3,7-DINITROFLUORANTHENE AND 3,9-DINITROFLUORANTHENE

3,7- and 3,9-Dinitrofluoranthenes were considered by a previous Working Group in June 1988 (IARC, 1989). New data have since become available, and these are included in the present monograph and have been taken into consideration in the evaluation.

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

3,7-Dinitrofluoranthene

Chem. Abstr. Serv. Reg. No.: 105735-71-5

Chem. Abstr. Name: 3,7-Dinitrofluoranthene

IUPAC Systematic Name: 3,7-Dinitrofluoranthene

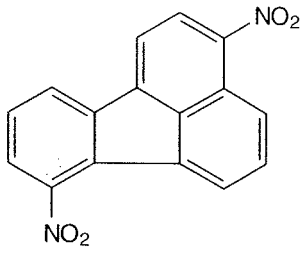
3,9-Dinitrofluoranthene

Chem. Abstr. Serv. Reg. No.: 22506-53-2

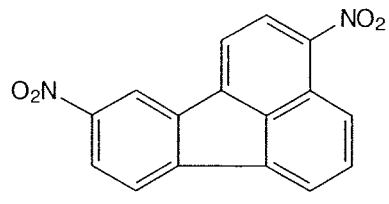
Chem. Abstr. Name: 3,9-Dinitrofluoranthene

IUPAC Systematic Name: 3,9-Dinitrofluoranthene

1.1.2 *Structural and molecular formulae and relative molecular mass*



3,7-Dinitrofluoranthene



3,9-Dinitrofluoranthene

$C_{16}H_8N_2O_4$ Relative molecular mass: 292.3

1.1.3 *Chemical and physical properties of the pure substance*

From Nakagawa *et al.* (1987), unless otherwise specified

3,7-Dinitrofluoranthene

(*a*) *Description*: Yellow needles
(*b*) *Melting-point*: 203–204 °C
(*c*) *Spectroscopy data*: Nuclear magnetic resonance, ultraviolet and mass spectral data have been reported (Ramdahl *et al.*, 1988)
(*d*) *Octanol/water partition coefficient (P)*: log P, 4.44
(*e*) *Conversion factor*: $mg/m^3 = 11.96 \times ppm$[1]

3,9-Dinitrofluoranthene

(*a*) *Description*: Yellow needles
(*b*) *Melting-point*: 222–224 °C
(*c*) *Spectroscopy data*: Nuclear magnetic resonance, ultraviolet and mass spectral data have been reported (Ramdahl *et al.*, 1988)
(*d*) *Octanol/water partition coefficient (P)*: log P, 4.44
(*e*) *Conversion factor*: $mg/m^3 = 11.96 \times ppm$[1]

1.1.4 *Technical products and impurities*

No data were available to the Working Group

1.1.5 *Analysis*

Tokiwa *et al.* (1990) reported a method to separate and identify dinitrofluoranthenes in airborne particulates. The particulate matter was collected on a silica fibre filter and extracted with dichloromethane. The crude extracts were applied to a column filled with silica gel and were eluted step by step with hexane, hexane : benzene (1 : 1, v/v), benzene, benzene : methanol (1 : 1, v/v) and methanol. The components were fractionated and identified by high-performance liquid chromatography and gas chromatography with mass spectrometry.

1.2 Production and use

No evidence was found that either 3,7- or 3,9-dinitrofluoranthene has been produced in commercial quantities or used for anything other than laboratory applications. 3,7- or 3,9-Dinitrofluoranthene can be synthesized by nitration of fluoranthene or 3-nitrofluoranthene in the presence of fuming nitric acid, with subsequent fractionation and purification by recrystallization (Nakagawa *et al.*, 1987; Horikawa *et al.*, 1991; Matsuoka *et al.*, 1993).

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[1] Calculated from: mg/m^3 = (relative molecular mass/24.45) × ppm, assuming temperature (25 °C) and pressure (101 kPa)

1.3 Occurrence

1.3.1 *Natural occurrence*

Neither 3,7- nor 3,9-dinitrofluoranthene is known to occur as a natural product.

1.3.2 *Occupational exposure*

No data were available to the Working Group

1.3.3 *Environmental occurrence*

3,7- and 3,9-Dinitrofluoranthenes were detected at a concentration of 0.028 mg/kg and 0.013 mg/kg, respectively, in particulates emitted from a diesel engine (Tokiwa *et al.*, 1986) and dinitrofluoranthenes have also been found in the incomplete combustion products of liquefied petroleum gas (Horikawa *et al.*, 1987).

In Sapporo, Hokkaido, Japan, in 1989, 3,7- and 3,9-dinitrofluoranthenes were detected in airborne particulates at a level of 0.01 mg/kg of particulate. 3,7-Dinitrofluoranthene has also been found in particulate emissions from a kerosene heater at 0.14 mg/kg of particulate (Tokiwa *et al.*, 1990, 1993).

1.4 Regulations and guidelines

No data were available to the Working Group.

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

3.1 Subcutaneous injection

Rat: Two groups of 21 and 11 male Fischer 344/DuCrj rats, six weeks of age, received twice-weekly subcutaneous injections of 0.05 mg 3,7-dinitrofluoranthene (> 99% pure) or 0.05 mg 3,9-dinitrofluoranthene (> 99% pure), respectively, in dimethyl sulfoxide (DMSO) for 10 weeks (total dose, 1 mg/rat). A vehicle-control group of 21 rats received injections of DMSO only. The rats were observed for 50 weeks, after which time surviving animals were killed. The mean survival time of 3,9-dinitrofluoranthene-treated rats was shorter than that of 3,7-dinitrofluoranthene-treated animals, both of which were reduced in comparison to controls. All organs were examined grossly and histopathological examination was carried out on all tumours and major organs. All rats treated with 3,7-dinitrofluoranthene and 10/11 rats treated with 3,9-dinitrofluoranthene developed subcutaneous tumours. Of the tumours that developed at the site of injection,

20/21 that were induced by 3,7-dinitrofluoranthene and 7/10 that were induced by 3,9-dinitrofluoranthene were classified as malignant fibrous histiocytomas, whereas the remainder showed typical features of rhabdomyosarcomas (1/21 and 3/10, respectively). The time of appearance of the subcutaneous tumours was earlier in the 3,9- than in the 3,7-dinitrofluoranthene-treated group: the first tumour in the 3,9-dinitrofluoranthene-treated group appeared on day 88 (average, 117), 10 weeks earlier than in the 3,7-dinitrofluoranthene-treated group (115; average, 186). No subcutaneous tumour was found in the control group (Tokiwa *et al.*, 1987).

3.2 Intrapulmonary implantation

Rat: A total of 84 male Fischer 344/DuCrj rats, 11 weeks of age, were divided into five groups that received pulmonary implants of 50, 100 or 200 μg 3,9-dinitrofluoranthene, 200 μg 3,7-dinitrofluoranthene in a mixture of equal volumes of beeswax and tricaprylin or the beeswax–tricaprylin mixture alone. The rats were anaesthetized, a left lateral thoracotomy was performed and 0.5 ml of the beeswax-tricaprylin mixture containing the chemicals was injected directly into the lower third of the left lung. After injection, the mixture formed a solid, defined pellet in the lung. All rats were observed for up to 100 weeks. The mean body weights of all treated groups were significantly decreased compared to those of controls. In 3,9-dinitrofluoranthene-treated rats, the earliest deaths caused by lung cancer were observed at weeks 99, 53 and 37 in the low-, mid- and high-dose groups, respectively. The earliest death in the 3,7-dinitrofluoranthene-treated group occurred at week 50. Lungs, liver, spleen and kidneys were examined grossly, and grossly apparent lesions and tissues from all major organs were examined microscopically. The incidence of lung tumours was 1/10 (10%), 7/10 (70%) and 19/21 (90.5%) in the low-, mid- and high-dose 3,9-dinitrofluoranthene-treated groups and 12/22 (54.5%) in the 3,7-dinitrofluoranthene-treated group. Most of the lung tumours induced by both chemicals were invasive squamous-cell carcinomas. No lung tumour was found in control rats (Horikawa *et al.*, 1991).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

No data were available to the Working Group.

4.1.2 *Experimental systems*

3,9-Dinitrofluoranthene was metabolized to an aminonitrofluoranthene (the isomeric structure of which could not be identified) by lung cytosol and microsomes from seven-to-nine-week-old male Fischer 344/N rats under anaerobic, but not under aerobic, condi-

tions. Pretreatment of the animals with 3-methylcholanthrene increased the microsomal but not the cytosolic reduction of 3,9-dinitrofluoranthene (Mitchell *et al.*, 1993).

4.2 Toxic effects

No data were available to the Working Group.

4.3 Reproductive and developmental effects

No data were available to the Working Group.

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see also Table 1 and Appendices 1 and 2)

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; Tokiwa *et al.*, 1993).

3,7-Dinitrofluoranthene was mutagenic at extremely low doses in *Salmonella typhimurium* strains and preferentially inhibited the growth of DNA repair-deficient *Bacillus subtilis*. In the *umu* test, *S. typhimurium* strains NM1011, which has increased nitrofurazone-reductase activity, and NM3009, which has high *O*-acetyltransferase and nitroreductase activities, were both particularly highly sensitive to the genetic activity of 3,7-dinitrofluoranthene.

3,7-Dinitrofluoranthene did not induce mutations to 6-thioguanine resistance in Chinese hamster V79 cells. In a Chinese hamster cell line (CHL), 3,7-dinitrofluoranthene induced chromosomal aberrations in the absence, but not in the presence, of rat-liver S9 mix.

In vivo, 3,7-dinitrofluoranthene induced micronuclei in mouse bone marrow.

3,9-Dinitrofluoranthene was mutagenic to *S. typhimurium* strains and preferentially inhibited the growth of DNA repair-deficient *B. subtilis*. The *umu* test with *S. typhimurium* NM1011, a strain with increased nitrofurazone-reductase activity, was particularly highly sensitive to 3,9-dinitrofluoranthene.

3,9-Dinitrofluoranthene did not induce mutations to 6-thioguanine resistance in Chinese hamster V79 lung cells. In a Chinese hamster cell line (CHL), 3,9-dinitrofluoranthene induced chromosomal aberrations in the absence, but not in the presence, of rat-liver S9 mix.

In vivo, 3,9-dinitrofluoranthene induced micronuclei in mouse bone marrow.

Table 1. Genetic and related effects of 3,7- and 3,9-dinitrofluoranthenes

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
3,7-Dinitrofluoranthene				
PRB, Prophage induction, SOS repair test, DNA strand breaks, cross-links or related damage in *Salmonella typhimurium* TA1535/pSK1002	+	0	0.03	Oda *et al.* (1992)
PRB, Prophage induction, SOS repair test, DNA strand breaks, cross-links or related damage in *Salmonella typhimurium* TA1535/pSK1002	+	0	0.001	Oda *et al.* (1993)
PRB, Prophage induction, SOS repair test, DNA strand breaks, cross-links or related damage in *Salmonella typhimurium* NM1000	(+)	0	0.003	Oda *et al.* (1993)
PRB, Prophage induction, SOS repair test, DNA strand breaks, cross-links or related damage in *Salmonella typhimurium* NM1011	+	0	0.003	Oda *et al.* (1992)
PRB, Prophage induction, SOS repair test, DNA strand breaks, cross-links or related damage in *Salmonella typhimurium* NM1011	+	0	0.0001	Oda *et al.* (1993)
PRB, Prophage induction, SOS repair test, DNA strand breaks, cross-links or related damage in *Salmonella typhimurium* NM1000	–	0	0.03	Oda *et al.* (1992)
PRB, Prophage induction, SOS repair test, DNA strand breaks, cross-links or related damage in *Salmonella typhimurium* NM2000	+	0	0.0003	Oda *et al.* (1993)
PRB, Prophage induction, SOS repair test, DNA strand breaks, cross-links or related damage in *Salmonella typhimurium* NM2009	+	0	0.00001	Oda *et al.* (1993)
PRB, Prophage induction, SOS repair test, DNA strand breaks, cross-links or related damage in *Salmonella typhimurium* NM3009	+	0	0.00001	Oda *et al.* (1993)
BSD, *Bacillus subtilis rec* strains, differential toxicity	+	0	0.005	Nakagawa *et al.* (1987)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	0.0005	Nakagawa *et al.* (1987)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	0.008	Nakagawa *et al.* (1987)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	+	(+)	0.001	Nakagawa *et al.* (1987)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	+	+	0.0005	Nakagawa *et al.* (1987)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	+	0.00013	Nakagawa *et al.* (1987)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
3,7-Dinitrofluoranthene (contd)				
SAS, *Salmonella typhimurium* TA97, reverse mutation	+	0	0.00025	Nakagawa *et al.* (1987)
SAS, *Salmonella typhimurium* TA98NR, reverse mutation	+	0	0.0005	Nakagawa *et al.* (1987)
SAS, *Salmonella typhimurium* TA98/1,8-DNP$_6$, reverse mutation	+	0	0.0005	Nakagawa *et al.* (1987)
SAS, *Salmonella typhimurium* TA1978, reverse mutation	–	0	0.5	Nakagawa *et al.* (1987)
G9H, Gene mutation, Chinese hamster lung V79 cells *hprt* locus	0	–	100	Tokiwa *et al.* (1988)
CIC, Chromosomal aberrations, Chinese hamster cells *in vitro*	+	–	2.5	Matsuoka *et al.* (1993)
MVM, Micronucleus test, mice *in vivo*	+		20 ip	Tokiwa *et al.* (1988)
3,9-Dinitrofluoranthene				
PRB, Prophage induction, SOS repair test, DNA strand breaks, cross-links or related damage in *Salmonella typhimurium* TA1535/pSK1002	+	0	0.003	Oda *et al.* (1992)
PRB, Prophage induction, SOS repair test, DNA strand breaks, cross-links or related damage in *Salmonella typhimurium* TA1535/pSK1002	+	0	0.0018	Oda *et al.* (1993)
PRB, Prophage induction, SOS repair test, DNA strand breaks, cross-links or related damage in *Salmonella typhimurium* NM1000	+	0	0.006	Oda *et al.* (1993)
PRB, Prophage induction, SOS repair test, DNA strand breaks, cross-links or related damage in *Salmonella typhimurium* NM1011	+	0	0.001	Oda *et al.* (1992)
PRB, Prophage induction, SOS repair test, DNA strand breaks, cross-links or related damage in *Salmonella typhimurium* NM1011	+	0	0.00056	Oda *et al.* (1993)
PRB, Prophage induction, SOS repair test, DNA strand breaks, cross-links or related damage in *Salmonella typhimurium* NM1000	–	0	0.01	Oda *et al.* (1992)
PRB, Prophage induction, SOS repair test, DNA strand breaks, cross-links or related damage in *Salmonella typhimurium* NM2000	+	0	0.0069	Oda *et al.* (1993)
PRB, Prophage induction, SOS repair test, DNA strand breaks, cross-links or related damage in *Salmonella typhimurium* NM2009	+	0	0.0001	Oda *et al.* (1993)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
3,9-Dinitrofluoranthene (contd)				
PRB, Prophage induction, SOS repair test, DNA strand breaks, cross-links or related damage in *Salmonella typhimurium* NM3009	+	0	0.00006	Oda *et al.* (1993)
BSD, *Bacillus subtilis rec* strains, differential toxicity	+	0	0.01	Nakagawa *et al.* (1987)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	0.001	Nakagawa *et al.* (1987)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	0.008	Nakagawa *et al.* (1987)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	+	+	0.001	Nakagawa *et al.* (1987)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	+	+	0.00013	Nakagawa *et al.* (1987)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	+	0.00013	Nakagawa *et al.* (1987)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	0	0.001	Horikawa *et al.* (1994)
SAS, *Salmonella typhimurium* TA97, reverse mutation	+	0	0.00025	Nakagawa *et al.* (1987)
SAS, *Salmonella typhimurium* TA98NR, reverse mutation	+	0	0.0005	Nakagawa *et al.* (1987)
SAS, *Salmonella typhimurium* TA98/1,8-DNP_6, reverse mutation	+	0	0.0005	Nakagawa *et al.* (1987)
SAS, *Salmonella typhimurium* TA1978, reverse mutation	+	0	0.25	Nakagawa *et al.* (1987)
G9H, Gene mutation, Chinese hamster lung V79 cells *hprt* locus	0	–	100	Tokiwa *et al.* (1988)
CIC, Chromosomal aberrations, Chinese hamster cells *in vitro*	+	–	2.5	Matsuoka *et al.* (1993)
MVM, Micronucleus test, mice *in vivo*	+		10 ip	Tokiwa *et al.* (1988)

[a] +, positive; (+), weak positive; –, negative; 0, not tested

[b] LED, lowest effective dose; HID, highest ineffective dose. In-vitro tests, μg/mL; in-vivo tests, mg/kg bw

5. Summary of Data Reported and Evaluation

5.1 Exposure data

3,7- and 3,9-Dinitrofluoranthenes are produced for laboratory use by nitration of fluoranthene. 3,7- and 3,9-Dinitrofluoranthenes have been detected at low levels in emissions from diesel engines, kerosene heaters and other combustion sources.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

3,7- and 3,9-Dinitrofluoranthenes were tested for carcinogenicity in rats by subcutaneous injection in one study and by pulmonary implantation in another study. Subcutaneous injection of 3,7- and 3,9-dinitrofluoranthenes induced a high incidence of subcutaneous tumours at the site of injection, most of which were malignant fibrous histiocytomas. Pulmonary implantation of 3,7- and 3,9-dinitrofluoranthenes induced a high incidence of lung tumours, most of which were squamous-cell carcinomas.

5.4 Other relevant data

3,7- and 3,9-Dinitrofluoranthenes are highly mutagenic to bacteria, particularly in the absence of an exogenous metabolic system. In mammalian cells *in vitro*, these compounds induced chromosomal aberrations but not gene mutations. *In vivo*, they induced micronuclei in mouse bone marrow.

5.5 Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of 3,7- and 3,9-dinitrofluoranthenes.

There is *sufficient evidence* in experimental animals for the carcinogenicity of 3,7- and 3,9-dinitrofluoranthenes.

Overall evaluation

3,7- and 3,9-Dinitrofluoranthenes are *possibly carcinogenic to humans (Group 2B).*

[1] For definition of the italicized terms, see Preamble, pp. 24–27.

6. References

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