Nitroarenes (Selected)

Introduction

The nitroarenes are a large class of structurally related chemicals normally found in particulate emissions from many combustion sources, most notably, diesel exhausts. These molecules are nitro-substituted derivatives of polycyclic aromatic hydrocarbons (arenes) with at least one nitro group covalently bound to a cyclic carbon atom (i.e., nitropolycyclic aromatic hydrocarbons, or nitro-PAHs) (Rosenkratz and Mermelstein 1985, Tokiwa and Ohnishi 1986). The nitroarenes result from incomplete combustion processes from sources such as kerosene heaters and fuel gas burners, in addition to diesel engines. Profiles for the following listed nitroarenes follow this introduction:

- 1,6-Dinitropyrene
- 1,8-Dinitropyrene
- 6-Nitrochrysene
- 1-Nitropyrene
- 4-Nitropyrene

Following are brief discussions of carcinogenicity and exposure for nitroarenes in general. Addtional information on carcinogenicity and exposure specific to each of the five listed nitroarenes is provided in the individual profiles.

These nitroarene compounds were first listed in the *Eighth Report on Carcinogens* (1998) as *reasonably anticipated to be human carcinogens* based on evidence of carcinogenicity from studies in experimental animals. Few members of this large class of chemicals have been rigorously evaluated in state-of-the-art cancer studies in rodents. Typically, the chemicals were administered by injection, over short periods, and with less-than-optimal time allowed for tumors to fully develop. Despite these limitations, the results of carcinogenicity studies of nitroarenes in animals were generally similar and demonstrated tumor formation both at the site of injection and at distant tissue sites. The mutagenic and carcinogenic properties of the nitroarene compounds vary. The mutagenicity of nitropyrenes in *Salmonella typhimurium* strains TA98 and TA98NR increased as the number of nitro groups increased (NTP 1999). The order of mutagenic potency in human cells, from most potent to least potent, was 1,6-dinitropyrene, followed by 1,8-dinitropyrene, followed by 1-nitropyrene (Durant 1996), and levels of DNA binding in the rat mammary gland were higher for 4-nitropyrene than for 1-nitropyrene (Chae *et al.* 1997).

The metabolic pathways for activation of these nitroarene molecules to create reaction products with the ability to cause gene mutations or changes in the structure of DNA have been described in tissues from humans and animals. The metabolic pathways are similar for the five listed nitroarenes. Two successive nitroreduction steps form an *N*-hydroxylamine group. This intermediate may be activated by loss of the *N*-hydroxyl group or by O-acetylation of the *N*-hydroxylamine group followed by removal of the acetate to form the DNA-reactive nitrenium ion, or it may be inactivated by further reduction to an amine. No adequate studies of the relationship between exposure to these chemicals and human cancer have been reported. However, exposure to diesel exhaust particulates is listed in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen* based on findings of elevated lung-cancer rates in occupational groups exposed to diesel exhaust and on supporting studies of cancer in experimental animals and studies on mechanisms of carcinogenesis. Whether the nitroarenes are responsible for or contribute to the carcinogenicity of diesel exhaust in humans has not been determined.

Nitroarenes are products of incomplete combustion in the presence of nitrating species (IPCS 2003). They have been identified in extracts of particles from the exhaust of diesel engines (IARC 1989). Nitroarene concentrations measured in diesel-exhaust extracts were higher for heavy-duty engines during operation and lower for engines at idle (IARC 1989, Yamazaki *et al.* 2000). Nitroarenes have also been identified in particulate matter from the incineration of municipal waste, coal fly ash, extracts of coke-oven emissions, and stack emissions from a facility manufacturing carbon electrodes. Concentrations of nitroarenes in ambient air are higher in heavily industrialized areas than in nonindustrialized urban areas, suburban areas, or rural areas (IARC 1989) and vary seasonally and diurnally. Higher concentrations in winter reflect increased emissions from heating sources, and diurnal variations reflect traffic patterns (IPCS 2003).

Because nitroarenes emitted to air are tightly bound to particulate matter, they may be removed from the atmosphere by wet and dry deposition and deposited on soil or surface water by settling and by precipitation. In Japan, all five listed nitroarenes were detected in particulates derived from coal burning (Taga *et al.* 2005) and in precipitation (Murahashi *et al.* 2001). Nitroarenes have been found in the indoor environment in particulate emissions from kerosene heaters and gas burners used for home heating and cooking (IPCS 2003). Before 1980, considerable amounts of all five listed nitroarenes were found in samples of carbon black that was known to be used in photocopiers. Some nitroarene compounds have also been identified in food products, especially in smoked and grilled meats, and in beverages, especially tea (IARC 1989).

References

Chae YH, Upadhyaya P, Ji BY, Fu PP, el-Bayoumy K. 1997. Comparative metabolism and DNA binding of 1-, 2-, and 4-nitropyrene in rats. *Mutat Res* 376(1-2): 21-28.

Durant JL, Busby WF Jr, Lafleur AL, Penman BW, Crespi CL. 1996. Human cell mutagenicity of oxygenated, nitrated and unsubstituted polycyclic aromatic hydrocarbons associated with urban aerosols. *Mutat Res* 371(3-4): 123-157.

IARC. 1989. 1,6-Dinitropyrene. In *Diesel and Gasoline Engine Exhausts and Some Nitroarenes*. IARC Monographs Evaluation of Carcinogenic Risks of Chemicals to Humans, vol. 46. Lyon, France: International Agency for Research on Cancer. pp. 215-230.

IPCS. 2003. *Environmental Health Criteria No. 229. Selected Nitro- and Nitro-oxy-polycyclic Aromatic Hydrocarbons*. International Programme on Chemical Safety. http://www.inchem.org/documents/ehc/ehc/ehc1229.htm.

Murahashi T, Ito M, Kizu R, Hayakawa K. 2001. Determination of nitroarenes in precipitation collected in Kanazawa, Japan. *Water Res* 35(14): 3367-3372.

NTP. 1999. *NTP Report on Carcinogens Background Document for 4-Nitropyrene*. National Toxicology Program. http://ntp.niehs.nih.gov/files/Nitropyrene-4.pdf. 19 pp.

Rosenkranz H, Mermelstein R. 1985. The genotoxicity, metabolism and carcinogenicity of nitrated polycyclic aromatic hydrocarbons. *J Environ Sci Health* C3(2): 221-272.

Taga R, Tang N, Hattori T, Tamura K, Sakai S, Toriba A, Kizu R, Hayakawa K. 2005. Direct-acting mutagenicity of extracts of coal burning-derived particulates and contribution of nitropolycyclic aromatic hydrocarbons. *Mutat Res* 581(1-2): 91-95.

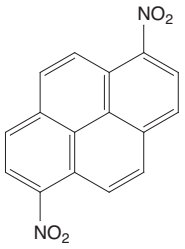
Tokiwa H, Ohnishi Y. 1986. Mutagenicity and carcinogenicity of nitroarenes and their sources in the environment. *Crit Rev Toxicol* 17(1): 23-60.

1,6-Dinitropyrene

CAS No. 42397-64-8

Reasonably anticipated to be a human carcinogen

First listed in the *Eighth Report on Carcinogens* (1998)



Carcinogenicity

1,6-Dinitropyrene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

1,6-Dinitropyrene caused tumors in several rodent species, at several different tissue sites, and by several different routes of exposure. Subcutaneous injection of 1,6-dinitropyrene caused cancer at the injection site (sarcoma) in male mice and in rats of both sexes and leukemia in female rats (IARC 1989). Exposure by intraperitoneal injection caused benign and malignant liver tumors (adenoma and carcinoma) in male mice and cancer of the peritoneal cavity (sarcoma) in female rats (IARC 1989, Iizasa *et al.* 1993). Intrapulmonary instillation of 1,6-dinitropyrene caused lung cancer (squamous-cell carcinoma) in male rats (IARC 1989, Iwagawa *et al.* 1989), and intratracheal instillation caused lung cancer (adenocarcinoma) and myeloid leukemia in hamsters of both sexes (IARC 1989). Administration of 1,6-dinitropyrene to female rats by stomach tube caused cancer of the pituitary gland (carcinoma) (IARC 1989, Imaida *et al.* 1991).

Studies on Mechanisms of Carcinogenesis

Pathways of 1,6-dinitropyrene metabolism leading to mutagenic and clastogenic metabolites and formation of DNA adducts have been described (IARC 1989). Furthermore, 1,6-dinitropyrene–induced tumors showed evidence of oncogene activation and mutations (Ishizaka *et al.* 1987, Smith *et al.* 1997). The potential modes of action in the carcinogenicity of 1,6-dinitropyrene therefore involve metabolic activation to reactive metabolites, oncogene activation, and genotoxicity.

The mutagenicity of 1,6-dinitropyrene is related to the ability of its metabolites to bind DNA. Reactive products of 1,6-dinitropyrene are formed by metabolism through two reductions of the 1-nitro group to form first a nitroso and then a *N*-hydroxy amino group at the 1-position. Activation occurs by O-acetylation of the *N*-hydroxylamine group, followed by removal of the acetate to create the active nitrenium ion, which reacts with deoxyguanosine at C-8 to form the DNA adduct. Both nitroreduction and acetylation dependent on acetyl coenzyme A are involved in the metabolism of 1,6-dinitropyrene to form the DNA adduct *N*-(deoxyguanosin-8-yl)-1-amino-6-nitropyrene (Beland 1986). This adduct forms in a dose-related manner in the liver, mammary gland, peripheral-blood lymphocytes, kidney, urinary bladder, and spleen lymphocytes of rats exposed to 1,6-dinitropyrene (Beland 1986, 1994, El-Bayoumy *et al.* 1994, Smith *et al.* 1995). Exposure of SV40-transformed hamster ovary cells to 1,6-dinitropyrene also caused formation of DNA adducts and amplified SV40 DNA (Neft 1993).

1,6-Dinitropyrene was genotoxic in a wide variety of assays in bacteria and mammalian cells, including human cells (IARC 1989). The most frequent mutations in *Salmonella typhimurium* were C:G to A:T or G:C transversions (Watanabe *et al.* 1997). Another metabolite of 1,6-dinitropyrene, 1-nitroso-6-nitropyrene, caused frameshift mutations at G:C base pairs in the *lacI* gene of *Escherichia coli* (Lambert *et al.* 1998, 2001). Intrapulmonary administration of single doses of 1,6-dinitropyrene that caused dose-dependent induction of lung tumors in rats also resulted in dose-dependent formation of DNA adducts in the lungs and liver and mutations in lymphocytes (Beland *et al.* 1994, Smith *et al.* 1995). Intratracheal administration of 1,6-dinitropyrene to *gpt*-delta transgenic mice induced mutations in the lungs (Hashimoto *et al.* 2006). Mutations in the K-*ras* proto-oncogene and *p53* tumor-suppressor gene were observed in 1,6-dinitropyrene–induced lung tumors and in the *hprt* gene of 6-thioguanine–resistant lymphocytes in rats exposed to 1,6-dinitropyrene. In the lung tumors, mutations were identified in K-*ras* codon 12 (5 mutations in 20 tumors) and *p53* exons 3, and 5 to 8 (9 of 20 tumors) and were mainly substitutions at G:C base pairs (Smith *et al.* 1997). Another study in rats reported that H-*ras* and N-*ras* were activated in 18% of 1,6-dinitropyrene–induced fibrosarcomas (Ishizaka *et al.* 1987).

In addition to gene mutations, 1,6-dintropyrene caused DNA damage, induction of unscheduled DNA synthesis, sister chromatid exchange, and chromosomal damage in cultured cells. It also caused morphological transformation of rat tracheal cells (IARC 1989, NTP 1999). Moreover, *in vivo* exposure to 1,6-dintropyrene transformed immortalized human bronchial epithelial cells (BEAS-2B) into malignant lung tumors (adenocarcinoma). The BEAS-2B cells were xenotransplanted into de-epithelialized rat tracheas, which were transplanted under the dorsal skin of nude mice and exposed to 1,6-dinitropyrene. The tumor cells did not contain the usual molecular genetic abnormalities found in lung adenocarcinoma (i.e., mutations in the K-*ras*, *p53*, or *Rb* genes), suggesting that other molecular alterations involving different oncogenes, tumor-suppressor genes, or growth-factor-related genes may have been responsible for transformation of the BEAS-2B cells. There is no evidence to suggest that mechanisms by which 1,6-dinitropyrene causes tumors in experimental animals would not also operate in humans.

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to 1,6-dinitropyrene.

Properties

1,6-Dinitropyrene is a nitro-substituted polycyclic aromatic hydrocarbon that exists at room temperature as a yellow to light-brown crystalline solid. It has a molecular weight of 292.3 and a melting point of 310°C. It is practically insoluble in water but moderately soluble in toluene (IARC 1989, IPCS 2003, HSDB 2009, Akron 2010).

Use

There is no evidence that 1,6-dinitropyrene has been used for any commercial purpose (IARC 1989). 1,6-Dinitropyrene is available for research purposes at a purity of 98% or higher. It is also available in ^{14}C- or ^{3}H-labeled form at a radiochemical purity of 98% or higher.

Production

One non-U.S. company was previously reported to synthesize 1,6-dinitropyrene at a purity higher than 99.9% (IARC 1989). In 2009, no commercial producers of 1,6-dinitropyrene were identified worldwide, but 1,6-dinitropyrene was available from four U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports of 1,6-dinitropyrene were found.

Exposure

The primary route of human exposure to 1,6-dinitropyrene is inhalation (IARC 1989). 1,6-Dinitropyrene was measured in diesel exhaust particulate extracts at concentrations of 1.2 mg/kg for heavy-duty engines during operation and up to 2.4 pmol/mg (0.7 mg/kg) for diesel engines at idle (IARC 1989, Yamazaki *et al.* 2000). 1,6-Dinitropyrene was measured in particulates derived from coal-burning at a concentration of 0.26 pmol/mg (0.08 mg/kg) (Taga *et al.* 2005). Concentrations measured in ambient air were higher in heavily industrialized areas (7.5 pg/m^3) than in nonindustrialized urban areas (0.48 pg/m^3), suburban areas (0.30 pg/m^3), or rural areas (0.12 pg/m^3) (IARC 1989). In Japan, 1,6-dinitropyrene was measured in precipitation at concentrations of up to 0.04 pmol/L (Murahashi *et al.* 2001) and in soil samples from various regions of the country at concentrations of 3 ng/g or less (Watanabe *et al.* 1998, 1999, 2000, 2003, 2005). No data were found on occupational exposure to 1,6-dinitropyrene. (See also the discussion of exposure in the Introduction for Nitroarenes [Selected], above.)

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

References

Akron. 2010. *The Chemical Database*. The Department of Chemistry at the University of Akron. http://ull.chemistry.uakron.edu/erd and search on CAS number. Last accessed: 1/11/10.

Beland FA. 1986. The metabolic activation and DNA adducts of dinitropyrenes. *Res Rep Health Eff Inst*(4): 3-30.

Beland FA, Fullerton NF, Smith BA, Heflich RH. 1994. Formation of DNA adducts and induction of mutations in rats treated with tumorigenic doses of 1,6-dinitropyrene. *Environ Health Perspect* 102(Suppl 6): 185-189.

ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. http://www.chemsources.com/chemonline.html and search on dinitropyrene. Last accessed: 9/3/09.

El-Bayoumy K, Johnson BE, Roy AK, Upadhyaya P, Partian SJ. 1994. Biomonitoring of nitropolynuclear aromatic hydrocarbons via protein and DNA adducts. *Res Rep Health Eff Inst*(64): 1-27, 29-37.

Hashimoto AH, Amanuma K, Hiyoshi K, Takano H, Masumura K, Nohmi T, Aoki Y. 2006. *In vivo* mutagenesis in the lungs of *gpt*-delta transgenic mice treated intratracheally with 1,6-dinitropyrene. *Environ Mol Mutagen* 47(4): 277-283.

HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB and search on CAS number. Last accessed: 9/3/09.

IARC. 1989. 1,6-Dinitropyrene. In *Diesel and Gasoline Engine Exhausts and Some Nitroarenes*. IARC Monographs Evaluation of Carcinogenic Risks of Chemicals to Humans, vol. 46. Lyon, France: International Agency for Research on Cancer. pp. 215-230.

Iizasa T, Momiki S, Bauer B, Caamano J, Metcalf R, Lechner J, Harris CC, Klein-Szanto AJ. 1993. Invasive tumors derived from xenotransplanted, immortalized human cells after *in vivo* exposure to chemical carcinogens. *Carcinogenesis* 14(9): 1789-1794.

Imaida K, Lee MS, Wang CY, King CM. 1991. Carcinogenicity of dinitropyrenes in the weanling female CD rat. *Carcinogenesis* 12(7): 1187-1191.

Ishizaka Y, Ochiai M, Ohgaki H, Ishikawa F, Sato S, Miura Y, Nagao M, Sugimura T. 1987. Active H-*ras* and N-*ras* in rat fibrosarcomas induced by 1,6-dinitropyrene. *Cancer Lett* 34(3): 317-324.

Iwagawa M, Maeda T, Izumi K, Otsuka H, Nishifuji K, Ohnishi Y, Aoki S. 1989. Comparative dose-response study on the pulmonary carcinogenicity of 1,6-dinitropyrene and benzo[*a*]pyrene in F344 rats. *Carcinogenesis* 10(7): 1285-1290.

Lambert IB, Carroll C, Laycock N, Duval L, Whiteway J, Lawford I, *et al*. 1998. The mutational specificity of 1-nitroso-6-nitropyrene in the *lacI* gene of *Escherichia coli* strains deficient in nucleotide excision repair. *Mutagenesis* 13(1): 9-18.

Lambert IB, Carroll C, Laycock N, Koziarz J, Lawford I, Duval L, *et al*. 2001. Cellular determinants of the mutational specificity of 1-nitroso-6-nitropyrene and 1-nitroso-8-nitropyrene in the *lacI* gene of *Escherichia coli*. *Mutat Res* 484(1-2): 19-48.

Murahashi T, Ito M, Kizu R, Hayakawa K. 2001. Determination of nitroarenes in precipitation collected in Kanazawa, Japan. *Water Res* 35(14): 3367-3372.

Neft RE, Roe AL, Smith BA, Beland FA. 1993. Dinitropyrene metabolism, DNA adduct formation, and DNA amplification in an SV40-transformed Chinese hamster embryo cell line. *Mol Carcinog* 7(4): 221-227.

NTP. 1999. *NTP Report on Carcinogens Background Document for 1,6-Dinitropyrene and 1,8-Dinitropyrene*. National Toxicology Program. http://ntp.niehs.nih.gov/files/Dinitropyrene.pdf.

Smith BA, Fullerton NF, Heflich RH, Beland FA. 1995. DNA adduct formation and T-lymphocyte mutation induction in F344 rats implanted with tumorigenic doses of 1,6-dinitropyrene. *Cancer Res* 55(11): 2316-2324.

Smith BA, Manjanatha MG, Pogribny IP, Mittelstaedt RA, Chen T, Fullerton NF, Beland FA, Heflich RH. 1997. Analysis of mutations in the K-*ras* and *p53* genes of lung tumors and in the *hprt* gene of 6-thioguanine-resistant T-lymphocytes from rats treated with 1,6-dinitropyrene. *Mutat Res* 379(1): 61-68.

Taga R, Tang N, Hattori T, Tamura K, Sakai S, Toriba A, Kizu R, Hayakawa K. 2005. Direct-acting mutagenicity of extracts of coal burning-derived particulates and contribution of nitropolycyclic aromatic hydrocarbons. *Mutat Res* 581(1-2): 91-95.

Watanabe T, Takashima M, Kasai T, Hirayama T. 1997. Comparison of the mutational specificity induced by environmental genotoxin nitrated polycyclic aromatic hydrocarbons in *Salmonella typhimurium his* genes. *Mutat Res* 394(1-3): 103-112.

Watanabe T, Ishida S, Minami H, Kasai T, Ogawa S, Wakabayashi K, Hirayama T. 1998. Identification of 1,6- and 1,8-dinitropyrene isomers as major mutagens in organic extracts of soil from Osaka, Japan. *Chem Res Toxicol* 11(12): 1501-1507.

Watanabe T, Ishida S, Kishiji M, Takahashi Y, Furuta A, Kasai T, Wakabayashi K, Hirayama T. 1999. High-performance liquid chromatography-fluorescence determination of dinitropyrenes in soil after column chromatographic clean-up and on-line reduction. *J Chromatogr A* 839(1-2): 41-48.

Watanabe T, Goto S, Matsumoto Y, Asanoma M, Hirayama T, Sera N, *et al.* 2000. Mutagenic activity of surface soil and quantification of 1,3-, 1,6-, and 1,8-dinitropyrene isomers in soil in Japan. *Chem Res Toxicol* 13(4): 281-286.

Watanabe T, Hasei T, Takahashi Y, Otake S, Murahashi T, Takamura T, Hirayama T, Wakabayashi K. 2003. Mutagenic activity and quantification of nitroarenes in surface soil in the Kinki region of Japan. *Mutat Res* 538(1-2): 121-131.

Watanabe T, Hasei T, Takahashi T, Asanoma M, Murahashi T, Hirayama T, Wakabayashi K. 2005. Detection of a novel mutagen, 3,6-dinitrobenzo[*e*]pyrene, as a major contaminant in surface soil in Osaka and Aichi Prefectures, Japan. *Chem Res Toxicol* 18(2): 283-289.

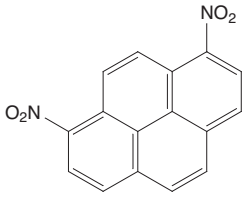
Yamazaki H, Hatanaka N, Kizu R, Hayakawa K, Shimada N, Guengerich FP, Nakajima M, Yokoi T. 2000. Bioactivation of diesel exhaust particle extracts and their major nitrated polycyclic aromatic hydrocarbon components, 1-nitropyrene and dinitropyrenes, by human cytochromes P450 1A1, 1A2, and 1B1. *Mutat Res* 472(1-2): 129-138.

1,8-Dinitropyrene

CAS No. 42397-65-9

Reasonably anticipated to be a human carcinogen

First listed in the *Eighth Report on Carcinogens* (1998)



Carcinogenicity

1,8-Dinitropyrene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

1,8-Dinitropyrene caused tumors in two rodent species, at several different tissue sites, and by several different routes of exposure. Subcutaneous injection of 1,8-dinitropyrene caused cancer at the injection site (sarcoma) in male mice and in rats of both sexes and leukemia in female rats (IARC 1989). Exposure by intraperitoneal injection caused

myelocytic leukemia and cancer of the peritoneal cavity (sarcoma) and mammary gland (adenocarcinoma) in female rats. Administration of 1,8-dinitropyrene to female rats by stomach tube also caused mammary-gland cancer (adenocarcinoma).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to 1,8-dinitropyrene.

Studies on Mechanisms of Carcinogenesis

Pathways of 1,8-dinitropyrene metabolism leading to mutagenic and clastogenic metabolites and formation of DNA adducts have been described (IARC 1989). Reactive products of 1,8-dinitropyrene are formed by metabolism through two reductions of the 1-nitro group to form first a nitroso and then a *N*-hydroxy amino group at the 1-position (Beland 1986). Activation occurs by O-acetylation of the *N*-hydroxylamine group followed by removal of the acetate to create the active nitrenium ion, which reacts with deoxyguansine at C-8 to form the DNA adduct.

1,8-Dinitropyrene is genotoxic in a wide variety of assays in bacteria and mammalian cells (IARC 1989). In *Salmonella typhimurium,* the most frequent mutations were C:G to A:T or G:C transversions (Watanabe *et al.* 1997), and a metabolite of 1,8-dinitropyrene, 1-nitroso-8-nitropyrene, caused mutations at G:C base pairs and frameshift mutations (Lambert *et al.* 2001). 1,8-Dinitropyrene also caused morphological transformation of cultured hamster embryo cells (IARC 1989). Exposure of SV40-transformed hamster ovary cells to 1,8-dinitropyrene caused formation of DNA adducts and amplified SV40 DNA (Neft 1993).

There is no evidence to suggest that the mechanisms by which 1,8-dinitropyrene causes tumors in experimental animals would not also operate in humans.

Properties

1,8-Dinitropyrene is a nitro-substituted polycyclic aromatic hydrocarbon that exists at room temperature as a yellow fluffy or light-brown crystalline solid (IARC 1989). It has a molecular weight of 292.3 and a melting point of over 300°C (HSDB 2009).

Use

1,8-Dinitropyrene has been reported to be a photosensitizer; however, there is no evidence that it has ever been used commercially for this or any other purpose (IARC 1989). 1,8-Dinitropyrene is available for research purposes at a purity of at least 99% and in ^{14}C- or ^{3}H-labeled form at a radiochemical purity of at least 98%.

Production

In 2009, no commercial producers of 1,8-dinitropyrene were identified worldwide, but 1,8-dinitropyrene was available from two U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports of 1,8-dinitropyrene were found.

Exposure

The routes of human exposure to 1,8-dinitropyrene are inhalation, ingestion, and dermal contact (IARC 1989). In Japan, 1,8-dinitropyrene was detected in soil samples in various regions of the country (Watanabe *et al.* 1998, 1999, 2000, 2003, 2005). No data were found on occupational exposure to 1,8-dinitropyrene. (See also the discussion of exposure in the Introduction for Nitroarenes [Selected], above.)

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

References

Beland FA. 1986. The metabolic activation and DNA adducts of dinitropyrenes. *Res Rep Health Eff Inst*(4): 3-30.

ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. http://www.chemsources.com/chemonline.html and search on dinitropyrene. Last accessed: 9/3/09.

HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB and search on CAS number. Last accessed: 9/3/09.

IARC. 1989. 1,8-Dinitropyrene. In *Diesel and Gasoline Engine Exhausts and Some Nitroarenes*. IARC Monographs Evaluation of Carcinogic Risks of Chemicals to Humans, vol. 46. Lyon, France: International Agency for Research on Cancer. pp. 231-246.

Lambert IB, Carroll C, Laycock N, Koziarz J, Lawford I, Duval L, *et al*. 2001. Cellular determinants of the mutational specificity of 1-nitroso-6-nitropyrene and 1-nitroso-8-nitropyrene in the *lacI* gene of *Escherichia coli*. *Mutat Res* 484(1-2): 19-48.

Neft RE, Roe AL, Smith BA, Beland FA. 1993. Dinitropyrene metabolism, DNA adduct formation, and DNA amplification in an SV40-transformed Chinese hamster embryo cell line. *Mol Carcinog* 7(4): 221-227.

Watanabe T, Takashima M, Kasai T, Hirayama T. 1997. Comparison of the mutational specificity induced by environmental genotoxin nitrated polycyclic aromatic hydrocarbons in *Salmonella typhimurium* his genes. *Mutat Res* 394(1-3): 103-112.

Watanabe T, Ishida S, Minami H, Kasai T, Ogawa S, Wakabayashi K, Hirayama T. 1998. Identification of 1,6- and 1,8-dinitropyrene isomers as major mutagens in organic extracts of soil from Osaka, Japan. *Chem Res Toxicol* 11(12): 1501-1507.

Watanabe T, Ishida S, Kishiji M, Takahashi Y, Furuta A, Kasai T, Wakabayashi K, Hirayama T. 1999. High-performance liquid chromatography-fluorescence determination of dinitropyrenes in soil after column chromatographic clean-up and on-line reduction. *J Chromatogr A* 839(1-2): 41-48.

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Watanabe T, Hasei T, Takahashi T, Asanoma M, Murahashi T, Hirayama T, Wakabayashi K. 2005. Detection of a novel mutagen, 3,6-dinitrobenzo[*e*]pyrene, as a major contaminant in surface soil in Osaka and Aichi Prefectures, Japan. *Chem Res Toxicol* 18(2): 283-289.

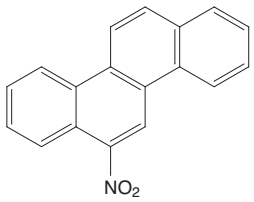
Yamazaki H, Hatanaka N, Kizu R, Hayakawa K, Shimada N, Guengerich FP, Nakajima M, Yokoi T. 2000. Bioactivation of diesel exhaust particle extracts and their major nitrated polycyclic aromatic hydrocarbon components, 1-nitropyrene and dinitropyrenes, by human cytochromes P450 1A1, 1A2, and 1B1. *Mutat Res* 472(1-2): 129-138.

6-Nitrochrysene

CAS No. 7496-02-8

Reasonably anticipated to be a human carcinogen

First listed in the *Eighth Report on Carcinogens* (1998)



Carcinogenicity

6-Nitrochrysene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

6-Nitrochrysene caused tumors in two rodent species, at several different tissue sites, and by two different routes of exposure. Intraperi-

toneal injection of 6-nitrochrysene caused malignant lymphoma and benign or malignant tumors of the lung (adenoma of adenocarcinoma) and liver (hepatocellular adenoma or carcinoma) in mice of both sexes (Busby *et al.* 1989, IARC 1989, El-Bayoumy *et al.* 1992, Imaida *et al.* 1992, Fu *et al.* 1994, Li *et al.* 1994). In newborn rats, intraperitoneal injection of 6-nitrochrysene caused benign or malignant colon tumors (adenoma or adenocarcinoma) in both sexes (Imaida *et al.* 1992). Injection of 6-nitrochrysene directly into the mammary gland of 30-day-old female rats caused benign and malignant tumors of the mammary gland (fibroadenoma, adenocarcinoma, and spindle-cell sarcoma) (El-Bayoumy *et al.* 1993).

Studies on Mechanisms of Carcinogenesis

In an initiation-promotion study using a phorbol ester as a tumor promoter, 6-nitrochrysene induced mainly benign skin tumors (papilloma) (El-Bayoumy *et al.* 1982). When given by intraperitoneal injection to transgenic mice carrying a human hybrid c-Ha-*ras* gene, 6-nitrochrysene caused lung and forestomach tumors (Ogawa *et al.* 1996). Injection of 6-nitrochrysene metabolites (1,2-dihydroxy-1,2-dihydro-6-nitrochrysene, 6-aminochrysene, 1,2-dihydroxy-3,4-epoxy-1,2,3,4-tetrahydro-6-nitrochrysene, or 1,2-dihydroxy-1,2-dihydro-6-aminochrysene) directly into the mammary gland of 30-day-old female rats caused cancer of the mammary gland (adenocarcinoma) (El-Bayoumy *et al.* 2002), but none of the metabolites was as potent as 6-nitrochrysene.

Pathways of 6-nitrochrysene metabolism leading to mutagenic and carcinogenic metabolites have been described (El-Bayoumy *et al.* 2002). Two different DNA-reactive metabolites are formed by two different pathways; however, an intermediate product in the second pathway can also feed into the first pathway (Li *et al.* 1994). One pathway involves ring hydroxylation followed by nitroreduction to form *trans*-1,2-dihydro-1,2-dihydroxy-6-aminochrysene, which can form a DNA-reactive epoxide (1,2-dihydro-1,2-dihydroxy-6-aminochrysene-3,4-epoxide). The other pathway is similar to that which activates 1,6-dinitropyrene, 1,8-dinitropyrene, and 1-nitropyrene; it proceeds by two steps of nitroreduction to form *N*-hydroxy-6-aminochrysene, which can then react with deoxyguanosine or deoxyadenosine to form at least three different DNA adducts. *N*-hydroxy-6-aminochrysene can also be ring hydroxylated to form *trans*-1,2-dihydro-1,2-dihydroxy-6-aminochrysene, the precursor of the 3,4-epoxide in the first pathway. 6-Nitrochrysene–DNA adducts were detected in tumor target tissues (lung, liver, colon, and mammary gland) in rats exposed to 6-nitrochrysene, and adducts of its metabolites were found in cells from target tissues exposed *in vitro.* Moreover, 6-nitrochrysene adducts caused mutations in the *hprt* gene of Chinese hamster ovary cells, mostly at A:T base pairs (Manjanatha *et al.* 1996). 6-Nitrochrysene was genotoxic in several assays in bacteria and mammalian cells and caused morphological transformation of finite-lifespan cells *in vitro* (IARC 1989).

In 6-nitrochrysene–induced mammary-gland tumors from female transgenic rats (Big Blue F344 × Sprague-Dawley F_1), the types of mutations observed (mainly A:T to G:C or T:A base-pair mutations) were consistent with the structure of 6-nitrochrysene–DNA adducts detected in this target organ (Boyiri *et al.* 2004). The metabolite with a mutational profile most similar to that of 6-nitrochrysene was *trans*-1,2-dihydroxy-1,2-dihydro-*N*-hydroxy-6-aminochrysene, which arises from both ring oxidation and nitroreduction (Guttenplan *et al.* 2007). Mutations in the K-*ras* proto-oncogene (involving C:G and A:T base pairs at codons 12, 13, and 61) were found in lung tumors (adenoma and adenocarcinoma) induced by 6-nitrochrysene or some of its metabolites, such as *trans*-1,2-dihydro-1,2-dihydroxy-6-aminochrysene, which is consistent with a role for the major adduct formed by this metabolite in formation of these tumors (Li *et al.* 1994). These findings support the possibility that the tumors caused by 6-nitrochysene are at least in part a result of DNA damage. There is no evidence to suggest that mechanisms by which 6-nitrochrysene causes tumors in experimental animals would not also operate in humans.

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to 6-nitrochrysene.

Properties

6-Nitrochrysene is a nitro-substituted polycyclic aromatic hydrocarbon that exists at room temperature as chrome-red to light-yellow to orange-yellow needles or prism-shaped crystals. It has a molecular weight of 273.3 and a melting point of 209°C, and it sublimes without decomposition. It is practically insoluble in water; slightly soluble in cold ethanol, diethyl ether, and carbon disulfide; slightly more soluble in benzene and acetic acid; and soluble in hot nitrobenzene (IARC 1989, WHO 2003).

Use

There is no evidence that 6-nitrochrysene has been used commercially for any purpose. 6-Nitrochrysene is used as an internal standard in the chemical analysis of nitroarenes (IARC 1989). It is available for research purposes at a purity of at least 98% and as a reference material at a certified purity of 98.9%.

Production

6-Nitrochrysene was first synthesized in 1890 (IARC 1989). In 2009, no commercial producers of 6-nitrochrysene were identified worldwide, but 6-nitrochrysene was available from three U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports of 6-nitrochrysene were found.

Exposure

The routes of human exposure to 6-nitrochrysene are inhalation, ingestion, and dermal contact. 6-Nitrochrysene was measured in diesel exhaust particulate extracts at a concentration of 0.78 µg/g (0.78 mg/kg) for heavy-duty engines during operation (IPCS 2003). The median concentration of hemoglobin adducts of 6-nitrochrysene measured in the blood of 29 bus-garage workers as an indicator of personal exposure to diesel exhaust was the same as in the control groups of urban and rural residents (Zwirner-Baier and Neumann 1999). No data were found on occupational exposure to 6-nitrochrysene. (See also the discussion of exposure in the Introduction for Nitroarenes [Selected], above.)

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements..

References

Boyiri T, Guttenplan J, Khmelnitsky M, Kosinska W, Lin JM, Desai D, Amin S, Pittman B, El-Bayoumy K. 2004. Mammary carcinogenesis and molecular analysis of *in vivo* cII gene mutations in the mammary tissue of female transgenic rats treated with the environmental pollutant 6-nitrochrysene. *Carcinogenesis* 25(4): 637-643.

Busby WF Jr, Stevens EK, Martin CN, Chow FL, Garner RC. 1989. Comparative lung tumorigenicity of parent and mononitro-polynuclear aromatic hydrocarbons in the BLU:Ha newborn mouse assay. *Toxicol Appl Pharmacol* 99(3): 555-563.

ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. http://www.chemsources.com/chemonline.html and search on nitrochrysene. Last accessed: 9/3/09.

El-Bayoumy K, Hecht SS, Hoffmann D. 1982. Comparative tumor initiating activity on mouse skin of 6-nitrobenzo[*a*]pyrene, 6-nitrochrysene, 3-nitroperylene, 1-nitropyrene and their parent hydrocarbons. *Cancer Lett* 16(3): 333-337.

El-Bayoumy K, Desai D, Upadhyaya P, Amin S, Hecht SS. 1992. Comparative tumorigenicity of nitrochrysene isomers in newborn mice. *Carcinogenesis* 13(12): 2271-2275.

El-Bayoumy K, Rivenson A, Upadhyaya P, Chae YH, Hecht SS. 1993. Induction of mammary cancer by 6-nitrochrysene in female CD rats. *Cancer Res* 53(16): 3719-3722.

El-Bayoumy K, Desai D, Boyiri T, Rosa J, Krzeminski J, Sharma AK, Pittman B, Amin S. 2002. Comparative tumorigenicity of the environmental pollutant 6-nitrochrysene and its metabolites in the rat mammary gland. *Chem Res Toxicol* 15(7): 972-978.

Fu PP, Dooley KL, Von Tungeln LS, Bucci T, Hart RW, Kadlubar FF. 1994. Caloric restriction profoundly inhibits liver tumor formation after initiation by 6-nitrochrysene in male mice. *Carcinogenesis* 15(2): 159-161.

Guttenplan JB, Zhao ZL, Kosinska W, Norman RG, Krzeminski J, Sun YW, Amin S, El-Bayoumy K. 2007. Comparative mutational profiles of the environmental mammary carcinogen, 6-nitrochrysene and its metabolites in a lacI mammary epithelial cell line. *Carcinogenesis* 28(11): 2391-2397.

IARC. 1989. 6-Nitrochrysene. In *Diesel and Gasoline Engine Exhausts and Some Nitroarenes*. IARC Monographs Evaluation of Carcinogic Risks of Chemicals to Humans, vol. 46. Lyon, France: International Agency for Research on Cancer. pp. 267-276.

Imaida K, Uneyama C, Ogasawara H, Hayashi S, Fukuhara K, Miyata N, Takahashi M. 1992. Induction of colon adenocarcinomas in CD rats and lung adenomas in ICR mice by 6-nitrochrysene: comparison of carcinogenicity and aryl hydrocarbon hydroxylase induction in the target organs of each species. *Cancer Res* 52(6): 1542-1545.

IPCS. 2003. *Environmental Health Criteria No. 229. Selected Nitro- and Nitro-oxy-polycyclic Aromatic Hydrocarbons*. International Programme on Chemical Safety. http://www.inchem.org/documents/ehc/ehc/ehc1229.htm.

Li EE, Heflich RH, Bucci TJ, Manjanatha MG, Blaydes BS, Delclos KB. 1994. Relationships of DNA adduct formation, K-*ras* activating mutations and tumorigenic activities of 6-nitrochrysene and its metabolites in the lungs of CD-1 mice. *Carcinogenesis* 15(7): 1377-1385.

Manjanatha MG, Li EE, Fu PP, Heflich RH. 1996. H- and K-*ras* mutational profiles in chemically induced liver tumors from B6C3F$_1$ and CD-1 mice. *J Toxicol Environ Health* 47(2): 195-208.

Ogawa K, Imaida K, Masui T, Kawabe M, Hasegawa R, Kato K, Ito N, Shirai T. 1996. Chemically induced lung and forestomach neoplasias in transgenic mice carry mutant forms of the human c-Ha-*ras* transgene. *Carcinogenesis* 17(2): 341-345.

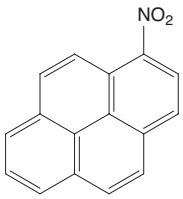
Zwirner-Baier I, Neumann HG. 1999. Polycyclic nitroarenes (nitro-PAHs) as biomarkers of exposure to diesel exhaust. *Mutat Res* 441(1): 135-144.

1-Nitropyrene

CAS No. 5522-43-0

Reasonably anticipated to be a human carcinogen

First listed in the *Eighth Report on Carcinogens* (1998)



Carcinogenicity

1-Nitropyrene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

1-Nitropyrene caused tumors in two rodent species, at several different tissue sites, and by several different routes of exposure. It caused benign or malignant mammary-gland tumors (fibroadenoma or adenocarcinoma) in 30-day-old female rats, in newborn male and female rats exposed by stomach tube (El-Bayoumy *et al.* 1995), and in female rats exposed by intraperitoneal or subcutaneous injection (IARC 1989). Subcutaneous injection of 1-nitropyrene also caused cancer at the injection site (sarcoma) in rats of both sexes. Lung tumors were observed in male hamsters exposed by intratracheal instillation (1-nitropyrene was adsorbed on carbon-black particles) (Moon *et al.* 1990) and in female strain A/J mice and newborn male CD-1 mice exposed by intraperitoneal injection (IARC 1989). In the A/J mice (a strain with a high spontaneous rate of lung tumors), both tumor incidence and the number of tumors per mouse were increased. In the newborn CD-1 mice, 1-nitropyrene also caused benign or malignant liver tumors (adenoma or carcinoma).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to 1-nitropyrene.

Studies on Mechanisms of Carcinogenesis

A DNA-binding metabolite of 1-nitropyrene is responsible for its genotoxic effects. 1-Nitropyrene is metabolized by two reductions of the 1-nitro group to form first a nitroso and then a *N*-hydroxylamine group at the 1-position (Beland 1986). Activation occurs by loss of the *N*-hydroxyl group or by O-acetylation of the *N*-hydroxylamine group, followed by removal of the acetate, either of which creates the active nitrenium ion, which reacts with deoxyguanosine at C-8 to form the DNA adduct. 1-Nitropyrene formed DNA adducts *in vitro* and *in vivo* and was genotoxic in a wide variety of assays in bacteria and mammalian cells, including human cells and cells from likely target tissue sites (IARC 1989). In particular, DNA adducts were detected in the lung following intratracheal instillation of 1-nitropyrene, indicating potential genotoxic activity in a likely target organ in humans (IARC 1989, NTP 1996, 1999). 1-Nitropyrene also consistently caused morphological transformation of both finite-life-span and immortal cell lines, including human cells. 1-Nitropyrene transformed rat tracheal epithelial cells *in vivo* following intratracheal administration, but not *in vitro*, suggesting that metabolic activation not present in the tracheal cells might be necessary for transformation (Ensell *et al.* 1998). Furthermore, subcutaneous injection with cell lines established from the transformed rat tracheal epithelial cells caused malignant tumors (squamous-cell carcinoma) in nude mice (Ensell *et al.* 1999).There is no evidence to suggest that mechanisms by which 1-nitropyrene causes tumors in experimental animals would not also operate in humans.

Properties

1-Nitropyrene is a nitro-substituted polycyclic aromatic hydrocarbon that exists as yellow needles or prisms at room temperature. It is practically insoluble in water, very soluble in diethyl ether, and soluble in ethanol, benzene, toluene, and tetrahyrofluorenone (IARC 1989, HSDB 2010). It is stable under normal temperatures and pressures, but decomposes following exposure to ultraviolet or visible light (Akron 2010, IARC 1989). Physical and chemical properties of 1-nitropyrene are listed in the following table.

Property	Information
Molecular weight	247.3[a]
Melting point	155°C[a]
Log K_{ow}	5.06[a]
Water solubility	0.0118 mg/L at 25°C[b]
Vapor pressure	5.52×10^{-8} mmHg at 25°C[b]

Sources: [a]HSDB 2010, [b]ChemIDplus 2010.

Use

1-Nitropyrene has been reported to be a chemical photosensitizer, and one non-U.S. company was reported to have used it as an intermediate in the production of 1-azidopyrene, which is used in photo-

sensitive printing. 1-Nitropyrene is available for research purposes at a purity of 97% or of greater than 99.5% with no more than 0.1% total dinitropyrenes and pyrene. It also is available as a reference material at a purity of 99.68% (IARC 1989).

Production

In 1989, one non-U.S. company was reported to produce 1-nitropyrene by the reaction of pyrene with nitric acid (IARC 1989). In 2010, no U.S. commercial producers of 1-nitropyrene were identified, but 1-nitropyrene was available from 14 suppliers worldwide, including 7 U.S. suppliers (ChemSources 2010). No data on U.S. imports or exports of 1-nitropyrene were found.

Exposure

The routes of human exposure to 1-nitropyrene are inhalation, ingestion, and dermal contact (HSDB 2010). Measurement of 1-nitropyrene in diesel exhaust has frequently been used as an indicator of the presence of over 200 different nitro-PAHs (Scheepers *et al.* 2003). 1-Nitropyrene has also been detected in the fumes from soybean cooking oil (Wu *et al.* 1998) and in dried herbs such as basil, chervil, marjoram, oregano, and sage (Spitzer *et al.* 2000). 1-Nitropyrene was measured in diesel exhaust particulate extracts at concentrations of 5.0 mg/kg for heavy-duty engines during operation, up to 93 mg/kg for a six-cylinder passenger-vehicle engine during operation, and up to 63 pmol/mg (15.6 mg/kg) for engines at idle (IARC 1989, Yamazaki *et al.* 2000, IPCS 2003). Emissions of 1-nitropyrene also depend on the composition of the diesel fuel; emissions from the same engine were much lower for Swedish diesel fuel classified as environmentally friendly (MK1) than for European Program on Emissions Fuels and Engine Technologies reference fuels (Westerholm *et al.* 2001). 1-Nitropyrene was measured in particulates derived from coal-burning at a concentration of 5.3 pmol/mg (1.3 mg/kg) (Taga *et al.* 2005).

Concentrations of 1-nitropyrene in ambient air were higher in heavily industrialized areas (0.057 ng/m^3) than in non-industrialized urban areas (0.030 ng/m^3), suburban areas (0.022 ng/m^3), or rural areas (0.013 ng/m^3) (IARC 1989). In Japan, concentrations varied from a high of 413 pg/m^3 in Sapporo in winter to a low of 11.3 pg/m^3 in Kanazawa in summer at night. In Japan, 1-nitropyrene was detected in precipitation and at low concentrations in river water and lower concentrations in seawater on the days after precipitation (Murahashi *et al.* 2001). 1-Nitropyrene has also been detected in soil, sewage sludge, sediment, and incinerator ash (IPCS 2003). It is expected to be immobile in soil (HSDB 2010).

The median concentration of hemoglobin adducts of 1-nitropyrene measured in the blood of 29 bus-garage workers as an indicator of personal exposure to diesel exhaust was 0.13 pmol/g hemoglobin, which was lower than in the control group of urban residents (0.16 pmol/g) and higher than in rural residents (0.10 pmol/g) (Zwirner-Baier and Neumann 1999). The concentration of 1-nitropyrene in lung-tissue specimens collected in Fukuoka, Japan, from 1991 to 1996 was 19.7 ± 10.5 pg/g of dry weight, which was lower than in lung specimens collected from 1961 to 1962, a period of heavy air pollution (Tokiwa *et al.* 1998).

Occupational exposure to 1-nitropyrene was documented for operators of diesel-powered machinery used in mining (IPCS 2003). In an oil-shale mine in Estonia, concentrations of 1-nitropyrene in respirable dust were much higher for underground than surface operations (Scheepers *et al.* 2003). (See also the discussion of exposure in the Introduction for Nitroarenes [Selected], above.)

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

References

Akron. 2010. *The Chemical Database*. The Department of Chemistry at the University of Akron. http://ull.chemistry.uakron.edu/erd and search on CAS number. Last accessed: 2/11/10.

Beland FA. 1986. *The Metabolic Activation and DNA Adducts of Dinitropyrenes.* Research Report No. 4. Boston: Health Effects Institute. 30 pp.

ChemIDplus. 2010. *ChemIDplus Advanced*. National Library of Medicine. http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp and select Registry Number and search on CAS number. Last accessed: 2/11/10.

ChemSources. 2010. *Chem Sources - Chemical Search*. Chemical Sources International. http://www.chemsources.com/chemonline.html and search on nitropyrene. Last accessed: 2/11/10.

El-Bayoumy K, Chae YH, Upadhyaya P, Rivenson A, Kurtzke C, Reddy B, Hecht SS. 1995. Comparative tumorigenicity of benzo[*a*]pyrene, 1-nitropyrene and 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine administered by gavage to female CD rats. *Carcinogenesis* 16(2): 431-434.

Ensell MX, Whong WZ, Heng ZC, Nath J, Ong T. 1998. *In vitro* and *in vivo* transformation in rat tracheal epithelial cells exposed to diesel emission particles and related compounds. *Mutat Res* 412(3): 283-291.

Ensell MX, Hubbs A, Zhou G, Battelli L, Nath J, Ong T. 1999. Neoplastic potential of rat tracheal epithelial cell lines induced by 1-nitropyrene and dibenzo(*a,i*)pyrene. *Mutat Res* 444(1): 193-199.

HSDB. 2010. *Hazardous Substances Data Bank*. National Library of Medicine. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB and search on CAS number. Last accessed: 2/11/10.

IARC. 1989. 1-Nitropyrene. In *Diesel and Gasoline Engine Exhausts and Some Nitroarenes*. IARC Monographs Evaluation of Carcinogenic Risks of Chemicals to Humans, vol. 46. Lyon, France: International Agency for Research on Cancer. pp. 321-358.

IPCS. 2003. *Environmental Health Criteria No. 229. Selected Nitro- and Nitro-oxy-polycyclic Aromatic Hydrocarbons*. International Programme on Chemical Safety. http://www.inchem.org/documents/ehc/ehc/ehc1229.htm.

Moon RC, Rao KV, Detrisac CJ. 1990. *Respiratory Carcinogenesis of Nitroaromatics.* Research Report No. 32. Boston: Health Effects Institute. 29 pp.

Murahashi T, Ito M, Kizu R, Hayakawa K. 2001. Determination of nitroarenes in precipitation collected in Kanazawa, Japan. *Water Res* 35(14): 3367-3372.

NTP. 1996. *NTP Technical Report on the Toxicity Studies of 1-Nitropyrene (CAS No. 5522-43-0) Administered by Inhalation to F344/N Rats.* Technical Report Series no. 34. Research Triangle Park, NC: National Toxicology Program. 62 pp.

NTP. 1999. *NTP Report on Carcinogens Background Document for 1-Nitropyrene*. National Toxicology Program. http://ntp.niehs.nih.gov/files/Nitropyrene-1.pdf.

Scheepers PT, Micka V, Muzyka V, Anzion R, Dahmann D, Poole J, Bos RP. 2003. Exposure to dust and particle-associated 1-nitropyrene of drivers of diesel-powered equipment in underground mining. *Ann Occup Hyg* 47(5): 379-388.

Spitzer B, Cichna M, Markl P, Sontag G, Knopp D, Niessner R. 2000. Determination of 1-nitropyrene in herbs after selective enrichment by a sol-gel-generated immunoaffinity column. *J Chromatogr A* 880(1-2): 113-120.

Taga R, Tang N, Hattori T, Tamura K, Sakai S, Toriba A, Kizu R, Hayakawa K. 2005. Direct-acting mutagenicity of extracts of coal burning-derived particulates and contribution of nitropolycyclic aromatic hydrocarbons. *Mutat Res* 581(1-2): 91-95.

Tokiwa H, Nakanishi Y, Sera N, Hara N, Inuzuka S. 1998. Analysis of environmental carcinogens associated with the incidence of lung cancer. *Toxicol Lett* 99(1): 33-41.

Westerholm R, Christensen A, Tornqvist M, Ehrenberg L, Rannug U, Sjogren M, *et al.* 2001. Comparison of exhaust emissions from Swedish environmental classified diesel fuel (MK1) and European Program on Emissions, Fuels and Engine Technologies (EPEFE) reference fuel: a chemical and biological characterization, with viewpoints on cancer risk. *Environ Sci Technol* 35(9): 1748-1754.

Wu PF, Chiang TA, Wang LF, Chang CS, Ko YC. 1998. Nitro-polycyclic aromatic hydrocarbon contents of fumes from heated cooking oils and prevention of mutagenicity by catechin. *Mutat Res* 403(1-2): 29-34.

Yamazaki H, Hatanaka N, Kizu R, Hayakawa K, Shimada N, Guengerich FP, Nakajima M, Yokoi T. 2000. Bioactivation of diesel exhaust particle extracts and their major nitrated polycyclic aromatic hydrocarbon components, 1-nitropyrene and dinitropyrenes, by human cytochromes P450 1A1, 1A2, and 1B1. *Mutat Res* 472(1-2): 129-138.

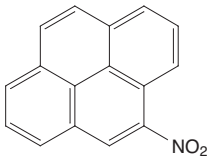
Zwirner-Baier I, Neumann HG. 1999. Polycyclic nitroarenes (nitro-PAHs) as biomarkers of exposure to diesel exhaust. *Mutat Res* 441(1): 135-144.

4-Nitropyrene

CAS No. 57835-92-4

Reasonably anticipated to be a human carcinogen

First listed in the *Eighth Report on Carcinogens* (1998)



Carcinogenicity

4-Nitropyrene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

4-Nitropyrene caused tumors in two rodent species, at several different tissue sites, and by several different routes of administration. Intraperitoneal injection of 4-nitropyrene caused benign and malignant tumors of the lung in newborn mice of both sexes and of the liver in newborn male mice (IARC 1989). In female rats, it caused benign or malignant mammary-gland tumors (adenoma, fibroadenoma, or adenocarcinoma) (Imaida *et al.* 1991). In newborn female rats, subcutaneous injection of 4-nitropyrene caused cancer at the injection site (sarcoma), mammary-gland cancer (adenocarcinoma), leukemia, and Zymbal-gland tumors (IARC 1989, Imaida *et al.* 1995). Injections of 4-nitropyrene directly into the mammary gland of 30-day-old female rats caused benign or malignant mammary-gland tumors (fibroadenoma or adenocarcinoma) (Imaida *et al.* 1991, El-Bayoumy *et al.* 1993).

Studies on Mechanisms of Carcinogenesis

Metabolic pathways for 4-nitropyrene include both ring oxidation and nitroreduction (Upadhyaya *et al.* 1994), resulting in mutagenic metabolites. DNA adducts were detected *in vitro* (Sun *et al.* 2004) and in the liver and mammary glands of rats exposed to 4-nitropyrene *in vivo* (Chae *et al.* 1997). Analysis of liver and mammary-gland DNA obtained from exposed rats yielded four radioactive peaks that coeluted with markers derived from the nitroreductive pathway, indicating that nitroreduction is primarily responsible for DNA adduct formation in these tissues (Chae *et al.* 1999). 4-Nitropyrene was genotoxic in bacteria and caused morphological transformation of BALB/3T3 mouse embryonic fibroblast cells *in vitro* (NTP 1999). There is no evidence to suggest that mechanisms by which 4-nitropyrene causes tumors in experimental animals would not also operate in humans.

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to 4-nitropyrene.

Properties

4-Nitropyrene is a nitro-substituted polycyclic aromatic hydrocarbon that exists as orange needles at room temperature (IARC 1989). It is practically insoluble in water but soluble in organic solvents such as acetone, benzene, dimethyl sulfoxide, and methylene chloride (WHO 2003). Physical and chemical properties of 4-nitropyrene are listed in the following table.

Property	Information
Molecular weight	247.3[a]
Melting point	190°C to 192°C[a]
Boiling point	472°C[b]
Water solubility	0.017 mg/L at 25°C[b]
Vapor pressure	3.3×10^{-8} mm Hg at 25°C[b]

Sources: [a]IARC 1989, [b]WHO 2003.

Use

4-Nitropyrene is used only as a laboratory chemical (IARC 1989); there is no evidence that it has ever been used for commercial purposes.

Production

4-Nitropyrene is produced only for laboratory use (IARC 1989). In 2009, no commercial producers of 4-nitropyrene were identified worldwide, but 4-nitropyrene was available from one U.S. supplier (ChemSources 2009). No data on U.S. imports or exports of 4-nitropyrene were found.

Exposure

The routes of human exposure to 4-nitropyrene are inhalation, ingestion, and dermal contact. 4-Nitropyrene was measured in diesel exhaust particulate extracts at concentrations of 0.07 µg/g (0.07 mg/kg) for heavy-duty engines during operation and up to 0.04 pmol/mg (0.01 mg/kg) for engines at idle (IPCS 2003). 4-Nitropyrene was measured in particulates derived from coal-burning at a concentration of 2.29 pmol/mg (0.57 mg/kg) (Taga *et al.* 2005). No data were found on occupational exposure to 1,6-dinitropyrene. (See also the discussion of exposure in the Introduction for Nitroarenes [Selected], above.)

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

References

Chae YH, Upadhyaya P, Ji BY, Fu PP, el-Bayoumy K. 1997. Comparative metabolism and DNA binding of 1-, 2-, and 4-nitropyrene in rats. *Mutat Res* 376(1-2): 21-28.

Chae YH, Ji B-Y, Lin J-M, Fu PP, Cho BP, El-Bayoumy K. 1999. Nitroreduction of 4-nitropyrene is primarily responsible for DNA adduct formation in the mammary gland of female CD rats. *Chem Res Toxicol* 12: 180-186.

ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. http://www.chemsources.com/chemonline.html and search on nitropyrene. Last accessed: 9/3/09.

El-Bayoumy K, Rivenson A, Upadhyaya P, Chae YH, Hecht SS. 1993. Induction of mammary cancer by 6-nitrochrysene in female CD rats. *Cancer Res* 53(16): 3719-3722.

IARC. 1989. 4-Nitropyrene. In *Diesel and Gasoline Engine Exhausts and Some Nitroarenes*. IARC Monographs Evaluation of Carcinogic Risks of Chemicals to Humans, vol. 46. Lyon, France: International Agency for Research on Cancer. pp. 367-373.

IPCS. 2003. *Environmental Health Criteria No. 229. Selected Nitro- and Nitro-oxy-polycyclic Aromatic Hydrocarbons*. International Programme on Chemical Safety. http://www.inchem.org/documents/ehc/ehc/ehc1229.htm.

Imaida K, Hirose M, Tay L, Lee MS, Wang CY, King CM. 1991. Comparative carcinogenicities of 1-, 2-, and 4-nitropyrene and structurally related compounds in the female CD rat. *Cancer Res* 51(11): 2902-2907.

Imaida K, Lee MS, Land SJ, Wang CY, King CM. 1995. Carcinogenicity of nitropyrenes in the newborn female rat. *Carcinogenesis* 16(12): 3027-3030.

NTP. 1999. *NTP Report on Carcinogens Background Document for 4-Nitropyrene*. National Toxicology Program. http://ntp.niehs.nih.gov/files/Nitropyrene-4.pdf.

Sun YW, Guengerich FP, Sharma AK, Boyiri T, Amin S, el-Bayoumy K. 2004. Human cytochromes P450 1A1 and 1B1 catalyze ring oxidation but not nitroreduction of environmental pollutant mononitropyrene isomers in primary cultures of human breast cells and cultured MCF-10A and MCF-7 cell lines. *Chem Res Toxicol* 17(8): 1077-1085.

Taga R, Tang N, Hattori T, Tamura K, Sakai S, Toriba A, Kizu R, Hayakawa K. 2005. Direct-acting mutagenicity of extracts of coal burning-derived particulates and contribution of nitropolycyclic aromatic hydrocarbons. *Mutat Res* 581(1-2): 91-95.

Upadhyaya P, Von Tungeln LS, Fu PP, el-Bayoumy K. 1994. *In vitro* and *in vivo* metabolism of the carcinogen 4-nitropyrene. *Chem Res Toxicol* 7(5): 690-695.