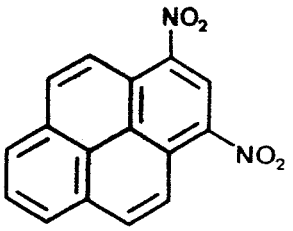
1,3-DINITROPYRENE

1. Chemical and Physical Data

1.1 Synonyms

Chem. Abstr. Services Reg. No.: 75321-20-9
Chem. Abstr. Name: Pyrene, 1,3-dinitro-
IUPAC Systematic Name: 1,3-Dinitropyrene

1.2 Structural and molecular formulae and molecular weight



$C_{16}H_8N_2O_4$ Mol. wt: 292.3

1.3 Chemical and physical properties of the pure substance

(*a*) *Description*: Light-brown needles, recrystallized from benzene and methanol (Buckingham, 1985); orange crystalline solid (Chemsyn Science Laboratories, 1988)

(*b*) *Melting-point*: 274–276°C (Buckingham, 1985); 297–298°C (Chemsyn Science Laboratories, 1988)

(*c*) *Spectroscopy data*: Ultra-violet (Paputa-Peck *et al.*, 1983), infra-red (Hashimoto & Shudo, 1984), nuclear magnetic resonance (Kaplan, 1981; Paputa-Peck *et al.*, 1983; Hashimoto & Shudo, 1984) and mass (Schuetzle & Jensen, 1985) spectral data have been reported.

(*d*) *Solubility*: Moderately soluble in toluene (Chemsyn Science Laboratories, 1988)

1.4 Technical products and impurities

1,3-Dinitropyrene is available for research purposes at ≥99% purity (Aldrich Chemical Co., 1988; Chemsyn Science Laboratories, 1988). It is also available in ^{14}C- or ^{3}H-labelled form at ≥98% radiochemical purity (Chemsyn Science Laboratories, 1988).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

Mixtures of 1,3-, 1,6- and 1,8-dinitropyrenes are produced by the nitration of pyrene, and 1,3-dinitropyrene has been isolated and purified from such preparations (Yoshikura *et al.*, 1985). No evidence was found that it has been produced in commercial quantities or used for other than laboratory applications.

2.2 Occurrence

(*a*) *Engine exhaust*

Levels of 1,3-dinitropyrene in exhaust particulate emissions from mobile sources and in the extracts from these particles are given in Table 1.

Table 1. 1,3-Dinitropyrene levels in diesel exhaust particles and their extracts

Sample[a]	Concentration (mg/kg particulate matter)	Reference
HDD (mining), 100% load, 1200 rpm	0.52	Draper (1986)
HDD (mining), 75% load, 1800 rpm	1.6	Draper (1986)
Diesel emissions (LDD)	0.3	Salmeen *et al.* (1984)
Diesel emissions (LDD)	0.6	Nishioka *et al.* (1982)
Diesel emissions (LDD)	<0.5	Schuetzle (1983)
Diesel emissions (LDD)	≤0.005	Gibson (1983)

[a]HDD, heavy-duty diesel; LDD, light-duty diesel

(*b*) *Other occurrence*

Small amounts of dinitropyrenes are generated by kerosene heaters, which are used extensively in Japan for heating residences and offices (Tokiwa *et al.*, 1985). Such open, oil-burning space heaters were found to emit dinitropyrenes at a rate of 0.2 ng/h after only 1 h of operation; 1,3-dinitropyrene was found at 0.53 ± 0.59 mg/kg particulate extract, accounting for 2.9% of the mutagenicity of the fraction. Gas and liquefied petroleum gas

(LPG) burners, widely used for home heating and cooking, also produced detectable amounts of dinitropyrenes. A level of 0.6 mg/kg particulate extract of 1,3-dinitropyrene was found in emissions from one gas burner, representing 7.9% of the mutagenic activity. The authors suggested that dinitropyrenes result from the incomplete combustion of fuel in the presence of at least a few micrograms per cuber metre of nitrogen dioxide.

According to Takayama *et al.* (1985) and Pitts (1987), several dinitropyrenes have been detected in respirable particles from ambient atmospheric samples. Tanabe *et al.* (1986) measured 1,3-dinitropyrene at up to 4.7 pg/m^3 air and up to 56.2 ng/g particulate matter in the ambient atmosphere in Tokyo, Japan. Gibson (1986) found no 1,3-dinitropyrene in the ambient air at six sites in the USA, under various conditions; the detection limit was 0.001 μg/g particulate matter.

Toners for use in photocopy machines have been produced in quantity since the late 1950s and have seen widespread use. 'Long-flow' furnace black was first used in photocopy toners in 1967; its manufacture involved an oxidation whereby some nitration also occurred. Subsequent changes in the production technique reduced the total extractable nitropyrene content from an uncontrolled level of 5–100 mg/kg to below 0.3 mg/kg (Rosenkranz *et al.*, 1980; Sanders, 1981; Butler *et al.*, 1983), and toners produced from this carbon black since 1980 have not been found to contain detectable levels of mutagenicity or, hence, nitropyrenes (Rosenkranz *et al.*, 1980; Butler *et al.*, 1983).

A pre-1979 carbon black sample was reported to contain 6.3 mg/kg 1,3-dinitropyrene (Sanders, 1981); and a formerly available commercial carbon black was also found to contain this compound (Ramdahl & Urdal, 1982). A sample made in 1980 contained 0.07 mg/kg 1,3-dinitropyrene (Giammarise *et al.*, 1982).

2.3 Analysis

See the monograph on 1-nitropyrene.

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals[1]

(a) Oral administration

Rat: A group of 36 female weanling CD rats received oral intubations of 10 μmol-[3 mg]/kg bw 1,3-dinitropyrene (purity, >99%) dissolved in dimethyl sulfoxide (DMSO; 1.7 μmol[0.5 mg]/ml DMSO) three times per week for four weeks (average total dose, 16 μmol[4.7 mg]/rat) and were observed for 76–78 weeks (King, 1988). A vehicle control group

[1]The Working Group was aware of a study in progress in mice by single subcutaneous injection (IARC, 1988).

of 36 animals received DMSO only. Average survival times of treated and control animals were 527 and 517 days, respectively. Three rats (9%) administered 1,3-dinitropyrene and none of the controls developed leukaemia. Mammary tumours (11 adenocarcinomas and 7 fibroadenomas) were found in 12/35 treated animals, but their incidence did not differ from that observed in vehicle controls (6 and 13 in 12/35). [The Working Group noted the short duration of both treatment and observation and that, in parallel studies, positive results were obtained with 1,6- and 1,8-dinitropyrene.]

(*b*) *Subcutaneous administration*

Mouse: A group of 20 male BALB/c mice, six weeks old, received subcutaneous injections of 0.05 mg 1,3-dinitropyrene (purity, >99.9%) dissolved in 0.2 ml DMSO once a week for 20 weeks (total dose, 1 mg; Otofuji *et al.*, 1987). A positive control group of 20 males received injections of 0.05 mg benzo[*a*]pyrene; a further 20 mice served as untreated controls. Animals were observed for 60 weeks or until moribund. The first subcutaneous tumour in the benzo[*a*]pyrene-treated group was seen in week 21, and all 16 mice surviving beyond this time developed tumours at the injection site which were diagnosed histologically as malignant fibrous histiocytomas [a term used as a specific diagnosis for some subcutaneous and intraperitoneal sarcomas]. No subcutaneous tumour was found in 1,3-dinitropyrene-treated or untreated controls up to 60 weeks. Some tumours developed in the lungs, liver and spleen of 1,3-dinitropyrene-treated animals, but the incidence was not statistically different from those in the positive or DMSO controls. [The Working Group noted the small number of animals used and the relatively short observation period.]

Rat: Ten male Fischer 344/DuCrj rats, six weeks old, received subcutaneous injections of 0.2 mg 1,3-dinitropyrene ([purity unspecified] impurities: 0.6% 1,6-dinitropyrene, <0.05% other nitropyrenes) dissolved in 0.2 ml DMSO twice a week for ten weeks (total dose, 4 mg; Ohgaki *et al.*, 1984). A control group of 20 rats received injections of 0.2 ml DMSO only. The animals were killed between days 169 and 347. Subcutaneous sarcomas developed at the site of injection in all treated rats between days 119 and 320. No 'tumorous' change was observed in other organs of the treated rats, and no tumour developed among control animals. [The Working Group noted the possible influence of the contamination with 1,6-dinitropyrene.]

A group of 43 female newborn CD rats received subcutaneous injections of 1,3-dinitropyrene (purity, >99%; total dose, 6.3 μmol [1.9 mg]) dissolved in DMSO (1.7 μmol[0.5 mg]/ml DMSO) into the suprascapular region once a week for eight weeks (King, 1988). A group of 40 animals injected with DMSO alone served as controls. The average length of survival was 468 days for treated animals and 495 days for controls. At the time of sacrifice, 67 weeks after the first treatment, 5/43 treated rats had developed malignant fibrous histiocytomas at the site of injection; no tumour of this type was found among vehicle controls ($p < 0.05$). Mammary tumours (six adenocarcinomas and three fibroadenomas) were observed in 9/43 treated animals and in 8/37 control animals (one adenocarcinoma, six fibroadenomas).

(*c*) *Intraperitoneal administration*

Mouse: Groups of 90 or 100 male and female newborn CD-1 mice received three intraperitoneal injections of 1,3-dinitropyrene (total dose, 200 nmol [58.5 μg]; purity, >99%) in 10, 20 and 40 μl DMSO on days 1, 8 and 15 after birth; a total dose of 560 nmol [140 μg] benzo[*a*]pyrene (purity, >99%); or three injections of DMSO only (Wislocki *et al.*, 1986). Treatment of a second vehicle control group was begun ten weeks after that of the other groups. At 25–27 days, when the mice were weaned, 30 males and 39 females in the treated group, 37 males and 27 females in the positive control group, and 28 and 31 males and 45 and 34 females in the two vehicle control groups were still alive. All remaining mice were killed after one year. In the group injected with 1,3-dinitropyrene, 6/30 male mice developed liver adenomas; this incidence was not significantly greater than that in the vehicle controls. No increase in the incidences of lung adenomas or malignant lymphomas was observed in males or females as compared to DMSO-treated animals. Benzo[*a*]pyrene induced liver tumours (adenomas and carcinomas) in 18/37 males and in 0/27 females, and the numbers of animals with lung adenomas (males, 13/37; females, 13/27) were significantly higher than those in DMSO controls. Malignant lymphomas were seen in 2/37 males and 4/27 females treated with benzo[*a*]pyrene. The numbers of animals with tumours in the two groups treated with DMSO only were 2/28 and 5/45 males with liver adenomas, 1/28 male with a lung adenoma and 4/45 with lung adenomas and carcinomas; only 2/34 females in the second vehicle control group had lung tumours. [The Working Group noted the short duration of the study.]

Rat: A group of 36 female weanling CD rats received intraperitoneal injections of 10 μmol[3 mg]/kg bw 1,3-dinitropyrene (purity, >99%) dissolved in DMSO (1.7 μmol[0.5 mg]/ml DMSO) three times per week for four weeks (total dose, 16 μmol[4.7 mg]/rat); 36 control animals were treated with DMSO only (King, 1988). Animals were sacrificed when moribund or after 76–78 weeks. At this time, malignant fibrous histiocytomas were found in the peritoneal cavity of two treated rats, and two animals had leukaemia. Neither malignancy developed in 31 surviving controls. Mammary tumours were observed in 19/36 treated rats (9 adenocarcinomas and 12 fibroadenomas) and in 7/31 controls (3 and 5, respectively); the difference in the total number of tumours was statistically significant ($p < 0.05$). [The Working Group noted the high and variable spontaneous incidence of mammary tumours seen in these studies.]

3.2 Other relevant data

(*a*) *Experimental systems*

(i) *Absorption, distribution, excretion and metabolism*

Under an argon atmosphere, rat and dog liver cytosol catalysed the reduction of 1,3-dinitropyrene to 1-amino-3-nitropyrene, 1-nitro-3-nitrosopyrene and 1,3-diaminopyrene. During this reduction, metabolites were formed that bound to exogenous DNA. When acetyl coenzyme A was added to the rat liver cytosolic incubations, 1-acetylamino-3-nitropyrene was also detected as a metabolite, and the extent of binding to DNA was

increased 19-fold (Djurić *et al.*, 1985). Subsequent studies showed that *Salmonella typhimurium* TA98 and rat liver microsomes obtained from a 105 000 *g* supernatant also reduced 1,3-dinitropyrene to 1-nitro-3-nitrosopyrene and 1-amino-3-nitropyrene (Djurić *et al.*, 1986).

1-Amino-3-nitropyrene and 1,3-diaminopyrene were detected as metabolites in rat mammary gland cytosol incubated with 1,3-dinitropyrene under anaerobic conditions. When incubations were conducted in the presence of acetyl coenzyme A, binding to exogenous tRNA occurred. Metabolism was not detected in intact rat mammary gland cells (King *et al.*, 1986; Imaida *et al.*, 1988).

Hsieh *et al.* (1986) used ^{32}P-postlabelling to detect a low level of DNA adduct formation (fewer than five adducts per 10^6 nucleotides) in C3H 10T1/2 mouse embryo fibroblasts incubated with 1,3-dinitropyrene.

(ii) *Toxic effects*

Intraperitoneal administration of 1,3-dinitropyrene to young male Sprague-Dawley rats (three times at 2.5 mg/kg bw) resulted in a four-fold increase in 1-nitropyrene reductase activity in liver microsomes over that in controls (Chou *et al.*, 1987).

(iii) *Genetic and related effects*

The genetic and related effects of nitroarenes and of their metabolites have been reviewed (Rosenkranz & Mermelstein, 1983; Beland *et al.*, 1985; Rosenkranz & Mermelstein, 1985; Tokiwa & Ohnishi, 1986).

1,3-Dinitropyrene (0.0015 μg/ml) induced DNA damage in *Salmonella typhimurium* (Nakamura *et al.*, 1987) and preferentially inhibited the growth of DNA repair-deficient *Bacillus subtilis* (Horikawa *et al.*, 1986 (0.03–1.0 μg/disc); Tokiwa *et al.*, 1986 (0.1 μg/disc)). It was mutagenic to *Escherichia coli* WP2 *uvrA* pKM101 (McCoy *et al.*, 1985a) and to *S. typhimurium* TA96, TA97, TA98, TA100, TA102, TA104, TA1537 and TA1538 (Rosenkranz *et al.*, 1980; Löfroth, 1981; Mermelstein *et al.*, 1981; Pederson & Siak, 1981; Morotomi & Watanabe, 1984; McCoy *et al.*, 1985b; Rosenkranz *et al.*, 1985; Tokiwa *et al.*, 1985).

1,3-Dinitropyrene (up to 500 μg/ml) did not induce gene conversion in the yeast *Saccharomyces cerevisiae* D4 (McCoy *et al.*, 1983).

It induced marginal DNA damage in primary mouse hepatocytes, as measured by alkaline elution, at 5–20 μM (Møller & Thorgeirsson, 1985). It induced unscheduled DNA synthesis in rat and mouse hepatocytes at $1.1 \times 10^{-5} - 1.1 \times 10^{-2}$ mg/ml (Mori *et al.*, 1987). 1,3-Dinitropyrene (0.5–2.0 μg/ml) induced the synthesis of polyoma virus DNA in polyoma virus-transformed rat fibroblasts (Lambert & Weinstein, 1987).

1,3-Dinitropyrene induced unscheduled DNA synthesis in cultured human hepatoma-derived HepG2 cells (Eddy *et al.*, 1986). As reported in an abstract, it induced unscheduled DNA synthesis in human hepatocytes (Yoshimi *et al.*, 1987).

1,3-Dinitropyrene (0.1–10 μg/ml) induced mutation to diphtheria toxin resistance in cultured Chinese hamster lung fibroblasts (Nakayasu *et al.*, 1982) and to ouabain resistance in Chinese hamster V79 cells (1–10 μg/ml; Takayama *et al.*, 1983; Katoh *et al.*, 1984). It also

marginally induced mutation to 6-thioguanine resistance in Chinese hamster CHO cells in the absence of an exogenous metabolic system (0.2–2 μg/ml) but was unequivocally active at 2 μg/ml in the presence of activation (Li & Dutcher, 1983).

1,3-Dinitropyrene induced mutations at the *hprt* locus of cultured human hepatoma-derived HepG2 cells (Eddy *et al.*, 1986).

As reported in an abstract, 1,3-dinitropyrene (2 μg/ml) induced chromosomal aberrations in cultured Chinese hamster lung fibroblasts in the absence of an exogenous metabolic system (Matsuoka *et al.*, 1987). As reported in an abstract, no transformation activity was observed when 1,3-dinitropyrene was tested at concentrations of up to 250 μg/ml in BALB/c 3T3 cells (Tu *et al.*, 1982).

(*b*) *Humans*

No data were available to the Working Group.

3.3 Epidemiological studies and case reports of carcinogenicity in humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Exposure data

1,3-Dinitropyrene has been detected in some carbon blacks and in particulate emissions from diesel engines, kerosene heaters and gas burners. It has been found at low concentrations in ambient air.

4.2 Experimental data

1,3-Dinitropyrene was tested for carcinogenicity in single experiments in rats by oral administration, in mice, rats and newborn rats by subcutaneous injection and in newborn mice and in weanling rats by intraperitoneal injection. It was carcinogenic to rats, producing sarcomas at the site of its subcutaneous injection. The tests by oral and intraperitoneal routes in rats and by subcutaneous and intraperitoneal injection in mice were inadequate for evaluation.

4.3 Human data

No data were available to the Working Group.

4.4 Other relevant data

Metabolism of 1,3-dinitropyrene led to DNA binding *in vitro*. 1,3-Dinitropyrene caused DNA damage and mutation in cultured rodent and human cells and in bacteria. It did not cause gene conversion in yeast.

4.5 Evaluation[1]

There is *limited evidence* for the carcinogenicity in experimental animals of 1,3-dinitropyrene.

No data were available from studies in humans on the carcinogenicity of 1,3-dinitropyrene.

Overall evaluation

1,3-Dinitropyrene *is not classifiable as to its carcinogenicity to humans (Group 3).*

5. References

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[1]For definitions of the italicized terms, see Preamble, pp. 25–28.

Summary table of genetic and related effects of 1,3-dinitropyrene

Nonmammalian systems													Mammalian systems																									
Prokaryotes		Lower eukaryotes				Plants			Insects				*In vitro*																*In vivo*									
													Animal cells								Human cells								Animals							Humans				
D	G	D	R	G	A	D	G	C	R	G	C	A	D	G	S	M	C	A	T	I	D	G	S	M	C	A	T	I	D	G	S	M	C	DL	A	D	S	M	C	A
+	+		−[1]										+	+							+[1]	+[1]																		

A, aneuploidy; C, chromosomal aberrations; D, DNA damage; DL, dominant lethal mutation; G, gene mutation; I, inhibition of intercellular communication; M, micronuclei; R, mitotic recombination and gene conversion; S, sister chromatid exchange; T, cell transformation

In completing the table, the following symbols indicate the consensus of the Working Group with regard to the results for each endpoint:

\+ considered to be positive for the specific endpoint and level of biological complexity

+[1] considered to be positive, but only one valid study was available to the Working Group

−[1] considered to be negative, but only one valid study was available to the Working Group

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