Vol. 23*. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Some Metals and Metallic Compounds. IARC, Lyon, France, pp. 325-415.

IRIS (Integrated Risk Information System), 2005. United States National Library of Medicine, National Institute of Health, Department of Health and Human Services 8600 Rockville Pike, Bethesda, MD 20894. http://toxnet.nlm.nih.gov

Landis, J.R.; Flegal, K.M. (1988) A generalized Mantel-Haenszel analysis of the regression of blood pressure on blood lead using NHANES II data. *Environ. Health Prospect*. 78:35-41.

McMichael, A.J.; Baghurst, P.A.; Wigg, N.R.; et al. (1988) Port Pirie cohort study: environmental exposure to lead and children's ability at the age of four years. *N. Engl. J. Med.* 319:468-475. (Cited in EPA, 1990)

Pirkle, J.L.; Schwartz, J.; Landis, J.R.; Harlan, W.R. (1985) The relationship between blood lead levels and blood pressure and its cardiovascular risk implication. *Am. J. Epidemiol*. 121:246-258. (cited in EPA, 1986e).

Pocock, S.J.; Shaper, A.G.; Ashby, D. Delves, T.; Whitehead, T.P. (1984) Blood lead concentration, blood pressure, and renal function. *Br. Med. J*. 289:872-874. (cited in EPA, 1986e).

Schroeder, S.R.; Hawk, B.; (1986) Child-caregiver environmental factors related to lead exposure and IQ. In: *Toxic Substances and Mental Retardation: Neurobehavioral Toxicology and Teratology*, S.R. Schroeder, Ed., Washington, D.C. (AAMD Monograph Series). (cited in EPA, 1986d)

Schwartz, J. (1991) Lead, blood pressure, and cardiovascular disease in men and women. *Environ. Health Perspect*. 91:71-75.

Stiles, K.M.; Bellinger, D.C. (1993) Neuropsychological correlates of low-level lead exposure in school-age children: A prospective study. *Neurotoxicol. Teratol*. 15:27-35.

Stollery, B.T.; Broadbent, D.E.; Banks, H.A.; Lee, W.R. (1991) Short-term prospective study of cognitive functioning in lead workers. *Br. J. Ind. Med*. 48:739-749.

U.S. Environmental Protection Agency (EPA). 1986a. *Air Quality Criteria for Lead. Vol. I of IV*. Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA-600/8-83/028aF. Available from NTIS, Springfield, VA; PB87-142378.

U.S. Environmental Protection Agency (EPA). 1986b. *Air Quality Criteria for Lead. Vol. II of IV*. Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA-600/8-83/028bF. Available from NTIS, Springfield, VA; PB87-142378.

U.S. Environmental Protection Agency (EPA). 1986c. *Air Quality Criteria for Lead. Vol. III of IV*. Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA-600/8-83/028cF. Available from NTIS, Springfield, VA; PB87-142378.

U.S. Environmental Protection Agency (EPA). 1986d. *Air Quality Criteria for Lead. Vol. IV of IV*. Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA-600/8-83/028dF. Available from NTIS, Springfield, VA; PB87-142378.

U.S. Environmental Protection Agency (EPA). 1986e. Lead effects on cardiovascular function, early development, and stature: an addendum to EPA Air Quality Criteria for Lead (1986). In: *Air Quality Criteria for Lead, Vol. I*. Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA-600/8-83/028aF. Available from NTIS, Springfield, VA; PB87-142378. pp. A1-67.

U.S. Environmental Protection Agency (EPA). 1989a. *Evaluation of the Potential Carcinogenicity of Lead and Lead Compounds*. Office of Health and Environmental Assessment. EPA/600/8-89/045A.

U.S. Environmental Protection Agency (EPA). 1989b. *Review of the National Ambient Air Quality Standards for Lead: Exposure Analysis Methodology and Validation.* OAQPS Staff Report. Office of Air Quality Planning and Standards, Research Triangle Park, NC. PB89207914/AS.

U.S. Environmental Protection Agency (EPA). 1990. *Air Quality Criteria for Lead: Supplement to the 1986 Addendum*. Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA-600/8-89/049F.

U.S. Environmental Protection Agency (EPA). 1994. *Interim Soil Lead Guidance for CERCLA Sites and RCRA Corrective Action Facilities*. OSWER Directive 9355.4-12. Office of Solid Waste and Emergency Response, Washington, D.C.

Vimpani, G.V.; Wigg, N.R.; Robertson, E.F.; et al. (1985) The Port Pirie cohort study: blood lead concentration and childhood developmental assessment. In: *Lead Environmental Health - The Current Issues,* L.J. Goldwater, L.M. Wysocki, R.A. Volpe, Eds., Edited proceedings, May, Duke University Press, Durham, NC. pp. 139-155. (cited in EPA, 1990)

Vimpani, G.; Baghurst, P.; McMichael, A.J.; et al. (1989) "The effects of cumulative lead exposure on pregnancy outcome and childhood development during the first four years." Presented at: Conference on Advances in Lead Research: Implications for Environmental Research. Research Triangle Park, NC, National Institute of Environmental Health Sciences, January.

Wigg, N.R.; Vimpani, G.V.; McMichael, A.J.; et al. (1988) Port Pirie cohort study: childhood blood lead and neuropsychological development at age two years. *J. Epidemiol. Commun. Health.* 42:213-219. (cited in EPA, 1990)

**Toxicity Summary for 1,1,2,2-TETRACHLOROETHANE**

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*Managed by Martin Marietta Energy Systems, Inc., for the U.S. Department of Energy under Contract No. DE-AC05-84OR21400

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1,1,2,2-Tetrachloroethane (CAS No. 79-34-5) is a two-carbon chain molecule with two chlorine atoms on each carbon atom. Uses of 1,1,2,2-tetrachloroethane have been as a chemical intermediate, industrial solvent, and extractant. 1,1,2,2-Tetrachloroethane was found on at least 278 of the hazardous waste sites on the United States Environmental Protection Agency's National Priorities List. Chemical degradation occurs by the loss of chlorine atoms, and the half-life of 1,1,2,2-tetrachloroethane in air is about 2 months and in groundwater 1 to 3 months. Bioaccumulation of 1,1,2,2-tetrachloroethane in fish and other aquatic organisms is not expected to be significant (ATSDR;1994).

Two human studies suggested that between 50 and 97% of inspired 1,1,2,2-tetrachloroethane was retained (Lehman and Schmidt-Kehl 1936, Morgan et al. 1970). Mouse and rat gavage studies indicated that 100% of 1,1,2,2-tetrachloroethane was absorbed (Dow Chemical Company 1988). Animal metabolites were trichloroethane, trichloroacetic acid, dichloroacetic acid, glyoxylic acid, and oxalic acid (Ikeda and Ohtsuji 1972, Mitoma et al. 1985, Yllner 1971). Vinyl chloride is another possible metabolite (Hallen et al. 1986). Human and animal studies indicate that the majority of 1,1,2,2-tetrachloroethane is metabolized (ATSDR 1994). Ten percent or less of the parent compound is exhaled in humans and animals.

Humans acutely exposed by the oral route had clinical signs inclusive of pulmonary congestion and edema (Hepple 1927, Mant 1953), lung collapse (Mant 1953) shallow breathing during unconsciousness, low blood pressure, a faint pulse (Sherman 1953, Ward 1955), and epicardial and endocardial anoxic hemorrhage (Mant 1953). Acute inhalation exposure studies of humans to concentrations ranging from 116 to 262 ppm for 10 to 30 minutes resulted in mucosal irritation, nausea and vomiting, eye mucosal irritation, and dizziness (Lehman and Schmidt-Kehl 1936).

A man died after cleaning a spill of 1,1,2,2-tetrachloroethane with his bare hands. His spleen was found to be enlarged with nodular areas on the surface (Coyer 1944). Chronic exposures in humans have resulted in reports of headache, tremors, dizziness, numbness, drowsiness, gastrointestinal distress, liver destruction, fatty degeneration in the liver (Hamilton 1917, Koelsch 1915, Lobo-Mendonca 1963, Minot and Smith 1921, Willcox et al. 1915). Jaundice and enlarged livers have also been reported in exposed workers (Coyer 1944, Horiguchi et al. 1964, Jeney et al. 1957, Koelsch;1915).

Acute oral lethal concentrations in rats range from 200 to 330 mg/kg (ATSDR 1994). Centrilobular swelling was observed in mice after an oral dose of 75 mg/kg/day given for 4 days (Dow Chemical Company 1988). Body weight loss and central nervous system depression and debilitation occurred in 16% of the rats receiving 300 mg/kg/day for 3 to 4 days (Dow Chemical Company 1988). Rats orally administered a single dose of 100 mg/kg displayed necrosis and fatty degeneration of the liver, increased serum leucine aminopeptidase, increased liver ascorbic acid, and increased liver triglyceride levels (Schmidt et al. 1980a). Rats orally treated for 17 weeks with a dose of 3.2;mg/kg/day exhibited chronic inflammation of the kidney (Gohlke et al.

1977). Rats had a body weight loss of 38% for the males and 24% for the females after 6 weeks of 178 mg/kg/day but apparently recovered by the end of the 78-week treatment regiment (NCI 1978). At the 280 mg/kg/day dosage, rats died after 70 weeks. At the end of the 78 weeks of 284 mg/kg/day, male mice died of tubular nephrosis and female mice demonstrated hydronephrosis (NCI 1978). [These NCI (1978)dosages were time-weighted averages of the different doses given.]

Lethal exposure concentrations and exposure times for rats were approximately 1000 ppm after 4 to 6 hours (Carpenter et al. 1949, Deguchi 1972, Schmidt et al. 1980b, Smyth et al. 1969) and 5100;ppm after 30 minutes (Price et al. 1978). One of 10 rats exposed to 6300 ppm for 30 minutes exhibited myocardial damage (Price et al. 1978). Mice exposed to 600 ppm for 3 hours developed fatty changes in the liver (Tomokuni 1969, 1970; Hayrack et al. 1962). Exposure of rats to 130 ppm for 15 weeks resulted in increased liver weights, granulation and vacuolization of the liver, and liver hyperplasia (Truffert et al. 1977). Rabbits exposed to 15 ppm for 7 to 11 months exhibited signs of liver degeneration (Navrotskiy et al. 1971). One monkey exposed to a time-weighted average of 1974;ppm for 2 hours/day, 6 days/week for 9 months (no control) had transient diarrhea, anorexia, centrilobular vacuolization, and fatty degeneration of the liver (Hayrack et al. 1962).

The dermal $LD_{50}$ value in rabbits was determined to be 6.36 g/kg (Smyth et al. 1969). Thickening of the cellular nucleus and pseudoeosinophilic infiltration was observed after dermal application of 514 mg/cm$^2$ for 16 hours on guinea pigs (Kronevi et al. 1981).

Army workers exposed to 1,1,2,2-tetrachloroethane vapor in a clothing processing plant had a very slight increase in death due to genital cancers, leukemia, or other lymphomas than workers not employed in a clothing plant (Norman et al. 1981). Male and female mice orally administered 142 and 284 mg/kg/day for 78 weeks had an increase in hepatocellular carcinomas (NCI 1978). Based on these results, 1,1,2,2-tetrachloroethane has been classified as Group C, possible human carcinogen (IRIS 2005).

**REFERENCES**

ATSDR (Agency for Toxic Substances and Disease Registry). 1994. *Toxicological Profile for 1,1,2,2-tetrachloroethane*. Draft for Public Comment. Update. Prepared by Research Triangle Institute under Contract No. 205-93-0606. U.S. Department of Health and Human Services, Public Health Service.

Carpenter, C. P., Smyth, H. F., and Pozzani, U. C. 1949. The assay of acute vapor toxicity and the grading in 6 from the results on 96 chemical compounds. *J. Ind. Hyg. Tox*. 31:343-346 (cited in ATSDR 1994).

Coyer, H. A. 1944.Tetrachloroethane poisoning. *Ind. Med*.13:230-233 (cited in ATSDR 1994).

Dow Chemical Company. 1988. *The metabolism and hepatic macromolecular interactions of 1,1,2,2-tetrachloroethane (TCE) in mice and rats*. D002628 (cited in ATSDR 1994).

Deguchi, T. 1972. [A fundamental study of the threshold limit values for solvent mixtures in the air--Effects of single and mixed chlorinated hydrocarbons upon the level of serum transaminases in rats.] *Osaka City Med*. J. 21:187-209 (cited in ATSDR 1994).

EPA. 1995b. *Health Effects Assessment Summary Tables*. Annual FY-95. Prepared for the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, Ohio, for the Office of Emergency and Remedial Response.

Gohlke, R., Schmidt, P., and Bahmann, H. 1977. 1,1,2,2-tetrachloroethane and heat stress in animal experiment. Morphological results. *Z. Gesame Hyg. IHRE Grenzgeb*. 20:278-282 (German) (cited in ATSDR 1994).

Hallen, R. T., Pyne, J. W. Jr., and Molton, P. M. 1986. Transformation of chlorinated ethenes and ethanes by anaerobic microorganisms. In: *192nd National Meeting ACS Division Environmental Chemistry*, 26: 326-344 (cited in ATSDR 1994).

Hamilton, A. 1917. Military medicine and surgery. *J. Am. Med. Assoc*. 69:2037-2039 (cited in ATSDR 1994).

Hepple, R. A. 1927. An unusual case of poisoning. *J. Army Med Corps*. 49:442-445 (cited in ATSDR 1994).

Horiguchi, S., Morioka, S., Utsunomiya, T., et al. 1964. [A survey of the actual conditions of artificial pearl factories with special reference to the work using tetrachloroethane.] *Jpn. J. Ind. Health* 6:251-256 (cited in ATSDR 1994).

Hayrack, K., Horuguchi, S., Hashimoto, K., et al. 1962. Studies on the industrial tetrachloroethane poisoning. *Osaka City Med*. J. 8:29-38 (cited in ATSDR 1994).

Ikeda, M., and Ohtsuji, H. 1972. Comparative study of the excretion of Fujiwara reaction-positive substances in urine of humans and rodents given trichloro- or tetrachloro-derivatives of ethane and ethylene. *Br. J. Ind. Med*. 29: 99-184 (cited in ATSDR 1994).

IRIS (Integrated Risk Information System), 2005. United States National Library of Medicine, National Institute of Health, Department of Health and Human Services 8600 Rockville Pike, Bethesda, MD 20894. http://toxnet.nlm.nih.gov

Jeney, E. Bartha, F., Kondor, L., et al. 1957. [Prevention of industrial tetrachloroethane intoxication-Part III.] *Egeszsegtudomany* 1:155-164 (Hungarian) (cited in ATSDR 1994).

Koelsch, F. 1915. Industrial poisonings by celluloid varnishes in the airplane industry. *Muench Medizin Wochensch* 62: 1567-1569 (cited in ATSDR 1994).

Kronevi, T., Wahlberg, J. E., and Holmberg, B. 1981. Skin pathology following epicutaneous exposure to seven organic solvents. *Int. J. Tissue React*. 3: 21-30 (cited in ATSDR 1994).

Lehman, K. B., and Schmidt-Kehl, L. 1936. Study of the 13 most important chlorohydrocarbons form the standpoint of industrial hygienics. *Arch. Hyg*. 116: 132-268 (German) (cited in ATSDR 1994).

Lobo-Mendonca, R. 1963. Tetrachloroethane--A survey. *Br. J. Ind. Med*. 20:51-56 (cited in ATSDR 1994).

Mant, A. K. 1953. Acute tetrachlorethane poisoning. A report on two fatal cases. *Br. Med. J*. 665-656 (cited in ATSDR 1994).

Minot, G. R. and Smith, L. W. 1921. The blood in tetrachloroethane poisoning. *Arch. Int. Med*. 28:687-702 (cited in ATSDR 1994).

Mitoma, C., Steeger, T., Jackson, S. E., et al., 1985. Metabolic disposition study of chlorinated hydrocarbons in rats and mice. *Drug Chem. Toxicol*. 3: 183-194 (cited in ATSDR 1994).

NCI. 1978. *Bioassay of 1,1,2,2-tetrachloroethane for possible carcinogenicity.* NTIS PB277 4537GA, DHEW/PUB/NIH-78-827. p. 90 (cited in ATSDR 1994).

Navrotskiy, V. K., Kashin, L. M., Kulinskoya, I. L. 1971. Comparative assessment of the toxicity of a number of industrial poisons when inhaled in low concentrations for porlonged periods. *Trudy S'ezda Gig Ukran*. 8:224-226 (Russian) (cited in ATSDR 1994).

Norman, J. E. Jr., Robinette, C. D., Fraumeni, J. F., Jr. 1981. The mortality experience of Army World War II chemical processing companies. *J. Occ. Med*. 23:818-822 (cited in ATSDR 1994).

Price, N. H., Allen, S. D., Daniels, A. U., et al. 1978. *Toxicity data for establishing "immediately dangerous to life and health" (IDLH) values*. NTIS PB87-163531 (cited in ATSDR 1994).

Schmidt, P., Gohlke, R., Just, A., et al. 1980a. Combined action of hepatotoxic substances and increased environmental temperature on the liver of rats. *J. Hyg. Epidemiol. Microbiol. Immunol*. (Prague) 24:271-277 (cited in ATSDR 1994).

Schmidt, P., Burck, D., Buerger, A., et al., 1980b. [On the hepatotoxicity of benzene, 1,1,2,2-tetrachloroethane and carbon tetrachloride]. *Gesamte Hyg. Ihre Grenzgeb*. (German).

Sherman, J. B. 1953. Eight cases of acute tetrachloroethane poisoning. *J. Trop. Med. Hyg*. 56:139-140 (cited in ATSDR 1994).

Smyth, H. F. Jr., Carpenter, C. P., Weil, C. S., et al. 1969. Range-finding toxicity data-List VII. *Am. Ind. Hyg. Assoc. J*. 30: 470-476 (cited in ATSDR 1994).

Tomokuni, K. 1969. Studies on hepatotoxicity induced by chlorinated hydrocarbons. Lipid and ATP metabolisms in the liver of mice exposed to 1,1,2,2-tetrachloroethane. *Acta Med Okayama* 23:273-282 (cited in ATSDR 1994).

Tomokuni, K. 1970. Hepatotoxicity induced by chlorinated hydrocarbons. II. Lipid metabolism and absorption spectrum of microsomal lipids in the mice exposed to 1,1,2,2-tetrachloroethane. *Acta Med Okayama* 24:315-322 (cited in ATSDR 1994).

Truffert, L., Girard-Wallon, C., Emmerich, E., et al. 1977. Early experimental demonstration of the hepatotoxicity of some chlorinated solvents by the study of the synthesis of hepatic DNA. *Arch. Mal. Prof. Med. Trav. Secur. Soc*. 38:261-263 (French) (cited in ATSDR 1994).

Yllner, S. 1971. Metabolism of 1,1,2,2-tetrachloroethane-14C in the mouse. *Acta Pharmacol. Toxicol.* 29: 499-512 (cited in ATSDR 1994).

Ward, J. M. 1955. Accidental poisoning with tetrachloroethane. *Br. Med*. J. 1:1136 (cited in ATSDR 1994).

Willcox, W. H., Spilsbury, B. H., and Legge, T. M. 1915. An outbreak of toxic jaundice of a new type amongst aeroplane workers-Its clinical and toxicological aspect. *Trans. Med. Soc. London* 38:129-156 (cited in ATSDR 1994).

**Toxicity Summary for ARSENIC**

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*Managed by Martin Marietta Energy Systems, Inc., for the U.S. Department of Energy under Contract No. DE-AC05-84OR21400.

The toxicity of inorganic arsenic (As) depends on its valence state (-3, +3, or +5), and also on the physical and chemical properties of the compound in which it occurs. Trivalent ($As^{+3}$) compounds are generally more toxic than pentavalent ($As^{+5}$) compounds, and the more water soluble compounds are usually more toxic and more likely to have systemic effects than the less soluble compounds, which are more likely to cause chronic pulmonary effects if inhaled. One of the most toxic inorganic arsenic compounds is arsine gas ($AsH_3$). It should be noted that laboratory animals are generally less sensitive than humans to the toxic effects of inorganic arsenic. In addition, in rodents the critical effects appear to be immunosuppression and hepato-renal dysfunction, whereas in humans the skin, vascular system, and peripheral nervous system are the primary target organs.

Water soluble inorganic arsenic compounds are absorbed through the G.I. tract (>90%) and lungs; distributed primarily to the liver, kidney, lung, spleen, aorta, and skin; and excreted mainly in the urine at rates as high as 80% in 61 hr following oral dosing (U.S. EPA, 1984; ATSDR, 1989; Crecelius, 1977). Pentavalent arsenic is reduced to the trivalent form and then methylated in the liver to less toxic methylarsinic acids (ATSDR, 1989).

Symptoms of acute inorganic arsenic poisoning in humans are nausea, anorexia, vomiting, epigastric and abdominal pain, and diarrhea. Dermatitis (exfoliative erythroderma), muscle cramps, cardiac abnormalities, hepatotoxicity, bone marrow suppression and hematologic abnormalities (anemia), vascular lesions, and peripheral neuropathy (motor dysfunction, paresthesia) have also been reported (U.S. Air Force, 1990; ATSDR, 1989; Franzblau and Lilis, 1989; U.S. EPA, 1984; Armstrong et al., 1984; Hayes, 1982; Mizuta et al., 1956). Oral doses as low as 20-60 g/kg/day have been reported to cause toxic effects in some individuals (ATSDR, 1989). Severe exposures can result in acute encephalopathy, congestive heart failure, stupor, convulsions, paralysis, coma, and death. The acute lethal dose to humans has been estimated to be about 0.6 mg/kg/day (ATSDR, 1989). General symptoms of chronic arsenic poisoning in humans are weakness, general debility and lassitude, loss of appetite and energy, loss of hair, hoarseness of voice, loss of weight, and mental disorders (Hindmarsh and McCurdy, 1986). Primary target organs are the skin (hyperpigmentation and hyperkeratosis) [Terada et al. 1960; Tseng et al., 1968; Zaldivar 1974; Cebrian et al., 1983; Huang et al., 1985], nervous system (peripheral neuropathy) [Hindmarsh et al., 1977, 1986; Valentine et al., 1982; Heyman et al., 1956; Mizuta et al., 1956; Tay and Seah, 1975], and vascular system [Tseng et al., 1968; Borgano and Greiber, 1972; Salcedo et al., 1984; Wu et al., 1989; Hansen, 1990]. Anemia, leukopenia, hepatomegaly, and portal hypertension have also been reported (Terada et al., 1960; Viallet et al., 1972; Morris et al., 1974; Datta, 1976). In addition, possible reproductive effects include a high male to female birth ratio (Lyster, 1977).

In animals, acute oral exposures can cause gastrointestinal and neurological effects (Heywood and Sortwell, 1979). Oral $LD_{50}$ values range from about 10 to 300 mg/kg (ASTDR, 1989; U.S. Air Force, 1990). Low subchronic doses can result in immunosuppression, (Blakely et al., 1980) and hepato-renal effects (Mahaffey et al., 1981; Brown et al., 1976; Woods and Fowler, 1977, 1978; Fowler and Woods, 1979; Fowler et al., 1979). Chronic exposures have also resulted in mild

hyperkeratosis and bile duct enlargement with hyperplasia, focal necrosis, and fibrosis (Baroni et al., 1963; Byron et al., 1967). Reduction in litter size, high male/female birth ratios, and fetotoxicity without significant fetal abnormalities occur following oral exposures (Schroeder and Mitchener, 1971; Hood et al., 1977; Baxley et al., 1981); however, parenteral dosing has resulted in exencephaly, encephaloceles, skeletal defects, and urogenital system abnormalities (Ferm and Carpenter, 1968; Hood and Bishop, 1972; Beaudoin, 1974; Burk and Beandoin, 1977).

Acute inhalation exposures to inorganic arsenic can damage mucous membranes, cause rhinitis, pharyngitis and laryngitis, and result in nasal septum perforation (U.S. EPA, 1984). Chronic inhalation exposures, as occurring in the workplace, can lead to rhino-pharyno-laryngitis, tracheobronchitis, (Lundgren, 1954); dermatitis, hyperpigmentation, and hyperkeratosis (Perry et al., 1948; Pinto and McGill, 1955); leukopenia (Kyle and Pease, 1965; Hine et al., 1977); peripheral nerve dysfunction as indicated by abnormal nerve conduction velocities (Feldman et al., 1979; Blom et al., 1985; Landau et al., 1977); and peripheral vascular disorders as indicated by Raynaud's syndrome and increased vasospastic reactivity in fingers exposed to low temperatures (Lagerkvist et al., 1986). Higher rates of cardiovascular disease have also been reported in some arsenic-exposed workers (Lee and Fraumeni, 1969; Axelson et al., 1978; Wingren and Axelson, 1985). Possible reproductive effects include a high frequency of spontaneous abortions and reduced birth weights (Nordström et al., 1978a,b). Arsine gas ($AsH_3$), at concentrations as low as 3-10 ppm for several hours, can cause toxic effects. Hemolysis, hemoglobinuria, jaundice, hemolytic anemia, and necrosis of the renal tubules have been reported in exposed workers (ACGIH, 1986; Fowler and Weissberg, 1974).

Animal studies have shown that inorganic arsenic, by intratracheal instillation, can cause pulmonary inflammation and hyperplasia (Webb et al., 1986, 1987), lung lesions (Pershagen et al., 1982), and immunosuppression (Hatch et al. (1985). Long-term inhalation exposures have resulted in altered conditioned reflexes and CNS damage (Rozenshstein, 1970). Reductions in fetal weight and in the number of live fetuses, and increases in fetal abnormalities due to retarded osteogenesis have been observed following inhalation exposures (Nagymajtenyi et al., 1985).

Epidemiological studies have revealed an association between arsenic concentrations in drinking water and increased incidences of skin cancers (including squamous cell carcinomas and multiple basal cell carcinomas), as well as cancers of the liver, bladder, respiratory and gastrointestinal tracts (U.S. EPA, 1987; IARC, 1987; Sommers et al., 1953; Reymann et al., 1978; Dobson et al., 1965; Chen et al., 1985, 1986). Occupational exposure studies have shown a clear correlation between exposure to arsenic and lung cancer mortality (IARC, 1987; IRIS 2005). The U.S. EPA has placed inorganic arsenic in weight-of-evidence group A, human carcinogen (IRIS, 2005).

**REFERENCES**

Armstrong, C.W.; Stroube, R.B.; Rubio, T.; Siudyla, E.A.; Miller, G.B. 1984. Outbreak of fatal arsenic poisoning caused by contaminated drinking water. Arch. Environ. Health 39:276-279.

ATSDR (Agency for Toxic Substances and Disease Registry). 1989. Toxicological Profile for Arsenic. Agency for Toxic Substances and Disease Registry, U.S. Public Health Service, Atlanta, GA. ATSDR/TP-88/02.

Axelson, O.; Dahlgren, E.; Jasson, C.-D.; Rehnlund, S.O. 1978. Arsenic exposure and mortality: a case-referent study from a Swedish copper smelter. Br. J. Ind. Med. 35:8-15. (Cited in ATSDR, 1989)

Baroni, C; van Esch, G.J.; Saffiotti, U. 1963. Carcinogenesis tests of two inorganic arsenicals. Arch. Environ. Health 7:668-674.

Baxley, M.N; Hood, R.D.; Vedel, G.C.; Harrison, W.P.; Szczech, G.M. 1981. Prenatal toxicity of orally administered sodium arsenite in mice. Bull. Environ. Contam. Toxicol. 26:749-756.

Beaudoin, A.R. 1974. Teratogenicity of sodium arsenate in rats. Teratology 10:153-158. (Cited in U.S. EPA, 1984).

Blakely, B. R.; Sisodia, C.S.; Mukkur, T.K. 1980. The effect of methylmercury, tetraethyl lead, and sodium arsenite on the humoral immune response in mice. Toxicol. Appl. Pharmacol. 52:245-254.

Blom, S.; Lagerkvist, B.; Linderholm, H. 1985. Arsenic exposure to smelter workers: clinical and neurophysiological studies. Scand. J. Work Environ. Health 11:265-270.

Borgono, J.M.; Greiber, R. 1972. Epidemiological study of arsenism in the city of Antofagasta. In: Trace Substances in Environmental Health, vol. 5. D.C. Hemphill, ed. University of Missouri, Columbia, MS. pp. 13-24.

Brown, M.M.; Rhyne, B.C.; Goyer, R.A.; Fowler, B.A. 1976. Intracellular effects of chronic arsenic administration on renal proximal tubule cells. J. Toxicol. Environ. Health 1:505-514.

Burk, D.; Beaudoin, A.R. 1977. Arsenate-induced renal agenesis in rats. Teratology 16:247-260.

Byron, W.R.; Bierbower, G.W.; Brouwer, J.B.; Hansen, W.H. 1967. Pathologic changes in rats and dogs from two-year feeding of sodium arsenite or sodium arsenate. Toxicol. Appl. Pharmacol. 10:132-147.

Cebrian, M.E.; Albores, A.; Aguilar, M.: Blakely, E. 1983. Chronic arsenic poisoning in the north of Mexico. Hum. Toxicol. 2:121-133.

Chen, C.J.; Chuang, Y.C.; Lin, T.M.; Wu, H.Y. 1985. Malignant neoplasms among residents of a Blackfoot disease-endemic area in Taiwan: High-arsenic artesian well water and cancers. Cancer Res. 45:5895-5899.

Chen, C.J.; Chuang, Y.C.; You, S.L.; Lin, T.M.; Wu, H.Y. 1986. A retrospective study on malignant neoplasms of bladder, lung, and liver in a Blackfoot disease-endemic area in Taiwan. Br. J. Cancer 53:399-405.

Chen, C.J.; Wu, S.; Lee, J.; et al. 1986. Atherogenicity and carcinogenicity of high-arsenic artesian well water: Multiple risk factors andf related malignant neoplasms of blackfoot disease. Arteriosclerosis 8:452-460. (Cited in Hansen, 1990).

Crecelius, E.A. 1977. Changes in the chemical speciation of arsenic following ingestion by man. Environ. Health Perspect. 19:147-150. (Cited in U.S. EPA, 1984).

Datta, D.V. 1976. Arsenic and noncirrhotic portal hypertension. Lancet 1:433.

Dobson, R.L.; Young, M.R.; Pinto, J.S. 1965. Palmar keratoses and cancer. Arch. Dermatol. 92:553-556.

Feldman, R.G.; Niles, C.A.; Kelly-Heyes, M.; Sax, D.S.; Dixon, W.J.; Thompson, D.J.; Landau, E. 1979. Peripheral neuropathy in arsenic smelter workers. Neurology 29:939-944.

Ferm, V.H.; Carpenter, S.J. 1968. Malformations induced by sodium arsenate. J. Reprod. Fert. 17:199-201.

Fowler, B.A.; Woods, J.S. 1979. The effects of prolonged oral arsenate exposure on liver mitochondria of mice: morphometric and biochemical studies. Toxicol. Appl. Pharmacol. 50:177-187.

Fowler, B.A.; Woods, J.S.; Schiller, C.M. 1979. Studies of hepatic mitochondria structure and function: Morphometric and biochemical evaluation of *in vivo* perturbation by arsenate. Lab. Invest. 42:313-320.

Franzblau, A.; Lilis, R. 1989. Acute arsenic intoxication from environmental arsenic exposure. Arch. Environ. Health 44(6):385-390.

Hansen, E.S. 1990. Shared risk factors for cancer and artherosclerosis - a review of the epidemiological evidence. Mutat. Res. 239:163-179.

Hatch, G.E.; Boykin, E.; Graham, J.A.; Lewtas, J.; Pott, F.; Loud, K.; Mumford, J.L. 1985. Inhalable particles and pulmonary host defense: *in vivo* and *in vitro* effects of ambient air and combustion particles. Environ. Res. 36:67-80.

Hayes, W.J., Jr. 1982. Pesticide Studies in Man. Williams and Eilkins, Baltimore, MD. pp. 41-50.

Heyman, A.; Pfeiffer, J.B.; Willett, R.W.; Taylor, H.M. 1956. Peripheral neuropathy caused by arsenical intoxication. New England J. Med. 254(9): 401-409.

Heywood. R.; Sortwell, R.J. 1979. Arsenic intoxication in the rhesus monkey. Toxicol. Lett. 3:137-144.

Hindmarsh, J.T.; McCurdy, R.F. 1986. Clinical and environmental aspects of arsenic toxicity. CRC Crit. Rev. Clin. Lab. Sci. 23:315-347.

Hindmarsh, J.T.; McLetchie, O.R.; Heffernan, L.P.; Haynie, O.A.; Ellenberger, H.A.; McCurdy, R.F.; Thiebaux, H.J. 1977. Electromyographic abnormalities in chronic environmental arsenicalism. J. Anal. Toxicol. 1:270-276.

Hine, C.H.; Pinto, S.S.; Nelson, K.W. 1977. Medical problems associated with arsenic exposure. J. Occup. Med. 19(6):391-396.

Hood, R.D.; Bishop, S.L. 1972. Teratogenic effects of sodium arsenate in mice. Arch. Environ. Health 24:62-65.

Hood, R.D.; Thacker, G.T.; Patterson, B.L. 1977. Effects in the mouse and rat of prenatal exposure to arsenic. Environ. Health Perspect. 19:219-222. (Cited in ATSDR, 1989).

Huang, Y.Z.; Qian, X.C.; Wang, G.Q.; Xiao, B.-Y.; Ren, D.D.; Feng, Z.Y.; Wu, J.Y.; Xu, R.J.; Zhang, F. 1985. Endemic chronic arsenism in Xinjiang. Chin. Med. J. (Eng). 98:219-222.

IARC (International Agency for Research on Cancer (IARC). 1987. Overall Evaluations of Carcinogenicity: an Updating of IARC Monographs Volumes 1 to 42. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, supplement 7. Geneva.

IRIS (Integrated Risk Information System), 2005. United States National Library of Medicine, National Institute of Health, Department of Health and Human Services 8600 Rockville Pike, Bethesda, MD 20894. http://toxnet.nlm.nih.gov

Kyle, R.A.; Pease, G.L. 1965. Hematologic aspects of arsenic intoxication. New Eng. J. Med. 273(1):18-23.

Lagerkvist, B.E.A.; Linderholm, H.; Nordberg, G.F. 1986. Vasospastic tendency and Raynaud's phenomenon in smelter workers exposed to arsenic. Environ. Res. 39:465-474.

Landau, E.D.; Thompson, D.J.; Feldman, R.G.; Goble, G.J.; Dixon, W.J. 1977. Selected Noncarcinogenic Effects of Industrial Exposure to Inorganic Arsenic. U.S. Environmental Protection Agency, Washington, DC. EPA 659/6-77-018.

Lee, A.M.; Fraumeni, J.F., Jr. 1969. Arsenic and respiratory cancer in man - an occupational study. J. Natl. Cancer Inst. 42:1045-1052.

Lundgren, K.D. 1954. Damage in the respiratory organs of workers at a smeltery. Nord. Hyg. Tidskr. 3:66-82.

Lyster, W.R. 1977. Arsenic and sex ratio in man. Med. J. Austral. 2:442.

Mahaffey, K.R.; Capar, S.G.; Gladen, B.C.; Fowler, B.A. 1981. Concurrent exposure to lead, cadmium, and arsenic: effects on toxicity and tissue metal concentrations in the rat. J. Lab. Clin. Med. 98:463-481.

Mizuta, N,; Mizuta, M.; Ita, F.; Ito, T.; Uchida, H.; Watanabe, Y.; Akama, H.; Murakami, T.; Hayashi, F.; Nakamura, K.; Yamaguchi, T.; Mizuia, W.; Oishi, S.; Matsumura, H. 1956. An outbreak of acute arsenic poisoning caused by arsenic-contaminated soy sauce (shoye). A clinical report of 220 cases. Bull. Yamaguchi Med. Sch. 4:131-150. (Cited in U.S. EPA, 1984).

Morris, J.S.; Schmid, M.; Newman, S.; Scheuer, P.J.; Sherlock, S. 1974. Arsenic and noncirrhotic portal hypertension. Gastroenterology 64:86-94.

Nagymjtenyi, L.; Selypes, A.; Berencsi, G. 1985. Chromosomal aberrations and fetotoxic effects of atmospheric arsenic exposure in mice. J. Appl. Toxicol. 5:61-63. (Cited in ATSDR, 1989).

Nordström, S.; Beckman, L.; Nordenson, I. 1978a. Occupational and environmental risks in and around a smelter in northern Sweden. I. Variations in birth weight. Hereditas 88:43-46.

Nordström, S.; Beckman, L.; Nordenson, I. 1978b. Occupational and environmental risks in and around a smelter in northern Sweden. III. Frequencies of spontaneous abortions. Hereditas 88:51-54.

Perry, K.; Bowler, R.G.; Buckell, H.M.; Druett, H.A.; Schilling, R.S.F. 1948. Studies in the incidence of cancer in a factory handling inorganic compounds of arsenic - II: clinical and environmental investigations. Br. J. Ind. Med. 5:6-15.

Pinto, S.S.; McGill, C.M. 1953. Arsenic trioxide exposure in industry. Ind. Med. Surg. 22:281-287. (Cited in U.S. EPA, 1984)

Reymann, F.; Moller, R.; Nielsen, A. 1978. Relationship between arsenic intake and internal malignant neoplasms. Arch. Dermatol. 114:378-381.

Rozenshstein, I.S. 1970. Sanitary toxicological assessment of low concentrations of arsenic trioxide in the atmosphere. Hyg. Sanit. 34:16-22. (Cited in U.S. EPA, 1984).

Salcedo, J.C.; Portales, A.; Landecho, E.; Diaz, R. 1984. Transverse study of a group of patients with vasculopathy from chronic arsenic poisoning in communities of the Francisco de Madero and San Pedro Districts, Coahuila, Mexico. Revista de la Facultad de Medicina de Torreon 12:16. (Cited in ATSDR, 1989).

Schroeder, H.A., Mitchener, M. 1971. Toxic effects of trace elements on the reproduction of mice and rats. Arch. Environ. Health 23:102-106.

Sommers, S.C.; McManus, R.G. 1953. Multiple arsenical cancers of the skin and internal organs. Cancer 6:347-359.

Tay, C.H.; Seah, C.S. 1975. Arsenic poisoning from anti-asthmatic herbal preparations. Med. J. Aust. 2:424-428.

Terada, H.; Katsuta, K.; Sasakawa, T.; Saito, T.; Shrota, H.; Fukuchi, K.; Sekiya, E.; Yokoyama, Y.; Hirokawa, S.; Watanabe, G.; Hasegawa, K.; Shina, T.O.; Sekiguchi, E. 1960. Clinical observations of chronic toxicosis by arsenic. Nihon Rinsho 18:2394-2403.

Tseng, W.P.; Chu, H.M.; How, S.W.; Fong, J.M.; Lin, C.S.; Yeh, S. 1968. Prevalence of skin cancer in an endemic area of chronic arsenium in Taiwan. J. Natl. Cancer Inst. 40:453-463.

U.S. Air Force. 1990. Arsenic. In: The Installation Restoration Program Toxicology Guide, vol. 5. Wright-Patterson Air Force Base, OH. pp. 75-1 to 75-102.

U.S. EPA. 1984. Health Assessment Document for Arsenic. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA 600/8-32-021F.

U.S. EPA. 1987. Special Report on Ingested Arsenic: Skin Cancer; Nutritional Essentiality. Prepared for the Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC. EPA/625/3-87/013.

Valentine, J.L.; Campion, D.S.; Schluchter, M.D.; Massey, F.J. 1982. Arsenic effects on human nerve conduction. In: Proceedings of the Fourth International Symposium on Trace Element Metabolism in Man and Animals, J.M. Gawthorne, J.M. Howell, and C.L. White, eds. Springer-Verlag, New York. pp. 409-412.

Viallet, A.; Guillaume, L.; Cote, J.; Legare, A.; Lavoie, P. 1972. Presinusoidal portal hypertension following chronic arsenic intoxication. Gastroenterology 62:177

Webb, D.R.; Wilson, S.E.; Carter, D.E. 1986. Comparative pulmonary toxicity of gallium arsenide, gallium (III) oxide, and arsenic (III) oxide intratracheally instilled into rats. Toxicol. Appl. Pharmacol. 82:405-416.

Webb, D.R.; Wilson, S.E.; Carter, D.E. 1987. Pulmonary clearance and toxicity of respirable gallium arsenide particulates intratracheally instilled into rats. Am. Ind. Hyg. Assoc. J. 48(7):660-667.

Wingren, G.; Axelson, O. 1985. Mortality pattern in a glass producing area in S.E. Sweden. British J. Indust. Med. 42:411-414.

Woods, J.S.; Fowler, B.A. 1977. Effects of chronic arsenic exposure on hematopoietic function in adult mammalian liver. Environ. Health Perspect. 19:209-213.

Woods, J.S.; Fowler, B.A. 1978. Altered regulation of mammalian hepatic heme biosynthesis and urinary porphyrin excretion during prolonged exposure to sodium arsenate. Toxicol. Appl. Pharmacol. 43:361-371.

Wu, M.M.; Kuo, T.L.; Hwang, Y.H.; Chen, C.J. 1989. Dose-response relation between arsenic concentration in well water and mortality from cancers and vascular diseases. Am. J. Epidemiol. 130:1123-1132.

Zaldivar, R. 1974. Arsenic contamination of drinking water and foodstuffs causing endemic chronic poisoning. Beitr. Path. 151:384-400.

**Toxicity Summary for TETRACHLOROETHYLENE**

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*Managed by Martin Marietta Energy Systems, Inc., for the U.S. Department of Energy under Contract No. DE-AC05-84OR21400.

Tetrachloroethylene (CAS No. 127-18-4) is a halogenated aliphatic hydrocarbon with a vapor pressure of 17.8 mm Hg at 25C (U.S. EPA, 1982). The chemical is used primarily as a solvent in industry and, less frequently, in commercial dry-cleaning operations (ATSDR, 1990). Occupational exposure to tetrachloroethylene occurs via inhalation, resulting in systemic effects, and via dermal contact, resulting in local effects. Exposure to the general population can occur through contaminated air, food and water (ATSDR, 1990).

The respiratory tract is the primary route of entry for tetrachloroethylene (NTP, 1986; U.S. EPA, 1988). The chemical is rapidly absorbed by this route and reaches an equilibrium in the blood within 3 hours after the initiation of exposure (Hake and Stewart, 1977). Tetrachloroethylene is also significantly absorbed by the gastrointestinal (g.i.) tract, but not through the skin (Koppel et al., 1985; ATSDR, 1990). The chemical accumulates in tissues with high lipid content, where the half-life is estimated to be 55 hours (Stewart, 1969; ATSDR, 1990), and has been identified in perirenal fat, brain, liver, placentofetal tissue, and amniotic fluid (Savolainen et al., 1977). The proposed first step for the biotransformation of tetrachloroethylene is the formation of an epoxide thought to be responsible for the carcinogenic potential of the chemical (Henschler and Hoos, 1982; Calabrese and Kenyon, 1991). Tetrachloroethylene is excreted mainly unchanged through the lungs, regardless of route of administration (NTP, 1986). The urine and feces comprise secondary routes of excretion (Monster et al., 1979; Ohtsuki et al., 1983). The major urinary metabolite of tetrachloroethylene, trichloroacetic acid, is formed via the cytochrome P-450 system (ATSDR, 1990).

The main targets of tetrachloroethylene toxicity are the liver and kidney by both oral and inhalation exposure, and the central nervous system by inhalation exposure. Acute exposure to high concentrations of the chemical (estimated to be greater than 1500 ppm for a 30-minute exposure) may be fatal to humans (Torkelson and Rowe, 1981). Chronic exposure causes respiratory tract irritation, headache, nausea, sleeplessness, abdominal pains, constipation, cirrhosis of the liver, hepatitis, and nephritis in humans; and microscopic changes in renal tubular cells, squamous metaplasia of the nasal epithelium, necrosis of the liver, and congestion of the lungs in animals (Chmielewski et al., 1976; Coler and Rossmiller, 1953; Stewart et al., 1970; von Ottingen, 1964; Stewart, 1969; NTP, 1986).

Some epidemiology studies have found an association between inhalation exposure to tetrachloroethylene and an increased risk for spontaneous abortion, idiopathic infertility, and sperm abnormalities among dry-cleaning workers, but others have not found similar effects (Kyyronen et al, 1989; van der Gulden and Zielhuis, 1989). The adverse effects in humans are supported in part by the results of animal studies in which tetrachloroethylene induced fetotoxicity (but did not cause malformations) in the offspring of treated dams (Schwetz et al., 1975; Beliles et al., 1980; Nelson et al., 1980).

Epidemiology studies of dry cleaning and laundry workers have demonstrated excesses in mortality due to various types of cancer, including liver cancer, but the data are regarded as inconclusive because of various confounding factors (Lynge and Thygesen, 1990; U.S. EPA,

1988). The tenuous finding of an excess of liver tumors in humans is strengthened by the results of carcinogenicity bioassays in which tetrachloroethylene, administered either orally or by inhalation, induced hepatocellular tumors in mice (NCI, 1977; NTP, 1986). The chemical also induced mononuclear cell leukemia and renal tubular cell tumors in rats. Tetrachloroethylene was negative for tumor initiation in a dermal study and for tumor induction in a pulmonary tumor assay (Van Duuren et al., 1979; Theiss et al., 1977).

Although U.S. EPA's Science Advisory Board recommended a weight-of-evidence classification of C-B2 continuum (C = possible human carcinogen; B2 = probable human carcinogen), the agency has not adopted a current position on the weight-of-evidence classification (IRIS, 2005).

**REFERENCES**

ATSDR (Agency for Toxic Substances and Disease Registry). 1990. Toxicological Profile for Tetrachloroethylene. Public Health Service, U.S. Department of Health and Human Services, Chamblee, GA.

Beliles, R.P., D.J. Bursisk and F.J. Meclec. 1980. Teratogenic, mutagenic risk of workplace contaminants; trichloroethylene, perchloroethylene and carbon disulfide. Unpublished studies U.S. Dept. of Health, Education and Welfare. Contract 210-77-0047, Litton Bionetics Inc., Kensington, MD. (Cited in EPA, 1988)

Buben, J.A. and E.J. O'Flaherty. 1985. Delineation of the role of metabolism in the hepatotoxicity of trichloroethylene and perchloroethylene: A dose-effect study. Toxicol. Appl. Pharmacol. 78: 105-122.

Calabrese, E.J. and E.M. Kenyon. 1991. Air Toxics and Risk Assessment. Lewis Publishers, Chelsea, MI. p. 531-535.

Chmielewski, J., R. Tomaszewski, P. Glombiowski, et al. 1976. Clinical observations of the occupational exposure to tetrachloroethylene. Bull. Inst. Marit. Trop. Med. Gdynia. 27(2): 197-205. (Cited in U.S. EPA, 1988)

Coler, H.R. and H.R. Rossmiller. 1953. Tetrachloroethylene exposure in a small industry. Ind. Hyg. Occup. Med. 8: 227.

Hake, C. and R. Stewart. 1977. Human exposure to tetrachloroethylene: inhalation and skin contact. Environ. Health Perspect. 21: 231-238.

Henschler, D. and R. Hoos. 1982. Metabolic activation and deactivation mechanisms of di, tri, and tetrachloroethylenes. In Snyder, R., et al., Eds. Biological Reactive Intermediates-II: Chemical Mechanisms and Biological Effects. Plenum Press, New York. p. 659-666.

IRIS (Integrated Risk Information System), 2005. United States National Library of Medicine, National Institute of Health, Department of Health and Human Services 8600 Rockville Pike, Bethesda, MD 20894. http://toxnet.nlm.nih.gov

Kyyronen, P., H. Taskinen, M.-L. Lindbohm, K. Hemminki, O.P. Heinonen. 1989. Spontaneous abortions and congenital malformations among women exposed to tetrachloroethylene in dry cleaning. J. Epidemiol. Comm. Health 43: 346-351.

Lynge, E. and L. Thygesen. 1990. Primary liver cancer among women in laundry and dry-cleaning work in Denmark. Scand J. Work Environ. Health 16: 108-112.

Monster, A.C., G. Boersma and H. Steenweg. 1979. Kinetics of tetrachloroethylene in volunteers: Influence of exposure concentration and work load. Int. Arch. Occup. Environ. Health 53: 331-336.

NCI (National Cancer Institute). 1977. Bioassay of Tetrachloroethylene for Possible Carcinogenicity. Department of Health, Education, and Welfare, Bethesda, MD. NCI TR 13.

Nelson, B.K., B.J. Taylor, J.V. Setzer and R.W. Hornung. 1980. Behavioral teratology of perchloroethylene in rats. J. Environ. Pathol. Toxicol. 3: 233-250.

NTP (National Toxicology Program). 1986. NTP Technical Report on the Toxicology and Carcinogenesis Tetrachloroethylene (Perchloroethylene) in F344/N Rats and B6C3$F_1$ Mice (Inhalation Studies). National Toxicology Program, U.S. Dept. of Health and Human Services, Research Triangle Park, NC. NTP TR 311.

Ohtsuki, T., K. Sato, A. Koizumi, M. Kumai and M. Ikeda. 1983. Limited capacity of humans to metabolize tetrachloroethylene. Int. Arch. Occup. Environ. Health 51: 381-390.

Rampy, L., J. Quast, B. Leong and P. Gehring. 1978. Results of a long-term inhalation toxicity

Savolainen, H., P. Pfaffli, M. Tengen and H. Vaino 1977. Biochemical and behavioural effects of inhalation exposure to tetrachloroethylene and dichloromethane. J. Neuropathol. Exp. Neurol. 36: 941-949.

Schwetz, B., B. Leong and P. Gehring. 1975. The effects of maternally inhaled trichloroethylene, perchloroethylene, methylchloroform, and methylene chloride on embryonal and fetal development in mice and rats. Toxicol. Appl. Pharmacol. 32: 84-92.

Stewart, R. 1969. Acute tetrachloroethylene intoxication. J. Am. Med. Assoc. 208: 1490-1493.

Stewart, R.D., E.D. Baretta, H.C. Dodd and T.R. Torkelson. 1970. Experimental human exposure to tetrachloroethylene. Arch. Environ. Health 20: 224-229.

Theiss, J., G. Stoner, M. Shimkin and E. Weisburger. 1977. Tests for carcinogenicity of orgnanic contaminants of United States drinking waters by pulmonary response in Strain A mice. Cancer Res. 37: 2717-2720.

Torkelson, T.R. and V.K. Rowe. 1981. Tetrachloroethylene. In: Patty's Industrial Hygiene and Toxicology, 3rd ed. Clayton, G.D. and F.E. Clayton, Eds. John Wiley & Sons, New York. p. 3560-3568, 3586-3601.

U.S. EPA (U.S. Environmental Protection Agency). 1982. Health Assessment Document for Tetrachloroethylene (Perchloroethylene). Final Report. Office of Health and Environmental Assessment, Washington, DC. EPA/600/8-82/005F.

U.S. EPA (U.S. Environmental Protection Agency). 1985. Health Assessment Document for Tetrachloroethylene (Perchloroethylene). Final draft. Office of Solid Waste and Emergency Response, Environmental Criteria and Assessment Office, U.S. EPA, Research Triangle Park, NC. EPA 600/8-82-005F. NTIS PB 84-162882.

U.S. EPA (U.S. Environmental Protection Agency). 1987. Health Assessment Document for Tetrachloroethylene (Perchloroethylene). Addendum. Office of Solid Waste and Emergency

Response, Environmental Criteria and Assessment Office, U.S. EPA, Research Triangle Park, NC. EPA 600/8-82-005FA.

U.S. EPA (U.S. Environmental Protection Agency). 1988. Updated Health Effects Assessment for Tetrachloroethylene. Final draft. Prepared for Office of Solid Waste and Emergency Response. Environmental Criteria and Assessment Office, U.S. EPA, Cincinnati, OH. ECAO-CIN-H009a.

U.S. EPA (U.S. Environmental Protection Agency). 1992a. Health Effects Summary Tables. FY-1992 Annual. Office of Research and Development, Office of Emergency and Remedial Response, U.S. Environmental Protection Agency, Washington, DC.

U.S. EPA (U.S. Environmental Protection Agency). 1992b. Superfund Health Risk Technical Support Center Fact Sheet. Tetrachloroethylene. December 14, 1992.

van der Gulden, J.W. and G.A. Zielhuis. 1989. Reproductive hazards related to perchloroethylene. A review. Int. Arch. Occup. Environ. Health 61: 235-242.

Van Duuren, B. B. Goldschmide, G. Lowengart et al. 1979. Carcinogenicity of halogenated olefinic and aliphatic hydrocarbons in mice. J. Natl. Cancer Inst. 63: 1433-1439.

von Oettingen, W.R. 1964. In: The Halogenated Hydrocarbons of Industrial and Toxicological Importance. Elsevier Press, Amsterdam. p. 271-283.

**Toxicity Summary for TRICHLOROETHENE**

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*Managed by Martin Marietta Energy Systems, Inc., for the U.S. Department of Energy under Contract No. DE-AC05-84OR21400.

Trichloroethene (TCE) is an industrial solvent used primarily in metal degreasing and cleaning operations. TCE can be absorbed through the lungs, mucous membranes, gastrointestinal tract, and the skin. TCE is extensively metabolized in humans to trichloroacetic acid and trichloroethanol, as well as to several minor metabolites, with most of the absorbed dose excreted in urine (ATSDR, 1989; U.S. EPA, 1985).

Human and animal data indicate that exposure to TCE can result in toxic effects on a number of organs and systems, including the liver, kidney, blood, skin, immune system, reproductive system, nervous system, and cardiovascular system. In humans, acute inhalation exposure to TCE causes central nervous system symptoms such as headache, dizziness, nausea, and unconsciousness (U.S. EPA, 1985). Among the reported effects from occupational exposure studies are fatigue, light-headedness, sleepiness, vision distortion, abnormal reflexes, tremors, ataxia, nystagmus, increased respiration, as well as neurobehavioral or psychological changes. Cardiovascular effects include tachycardia, extrasystoles, EKG abnormalities, and precordial pain (Landrigan et al., 1987; Grandjean et al., 1955; Milby, 1968). The use of TCE as an anesthetic has been associated with cardiac arrhythmias (U.S. EPA, 1985).

Cases of severe liver and kidney damage, including necrosis, have been reported in humans following acute exposure to TCE (Defalque, 1961), but these effects generally are not associated with long-term occupational exposures. In animals, TCE has produced liver enlargement with hepatic biochemical and/or histological changes (Nomiyama et al., 1986; Kjellstrand et al., 1981, 1983; Stott et al., 1982; Tucker et al., 1982) and kidney enlargement, renal tubular alterations and/or toxic nephropathy (NTP, 1982, 1986a, 1988). Also observed in animals were hematological effects (Tucker et al., 1982; Mazza and Brancaccio, 1967) and immunosuppression (Sanders et al., 1982). Inhalation studies with rats indicate that TCE is a developmental toxicant causing skeletal ossification anomalies and other effects consistent with delayed maturation (Healy et al., 1982; Dorfmueller et al., 1979). TCE may cause dermatitis and dermographism (U.S. EPA, 1985).

The carcinogen assessment for TCE has been withdrawn following further review. A new carcinogen summary is in preparation by the EPA (IRIS, 2005).

**REFERENCES**

ATSDR (Agency for Toxic Substances and Disease Registry). 1989. Toxicological Profile for Trichloroethylene. Prepared by Syracuse Research Corporation, under Contract No. 68-C8-0004 for ATSDR, U.S. Public Health Service. ATSDR/TP-88/24.

Bell, Z.G., K.H. Olson and T.J. Benja. 1978. Final Report of Audit Findings of the Manufacturing Chemists Association: Administered Trichloroethylene Chronic Inhalation Study at Industrial Biotest Laboratories, Inc., Decatur, IL. Unpublished. (Cited in U.S. EPA, 1987)

Defalque, J.R. 1961. Pharmacology and toxicology of trichloroethylene. A critical review of the world literature. Clin. Pharmacol. Ther. 2: 665-688. (Cited in IARC, 1979)

Dorfmueller, M.A., S.P. Henne, R.G. York, et al. 1979. Evaluation of teratogenicity and behavioral toxicity with inhalation exposure of maternal rats to trichloroethylene. Toxicology 14: 153-166.

Fukuda, K., K. Takemoto and H. Tsuruta. 1983. Inhalation carcinogenicity of trichloroethylene in mice and rats. Ind. Health 21: 243-254.

Grandjean, E., R. Munchinger, V. Turrian, et al. 1955. Investigations into the effects of exposure to trichloroethylene in mechanical engineering. Brit. J. Ind. Med. 12: 131-142.

Healy, T.E.J., T.R. Poole and A. Hopper. 1982. Rat fetal development and maternal exposure to trichloroethylene at 100 ppm. Br. J. Anaesth. 54: 337-341.

IRIS (Integrated Risk Information System), 2005. United States National Library of Medicine, National Institute of Health, Department of Health and Human Services 8600 Rockville Pike, Bethesda, MD 20894. http://toxnet.nlm.nih.gov

Kjellstrand, P., M. Kanje, L. Manson, et al. 1981. Trichloroethylene: Effects on body and organ weights in mice, rats, and gerbils. Toxicology 21: 105-115.

Landrigan, P.J., G.F. Stein, J.R. Kominski, et al. 1987. Common-source community and industrial exposure to trichloroethylene. Arch. Environ. Health 42: 327-332.

Maltoni, C., G. Lefemine and G. Cotti. 1986. Experimental Research on Trichloroethylene Carcinogenesis. C. Maltoni and M.A. Mehlman, Eds., Archives of Industrial Carcinogenesis Series, Vol. V. Princeton Scientific Publishing Co., Princeton, NJ, p. 393. (Cited in ATSDR, 1989)

Maltoni, C., G. Lefemine, G. Cotti, et al. 1988. Long-term carcinogenicity bioassays on trichloroethylene administered by inhalation to Sprague-Dawley rats and Swiss and B6C3$F_1$ mice. Ann. N.Y. Acad. Sci. 534: 316-342.

Mazza, V. and A. Brancaccio. 1967. Characteristics of the formed elements of the blood and bone marrow in experimental trichloroethylene intoxication. Folia Med. 50: 318-324. (Cited in U.S. EPA, 1985)

Milby, T.H. 1968. Chronic trichloroethylene intoxication. J. Occup. Med. 10: 252-254.

NCI (National Cancer Institute). 1976. Carcinogenesis Bioassay of Trichloroethylene. CAS No. 79-01-6. U.S. Department of Health, Eduction, and Welfare, National Institutes of Public Health, 76-802. NCI-CG-TR-2.

Nomiyama, K., H. Nomiyama and H. Arai. 1986. Reevaluation of subchronic toxicity of trichloroethylene. Toxicol. Lett. 31(Suppl.): 225.

NTP (National Toxicology Program). 1982. Carcinogenesis Bioassay of Trichloroethylene in F344 Rats and B6C3$F_1$ Mice. CAS No. 79-01-6. U.S. Department of Health and Human Services, National Institutes of Health, Bethesda, MD. NTP 81-84, NIH Publ. 82-1799.

NTP (National Toxicology Program). 1986a. Toxicology and Carcinogenesis Studies of Trichloroethylene (CAS No. 79-01-6) in F344 Rats and B6C3$F_1$ Mice. U.S. Department of Health and Human Services, National Institutes of Health, Bethesda, MD. NTP TR 243.

NTP (National Toxicology Program). 1988. Toxicology and Carcinogenesis Studies of Trichloroethylene (CAS No. 79-01-6) in Four Strains of Rats (ACI, August, Marshall, Osborne-Mendel) (Gavage Studies). U.S. Department of Health and Human Services, National Institutes of Health, Bethesda, MD. NTP TR 273.

Sanders, V.M., A.N. Tucker, K.L. White, Jr., et al. 1982. Humoral and cell-mediated immune status in mice exposed to trichloroethylene in drinking water. Toxicol. Appl. Pharmacol. 62: 358-368.

Stott, W.T., J.F. Quast and P.G. Watanabe. 1982. Pharmacokinetics and macromolecular interactions of trichloroethylene in mice and rats. Toxicol. Appl. Pharmacol. 62: 137-151.

Tucker, A.N., V.M. Sanders, D.W. Barnes, et al. 1982. Toxicology of trichloroethylene in the mouse. Toxicol. Appl. Pharmacol. 62: 351-357.

U.S. EPA. 1985. Health Assessment Document for Trichloroethylene. Final Report. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA/600/8-82/006F.

U.S. EPA. 1987. Addendum to the Health Assessment Document for Trichloroethylene. Updated Carcinogenicity Assessment for Trichloroethylene. External Review Draft. Office of Health and Environmental Assessment, Office of Research and Development, Washington, DC. EPA/600/8-82/006FA, PB87-228045.

**1, 4-Dioxane Fact Sheet: Support Document (CAS No. 123-9-1)**

United States Environmental Protection Agency Pollution Prevention and Toxics EPA 749-F-95-010a

This summary is based on information retrieved from a systematic search limited to secondary sources. These sources include online databases, unpublished EPA information, government publications, review documents, and standard reference materials. The literature search was done in February of 1995. No attempt has been made to verify information in these databases and secondary sources.

In 1985, 90 percent of 1,4-dioxane produced in the U.S. was used as a stabilizer for chlorinated solvents such as 1,1,1-trichloroethane (HSDB 1995). Although this application continues to be the primary one, it is quickly being phased out (FerroCorp. 1995). The primary use of 1,4-dioxane is as a solvent for various applications, primarily in the manufacturing sector. Other solvent applications include those for cellulose acetate, dyes, fats, greases, lacquers, mineral oil, paints, resins, varnishes, and waxes. 1,4-Dioxane is also used in paint and varnish strippers, as a wetting agent and dispersing agent in textile processing, dye baths, stain and printing compositions, and in the preparation of histological slides. Additionally, 1,4-dioxane is used in cosmetics, deodorants, fumigants, automotive coolant liquid, and scintillation counters (Chemical Marketing Reporter 1988; Sax and Lewis 1993; Sittig 1991; USITC 1994).

Systemic toxicity has been observed following oral, inhalation and dermal exposure, indicating that absorption occurs by these routes. Rowe and Wolf (1981) report that 1,4-dioxane and its metabolites are excreted in urine, and that unchanged 1,4-dioxane is found in expired air (IARC 1976). The major urinary metabolite of 1,4-dioxane is hydroxyethoxyacetic acid, as determined in studies with rats and with human volunteers and dioxane plant personnel (Rowe and Wolf 1982). A second minor urinary metabolite may be diethylene glycol. Dioxane has low acute toxicity. The liquid is painful and irritating to the eyes, irritating to the skin upon prolonged or repeated contact, and can be absorbed through the skin in toxic amounts. Dioxane vapor has poor warning properties and can be inhaled in amounts that may cause serious systemic injury, particularly to the liver and kidneys. Exposure of 12 volunteers to a concentration of 1080 mg/m3 (300 ppm) 1,4-dioxane in air for 15 minutes produced irritation of the eyes, nose and throat (IARC 1976). Five deaths due to acute inhalation exposure to 1,4-dioxane have been reported; hemorrhagic nephritis and liver necrosis were recorded at autopsy (IARC 1976). Other workers in the same plant suffered from nausea, vomiting, and irritation of the eyes and respiratory passages (ACGIH 1991). Death of a worker, probably attributable to one week's inhalation exposure to about 1800 mg/m3 has been reported. In that case, there was also the possibility of skin absorption since the dioxane was also used as a solvent to remove glue from hands (IARC 1976). Epidemiologic studies of workers exposed to low levels of 1,4-dioxane have not shown adverse effects. Dose-related liver and kidney damage have been observed in several species of animals exposed by oral, inhalation, and dermal routes. Dioxane is not considered to be a skin irritant in the workplace, but prolonged and repeated contact can cause eczema, as can any effective fat solvent (Rowe and Wolf 1982). Impaired neurological function has been observed in humans exposed to high levels of 1,4-dioxane by inhalation, and in animals exposed by the inhalation, oral, or dermal routes. These effects include incoordination, narcosis, vertigo, behavioral effects, and coma. Among symptoms observed in cases of fatal industrial 1,4-dioxane inhalation poisoning (possibly combined with dermal absorption) were drowsiness, vertigo, headache, and coma (Rowe and Wolf 1982).

No evidence of adverse effects was found in chromosomal analyses performed on 6 members of a cohort in an epidemiologic study of dioxane workers (Rowe and Wolf 1982). 1,4-Dioxane induced DNA strand breaks in rat hepatocytes in vitro. It was not mutagenic to bacteria (IARC 1976). The chemical was negative in the mouse lymphoma assay, negative for the induction of chromosomal aberrations in cultured Chinese hamster ovary (CHO) cells and weakly positive in the CHO sister-chromatid exchange assay (ACGIH 1991). There is very little information on the developmental/reproductive toxicity of 1,4-dioxane. There is evidence of fetal toxicity in one rat study at high doses (Rowe and Wolf 1982).

EPA classifies 1,4-dioxane as B2, a probable human carcinogen, based on the induction of nasal cavity and liver carcinomas in multiple strains of rats, liver carcinomas in mice, and gall bladder carcinomas in

guinea pigs. Human carcinogenicity data for 1,4-dioxane are inadequate. In three epidemiologic studies on workers exposed to 1,4-dioxane, no increase was observed in the number of cancer deaths over that expected (IRIS 2005).

**REFERENCES**


Chemical Marketing Reporter. 1988. "1,4-dioxane has more sources than expected, says Gelman." 234: 17.

Ferro Corporation. 1995. EPA conversation with Ferro Corp. representative, May 1, 1995.

IARC. 1976. International Agency for Research on Cancer. 1,4-Dioxane. In: IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Vol. 11. IARC, Lyon, pp. 247-256.

IRIS (Integrated Risk Information System), 2005. United States National Library of Medicine, National Institute of Health, Department of Health and Human Services 8600 Rockville Pike, Bethesda, MD 20894. http://toxnet.nlm.nih.gov

Rowe VK, Wolf MA. 1982. Derivatives of glycols. Patty's Industrial Hygiene and Toxicology, 3rd ed., Vol. 2C. Clayton GD and Clayton FE, eds. John Wiley & Sons: New York. pp. 3947-3956.

Sax, N. and R.J. Lewis. 1993. Hawley's Condensed Chemical Dictionary. 12th edition. Van Nostrand Reinhold: New York.

Sittig, M. 1991. Handbook of Toxic and Hazardous Chemicals andCarcinogens, Third edition. Noyes Publications: New Jersey.

U.S. ITC. ( United States International Trade Commission.) 1994. Synthetic Organic Chemicals: United States Production and Sales,1992. 76th edition. USITC Publication 2720, February 1994.

ACGIH. 1991. American Conference for Governmental IndustrialHygienists, Inc. TLVs . Documentation of the Threshold Limit Values and Biological Exposure Indices. ACGIH, Cincinnati, OH.

**Toxicity Summary for 1,1-DICHLOROETHANE**

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1,1-Dichloroethane is used primarily as an intermediate in manufacturing vinyl chloride and 1,1,1-trichloroethane; it is also used as a cleaning agent and degreaser and as a solvent for plastics, oils, and fats (ATSDR, 1990).

The available evidence indicates that 1,1-dichloroethane can be readily absorbed following inhalation and oral exposures (ATSDR, 1990). The anesthetic effects of 1,1-dichloroethane are evidence that the chemical reaches the central nervous system (CNS). Acetic acid is a major metabolite, and 2,2-dichloroethanol, chloroacetic acid, and dichloroacetic acid are minor metabolites (McCall et al., 1983). In animal studies, orally administered 1,1-dichloroethane was excreted primarily in expired air as the unmetabolized chemical (Mitoma et al., 1985).

No information is available on the oral toxicity of 1,1-dichloroethane to humans. In animals, a drinking water concentration of up to 2500 mg/L for 52 weeks caused no adverse effects in male mice (Klaunig et al., 1986), and maximum gavage doses of 764 mg/kg/day (male Osborne-Mendel rats), 950 mg/kg (female Osborne-Mendel rats), 2885 mg/kg (male $B6C3F_1$ mice), and 3331 mg/kg (female $B6C3F_1$ mice), 5 days/week for 78 weeks (3 weeks on, 1 week off) resulted in no histopathological changes (NCI, 1978).

At high vapor concentrations (26,000 ppm), 1,1-dichloroethane induces anesthesia and can cause cardiac arrhythmia in humans, but no fatalities have occurred (ATSDR, 1990). Adverse effects following subchronic or chronic exposures to humans have not been reported. In animal studies, 1,1-dichloroethane did not cause developmental or reproductive effects but did delay rib ossification in rats (Schwetz et al., 1974). Kidney damage was observed in cats exposed to 2025 $mg/m^3$ (6 hours/day, 5 days/week) for 13 weeks followed by 4050 $mg/m^3$ for an additional 13 weeks; however, similar effects were not seen in rats, rabbits, or guinea pigs.

1,1-Dichloroethane is placed in Group C, possible human carcinogen based on no human data and limited evidence of carcinogenicity in two animal species (rats and mice) (IRIS,2005).

**REFERENCES**

ATSDR (Agency for Toxic Substances and Disease Registry). 1990. *Toxicological Profile for 1,1-Dichloroethane*. U.S. Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA. 103 pp. ATSDR/TP-90-12.

IRIS (Integrated Risk Information System), 2005. United States National Library of Medicine, National Institute of Health, Department of Health and Human Services 8600 Rockville Pike, Bethesda, MD 20894. http://toxnet.nlm.nih.gov

Klaunig, J.E., R.J. Ruch, and M.A. Pereira. 1986. "Carcinogenicity of chlorinated methane and ethane compounds administered in drinking water to mice." *Environ. Health Perspect*. 69:89-95. (Cited in ATSDR, 1990).

McCall, S.N., P. Jurgens, and K.M. Ivanetich. 1983. "Hepatic microsomal metabolism of dichloroethanes." *Biochem. Pharmacol*. 3:207-213. (Cited in ATSDR, 1990).

Mitoma, C., T. Steeger, S.E. Jackson, et al. 1985. "Metabolic disposition study of chlorinated hydrocarbons in rats and mice." *Drug Chem. Toxicol*. 8:183-194. (Cited in ATSDR, 1990).

NCI (National Cancer Institute). 1978. *Carcinogenesis Bioassay of 1,1-Dichloroethane*. NCI Carcinogenesis Technical Report Series Number 66, NCI-CG-TR-66, DHEW Publications No. (NIH) 78-1316.

Schwetz, B.A.; B.K.G. Leong, and P.J. Gehring. 1974. "Embryo- and fetotoxicity of inhaled carbon tetrachloride, 1,1-dichloroethane, and methyl ethyl ketone in rats." *Toxicol. Appl. Pharmacol*. 28:452-464. (Cited in U.S. Air Force, 1989).

# Toxicity Summary for 1,1-DICHLOROETHYLENE

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1,1-Dichloroethylene (CAS No. 75-35-4), also known as 1,1-dichloroethene and vinylidine chloride, is a colorless liquid that is used primarily in the production of polyvinylidine chloride (PVC) copolymers and as an intermediate for synthesis of organic chemicals. The major application for PVC copolymers is the production of flexible films for food packaging such as Saran® wrap (ATSDR, 1993).

1,1-Dichloroethylene does not occur naturally (IARC, 1986) but is found in the environment due to releases associated with its production and transport and with the production of its polymers. Because of its high volatility, releases to the atmosphere are the greatest source of ambient 1,1-dichloroethylene. Smaller amounts are released to surface waters and soils (ATSDR, 1993). Loss of 1,1-dichloroethylene from water and soils is primarily due to volatilization. In the atmosphere, reaction with photochemically generated hydroxyl radicals is expected to be the predominant removal mechanism (EPA, 1987). Human exposure to 1,1-dichloroethylene is potentially highest in workplace settings and in the vicinity of hazardous waste sites where the compound may contaminate environmental media (ATSDR, 1993).

The primary effect of acute exposure to high concentrations (approximately 4000 ppm) of 1,1-dichloroethylene vapor in humans is central nervous system (CNS) depression which may progress to unconsciousness (Gosselin et al., 1984). Occupational exposure has been reported to cause liver dysfunction in workers (Tierney et al., 1979). 1,1-Dichloroethylene is irritating when applied to the skin and prolonged contact can cause first degree burns (Tierney et al., 1979). Direct contact with the eyes may cause conjunctivitis and transient corneal injury (IARC, 1986).

In experimental animals, the liver and kidneys are target organs for the toxic effects of 1,1-dichloroethylene. Subchronic oral exposure for 90 days to 1,1-dichloroethylene in drinking water produced slight hepatotoxic effects at 200 ppm (Rampy et al., 1977), and chronic oral exposure to drinking water for 2 years produced hepatocellular changes in males at >=100 ppm and in females at >=50 ppm (Quast et al., 1983). Gavage administration of 10 mg/kg/day, 5 days/week for 2 years produced chronic inflammation of the kidney in male and female rats and liver necrosis in male and female mice (NTP, 1982). Exposure by inhalation to 55 ppm 1,1-dichloroethylene, 6 hours/day, 5 days/week for up to 1 year produced fatty liver changes in rats and focal degeneration and necrosis in mice (Lee et al., 1977).

In a three-generation study, no treatment-related effects on reproduction or neonatal development were seen in male and female Sprague-Dawley rats administered up to 200 ppm of 1,1-dichloroethylene in the drinking water (Nitschke et al., 1983). However, inhalation exposure during gestation produced increased resorptions and minor skeletal alterations in rodents at concentrations that caused maternal toxicity. These effects were reported in rats and mice at >=15 ppm (Short et al., 1977a) and in rats and rabbits at >=80 ppm and >=160 ppm, respectively (Murray et al., 1979).

An epidemiology study using a small cohort found no association between the occurrence of cancer or cancer mortality and exposure to 1,1-dichloroethylene (Ott et al., 1976). Oral carcinogenicity bioassays (drinking water or gavage exposures) with experimental animals gave

generally negative results (NTP, 1982; Quast et al., 1983; Maltoni et al., 1984, 1985). In one inhalation study (Maltoni et al., 1985), statistically significant increases in renal adenocarcinomas were noted in male Swiss mice exposed to 25 ppm for 12 months. Also observed were statistically significant increases in mammary gland carcinomas in females and lung tumors in both sexes. Results of other inhalation studies with rats, mice, and hamsters have been negative (Hong et al., 1981; Maltoni et al., 1984; Quast et al., 1986).

Based on EPA guidelines, 1,1-dichloroethylene was assigned to weight-of-evidence group C, possible human carcinogen (IRIS, 2005).

**REFERENCES**


ATSDR (Agency for Toxic Substances and Disease Registry). 1993. 1,1-Dichloroethylene, Update. U.S. Department of Health and Human Services, Public Health Service.

EPA (U.S. Environmental Protection Agency). 1987. Health Effects Assessment for 1,1-Dichloroethylene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Emergency and Remedial Response, Washington, DC. ECAO-CIN-HO51a.

Gosselin, R.E., R.P. Smith, H.C. Hodge, et al. 1984. *Clinical Toxicology of Commercial Products, 5th ed*. The Williams and Wilkins Co., New York, p. II-163.

Hong, C.B., J.M. Winston, L.P. Thornburg, et al. 1981. Follow-up study on the carcinogenicity of vinyl chloride and vinylidine chloride in rats and mice: Tumor incidence and mortality subsequent to exposure. *J. Toxicol. Environ. Health* 7: 909-924.

IRIS (Integrated Risk Information System), 2005. United States National Library of Medicine, National Institute of Health, Department of Health and Human Services 8600 Rockville Pike, Bethesda, MD 20894. http://toxnet.nlm.nih.gov

IARC (International Agency for Research on Cancer). 1986. Vinylidine chloride. In: *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 39*. IARC, Lyon, France, pp. 195-226.

Lee, C.C., J.C. Bhandari, J.M. Winston, et al. 1977. Inhalation toxicity of vinyl chloride and vinylidine chloride. *Environ. Health Perspect*. 21: 25-32.

Maltoni, C., G. Cotti and P. Chieco. 1984. Chronic toxicity and carcinogenicity bioassays of vinylidine chloride. *Acta Oncol*. 5: 91-145. (Cited in IARC, 1986)

Maltoni, C., G. Lefemine, P. Chieco, et al. 1985. Experimental research on vinylidine carcinogenesis. In: *Archives of Research on Industrial Carcinogenesis, Vol. 3*, C. Maltoni and M. Mehlman, Eds. Princeton Scientific Publishers, Princeton, NJ. (Cited in EPA, 1992)

Nitschke, K.D., F.A. Smith, J.F. Quast, et al. 1983. A three-generation rat reproductive toxicity study of vinylidine chloride in the drinking water. *Fund. Appl. Toxicol*. 3: 75-79.

NTP (National Toxicology Program). 1982. *Carcinogenesis Bioassay of Vinylidine Chloride (CAS No. 75-35-4) in F344 Rats and B6C3F$_1$ Mice (Gavage Study)*. NTP Tech. Rep. Series No. 228. NTP-80-82; NIH Publ. No. 82-1784.

Ott, M.G., W.A. Fishbeck, J.C. Townsend and E.J. Schneider. 1976. A health study of employees exposed to vinylidine chloride. *J. Occup. Med.* 18: 735-738.

Quast, J.F., C.G. Humiston, C.E. Wade et al. 1983. A chronic toxicity and oncogenicity study in rats and subchronic toxicity study in dogs on ingested vinylidine chloride. *Fund. Appl. Toxicol*. 3: 55-62.

Quast, J.F., M.J. McKenna, L.W. Rampy and J.M. Norris. 1986. Chronic toxicity and oncogenicity study on inhaled vinylidine chloride in rats. *Fund. Appl. Toxicol*. 6: 105-144.

Rampy, L.W., J.F. Quast, C.G. Humiston, et al. 1977. Interim results of two-year toxicological studies in rats of vinylidine chloride incorporated in the drinking water or administered by repeated inhalation. *Environ. Health Perspect.* 21: 333-343.

Short, R.D., Jr., J.L. Minor, J.M. Winston, et al. 1977a. *Toxicity Studies of Selected Chemicals. Task II. The Developmental Toxicity of Vinylidine Chloride Inhaled by Rats and Mice during Gestation*. Prepared by Midwest Research Institute, Kansas City, MO for the Office of Toxic Substances, U.S. Environmental Protection Agency. EPA-560/6-77-022. (Cited in EPA, 1983)

Tierney D.R., T.R. Blackwood and M.R. Piana. 1979. *Status Assessment of Toxic Chemicals: Vinylidine chloride.* Prepared by Monsanto Research Corporation for Office of Research and Development, U.S. Environmental Protection Agency, Cincinnati, OH. EPA 600/2-79-2100; PB80-146442.

**Toxicity Summary for BENZO[A]PYRENE**

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*Managed by Martin Marietta Energy Systems, Inc., for the U.S. Department of Energy under Contract No. DE-AC05-84OR21400.

Benzo[*a*]pyrene is a polycyclic aromatic hydrocarbon (PAH) that can be derived from coal tar. Benzo[*a*]pyrene occurs ubiquitously in products of incomplete combustion of fossil fuels and has been identified in ambient air, surface water, drinking water, waste water, and char-broiled foods (IARC, 1983). Benzo[*a*]pyrene is primarily released to the air and removed from the atmosphere by photochemical oxidation and dry deposition to land or water. Biodegradation is the most important transformation process in soil or sediment (ATSDR, 1990).

Benzo[*a*]pyrene is readily absorbed following inhalation, oral, and dermal routes of administration (ATSDR, 1990). Following inhalation exposure, benzo[*a*]pyrene is rapidly distributed to several tissues in rats (Sun et al., 1982; Weyand and Bevan, 1986). The metabolism of benzo[*a*]pyrene is complex and includes the formation of a proposed ultimate carcinogen, benzo[*a*]pyrene 7,8 diol-9,10-epoxide (IARC, 1983). The major route of excretion is hepatobiliary followed by elimination in the feces (EPA, 1991).

No data are available on the systemic (non-carcinogenic) effects of benzo[*a*]pyrene in humans. In mice, genetic differences appear to influence the toxicity of benzo[*a*]pyrene. Subchronic dietary administration of 120 mg/kg benzo[*a*]pyrene for up to 180 days resulted in decreased survival due to hematopoietic effects (bone narrow depression) in a "nonresponsive" strain of mice (i.e., a strain whose cytochrome P-450 mediated enzyme activity is not induced as a consequence of PAH exposure). No adverse effects were noted in "responsive" mice (i.e., a strain capable of inducing increased cytochrome P-450 mediated enzyme activity as a consequence of PAH exposure) (Robinson et al., 1975). Immunosuppression has been reported in mice administered daily intraperitoneal injections of 40 or 160 mg/kg of benzo[*a*]pyrene for 2 weeks, with more pronounced effects apparent in "nonresponsive" mice (Blanton et al., 1986; White et al., 1985). In utero exposure to benzo[*a*]pyrene has produced adverse developmental/reproductive effects in mice. Dietary administration of doses as low as 10 mg/kg during gestation caused reduced fertility and reproductive capacity in offspring (Mackenzie and Angevine, 1981), and treatment by gavage with 120 mg/kg/day during gestation caused stillbirths, resorptions, and malformations (Legraverend et al., 1984). Similar effects have been reported in intraperitoneal injection studies (ATSDR, 1990).

Numerous epidemiologic studies have shown a clear association between exposure to various mixtures of PAHs containing benzo[*a*]pyrene (e.g., coke oven emissions, roofing tar emissions, and cigarette smoke) and increased risk of lung cancer and other tumors. However, each of the mixtures also contained other potentially carcinogenic PAHs; therefore, it is not possible to evaluate the contribution of benzo[*a*]pyrene to the carcinogenicity of these mixtures (IARC, 1983; EPA, 1991). An extensive data base is available for the carcinogenicity of benzo[*a*]pyrene in experimental animals. Dietary administration of benzo[*a*]pyrene has produced papillomas and carcinomas of the forestomach in mice (Neal and Rigdon, 1967), and treatment by gavage has produced mammary tumors in rats (McCormick et al., 1981) and pulmonary adenomas in mice (Wattenberg and Leong, 1970). Exposure by inhalation and intratracheal instillation has resulted in benign and malignant tumors of the respiratory and upper digestive tracts of hamsters (Ketkar et al., 1978; Thyssen et al., 1981). Numerous topical application studies have shown that

benzo[*a*]pyrene induces skin tumors in several species, although mice appear to be the most sensitive species. Benzo[*a*]pyrene is a complete carcinogen and also an initiator of skin tumors (IARC, 1973; EPA, 1991). Benzo[*a*]pyrene has also been reported to induce tumors in animals when administered by other routes, such as intravenous, intraperitoneal, subcutaneous, intrapulmonary, and transplacental.

Based on United States Environmental Protection Agency (EPA) guidelines, benzo[*a*]pyrene was assigned to weight-of-evidence group B2, probable human carcinogen (IRIS, 2005).

**REFERENCES**


ATSDR (Agency for Toxic Substances and Disease Registry). 1990. *Toxicological Profile for Benzo(a)pyrene*. Prepared by ICF-Clement, under Contract No. 68-02-4235. ATSDR/TP-88-05.

Blanton, R.H., M. Lyte, M.J. Myers, and P.H. Bick. 1986. Immunomodulation by polyaromatic hydrocarbons in mice and murine cells. *Cancer Res*. 46: 2735-2739.

IARC (International Agency for Research on Cancer). 1973. Benzo(a)pyrene. In: *IARC Monographs on the Evaluation of Carcinogenic Risk of the Chemical to Man. Certain Polycyclic Aromatic Hydrocarbons and Heterocyclic Compounds, Vol. 3.* World Health Organization, Lyon, France, pp. 91-136.

IARC (International Agency for Research on Cancer). 1983. Benzo[*a*]pyrene. In: I*ARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Polynuclear Aromatic Compounds. Part 1. Chemical, Environmental and Experimental Data, Vol. 32.* World Health Organization, Lyon, France, pp. 33-224.

IRIS (Integrated Risk Information System), 2005. United States National Library of Medicine, National Institute of Health, Department of Health and Human Services 8600 Rockville Pike, Bethesda, MD 20894. http://toxnet.nlm.nih.gov

Ketkar, M., G. Reznik, P. Schneider and U. Mohr. 1978. Investigations on the carcinogenic burden by air pollution in man. Intratracheal instillation studies with benzo[a]pyrene in bovine albumin in Syrian hamsters. *Cancer Lett*. 4: 235-239.

Legraverend C., T.M. Guenthner and D.W. Nebert. 1984. Importance of the route of administration for genetic differences in benzo[a]pyrene-induced *in utero* toxicity and teratogenicity. *Teratology* 29: 35-47.

MacKenzie, K.M. and D.M. Angevine. 1981. Infertility in mice exposed *in utero* to benzo[a]pyrene. *Biol. Reprod*. 24: 183-191. (Cited in IARC, 1983)

Neal, J. and R.H. Rigdon. 1967. Gastric tumors in mice fed benzo[a]pyrene: A quantitative study. *Tex. Rep. Biol. Med.* 25: 553-557. (Cited in U.S. EPA, 1994)

Robinson, J.R., J.S. Felton, R.C. Levitt, et al. 1975. Relationship between "aromatic hydrocarbon responsiveness" and the survival times in mice treated with various drugs and environmental compounds. *Mol. Pharmacol.* 11: 850-865. (Cited in ATSDR, 1990; IARC, 1983)

Sun, J.D., R.K. Wolff and G.M. Kanapilly. 1982. Deposition, retention, and biological fate of inhaled benzo[a]pyrene adsorbed onto ultrafine particles and as a pure aerosol. *Toxicol. Appl. Pharmacol.* 65: 231-244.

Thyssen, J., J. Althoff, G. Kimmerle and U. Mohr. 1981. Inhalation studies with benzo[*a*]pyrene in Syrian golden hamsters. *J. Natl. Cancer Inst.* 66: 575-577.

United States Environmental Protection Agency (EPA). 1991. *Drinking Water Criteria for Polycyclic Aromatic Hydrocarbons (PAHs)*. Prepared by the Environmental Criteria and Assessment, Office, Office of Health and Environmental Assessment, Cincinnati, OH, for the Office of Water, Washington, DC. ECAO-CIN-D010.

Wattenberg, L.W. and J.L. Leong. 1970. Inhibition of the carcinogenic action of benzo[a]pyrene by flavones. *Cancer Res.* 30: 1922-1925.

Weyand, E.H. and D.R. Bevan. 1986. Benzo(a)pyrene disposition and metabolism in rats following intratracheal instillation. *Cancer Res.* 46: 5655-5661.

White, K.L., H.H. Lysy and M.P. Holsapple. 1985. Immunosuppression by polycyclic aromatic hydrocarbons. A structure-activity relationship in B6C3$F_1$ and DBA/2 mice. *Immunopharmacology* 9: 155-164. (Cited in U.S. EPA, 1991)

**Toxicity Summary for *cis*- and *trans*-1,2-DICHLOROETHYLENE**

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*Managed by Martin Marietta Energy Systems, Inc., for the U.S. Department of Energy under contract No. DE-AC05-84OR21400.

1,2-Dichloroethene exists in two isomeric forms, *cis*-1,2-dichloroethene and *trans*-1,2-dichloroethene, that are colorless, volatile liquids with a slightly acrid odor. Although not used extensively in industry, 1,2-dichloroethene is used in the production of other chlorinated solvents and as a solvent for dyes, perfumes, and lacquers (Sax and Lewis 1989, Budavari et al. 1989). Humans are exposed to 1,2-dichloroethene primarily by inhalation, but exposure can also occur by oral and dermal routes.

Limited information exists on the absorption, distribution, and excretion of 1,2-dichloroethene in either humans or animals. In vitro studies have shown that the mixed function oxidases will metabolize 1,2-dichloroethene; the final metabolic products are dependent on the initial isomer of 1,2-dichloroethene (Costa and Ivanetich 1984, Henschler 1977, Liebman and Ortiz 1977).

Information on the toxicity of 1,2-dichloroethene in humans and animals is limited. Workers exposed to 1,2-dichloroethene have been reported to suffer from drowsiness, dizziness, nausea, fatigue, and eye irritation (ATSDR 1990). Acute and subchronic oral and inhalation animal studies of *trans*-1,2-dichloroethene and acute inhalation animal studies of *cis*-1,2-dichloroethene suggest that the liver is the primary target organ. The toxicity is expressed in increased activities of liver associated enzymes, fatty degeneration, and necrosis (McCauley et al. n.d., Barnes et al. 1985, Freundt et al. 1977). Secondary target organs include the central nervous system and lung.

No information was available concerning the chronic, developmental, or reproductive toxicity of *cis*-1,2-dichloroethene or *trans*-1,2-dichloroethene. No cancer bioassays or epidemiological studies were available to assess the carcinogenicity of 1,2-dichloroethene. EPA has placed both *cis*-1,2-dichloro-ethene and *trans*-1,2-dichloroethene in weight-of-evidence group D, not classifiable as to human carcinogenicity, based on the lack of human or animal carcinogenicity data and on essentially negative mutagenicity data (IRIS, 2005).

**REFERENCES**

ATSDR (Agency for Toxic Substances and Disease Registry). 1990. *Draft Toxicological Profile for 1,2-dichloroethene*. Prepared by Clement Assoc., Inc. under contract 205-88-0608. U.S. Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA, p. 1-101.

Barnes, D.W., V.M. Sanders, K.L. White, G.M. Shopp and A.E. Munson. 1985. Toxicology of *trans*-1,2-dichloroethylene in the mouse. *Drug and Chem. Toxicol*. 8(5): 373-392.

Budavari, S., M.J. O'Neil, A. Smith and P.E. Heckelman. 1989. In: *The Merck Index*, 11th ed., Merck & Co., Inc., Rahway, NJ, p. 15.

Costa, A.K. and K.M. Ivanetich. 1984. Chlorinated ethylenes: Their metabolism and effect on DNA repair in rat hepatocytes. *Carcinogenesis* 5: 1629-1636.

Freundt, K.J., G.P. Liebaldt and E. Lieberwirth. 1977. Toxicity studies on *trans*-1,2-dichloroethene. *Toxicology* 7: 141-153.

Henschler, D. 1977. Metabolism and mutagenicity of halogenated olefins -- A comparison of structure and activity. *Environ. Health Perspec*. 21: 61-64.

IRIS (Integrated Risk Information System), 2005. United States National Library of Medicine, National Institute of Health, Department of Health and Human Services 8600 Rockville Pike, Bethesda, MD 20894. http://toxnet.nlm.nih.gov

Liebman, K.C. and E. Ortiz. 1977. Metabolism of halogenated ethylenes. *Environ. Health Perspec*. 21: 91-97.

McCauley, P.T., M. Robinson, L.W. Condie and M. Parvell. n.d. *The effects of subacute and subchronic oral exposure to cis-1,2-dichloroethylene in rats*. Health Effects Research Laboratory, EPA, Cincinnati, OH.

Sax, N.I. and R.J. Lewis. 1989. In: *Properties of Industrial Materials*, 7th ed., Volume III, Van Nostrand Reinhold Co., New York, NY, p. 1152.

**Toxicity Summary for DIBENZ[A,H]ANTHRACENE**

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*Managed by Lockheed Martin Energy Systems, Inc., for the U.S. Department of Energy under Contract No. DE-AC05-84OR21400

Dibenz[*a,h*]anthracene is a polycyclic aromatic hydrocarbon (PAH) with five aromatic rings. No commercial production or use of dibenz[*a,h*]anthracene is known. It occurs as a component of coal tars, shale oils, and soots (IARC, 1985) and has been detected in gasoline engine exhaust, coke oven emissions, cigarette smoke, charcoal broiled meats, vegetation near heavily traveled roads, and surface water and soils near hazardous waste sites (ATSDR, 1993; IARC, 1983).

Dibenz[*a,h*]anthracene is poorly absorbed from the gastrointestinal tract and is primarily excreted via feces (Chang, 1943). Following absorption, dibenz[*a,h*]anthracene is distributed to various tissues, with highest accumulation in the liver and kidneys (Daniel et al., 1967). Dibenz[*a,h*]anthracene is metabolized by mixed function oxidases to dihydrodiols. Epoxidation of the 3,4-dihydrodiol may lead to the formation of a diol-epoxide, the putative ultimate carcinogenic metabolite of dibenz[*a,h*]anthracene (Buening et al., 1979).

No human studies were available to evaluate the toxicity of dibenz[*a,h*]anthracene. In animals, depressed immune responses were observed in mice following single or multiple subcutaneous injections of dibenz[*a,h*]anthracene (White et al., 1985). Weekly subcutaneous. injections of 0.05% dibenz[*a,h*]anthracene for 40 weeks produced lymphoid tissue changes, decreased spleen weights, and liver and kidney lesions in mice (Hoch-Ligeti, 1941). Weekly intramuscular injections of 20 mg/kg promoted the development of arteriosclerotic plaques in chickens (Penn and Snyder, 1988).

No epidemiologic studies or case reports addressing the carcinogenicity of dibenz[*a,h*]anthracene in humans were available. In animals, dibenz[*a,h*]anthracene has produced tumors by different routes of administration, having both local and systemic carcinogenic effects.

After oral administration, dibenz[*a,h*]anthracene produced tumors at several sites. Male and female mice fed dibenz[*a,h*]anthracene (0.85 mg/day for males, 0.76 mg/day for females) in an aqueous olive oil emulsion developed pulmonary adenomatosis, alveologenic carcinomas of the lung, hemangio-endotheliomas of the pancreas and mesentery/abdominal lymph nodes, and mammary carcinomas (females) after 200 days (Snell and Stewart, 1962). A single oral dose of 1.5 mg dibenz[*a,h*]anthracene in polyethylene glycol produced a low incidence of forestomach papillomas in mice (Berenblum and Haran, 1955). Mammary carcinomas developed in mice treated by gavage with a total dose of 15 mg over a 15-week period (Biancifiori and Caschera, 1962).

Carcinogenic as well as tumor-initiating activity of dibenz[*a,h*]anthracene has been demonstrated in topical application studies with mice. Repeated dermal application of 0.001 to 0.01% solutions produced a high incidence of skin papillomas and carcinomas in mice (Wynder and Hoffmann, 1959; Van Duuren et al., 1967). In initiation-promotion assays, the compound was active as an initiator of skin carcinogenesis in mice (Buening et al., 1979; Platt et al., 1990). However, no skin tumors were observed in Syrian golden hamsters that received topical dibenz[*a,h*]anthracene applications over a 10-week period (Shubik et al., 1960).Injection site sarcomas developed in mice injected subcutaneously with dibenz[*a,h*]anthracene (Pfeiffer, 1977). In newborn mice, a

single subcutaneous injection of dibenz[*a,h*]anthracene induced local sarcomas and lung adenomas (Platt et al., 1990) and three intraperitoneal injections induced a high incidence of pulmonary tumors (Buening et al., 1979). A number of earlier studies have also demonstrated the carcinogenicity of dibenz[*a,h*]anthracene when administered by various parenteral routes in several animal species (IARC, 1973).

Based on no human data and sufficient evidence for carcinogenicity in animals, EPA has assigned dibenz[*a,h*]anthracene a weight-of-evidence classification of B2, probable human carcinogen (IRIS, 2005).

**REFERENCES**


ATSDR (Agency for Toxic Substances and Disease Registry). 1993. *Toxicological Profile for Polycyclic Aromatic Hydrocarbons (PAHs). Draft for Public Comment. Update*, prepared by Clement International Corporation, under Contract No. 205-88-0608, for the U.S. Department of Health and Human Services, Public Health Service.

Berenblum, I. and N. Haran. 1955. The influence of croton oil and of polyethylene glycol-400 on carcinogenesis in the forestomach of the mouse. *Cancer Res*. 15: 510-516. (Cited in EPA, 1991)

Biancifiori, C. and F. Caschera. 1962. The relation between pseudo-pregnancy and the chemical induction of mammary and ovarian tumors in BALB/c mice. *Br. J. Cancer* 16: 722-730. (Cited in EPA, 1995)

Buening, M. K., W. Levi n, A. W. Wood, et al. 1979. Tumorigenicity of the dihydrodiols of dibenzo(*a,h*)anthracene on mouse skin and in newborn mice. *Cancer Res*. 39: 1310-1314.

Chang, L. H. 1943. The fecal excretion of polycyclic hydrocarbons following their administration to the rat. *J. Biol. Chem*. 151: 93-99. (Cited in ATSDR, 1993)

Daniel, P. M., O. E. Pratt and M. M. L. Prichard. 1967. Metabolism of labelled carcinogenic hydrocarbons in rats. *Nature* 215: 1142-1146.

Hoch-Ligeti, C. 1941. Studies on the changes in the lymphoid tissue of mice treated with carcinogenic and noncarcinogenic hydrocarbons. *Cancer Res*. 1: 484-488.

IARC (International Agency for Research on Cancer). 1973. Dibenz(a,h)anthracene. In: *IARC Monographs on the Evaluation of Carcinogenic Risk of the Chemical to Man. Certain Polycyclic Aromatic Hydrocarbons and Heterocyclic Compounds*, Vol. 3, World Health Organization, Lyon, France, pp. 178-196.

IARC (International Agency for Research on Cancer). 1983. *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Polynuclear Aromatic Compounds, Part 1, Chemical, Environmental and Experimental Data*, Vol. 32. World Health Organization, Lyon, France, pp. 33-224.

IARC (International Agency for Research on Cancer). 1985. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Polynuclear Aromatic Compounds, Part 4, Bitumens, Coal-tars and Derived Products, Shale-oils and Soots, Vol. 35. In: *IARC Monographs on the Evaluation of Carcinogenic Risk of the Chemical to Man*, World Health Organization, Lyon, France, pp. 88, 91, 164, 225.

IRIS (Integrated Risk Information System), 2005. United States National Library of Medicine, National Institute of Health, Department of Health and Human Services 8600 Rockville Pike, Bethesda, MD 20894. http://toxnet.nlm.nih.gov

Penn, A. and C. Snyder. 1988. Arteriosclerotic plaque development is 'promoted' by polynuclear aromatic hydrocarbons. *Carcinogenesis* 9: 2185-2189.

Pfeiffer, E. H. 1977. Oncogenic interaction of carcinogenic and non-carcinogenic polycyclic aromatic hydrocarbons in mice. In: *Air Pollution and Cancer in Man,* V. Mohr, et al., Eds. International Agency for Research on Cancer, Lyon, France, pp. 69-77. (Cited in EPA, 1991).

Platt, K. L., E. Pfeiffer, P. Petrovic, et al. 1990. Comparative tumorigenicity of picene and dibenz[*a,h*]anthracene in the mouse. *Carcinogenesis* 11: 1721-1726.

Shubik, P., G. Pietra and G. Della Porta. 1960. Studies of skin carcinogenesis in the Syrian golden hamster. Cancer Res. 20: 100-105.

Snell, K. C. and H. L. Stewart. 1962. Pulmonary adenomatosis induced in DBA/2 mice by oral administration of dibenz[*a,h*]anthracene. *J. Natl. Cancer Inst*. 28: 1043-1049.

Van Duuren, B. L., L. Langseth, B. M. Goldschmidt and L. Orris. 1967. Carcinogenicity of epoxides, lactones and peroxy compounds. VI. Structure and carcinogenic activity. *J. Natl. Cancer Inst*. 39: 1217. (Cited in IARC, 1973; EPA, 1991)

White, K. L., Jr., H. H. Lysy and M. P. Holsapple. 1985. Immunosuppression by polycyclic aromatic hydrocarbons: A structure-activity relationship in B6C3F1 and DBA/2 mice. *Immunopharmacol*. 9: 155-164.

Wynder, E. L. and D. Hoffmann. 1959. A study of tobacco carcinogenesis. VII. The role of higher polycyclic hydrocarbons. *Cancer* 12: 1079-1086.