MAGENTA AND CI BASIC RED 9

These substances were considered by a previous Working Group, in 1973 (IARC, 1974a). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the evaluation.

Magenta is a mixture of several closely related homologues in varying proportions, with zero (CI Basic Red 9), one (magenta I) and two (magenta II) methyl functions on a 4,4′,4″-triaminotriarylmethane structure in the form of their hydrochloride salts. Small amounts of magenta III (with three methyl functions) may be present in magenta. The term 'basic fuchsin' has been used as a synonym for magenta, but also for CI Basic Red 9 and magenta I.

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Synonyms, structural and molecular data*

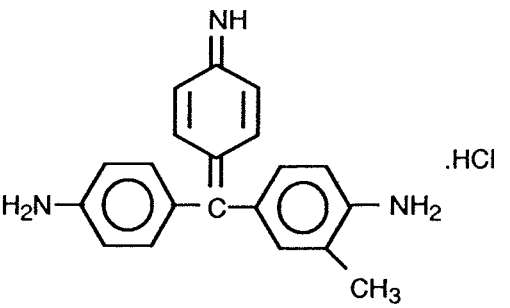
Magenta I

Chem. Abstr. Serv. Reg. No.: 632-99-5; replaces 8053-09-6

Chem. Abstr. Name: 4-[(4-Aminophenyl)(4-imino-2,5-cyclohexadien-1-ylidene)methyl]-2-methylbenzenamine, monohydrochloride

Colour Index No.: 42510

Synonyms: Basic fuchsin; basic fuchsine; basic magenta; Basic Violet 14; CI Basic Violet 14; CI Basic Violet 14, monohydrochloride; fuchsin; fuchsine; rosaniline; rosaniline chloride; rosaniline hydrochloride; rosanilinium chloride



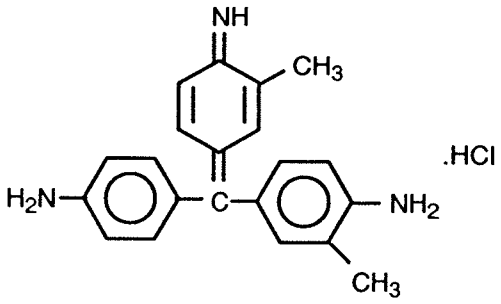
$C_{20}H_{19}N_3.HCl$ Mol. wt: 337.85

Magenta II

Chem. Abstr. Serv. Reg. No.: 26261-57-4

Chem. Abstr. Name: 4-[(4-Aminophenyl)(4-imino-3-methyl-2,5-cyclohexadien-1-ylidene)methyl]-2-methylbenzenamine, monohydrochloride

Synonym: Dimethyl fuchsin



$C_{21}H_{21}N_3.HCl$ Mol. wt: 351.9

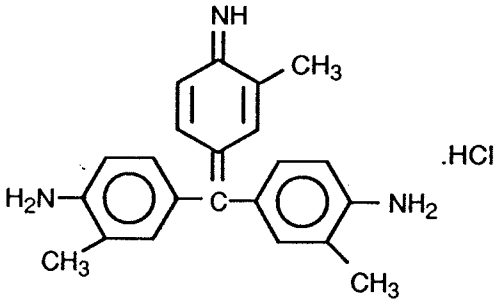
Magenta III

Chem. Abstr. Serv. Reg. No.: 3248-91-7; replaces 100359-07-7

Chem. Abstr. Name: 4-[(4-Amino-3-methylphenyl)(4-imino-3-methyl-2,5-cyclohexadien-1-ylidene)methyl]-2-methylbenzenamine, monohydrochloride

Colour Index No.: 42520

Synonyms: Basic Violet 2; CI Basic Violet 2; neofuchsine; new fuchsine; new magenta; trimethyl fuchsin; isorubine



$C_{22}H_{23}N_3.HCl$ Mol. wt: 365.9

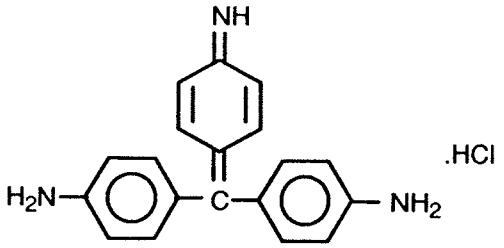
CI Basic Red 9

Chem. Abstr. Serv. Reg. No.: 569-61-9; replaces 70426-60-7; 131883-55-1

Chem. Abstr. Name: 4-[(4-Aminophenyl)(4-imino-2,5-cyclohexadien-1-ylidene)methyl]-benzenamine, monohydrochloride

Colour Index No.: 42500

Synonyms: Basic fuchsin; basic parafuchsine; Basic Red 9; basic rubine; CI Basic Red 9, monohydrochloride; *para*-fuchsin; *para*-fuchsine; parafuchsin; parafuchsine; para-magenta; pararosaniline; pararosaniline chloride; pararosaniline hydrochloride; *para*-rosaniline hydrochloride



$C_{19}H_{17}N_3.HCl$ Mol. wt: 323.82

1.1.2 *Chemical and physical properties of the substances*

Magenta I (CI 42510)

(*a*) *Description*: Dark-green crystalline powder (Green, 1990)
(*b*) *Melting-point*: 250 °C (decomposes) (Green, 1990)
(*c*) *Spectroscopy data*: Infrared and ultraviolet spectral data have been reported (Sadtler Research Laboratories, 1980; Pouchert, 1981, Green, 1990; Sadtler Research Laboratories, 1991).
(*d*) *Solubility*: Soluble in water (4 mg/ml), ethanol (30 mg/ml), ethylene glycol methyl ether (30 mg/ml) (Green, 1990) and methanol (Sadtler Research Laboratories, 1980)
(*e*) *Reactivity*: Destroyed by strong oxidizing agents; readily reduced to leuco-bases with a variety of reducing reagents; sensitive to photochemical oxidation (Bannister & Elliott, 1983)

CI Basic Red 9 (CI 42500)

(*a*) *Description*: Dark-green crystalline powder (Green, 1990)
(*b*) *Melting-point*: 268–270 °C (decomposes) (Green, 1990)
(*c*) *Spectroscopy data*: Infrared, ultraviolet and nuclear magnetic resonance spectral data have been reported (Sadtler Research Laboratories, 1980; Pouchert, 1981; US National Toxicology Program, 1986; Green, 1990; Sadtler Research Laboratories, 1991).
(*d*) *Solubility*: Soluble in water (2–3 mg/ml), ethanol (2–25 mg/ml), ethylene glycol methyl ether (50–70 mg/ml) (Green, 1990) and methanol (Sadtler Research Laboratories, 1980)
(*e*) *Reactivity*: Destroyed by strong oxidizing agents; readily reduced to leuco-bases with a variety of reducing reagents sensitive to photochemical oxidation (Bannister & Elliott, 1983)

1.1.3 *Trade names, technical products and impurities*

Magenta I

Some trade names are: Aizen Magenta; Astra Fuchsine B; Basic Magenta E 200; C-WR Violet 8; Calcozine Fuchsine HO; Calcozine Magenta RTN; Calcozine Magenta XX; Cerise

B; Diabasic Magenta; Diamond Fuchsine; Fuchsine A; Fuchsine CS; Fuchsine G; Fuchsine HO; Fuchsine N; Fuchsine RTN; Fuchsine SBP; Fuchsine Y; Magenta DP; Magenta E; Magenta G; Magenta PN; Magenta S; Magenta Superfine; Orient Basic Magenta; 12418 Red

Magenta, a cationic triarylmethane dye, is commonly, but not always, a homologous mixture of dyes; in a given lot, any homologue may be dominant. The Biological Stain Commission has determined, however, that for a lot to perform satisfactorily in all the usual applications embraced by the protocol of the Commission, CI Basic Red 9 (CI 42500) must comprise not less than 50% of the total dye present; other components that may be found are magenta I (CI 42510), magenta II and magenta III (CI 42520). Both CI Basic Red 9 and magenta III can be produced directly as pure products; however, to obtain pure magenta I and magenta II, free of the other homologue, chromatographic separation must be used (Green, 1990).

Magenta I is commercially available as a biological stain-grade product (Aldrich Chemical Co., 1992).

CI Basic Red 9

Some trade names are: Calcozine Magenta N; Fuchsine DR 001; Fuchsine SP; Fuchsine SPC; Orient Para Magenta Base

CI Basic Red 9 is available commercially as a certified biological stain at a purity of approximately 95%; it is also available at a purity of at least 88% (Aldrich Chemical Co., 1992).

1.1.4 *Analysis*

A rapid method for the assay of triarylmethane dyes (Knecht method) is titration with titanium trichloride to a colourless end-point (Bannister & Elliott, 1983).

1.2 Production and use

1.2.1 *Production*

The first triarylmethane dyes were synthesized in the late 1850s. Their structure was established by Otto Fischer and Emil Fischer in 1878 after the identification of pararosaniline (CI Basic Red 9) (Bannister & Elliott, 1983). Magenta was being produced for sale in England before 1874 (Bannister & Olin, 1965). It has been produced commercially in the USA since at least 1921 (US Tariff Commission, 1922).

In the United Kingdom, the process for manufacturing magenta has involved condensation of *ortho*-toluidine (see IARC, 1982a, 1987a) and formaldehyde (see IARC, 1982b, 1987b) in the presence of nitrotoluene, resulting mainly in the production of magenta III (Howe, 1977).

Magenta I is prepared by the reaction of a mixture of aniline (see IARC 1982c, 1987c), *ortho*- and *para*-toluidine and their hydrochlorides with nitrobenzene or a mixture of nitrobenzene and *ortho*-nitrotoluene in the presence of ferrous chloride, ferrous oxide and zinc chloride (US National Library of Medicine, 1992a). CI Basic Red 9 is prepared by the

reaction of aniline with formaldehyde in the presence of hydrogen chloride, forming 4,4′-methylenedianiline (see IARC, 1986), which is then heated with aniline and aniline hydrochloride in the presence of nitrobenzene and ferric chloride (US National Library of Medicine, 1992a).

CI Basic Red 9 (CI 42500) is produced by one company in Brazil and by two companies in the USA, and magenta I (CI 42510) is produced by one company each in India and the United Kingdom (Chemical Information Services, 1991).

No recent data were available on the production of magenta or CI Basic Red 9. US production data for magenta I were last reported for 1964, when the combined production of five US producers was reported as 53 tonnes (US Tariff Commission, 1965). US production of CI Basic Red 9 was estimated as greater than 0.9 tonnes in 1972 and 0.5 tonnes in 1975 (US National Library of Medicine, 1992a).

1.2.2 *Use*

The triarylmethane dyes have been used extensively as textile dyes. Magenta and CI Basic Red 9 are of brilliant hue, exhibit high tinctorial strength, are relatively inexpensive and may be applied to a wide range of substrates. They are not, however, very stable to light and washing, and the use of triarylmethane dyes on textiles has decreased as dyes of other chemical classes with superior properties have become available. Interest in this class of dyes was revived with the introduction of polyacrylonitrile fibres (see IARC, 1979). Triarylmethane dyes are readily adsorbed on these fibres and are surprisingly more light- and wash-fast than when they are used on natural fibres. The most important commercial black dye for acid-modified fibres is a mixture of the classical triarylmethane dyes, malachite green and magenta I (Bannister & Elliott, 1983).

Current use of triarylmethane dyes is mainly for nontextile purposes. Substantial quantities are used in the preparation of organic pigments for printing inks and in printing, in which cost and brilliance are more important than light fastness. Triarylmethane dyes and their colourless precursors (carbinols and lactones) are used extensively in high-speed photoduplicating and photoimaging systems. They are also used for specialty applications such as tinting automobile antifreeze solutions and toilet sanitary preparations, in the manufacture of carbon paper, in ink for typewriter ribbons and in jet printing for high-speed computer printers. Triarylmethane dyes may be used to colour other substrates, such as leather, fur, anodized aluminium, glass, waxes, polishes, soaps, plastics, drugs and cosmetics. They are also used extensively as microbiological stains (Bannister & Elliott, 1983).

CI Basic Red 9 can be *N*-phenylated with excess aniline and benzoic acid to form *N*,*N*′,*N*″-triphenylaminotriphenylmethane hydrochloride (Spirit Blue; CI Solvent Blue 23) (Bannister & Elliott, 1983).

1.3 Occurrence

1.3.1 *Natural occurrence*

Magenta and CI Basic Red 9 are not known to occur as natural products.

1.3.2 *Occupational exposure*

At one textile plant where socks were dyed, several classes of compounds were used for dyeing acrylic/modacrylic, wool, nylon, polyester and cotton fibres. Over 200 dyes were handled during the survey at this facility, comprising acid, disperse, basic (including magenta I), reactive and direct dyes. Spectrophotometric estimates of the average airborne concentration of active colourant were 90 $\mu g/m^3$ using personal filters and 60 $\mu g/m^3$ using area filters (US Environmental Protection Agency, 1990).

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 12 691 workers, including 8288 women, were potentially exposed to magenta I in six industries and that a total of 907 workers, including 733 women, may have been exposed to CI Basic Red 9 in four industries (US National Library of Medicine, 1992b).

1.4 Regulations and guidelines

Magenta I is allowed for use exclusively in cosmetic products not intended to come into contact with the mucous membranes (Commission of the European Communities, 1976, 1990, 1991).

2. Studies of Cancer in Humans

2.1 Case report

Rehn (1895) described three cases of bladder cancer among 45 workers employed in the manufacture of magenta (fuchsin) at a dye factory in Frankfurt, Germany. The cases had worked in the process for 15–29 years. The author mentioned that the process involved exposure to aniline, toluidine and nitrobenzene.

2.2 Cohort studies

Case and Pearson (1954) studied men who had been employed for at least six months between 1910 and 1952 in the manufacture of magenta in the British chemical industry. Detailed job histories were derived from nominal rolls of employees in factories. Workers who had been exposed to benzidine or 1- or 2-naphthylamine were excluded. Bladder cancer occurrence was determined from factory and hospital records. Deaths were identified from alphabetical lists of death certificates, and the numbers were compared with mortality rates for England and Wales for the same period (1921[Case *et al.*, 1954]–52). Results were analysed for subjects who had worked in magenta manufacture, with and without concomitant exposure to auramine. Among 85 subjects who had been engaged in the manufacture of magenta and not in the manufacture of auramine, five cases of bladder cancer were observed, with exposures ranging from one to 19 years, and three deaths from bladder cancer, with 0.13 expected (standardized mortality ratio [SMR], 23.08; $p < 0.005$). One case of bladder cancer was observed among nine subjects who had been exposed to both magenta

and auramine, but no death was seen from this cause (0.02 expected). [The Working Group noted that the process for the manufacture of magenta involved exposure to other aromatic amines used as intermediates.]

Rubino *et al.* (1982) studied 53 male workers who had been employed for at least one month in the manufacture of 'new fuchsin' (magenta III) and safranine T between 1922 and 1970 at a factory in the Province of Torino, Italy. Manufacture and use of magenta III had been discontinued in 1970–72. These workers were a subset of a cohort of 906 workers. Subjects engaged in the manufacture and use of 1- or 2-naphthylamine or benzidine were excluded from the study. Subjects and their work histories were identified from factory personnel records, and the workers were followed for mortality from 1946 to 1976, as identified from factory records and from municipal registries of current residence. Working conditions were reported to have resulted in severe exposure to magenta. Five deaths from bladder cancer were observed, while 0.08 were expected (SMR, 62.50; $p < 0.001$) on the basis of mortality rates for Italy in 1951–76. The cases had had exposure to magenta III (CI No. 42520) and safranine T (Basic Red 2, CI No. 50240) for 12–40 years. The authors noted that the processes for the manufacture of magenta and safranine T involved exposure to *ortho*-toluidine, *ortho*-aminoazotoluene (see IARC, 1975), 2,5-diaminotoluene (see IARC, 1978), 4,4′-methylenebis(2-methylaniline) (see IARC, 1974b, 1987d) and *ortho*-nitrotoluene.

Follow-up to 1981 (Decarli *et al.*, 1985) and 1989 (Piolatto *et al.*, 1991) of the 906 workers included 54 workers employed in the manufacture of magenta III and safranine T. No additional death from bladder cancer was reported after 1976.

2.3 Case–control study

Vineis and Magnani (1985) studied 512 prevalent and incident male cases of bladder cancer and 596 hospital-based controls between 1978 and 1983 in the Province of Torino, Italy—the same area considered in the cohort study described above. Complete occupational histories and related information were obtained by hospital interviews. Exposures to specific chemicals, including magenta, were estimated from ILO occupation and industry titles, using information on the industrial uses of these chemicals as described in published sources. On the basis of industrial branches in which magenta exposure could have occurred, 41 cases were classified as having been exposed prior to the age of 60, to give a relative risk of 1.8 (95% confidence interval, 1.1–2.9). On the basis of job titles in which exposure to magenta could have occurred, two cases were classified as having been exposed prior to the age of 60, with an associated relative risk of 3.0 (95% confidence interval, 0.4–20.0). [The Working Group noted that exposure to other aromatic amines could not be excluded].

3. Studies of Cancer in Experimental Animals

3.1 Oral administration

3.1.1 *Mouse*

Magenta I

Groups of 30 male and 30 female stock mice [strain and age unspecified] were treated intragastrically with 0 or 6 mg magenta I [purity unspecified] in arachis oil twice weekly for 52 weeks [about 600 mg/kg bw per week], to give a total dose of 624 mg per mouse. Controls were given subcutaneous injections of arachis oil. The mice were held as long as possible, and at 90 weeks 21/30 control and 23/30 treated males and 21/30 control and 17/30 treated females were still alive. Only gross lesions were examined microscopically. No treatment-related increase in the incidence of tumours was observed in mice of either sex; one liver-cell tumour was observed in a treated female (Bonser *et al.*, 1956). [The Working Group noted the inadequate study design.]

CI Basic Red 9

Groups of 50 male and 50 female $B6C3F_1$ mice, 6–10 weeks of age, were administered 0, 500 or 1000 mg/kg of diet (ppm) CI Basic Red 9 in the diet for 103 weeks and were killed at 110–115 weeks of age. Two lots of the test chemical were used, with purities of 93 and 99% (water was the major impurity). Mean body weights of treated mice were lower than those of controls throughout the study. At the end of the experiment, 42/50 control, 32/50 low-dose and 36/50 high-dose males and 31/50 control, 12/50 low-dose and 6/50 high-dose females were alive ($p < 0.001$). In male mice, CI Basic Red 9 caused a dose-related increase in the incidence of hepatocellular carcinomas (control, 10/50; low-dose, 20/50; high-dose, 27/50; $p < 0.001$, incidental tumour trend test). The incidence of hepatocellular adenomas was 22/50 (control), 21/50 (low-dose) and 17/50 (high-dose). The combined incidence of liver tumours was 29/50 (control), 37/50 (low-dose) and 41/50 (high-dose) ($p = 0.005$, incidental tumour trend test). In female mice, the compound caused a dose-related increase in the incidence of hepatocellular carcinomas (control, 3/49; low-dose, 19/50; high-dose, 37/49; $p < 0.001$, Cochran-Armitage trend test). The incidence of hepatocellular adenomas was 2/49 control, 18/50 low-dose ($p < 0.001$, Fischer exact test) and 4/49 high-dose. The combined incidence of liver tumours in females was 5/49 control, 35/50 low-dose and 41/49 high-dose ($p < 0.001$, Cochran-Armitage trend test). An increase in the incidence of benign and malignant adrenal phaeochromocytomas (combined) was found in females (control, 1/48; low-dose, 8/47; high-dose, 8/45; $p = 0.015$, Cochran-Armitage trend test) (US National Toxicology Program, 1986).

3.1.2 *Rat*

Magenta I

Groups of 40 male and 40 female Sprague-Dawley rats, 12 weeks old, were treated intragastrically with 0 or 400 mg/kg bw magenta I (CI 42510) [purity unspecified] in 0.9%

saline solution twice a week. Controls were given saline only. After two weeks, the dose of 400 mg/kg was found to be toxic, and treatment was discontinued for one week; after a further six weeks, half of the original dose (200 mg/kg bw) was used for the remaining treatment, for life. Average survival times were 104 weeks for control males, 59 weeks for treated males, 92 weeks for control females and 49 weeks for treated females. No treatment-related increase in the incidence of tumours was observed in rats of either sex (Ketkar & Mohr, 1982). [The Working Group noted the poor survival in the treated groups and the inadequate reporting of the study.]

CI Basic Red 9

In the same study, groups of 40 male and 40 female Sprague-Dawley rats, 12 weeks old, were treated intragastrically twice a week with 0 or 600 mg/kg bw CI Basic Red 9 [purity unspecified] in 0.9% saline. The dose of 600 mg/kg was found to be toxic and, after 12 weeks, treatment was discontinued for one week; after a further six weeks, half of the original dose (300 mg/kg bw) was used for the remaining treatment, for life. Average survival times were 104 weeks for control males, 70 weeks for treated males, 92 weeks for control female and 69 weeks for treated females. No treatment-related increase in the incidence of tumours was observed in rats of either sex (Ketkar & Mohr, 1982). [The Working Group noted the poor survival in the treated groups and the inadequate reporting of the study.]

Groups of 50 male and 50 female Fischer 344/N rats, six to seven weeks of age, were administered 0, 1000 or 2000 mg/kg of diet (ppm) (males) and 0, 500 or 1000 ppm (females) CI Basic Red 9 in the diet for 103 weeks and were killed at 110–113 weeks of age. Two lots of the test chemical were used, with purities of 93 and 99% (water was the major impurity). Increased mortality was seen in high-dose males and females, and, at the end of the experiment, 36/50 control, 29/50 low-dose and 0/50 high-dose males and 37/50 control, 35/50 low-dose and 14/50 high-dose females were still alive. CI Basic Red 9 caused significant increases in the incidences of benign and malignant tumours at various sites in both males and females (Table 1) (US National Toxicology Program, 1986).

3.1.3 *Hamster*

Magenta I

Groups of 40 male and 40 female outbred Syrian golden hamsters, 12 weeks old, were treated intragastrically with 0, 400 or 600 mg/kg bw magenta I (CI 42510) [purity unspecified] in 0.9% saline solution twice a week for life. In the high-dose group, the majority of animals died within the first 10 weeks of treatment; the lower dose was well tolerated, and body weight development and average survival times were similar to those of controls. After 72 weeks of treatment, 17/40 control and 17/40 low-dose males and 3/40 control and 0/40 low-dose females were still alive; by 88 weeks of treatment, all treated and control animals had died. No treatment-related increase in the incidence of tumours was observed in hamsters of either sex (Green *et al.*, 1979). [The Working Group noted the high mortality in the control and treated groups, especially in females.]

Table 1. Trends in tumour incidences at specific sites in Fischer 344/N rats fed diets containing CI Basic Red 9

Tumour site and type	Control	Low-dose	High-dose	p (trend)[a]
Males				
Dose (mg/kg diet)	0	1000	2000	
Skin				
Squamous-cell carcinoma	0/50	1/50	10/50	< 0.001
Trichoepithelioma	0/50	0/50	7/50	= 0.001
Sebaceous adenoma	0/50	0/50	5/50	= 0.006
Subcutis				
Fibroma	2/50	20/50	16/50	< 0.001
Zymbal gland				
Carcinoma	1/50	1/50	13/50	< 0.001
Thyroid gland				
Follicular adenoma	0/49	0/46	9/44	< 0.001
Follicular carcinoma	0/49	5/46	18/44	< 0.001
Combined	0/49	5/46	25/44	< 0.001
Liver				
Hepatocellular neoplastic nodule	5/50	14/50	6/50	= 0.447
Hepatocellular carcinoma	0/50	2/50	8/50	= 0.001
Combined	5/50	15/50	14/50	= 0.021
Females				
Dose (mg/kg diet)	0	500	1000	
Subcutis				
Fibroma	0/50	15/50	10/50	= 0.005
Zymbal gland				
Carcinoma	0/50	2/50	7/50	= 0.003
Thyroid				
Follicular adenoma	0/47	0/48	4/50	= 0.017
Follicular carcinoma	0/47	2/48	2/50	> 0.05
Combined	0/47	2/48	6/50	= 0.009

From US National Toxicology Program (1986)
[a]Cochran-Armitage trend test

CI Basic Red 9

In the same study, similar groups of hamsters were treated intragastrically with 0, 300 or 600 mg/kg bw CI Basic Red 9 [purity unspecified] in 0.9% saline solution twice a week for life. In the high-dose group, the majority of animals died within the first 10 weeks of treatment; the lower dose was well tolerated, and body weight development and average survival times were similar to those of controls. After 72 weeks of treatment, 17/40 control and 15/40 low-dose males and 3/40 control and 3/40 low-dose females were still alive; by 88 weeks of treatment, all treated and control animals had died. No treatment-related increase in the incidence of tumours was observed in hamsters of either sex (Green *et al.*, 1979). [The

Working Group noted the high mortality in control and treated animals, especially in females.]

3.2 Subcutaneous administration

Rat

In a study reported in a short communication, a group of 20 BD III rats [sex unspecified] was treated once a week with 10 mg of an aqueous solution of 1% CI Basic Red 9 [purity unspecified] for a maximum of 515 days (total dose, 650 mg). The mean life span was 545 days in treated rats and 780 days in controls. The first local sarcoma appeared at 300 days, after a total dose of 370 mg of the dye. Spindle-cell sarcomas were found in 7/12 rats surviving after the appearance of the first tumour, compared to a spontaneous incidence of sarcomas in these rats of less than 0.5% (Druckrey *et al.*, 1956).

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*

No data were available to the Working Group.

4.2.2 *Experimental systems*

CI Basic Red 9 (93% pure) was tested for subchronic toxicity in groups of 10 male and 10 female Fischer 344/N rats and B6C3F$_1$ mice fed diets containing 0, 250, 500, 1000, 2000 or 4000 ppm (mg/kg) CI Basic Red 9 for 13 weeks (US National Toxicology Program, 1986). Body weight gain was reduced in female rats at the two highest doses, by 14 and 37%, and in male rats at the high dose, by 40%. Two females and one male rat in the high-dose group died before the end of the study. Adenomatous goitre was seen in 9/9 females and 9/10 males in the high-dose group; diffuse hyperplasia of the thyroid gland occurred in 7/10 females given 2000 ppm and in 1/10 males given 4000 ppm. Pituitary basophilic hypertrophy was found in 8/9 female and 5/7 male rats that received 4000 ppm and in 1/10 female and 1/9 male rats that received 2000 ppm. None of these lesions was found in controls. Fatty changes in the liver were observed in 1/10 male and 4/10 female rats in the high-dose groups. In mice, body weight gain was at least 10% lower than that in controls in males in the high-dose group and in females that received 1000 ppm or more. Clinical signs of toxicity were not observed.

A longer study was performed in rats to observe effects on the thyroid gland (US National Toxicology Program, 1986). Groups of 10 male Fischer 344/N rats were fed diets containing 0 or 2000 ppm (mg/kg) and groups of 10 females, 0 or 1000 ppm CI Basic Red 9

(93 and 99% pure) for 52 weeks. Thyroid glands were palpated regularly; serum thyroxin levels were determined during the first and second week of quarantine and at weeks 13, 26, 39 and 52. The final mean body weights of treated males were 13% lower than that of controls and those of females were 9% lower. Of the male rats, 1/10 had hyperplasia, 1/10 an adenoma and 1/10 a carcinoma of the follicular epithelium of the thyroid gland at the end of treatment. Follicular cysts of the thyroid gland were observed in 2/10 females and 1/10 males. The relative weight of thyroid glands was 1.69 times that of the controls in males and 1.13 times that of controls in females. The concentration of thyroxin was significantly lower than that of controls by week 13 in males and by week 52 in females. The ratio of thyroxin level in dosed groups to that in controls was 0.52 in males and 0.64 in females at 52 weeks. Four of 10 males had fatty changes of the liver, two had focal necrosis of the liver and one, a neoplastic nodule.

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 2 and Appendices 1 and 2)

No data were available on the genetic and related effects of magenta.

CI Basic Red 9 induced repairable DNA damage in bacterial differential toxicity assays, in the absence of activation. It was generally not mutagenic to *Salmonella typhimurium*; some activity was observed in the presence of exogenous activating systems, especially those derived from Syrian hamster liver. It induced forward mutation in *Escherichia coli* in the absence of exogenous metabolism. It did not induce mitotic recombination in *Saccharomyces cerevisiae*.

Conflicting reports were obtained for induction of unscheduled DNA synthesis in rat hepatocytes *in vitro*: in a single study, it induced unscheduled DNA synthesis in primary hepatocytes from Syrian hamsters but not from rats. The compound gave inconclusive responses in two tests for mutation at the *tk* locus in mouse lymphoma L5178Y cells and positive responses in another. CI Basic Red 9 did not induce chromosomal rearrangement or sister chromatid exchange in Chinese hamster ovary cells. It induced morphological transformation of Syrian hamster embryo cells in the presence, but not in the absence, of an exogenous activating system from hamster liver. It also induced transformation of BALBc/3T3 mouse cells and enhanced Rauscher leukaemia virus-induced transformation of Fischer rat embryo cells.

Oral administration of CI Basic Red 9 to mice or rats resulted in urine that was mutagenic to *S. typhimurium*. The dye did not induce mitotic recombination in *S. cerevisiae* or mutation in *S. typhimurium* recovered from the peritoneal cavity of mice, and it did not induce mutation in *S. typhimurium* after intramuscular administration.

Table 2. Genetic and related effects of CI Basic Red 9 (*para*-rosaniline)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
PRB, Prophage induction, SOS repair test, DNA strand breaks, cross-links or related damage	-	0	500.0000	Speck *et al.* (1978)
ECL, *Escherichia coli pol* A^+/pol A^-W3110-P3478 differential toxicity (liquid suspension)	+	0	20.0000	Rosenkranz & Poirier (1979)
BRD, *Escherichia coli* WP2/WP67/CM871, differential toxicity	+	-	155.0000	De Flora *et al.* (1984a)
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	-	250.0000	Simmon (1979a)
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	-	1070.0000	De Flora (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	+[b]	167.0000	Dunkel *et al.* (1984)
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	+	17.0000	Mortelmans *et al.* (1986)
SA2, *Salmonella typhimurium* TA102, reverse mutation	-	-	0.0000	De Flora *et al.* (1984b)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	-	-	125.0000	Rosenkranz & Poirier (1979)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	-	-	250.0000	Simmon (1979a)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	-	-	1070.0000	De Flora (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	-	-	167.0000	Dunkel *et al.* (1984)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	-	(+)	500.0000	Mortelmans *et al.* (1986)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	-	-	250.0000	Simmon (1979a)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	-	-	1070.0000	De Flora (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	-	-	167.0000	Dunkel *et al.* (1984)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	-	-	167.0000	Mortelmans *et al.* (1986)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	-	-	125.0000	Rosenkranz & Poirier (1979)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	-	-	250.0000	Simmon (1979a)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	-	-	1070.0000	De Flora (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	-	-	167.0000	Dunkel *et al.* (1984)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	-	250.0000	Simmon (1979a)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	-	1070.0000	De Flora (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	(+)[c]	167.0000	Dunkel et al. (1984)
SA9, *Salmonella typhimurium* TA98, reverse mutation[d]	0	+	0.0000	Arni et al. (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	+	50.0000	Mortelmans *et al.* (1986)
SAS, *Salmonella typhimurium* TA1586, reverse mutation	-	-	250.0000	Simmon (1979a)

Table 2 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	(+)	1600.0000	De Flora *et al.* (1984b)
ECF, *Escherichia coli* exclusive of strain K12, forward mutation	+	(+)	5000.0000	Hayes *et al.* (1984)
ECW, *Escherichia coli* WP2 *uvrA*, reverse mutation	–	–	167.0000	Dunkel *et al.* (1984)
SCH, *Saccharomyces cerevisiae*, homozygosis by mitotic recombination	–	–	300.0000	Simmon (1979b)
URP, Unscheduled DNA synthesis, rat primary hepatocytes *in vitro*	–	0	1.0000	Williams *et al.* (1982)
URP, Unscheduled DNA synthesis, rat primary hepatocytes *in vitro*	+	0	2.2000	US National Toxicology Program (1986)
URP, Unscheduled DNA synthesis, rat primary hepatocytes *in vitro*	–	0	3.2400	Kornbrust & Barfknecht (1984)
UIA, Unscheduled DNA synthesis, Syrian hamster primary hepatocytes *in vitro*	+	0	3.2400	Kornbrust & Barfknecht (1984)
G5T, Gene mutation, mouse lymphoma L5178Y cells *tk* locus	+	+	1.0000	Mitchell *et al.* (1988)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus	?	–	7.5000	Myhr & Caspary (1988)
SIC, Sister chromatid exchange, Chinese hamster cells *in vitro*	–	–	15.0000	Anderson *et al.* (1990)
CIC, Chromosomal aberrations, Chinese hamster cells *in vitro*	–	–	50.0000	Anderson *et al.* (1990)
TBM, Cell transformation, BALB/c 3T3 mouse cells	+	0	0.0400	Dunkel *et al.* (1981)
TCS, Cell transformation, Syrian hamster embryo cells, clonal assay	–	0	1.0000	Pienta *et al.* (1977)
TCS, Cell transformation, Syrian hamster embryo cells, clonal assay	–	+	2.0000	Pienta & Kawalek (1981)
TRR, Cell transformation, RLV/Fischer rat embryo cells	+	0	1.4000	Dunkel *et al.* (1981)
BFA, Urine from mouse, microbial mutagenicity	+	+	0.0000 × 1 po	Haworth *et al.* (1981); abstr.
BFA, Urine from mouse and rat, microbial mutagenicity	+	+	120.0000 × 2 po	Lawlor *et al.* (1987)
HMM, Host-mediated assay, *Salmonella typhimurium* in mice	–		1600.0000 × 1 po	Simmon *et al.* (1979)
HMM, Host-mediated assay, *Salmonella typhimurium* in mice	–		1600.0000 × 1 im	Simmon *et al.* (1979)
HMM, Host-mediated assay, *Saccharomyces cerevisiae* in mice	–		1600.0000 × 1 po	Simmon *et al.* (1979)

+, positive; (+), weakly positive; –, negative; 0, not tested; ?, inconclusive (variable response in several experiments within an adequate study)

[a]In-vitro tests, μg/ml; in-vivo tests, mg/kg bw; 0.0000, not given

[b]Positive in 2/4 laboratories

[c]Positive in 1/4 laboratories

[d]Automated COBAS Bact apparatus also positive

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Magenta and CI Basic Red 9, a common constituent of magenta, were first produced commercially in the late nineteenth century in Germany. As the industry developed in the early twentieth century, it converted in some countries, such as Italy and the United Kingdom, from production of magenta (prepared from a mixture of aniline and *ortho*-toluidine) to production of magenta III (prepared from *ortho*-toluidine without aniline).

Magenta and CI Basic Red 9 have been used to dye textile fibres, in the preparation of pigments for printing inks and in other specialty applications, such as biological stains.

5.2 Human carcinogenicity data

Two small cohorts of workers engaged in the manufacture of magenta were studied in the United Kingdom and Italy. Marked excesses of cancer of the urinary bladder were identified. Although efforts were made to exclude workers exposed to 2-naphthylamine and benzidine, both cohorts may also have been exposed to aromatic amines present as intermediates and suspected to be urinary bladder carcinogens, such as *ortho*-toluidine.

5.3 Animal carcinogenicity data

No adequate study was available to evaluate the carcinogenicity in experimental animals of magenta or of magenta I, magenta II or magenta III.

CI Basic Red 9 was tested for carcinogenicity in one study in mice and in one study in rats by oral administration in the diet and in one study in rats by subcutaneous administration. After oral administration, the compound induced hepatocellular carcinomas in male and female mice and in male rats; adrenal gland phaeochromocytomas in female mice; benign and malignant skin tumours in male rats; and subcutaneous fibromas, thyroid gland follicular-cell tumours and Zymbal gland carcinomas in male and female rats. Subcutaneous administration to rats resulted in a high incidence of local sarcomas.

5.4 Other relevant data

CI Basic Red 9 lowers thyroxin levels and caused hypertrophy of the thyroid in rats and mice.

CI Basic Red 9 induced DNA damage in bacteria, but conflicting results were obtained in assays for gene mutation. Mitotic recombination was not induced in yeast. In cultured mammalian cells, there was no induction of sister chromatid exchange or chromosomal aberrations, but DNA damage and cell transformation were induced; assays for gene mutation gave inconsistent results.

5.5 Evaluations[1]

There is *inadequate evidence* in humans for the carcinogenicity of magenta.

There is *inadequate evidence* in humans for the carcinogenicity of CI Basic Red 9.

There is *sufficient evidence* that the manufacture of magenta entails exposures that are carcinogenic.

There is *sufficient evidence* in experimental animals for the carcinogenicity of CI Basic Red 9.

There is *inadequate evidence* in experimental animals for the carcinogenicity of magenta.

Overall evaluation

The manufacture of magenta *entails exposures that are carcinogenic (Group 1).*

CI Basic Red 9 *is possibly carcinogenic to humans (Group 2B).*

Magenta containing CI Basic Red 9 is *possibly carcinogenic to humans (Group 2B).*

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

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