RIPAZEPAM

1. Exposure Data

1.1 Chemical and physical data

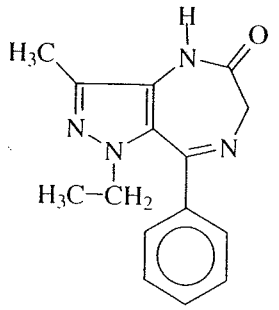
1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 26308-28-1

Chem. Abstr. Name: 1-Ethyl-4,6-dihydro-3-methyl-8-phenylpyrazolo[4,3-*e*][1,4]diazepin-5(1*H*)-one

IUPAC Systematic Name: 1-Ethyl-4,6-dihydro-3-methyl-8-phenylpyrazolo[4,3-*e*]-[1,4]diazepin-5(1*H*)-one

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_{15}H_{16}N_4O$ Relative molecular mass: 268.32

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Pale-yellow crystalline solid (Fitzgerald *et al.*, 1984)

(*b*) *Melting-point*: 221–223 °C (DeWald *et al.*, 1973)

1.1.4 *Technical products and impurities*

One trade name of the chemical is available: Pyrazapon.

1.1.5 *Analysis*

No information on the analysis of ripazepam was available to the Working Group.

1.2 Production and use

1.2.1 *Production*

Ripazepam can be prepared by reacting 4-amino-1-ethyl-3-methylpyrazol-5-yl phenyl ketone and glycine ethyl ester hydrochloride in piperidine/pyridine solvent. The resulting intermediate is reacted with ammonium hydroxide in dichloromethane/ethyl acetate, and ripazepam is recrystallized from toluene (DeWald *et al.*, 1973).

1.2.2 *Use*

Ripazepam is a pyrazolodiazepine that demonstrated anxiolytic effects in pharmacological tests in animals, but was apparently never marketed for human use (Poschel *et al.*, 1974; Fitzgerald *et al.*, 1984).

1.3 Occurrence

Ripazepam is not known to occur as a natural product.

1.4 Regulations and guidelines

No information was available to the Working Group.

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

3.1 Oral administration

3.1.1 *Mouse*

Groups of 50 male and 50 female albino CD-1 mice, five to six weeks of age, were given 0, 15 or 150 mg/kg bw ripazepam (100% pure) in the diet for up to 78 weeks. The ripazepam concentration in the food was adjusted weekly for changes in body weight and food consumption. The ripazepam/diet mixtures were prepared freshly each week and offered *ad libitum*. In treated mice, body-weight gains exceeded those of controls at both doses in females and at 15 mg/kg bw in the males. Food consumption was similar in control and treated mice. From graphic presentations, there appeared to be a slight increase in mortality among high-dose males beginning at about week 40. Mortality rates were similar in all groups of female mice [statistics and exact numbers not given]. At 78 weeks, survival was 60–70% in all groups and all surviving animals were killed. Major organs [not specified] and visually apparent lesions were examined histologically. Data on the incidence of liver tumours are presented in Table 1 (Fitzgerald *et al.*, 1984).

Table 1. Incidence of benign and malignant hepatocellular tumours in mice and rats treated with ripazepam

Dose (mg/kg bw)	Mouse				Rat			
	Adenoma (neoplastic nodules)		Carcinoma		Adenoma (neoplastic nodules)		Carcinoma	
	Male	Female	Male	Female	Male	Female	Male	Female
0	10/50	5/50	0/50	0/50	5/50	4/50	0/50	0/50
15	15/50	2/50	0/50	0/50	4/50	6/50	0/50	0/50
150	33/50	11/50	1/50	0/50	9/50	6/50	1/50	2/50

From Fitzgerald *et al.* (1984)

3.1.2 *Rat*

Groups of 50 male and 50 female albino CD rats, five to six weeks of age, were given 0, 15 or 150 mg/kg bw ripazepam (100% pure) in the diet for up to 104 weeks. The ripazepam concentration in the food was adjusted weekly for changes in body weight and food consumption. The ripazepam/diet mixtures were prepared freshly each week and offered *ad libitum*. In treated rats, body-weight gains were depressed by 21% in male and by 36% in female rats given 150 mg/kg bw ripazepam. Food consumption was decreased slightly (7%) only in female rats at the 150-mg/kg dose. Mortality rates were similar in all groups. All surviving animals were killed at 104 weeks. Histological examinations were performed on major organs [not specified] and visually apparent lesions. An increase in centrilobular hypertrophy of hepatocytes, primarily at the 150-mg/kg bw dose level, was observed in treated rats. No significant increase in the incidence of tumours in treated groups was observed for either sex. Data on the incidence of liver tumours are presented in Table 1 (Fitzgerald *et al.*, 1984).

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

No data were available to the Working Group.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Ripazepam is a pyrazolodiazepine with anxiolytic properties which has never been marketed for human use.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Ripazepam was tested for carcinogenicity in one experiment in mice and in one experiment in rats by oral administration in the diet. An increased incidence of benign liver tumours was found in male mice. No increase in the incidence of tumours was found in female mice or in rats of either sex.

5.4 Other relevant data

No data were available to the Working Group on the metabolism, toxicity, reproductive or genetic and related effects of ripazepam.

5.5 Evaluation[1]

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

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

Overall evaluation

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

6. References

DeWald, H.A., Nordin, I.C., L'Italien, Y.J. & Parcell, R.F. (1973) Pyrazolodiazepines. 1,3- (and 2,3-) Dialkyl-4,6-dihydro-8-arylpyrazolo[4,3-*e*][1,4]diazepin-5-ones as antianxiety agents. *J. med. Chem.*, **16**, 1346–1354

Fitzgerald, J.E., de la Iglesia, F.A. & McGuire, E.J. (1984) Carcinogenicity studies in rodents with ripazepam, a minor tranquilizing agent. *Fundam. appl. Toxicol.*, **4**, 178–190

Poschel, B.P.H., McCarthy, D.A., Chen, G. & Ensor, C.R. (1974) Pyrazapon (CI-683): a new antianxiety agent. *Psychopharmacologia*, **35**, 257–271

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