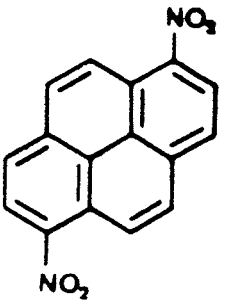
# 1,6-DINITROPYRENE

## 1. Chemical and Physical Data

### 1.1 Synonyms

*Chem. Abstr. Services Reg. No.*: 42397-64-8
*Chem. Abstr. Name*: Pyrene, 1,6-dinitro-
*IUPAC Systematic Name*: 1,6-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); yellow crystalline solid (Chemsyn Science Laboratories, 1988)

(*b*) *Melting-point*: >300°C (Buckingham, 1985); 310°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

1,6-Dinitropyrene is available for research purposes at 98% (Aldrich Chemical Co., 1988) or ≥99% purity (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

(*a*) *Production*

Mixtures of 1,3-, 1,6- and 1,8-dinitropyrenes are produced by the nitration of pyrene, and 1,6-dinitropyrene has been isolated and purified from such preparations (Yoshikura *et al.*, 1985). The Katsura Chemical Co., Tokyo, Japan, synthesized >99.9% pure 1,6-dinitropyrene for Takayama *et al.* (1985), according to the method of Hashimoto and Shudo (1984).

(*b*) *Use*

No evidence was found that 1,6-dinitropyrene has been used for other than laboratory applications.

### 2.2 Occurrence

(*a*) *Engine exhaust*

1,6-Dinitropyrene has been found at levels of 0.81 mg/kg (Manabe *et al.*, 1985) and 1.2 mg/kg (Nakagawa *et al.*, 1983) in extracts of particles from the exhaust of heavy-duty diesel engines, and at 0.4 ± 0.2 mg/kg extract (Salmeen *et al.*, 1984), 0.6 mg/kg extract (Nishioka *et al.*, 1982) and 0.033–0.034 mg/kg particles (Gibson, 1983) from the exhaust of light-duty diesel engines.

(*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; a mixture of 1,6- and 1,8-dinitropyrenes was found at 3.25 ± 0.63 mg/kg particulate extract, accounting for 13% of the mutagenic activity of the sample. Gas and liquefied petroleum gas (LPG) burners, widely used for home heating and cooking, also produced detectable amounts of dinitropyrenes: 1.88 mg/kg extract (36.8% of mutagenicity) and 0.88 mg/kg extract (25.2% of mutagenicity), respectively. The authors suggested that dinitropyrenes result from the incomplete combustion of fuel in the presence of at least a few micrograms per cubic 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. Gibson (1986) reported higher amounts in heavy industrialized areas than in nonindustrialized urban and suburban sites. Levels of 1,6-dinitropyrene in samples of airborne particulates are given in Table 1.

**Table 1. 1,6-Dinitropyrene levels in atmospheric particulates**

| Sample source | Concentration | | Reference |
|---|---|---|---|
| | Particulate extract (mg/kg) | Atmosphere (pg/m³) | |
| Tokyo, Japan | 0.0047–0.105 | 0.33–8.74 | Tanabe *et al.* (1986) |
| Bermuda (remote) | | | Gibson (1986) |
| Summer | 0.0081 | 0.15[a] | |
| Winter | 0.0083 | 0.12[a] | |
| Delaware, USA (rural) | | | Gibson (1986) |
| Summer | 0.0049 | 0.12[a] | |
| Warren, MI, USA (suburban) | | | Gibson (1986) |
| Winter | <0.006 | 0.15[a] | |
| Summer | 0.0046 | 0.30[a] | |
| Detroit, MI, USA (urban) Summer | 0.0036 | 0.48[a] | Gibson (1986) |
| River Rouge, MI, USA (industrial) | | | Gibson (1986) |
| Summer | 0.046 | 4.44[a] | |
| Dearborn, MI, USA (industrial) | | | Gibson (1986) |
| Summer | 0.041 | 7.50[a] | |
| Southeast, MI, USA | | | Siak *et al.* (1985) |
| Summer | 0.31 (mean) | 0.026 (mean) | |
| Santiago, Chile (urban) | 0.2 | – | Tokiwa *et al.* (1983) |

[a]Calculated by the Working Group

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).

Some carbon black samples have also been found to contain 1,6-dinitropyrene: 21 mg/kg in a pre-1979 aftertreated carbon black (Sanders, 1981) and in a commercial sample (Ramdahl & Urdal, 1982). A sample made in 1980 was found to contain 0.13 mg/kg 1,6-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 1,6-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 of 36 animals received DMSO only. Two rats treated with 1,6-dinitropyrene and none of the controls developed leukaemia. Mammary tumours were found in 17/36 treated (19 adenocarcinomas and 11 fibroadenomas) and in 12/35 control rats (6 adenocarcinomas and 13 fibroadenomas); the difference between the groups was not statistically significant. [The Working Group noted the short duration of both treatment and observation.]

(*b*) *Intratracheal instillation*

*Hamster*: A group of ten male and ten female Syrian golden hamsters, ten weeks old, received intratracheal instillations of 0.5 mg 1,6-nitropyrene (purity, >99.9%) suspended in 0.2 ml saline once a week for 26 weeks (total dose, 13 mg; Takayama *et al.*, 1985). A group of ten males and ten females received instillations of saline only and served as controls. The experiment was terminated at 11 months. Lung adenocarcinomas developed in ten males and nine females treated with 1,6-nitropyrene in weeks 20–48; 65% had multiple tumour nodules. In addition, myeloid leukaemia developed in six males and six females. No such tumour was detected among controls.

(*c*) *Intrapulmonary administration*

*Rat*: A group of 28 male Fischer 344/DuCrj rats, 10–11 weeks old, received a single injection of 0.05 ml beeswax-tricaprylin containing 0.15 mg 1,6-dinitropyrene (purity,

[1]The Working Group was aware of studies in progress in rats by single intrapleural instillation and in mice by single subcutaneous injection (IARC, 1988).

>99.9%) directly into the lower third of the left lung after left lateral thoracotomy (Maeda *et al.*, 1986). A group of 19 rats received a single injection of 0.05 ml beeswax-tricaprylin containing 0.5 mg 3-methylcholanthrene [purity unspecified], and another group of 31 rats received an injection of beeswax-tricaprylin only. Animals were observed for 72 weeks after treatment, at which time the experiment was terminated. Of the 1,6-dinitropyrene-treated rats, 21/28 (75%) developed squamous-cell carcinomas and 2/28 developed undifferentiated carcinomas. Squamous-cell carcinomas were induced in all 19 rats treated with 3-methylcholanthrene earlier than in 1,6-dinitropyrene-treated rats. No squamous-cell carcinoma was observed in the control group ($p < 0.005$). Distant metastases of induced tumours were observed in four 1,6-dinitropyrene-treated and one 3-methylcholanthrene-treated rats. The incidence of Leydig-cell tumours of the testis was significantly lower in 1,6-dinitropyrene- and 3-methylcholanthrene-treated rats than in the controls ($p < 0.05$). The incidences of other tumours did not differ among the groups.

(*d*) *Subcutaneous administration*

*Mouse*: A group of 20 male BALB/c mice, six weeks old, received subcutaneous injections of 0.1 mg 1,6-dinitropyrene (purity, >99.9%) dissolved in 0.2 ml DMSO once a week for 20 weeks (total dose, 2 mg; Tokiwa *et al.*, 1984). A further group of 20 mice treated with 0.2 ml DMSO only served as vehicle controls. Animals were observed for 60 weeks or, for mice with tumours at the site of injection, until moribund. The first tumour in the 1,6-dinitropyrene-treated group was seen on day 112; 45 weeks after the first treatment, 10/20 mice had 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 detected in vehicle controls ($p < 0.002$). Lung tumours were found in 6/20 treated and 7/20 control mice.

*Rat*: Ten male Fischer 344/DuCrj rats, six weeks old, received subcutaneous injections of 0.2 mg 1,6-dinitropyrene ([purity unspecified] impurities: <0.05% each of 1,3-dinitropyrene, 1,8-dinitropyrene, 1,3,6-trinitropyrene and 1,3,6,8-tetranitropyrene) dissolved in 0.2 ml DMSO twice a week for ten weeks (total dose, 4 mg; Ohgaki *et al.*, 1985). A control group of 20 rats received injections of 0.2 ml DMSO only. Treated animals were killed on day 320 and control rats on day 650. Sarcomas developed at the site of injection in all treated rats between days 103 and 123. No tumour developed at the injection site among control animals, although 16 interstitial-cell tumours of the testis, two C-cell adenomas of the thyroid gland, two pancreatic islet-cell adenomas and one phaeochromocytoma were seen.

A group of 46 female newborn CD rats received subcutaneous injections of 1,6-dinitropyrene (purity, >99%) dissolved in DMSO (1.7 μmol[0.5 mg]/ml DMSO) into the suprascapular region once a week for eight weeks (total dose, 6.3 μmol[1.8 mg]; King, 1988). A group of 40 animals injected with DMSO alone served as controls. The average survival time was 149 days for treated rats and 495 days for controls. Malignant fibrous histiocytomas developed rapidly at the site of injection among treated rats; the first tumour was seen 15 weeks after the initial treatment, and by 18 weeks all rats had developed this

tumour. In addition, nine rats had leukaemia. Vehicle controls developed neither malignancy ($p < 0.0001$ and $p < 0.005$). Mammary tumours (mainly adenocarcinomas) were seen in 5/46 treated rats; 8/40 controls had mammary tumours (mainly fibroadenomas).

(*e*) *Intraperitoneal administration*

*Mouse*: Groups of 90 or 100 male and female newborn CD-1 mice received three intraperitoneal injections of 1,6-dinitropyrene (purity, >99%; total dose, 200 nmol [58.7 μg] 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%) as three injections; 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, 25 males and 29 females in the treated group, 37 males and 37 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 1,6-dinitropyrene, 8/25 male mice developed liver tumours (three with adenomas, five with carcinomas); this incidence was significantly greater than that in the vehicle controls ($p < 0.025$). No increase in the incidences of lung tumours or malignant lymphomas was observed in males or females as compared to DMSO-treated animals. Benzo[*a*]pyrene induced liver tumours in 18/37 males and 0/27 females and lung adenomas in 13/37 males and 13/27 females; the latter incidences were significantly higher than those in DMSO controls ($p < 0.005$). Malignant lymphomas were seen in 2/37 males and 4/27 females treated with benzo[*a*]pyrene. In the two DMSO-treated groups, 2/28 and 5/45 males had liver adenomas and 1/28 and 4/45 had lung tumours, and 0/31 and 0/34 females had liver tumours and 0/31 and 2/34 had lung tumours.

*Rat*: A group of 36 female weanling CD rats received intraperitoneal injections of 10 μmol[3 mg]/kg bw 1,6-dinitropyrene (purity, >99%) dissolved in 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); 36 control animals were treated with DMSO only (King, 1988). Treatment with 1,6-dinitropyrene resulted in some early deaths 12–15 weeks after the initial treatment. Tumours were first identified in a rat autopsied 17 weeks after the first injection. All 23 1,6-dinitropyrene-treated animals that survived longer than 21 weeks had developed malignant fibrous histiocytomas in the peritoneal cavity, but none of the vehicle controls, observed for 76–78 weeks, developed these tumours ($p < 0.0001$). Mammary tumours developed in both groups at approximately the same incidence.

## 3.2 Other relevant data

(*a*) *Experimental systems*

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

In preweanling male CD mice treated with a single intraperitoneal dose of 115 nmol [33.6 μg] [$^3$H]1,6-dinitropyrene, analysis of lung and liver DNA 24 h later indicated the

presence of one major adduct, *N*-(deoxyguanosin-8-yl)-1-amino-6-nitropyrene (Delclos *et al.*, 1987). In male Sprague-Dawley rats treated with an intraperitoneal dose of 200 μg/kg bw [$^3$H]1,6-dinitropyrene, DNA binding was detected in the mammary epithelium, liver, lung, kidney and urinary bladder; *N*-(deoxyguanosin-8-yl)-1-amino-6-nitropyrene was detected in the urinary bladder, liver, kidney and mammary epithelium. Pretreatment of these animals with 1-nitropyrene, which induced nitroreductase, did not affect DNA binding, except in the kidney where it was increased 1.6-fold (Djurić *et al.*, 1988).

Under an argon atmosphere, rat and dog liver cytosol catalysed the reduction of 1,6-dinitropyrene to 1-amino-6-nitropyrene, 1-nitro-6-nitrosopyrene and 1,6-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-6-nitropyrene was also detected as a metabolite, and the extent of binding was increased 24-fold (Djurić *et al.*, 1985). Subsequent studies showed that *Salmonella typhimurium* TA98, rat liver microsomes obtained from a 105 000 *g* supernatant and human liver cytosol also reduced 1,6-dinitropyrene to 1-nitro-6-nitrosopyrene and 1-amino-6-nitropyrene (Djurić *et al.*, 1986, 1988).

1-Nitro-6-nitrosopyrene, 1-amino-6-nitropyrene and 1,6-diaminopyrene were detected as metabolites in rat mammary gland cytosol incubated with 1,6-dinitropyrene under anaerobic conditions. When incubations were conducted in the presence of acetyl coenzyme A, binding to exogenous tRNA occurred. Incubation with intact rat mammary gland cells resulted in the formation of 1-amino-6-nitropyrene (King *et al.*, 1986; Imaida *et al.*, 1988).

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

A Fischer 2408 rat fibroblast cell line, H3, transformed by a temperature-sensitive mutant of polyoma virus, metabolized 1,6-dinitropyrene to several polar products; one major and several minor DNA adducts were formed at the same time (Lambert & Weinstein, 1987).

Incubation of 1,6-dinitropyrene with purified nitroreductases from the anaerobic bacterium, *Bacteroides fragilis*, in the presence of various polynucleotides resulted in preferential binding to the deoxyguanine moiety of poly(dG) nucleic acids, binding to the deoxy adenine moiety poly(dA) being about 75% lower (Kinouchi & Ohnishi, 1986).

(ii) *Toxic effects*

A group of 28 male Fischer 344 rats was given a single injection of 0.15 mg 1,6-dinitropyrene directly into the lower third of the left lung after left lateral thoracotomy. Squamous metaplasia of the lung was seen in two animals and granulomatous lesions containing foreign-body giant cells in three (Maeda *et al.*, 1986).

Intraperitoneal administration of 1,6-dinitropyrene to young male Sprague Dawley rats (three times at 2.5 mg/kg bw) resulted in a 2.5-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).

1,6-Dinitropyrene (0.005 μg/ml) induced DNA damage in *S. typhimurium* (Nakamura *et al.*, 1987) and preferentially inhibited the growth of DNA repair-deficient *Bacillus subtilis* (Horikawa *et al.*, 1986 (0.02–0.06 μg/disc); Tokiwa *et al.*, 1986 (0.04 μg/disc)). It was mutagenic to *Escherichia coli* WP2 *uvrA* pkM101 (Tokiwa *et al.*, 1984; 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; Tokiwa *et al.*, 1981; Nakayasu *et al.*, 1982; Ashby *et al.*, 1983; Morotomi & Watanabe, 1984; Tokiwa *et al.*, 1984; McCoy *et al.*, 1985b; Rosenkranz *et al.*, 1985; Tokiwa *et al.*, 1985; El-Bayoumy & Hecht, 1986; Fifer *et al.*, 1986; Fu *et al.*, 1986).

Conflicting results have been reported concerning the induction by 1,6-dinitropyrene of gene conversion in the yeast, *Saccharomyces cerevisiae*: positive results were reported in strain JDI (Wilcox & Parry, 1981 (1.6–25 μg/ml); Wilcox *et al.*, 1982 (2.9–4.4 ng/ml)) and negative results in strain D4 (McCoy *et al.*, 1983 (up to 500 μg/ml)). It has been suggested that these differences reflect intracellular oxygen levels (Rosenkranz & Mermelstein, 1983).

As determined by alkaline elution, 1,6-dinitropyrene induced a marginal effect on the formation of single-strand DNA breaks in primary mouse hepatocytes at 5–20 μM (Møller & Thorgeirsson, 1985) and in Chinese hamster V79 cells at the only concentration tested, 15 μM (Saito *et al.*, 1984), but not in cultured rat hepatoma cells at up to 10 μM (Møller & Thorgeirsson, 1985). 1,6-Dinitropyrene (15 μM) did not induce DNA-protein cross-links in cultured rat hepatoma cells (Møller & Thorgeirsson, 1985). When tested at 0.5-2 μg/ml, it induced the synthesis of viral DNA in polyoma virus-transformed rat fibroblasts (Lambert & Weinstein, 1987).

1,6-Dinitropyrene induced unscheduled DNA synthesis in mouse (Mori *et al.*, 1987 ($1.0 \times 10^{-5}$–$1.0 \times 10^{-2}$ mg/ml)), rat (Butterworth *et al.*, 1983 (0.00005–0.005 mM); Mori *et al.*, 1987 ($1.0 \times 10^{-5}$–$1.0 \times 10^{-2}$ mg/ml)) and human (Butterworth *et al.*, 1983 (0.00005–0.005 mM); Yoshimi *et al.*, 1987)) hepatocytes, and in rat (Doolittle & Butterworth, 1984 (0.05–0.5 μM)) and human (Sugimura & Takayama, 1983 ($10^{-4}$M); Doolittle *et al.*, 1985 (0.5–5.0 μM)) cultured tracheal or bronchial epithelial cells. It induced unscheduled DNA synthesis in rabbit lung Clara and alveolar type II cells (Haugen *et al.*, 1986 (0.63–10 ng/ml)), but not in human hepatoma-derived HepG2 cells (Eddy *et al.*, 1985, 1986 (up to 2 μg/ml)) or in isolated rat spermatocytes (Working & Butterworth, 1984 (0.05–5 μM)).

1,6-Dinitropyrene (0.05–5 μg/ml) induced mutations at the *hprt* locus of cultured Chinese hamster CHO cells (Li & Dutcher, 1983 (0.2–2 μg/ml); Edgar & Brooker, 1985) and was weakly active at 5–20 μM (Fifer *et al.*, 1986); it did not induce this mutation in human hepatoma-derived HepG2 cells at up to 2 μg/ml (Eddy *et al.*, 1985, 1986). It induced mutation to ouabain resistance (only one dose tested, 0.1 μg/ml) in Chinese hamster V79 cells (Katoh *et al.*, 1984) and to diphtheria toxin resistance (0.1–10 μg/ml; Nakayasu *et al.*, 1982) in cultured Chinese hamster lung fibroblasts.

1,6-Dinitropyrene (0.05–5 μg/ml) induced sister chromatid exchange and chromosomal aberrations in cultured Chinese hamster CHO cells (Edgar & Brooker, 1985). It induced chromosomal aberrations, primarily of the chromatid type, in cultured rat (Wilcox *et al.*, 1982; Danford *et al.*, 1982 (0.01–2.5 μg/ml)) and Chinese hamster liver epithelial cells (Danford *et al.*, 1983 (2 mg/ml)) and in human fibroblasts (Wilcox *et al.*, 1982 (0.02–5.0 μg/ml)). As reported in an abstract, 1,6-dinitropyrene (0.1 μg/ml) induced chromosomal aberrations in cultured Chinese hamster lung fibroblasts (Matsuoka *et al.*, 1987).

Oral administration of 1,6-dinitropyrene to rats (50 mg/kg bw) did not result in the induction of unscheduled DNA synthesis in either hepatocytes (Butterworth *et al.*, 1983) or spermatocytes (Working & Butterworth, 1984).

1,6-Dinitropyrene-induced rat fibrosarcomas contained activated H-*ras* and N-*ras* oncogenes (Ishizaka *et al.*, 1987).

(*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

1,6-Dinitropyrene has been detected in some carbon blacks and in particulate emissions from diesel engines, kerosene heaters and gas burners. It has also been found at low concentrations in ambient air.

### 4.2 Experimental data

1,6-Dinitropyrene was tested for carcinogenicity by intratracheal instillation in hamsters, by intrapulmonary injection in rats, by subcutaneous injection in mice and rats and by intraperitoneal injection in newborn mice and weanling rats. After intratracheal instillation, it induced adenocarcinomas of the lung and leukaemia. After intrapulmonary injection, it induced a high incidence of squamous-cell carcinomas of the lung. After subcutaneous injection, it induced a high incidence of sarcomas at the injection site in weanling and newborn rats and in mice and leukaemia in newborn rats. After intraperitoneal injection, it increased the incidence of liver-cell tumours in male mice and induced sarcomas of the peritoneal cavity in rats. A study by oral administration in rats was inadequate for evaluation.

### 4.3 Human data

No data were available to the Working Group.

### 4.4 Other relevant data

Metabolism of 1,6-dinitropyrene led to DNA adduct formation *in vivo* and *in vitro*. 1,6-Dinitropyrene induced DNA damage and chromosomal aberrations but not mutations in cultured human cells. It induced DNA damage, mutation, sister chromatid exchange and chromosomal aberrations in cultured rodent cells, and DNA damage and mutation in bacteria.

### 4.5 Evaluation[1]

There is *sufficient evidence* for the carcinogenicity in experimental animals of 1,6-dinitropyrene.

No data were available from studies in humans on the carcinogenicity of 1,6-dinitropyrene.

#### Overall evaluation

1,6-Dinitropyrene *is possibly carcinogenic to humans (Group 2B).*

## 5. References

Aldrich Chemical Co. (1988) *Aldrich Catalog/ Handbook of Fine Chemicals 1988*–1989, Milwaukee, WI, p. 633

Ashby, J., Paton, D., Wilcox, P. & Parry, J.M. (1983) Synthesis of 1,6-diaminopyrene from 1,6-dinitropyrene and its S9 dependent mutagenicity to *S. typhimurium*. *Carcinogenesis*, *4*, 787–789

Beland, F.A., Heflich, R.H., Howard, P.C. & Fu, P.P. (1985) The in vitro metabolic activation of nitro polycyclic aromatic hydrocarbons. In: Harvey, R.G., ed., *Polycyclic Hydrocarbons and Carcinogenesis (ACS Symposium Series No. 283)*, Washington DC, American Chemical Society, pp. 371–396

Buckingham, J., ed. (1985) *Dictionary of Organic Compounds*, 5th ed., 3rd Supplement, New York, Chapman & Hall, p. 182 (D-30522)

Butler, M.A., Evans, D.L., Giammarise, A.T., Kiriazides, D.K., Marsh, D., McCoy, E.C., Mermelstein, R., Murphy, C.B. & Rosenkranz, H.S. (1983) Application of *Salmonella* assay to carbon blacks and toners. In: Cooke, M. & Dennis, A.J., eds, *Polynuclear Aromatic Hydrocarbons, 7th International Symposium, Formation, Metabolism and Measurement*, Columbus, OH, Battelle, pp. 225–241

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

## Summary table of genetic and related effects of 1,6-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

? considered to be equivocal or inconclusive (e.g., there were contradictory results from different laboratories; there were confounding exposures; the results were equivocal)

Butterworth, B.E., Earle, L.L., Strom, D., Jirtle, R. & Michalopoulos, G. (1983) Induction of DNA repair in human and rat hepatocytes by 1,6-dinitropyrene. *Mutat. Res., 122*, 73–80

Chemsyn Science Laboratories (1988) *1,6-Dinitropyrene* (*Product Code U1036*), Lenexa, KS, pp. 69–71

Chou, M.W., Wang, B., Von Tungeln, L.S., Beland, F.A. & Fu, P.P. (1987) Induction of rat hepatic cytochromes P-450 by environmental nitropolycyclic aromatic hydrocarbons. *Biochem. Pharmacol., 36*, 2449–2454

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