

CHEMICAL AGENTS AND RELATED OCCUPATIONS

VOLUME 100 F
A REVIEW OF HUMAN CARCINOGENS

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, 20-27 October 2009

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IARC MONOGRAPHS
ON THE EVALUATION
OF CARCINOGENIC RISKS
TO HUMANS

MAGENTA AND MAGENTA PRODUCTION

Magenta and magenta production were considered by previous IARC Working Groups in 1973, 1986, 1987, and 2008 ([IARC, 1974](#), [1987a](#), [b](#), [2010](#)). Since that time new data have become available, which have been incorporated in this *Monograph*, and taken into consideration in the present evaluation.

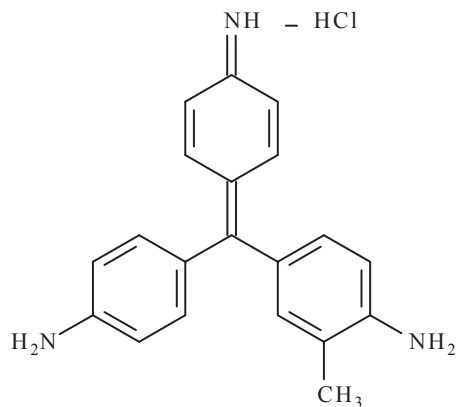
1. Exposure Data

Historically, the dye name Magenta has been used to refer to the mixture Basic Fuchsin, with its four major constituents Basic Red 9 (Magenta 0), Magenta I (Rosanilin), Magenta II, and Magenta III (New Fuchsin). Although samples of Basic Fuchsin can vary considerably in the proportions of these four constituents, today all except Magenta II are available commercially under their own name. Of these, Magenta I and Basic Red 9 are the most common ([IARC, 2010](#)).

1.1 Identification of the agents

1.1.1 Magenta I

Chem. Abstr. Serv. Reg. No.: 632-99-5
CAS Name: 4-[(4-Aminophenyl)(4-imino-2,5-cyclohexadien-1-ylidene)methyl]-2-methylbenzenamine, hydrochloride (1:1)



$C_{20}H_{19}N_3 \cdot HCl$

Relative molecular mass: 337.85

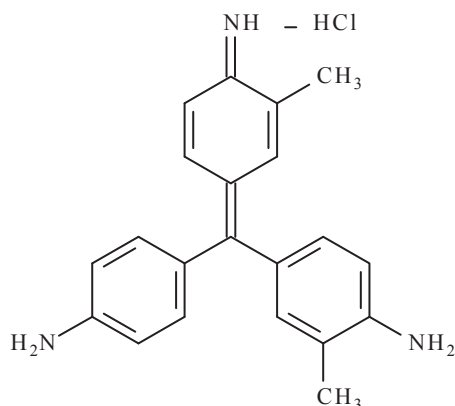
Description: Metallic green, lustrous crystals

Melting-point: Decomposes above 200 °C

Solubility: Slightly soluble in water (4 mg/mL); soluble in ethanol (30 mg/mL) and ethylene glycol methyl ether (30 mg/mL); insoluble in diethyl ether

1.1.2 Magenta II

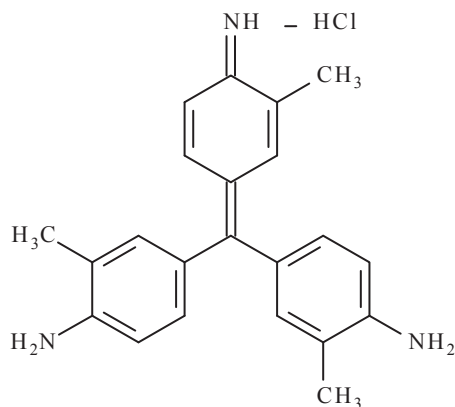
Chem. Abstr. Serv. Reg. No.: 26261-57-4
 CAS Name: 4-[(4-Aminophenyl)(4-imino-3-methyl-2,5-cyclohexadien-1-ylidene)methyl]-2-methylbenzenamine, hydrochloride (1:1)



$C_{21}H_{22}N_3 \cdot HCl$
 Relative molecular mass: 351.87
 No information regarding the chemical and physical properties of Magenta II was available to the Working Group.

1.1.3 Magenta III

Chem. Abstr. Serv. Reg. No.: 3248-91-7
 CAS Name: 4,4'-[(4-imino-3-methyl-2,5-cyclohexadien-1-ylidene)methylene]bis[2-methylbenzenamine], hydrochloride (1:1)

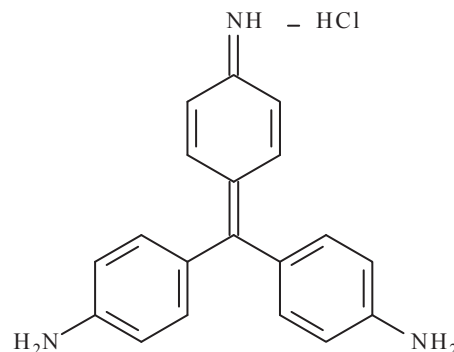


$C_{22}H_{23}N_3 \cdot HCl$
 Relative molecular mass: 365.90

Description: Green crystalline powder
Solubility: Soluble in water (20 mg/mL), ethanol (20 mg/mL), and ethylene glycol methyl ether (20 mg/mL)

1.1.4 Basic Red 9 (Magenta 0)

Chem. Abstr. Serv. Reg. No.: 569-61-9
 CAS Name: 4,4'-[(4-imino-2,5-cyclohexadien-1-ylidene)methylene]bis[benzenamine], hydrochloride (1:1)



$C_{19}H_{17}N_3 \cdot HCl$
Description: Pale violet powder
Melting-point: 269 °C (decomposes)
Solubility: Slightly soluble in water (3 mg/mL); soluble in ethanol (25 mg/mL) and ethylene glycol methyl ether (70 mg/mL)

From [Green \(1990\)](#), [O'Neil \(2006\)](#), and [Lide \(2008\)](#).

1.2 Manufacturing processes

Magenta was among the first synthetic dyes to be produced in the 1850s. It has been produced commercially in the United States of America (USA) since at least 1921 ([IARC, 2010](#)).

In the United Kingdom, the process for manufacturing Magenta has involved condensation of *ortho*-toluidine and formaldehyde in the presence of nitrotoluene, resulting mainly in the production of Magenta III. Magenta I is prepared by the reaction of a mixture of aniline, *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. CI Basic Red 9 is prepared by the reaction of aniline with formaldehyde in the presence of hydrogen chloride, forming 4,4'-methylenedianiline, which is then heated with aniline and aniline hydrochloride in the presence of nitrobenzene and ferric chloride (IARC, 2010).

1.3 Human exposure

1.3.1 Occupational exposure

The only well described groups of workers exposed during magenta production include those in a dyestuff-manufacturing plant in Ludwigshafen, Germany (Rehn, 1895), in the manufacture of magenta in the chemical industry in the United Kingdom (1910–52) (Case & Pearson, 1954) and the in manufacture of 'new fuchsin' in an Italian dyestuffs factory (Rubino *et al.*, 1982; Piolatto *et al.*, 1991). Reported exposures were based on duration of exposure, years since first exposure, age at first exposure, job category or years since last exposure. No environmental or biological measurements have been reported for these plants or any other plants historically or currently producing magenta.

Production of magenta may involve exposure to process chemicals (e.g. aniline, *ortho*- and *para*-toluidine, and – historically – arsenic acid). Exposure to other chemicals used and produced at the same location may also occur (e.g. benzidine, 1-naphthylamine, 2-naphthylamine, auramine, aniline) (Case & Pearson, 1954).

2. Cancer in Humans

Magenta production was last reviewed in IARC Monograph Volume 99 (IARC, 2010). A 23-fold excess of bladder tumours was found

in men engaged in the manufacture of magenta ($P < 0.005$), compared with mortality rates for the male population in England and Wales (Case & Pearson, 1954). Although care had been taken to eliminate from the analysis those workers who were recorded as also having been in contact with auramine, 1- or 2-naphthylamine or benzidine, exposure to non-magenta bladder carcinogens could not be entirely excluded. Rubino *et al.* (1982) reported two deaths from bladder cancer after exposure to magenta in the manufacture of 'new fuchsin' (Magenta III) (see Table 2.1, available at <http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-08-Table2.1.pdf>). Bladder cancer was associated with employment in industries with potential magenta exposure in Torino, Italy (Vineis & Magnani, 1985; see Table 2.2, available at <http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-08-Table2.2.pdf>). These studies indicate that excess bladder cancer risks are caused by the production of magenta, but co-exposures preclude a conclusion for magenta itself.

3. Cancer in Experimental Animals

Studies on the carcinogenicity of magenta in the mouse, rat, and hamster after oral administration, and studies on the carcinogenicity of CI Basic Red 9 in these species after oral administration or subcutaneous injection, have been reviewed in previous IARC Monographs (IARC, 1974, 1987b, 1993, 2010). There have been no additional carcinogenicity studies in animals reported since the most recent evaluation (IARC, 2010).

3.1 Magenta

Magenta was tested for carcinogenicity by oral administration in one experiment in mice (Bonser *et al.*, 1956), one experiment in rats

Table 3.1 Carcinogenicity studies of oral administration of Magenta (CI Basic Red 9) in experimental animals

Species, strain (sex) Duration Reference	Route Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
CI Basic Red 9				
Mouse, B6C3F ₁ (M, F) 103 wk NTP (1986)	Feed Groups of 50 M and 50 F mice were fed a diet containing 0, 500 or 1000 ppm CI Basic Red 9 for 103 wk.	Hepatocellular carcinomas:		Purity 93–99%
		M–10/50, 20/50, 27/50	<i>P</i> < 0.001 (trend)	
		F–3/49, 19/50, 37/49	<i>P</i> < 0.001 (trend)	
		Adrenal pheochromocytomas (benign or malignant):		
		F–1/48, 8/47, 8/45	<i>P</i> = 0.015 (trend)	
Rat, F344/N (M, F) 103 wk NTP (1986)	Feed Groups of 50 M and 50 F rats were fed a diet containing 0, 1000 or 2000 ppm CI Basic Red 9 for 103 wk.	Hepatocellular carcinomas:		Purity 93–99%
		M–0/50, 2/50, 8/50	<i>P</i> = 0.001 (trend)	
		Thyroid-follicular cell carcinomas:		
		M–0/49, 5/46, 18/44	<i>P</i> < 0.001 (trend)	
		F–0/47, 2/48, 2/50	NS	
		Thyroid-follicular cell adenomas or carcinomas:		
		M–0/49, 5/46, 25/44	<i>P</i> < 0.001 (trend)	
		F–0/47, 2/48, 6/50	<i>P</i> = 0.009 (trend)	
		Zymbal gland carcinomas:		
		M–1/50, 1/50, 13/50	<i>P</i> < 0.001 (trend)	
		F–0/50, 2/50, 7/50	<i>P</i> = 0.003 (trend)	
		Subcutaneous-fibromas:		
		M–2/50, 20/50, 16/50	<i>P</i> < 0.001 (trend)	
		F–0/50, 15/50, 10/50	<i>P</i> = 0.005 (trend)	
		Skin-squamous cell carcinomas:		
M–0/50, 1/50, 10/50	<i>P</i> < 0.001 (trend)			
Skin-trichoepitheliomas:				
M–0/50, 0/50, 7/50	<i>P</i> = 0.001 (trend)			
Skin-sebaceous adenomas:				
M–0/50, 0/50, 5/50	<i>P</i> = 0.006 (trend)			

F, female; M, male; NS, not significant; wk, week or weeks

([Ketkar & Mohr, 1982](#)) and one experiment in hamsters ([Green et al., 1979](#)). These studies were found to be inadequate to evaluate the carcinogenicity of magenta in experimental animals.

3.2 CI Basic Red 9

CI Basic Red 9 was tested for carcinogenicity by oral administration in one study in mice, ([NTP, 1986](#)) in two studies in rats ([Ketkar & Mohr, 1982](#); [NTP, 1986](#)) and one study in hamsters ([Green et al., 1979](#)). It has also been tested by subcutaneous injection in one study in rats ([Druckrey et al., 1956](#)). Only the study by [NTP \(1986\)](#) was adequate to evaluate the carcinogenicity of CI Basic Red 9 in experimental animals.

After oral administration in the diet, CI Basic Red 9 increased the incidence of hepatocellular carcinomas in male and female mice and in male rats. It increased the incidence of adrenal gland pheochromocytomas (benign or malignant) in female mice, and of benign (trichoepitheliomas and sebaceous adenomas) and malignant (squamous cell carcinomas) skin tumours in male rats. In rats, it also increased the incidence of subcutaneous fibromas and Zymbal gland carcinomas in males and females, of thyroid follicular-cell carcinomas in males, and of thyroid follicular-cell adenomas and carcinomas combined in females ([NTP, 1986](#); [Table 3.1](#)). In an early study, subcutaneous injection of Basic Red 9 (parafuchsin) in rats resulted in a high incidence of local sarcomas ([Druckrey et al., 1956](#)). [The Working Group noted that this study lacks detail and has no concurrent controls.]

4. Other Relevant Data

A general Section on “Aromatic amines: metabolism, genotoxicity, and cancer susceptibility” appears as Section 4.1 in the *Monograph* on 4-aminobiphenyl in this volume.

No studies in laboratory animals or in humans were found on the metabolism of magenta. No adequate studies were available on the carcinogenicity of magenta in experimental animals. However, the related compound CI Basic Red 9, which is a component of commercial magenta, induced liver tumours in rats and mice. Excess risk for cancer of the urinary bladder was reported in workers involved in the manufacture of magenta. Magenta was mutagenic in *S. typhimurium* strains TA98, TA100, and TA1535 when tested in the presence of metabolic activation ([Mortelmans et al., 1986](#)).

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of magenta production. Magenta production causes cancer of the urinary bladder.

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

There are insufficient mechanistic data relevant to the carcinogenicity of magenta in humans or experimental animals.

Magenta production is *carcinogenic to humans (Group 1)*.

Magenta is *possibly carcinogenic to humans (Group 2B)*.

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