Nitroarenes (Selected)

Introduction

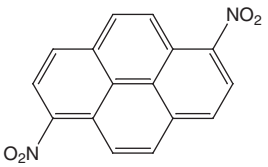
The nitroarenes comprise a large class of structurally related chemicals that are normally found in particulate emissions from many combustion sources, most notably, diesel exhausts. These compounds were first listed in the *Eighth Report on Carcinogens* (1998) as *reasonably anticipated to be a human carcinogen* based on carcinogenicity results with experimental animals. Few of this large class of chemicals have been rigorously evaluated in "state-of-the-art" rodent cancer studies. Typically, the chemicals were administered by injection, over short periods of time, and with less than optimal time allowed for tumors to fully develop. Despite these factors, the experimental carcinogenesis results are generally similar and demonstrate tumor formation at the site of injection and at sites away from the site of injection. The chemicals also show genotoxic activity in a variety of *in vitro* and *in vivo* assays, and metabolic pathways for the creation of reaction products with the ability to cause gene mutations or changes in the structure of DNA have been described in tissues from animals as well as humans. No adequate human 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 supporting animal and mechanistic studies. Whether the nitroarenes are responsible for, or contribute to, the human carcinogenicity of diesel exhaust has not been determined.

Profiles for the following nitroarenes follow this introduction. The CAS Registry Number for each compound is listed in parentheses after the name.

- 1,6-Dinitropyrene (42397-64-8)
- 1,8-Dinitropyrene (42397-65-9)
- 6-Nitrochrysene (7496-02-8)
- 1-Nitropyrene (5522-43-0)
- 4-Nitropyrene (57835-92-4)

Nitroarenes (Selected) 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 malignant tumor formation in multiple species of experimental animals, at multiple sites and by multiple routes of exposure (IARC 1989).

When administered by subcutaneous injections, 1,6-dinitropyrene induced injection-site sarcomas in male mice and male and female rats, and leukemia in female rats (Tokiwa *et al.* 1984, Ohgaki *et al.* 1985, Imaida *et al.* 1995). Intraperitoneal injections of 1,6-dinitropyrene caused an increased incidence of liver-cell tumors in male mice (Wislocki *et al.* 1986) and induced sarcomas of the peritoneal cavity in female rats (Imaida *et al.* 1991). In two studies, squamous cell carcinomas of the lung were induced in male rats receiving 1,6-dinitropyrene by intrapulmonary injection (Maeda *et al.* 1986, Iwagawa *et al.* 1989). The incidences of myeloid leukemia and lung adenocarcinomas were significantly increased in male and female hamsters receiving 1,6-dinitropyrene by intratracheal instillation (Takayama *et al.* 1985). 1,6-Dinitropyrene induced carcinoma of the pituitary gland in an oral study of short-term duration in rats (Imaida *et al.* 1991).

No adequate data were available to evaluate the carcinogenicity of 1,6-dinitropyrene in humans.

Additional Information Relevant to Carcinogenicity

Intratracheal administration of 1,6-dinitropyrene to rats previously inoculated to de-epithelialized trachea with an immortalized bronchial cell line, caused tumors when the tracheas were then implanted subcutaneously into nude mice (Iizasa *et al.* 1993). 1,6-Dinitropyrene is genotoxic in a wide variety of assays in bacteria and mammalian cells including human cells. 1,6-Dinitropyrene also demonstrates evidence of cell transformation activity *in vitro* in rat tracheal epithelial cells. Metabolic pathways leading to mutagenic and clastogenic metabolites and DNA adducts of 1,6-dinitropyrene have been described (IARC 1989).

No data were available that would suggest that the mechanisms thought to account for tumor induction by 1,6-dinitropyrene in experimental animals would not also operate in humans.

Properties

1,6-Dinitropyrene occurs as light-brown needles or as a yellow crystalline solid. The water solubility was not reported, but it is moderately soluble in toluene. The melting point is greater than 300°C (IARC 1989).

Use

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

Production

One foreign company synthesized >99.9% pure 1,6-dinitropyrene (IARC 1989). One U.S. company produced 1,6-dinitropyrene (SRI 1992), and there are at least four U.S. suppliers (Chem Sources 2001). No data on imports or exports were available.

Exposure

The primary route of potential human exposure to 1,6-dinitropyrene is inhalation. Detectable levels have been found in ambient atmospheric samples. Higher amounts have been reported in heavy industrialized areas when compared to nonindustrialized urban and suburban sites. 1,6-Dinitropyrene has been found in various concentrations in extracts of particles from the exhaust of heavy-duty and light-duty diesel engines. It has also been found in small amounts in particulate emissions from kerosene heaters and gas burners used for home heating and cooking. Prior to 1980, some carbon black samples, known to be used in photocopy machines, were found to contain considerable quantities of 1,6-dinitropyrene (IARC 1989). 1,6-Dinitropyrene is not listed in the National Occupational Exposure Survey or the National Occupational Hazard Survey conducted by NIOSH.

Regulations

No specific regulations or guidelines relevant to reduction of exposure to 1,6-dinitropyrene were identified.

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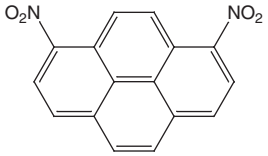
Nitroarenes (Selected)
1,8-Dinitropyrene
CAS No. 42397-65-9

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 malignant tumor formation in multiple species of experimental animals, at multiple sites, and by multiple routes of exposure (IARC 1989). When administered by subcutaneous injections, 1,8-dinitropyrene induced injection-site sarcomas in male mice and male and female rats, and leukemia in female rats (Imaida *et al.* 1995, Ohgaki *et al.* 1984, 1985, Otofuji *et al.* 1987). Intraperitoneal injections of 1,8-dinitropyrene induced sarcomas of the peritoneal cavity, leukemia, and mammary adenocarcinoma in female rats (Imaida *et al.* 1991, 1995). The incidences of mammary tumors, including adenocarcinomas, were increased in female rats receiving 1,8-dinitropyrene by gavage (Imaida *et al.* 1991, IARC 1989).

No adequate data were available to evaluate the carcinogenicity of 1,8-dinitropyrene in humans.

Additional Information Relevant to Carcinogenicity

1,8-Dinitropyrene is genotoxic in a wide variety of assays in bacteria and mammalian cells demonstrating evidence of cell transformation activity *in vitro*, and metabolic pathways leading to mutagenic and clastogenic metabolites and DNA adducts have been described (IARC 1989).

No data were available that would suggest that the mechanisms thought to account for tumor induction of 1,8-dinitropyrene in experimental animals would not also operate in humans.

Properties

1,8-Dinitropyrene occurs as light-brown needles or as a yellow, fluffy, crystalline solid. It has a melting point of ≥300°C (IARC 1989). When heated to decomposition, 1,8-dinitropyrene emits toxic fumes of nitrogen oxides. No information on the solubility of 1,8-dinitropyrene was found in the published literature.

Use

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

Production

One U.S. company produced 1,8-dinitropyrene (SRI 1992), and two U.S. suppliers were identified (Chem Sources 2001). No data on imports or exports of 1,8-dinitropyrene were available.

Exposure

The primary route of potential human exposure to 1,8-dinitropyrene is inhalation. Detectable levels have been found in respirable particulates from ambient atmospheric samples. Higher amounts have been reported in heavy industrialized areas when compared to nonindustrialized urban and suburban sites. 1,8-Dinitropyrene has been found in various concentrations in extracts of particles from the exhaust of heavy-duty and light-duty diesel engines. It has also been found in small amounts in particulate emissions from kerosene heaters and gas burners used for home heating and cooking. Prior to 1980, some carbon black samples, known to be used in photocopy machines, were found to contain considerable quantities of 1,8-dinitropyrene (IARC 1989). 1,8-Dinitropyrene is not listed in the National Occupational Exposure Survey or the National Occupational Hazard Survey conducted by NIOSH.

Regulations and Guidelines

No specific regulations or guidelines relevant to reduction of exposure to 1,8-dinitropyrene were identified.

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Imaida, K., M. S. Lee, C. Y. Wang and C. M. King. 1991. Carcinogenicity of dinitropyrenes in the weanling female CD rat. Carcinogenesis 12(7): 1187-91.
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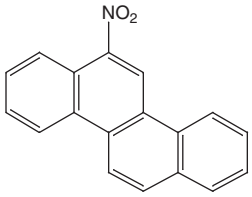
Nitroarenes (Selected) 6-Nitrochrysene CAS No. 7496-02-8

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 at multiple sites in multiple species of experimental animals (IARC 1989). In seven studies, when administered by intraperitoneal injection, 6-nitrochrysene caused lung tumors in male and female mice and also induced liver tumors in female and/or male mice in three of these studies and malignant lymphoma in one study (Busby *et al.* 1985, 1989, El-Bayoumy *et al.* 1992, Li *et al.* 1994, Fu *et al.* 1994, Imaida *et al.* 1992, Wislocki *et al.* 1986). Dysplastic and/or adenomatous lesions of the colon were increased in male and female rats, and colon adenocarcinomas were increased in male rats receiving 6-nitrochrysene by intraperitoneal injection (Imaida *et al.* 1992). Mammary fibroadenoma, adenocarcinoma, and spindle cell sarcomas were increased in female rats receiving 6-nitrochrysene by injection into the mammary gland (El-Bayoumy *et al.* 1993).

No data were available to evaluate the carcinogenicity of 6-nitrochrysene in humans.

Additional Information Relevant to Carcinogenicity

6-Nitrochrysene induced skin tumors, mainly papillomas, in a dermal initiation-promotion study in which 6-nitrochrysene was used as the initiator, followed by promotion with a phorbol ester (El-Bayoumy *et al.* 1982). It also caused lung and forestomach tumors when given by intraperitoneal injection to transgenic mice carrying a human hybrid c-Ha-*ras* gene (Ogawa *et al.* 1996). 6-Nitrochrysene is genotoxic in several assays in bacteria and mammalian cells and induces cell transformation in finite lifespan cells *in vitro*. Metabolic pathways leading to mutagenic and clastogenic metabolites and DNA adducts have been described (IARC 1989). The presence of 6-nitrochrysene-DNA adducts in tumor target tissue supports the possibility that tumors induced by this chemical are at least in part a result of chemical-induced DNA damage.

No data were available that would suggest that the mechanisms thought to account for tumor induction by 6-nitrochrysene in experimental animals would not also operate in humans.

Properties

6-Nitrochrysene occurs as chrome-red, thick prismatic crystals; orange-yellow needles; and light-yellow needles. It can be transferred from a solid state to a vapor state without decomposition, and has a melting point of 209°C. 6-Nitrochrysene is slightly soluble in cold ethanol, diethyl ether, and carbon disulfide; slightly more soluble in benzene and acetic acid; and soluble in hot nitrobenzene. Heating 6-nitrochrysene with tin and concentrated hydrochloric acid in acetic acid at 100°C forms 6-aminochrysene. 6-Nitrochrysene also reacts with bromine to form 12-bromo-6-nitrochrysene, and it reacts with fuming nitric acid to form 6,12-dinitrochrysene (IARC 1989).

Use

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

Production

6-Nitrochrysene was first synthesized in 1890 (IARC 1989). One U.S. company produced 6-nitrochrysene (SRI 1992), and Chem Sources (2001) identified five U.S. suppliers. No data on imports or exports of 6-nitrochrysene were available.

Exposure

The primary route of potential human exposure to 6-nitrochrysene is inhalation. Low concentrations of 6-nitrochrysene have been found in ambient airborne particulates. Prior to 1980, some carbon black samples, known to be used in photocopy machines, were found to contain considerable quantities of nitropyrenes (IARC 1989). 6-Nitrochrysene is not listed in the National Occupational Exposure Survey or the National Occupational Hazard Survey conducted by NIOSH.

Regulations and Guidelines

No specific regulations or guidelines relevant to reduction of exposure to 6-nitrochrysene were identified.

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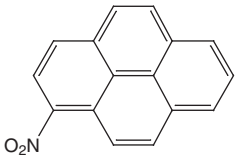
Nitroarenes (Selected)
1-Nitropyrene
CAS No. 5522-43-0

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 malignant tumor formation in multiple species of experimental animals, at multiple sites and by multiple routes of exposure (IARC 1989).

Intraperitoneal (i.p.) injections of 1-nitropyrene in the strain A mouse increased lung tumors in males and females, and the numbers of adenomas per mouse lung also increased (El-Bayoumy and Hecht 1983, El Bayoumy *et al.* 1984). When administered by subcutaneous injections, 1-nitropyrene induced injection-site sarcomas in male and female rats and mammary tumors (including adenocarcinomas) in female rats (Hirose *et al.* 1984, Imaida *et al.* 1995). Intraperitoneal injections of 1-nitropyrene in mice caused liver-cell tumors in males (Wislocki *et al.* 1986). A study in female rats injected i.p. with 1-nitropyrene showed increased mammary tumors; a second i.p. study demonstrated a nonstatistically significant increase in mammary tumors (IARC 1989, Imaida *et al.* 1991). Mammary gland tumors were also increased following oral administration of 1-nitropyrene to female rats (El-Bayoumy *et al.* 1988, 1995). Intratracheal administration of 1-nitropyrene, adsorbed onto carbon black particles, to hamsters demonstrated a weak, but significant, increase in lung tumors over particle only controls (Moon *et. al.* 1990).

No data were available to evaluate the carcinogenicity of 1-nitropyrene in humans.

Additional Information Relevant to Carcinogenicity

1-Nitropyrene is genotoxic in a wide variety of assays in bacteria and mammalian cells including human cells and cells from likely target organs (i.e. lung). Further, 1-nitropyrene demonstrates consistent evidence of cell transformation activity *in vitro* in both finite life-span and immortal cell lines including human cells, and has demonstrated the ability to form DNA adducts *in vitro* and *in vivo*. Importantly, adducts have been detected in the lung following intratracheal instillation of 1-nitropyrene thus supporting potential genotoxic activity in a likely target organ in humans (IARC 1989, Chan 1996).

No data were available that would suggest that the mechanisms thought to account for tumor induction of 1-nitropyrene in experimental animals would not also operate in humans.

Properties

1-Nitropyrene occurs as yellow needles or prisms from ethanol, and it has a melting point of 155°C. It is partially insoluble in water (0.02 mg/L @ 25°C); very soluble in diethyl ether, and soluble in acetone, ethanol, benzene, toluene, and tetrahydrofluorenone. 1-Nitropyrene reacts with ethanolic potassium hydroxide and with zinc powder in ethanol (in the presence of catalytic amounts of ammonium chloride or ammonia) to form 1,1′-azoxypyrene. 1-Nitropyrene degrades to 2-propanol following exposure to ultraviolet/visible light. When heated to decomposition, 1-nitropyrene emits toxic fumes of nitrogen oxides (IARC 1989, HSDB 2003).

Use

1-Nitropyrene has been reported to be a chemical photosensitizer. One foreign company used 1-nitropyrene as an intermediate in the production of 1-azidopyrene, which is used in photosensitive printing. It is available for research purposes at 97% or ≥99.5% purity with ≤0.1% total dinitropyrenes and pyrene. It is available at a purity of 99.68% as a reference material (IARC 1989).

Production

Since 1972, one foreign company has produced 1-nitropyrene by the reaction of pyrene with nitric acid (IARC 1989). One U.S. producer (SRI 1992) and 11 U.S. suppliers were identified (Chem Sources 2001). No data on imports or exports of 1-nitropyrene were available.

Exposure

The primary route of potential human exposure to 1-nitropyrene is inhalation. It is one of the most abundant mononitroarenes detected in ambient air. Concentrations in ambient air are generally less than 0.1 ng/m^3 and less than 0.5 mg/kg in airborne particulates. 1-Nitropyrene has also been detected in stack gases from coal-fired power plants and aluminum smelters, in particulate emissions from many stationary combustion sources and diesel engines, in used oil from diesel and gasoline engines, in fly-ash extracts from commercial power plants, and particles emitted from fireplaces and coal-fired boilers. Prior to 1980, some carbon black samples, known to be used in photocopy machines, were found to contain considerable quantities of nitropyrenes. 1-Nitropyrene has also been detected in the wastewater from gasoline service stations and in river sediment (IARC 1989). 1-Nitropyrene is not listed in the National Occupational Exposure Survey or the National Occupational Hazard Survey conducted by NIOSH.

Regulations

EPA

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements

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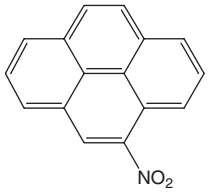
Nitroarenes (Selected)
4-Nitropyrene
CAS No. 57835-92-4

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 malignant tumor formation at multiple tissue sites in multiple species of experimental animals (IARC 1989). Intraperitoneal injections of 4-nitropyrene caused an increased incidence of liver tumors in male mice, lung tumors in male and female mice (Wislocki *et al.* 1986), and mammary adenocarcinomas in female rats (Imaida *et al.* 1991). When administered by subcutaneous injections, 4-nitropyrene induced sarcomas at the injection site, and increased incidences of mammary adenocarcinomas, leukemia, and tumors of the Zymbal gland in female rats (Imaida *et al.* 1995, IARC 1989). In two studies, female rats receiving mammary gland injections of 4-nitropyrene showed an increased incidence of mammary tumors (Imaida *et al.* 1991, El-Bayoumy *et al.* 1993).

No data were available to evaluate the carcinogenicity of 4-nitropyrene in humans.

Additional Information Relevant to Carcinogenicity

Although not as reactive or potent as some of the mononitro- or dinitropyrenes, 4-nitropyrene is genotoxic in bacterial cells and induces cell transformation in BALB cells *in vitro*. Metabolic pathways for 4-nitropyrene, leading to mutagenic and likely DNA adducts, have also been described (IARC 1989).

No data were available that would suggest that the mechanisms thought to account for tumor induction by 4-nitropyrene in experimental animals would not also operate in humans.

Properties

4-Nitropyrene occurs as slender orange needles. It has a melting point of 190°C to 192°C (IARC 1989). When heated to decomposition, 4-nitropyrene emits toxic fumes of nitrogen oxides.

Use

4-Nitropyrene is used only as a laboratory chemical. There is no evidence that 4-nitropyrene has ever been used for commercial applications (IARC 1989).

Production

No evidence has been found that 4-nitropyrene has been produced for other than laboratory use (IARC 1989). One U.S. producer (SRI 1992) and one U.S. supplier (Chem Sources 2001) were identified. No data on imports or exports of 4-nitropyrene were available.

Exposure

The primary route of potential human exposure to 4-nitropyrene is inhalation. Low concentrations of 4-nitropyrene were found in ambient airborne particulates in one study. Prior to 1980, some carbon black samples, known to be used in photocopy machines, were found to contain considerable quantities of nitropyrenes (IARC 1989). 4-Nitropyrene is not listed in the National Occupational Exposure Survey or the National Occupational Hazard Survey conducted by NIOSH.

Regulations and Guidelines

No specific regulations or guidelines relevant to reduction of exposure to 4-nitropyrene were identified.

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