

## DIESEL AND GASOLINE ENGINE EXHAUSTS AND SOME NITROARENES

VOLUME 105

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 5-12 June 2012

LYON, FRANCE - 2014

IARC MONOGRAPHS  
ON THE EVALUATION  
OF CARCINOGENIC RISKS  
TO HUMANS

# 1,3-DINITROPYRENE

1,3-Dinitropyrene was evaluated by a previous IARC Working Group in 1988 ([IARC, 1989](#)). New data have since become available, and these have been taken into consideration in the present evaluation.

## 1. Exposure Data

### 1.1 Chemical and physical data

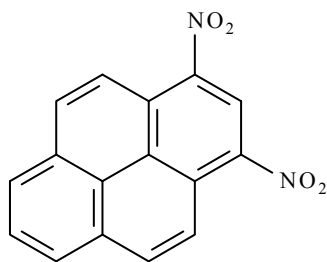
#### 1.1.1 Nomenclature

*Chem. Abstr. Serv. Reg. No.:* 75 321-20-9

*Chem. Abstr. Name:* Pyrene, 1,3-dinitro-

*IUPAC Systematic Name:* 1,3-Dinitropyrene

#### 1.1.2 Structural and molecular formulae and relative molecular mass



$C_{16}H_8N_2O_4$

*Relative molecular mass:* 292.3

#### 1.1.3 Chemical and physical properties of the pure substance

*Description:* Light-brown needles, recrystallized from benzene and methanol ([Buckingham, 1985](#))

*Melting-point:* 274–276 °C ([Buckingham, 1985](#)); 295–297 °C ([Paputa-Peck et al., 1983](#))

*Spectroscopy data:* Ultraviolet ([Paputa-Peck et al., 1983](#)), infrared ([Hashimoto & Shudo, 1984](#)), nuclear magnetic resonance ([Kaplan, 1981](#); [Paputa-Peck et al., 1983](#); [Hashimoto & Shudo, 1984](#)) and mass spectral data ([Schuetzle & Jensen, 1985](#)) have been reported. The National Institute of Standards and Technology Chemistry WebBook provides extensive spectroscopic data ([Linstrom & Wallard, 2011](#)).

*Solubility:* Moderately soluble in toluene ([Chemsyn Science Laboratories, 1988](#))

#### 1.1.4 Technical products and impurities

1,3-Dinitropyrene is available for research purposes at a purity of 99% ([Sigma-Aldrich, 2012](#)). The ChemicalBook web site lists nine companies that supply 1,3-dinitropyrene ([ChemicalBook, 2012](#)).

## 1.2 Analysis

For analytical methods of nitro-polycyclic aromatic hydrocarbons (PAHs) in general, the reader is referred to Section 1.2.2(d) of the

*Monograph on Diesel and Gasoline Engine Exhausts* in this Volume.

A variety of analytical methods have been used to separate and quantify specific dinitropyrenes in environmental samples. [Hayakawa et al. \(1992\)](#) used the reduction of the nitro groups off-line with sodium hydrosulfide followed by separation of the mixture of amino derivatives of nitropyrenes and dinitropyrenes using high-performance liquid chromatography with chemiluminescence detection. In a later modification of this method, nitro-PAHs were separated from extraneous substances using a clean-up column and reduced to their amino derivatives on a platinum/rhodium-coated alumina reducer column. The derivatives were concentrated on a concentrator column and eluted into a separator column, and the components were measured by chemiluminescence induced by a solution of bis(2,3,6-trichlorophenyl)oxalate and hydrogen peroxide ([Hayakawa et al., 2001](#)). [Hutzler et al. \(2011\)](#) reported the high sensitivity and specificity of liquid chromatography with an atmospheric-pressure photoionization source attached to an API 4000 mass spectrometer.

The measurement of dinitropyrene vapour in environmental samples is challenging because of the very low concentrations, which limited some of the earlier studies. [Araki et al. \(2009\)](#) developed an apparatus to collect nitropyrene vapours downstream of a quartz fibre filter in a high-volume sampler at 300 L/min. The specially designed cylindrical vapour collector (8 cm in diameter, 8 cm in length) contained two layers of XAD-4 resin, the first 4 cm deep and the second 2 cm deep, each followed by a 1-cm thick sheet of polyurethane foam. Dinitropyrenes were measured by gas chromatography-mass spectrometry (MS) with an electron ionizing detector.

[Crimmins & Baker \(2006\)](#) achieved high sensitivity using a programmed temperature vapourization method for injecting a large volume of gas into a gas chromatograph with a mass spectrometer as a detector. MS was

performed using negative chemical ionization with methane ionization gas (40 mL/minute) at a temperature of 200 °C. Excellent reproducibility was obtained, with a relative standard deviation of 1.4–3.7% for three dinitropyrene compounds, but the limits of detection of the instrument were relatively high: 0.53 pg for 1,3-dinitropyrene, 2.85 pg for 1,6-dinitropyrene and 1.7 pg for 1,8-dinitropyrene, which were at least one order of magnitude higher than that for 1-nitropyrene (0.17 pg). When the method was applied to the National Institute of Standards and Technology standardized reference materials 1649 and 1650 prepared from samples of diesel engine exhaust, none of the dinitropyrenes could be detected because of matrix effects at the inlet.

### 1.3 Production and use

1,3-Dinitropyrene is produced by the nitration of 1-nitropyrene, and have been isolated and purified from such preparations ([Yoshikura et al., 1985](#)).

No evidence was found that 1,3-dinitropyrene has been produced in commercial quantities or used for purposes other than laboratory applications.

### 1.4 Occurrence

#### 1.4.1 Engine exhaust

The reader is also referred to the *Monographs on Diesel and Gasoline Engine Exhausts and 1-Nitropyrene* in this Volume.

During combustion in diesel and gasoline engines, pyrene is nitrated to form 1-nitropyrene, which is further nitrated to form small amounts of 1,3-, 1,6- and 1,8-dinitropyrene ([Heeb et al., 2008](#)). A variety of tests of diesel engine emissions were performed in the 1980s, which showed a range of 1,3-dinitropyrene concentrations in the particulate matter (PM) of up to 1600 pg/mg ([Table 1.1](#); reviewed in [Fu](#)

**Table 1.1 Levels of 1,3-dinitropyrene in diesel engine exhaust particles and their extracts**

Reference	Vehicle/engine	Concentration of 1,3-DNP (pg/mg particulate matter)
<a href="#">Nishioka et al. (1982)</a>	Passenger cars (LDD)	ND–600 <sup>a</sup>
<a href="#">Gibson (1983)</a>	Diesel cars, 1978–82 (LDD)	≤ 5
<a href="#">Nakagawa et al. (1983)</a>	Idling 6-tonne bus from 1970 (HDD), 1200 rpm	Detected
<a href="#">Schuetzle &amp; Perez (1983)</a>	<i>Heavy-duty vehicle</i>	
	Idle	< 800
	High-speed, no load	600
	High-speed, full load	400
<a href="#">Salmeen et al. (1984)</a>	Passenger cars (LDD)	300 ± 200
<a href="#">Draper (1986)</a>	Commercial mining engine (HDD), 100% load, 1–200 rpm	520
	Commercial mining engine (HDD), 75% load, 1–800 rpm	1600
<a href="#">Hayakawa et al. (1992)</a>	Idling engine (LDD)	81.8 <sup>b</sup>

<sup>a</sup> Range of three different engines

<sup>b</sup> Using a much more sensitive analytical method

DNP, dinitropyrene; HDD, heavy-duty diesel; LDD, light-duty diesel; ND, not detected

**Table 1.2 Mass concentrations in particulate matter from diesel and gasoline engine exhausts from tailpipes in 1992**

	No. of samples	Concentration (pg/mg) <sup>a</sup>			
		1-NP	1,3-DNP	1,6-DNP	1,8-DNP
Gasoline engine, idle	8	444 ± 210	64 ± 44	128 ± 106	102 ± 53
Diesel engine, idle	7	12 600 ± 13 100	67 ± 44	67 ± 47	61 ± 41

<sup>a</sup> Values are means ± standard deviations

DNP, dinitropyrene; NP, nitropyrene

From [Hayakawa et al. \(1992, 1994\)](#)

[& Herreno-Saenz, 1999](#)). The production of dinitropyrenes appears to depend on engine size and operating conditions.

Using a more sensitive method than in earlier studies, [Hayakawa et al. \(1992, 1994\)](#) examined nitroarenes in PM emissions from 15 diesel and gasoline engine vehicles ([Table 1.2](#)). Exhausts from idling diesel and gasoline engines contained approximately the same mass concentration of 1,3-dinitropyrene [64–67 pg/mg]; however, the ratio of the concentrations of 1,3-dinitropyrene to 1-nitropyrene was 14% for gasoline and 0.5% for diesel engine exhaust, which was assumed to be the result of differences in combustion conditions. The diesel engines produced many more particulates, and their total emissions of

1,3-dinitropyrene were therefore much greater. In emissions from mixed traffic, the air concentration ratio of 1,3-dinitropyrene to 1-nitropyrene decreases as the relative number of diesel vehicles increases.

In the past decade, particulate filters have been developed to filter PM from diesel engine exhausts to control emissions. The accumulated soot particles and organic carbon components, including PAHs and nitro-PAHs, that collect on the filters are removed by oxidation, aided by catalytic coatings or catalysts added to the fuel (see Section 1.1 in the *Monograph* on Diesel and Gasoline Engine Exhausts in this Volume).

In a series of laboratory tests, a range of various types of diesel particulate filter was tested

to compare their impact on PAH and nitro-PAH emissions (Heeb *et al.*, 2010). All filters tested, which removed 99% of the particles, also removed most PAH components. However, low-oxidation filters produced 63% more 1-nitropyrene than the amount present in the unfiltered exhaust; although the quantities of dinitropyrenes were not measured, they would also be expected to increase similarly.

Carrara & Niessner (2011) examined the formation of 1-nitropyrene in high- and low-oxidation filters operating at temperatures of 293–573 °K (20–300 °C). The lower temperatures produced more 1-nitropyrene on the filter, with a peak at ~100 °C that declined at higher temperatures. Measurements at 250 °C showed that < 2% of the 1-nitropyrene was on the filter and 47% ± 12% was on the vapour collector (losses of vapour were noted). Although they were not measured in the samples, dinitropyrenes would be expected to be affected similarly.

#### 1.4.2 Environmental occurrence

##### (a) Air

The nitration of pyrene in atmospheric processes leads to the formation of 2- but not 1-nitropyrene, because the oxidants involved differ from those that are present during combustion, which produces 1-nitropyrene (Pitts, 1987). Thus, dinitropyrenes cannot be formed by atmospheric processes.

The earliest reports of 1,3-dinitropyrene in atmospheric air date back to the early 1980s. The presence of dinitropyrenes [not further characterized] in respirable particles from ambient atmospheric samples was inferred from mutagenicity testing of polycyclic organic matter extracts (Pitts, 1987). Tanabe *et al.* (1986) found levels of 1,3-dinitropyrene of up to 4.7 pg/m<sup>3</sup> in the air and up to 56.2 pg/mg in PM 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 Working Group noted that the limit of detection of the analytical method used was 1 pg/mg PM and may have been too high.] Similarly, 1,3-dinitropyrene was not detected in another study in the Michigan area (Siak *et al.*, 1985).

In the early 1990s, Hayakawa and colleagues developed sensitive methods for the detection of nitro- and dinitropyrenes (see Section 1.2) and used them to perform a series of studies on PAHs and nitro-PAHs in Japan, and later in the countries surrounding the Sea of Japan. In a first study of atmospheric air, they determined that 94.3% of the 1,3-, 1,6- and 1,8-dinitropyrene, and 99.8% of the 1-nitropyrene in the air came from diesel engine emissions (Murahashi *et al.*, 1995). They later compared the atmospheric formation of nitropyrenes from highway emission sources (Hayakawa *et al.*, 2002). Samples were taken at three sites at varying distances from a highway (two urban and one suburban) in Kanazawa, Japan, using a high-volume sampler to collect total suspended particulates; 24-hour samples were collected for 6 consecutive days during each of the four seasons in 1989–96 (total, 84 samples; Table 1.3). Air concentrations of nitropyrenes rapidly declined with distance from the highway. A characteristic pattern of similar air concentrations of dinitropyrene isomers, within a factor of two, was observed; also, concentrations of dinitropyrenes were two orders of magnitude lower (approximately 0.5%) those of the parent compound, 1-nitropyrene.

A short series of five, 24-hour roadside samples were collected in Kanazawa, Japan in 2007 (Araki *et al.*, 2009). The concentration pattern was similar to that in earlier samples (Table 1.3), and the levels of dinitropyrenes in PM were less than 1% of those of 1-nitropyrene. Compared with the earlier samples, no evidence of a decline over time was found. The authors also examined the vapour-PM partitioning of the nitro-PAHs using a newly designed, high-volume vapour collector. No dinitropyrenes

**Table 1.3 Airborne concentrations of 1-nitropyrene and isomers of dinitropyrene**

Reference	Location, site	No. of samples	Airborne concentrations (pg/mg <sup>3</sup> ) <sup>a,b</sup>			
			1-NP	1,3-DNP	1,6-DNP	1,8-DNP
<a href="#">Hayakawa et al. (2002)</a>	<i>Kanazawa, Japan, 1989–96</i>					
	2 m from an urban roadside	84	170 (35–400)	0.61 (0.29–1.8)	1.1 (0.41–2.6)	1.0 (0.32–2.9)
	10 m from an urban roadside	84		0.2 (0.06–0.64)	0.24 (0.05–0.67)	0.23 (0.03–0.73)
	Suburban area not near roads	84	54 (7.4–150) 5.4 (1.0–16)	0.023 (0.006–0.06)	0.025 (0.008–0.04)	0.025 (0.003–0.06)
<a href="#">Araki et al. (2009)</a>	<i>Kanazawa, Japan, 2007</i>					
	Urban roadside in winter	5	18.8 ± 7.41	0.12 ± 0.06	0.17 ± 0.088	[0.61] <sup>c</sup> ± 0.17
<a href="#">Schauer et al. (2004)</a>	<i>Munich area, Germany</i>					
	Urban site, September–23 October 2002	10	22 ± 6	16 ± 5	4.8 ± 3.4	ND
	Rural site, 28 August–15 September 2002	5	6.6 ± 3.9	4.0 ± 1.6	3.0 ± 1.8	ND
	Alpine site, 30 October–26 November 2002	9	2.2 ± 0.7	0.1 ± 0.1	0.6 ± 0.5	ND

<sup>a</sup> Values are means (range) or means ± standard deviations

<sup>b</sup> Reported values for 1,3-, 1,6- and 1,8-DNP in fmol/m<sup>3</sup> were multiplied by 0.292 pg/fmol and those of 1-NP were multiplied by 0.247 pg/fmol for the conversion to pg/m<sup>3</sup>.

<sup>c</sup> The value reported in the article (21 fmol/m<sup>3</sup>) conflicts with the reported range of 1.3–2.9 fmol/m<sup>3</sup>. The Working Group therefore assumed that the correct value is 2.1 fmol/m<sup>3</sup>, or 0.61 pg/m<sup>3</sup>.

DNP, dinitropyrene; m, metres; ND, not detected; NP, nitropyrene

**Table 1.4 Mass concentrations of 1-nitropyrene and three isomers of dinitropyrene in airborne particulate matter**

Reference	Location, study period	No. of samples	Concentration (pg/mg) <sup>a</sup>			
			1-NP	1,3-DNP	1,6-DNP	1,8-DNP
<a href="#">Kakimoto et al. (2002)</a>	Kitakyushu, Japan Industrial city centre, 1997	20	230 ± 96	4.1 ± 0.18	7.9 ± 6.5	5.9 ± 1.8
	Sapporo, Japan Roadside of highway, 1997	20	2700 ± 1600	11 ± 9.4	10 ± 8.8	16 ± 9.4
	Tokyo, Japan Roadside of highway, 1997	20	940 ± 490	4.7 ± 0.85	5.0 ± 3.2	8.2 ± 3.2
<a href="#">Albinet et al. (2006)</a>	Sollières, France Rural site, winter 2002–03	13	10.6 (2.7–28.9)	3.7 (0.0–27.7)	1.3 (0.0–4.4)	9.5 (0.0–27.2)

<sup>a</sup> Values are means ± standard deviations (range)  
DNP, dinitropyrene; NP, nitropyrene

were detected in the gas phase samples, whereas ~10% of the 1-nitropyrene was present in the gas phase. Nitro-PAHs were generally less volatile than their parent compounds.

1-Nitropyrene and related dinitropyrene isomers are not formed in the atmosphere, but can be removed by atmospheric processes such as photo-degradation; as a result, their concentration declines more rapidly than through dilution and dispersion alone ([Morel et al., 2006](#)). [Kakimoto et al. \(2002\)](#) noted that the levels of 1-nitropyrene and dinitropyrene in airborne PM declined more rapidly with distance than the un-nitrated PAHs, which implies an active removal process. Also, the levels of dinitropyrenes in the PM collected close to the roadside in Sapporo and Tokyo, Japan, were 0.2–0.9% of those of 1-nitropyrene ([Table 1.4](#)), whereas at a distance from the roadside, in Kitakyushu, Japan, levels of dinitropyrenes were 1.7–34% of those of the 1-nitropyrene, which indicates that 1-nitropyrene is removed more rapidly than dinitropyrenes.

To link the levels to the sources, the authors also recorded the percentage of diesel-powered vehicles registered in each city and the volume of kerosene purchased per home. Levels of each dinitropyrene and 1-nitropyrene in PM increased with the percentage of diesel-powered

vehicles registered in the cities. Atmospheric concentrations of 1-nitropyrene and of each dinitropyrene were 1.3–4.3-fold higher in the winter (with the exception of 1,3-dinitropyrene in Kitakyushu), but most differences were not significant ([Table 1.4](#)). Sapporo had the highest percentage of diesel vehicles compared with Kitakyushu and Tokyo (38.5% versus 20% and 26%, respectively) and the highest volume of kerosene used per home (1343 L versus 224 L and 85 L, respectively) ([Kakimoto et al., 2002](#)). This site also had the lowest dinitropyrene:1-nitropyrene ratio (0.011 versus 0.06 and 0.017, respectively). The differences in the number of vehicles and the amount of kerosene used may account in part for the variations between the three cities. Consistently, Sapporo had the highest airborne levels of each of the dinitropyrene isomers, but the differences were much smaller than those for 1-nitropyrene.

At a rural site in France, the levels of dinitropyrenes isomers were similar to those in a previous study ([Albinet et al., 2006](#)).

[Schauer et al. \(2004\)](#) collected a series of air samples in Germany during the autumn and summer of 2002 in urban (Munich), rural (Hohenpeissenberg) and high alpine (Zugspitze) locations to measure the levels of PAHs and nitro-PAHs. The method of analysis used nitro-PAH

**Table 1.5 Distribution of particulate matter, dinitropyrene isomers and 1-nitropyrene by particle size**

PM size ( $\mu\text{m}$ )	PM ( $\mu\text{g}/\text{m}^3$ (%))	1,3-DNP <sup>a</sup> ( $\text{pg}/\text{m}^3$ (%))	1,6-DNP <sup>a</sup> ( $\text{pg}/\text{m}^3$ (%))	1,8-DNP <sup>a</sup> ( $\text{pg}/\text{m}^3$ (%))	1-NP <sup>a</sup> ( $\text{pg}/\text{m}^3$ (%))
> 7	24 (36%)	0.02 (3%)	0.04 (5%)	0.06 (9%)	4.99 (3%)
3.3–7	7.1 (11%)	0.04 (5%)	0.05 (6%)	0.07 (10%)	8.10 (4%)
2–3.3	4.6 (7%)	0.04 (5%)	0.05 (6%)	0.06 (8%)	7.46 (4%)
1.1–2	4.4 (7%)	0.05 (6%)	0.06 (7%)	0.06 (8%)	10.20 (5%)
< 1.1	26 (39%)	0.62 (81%)	0.62 (76%)	0.46 (65%)	155 (84%)
Total	66.1	0.77	0.82	0.70	186

<sup>a</sup> Values were converted from  $\text{fmol}/\text{m}^3$  to  $\text{pg}/\text{m}^3$  using a conversion factor of 0.292  $\text{pg}/\text{fmol}$  for DNPs and 0.247  $\text{pg}/\text{fmol}$  for 1-NP.

DNP, dinitropyrene; NP, nitropyrene; PM, particulate matter

From [Hayakawa et al. \(1995\)](#)

reduction to amino-PAHs and fluorescence detection, which appears to be less sensitive than the chemiluminescence detection used by Hayakawa's group. The air concentrations for 1,3- and 1,6-dinitropyrene were among the highest observed for the urban and rural areas ([Table 1.3](#)). The concentrations of 1,3-dinitropyrene were almost of the same magnitude as those of 1-nitropyrene, which differed considerably from the Japanese data that showed a difference of at least 100-fold between the concentrations of 1-nitropyrene and the dinitropyrenes isomers. [The Working Group noted that the values for dinitropyrenes seemed to be unreasonably high.]

In the autumn of 1993, [Hayakawa et al. \(1995\)](#) collected size-fractionated PM with an Andersen high-volume sampler for 6 days in downtown Kanazawa, Japan ([Table 1.5](#)). Approximately one-third (36%) of the particulate mass comprised particles > 7  $\mu\text{m}$  and another third (39%) comprised particles < 1.1  $\mu\text{m}$ . However, 81% of 1,3-, 76% of 1,6- and 65% of 1,8-dinitropyrene, and 84% of 1-nitropyrene were found in the smallest particles (< 1.1  $\mu\text{m}$ ), probably due to the predominant diesel emissions in the submicron PM sizes from nearby heavy traffic.

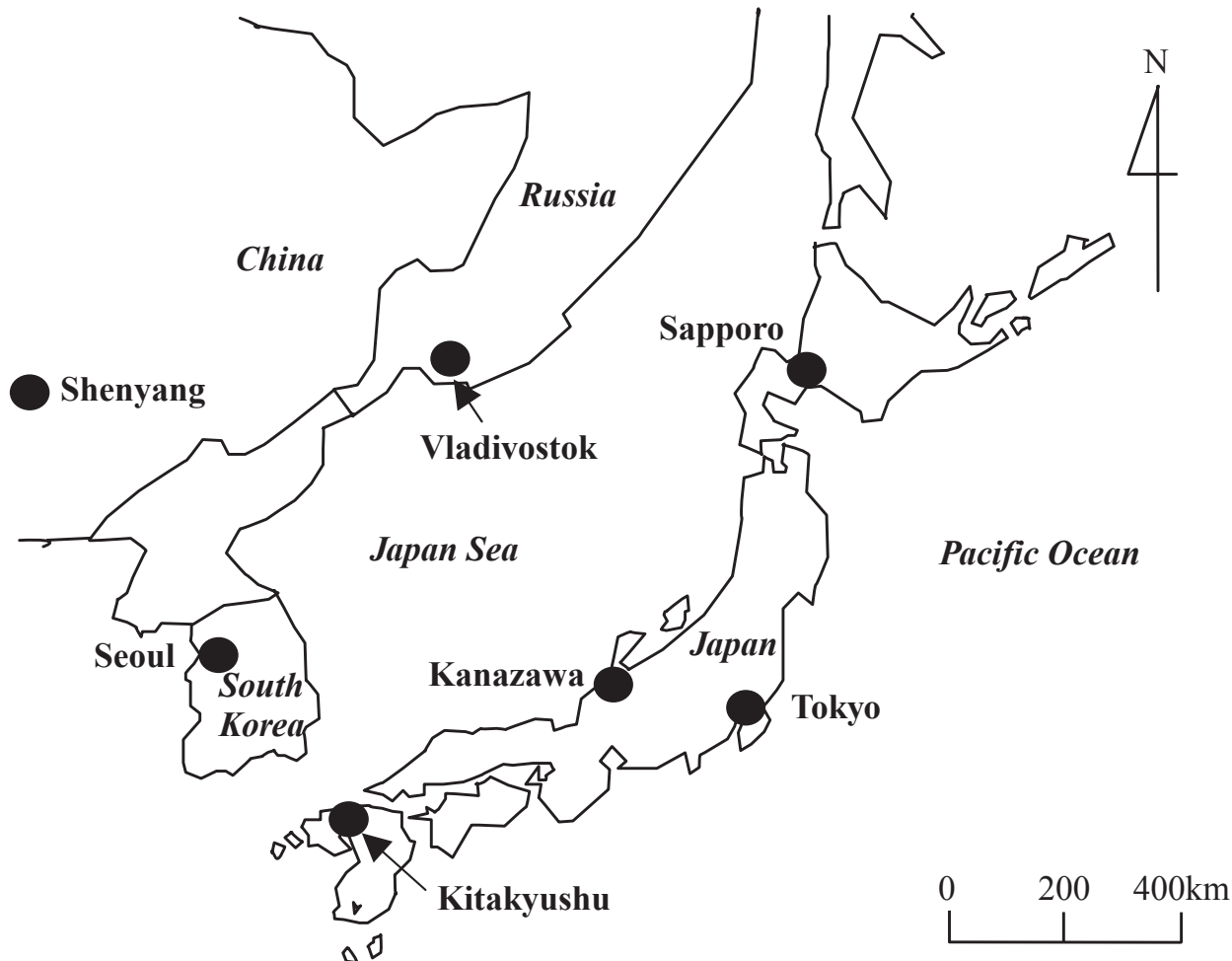
The authors later extended these studies to the Pan-Japan Sea area ([Tang et al., 2005](#)). The sampling sites are given in [Fig. 1.1](#). The amount

of 1-nitropyrene derived from pyrene associated with coal fires was much smaller than that from diesel engine emissions, which have much higher operating temperatures. Air samples were collected from six cities during the summer and winter seasons. Very clear seasonal differences were seen for all of the dinitropyrene isomers and 1-nitropyrene ([Table 1.6](#)). Lower levels in the summer were attributed to increased photochemical degradation, while higher levels in the winter were partially ascribed to stagnant weather conditions. In contrast, the patterns of the levels of nitropyrenes did not change with the seasons. [The Working Group noted that this observation indicates that coal burning was not a significant confounder.]

#### (b) Water

Nitropyrene and the dinitropyrene isomers were measured in rainwater, river water and sea water in Kanazawa ([Murahashi et al., 2001](#)), Japan, in the autumn and winter of 1996–97. The levels of dinitropyrenes were all approximately 0.01  $\text{pmol}/\text{L}$  in February and approximately 0.05  $\text{pmol}/\text{L}$  in September–October.



Fig. 1.1 Sampling locations in the study by Tang *et al.* (2005)

From [Tang \*et al.\* \(2005\)](#)

#### 1.4.3 Other sources

Small amounts of dinitropyrenes are generated by kerosene heaters, which are used extensively in Japan to heat 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 one hour of operations; 1,3-dinitropyrene was found at  $0.53 \pm 0.59$  pg/mg in the particulate extract.

Gas and liquefied petroleum gas burners are widely used for home heating and cooking, and also produce detectable amounts of dinitropyrenes. A level of 0.6 pg/mg particulate extract of 1,3-dinitropyrene was found in emissions

from one gas burner. Dinitropyrenes may result from the incomplete combustion of fuel in the presence of nitrogen dioxide ([Tokiwa \*et al.\*, 1985](#)).

Toners for photocopy machines have been produced commercially since the late 1950s and have been in widespread use since that time. [Löfroth \*et al.\* \(1980\)](#) and [Rosenkranz \*et al.\* \(1980\)](#) first discovered the presence of dinitropyrenes in the toner and on the copies. They traced these to impurities in the carbon black, the toner colorant. ‘Long-flow’ furnace black was first used in photocopy toners in 1967. Its manufacture involved an oxidation step whereby some nitration of pyrene also occurred. A carbon black

**Table 1.6 Seasonal concentrations of 1-nitropyrene and dinitropyrene isomers in cities around the Sea of Japan, 1997–2002**

Site, country, sampling date Season	No. of samples	Concentration (pg/m <sup>3</sup> ) <sup>a</sup>				Comments
		1-NP	1,3-DNP	1,6-DNP	1,8-DNP	
<i>Seoul, Republic of Korea, 2002</i>	4					330 000 cars
Summer		-	-	-	-	
Winter		173.6 ± 38.5	1.1 ± 0.1	1.1 ± 0.2	1.6 ± 0.4	
<i>Shenyang, China, 2001</i>	9					330 000 cars; energy from coal
Summer		29 ± 24	0.6 ± 0.5	0.4 ± 0.1	0.3 ± 0.1	
Winter		178.6 ± 19.0	2.0 ± 0.2	1.5 ± 0.2	0.9 ± 0.3	
<i>Vladivostok, the Russian Federation, 1999</i>	14					200 000 cars; energy from coal
Summer		17 ± 19	0.3 ± 0.3	0.2 ± 0.2	0.3 ± 0.2	
Winter		95.1 ± 76.6	1.2 ± 0.9	0.6 ± 0.7	0.5 ± 0.4	
<i>Kanazawa, Japan, 1999</i>	14					2 640 000 cars
Summer		25 ± 28	0.2 ± 0.2	0.4 ± 0.4	0.4 ± 0.4	
Winter		56.3 ± 56.1	0.8 ± 0.6	0.6 ± 0.4	0.4 ± 0.3	
<i>Sapporo, Japan, 1997</i>	20					1 210 000 cars; 38.5% diesel
Summer		126 ± 36	0.4 ± 0.1	0.4 ± 0.1	0.8 ± 0.2	
Winter		271.7 ± 109.9	1.2 ± 0.4	1.1 ± 0.4	1.6 ± 0.5	
<i>Tokyo, Japan, 1997</i>	20					3 630 000 cars; 20.5% diesel
Summer		44 ± 12	0.4 ± 0.2	0.2 ± 0.1	0.4 ± 0.2	
Winter		168.0 ± 61.8	0.7 ± 0.2	0.9 ± 0.4	1.4 ± 0.4	
<i>Kitakyushu, Japan, 1997</i>	20					550 000 cars; 26.3% diesel
Summer		5.7 ± 2.2	0.2 ± 0.1	0.1 ± 0.1	0.2 ± 0.1	
Winter		13.6 ± 8.6	0.1 ± 0.1	0.4 ± 0.6	0.3 ± 0.1	

<sup>a</sup> Values are means ± standard deviations

DNP, dinitropyrene; NP, nitropyrene

From [Tang et al. \(2005\)](#)

sample manufactured before 1979 was reported to contain 6.3 ng/mg 1,3-dinitropyrene ([Sanders, 1981](#)); using fused silica capillary gas chromatography/negative ion chemical ionization MS for analysis, a 'long-flow' furnace carbon black was also reported to contain 1,3-, 1,6- and 1,8-dinitropyrenes ([Ramdahl & Urdal, 1982](#)). Subsequent to this discovery, changes in the production process reduced the total extractable nitropyrene content from uncontrolled levels of 5–100 ng/mg to less than 0.3 ng/mg. Toners formulated from this modified carbon black (and sold since 1980) have resulted in no detectable levels of mutagenicity and, hence, of nitropyrenes ([Rosenkranz et al., 1980](#); [Butler et al., 1983](#)). A sample of carbon black made in 1980 contained 0.07 ng/mg 1,3-dinitropyrene ([Giammarise et al., 1982](#)), as detected by optimization of the extraction method.

## 2. Cancer in Humans

No data were available to the Working Group.

## 3. Cancer in Experimental Animals

### 3.1 Mouse

See [Table 3.1](#).

#### 3.1.1 Intraperitoneal administration

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%) or benzo[*a*]pyrene (total dose, 560 nmol [140 µg]; purity, > 99%) in 10, 20 and 40 µL of dimethyl sulfoxide (DMSO) or three injections of DMSO alone on days 1, 8 and 15 after birth. 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 males and 31 females in the vehicle-control group were still alive. All surviving mice were killed after 1 year.

No increase in the incidence of tumours was observed in any of the organs examined in males or females ([Wislocki et al., 1986](#)). [The Working Group noted the short duration of the study.]

#### 3.1.2 Subcutaneous administration

A group of 20 male BALB/c mice, aged 6 weeks, received subcutaneous injections of 0.05 mg of 1,3-dinitropyrene (purity, > 99.9%) dissolved in 0.2 mL of DMSO (total dose, 1 mg) once a week for 20 weeks. A positive-control group of 20 males received injections of 0.05 mg benzo[*a*]pyrene, and a further 20 mice served as controls. [The Working Group could not determine whether controls were injected with DMSO.] 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 malignant soft-tissue sarcomas]. No subcutaneous tumour was found in 1,3-dinitropyrene-treated mice or 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 that in the controls ([Otofuji et al., 1987](#)). [The Working Group noted the small number of animals used and the relatively short observation period.]

### 3.2 Rat

See [Table 3.2](#).

#### 3.2.1 Oral administration

A group of 36 female weanling Sprague-Dawley rats received intragastric intubations of 10 µmol [3 mg]/kg body weight (bw) of 1,3-dinitropyrene (purity, > 99%) dissolved in DMSO (1.7 µmol [0.5 mg]/mL) three times per week for 4 weeks

**Table 3.1 Studies of the carcinogenicity of 1,3-dinitropyrene in mice**

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Newborn CD1 (M, F) 12 mo <a href="#">Wislocki et al.(1986)</a>	Intraperitoneal administration 0 (control), 200 nmol [58.5 mg] 1,3-DNP (total dose) or 560 nmol [140 µg] B[a]P in 10, 20 or 40 µL DMSO once at 1, 8 and 15 d after birth Groups of 90 M, 100 F	<i>Liver (adenoma):</i> M–2/28 (7%), 6/30 (20%) F–0/31, 0/39 <i>Liver (carcinoma):</i> M–0/28, 0/30 F–0/31, 0/39 <i>Lung (adenoma):</i> M–1/28 (3%), 3/30 (10%) F–0/31, 3/39 (8%) <i>Lung (carcinoma):</i> M–0/28, 0/30 F–0/31, 0/39 <i>Malignant lymphoma:</i> M–1/28 (1%), 1/30 (3%) F–1/31 (1%), 3/39 (8%)	NS	Purity, > 99% Survival: 1,3-DNP–30 M, 39 F; controls–73 M, 65 F Short duration of the study Incidences of liver and lung tumours were increased in B[a]P-treated animals (positive-control group)
BALB/c (M) 60 wks or until moribund <a href="#">Otofuji et al. (1987)</a>	Subcutaneous injection 0.05 mg 1,3-DNP or B[a]P in 0.2 mL DMSO (total dose, 1 mg) once/wk for 20 wks Groups of 20 aged 6 wks including a control group [unclear if injected with DMSO]	<i>Subcutaneous (all tumours):</i> 0/13 (control), 0/18 <i>Lung (all tumours):</i> 3/13 (23%), 8/18 (44%) <i>Liver (all tumours):</i> 3/13 (23%), 2/18 (11%)	NS	Purity, > 99.9% Study limited by small number of animals and the relatively short observation period Incidence of subcutaneous tumours was increased in B[a]P-treated animals (positive-control group)

1,3-DNP, 1,3-dinitropyrene; B[a]P, benzo[a]pyrene; d, day; DMSO, dimethyl sulfoxide; F, female; M, male; mo, month; NS, not significant; wk, week

**Table 3.2 Studies of the carcinogenicity of 1,3-dinitropyrene in rats**

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
CD (F) 76–78 wks <a href="#">King (1988)</a> ; <a href="#">Imaida et al. (1991)</a>	Oral administration (intra-gastric intubation) 0 or 10 µmol [3 mg]/kg bw in DMSO (total dose, 16 µmol [4.7 mg]/rat), 3 ×/wk for 4 wks Groups of 36 weanlings	Leukaemia: 0/36, 3/36 (9%) Mammary gland (adenocarcinoma): 5/35 (14%), 5/35 (14%) Mammary gland (fibroadenoma): 9/35 (26%), 7/35 (20%) Adrenal gland (pheochromocytoma): 4/36 (11%), 3/35 (9%) Adrenal gland (cortical adenoma): 6/36 (17%), 10/35 (29%) Pituitary gland (carcinoma): 2/36 (6%), 12/35 (34%)* Pituitary gland (adenoma): 9/36 (25%), 5/35 (14%)	* $P < 0.05$	Purity, > 99.9% Study limited by the short duration of both treatment and observation periods and the use of a single dose.
CD (F) 76–78 wks <a href="#">King (1988)</a> ; <a href="#">Imaida et al. (1991)</a>	Intraperitoneal administration 0 or 10 µmol [3 mg]/kg bw in DMSO (total dose, 16 µmol [4.7 mg]/rat), 3 ×/wk for 4 wks Groups of 36 weanlings	Peritoneal cavity (malignant fibrous histiocytoma): 0/31, 2/36 (6%) Leukaemia: 0/31, 2/36 (6%) Mammary gland (adenocarcinoma): 3/31 (10%), 9/36 (25%) Mammary gland (fibroadenoma): 5/31 (16%), 12/36 (33%) Pituitary gland (carcinoma): 3/31 (10%), 3/36 (8%) Pituitary gland (adenoma): 10/31 (32%), 13/36 (36%)	$P < 0.05$ for mammary tumour-bearing animals	Purity, > 99.9% Study limited by the short duration of both treatment and observation periods and the use of a single dose.

**Table 3.2 (continued)**

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
F344/DuCrj (M) 347 d <a href="#">Ohgaki et al. (1984)</a>	Subcutaneous injection 0 or 0.2 mg in 0.2 mL DMSO (total dose, 4 mg), twice/wk for 10 wks Groups of 10 or 20 aged 6 wks	Injection site (subcutaneous sarcoma): 0/20, 10/10 (100%)	[ <i>P</i> < 0.0001]	Study limited because of the small number of animals studied, the short treatment and observation periods and the possible influence of the contamination with 1,6-dinitropyrene (0.6%).
CD (F) 67 wks <a href="#">King (1988); Imaida et al. (1991)</a>	Subcutaneous injection Suprascapular injection starting within 24 h of birth; 1st dose: 2.5 µmol/kg bw; 2nd and 3rd doses: 5 µmol/kg bw; 4th–8th doses: 10 µmol/kg bw (total dose, 6.3 µmol [1.9 mg]) in DMSO once/wk for 8 wks Treated group: 43 newborns; a group of 40 newborns served as vehicle controls	Injection site (malignant fibrous histiocyctomas): 0/40, 5/43 (12%)* Mammary gland (adenocarcinoma): 1/40 (2%), 6/43 (14%) Mammary gland (fibroadenoma): 6/40 (15%), 3/43 (7%) Mammary gland (adenoma): 1/40 (2%), 1/43 (2%)	* <i>P</i> < 0.05  NS	Purity, > 99.9% Study limited by the short duration of both treatment and observation periods and the use of a single dose.

bw, body weight; d, day; DMSO, dimethyl sulfoxide; F, female; h, hour; M, male, NS, not significant; wk, week

(average total dose, 16  $\mu\text{mol}$  [4.7 mg]/rat) and were observed for 76–78 weeks. A vehicle-control group of 36 animals received DMSO only. Average survival times of the 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 adenocarcinomas were found in 5 out of 35 (14%) and fibroadenomas in 7 out of 35 (20%) treated animals, but their incidence did not differ from that observed in vehicle controls (5 out of 35 and 9 out of 35, respectively). A significant increase in the incidence of pituitary carcinomas was also observed in treated animals (12 out of 35; 34%) compared with the control group (2 out of 36; 6%) (King, 1988; Imaida *et al.*, 1991). [The Working Group noted the short duration of both treatment and observation.]

### 3.2.2 Intraperitoneal administration

A group of 36 female weanling Sprague-Dawley rats received intraperitoneal injections of 10  $\mu\text{mol}$  [3 mg]/kg bw of 1,3-dinitropyrene (purity, > 99%) dissolved in DMSO (1.7  $\mu\text{mol}$  [0.5 mg]/mL) three times a week for 4 weeks (total dose, 16  $\mu\text{mol}$  [4.7 mg]/rat); 36 control animals were treated with DMSO only. Animals were killed when moribund or after 76–78 weeks. Malignant fibrous histiocytomas were found in the peritoneal cavity of two treated rats (6%), and two animals (6%) had leukaemia. Neither malignancy developed in 31 surviving controls. Mammary adenocarcinomas were observed in 9 out of 36 (25%) treated animals compared with 3 out of 31 (10%) controls, and fibroadenomas occurred in 12 out of 36 (33%) treated rats compared with 5 out of 31 (16%) controls; the difference in the number of mammary tumour-bearing animals was statistically significant ( $P < 0.05$ ). There was also an increased incidence of pituitary adenomas ( $P < 0.05$ ) (King, 1988; Imaida *et al.*, 1991).

### 3.2.3 Subcutaneous administration

Ten male Fischer 344/ DuCrj rats, aged 6 weeks, received subcutaneous injections of 0.2 mg of 1,3-dinitropyrene [purity unspecified] (impurities: 0.6% 1,6-dinitropyrene, < 0.05% other nitropyrenes) dissolved in 0.2 mL of DMSO twice a week for 10 weeks (total dose, 4 mg). A control group of 20 rats received injections of 0.2 mL DMSO alone. The animals were killed between days 169 and 347. Subcutaneous sarcomas developed at the site of the injection in all (100%) treated rats between days 119 and 320. No tumours were observed in other organs of the treated rats, and no tumours developed among control animals (Ohgaki *et al.*, 1984). [The Working Group noted that, while the study material was contaminated with 1,6-dinitropyrene, the 100% incidence of sarcomas that it caused would indicate that the small amount of the impurity had a minor effect, if any, on the outcome.]

A group of 43 female newborn Sprague-Dawley rats received subcutaneous injections into the suprascapular region of 1,3-dinitropyrene (purity, > 99%; total dose, 6.3  $\mu\text{mol}$  [1.9 mg]) dissolved in DMSO (1.7  $\mu\text{mol}$  [0.5 mg]/mL) starting within 24 hours after birth. A group of 40 or more animals injected with DMSO alone served as controls. The first dose was 2.5  $\mu\text{mol}$ /kg bw, the second and third doses were 5  $\mu\text{mol}$ /kg and doses 4–8 were 10  $\mu\text{mol}$ /kg. The average length of survival was 468 days for treated animals and 495 days for the controls. The animals were killed 67 weeks after the first treatment, and 5 out of 43 (12%;  $P < 0.05$ ) treated rats had developed malignant fibrous histiocytomas at the site of injection; no tumour of this type was found among the vehicle controls (0 out of 40). No increase in the incidence of mammary tumours was observed. Mammary tumours were observed in treated animals (6 out of 43 had adenocarcinoma (14%); 3 out of 43 had fibroadenoma (7%); and 1 out of 43 had adenoma (1%)) and in control animals

(1 out of 40 had adenocarcinoma (3%); 6 out of 40 had fibroadenoma (15%); and 1 out of 40 had adenoma (3%)) ([King, 1988](#); [Imaida et al., 1995](#)). [The Working Group noted that the study was limited by the short duration of both treatment and observation and the use of a single dose.]

## 4. Mechanistic and Other Relevant Data

### 4.1 Absorption, distribution, metabolism, excretion

#### 4.1.1 Humans

No data were available to the Working Group.

#### 4.1.2 Experimental systems

The metabolic activation of 1,3-dinitropyrene (reviewed previously in [IARC, 1989](#)) is caused by the reduction of one nitro group to yield the corresponding *N*-hydroxylamine derivative, which in turn can undergo acid-catalysed DNA binding or be converted into a highly reactive *O*-acetyl metabolite by bacteria and mammalian acetyl-transferases; several metabolizing systems were employed and the nitroreduction of 1,3-dinitropyrene by rat liver cytosol occurred to much lesser extent than that of 1,6- or 1,8-dinitropyrene ([Fu, 1990](#); [Beland & Marques, 1994](#)).

### 4.2 Genetic and related effects

#### 4.2.1 Humans

No data were available to the Working Group.

#### 4.2.2 Experimental systems

The genotoxicity of nitro-PAHs, including 1,3-dinitropyrene, in eukaryotic cells, including fungi, plants and mammalian cells, has been reported ([IARC, 1989](#); [IPCS, 2003](#)). The wide

differences in sensitivity to nitro-PAHs of prokaryotic and eukaryotic cells are probably due to interspecies differences in the types and concentrations of metabolizing enzyme present, as well as DNA repair or possibly other factors, including the duration of treatment ([Durant et al., 1996](#)).

The activation of 1,3-dinitropyrene to a mutagen in *Salmonella typhimurium* was mainly due to the enzymes in the bacteria itself ([IARC, 1989](#)). Overall, nitroreduction is an important mutagenic activation pathway in this system. The use of a nitroreductase-deficient strain revealed a clear decrease in mutagenic activity compared with the standard tester strain, which showed the maximum mutagenic potency of 1,3-dinitropyrene ([Crebelli et al., 1995](#)).

Genotoxicity studies of 1,3-dinitropyrene in bacterial systems other than the *Salmonella* microsome assay have been reported, and the results, with a few exceptions, were consistent with those in *Salmonella*. Other bacterial assays were also used, e.g. *S. typhimurium* TM677 (a quantitative bacterial forward mutation assay, based on resistance to 8-azaguanine). In general, the results were consistent with those observed in *S. typhimurium* TA98. 1,3-Dinitropyrene was a potent mutagen in *in vitro* studies in bacteria, but only marginal effects were observed *in vivo* in a host-mediated assay using the same bacterial strain ([McCoy et al., 1985](#); [IARC, 1989](#); [Mersch-Sundermann et al., 1991, 1992](#); [Shah et al., 1991](#); [Oda et al., 1992, 1993](#); [Busby et al., 1994](#); [Shimada et al., 1994](#); [Shane & Winston, 1997](#); [Yamazaki et al., 2000](#)).

In the yeast *Saccharomyces cerevisiae* D4, 1,3-dinitropyrene at doses of up to 500 µg/mL did not induce gene conversion; in primary mouse hepatocytes at 5–20 µM, it induced marginal DNA damage (as measured by alkaline elution); and in rat, mouse and human hepatocytes, 1,3-dinitropyrene ( $1.1 \times 10^{-5}$ – $1.1 \times 10^{-2}$  mg/mL) induced unscheduled DNA synthesis. At 0.5–2.0 µg/mL, it induced the synthesis of polyoma virus DNA



in polyoma virus-transformed rat fibroblasts (IARC, 1989).

1,3-Dinitropyrene (0.1–10 µg/mL) induced mutation to diphtheria toxin resistance in cultured Chinese hamster lung fibroblasts and to ouabain resistance in Chinese hamster V79 cells (1–10 µg/mL). At 0.2–2 µg/mL, it also induced mutation to 6-thioguanine resistance in Chinese hamster ovary cells in the absence of an exogenous metabolic system but was unequivocally active at 2 µg/mL and in the presence of metabolic activation. 1,3-Dinitropyrene (2 µg/mL) induced chromosomal aberrations in cultured Chinese hamster lung fibroblasts in the absence of an exogenous metabolic system but not morphological cell transformation at concentrations of up to 250 µg/mL in BALB/c3T3 cells (IARC, 1989).

The effects of nitro-PAHs, including 1,3-dinitropyrene, on cell signalling related to apoptosis have been reported (Landvik *et al.*, 2007). In Hepa1c1c7 cells, 1,3-dinitropyrene was a more effective inducer of apoptosis than 1,8-dinitropyrene, in contrast to the level of DNA damage that it causes and its carcinogenic activity. Both compounds induced cytochrome P450 1a1, and activated various intracellular signalling pathways related to apoptosis. Furthermore, 1,3-dinitropyrene was found to induce concentration-dependent lipid peroxidation, as measured using the fluoroprobe C<sub>11</sub>-BODIPY<sup>581/591</sup>. Products derived from lipid peroxidation can react with DNA leading to the formation of mutagenic etheno adducts (el Ghissassi *et al.*, 1995; Nair *et al.*, 2007).

### 4.3 Other relevant data

No data were available on the acute toxicity of 1,3-dinitropyrene. As previously reported (IARC, 1989), rats administered 1,3-dinitropyrene (about 3 mg/kg bw, three times a week for 4 weeks) orally showed no effects on body weight or survival. Before the appearance of tumours, local effects (ulcer and scar formation at the site

of injection) were noted in rats after repeated subcutaneous injections of 0.2 mg of 1,3-dinitropyrene per animal. Three intraperitoneal injections of 1,3-dinitropyrene (at 2.5 mg/kg bw) into young male Sprague-Dawley rats resulted in a fourfold increase in 1-nitropyrene reductase activity, a carcinogen-metabolizing enzyme, in the liver microsomes compared with controls (IARC, 1989).

Oral administration of 1,3-dinitropyrene to female weanling CD rats resulted in the development of leukaemia. Subcutaneous injection of 1,3-dinitropyrene into mice and rats did not result in significant tumorigenicity. However, subcutaneous injection of 1,3-dinitropyrene into newborn CD rats resulted in the formation of malignant fibrous histiocytomas at the site of injection (IARC, 1989).

### 4.4 Mechanistic considerations

See the *Monograph* on 1,8-Dinitropyrene in this Volume.

## 5. Summary of Data Reported

### 5.1 Exposure data

1,3-Dinitropyrene is formed by the nitration of 1-nitropyrene. No evidence was found that it has been produced in commercial quantities or used for purposes other than laboratory applications. During the combustion of diesel and gasoline engines, pyrene is nitrated to form 1-nitropyrene, which is further nitrated to form small amounts of dinitropyrenes. This leads to a content of 1,3-dinitropyrene in the range of 0.1–10% relative to that of 1-nitropyrene in diesel and gasoline exhaust particles and ~1% in airborne particulate matter. 1,3-Dinitropyrene is present in the 0.1–10 ng/g range in airborne particulate matter collected from ambient atmospheric samples. Air concentrations clearly

declined from values in the 1–10 pg/m<sup>3</sup> range at urban locations to values in the 0.01–0.1 pg/m<sup>3</sup> range at suburban and rural locations.

1,3-Dinitropyrene is also generated by kerosene heaters. No data on occupational exposure were available to the Working Group.

## 5.2 Human carcinogenicity data

No data were available to the Working Group.

## 5.3 Animal carcinogenicity data

1,3-Dinitropyrene was tested for carcinogenicity in mice in one study by intraperitoneal injection and in one study by subcutaneous injection, and in rats in one study by oral administration, one study by intraperitoneal injection and two studies by subcutaneous injection. In mice, neither intraperitoneal nor subcutaneous injection of 1,3-dinitropyrene produced an increase in the incidence of tumours at any site that was significantly different from that in controls. In rats, intragastric intubation of 1,3-dinitropyrene produced a significant increase in the incidence of pituitary carcinomas; intraperitoneal injection of 1,3-dinitropyrene caused a significant increase in the incidence of mammary tumours and pituitary adenomas; and subcutaneous injection of 1,3-dinitropyrene caused significant increases in the incidence of subcutaneous sarcomas in treated animals in one study and an increase in the formation of malignant histiocytomas at the injection site in another study.

## 5.4 Mechanistic and other relevant data

No data were available to the Working Group on the absorption, distribution, metabolism and excretion or the genetic and related effects of 1,3-dinitropyrene in humans. Metabolic activation of 1,3-dinitropyrene occurs by reduction

of one nitro group to yield the corresponding *N*-hydroxylamine, which may then be converted into the highly reactive *O*-acetyl metabolite. Mutagenicity assays in bacteria have shown that the activating enzymes are present in the bacteria themselves. 1,3-Dinitropyrene did not induce gene conversion in yeast. It was mutagenic in different mammalian systems, and induced chromosomal aberrations in Chinese hamster lung fibroblasts, but no cell transformation in BALB-c3T3 cells. 1,3-Dinitropyrene was an effective inducer of apoptosis in mammalian Hepa1c1c7 cells, and it enhanced lipid peroxidation.

Overall, these data provide *weak mechanistic evidence* to support the carcinogenicity of 1,3-dinitropyrene.

## 6. Evaluation

### 6.1 Cancer in humans

No data were available to the Working Group.

### 6.2 Cancer in experimental animals

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

### 6.3 Overall evaluation

1,3-Dinitropyrene is *possibly carcinogenic to humans (Group 2B)*.

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