D&C RED NO. 9 (CI Pigment Red 53:1)

This substance was considered by a previous Working Group, in 1974 (IARC, 1975). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the evaluation.

D&C Red No. 9 is a grade of CI Pigment Red 53:1 (Colour Index No. 15585:1), which is certified for use in drugs and cosmetics (US Food & Drug Administration, 1974).

1. Exposure Data

1.1 Chemical and physical data

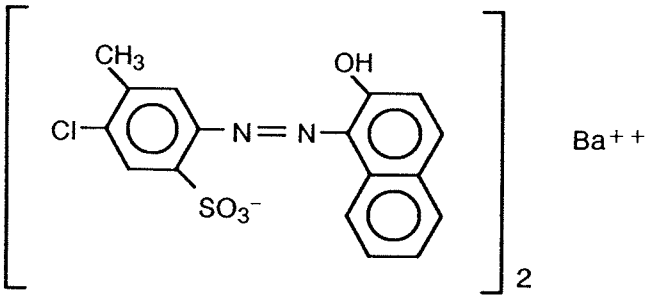
1.1.1 *Synonyms, structural and molecular data*

Chem. Abstr. Serv. Reg. No.: 5160-02-1; replaces 12237-52-4; 12238-39-0; 12238-41-4; 12238-43-6; 24777-23-9; 52627-68-6; 68894-03-1

Chem. Abstr. Name: 5-Chloro-2-[(2-hydroxy-1-naphthalenyl)azo]-4-methyl benzenesulfonic acid, barium salt (2:1)

Colour Index No.: 15585:1

Synonyms: CI Pigment Red 53, Ba salt; CI Pigment Red 53, barium salt (2:1); D and C Red No. 9; Pigment Red 53:1; Lake Red C; Red Lake C



$[C_{17}H_{12}ClN_2O_4S]_2.Ba$ Mol. wt: 888.6

1.1.2 *Chemical and physical properties*

(*a*) *Description*: Red powder (Benemelis, 1973)

(*b*) *Melting-point*: 343–345 °C (decomposes) (US National Toxicology Program, 1982)

(*c*) *Density*: 1.66 g/cm^3 (Benemelis, 1973)

(*d*) *Spectroscopy data*: Infrared and ultraviolet spectral data have been reported (US National Toxicology Program, 1982).

(*e*) *Solubility*: Slightly soluble in water and ethanol; insoluble in acetone and benzene (Society of Dyers and Colourists, 1982)

1.1.3 *Trade names, technical products and impurities*

D&C Red No. 9 is required to contain a minimum of 87% pure colour for sale as a drug and cosmetic colourant (US Food and Drug Administration, 1974).

Analysis of commercial samples of D&C Red No. 9 revealed the presence of 11 aromatic azo compounds (subsidiary colours), at levels of up to 27 ppm (mg/kg), derived from aromatic amine impurities in the Red Lake C Amine (2-amino-4-methyl-5-chlorobenzene-sulfonic acid) precursor (Naganuma *et al.*, 1983).

1.1.4 *Analysis*

The amount of pure colourant in colour additives can be determined by a titrimetric method using titanous chloride as an indicator (Williams, 1984).

1.2 Production and use

1.2.1 *Production*

The first commercial production of CI Pigment Red 53:1 was in 1903. The method of manufacture involves three steps: diazotization, preparation of the coupling intermediate and coupling. The diazotization step involves reacting 2-amino-4-methyl-5-chlorobenzene-sulfonic acid with hydrochloric acid and sodium nitrite to form the diazonium chloride moiety. The coupling step involves mixing the diazonium chloride solution with the coupling component (β-naphthol), then adding barium chloride to form CI Pigment Red 53:1 (Benemelis, 1973). To meet specifications for use in drugs and cosmetics, purified starting materials may be required (US Food and Drug Administration, 1979).

Production of US Food and Drug Administration-certified D&C Red No. 9 was 13 tonnes in 1970, 28 tonnes in 1975, 38 tonnes in 1980 and 0.5 tonnes in 1987; the last year in which it was approved as a D&C colour was 1988 (Marmion, 1991). Approximate US production of CI Pigment Red 53:1 was 430 tonnes in 1950, 990 tonnes in 1970, 1240 tonnes in 1975, 1770 tonnes in 1980, 2020 tonnes in 1985 and 1960 tonnes in 1990 (Benemelis, 1973; US International Trade Commission, 1977, 1981, 1986, 1991). CI Pigment Red 53:1 is produced by one company each in Belgium, Canada, Denmark, India and Japan and by four companies in the USA (Chemical Information Services, 1991).

1.2.2 *Use*

D&C Red No. 9 is used in some countries in the cosmetic and drug industry in such applications as a lipstick colourant, mouthwashes, dentifrices and drugs (Dry Color Manufacturers Association, 1987).

CI Pigment Red 53:1 (as Red Lake C) is widely used in printing inks. It has been used extensively in letter press and offset inks and also in gravure inks, in which its transparency is important. The non-resinated form is used in water- and solvent-based flexographic inks. It

also finds substantial use in coated papers and crayons. Because of its good heat resistance, it is used in polystyrene and rubber, in tin printing and in baking enamels (Society of Dyers and Colourists, 1971; Benemelis, 1973; Dry Color Manufacturers Association, 1987). Resinated CI Pigment Red 53:1 (as Red Lake C) is also used extensively in flexographic inks, in which it provides a stronger, cleaner, yellower colour than the non-resinated grade (Benemelis, 1973).

1.3 Occurrence

1.3.1 *Natural occurrence*

D&C Red No. 9 is not known to occur as a natural product.

1.3.2 *Occupational exposure*

No data were available to the Working Group.

On the basis of a survey conducted in the USA between 1981 and 1983, the US National Institute for Occupational Safety and Health estimated that a total of 122 313 workers, including 23 095 women, were potentially exposed occupationally to CI Pigment Red 53:1. The compound was observed in 43 industries, but the greatest number of potentially exposed workers were employed in the printing trades (US National Library of Medicine, 1992).

1.4 Regulations and guidelines

D&C Red No. 9 was provisionally allowed in the European Economic Community for use in cosmetic products (with a maximum of 3% in products intended to come into contact with mucous membranes) except those intended to be applied in the vicinity of the eyes, in particular eye make-up and eye make-up remover (Commission of the European Communities, 1976, 1990, 1991). This application was prohibited in 1992 (Commission of the European Community, 1992).

D&C Red No. 9 was provisionally listed by the US Food and Drug Administration for use in internally and externally applied drugs and cosmetics (US Food and Drug Administration, 1974; Dry Color Manufacturers Association, 1987), including (i) use in lipsticks and other cosmetics intended to be applied to the lips at not more than 3.0% pure pigment by weight of each lipstick or other lip cosmetic; (ii) use in a dentifrice at not more than 0.002% of the pure pigment by weight of the dentifrice or in a mouthwash at not more than 0.005% of the pure dye by weight of the mouthwash; and (iii) use in drugs subject to ingestion, other than mouthwashes and dentifrices at not more than 0.1 mg per day. In 1988, these applications were prohibited (US Food and Drug Administration, 1979, 1987, 1988).

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

3.1 Oral administration

3.1.1 *Mouse*

Groups of 50 male and 50 female B6C3F$_1$ mice, six weeks of age, were fed diets containing 1000 or 2000 mg/kg (ppm) D&C Red No. 9 (89.8% pure; major impurities, sodium and barium sulfates) for 103 weeks, followed by an observation period of two weeks before all survivors were killed. A control group of 50 males and 50 females was fed basal diet for 104 (males) and 105 (females) weeks. Mean body weights of treated males and control mice were comparable, although, after week 50, the mean body weights of high-dose females were slightly lower than those of controls. No significant difference was observed in survival in any group: males (control, 42/50; low-dose, 40/50; high-dose, 39/50) and females (control, 40/50; low-dose, 40/50; high-dose, 41/50). The incidence of hepatocellular carcinomas was significantly increased in treated males (control, 4/50; low-dose, 9/50; high-dose, 11/50; $p < 0.038$, Cochran-Armitage trend test). The historical incidence of hepatocellular carcinomas in male mice at the study laboratory was 65/297 (22%). The incidence of hepatocellular adenomas in males was 4/50 controls, 4/50 low-dose and 4/50 high-dose. The combined incidences of hepatocellular adenomas and carcinomas were not significantly different. No significant difference was found in the incidence of tumours of other sites. In female mice, no significant increase in tumours was observed at any site (US National Toxicology Program, 1982). [The Working Group considered that the marginally significant increase in trend of hepatocellular carcinomas in male mice is neither biologically significant nor related to treatment.]

3.1.2 *Rat*

Groups of 25 male and 25 female Osborne-Mendel rats, three weeks of age, were fed 0, 100, 500, 2500 or 10 000 mg/kg of diet (ppm) D&C Red No. 9 (purity, $\geq$ 86% [impurities unspecified]) for up to 103–108 weeks, when all surviving animals were killed. About 80% of rats in all groups survived 18 months or longer. There was no significant increase in the incidence of tumours at any site (Davis & Fitzhugh, 1962).

Groups of 50 male and 50 female Fischer 344/N rats, six weeks of age, were fed 0, 1000 or 3000 mg/kg of diet (ppm) D&C Red No. 9 (89.8% pure; major impurities, sodium and barium sulfates) for 103 weeks, followed by an observation period of one week before surviving animals were killed. Mean body weights were comparable in treated and control rats. Survival at the end of the study was males: 35/50 controls, 44/50 low dose, 30/50 high dose; females: 38/50 controls, 40/50 low dose and 41/50 high dose. The incidence of splenic sarcomas was significantly increased in high-dose males (26/48 *versus* 0/50 in low-dose and 0/50 in controls; $p < 0.001$, Fisher exact test). 'Neoplastic nodules of the liver' occurred in males: in 0/50 controls, 6/50 at the low dose and 7/49 at the high dose ($p = 0.02$, Cochran-Armitage trend test), and in females: in 1/50 controls, 1/50 at the low dose and 5/50 at the high dose (p for trend < 0.05, Cochran-Armitage trend test). The incidence in historical

controls at the study laboratory was 5/140 (3.6%) (US National Toxicology Program, 1982; Weinberger *et al.*, 1985).

3.2 Skin application

Mouse

Groups of 50 male and 50 female ICR (Swiss Webster-derived) mice [age unspecified] received topical applications of 1 mg D&C Red No. 9 (90.0% pure [impurities unspecified]) in 0.1 ml water to an area of approximately 6 cm^2 of clipped back skin, twice a week for 18 months. Three groups of 50 male and 50 female controls received applications of water alone. No difference in survival was observed at 18 months. No skin tumour was found. Although various tumours developed in the mammary glands and internal organs, no treatment-related difference in incidence was found (Carson, 1984).

4. Other Relevant Data

4.1 Absorption, distribution, metabolism and excretion

No data were available to the Working Group.

4.2 Toxic effects

4.2.1 *Humans*

D&C Red No. 9 has been associated with contact dermatitis following cosmetic use (Sugai *et al.*, 1977).

4.2.2 *Experimental systems*

D&C Red No. 9 was tested for toxicity in Fischer 344 rats and $B6C3F_1$ mice in a range-finding study for carcinogenicity testing (US National Toxicology Program, 1982). Groups of five males and five females of each species received feed containing 6000, 12 500, 25 000, 50 000 or 100 000 ppm (mg/kg) of the pigment for 14 days. None of the rats, but 1/5 male mice receiving 12 500 ppm, 4/5 males and 3/5 females receiving 25 000 ppm and all mice treated with higher doses died. The spleens of all dosed rats and mice were dark red and enlarged, and the livers and kidneys were dark red to reddish tan.

In a subchronic study, groups of 10 rats of each sex received feed containing 0, 3000, 6000, 12 500 or 50 000 ppm (mg/kg) D&C Red No. 9 for 91 days (US National Toxicology Program, 1982). The respective doses in mice were 0, 600, 1250, 2500, 5000 and 10 000 ppm. Mean body weight gains were not altered in any of the groups, but spleens were affected in all of them. Typically, in rats, congestion and lymphoreticular hyperplasia were seen; in addition, haemosiderosis of the liver was found in the high-dose male and female rats. All except one male and one female rat survived the treatment. Mice that received 1250 ppm or more had congestion of the spleen and haemosiderin deposits.

In Osborne Mendel rats, splenomegaly was a common finding after two years' feeding of up to 20 000 ppm (mg/kg) D&C Red No. 9 (Davis & Fitzhugh, 1962).

4.3 Reproductive and prenatal 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)

D&C Red No. 9 was not mutagenic to *Salmonella typhimurium* in most studies; the two weakly positive responses that were recorded were obtained at doses well above those at which precipitation was first observed (100 μg per plate). [The Working Group considered that the effect was due to a substance other than that which precipitated.] D&C Red No. 9 did not induce mutation at the *tk* locus in mouse lymphoma L5178Y cells, sister chromatid exchange or chromosomal damage in Chinese hamster ovary cells or unscheduled DNA synthesis in rat hepatocytes *in vitro*.

After oral administration to rats, D&C Red No. 9 did not induce unscheduled DNA synthesis in the liver or micronucleus formation in bone marrow.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

D&C Red No. 9 (a certified grade of CI Pigment Red 53:1) is used in lipsticks, mouthwashes, dentifrices and drugs in some countries. CI Pigment Red 53:1 has been used extensively since the 1940s as a pigment in printing inks, coated papers, crayons, rubber and baking enamels.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

D&C Red No. 9 was tested for carcinogenicity by administration in the diet in one study in mice and in two studies in rats and by skin painting in one study in mice. In one study, it produced splenic sarcomas in male rats and increased the incidence of neoplastic liver nodules in animals of each sex. No treatment-related increase in the incidence of tumours was observed in mice.

Table 1. Genetic and related effects of D&C Red No. 9

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	167.0000	Brown *et al.* (1979)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	0.0000	Muzzall & Cook (1979)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	5000.0000[b]	Zeiger *et al.* (1988)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	167.0000	Brown *et al.* (1979)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	0.0000	Muzzall & Cook (1979)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	5000.0000[b]	Zeiger *et al.* (1988)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	167.0000	Brown *et al.* (1979)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	0.0000	Muzzall & Cook (1979)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	0	5000.0000[b]	Zeiger *et al.* (1988)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	167.0000	Brown *et al.* (1979)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	167.0000	Brown *et al.* (1979)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	0.0000	Muzzall & Cook (1979)
SA9, *Salmonella typhimurium* TA98, reverse mutation	(+)	–	5000.0000[b]	Zeiger *et al.* (1988)
SAS, *Salmonella typhimurium* TA97, reverse mutation	(+)	–	5000.0000[b]	Zeiger *et al.* (1988)
URP, Unscheduled DNA synthesis, rat primary hepatocytes *in vitro*	–	0	50.0000	Kornbrust & Barfknecht (1985)
URP, Unscheduled DNA synthesis, rat primary hepatocytes *in vitro*	–	0	1.0000	Williams *et al.* (1989)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus	–	–	15.0000	Myhr & Caspary (1991)
SIC, Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	–	–	500.0000	Ivett *et al.* (1989)
CIC, Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	–	–	250.0000	Ivett *et al.* (1989)
UPR, Unscheduled DNA synthesis, rat hepatocytes *in vivo*	–		500.0000 × 1 po	Kornbrust & Barfknecht (1985)
UPR, Unscheduled DNA synthesis, rat hepatocytes *in vivo*	–		2000.0000 × 1 po	Westmoreland & Gatehouse (1992)
MVR, Micronucleus test, rat bone-marrow *in vivo*	–		2000.0000 × 1 po	Westmoreland & Gatehouse (1992)

(+), weakly positive; –, negative; 0, not tested
[a]In-vitro tests, μg/ml; in-vivo tests, mg/kg bw; 0.0000, not given
[b]Precipitate present at all doses

5.4 Other relevant data

D&C Red No. 9 caused splenic toxicity in rats and mice.

D&C Red No. 9 was inactive in all studies in which it was tested, including assays for gene mutation in bacteria and in cultured mammalian cells, DNA damage in cultured mammalian cells and in rodents *in vivo*, sister chromatid exchange and chromosomal aberrations in cultured mammalian cells and micronucleus formation in the bone marrow of rats treated orally.

5.5 Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of D&C Red No. 9.

There is *limited evidence* in experimental animals for the carcinogenicity of D&C Red No. 9.

Overall evaluation

D&C Red No. 9 *is not classifiable as to its carcinogenicity to humans (Group 3).*

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[1]For definition of the italicized terms, see Preamble, pp. 26–30.

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