

AZACITIDINE

This substance was considered by a previous Working Group, in October 1980, under the title 5-azacytidine (IARC, 1981). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

1. Chemical and Physical Data

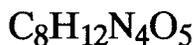
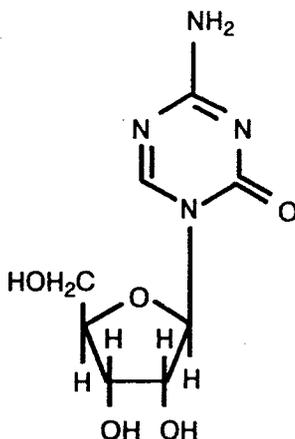
1.1 Synonyms

Chem. Abstr. Services Reg. No.: 320-67-2

Chem. Abstr. Name: 1,3,5-Triazin-2(1H)-one, 4-amino-1-β-ribofuranosyl

Synonyms: Antibiotic U 18496; 5-azacytidine; ladakamycin; NSC 102816; U-18496; WR-183027

1.2 Structural and molecular formulae and molecular weight



Mol. wt: 244.2

1.3 Chemical and physical properties of the pure substance

From Winkley and Robins (1970), unless otherwise specified

(a) *Description:* White crystalline powder

- (b) *Melting-point*: 235-237°C (decomposes)
- (c) *Optical rotation*: $[\alpha]_D^{26} = +26.6^\circ\text{C}$ ($c = 1.00$; in water)
- (d) *Solubility*: Soluble in warm water (40 mg/ml), cold water (14 mg/ml), 0.1 N hydrochloric acid (28 mg/ml) and 0.1 N sodium hydroxide (43 mg/ml); soluble in 35% ethanol (14.2-15.0 mg/l), acetone (1 mg/ml), chloroform (1 mg/ml), hexane (1 mg/ml) and dimethyl sulfoxide (52.7 mg/ml) (von Hoff *et al.*, 1975)
- (e) *Spectroscopy data*: Ultraviolet, infrared and nuclear magnetic resonance spectra have been reported (Beisler, 1978).
- (f) *Stability*: Very unstable in aqueous media, rapid degradation to complex products occurring within hours of dissolution in intravenous solutions at room temperature (Reynolds, 1989)

1.4 Technical products and impurities

Trade name: Mylosar

Azacitidine is available as a lyophilized powder in vials containing 100 mg of the compound with 100 mg mannitol for reconstitution as injections of 5 mg/ml (von Hoff *et al.*, 1975).

2. Production, Occurrence, Use and Analysis

2.1 Production and occurrence

(a) Production

Azacitidine, a pyrimidine analogue of cytidine with a nitrogen substituted for a 5-carbon, can be isolated from a culture of the bacterium *Streptovercillium ladakanus*, but has also been prepared by synthetic methods. One reported method involved treatment of the trimethylsilyl derivative of 4-amino-1,3,5-triazin-2-one with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide, followed by deacetylation to give azacitidine (Winkley & Robins, 1970).

Azacitidine is synthesized in the Federal Republic of Germany (Chemical Information Services, 1989-90).

(b) Occurrence

Azacitidine is produced by the bacterium *Streptovercillium ladakanus* (Winkley & Robins, 1970).

2.2 Use

Azacitidine is a cytostatic agent. It has been used mainly in the treatment of acute leukaemia, either as intravenous or intramuscular injections or as

intravenous infusions at a daily level of 40-750 mg/m² (Weiss *et al.*, 1972; Skoda, 1975; von Hoff *et al.*, 1975, 1976; von Hoff & Slavik, 1977; Wade, 1977; Glover *et al.*, 1987; Reynolds, 1989). It is used alone, or in combination with vincristine, vinblastine, prednisone, cytarabine or amsacrine, at a daily dose of 50-150 mg/m² azacitidine. It has also been tested for use in the treatment of a variety of solid tumours (Glover *et al.*, 1987).

2.3 Analysis

Azacitidine can be quantified in blood by microbiological assay (Pittillo & Woolley, 1969) and in plasma by high-performance liquid chromatography with ultraviolet detection (Rustum & Hoffman, 1987).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

(a) Intraperitoneal injection

Mouse: In a screening assay based on the accelerated induction of leukaemia in a strain highly susceptible to development of this neoplasm, 40 AKR female mice, two months of age, were given six intraperitoneal injections of azacitidine at 1.5 mg/kg bw [purity unspecified] over 20 days, and, because of toxicity, six injections of azacitidine at 0.8 mg/kg bw over the following 30 days. All treated mice had died of leukaemia by 60 days. A control group of 40 females survived free of disease for the observation time of 120 days (Vesely & Cihák, 1973).

In a screening assay based on the accelerated induction of lung tumours in a strain highly susceptible to development of this neoplasm, three groups of ten male and ten female A/He mice, six to eight weeks of age, received intraperitoneal injections of azacitidine [purity unspecified], in a vehicle composed of saline, polysorbate-80, carboxymethyl cellulose and benzyl alcohol, three times a week for eight weeks (total doses, 33, 62 and 90 mg/kg bw (which was the maximum tolerated dose)). Control groups received 24 intraperitoneal injections of 0.1 ml vehicle or were untreated. All animals were killed 24 weeks after the first injection. The numbers of mice with lung tumours, calculated on the basis of survivors of each sex, were 6/11 (54%), 5/15 (33%) and 8/19 (42%) in the groups receiving the high, mid and low doses, respectively. The results for untreated and vehicle-treated groups were expressed only as per cent tumour incidence; thus, 22% (males) and 17% (females) of untreated controls and 26% (males) and 23% (females) of

vehicle-treated controls developed lung tumours. The number of lung tumours per mouse (counted grossly) in animals of each sex treated with the highest dose was 0.73 ± 0.22 (SE), which was significantly higher ($p < 0.05$) than that in untreated (males, 0.22 ± 0.03 ; females, 0.17 ± 0.02) or vehicle-treated (males, 0.25 ± 0.05 ; females, 0.23 ± 0.04) control mice. With lower doses, the increase in the number of lung tumours per mouse was not statistically significant (Stoner *et al.*, 1973).

Groups of 35 male and 35 female B6C3F1 mice, 38 days of age, received intraperitoneal injections of azacitidine at 2.2 or 4.4 mg/kg bw (> 99% pure) in buffered saline three times a week for 52 weeks. Groups of 15 male and 15 female mice were untreated or received the vehicle only. Surviving mice were killed at 81 or 82 weeks. All high-dose females died before week 62, with no significant increase in the incidence of any tumour; of the low-dose females, 17/35 survived until termination of the experiment. Among males, 7/35 of the high-dose group and 13/35 of the low-dose group survived to the end of the study. The overall numbers of survivors in untreated and vehicle-treated groups were 25/30 and 20/30, respectively. In female mice of the low-dose group, lymphocytic and granulocytic neoplasms of the haematopoietic system were observed in 17/29 animals examined histologically, at a highly significant incidence ($p < 0.001$) compared with the vehicle-control group (0/14); 10 of the treated animals had granulocytic tumours (nine sarcomas, one leukaemia). A malignant lymphocytic lymphoma was observed in 1/15 untreated controls. No increase in the incidence of tumours was observed in male mice (National Cancer Institute, 1978).

Groups of 50 male and 50 female BALB/c/Cb/Se mice, eight weeks of age, were given intraperitoneal injections of azacitidine at 2.0 mg/kg bw in saline (99% pure) once a week for 50 weeks. Control groups received injections of saline. After 25 weeks, survival was reduced in exposed animals of each sex. The incidence of lymphoreticular neoplasms was increased, occurring in 12/50 ($p < 0.01$) males and 36/50 ($p < 0.001$) females, compared to 3/50 and 6/50 in control males and females, respectively. The incidence of lung adenomas was increased in treated males (27/50 *versus* 12/50 [$p < 0.01$]) but not in females. Mammary gland adenocarcinomas and adenoacanthomas were found in 7/50 treated females and in none of the controls. The incidence of skin tumours was increased in treated animals of each sex, occurring in 3/50 treated males compared to 0/50 controls [$p < 0.05$] and in 7/50 treated females compared to 1/50 controls [$p < 0.01$, log rank test] (Cavaliere *et al.*, 1987). [The Working Group noted that adenoacanthomas are not described as mammary tumours in reference sources; see Turusov (1973, 1976).]

Rat: Two groups of 12 or 8 male Fischer rats, weighing 160-180 g, were given intraperitoneal injections of azacitidine at 2.5 or 10 mg/kg bw [purity unspecified] in saline twice a week for nine months. A control group of 12 male rats was maintained without treatment. All rats were killed at 18 months. Interstitial-cell testicular

tumours were found in 1/8 high-dose animals and 9/12 low-dose animals compared to 0/12 controls. In the high-dose group, two squamous-cell carcinomas of the skin and one skin appendage tumour at the site of injection were found, compared to none in controls (Carr *et al.*, 1984). [The Working Group noted the small number of animals tested, and the absence in controls of testicular tumours, which occurred commonly in a second, shorter study by the same investigators (see below).]

Groups of 10, 10 or 100 young adult male Fischer rats, weighing 100-160 g, received intraperitoneal injections of azacitidine at 0.025, 0.25 or 2.5 mg/kg bw in saline [purity unspecified] three times a week for one year. A control group of 50 rats was injected with saline. At one year, when the study was terminated, 87/100 of animals at the high dose and 10/10 in each of the lower-dose groups were still alive. The highest dose increased the incidence of testicular interstitial-cell tumours to 56/87, compared to 10/49 in controls ($p < 0.001$). No other tumour was observed in controls. In the highest dose group, other tumours noted were four lymphomas, four renal tumours, one lung tumour, three skin tumours, two mesotheliomas and two sarcomas (Carr *et al.*, 1988). [The Working Group noted the short duration of the experiment and the small numbers of animals in some groups.]

(b) *Transplacental administration*

Mouse: Groups of 32-37 pregnant NMRI mice received intraperitoneal injections of azacitidine at 1 or 2 mg/kg bw in saline [purity unspecified] on day 12, 14 or 16 of gestation. A group of 53 control dams was injected with saline. The number of stillbirths was increased at the high dose; survival of offspring was decreased in all exposed groups. In exposed progeny, increased percentages of tumour-bearing animals and increased incidences of leukaemias and lymphomas, lung tumours and liver tumours were seen in some groups (see Table 1). Some increases in the incidence of soft-tissue sarcomas were also seen (Schmahl *et al.*, 1985).

(c) *Administration in combination with other compounds*

Rat: In the experiment by Carr *et al.* (1984), described above, groups of 6-10 male Fischer rats were given *N*-nitrosodiethylamine at 50 mg/kg bw 18 h after partial hepatectomy, alone or with azacitidine at 2.5 or 10 mg/kg bw by intraperitoneal injection. Liver tumours were found in 2/10 and 8/10 animals given the low and the high dose of azacitidine, respectively, but not in the group given the nitroso compound alone.

Table 1. Incidences of tumours in the progeny of NMRI mice given azacitidine by intraperitoneal injection^a

Treatment		Sex	No. of animals	Leukaemias and lymphomas		Lung tumours		Liver tumours	
mg/kg bw	day of gestation			No.	%	No.	%	No.	%
1	12	Males	165	81	49.1	30	18.2	15	9.1
		Females	158	80	50.6	33	20.9	6	3.8
2	12	Males	113	28	24.8	22	19.5	11	9.7
		Females	110	26	23.6	22	20.0	9	8.2
1	14	Males	178	42	23.6	29	16.3	12	6.7
		Females	171	26	15.2	31	18.1	20	11.7
2	14	Males	97	9	9.3	46	47.4	11	11.3
		Females	101	14	13.9	43	42.6	7	6.9
1	16	Males	153	97	63.4	81	52.9	14	9.2
		Females	160	98	61.3	99	61.9	8	5.0
2	16	Males	158	67	42.4	78	49.3	18	11.4
		Females	151	57	37.7	82	54.3	5	3.3
Controls		Males	293	84	28.7	57	19.5	14	4.8
		Females	279	82	29.4	53	19.0	11	3.9

^aFrom Schmahl *et al.* (1985)

3.2 Other relevant data

(a) *Experimental systems*

(i) *Absorption, distribution, excretion and metabolism*

Blood levels of azacitidine, determined by biological activity, in mice peaked within 0.5 h after intraperitoneal or oral administration. Maximal concentrations of azacitidine in blood after administration at 50 mg/kg bw were about 2 µg/ml after oral administration and 43 µg/ml after intraperitoneal injection (Neil *et al.*, 1975).

In a study using a microbiological assay, maximal concentrations were found in blood 15 min after intraperitoneal injection of 9.5 and 4.75 mg/kg bw (LD₁₀ and 0.5 LD₁₀) to mice. Elimination was rapid, and no azacitidine was detected in blood 1 h after injection of the high dose or 30 min after injection of the low dose. No drug was detected in liver, lung, brain, spleen or kidneys (Pittillo & Woolley, 1969).

In a further study, ¹⁴C activity in blood diminished rapidly in mice after intraperitoneal administration of labelled azacitidine (Raska *et al.*, 1965). The half-time for azacitidine and its radioactive metabolites was calculated by von Hoff and Slavic (1977) to be 3.8 h; radioactivity was retained in lymphatic organs.

As reported in an abstract, 50% of a dose [amount and route unspecified] administered to mice was excreted in the urine within 8 h; of the excreted radioactive material, 4% was associated with unchanged azacitidine. Six additional radioactive metabolites were found (Coles *et al.*, 1975). In beagle dogs, azacitidine, 5-azacytosine, urea and guanidine were observed after intravenous administration of azacitidine at 0.5 mg/kg bw; 33% of the administered dose was excreted in urine by 4 h (Coles *et al.*, 1974). In rabbits, most of the radioactivity (25-40%) was excreted in the urine after intravenous administration of labelled azacitidine at 15 mg/kg bw; only small amounts were excreted *via* the bile (Chan *et al.*, 1977).

Azacitidine is phosphorylated and inhibits uridine kinase and orotidylic acid hydroxylase (von Hoff *et al.*, 1975, 1976). It is readily deaminated in biological systems to 5-azauridine, which is degraded further (Cihák, 1974; Neil *et al.*, 1975; Glover & Leyland-Jones, 1987).

(ii) Toxic effects

As reported in an abstract, the intraperitoneal LD₅₀ for azacitidine in mice was 116 mg/kg bw and the oral LD₅₀, 572 mg; five daily doses increased the toxicity considerably (Palm & Kensler, 1971).

After phosphorylation, azacitidine is incorporated into DNA and RNA in L1210 leukaemia cells *in vitro* (Li *et al.*, 1970); it inhibits DNA synthesis in the liver of partially hepatectomized rats. Intraperitoneal injection of azacitidine at 10 µmol/100 g bw inhibited thymidine kinase and thymidylate kinase in rat liver (Cihák & Vesely, 1972).

Azacitidine is cytotoxic to Friend erythroleukaemia cells (Hickey *et al.*, 1986), L1210 leukaemia cells (Li *et al.*, 1970) and normal rat hepatocytes (Carr *et al.*, 1988) *in vitro*; after a dose of 1×10^{-4} M, 32% survival of rat hepatocytes was observed within 24 h.

(iii) Hypomethylation and effects on gene expression

After incorporation into DNA, azacitidine inhibits DNA methyl transferase noncompetitively, blocking cytosine methylation in newly replicated DNA. Since hypomethylation patterns in DNA are related to gene expression, this may be the mechanism by which azacitidine induces a range of biological effects (Glover *et al.*, 1987). A number of *in-vitro* and *in-vivo* studies have shown that azacitidine treatment affects both differentiation (Constantinides *et al.*, 1978; Taylor & Jones, 1979; Tsao *et al.*, 1984; Csordas & Schauenstein, 1986; Liu *et al.*, 1986; Sémat *et al.*, 1986; Rothrock *et al.*, 1988) and gene expression (Tennant *et al.*, 1982; Harrison *et al.*, 1983; Rothrock *et al.*, 1983; Sugiyama *et al.*, 1983; del Senno *et al.*, 1984; Waalkes & Poirier, 1985; Castelazzi *et al.*, 1986; Hickey *et al.*, 1986; Hoshino *et al.*, 1987; Ishikawa *et al.*, 1987; Price-Haughey *et al.*, 1987; Carr *et al.*, 1988; Stephanopoulos *et al.*, 1988; Wagner *et al.*, 1988).

(iv) *Effects on reproduction and prenatal toxicity*

Intraperitoneal administration of azacitidine at 1.5-2.5 mg/kg bw to mice for various periods during pregnancy induced very high or total resorption of conceptuses when treatment was given in the preimplantation period up to day 6; after this time, the incidence of resorptions was only slightly greater than the control level (Svata *et al.*, 1966; Seifertová *et al.*, 1968). Other workers have shown that single intraperitoneal doses of 1-2 mg/kg to mice during the period of embryogenesis can cause a high resorption rate and malformations in the majority of surviving fetuses, including major central nervous system defects, facial clefts and limb defects (Schmahl *et al.*, 1984; Takeuchi & Takeuchi, 1985).

Intraperitoneal injection of azacitidine at 1-4 mg/kg to mice at later stages of pregnancy, especially on day 15, can result in morphological changes in the brain (Langman & Shimada, 1971), and behavioural changes can be detected in offspring when tested as adults (Rodier *et al.*, 1973; Langman *et al.*, 1975; Rodier, 1979).

The primary mechanism by which azacitidine causes malformations in rats is thought to be induction of cell death, but inhibition of some but not all of the effects of azacitidine by administration of caffeine indicates that more than one mechanism may be involved (Kurishita & Ihara, 1987a,b).

(v) *Genetic and related effects*

In *Escherichia coli*, azacitidine caused DNA damage (Bhagwat & Roberts, 1987) and prophage induction (Barbe *et al.*, 1986). It was mutagenic to *E. coli* (Fucik *et al.*, 1965; Lal *et al.*, 1988) and induced base-pair but not frameshift mutations in *Salmonella typhimurium* (Marquardt & Marquardt, 1977; Podger, 1983; Call *et al.*, 1986; Levin & Ames, 1986; Schmuck *et al.*, 1986).

Azacitidine induced mitotic recombinations, mitotic gene conversions and reverse mutations but not mitotic chromosome loss in *Saccharomyces cerevisiae* (Zimmermann & Scheel, 1984). It induced mitotic recombinations, deletions and gene mutations in the wing spot assay in *Drosophila melanogaster* (Katz, 1985) and chromosomal aberrations in root meristem cells of *Vicia faba* (Fucik *et al.*, 1970).

Azacitidine inhibited DNA synthesis in Chinese hamster CHO cells (Tobey, 1972) and induced DNA strand breaks in HeLa cells (Snyder & Lachmann, 1989). It induced mutations at the *hprt* locus in Chinese hamster V79 cells in one study (at 5 μ M; Marquardt & Marquardt, 1977) but not in another (at 40 μ M; Landolph & Jones, 1982). It did not induce mutation at the *hprt* locus in Syrian hamster BHK cells (Bouck *et al.*, 1984), primary rat tracheal epithelial cells (Walker & Nettesheim, 1986) or mouse lymphoma L5178Y cells (at 4 μ M; McGregor *et al.*, 1989). Azacitidine induced mutations at the *hprt* and *tk* loci in human fibroblasts (Call *et al.*, 1986) and at the *tk* locus of mouse lymphoma L5178Y cells (Amacher & Turner, 1987; McGregor *et al.*, 1989). It did not induce ouabain-resistant mutations in

mouse C3H 10T $\frac{1}{2}$, Chinese hamster V79 (Landolph & Jones, 1982), Syrian hamster BHK (Bouck *et al.*, 1984) or primary rat tracheal epithelial cells (Walker & Nettesheim, 1986).

Azacitidine induced sister chromatid exchange in a cloned hamster cell line (Banerjee & Benedict, 1979), in CHO cells (Hori, 1983) and in human peripheral lymphocytes *in vitro* [only one concentration, 8 μ M, was tested] (Lavia *et al.*, 1985). In another study, azacitidine did not induce sister chromatid exchange in human lymphocytes (up to 9 μ M; Ioannidou *et al.*, 1989). It induced chromosomal aberrations in Chinese hamster Don cells (Karon & Benedict, 1972) and in human peripheral lymphocytes *in vitro* [only one concentration, 8 μ M, was tested] (Lavia *et al.*, 1985) but not in human lymphoblasts (10 μ M; Call *et al.*, 1986).

Azacitidine induced transformation in mouse C3H/10T $\frac{1}{2}$ (Benedict *et al.*, 1977), Syrian hamster BHK (Bouck *et al.*, 1984), mouse BALB/3T3 (Yasutake *et al.*, 1987) and primary rat tracheal epithelial cells (Walker & Nettesheim, 1986).

Azacitidine did not induce dominant lethal mutation in male mice after administration at 5 and 10 mg/kg bw intraperitoneally (Epstein *et al.*, 1972).

(b) *Humans*

The toxicity, cytostatic activity and mechanism of action of azacitidine have been reviewed (Cihák, 1974; von Hoff & Slavik, 1977; Glover & Leyland-Jones, 1987).

(i) *Pharmacokinetics*

After an intravenous injection of radiolabelled azacitidine, the α -phase half-time of radioactivity was 16-33 min (Israeli *et al.*, 1976), and the β -phase half-time was 3.4-6.2 h (Troetel *et al.*, 1972; Israeli *et al.*, 1976). After 30 min, less than 2% of the plasma radioactivity cochromatographed with azacitidine; at least two different metabolites or decomposition products were detected by thin-layer chromatography (Israeli *et al.*, 1976), and 73-98% of the injected radioactivity was detected in the urine within three days (Israeli *et al.*, 1976). Similar results were obtained by Troetel *et al.* (1972).

Less than 1% of radiolabelled azacitidine was bound to human serum albumin *in vitro* (Israeli *et al.*, 1976).

(ii) *Adverse effects*

The major toxic effects of the clinical use of azacitidine have been gastrointestinal, haematological and hepatic (von Hoff *et al.*, 1976; von Hoff & Slavik, 1977; Reynolds, 1989). Leukopenia is generally the dose-limiting toxicity; in a compilation of several studies with a total of 821 patients, the incidence of leukopenia (total leukocyte count, less than 1500/mm³) was 34% and was dose-related. Thrombocytopenia has been reported less frequently (von Hoff *et al.*,

1976; von Hoff & Slavik, 1977). Fatal hepatic damage was reported in four patients with previous hepatic dysfunction, who had been treated with azacitidine (Bellet *et al.*, 1973).

(iii) *Effects on reproduction and prenatal toxicity*

No data were available to the Working Group.

(iv) *Genetic and related effects*

No adequate study was available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity to humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Azacitidine is a cytostatic agent that has been used since the 1970s for the treatment of acute leukaemia.

4.2 Experimental carcinogenicity data

Azacitidine was tested for carcinogenicity by intraperitoneal injection in four studies in mice and in two studies in rats and by transplacental exposure in one study in mice. In one study in mice, it accelerated the development of leukaemias; in the two long-term studies and in the transplacental study, it increased the incidence of lymphoid neoplasms. In one of the long-term studies, the incidence of lung adenomas was increased in male mice and that of skin tumours in mice of each sex. In the transplacental study in mice, it also increased the incidences of lung and liver tumours. It accelerated the induction of lung tumours in mice. In rats, it increased the incidence of testicular tumours.

Intraperitoneal administration of azacitidine to rats enhanced the development of liver tumours induced by *N*-nitrosodiethylamine.

4.3 Human carcinogenicity data

No data were available to the Working Group.

4.4 Other relevant data

During the early stages of gestation, azacitidine induces embryomortality in mice; during the organogenesis period, multiple, gross structural malformations

can be induced; and during later stages of gestation, mainly central nervous system defects have been induced in mice.

Azacitidine is readily deaminated to azauridine and further degraded. It is incorporated into DNA and alters gene expression. In humans, it causes leukopenia.

Azacitidine causes hypomethylation of DNA both *in vivo* and *in vitro*.

In one study, azacitidine did not induce dominant lethal mutations in mice. Contradictory results have been reported with respect to the induction of chromosomal aberrations and sister chromatid exchange in human cells. In single studies, azacitidine induced gene mutations and DNA strand breaks in human cells. It induced chromosomal aberrations in Chinese hamster cells, sister chromatid exchange in cloned Chinese hamster cells, gene mutations in Chinese hamster and mouse lymphoma cells and transformation in various cell lines. It induced mitotic recombination and mutations in *Drosophila*. Azacitidine induced chromosomal aberrations in *Vicia faba*. In *Saccharomyces cerevisiae*, it induced gene mutations and mitotic recombination but not chromosomal loss. It induced mutations and DNA damage in *Salmonella typhimurium* and *Escherichia coli*. (See Appendix 1.)

4.5 Evaluation¹

There is *sufficient evidence* for the carcinogenicity of azacitidine in experimental animals.

No data were available from studies in humans on the carcinogenicity of azacitidine.

In making the overall evaluation, the Working Group also took note of the following information. Azacitidine is active in a broad spectrum of assays for genetic and related effects, including those involving mammalian cells. Furthermore, azacitidine, a pyrimidine analogue, is incorporated into DNA, causing hypomethylation.

Overall evaluation

Azacitidine is probably carcinogenic to humans (Group 2A).

¹For description of the italicized terms, see Preamble, pp. 26–29.

5. References

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