CARBAZOLE

Data were last reviewed in IARC (1983) and the compound was classified in *IARC Monographs* Supplement 7 (1987).

1. Exposure Data

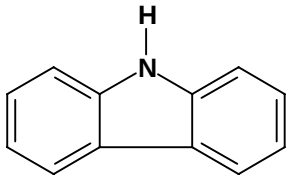
1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Services Reg. No.: 86-74-8

Systematic name: 9H-Carbazole

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_{12}H_9N$ Relative molecular mass: 167.2

1.1.3 *Physical properties* (for details, see IARC, 1983)

(*a*) *Boiling-point*: 355°C

(*b*) *Melting-point*: 247–248°C

(*c*) *Conversion factor*: $mg/m^3 = 6.84 \times ppm$

1.2 Production, use and human exposure

Carbazole occurs in the products of incomplete combustion of nitrogen-containing organic matter, e.g., tobacco. It in an important dye intermediate (IARC, 1983).

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

Carbazole was tested for carcinogenicity in mice by administration in the diet, by skin application and by subcutaneous injection. In the study by oral administration, a dose-dependent increase in the incidence of liver neoplastic nodules and hepatocellular carcinomas was observed. Papillomas and carcinomas of the forestomach occurred in animals that received the highest dose. The other studies in mice were considered inadequate for evaluation (IARC, 1983).

3.1 Intraperitoneal administration

Mouse: CD-1 mouse pups born to untreated dams were administered intraperitoneal doses of 5, 10 and 20 μL of either dimethyl sulfoxide (DMSO) or a 50 mM solution of carbazole in DMSO on days 1, 8 and 15 of postnatal life, respectively. The total dose of carbazole was 1.75 μmol per mouse. The effective numbers of mice (i.e., those alive at two months of age) were: DMSO control, 46 females, 38 males; carbazole-treated, 42 females, 34 males. All of the mice were killed at 52 weeks and examined for gross lesions. The liver, lungs and any gross lesions in other tissues were examined histologically. No increase in neoplasms was found (Weyand *et al*., 1993). [The Working Group noted the limited exposure.]

3.2 Administration with known carcinogens

3.2.1 *Rat*

In a screening assay for promoters of urinary bladder carcinogenesis, groups of male Fischer 344 rats, six weeks of age, were given drinking-water either alone or containing 0.05% *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine (BBN) for two weeks. Each of these groups was then subdivided into two groups, which received basal diet either alone or containing 0.6% carbazole for 22 weeks. On day 22 of the experiment, the left ureter of all rats was ligated. The rats were killed at week 24 and autopsied. The urinary bladder, kidneys, ureter and liver were examined histologically. No neoplasia or hyperplasia was observed in liver, kidneys or ureter. The proportions of the groups with papillary or nodular hyperplasia or with papilloma of the urinary bladder, respectively, were: BBN alone, 3/44 (7%) and 0/44; BBN and carbazole diet, 5/14 (36%) ($p < 0.05$) and 2/14 (14%); carbazole diet alone, 0/15 and 0/15 (Miyata *et al*., 1985).

Male Fischer 344 rats, six weeks of age, were given drinking-water either alone or containing 0.2% *N*-bis(2-hydroxypropyl)nitrosamine (DHPN) for one week. One week later, each of these groups was subdivided into two groups, which received basal diet either alone or containing 0.6% carbazole for 50 weeks. All rats were killed at the end of week 52 and autopsied. The urinary bladder, kidneys, liver, thyroid and lungs and any organ with gross abnormalities were examined histologically. The proportions of tumour-bearing rats and the multiplicity of certain tumours are shown in Table 1. Carbazole showed no promoting effect in liver, lung or thyroid and did not induce tumours in the

Table 1. Incidence and multiplicity of certain tumours in rats treated with carbazole in an initiation-promotion model

Treatment		DHPN	DHPN–Carbazole	Carbazole
Number of rats		20	19	20
Lung	Adenoma, no. (%)	18 (90)	17 (89)	Not
	No. per rat	2.25 ± 1.41	2.05 ± 1.18	recorded
	Carcinoma, no. (%)	16 (80)	11 (58)	
	No. per rat	1.60 ± 1.29	1.00 ± 0.88	
Thyroid	Adenoma, no. (%)	7 (35)	8 (42)	Not
	Carcinoma, no. (%)	14 (70)	15 (79)	recorded
	No. per rat (adenoma + carcinoma)	1.56 ± 1.31	1.67 ± 0.79	
Kidney	Renal cell, no. (%)	6 (30)	4 (21)	Not
	Nephroblastoma, no. (%)	2 (10)	4 (21)	recorded
	Pelvic papilloma, no. (%)	0	5 (26) ($p < 0.05$)	
	Pelvic carcinoma, no. (%)	4 (21)	7 (37)	
	Pelvic papilloma + carcinoma, no. (%)	4 (21)	11 (58) ($p < 0.05$)	
Bladder	Papilloma (%)	2 (11)	4 (21)	Not
	Carcinoma (%)	1 (5)	3 (16)	recorded
	Papilloma + carcinoma (%)	3 (15)	7 (37)	
Liver	Foci (%)	5 (25)	11 (58)	9 (45)
	Hyperplastic nodules (%)	1 (5)	0	1 (5)

From Shirai *et al*. (1988)

lung. It increased the incidence of transitional-cell tumours in the renal pelvis significantly and the incidence of urinary bladder tumours slightly, but not significantly (Shirai *et al*., 1988).

Male Fischer 344 rats [age unspecified] were given a single intraperitoneal injection of 200 mg/kg bw *N*-nitrosodiethylamine and then, two weeks later, they were divided into three equal groups and maintained for six weeks on basal diet, either alone (one group) or containing 33 ppm (mg/kg) carbazole (two groups). One week into this period, all rats were subjected to partial hepatectomy. All rats were killed eight weeks from the beginning of the experiment and their livers were assessed for development of glutathione-*S*-transferase placental form (GST-P)-positive foci by immunohistochemical staining and image analysis. There was no difference among the *N*-nitrosodiethylamine-treated rats in the area of liver foci between the groups on control and carbazole-containing diet (Hasegawa *et al*., 1989).

3.2.1 *Hamster*

A group of 40 Syrian golden hamsters [sex unspecified], six weeks of age, was given a single intraperitoneal injection of 20 mg/kg bw 2,2′-dioxo-*N*-nitrosodipropylamine

(DOPN), while another group of 80 animals was left untreated. Beginning one week later, half of each group continued to receive basal diet alone, while the other half received basal diet containing 0.2% carbazole until they were killed at week 40. The numbers of GST-P-positive foci, expressed as foci/cm^2, were: basal diet, 0; carbazole diet, 3.6 ± 1.3 ($p < 0.001$); DOPN + basal diet, 9.2 ± 4.1; DOPN + carbazole diet, 19.0 ± 7.6 ($p < 0.001$) (Moore *et al*., 1987).

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-Hydroxycarbazole has been reported to be a urinary metabolite of carbazole in rats and rabbits (IARC, 1983).

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*

Carbazole was not mutagenic to *Salmonella typhimurium* (IARC, 1983).

5. Evaluation

No epidemiological data relevant to the carcinogenicity of carbazole were available.

There is *limited evidence* in experimental animals for the carcinogenicity of carbazole.

Overall evaluation

Carbazole is *not classifiable as to its carcinogenicity to humans (Group 3)*.

6. References

Hasegawa, R., Mutai, M., Imaida, K., Tsuda, H., Yamaguchi, S. & Ito, N. (1989) Synergistic effects of low-dose hepatocarcinogens in induction of glutathione *S*-transferase P-positive foci in rat liver. *Jpn. J. Cancer Res*., **80**, 945–951

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