PRAZEPAM

1. Exposure Data

1.1 Chemical and physical data

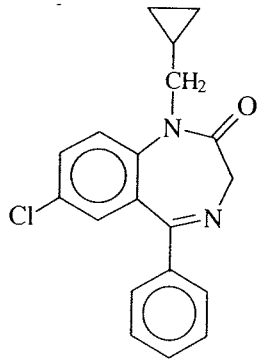
1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 2955-38-6

Chem. Abstr. Name: 7-Chloro-1-(cyclopropylmethyl)-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one

IUPAC Systematic Name: 7-Chloro-1-(cyclopropylmethyl)-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_{19}H_{17}ClN_2O$ Relative molecular mass: 324.81

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Colourless crystalline powder (Gennaro, 1995)

(*b*) *Melting-point*: 145–146 °C (Budavari, 1995)

(*c*) *Solubility*: Practically insoluble in water [1 g/more than 10 000 mL]; sparingly soluble in anhydrous ethanol and diethyl ether; soluble in acetone, chloroform and acetic anhydride (Society of Japanese Pharmacopoeia, 1992; Gennaro, 1995)

(*d*) *Octanol/water partition coefficient (P)*: log P, 3.7 (Dollery *et al.*, 1991)

1.1.4 *Technical products and impurities*

Prazepam is available as 10- and 20-mg tablets, 16.5-mg 'drops' and 5-, 10- and 20-mg capsules which also may contain anhydrous ethanol, corn starch, flavouring, lactose, magnesium stearate, microgranular cellulose, polyethylene glycol 400, precipitated

silica, propylene glycol, sodium saccharin, sodium lauryl sulfate, colloidal silicon dioxide, titanium dioxide, E 132 (Indigo carmine), D&C Yellow no. 10 (Quinoline Yellow), FD&C Blue no. 1 (Brilliant Blue FCF), FD&C Yellow 6 (Sunset Yellow FCF), FD&C green no. 3 (Fast Green FCF) (Farmindustria, 1993; Medical Economics, 1996).

Trade names and designations of the chemical and its pharmaceutical preparations include: Centrax; Demetrin; Equipaz; K 373; Lysanxia; Mono Demetrin; Prazene; Reapam; Sedapran; Settima; Trepidan; Verstran; W-4020.

1.1.5 *Analysis*

Several international pharmacopoeias specify potentiometric titration with perchloric acid as the assay for purity of prazepam and thin-layer chromatography for determining impurities and decomposition products. The assays for prazepam in capsules and tablets apply liquid chromatography or potentiometric titration with perchloric acid using standards. An assay for heavy metal impurities is also specified (Society of Japanese Pharmacopoeia, 1992; United States Pharmacopeial Convention, 1994). Spectrophotometry has also been used in the analysis for prazepam in pharmaceutical preparations (El-Yazbi *et al.*, 1986; Mañes *et al.*, 1987; Prada *et al.*, 1988).

Prazepam and its metabolites (including oxazepam) can be analysed in biological fluids by radioimmunoassay (Köhler-Schmidt & Bohn, 1983), electron capture gas chromatography (Nau *et al.*, 1978, Peat & Kopjak, 1979), gas chromatography with flame ionization detection (Quaglio & Bellini, 1984), gas chromatography–mass spectrometry (Maurer & Pfleger, 1987) and high-performance liquid chromatography (Peat & Kopjak, 1979; Lensmeyer *et al.*, 1982).

1.2 Production and use

1.2.1 *Production*

Prazepam is prepared by acylating 2-amino-5-chlorobenzophenone with cyclopropanecarbonyl chloride using triethylamine as an acid-receptor. The product is reduced with lithium aluminium hydride to give 2-cyclopropylmethylamino-5-chlorobenzhydrol, which is then oxidized with manganese dioxide to the corresponding benzophenone. This is acylated with phthalimidoacetyl chloride and the product cyclized with hydrazine hydrate to produce prazepam (Gennaro, 1995).

1.2.2 *Use*

Prazepam is a benzodiazepine used for the treatment of anxiety disorders (see the monograph on diazepam, pp. 39–41, for a brief overview of the pharmacology of therapeutic action for this class of drugs). The optimal dosage in adults, adjusted to the response of the patient, is usually 20–40 mg daily in divided doses or as a single nightly dose. In severe conditions, up to 60 mg daily has been given. In elderly or debilitated patients, treatment should be initiated with a daily dose of 10–15 mg (Reynolds, 1993).

Clinical uses of prazepam and other benzodiazepines have been reviewed (Hollister *et al.*, 1993). Prazepam was approved for use in the United States of America in 1976 and, in France, it was first marketed in 1979 (Parke-Davis, 1996).

Comparative data on sales of prazepam in several countries are shown in Table 1. Overall, sales worldwide declined by approximately 24% from 1990 to 1995 and prescriptions in the United States dropped to almost nil (see Table 2 in the monograph on diazepam, p. 43).

Table 1. Sales of prazepam in various countries[a] (no. of standard units[b], in thousands)

Country	1990	1995	Country	1990	1995
Africa			Europe		
South Africa	2 492	1 819	Belgium	10 913	9 900
North America			France	185 801	190 175
United States	65 399	1	Germany	15 246	8 702
South America			Greece	9 908	6 002
Argentina	480	239	Italy	45 244	41 032
Colombia	0	24	Netherlands	2 582	2 036
Asia			Portugal	206	962
Japan	14 161	8 074	Spain	1 515	1 165
Republic of Korea	4 205	2 947	Switzerland	3 454	2 836

[a] Data provided by IMS

[b] Standard dosage units, uncorrected for prazepam content

1.3 Occurrence

Prazepam is not known to occur as a natural product.

No quantitative data on occupational exposure levels were available to the Working Group.

The National Occupational Exposure Survey conducted between 1981 and 1983 in the United States by the National Institute for Occupational Safety and Health indicated that about 100 employees were potentially occupationally exposed to prazepam. The estimate was based on a survey of United States companies and did not involve measurements of actual exposure (United States National Library of Medicine, 1996).

1.4 Regulations and guidelines

Prazepam is listed in the French, Japanese and United States pharmacopoeias (Reynolds, 1993; Vidal, 1995).

2. Studies of Cancer in Humans

No data were available to the Working Group (see the monograph on diazepam, pp. 44–54, for a discussion of benzodiazepines).

3. Studies of Cancer in Experimental Animals

3.1 Oral administration

3.1.1 *Mouse*

Groups of 100 male and 100 female albino CF1 (control) or 50 male and 50 female mice (treated), eight weeks of age, were given 0, 8, 25 or 75 mg/kg bw prazepam (99% pure) mixed in the diet for up to 80 weeks. The prazepam concentration in the food was adjusted weekly for changes in body weight and food consumption. The prazepam/diet mixtures were prepared freshly each week. In treated mice, body-weight gains were similar to those of controls throughout the study. From graphic presentations, there appeared to be no significant effect on mortality (60–70% survival for males and females) [statistics and exact numbers not given.] All surviving animals were killed at 80 weeks. Major organs [unspecified] and visually apparent lesions were examined histologically. No significant increase in the incidence of tumours at any site was seen for either male or female mice. Data on incidence of hepatocellular tumours are presented in Table 2 (de la Iglesia *et al.*, 1981). [The Working Group noted that the study was terminated at 80 weeks.]

3.1.2 *Rat*

Groups of 115 male and 115 female SPF albino Wistar rats (control) or 65 male and 65 female rats (treated), eight weeks of age, were given 0, 8, 25 or 75 mg/kg bw prazepam (99% purity) mixed in the diet for up to 104 weeks. The prazepam concentration in the food was adjusted weekly for changes in body weight and food consumption. The prazepam/diet mixtures were prepared freshly each week. In treated rats, body-weight gains were similar to those of controls throughout the study. There appeared to be no significant effect on mortality (50–60% survival for males and about 60% for females) [statistics and exact numbers not given]. All surviving animals were killed at 104 weeks. Major organs [not specified] and visually apparent lesions were examined histologically. No significant increase in the incidence of tumours was seen for either male or female rats. Data on incidences of hepatocellular tumours are presented in Table 2 (de la Iglesia *et al.*, 1981).

3.2 Carcinogenicity of metabolites

See the monograph on oxazepam (pp. 119–123).

Table 2. Incidence of benign and malignant hepatocellular tumours in mice and rats treated with prazepam

Dose (mg/kg bw)	Mouse				Rat			
	Benign		Malignant		Benign		Malignant	
	Male	Female	Male	Female	Male	Female	Male	Female
0	1/100	1/100	7/100	1/100	1/115	1/115	0/115	0/115
8	0/50	1/50	5/50	0/50	0/65	0/65	0/65	0/65
25	1/50	2/50	4/50	1/50	2/65	1/65	1/65	0/65
75	1/50	0/50	4/50	0/50	1/65	3/65	1/65	0/65

From de la Iglesia *et al.* (1981)

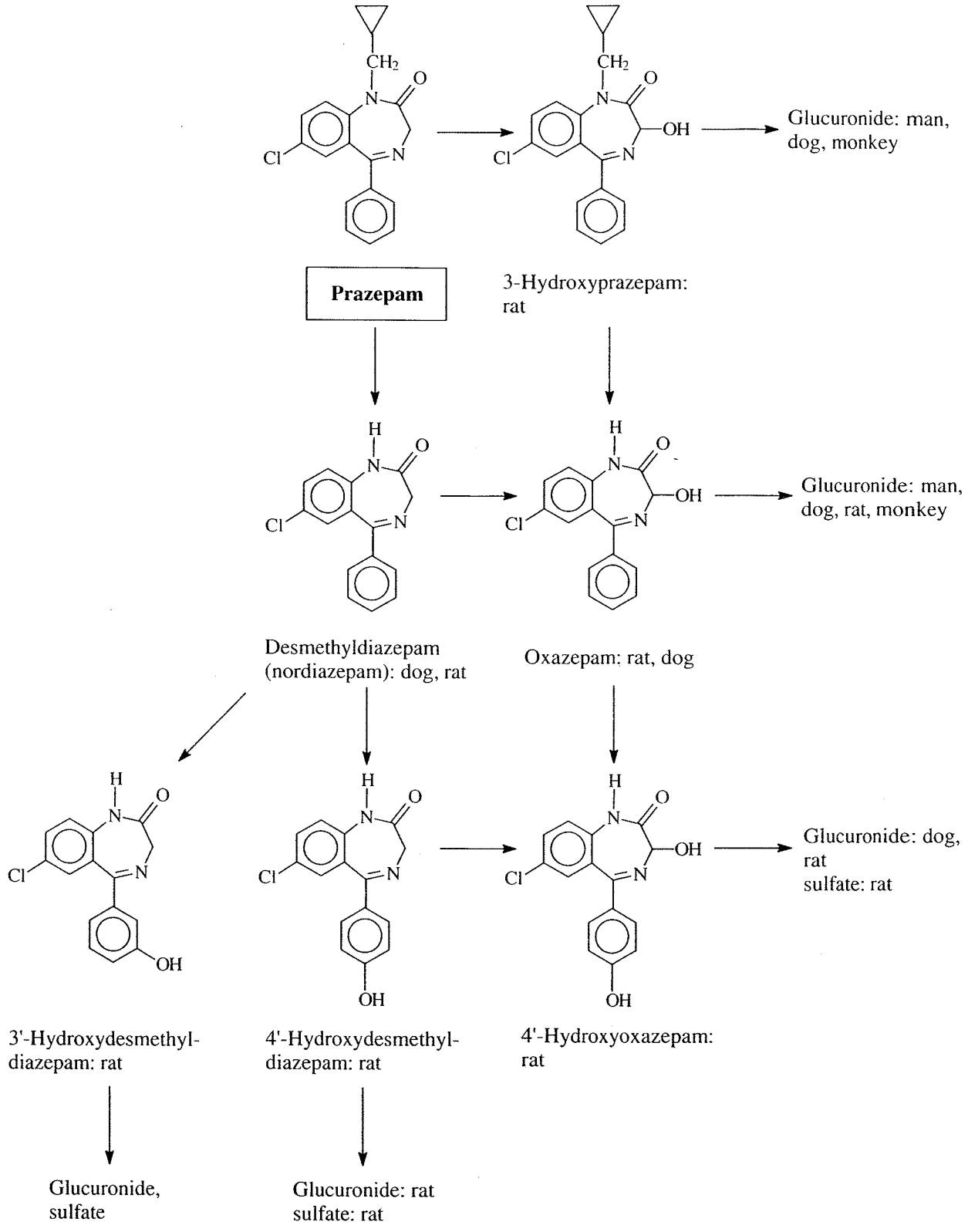
4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

Prazepam is rapidly absorbed after oral administration, the peak plasma concentration of the unchanged compound appearing within 0.5 h. While some authors have not seen measurable concentrations of prazepam in plasma after dosing with tablets, Smith *et al.* (1979) detected low concentrations (> 2.5 ng/mL) for brief periods in four of nine subjects after ingestion of tablets and in all nine subjects after ingestion of a solution. The bioavailability from tablets relative to the solution was 86%. The elimination half-life of the parent drug was approximately 1 h. The major non-conjugated compound in plasma was the N-dealkylated metabolite, *N*-desmethyldiazepam. Peak plasma concentrations of *N*-desmethyldiazepam following oral administration of prazepam tablets have been reported to be 321 ± 76 ng/mL at 4.25 ± 1.75 h (30-mg dose; Smith *et al.*, 1979), 235 ± 68 ng/mL at 12 h (30-mg dose; Chasseaud *et al.*, 1980) and 105 ± 12 ng/mL at 9.2 ± 3 h (20-mg dose; Greenblatt *et al.*, 1988). Allen *et al.* (1980) reported differences according to age and sex, with average peak plasma levels of 92–142 ng/mL being reached in an average of 10–20 h. The elimination half-life of *N*-desmethyldiazepam in these studies was reported to be 96 ± 34 h (Smith *et al.*, 1979), 82 [± 23 h] (Chasseaud *et al.*, 1980) and ranging from 29 to 224 h (Allen *et al.*, 1980). In this last study, the elimination half-life increased with age in men, but not in women. The major metabolic pathways of prazepam are N-dealkylation (Allen *et al.*, 1979; Chasseaud *et al.*, 1980) and 3-hydroxylation (DiCarlo *et al.*, 1970). The glucuronides of 3-hydroxyprazepam and oxazepam are the main metabolites eliminated in urine (Figure 1). Neither prazepam nor *N*-desmethyldiazepam was detected in 24-h urine samples of women given three 10-mg prazepam capsules (Chasseaud *et al.*, 1980).

Figure 1. Postulated metabolic pathways of prazepam



From Viau *et al.* (1973); Ishihama *et al.* (1978)

The plasma half-lives of [^{14}C]prazepam and of antipyrine were increased in male volunteers pretreated with unlabelled prazepam (0.4 mg/kg/day) for seven days (Vesell *et al.*, 1972).

4.1.2 *Experimental systems*

Prazepam metabolism has been studied in rats, dogs and monkeys. Prazepam is well absorbed after oral dosing in rats, and is rapidly and extensively metabolized. In the rat, the plasma half-life of prazepam and its metabolites was 2.5 h (Viau *et al.*, 1973). Nine identified metabolites in urine together accounted for only 50% of the dose of radioisotope, while faecal excretion of radioisotope exceeded urinary excretion. The major pathway was N-dealkylation, and all identified metabolites were derived from *N*-desmethyldiazepam. Hydroxylation at the 4-position of the 5-phenyl ring (4′-hydroxylation) was extensive. Ishihama *et al.* (1978) additionally found substantial amounts of 3′-hydroxydesmethyldiazepam in urine and faeces. Both groups noted substantial amounts of unidentified polar metabolites. Metabolism in dogs was more similar to the pattern in humans. The major metabolite was oxazepam (excreted as the glucuronide), and smaller amounts of 3-hydroxyprazepam and 4′-hydroxyoxazepam (excreted as the glucuronides) were recovered (DiCarlo *et al.*, 1969; DiCarlo & Viau, 1970). An even closer parallel to the human pattern was seen in cynomolgus monkeys, which excreted principally oxazepam and 3-hydroxyprazepam glucuronides, with only trace amounts of 4′-hydroxydesmethyldiazepam, as the sulfate conjugate (Kabuto *et al.*, 1978).

A preponderance of N-dealkylation over C_3-hydroxylation of prazepam was shown in metabolic studies using liver microsomes from Sprague-Dawley rats *in vitro*, pretreated with phenobarbital (Lu & Yang, 1989; Hooper *et al.*, 1992). This was also shown for humans (Lu *et al.*, 1991); these workers additionally showed that the 3-hydroxyprazepam was formed stereoselectively, with the 3*R*-enantiomer predominating in both rats and humans.

4.2 Toxic effects

4.2.1 *Humans*

(*a*) *Acute toxicity*

Prazepam has no significant effect on the cardiovascular system; however, respiratory depression may be observed following large doses or in sensitive individuals with chronic obstructive airway diseases (reviewed by Dollery *et al.*, 1991). In a review of fatal poisoning attributed to benzodiazepines in the United Kingdom during the 1980s, only one lethal intoxication with prazepam was recorded (Serfaty & Masterton, 1993).

(*b*) *Chronic toxicity*

There is no evidence to suggest that prazepam causes any organ toxicity other than effects associated with its pharmacological action on the central nervous system (reviewed by Dollery *et al.*, 1991).

4.2.2 *Experimental systems*

(*a*) *Acute toxicity*

Prazepam given intravenously to cats, dogs and rabbits caused convulsions at all doses (1–8 mg/kg bw) investigated. In contrast, oral administration of 3–36 mg/kg bw prazepam to mice suppressed convulsions induced by pentylenetetrazol, strychnine or electroshock with a similar potency to other benzodiazepines (Robichaud *et al.*, 1970). Intravenous administration of prazepam to dogs at doses of up to 10 mg/kg did not induce significant autonomic or cardiovascular effects.

(*b*) *Subacute and chronic toxicity*

In male Sprague-Dawley rats, intraperitoneal administration of 100 mg/kg bw prazepam for four days resulted in increased levels of hepatic microsomal cytochrome P450 and increased activities of hepatic ethylmorphine N-demethylase and aniline hydroxylase (Vesell *et al.*, 1972).

4.3 Reproductive and prenatal effects

4.3.1 *Humans*

No data were available to the Working Group

4.3.2 *Experimental systems*

Prazepam increased the incidence of congenital anomalies (mainly short tail and hydrops fetalis (subcutaneous oedema)) in rats. Body weights and organ weights of the offspring of rats treated orally with a daily dose of 100 mg/kg bw prazepam were decreased, but there was no adverse effect on behaviour, emotionality or learning ability of offspring (Kuriyama *et al.*, 1978a; Ota *et al.*, 1979a).

The fertility of male rats was suppressed by five weeks' treatment with 1000 mg/kg prazepam due to the retardation of spermatogenesis. Mating performance and fertility of female rats were inhibited by oral treatment with a daily dose of 1000 mg/kg prazepam, but recovered soon after discontinuation of treatment (Kuriyama *et al.*, 1978b) and Ota *et al.* (1979a) found no adverse effect on the fertility of the offspring.

No increase in the occurrence of congenital abnormalities was observed in rabbits which received daily oral doses of 5, 12.5, 25 or 50 mg/kg bw on gestational days 6–18 (Ota *et al.*, 1979b).

Chronic dietary administration of prazepam to breeding pairs of Swiss-Webster mice caused a significant decrease in mating performance and body weights at birth (Guerriero & Fox, 1976). Female mice which received prazepam prenatally had delay in the age of vaginal opening; however, the age of first oestrus was generally younger than that of controls due to disruption of normal hypothalamic-pituitary relations (Fox & Guerriero, 1978). Male mice which received prazepam prenatally and during early infancy exhibited enhanced performance of a Y-maze task as adults. The drug produced its greatest effects on learning measures when given prenatally (Fox *et al.*, 1977).

4.4 Genetic and related effects (see also Table 3 for references and Appendices 1 and 2)

No chromosomal damage was observed in *Nigella damascena*. No increase in DNA single-strand breaks and/or alkali-labile sites was observed in the liver of rats given orally a single dose or multiple daily doses of prazepam.

Table 3. Genetic and related effects of prazepam

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
PLC, *Nigella damascena*, chromosomal aberrations	–	NT	50	Moutschen *et al.* (1987)
DVA, DNA strand breaks, rat liver *in vivo*	–		325 po × 1	Carlo *et al.* (1989)
DVA, DNA strand breaks, rat liver *in vivo*	–		65 po × 15	Carlo *et al.* (1989)

[a] +, positive; (+), weak positive; –, negative; NT, not tested; ?, inconclusive
[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, μg/mL; in-vivo tests, mg/kg bw/day

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Prazepam is a benzodiazepine used since the late 1970s for treatment of anxiety.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Prazepam was tested for carcinogenicity in one experiment in mice and in one experiment in rats by oral administration in the diet. No significant increase in the incidence of tumours was found.

5.4 Other relevant data

Prazepam is rapidly and extensively absorbed in humans, but its plasma concentrations are low and of short duration as a consequence of its rapid conversion to *N*-des-

methyldiazepam and, to a lesser extent, 3-hydroxyprazepam. The elimination half-life is about 1 h.

Prazepam is extensively metabolized in rats, and the primary metabolite *N*-desmethyldiazepam is further converted to at least eight derivatives. Oxazepam is the major metabolite in dogs and monkeys.

There is no evidence to suggest that prazepam causes any organ toxicity other than effects associated with its pharmacological action on the central nervous system in humans or experimental animals.

There are no data on the teratogenicity of prazepam in humans. In one study, prazepam increased the incidence of short tail and hydrops fetalis (subcutaneous oedema) in rats. In a single study in the rabbit, it was not teratogenic.

The two available studies on genetic effects were negative.

5.5 Evaluation[1]

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

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

Overall evaluation

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

6. References

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[1]For definition of the italicized terms, see Preamble, pp. 22–25.

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