OXAZEPAM

This substance was considered by previous working groups in October 1976 (IARC, 1977) and March 1987 (IARC, 1987). Since that time, new data have become available, and these have been incorporated in the monograph and taken into consideration in the evaluation.

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 604-75-1

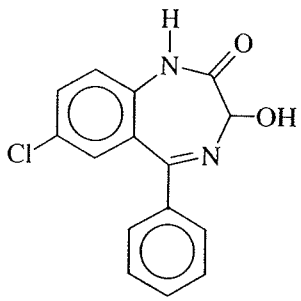
Deleted CAS Reg. No.: 61036-43-9

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

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

Synonyms: *N*-Desmethyltemazepam; nortemazepam

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_{15}H_{11}ClN_2O_2$ Relative molecular mass: 286.72

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Creamy white to pale-yellow powder (Gennaro, 1995)

(*b*) *Melting-point*: 205–206 °C (Budavari, 1995)

(*c*) *Spectroscopy data*: Infrared, ultraviolet, nuclear magnetic resonance and mass spectral data have been reported (Shearer & Pilla, 1974).

(*d*) *Solubility*: Practically insoluble in water (1 g/more than 10 000 mL); soluble in chloroform (1 g/270 mL), diethyl ether (1 g/2200 mL), ethanol (1 g/220 mL) (Gennaro, 1995) and dioxane (Budavari, 1995)

(*e*) *Stability*: Stable in light and nonhygroscopic (Gennaro, 1995); hydrolysed by acids (Shearer & Pilla, 1974)

(*f*) *Dissociation constants*: pK_as = 1.7 and 11.6 (American Hospital Formulary Service, 1995)

(*g*) *Octanol/water partition coefficient (P)*: log P, 1.99 (Dollery *et al.*, 1991)

1.1.4 *Technical products and impurities*

There are two enantiomeric forms of the oxazepam structure (asymmetric centre at C_3); oxazepam in pharmaceutical preparations is invariably the racemic mixture (British Pharmacopoeial Commission, 1993).

Oxazepam is available as 10-, 15- and 30-mg tablets and 10-, 15- and 30-mg capsules, which may also contain gelatin, lactose, magnesium stearate, methylcellulose, polacrilin potassium, titanium dioxide, D&C Red 22 (eosine), D&C Red 28, FD&C Blue 1 (Brilliant Blue FCF), FD&C Red 40 (Allura Red AC), FD&C Yellow 5 (tartrazine) or FD&C Yellow 6 (Sunset Yellow FCF) (Thomas, 1991; British Medical Association/-Royal Pharmaceutical Society of Great Britain, 1994; American Hospital Formulary Service, 1995; Medical Economics, 1996).

Trade names and designations of the chemical and its pharmaceutical preparations include: Abboxapam; Adumbran; Alepam; Alopam; Antoderin; Anxiolit; Anxiolit retard; Aplakil; Aslapax; Astress; Azutranquil; Benzotran; Bonare; Buxopax; CB 8092; Constantonin; Drimuel; Droxacepam; Durazepam; Enidrel; Hilong; Iranil; Isodin; Lederpam; Limbial; Murelax; Nesontil; Neurofren; Noctazepam; Novoxapam; Nozepam; Oxa; Oxabenz; Oxahexal; Oxa-10 L.U.T.; Oxanid; Oxa-Puren; Oxepam; Oxpam; Praxiten; Propax; Psicopax; Psiquiwas; Purata; Quen; Quilibrex; Ro 5-6789; Rondar; Sedokin; Serax; Serenal; Serenid; Serepax; Seresta; Serpax; Sigacalm; Sobile; Sobril; Tarchomin; Tazepam; Uskan; Vaben; Wy 3498; Zapex; Zaxopam.

1.1.5 *Analysis*

Several international pharmacopoeias specify potentiometric titration with tetrabutylammonium hydroxide or perchloric acid as the assay for purity of oxazepam, and thin-layer chromatography (TLC) or gas chromatography (GC) with flame ionization detection (FID) for determining impurities and decomposition products. Assays for oxazepam in capsules and tablets typically involve comparing ultraviolet absorbance with standards (Council of Europe, 1992; British Pharmacopoeial Commission, 1993; United States Pharmacopeial Convention, 1994). Other methods of analysis in pharmaceutical preparations include fluorimetry (Walash *et al.*, 1994), spectrophotometry (Prada *et al.*, 1988; El-Brashy *et al.*, 1993), mass spectrometry (MS) (McCarley & Brodbelt, 1993) and high-performance liquid chromatography (HPLC) (Bargo, 1983).

Oxazepam and its metabolites can be analysed in biological fluids and tissues by fluorescence polarization immunoassay (Simonsson *et al.*, 1995), fluorimetry (Walash *et al.*,

1994), GC (Nau *et al.*, 1978; Peat & Kopjak, 1979; Löscher, 1982), GC/MS (Maurer & Pfleger, 1987; Langner *et al.*, 1991) and HPLC (Peat & Kopjak, 1979; Lensmeyer *et al.*, 1982; Komiskey *et al.*, 1985; Mura *et al.*, 1987; Fernández *et al.*, 1991; Berrueta *et al.*, 1993; Chopineau *et al.*, 1994).

1.2 Production and use

1.2.1 *Production*

A method for preparing oxazepam was first reported in 1962 (Bell & Childress, 1962); commercial production of oxazepam in the United States of America was first reported in 1965 (United States Tariff Commission, 1967).

Oxazepam is prepared by acylating 2-amino-5-chlorobenzophenone with chloroacetyl chloride. Heating the product with sodium iodide yields the iodoacetamido compound. Treatment of the iodoacetamido compound with hydroxylamine effects dehydration and dehydrohalogenation to form a benzodiazepine derivative, which rearranges to oxazepam, with esterification, when treated with acetic anhydride. Saponification liberates oxazepam (Gennaro, 1995).

1.2.2 *Use*

Oxazepam is a benzodiazepine used in the treatment of anxiety disorders, insomnia and alcohol withdrawal symptoms (see the monograph on diazepam, pp. 39–41, for a brief overview of the pharmacology of therapeutic action for this class of drugs). The usual adult oral dose is 10–15 mg three or four times daily for the treatment of mild to moderate anxiety and 15–30 mg three or four times daily for the treatment of severe anxiety or for control of symptoms of alcohol withdrawal. A suggested initial dose for elderly or debilitated patients is 10 mg three times daily, which may be increased to 15 mg three or four times daily if necessary. Oxazepam (15–25 mg) may be given one hour before retiring for the treatment of insomnia associated with anxiety; up to 50 mg may occasionally be necessary. A dosage of oxazepam for children 6–12 years of age has not been clearly established (Reynolds, 1993; American Hospital Formulary Service, 1995; Medical Economics, 1996). Clinical uses of oxazepam and other benzodiazepines have been reviewed (Hollister *et al.*, 1993). Oxazepam is used extensively in elderly patients and patients with impaired hepatic function (Goodman Gilman *et al.*, 1990).

Comparative data on sales of oxazepam in several countries are shown in Table 1. Overall, sales declined by approximately 20% from 1990 to 1995. During the same period, prescriptions in the United States declined by approximately 13% (see Table 2 in the monograph on diazepam, p. 43).

Table 1. Sales of oxazepam in various countries[a] (number of standard units[b], in thousands)

Country	1990	1995	Country	1990	1995
Africa			Europe		
South Africa	14 177	13 992	Belgium	39 581	30 502
North America			France	182 475	137 808
Canada	84 407	84 985	Germany	367 014	245 363
Mexico	5 005	0	Greece	2 870	0
United States	97 602	106 913	Italy	44 115	33 200
South America			Netherlands	94 819	104 909
Argentina	4 199	3 327	Portugal	16 205	18 431
Brazil	141	23	Spain	35 856	10 850
Venezuela	6 390	219	Sweden	99 809	64 160
Asia			Switzerland	37 824	34 404
Republic of Korea	28 316	22 942	Turkey	680	0
Australia	78 027	57 015	United Kingdom	33 365	23 406

[a] Data provided by IMS

[b] Standard dosage units, uncorrected for oxazepam content

1.3 Occurrence

1.3.1 *Natural occurrence*

Oxazepam is not known to occur as a natural product. Oxazepam is a metabolite of other benzodiazepine pharmaceuticals, including diazepam, prazepam and temazepam (Langner *et al.*, 1991).

1.3.2 *Occupational exposure*

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 2650 employees were potentially occupationally exposed to oxazepam. 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

Oxazepam is listed in the following pharmacopoeias: British, Brazilian, Czech, European, French, Italian, Nordic and United States (Reynolds, 1993; Vidal, 1995).

2. Studies of Cancer in Humans

Oxazepam, together with triazolam, was included in the 'other benzodiazepines' category in the comprehensive case–control study by Rosenberg *et al.* (1995) reviewed in detail in the monograph on diazepam (pp. 51–53). Too few subjects had used oxazepam to allow analysis of this drug as a separate category, but no elevated risk was associated with the general category 'sustained use of other benzodiazepines' for any cancer, including cancer of the large bowel (relative risk (RR), 1.5; 95% confidence interval (CI), 0.9–2.4), malignant melanoma (RR, 0.7; 95% CI, 0.3–1.6), lung cancer (RR, 1.4; 95% CI, 0.6–3.2), breast cancer (RR, 0.8; 95% CI, 0.4–1.4) and endometrial cancer (RR, 0.8; 95% CI, 0.3–2.5). Sustained use was defined as ≥ 4 days per week for at least one month that began ≥ 2 years before admission to the hospital. [See additional comments on this study in the monograph on diazepam.]

3. Studies of Cancer in Experimental Animals

3.1 Oral administration

3.1.1 *Mouse*

Groups of 14 male and 14 female Swiss-Webster mice, three months of age, were given oxazepam [purity not specified] in the diet for nine months at concentrations of 500 or 1500 mg/kg diet (ppm) or were given a control diet. After 12 months of age, all mice were given the control diet for a further two months; then, all surviving animals were killed. Selected tissues [list of organs examined not given] were evaluated histologically. In surviving animals, an increased incidence of hepatocellular adenomas (males: control, 0/13; low-dose, 3/12 (25%); high-dose, 8/13 (62%); females: controls, 0/10; low-dose, 0/10; high-dose, 5/8 (63%)) was seen (Fox & Lahcen, 1974). [The Working Group noted that the tumour incidence was given as a percentage of animals surviving at the end of the study and not of total animals.]

The incidences of liver tumours from the following two studies are presented in Table 2.

Groups of 60 male and 60 female Swiss-Webster mice, six to seven weeks of age, were given oxazepam (purity, > 99%) in the diet at concentrations of 0, 2500 or 5000 mg/kg diet (ppm) for up to 57 weeks, at which time the study was terminated due to excessive treatment-related mortality. The oxazepam/diet mixtures were prepared freshly every two weeks. Consumption of diet containing 2500 and 5000 ppm oxazepam resulted in average daily intakes of 270 and 570 mg/kg bw for males and 320 and 670 mg/kg bw for females. The body weights of the treated males were similar to those of the controls during the early weeks, but fell below those of the controls by week 17. The females had greater body weight than the controls until week 29, after which the body weights of the

Table 2. Liver tumours in oxazepam-treated mice

Strain	Sex	Dose (ppm)	No. of mice examined	No. of tumours		
				Adenomas	Carcinomas	Hepato-blastomas
Swiss-Webster (study terminated at 57 weeks)	Male	0	60	1	0	
		2500	60	35[a]	5[b]	
		5000	60	50[a]	19[c]	
	Female	0	60	0	1	
		2500	59	22[a]	1	
		5000	59	47[a]	11[c]	
B6C3F1 (study terminated at 105 weeks)	Male	0	49	17	9	0
		125	50	18	5	2
		2500	50	34[c]	45[c]	21[c]
		5000	50	32[c]	50[c]	13[c]
	Female	0	50	25	9	0
		125	50	35	5	1
		2500	50	35[c]	49[c]	8[c]
		5000	50	36[c]	44[c]	8[c]

From United States National Toxicology Program (1993)
[a] $p < 0.001$; logistic regression test
[b] $p = 0.003$; life table test
[c] $p < 0.001$; life table test

high-dose females were similar to those of the controls, while those of the low-dose females remained slightly higher. Food consumption was slightly lower in exposed males and females than in controls. At 57 weeks, there was a significant reduction in the numbers of exposed mice surviving compared with controls (males: control, 45/60; low-dose, 19/60; high-dose, 10/60; females: control, 47/60; low-dose, 28/59; high-dose, 17/59). All surviving animals were killed at 57 weeks. Complete histological examination was performed for all animals except two lost females. Systemic amyloidosis was the principal cause of death in mice dying before the study was terminated. The lower survival of mice receiving oxazepam was attributed to an increase in the extent and severity of amyloid deposits in many organs. A significant increase in the incidence of benign and malignant hepatocellular tumours was observed for male and female mice (Fisher's exact test and Cochran–Armitage linear trend test). The incidences of eosinophilic foci were also increased in exposed mice (males: control, 0/60; low-dose, 22/60 and high-dose, 22/60; females: control, 0/60; low-dose, 20/59 and high-dose, 14/59) and there was evidence of increased centrilobular hepatocyte hypertrophy (males: control, 12/60; low-dose, 46/60 and high-dose, 47/60; females: control, 3/60, low-dose, 51/59 and high-dose, 53/59) (United States National Toxicology Program, 1993; Bucher *et al.*, 1994).

Groups of 50 male and 50 female B6C3F1 mice, six weeks of age, were given oxazepam (purity, > 99%) in the diet at concentrations of 0, 125, 2500 or 5000 mg/kg diet

(ppm) for up to 105 weeks. Consumption of diets containing 125, 2500 and 5000 ppm oxazepam resulted in average daily intakes of 12, 310 and 690 mg/kg bw for males and 15, 350 and 780 mg/kg bw for females. Body-weight gain of treated males and females was similar to that of controls until about week 15, after which weight gain for mice exposed to 2500 and 5000 ppm was reduced in relation to controls, resulting in body weights 30–40% lower than those of the controls throughout the remainder of the study. Mean body weights of male mice exposed to 125 ppm oxazepam were similar to those of the controls, while those of female mice receiving 125 ppm were 10–15% lower than those of the controls after about week 45. Food consumption by exposed males and exposed females was similar to that of controls. At 105 weeks, survival of mice receiving 2500 and 5000 ppm was significantly lower than that of controls (males: control, 45/50; low-dose, 44/50; mid-dose, 15/50; high-dose, 0/50; females: 39/50, 41/50, 2/50, 0/50, respectively). All surviving animals were killed at 105 weeks. Complete histological examination was performed on all animals except one control male. The early deaths of the mice were attributed to marked increases in the incidence of hepatoblastoma, hepatocellular adenoma and hepatocellular carcinoma. Moderate hypertrophy of centrilobular hepatocytes occurred in mice receiving 2500 and 5000 ppm oxazepam (males: control, 0/49; low-dose, 2/50; mid-dose, 26/50 and high-dose, 43/50; females: control, 0/50; low-dose, 2/50; mid-dose, 11/50 and high-dose, 29/50). An increase in the incidence of follicular-cell hyperplasia of the thyroid gland occurred in all exposed groups of mice (males: control, 4/49; low-dose, 22/50; mid-dose, 49/50 and high-dose, 47/50; females: control, 16/50; low-dose, 34/50; mid-dose, 49/50 and high-dose, 44/50) and the incidence of thyroid gland follicular-cell adenoma was increased in exposed females (control, 0/50; low-dose, 4/50; mid-dose, 5/50 and high-dose, 6/50) (United States National Toxicology Program, 1993; Bucher *et al.*, 1994). [The Working Group noted that the two highest dose levels may have been toxic.]

The hepatocellular adenomas, carcinomas and hepatoblastomas from the B6C3F1 mice exposed to oxazepam in the diet in the above study were analysed for the presence of activated *ras* proto-oncogenes (Devereux *et al.*, 1994) (see Section 4.4.2).

3.1.2 *Rat*

To study preneoplastic events, groups of 10 male Fischer 344 rats, weighing 150 g [age not specified] were given 0 (control), 20 and 200 mg/kg bw oxazepam (> 99% pure) suspended in 10% arabic gum solution daily by gastric instillation for 14 weeks. No iron-excluding hepatocellular focus was found in the controls or the group receiving 20 mg/kg oxazepam. Four hepatocellular foci were found in one rat receiving oxazepam at the highest dose (Remandet *et al.*, 1984).

3.2 Administration with known carcinogens

3.2.1 *Mouse*

Groups of 40 male B6C3F1 mice, five weeks of age, were given either 0 or 90 mg/kg bw *N*-nitrosodiethylamine (NDEA) in tricaprylin as a single intraperitoneal injection. At

seven weeks of age, the mice were given 500 or 1500 mg/kg diet (ppm) oxazepam [purity not specified] in the diet or 500 mg/L (ppm) phenobarbital in the drinking water. Eight mice per group were killed at 9, 21 and 33 weeks of exposure and the remainder were killed after 53 weeks of exposure. Complete necropsy was performed on each animal, and liver, lung, spleen, thyroid, kidney and visually apparent lesions in other organs were examined histologically. Between 33 and 53 weeks of exposure, there was an increase in the incidence of hepatocellular tumours in animals treated with NDEA and oxazepam (see Table 3) (Diwan *et al.*, 1986).

Table 3. Incidence of liver tumours in B6C3F1 mice

Treatment	Hepatocellular adenomas	Hepatocellular carcinomas
NDEA	10/16	0/16
NDEA + 500 ppm oxazepam	14/16[a]	3/16[a]
NDEA + 1500 ppm oxazepam	15/15[b]	8/15[c]
NDEA + 500 ppm phenobarbital	16/16	10/16
500 ppm oxazepam	2/16	0/13
1500 ppm oxazepam	0/15	0/15
500 ppm phenobarbital	0/16	0/16

From Diwan *et al.* (1986)
[a] [$p = 0.1$; Fisher's exact test versus NDEA controls]
[b] [$p = 0.01$; Fisher's exact test versus NDEA controls]
[c] [$p = 0.001$; Fisher's exact test versus NDEA controls]

3.2.2 *Rat*

Three groups of eight male Wistar rats [age not specified] were given 200 mg/kg bw NDEA as a single intraperitoneal injection. Two weeks later, the animals were given 3000 mg/kg diet (ppm) 2-acetylaminofluorene (2-AAF) in the diet for 14 days and 2 mL/kg bw carbon tetrachloride as a single gastric instillation at the mid-point of the 2-AAF treatment. One week later, the three groups were given basal diet (control), 1000 mg/kg (ppm) oxazepam [purity unspecified] or 500 mg/kg (ppm) phenobarbital in the diet for 30 weeks. At the end of the study, livers were weighed and examined and samples from each lobe plus visually apparent tumours were examined. Both oxazepam and phenobarbital increased the incidence of hepatocellular carcinomas (controls, 0/8; oxazepam, 5/8 (62%); phenobarbital, 7/8 (87%)) (Préat *et al.*, 1987).

Three groups of eight female Sprague-Dawley rats [age not specified] were partially hepatectomized and then given 10 mg/kg bw NDEA as a single intraperitoneal injection and held for two months. The rats were subsequently given basal diet (control), 1000 mg/kg (ppm) oxazepam [purity unspecified] or 500 mg/kg (ppm) phenobarbital in the diet for 57 weeks. At the end of the study, livers were weighed, examined and samples from each lobe as well as visually apparent tumours were examined. There was no significant increase in the incidence of hepatocellular carcinomas (controls, 0/8;

oxazepam, 2/8 (25%); phenobarbital, 0/8) (Préat *et al.*, 1987) [The Working Group noted the small numbers of animals.]

Groups of 10 or 20 male Fischer 344 rats, weighing 170 g [age not specified], were fed diets containing 200 mg/kg (ppm) 2-AAF for eight weeks. The daily dose was estimated to be approximately 15 mg/kg bw. In one group of 10 rats, this was followed by 12 weeks' treatment with 200 mg/kg bw oxazepam (purity > 99%) daily by gastric instillation. There was no significant increase in the incidence of neoplastic nodules of the liver: untreated controls (20 rats), 0 neoplastic nodule/liver; 2-AAF alone (20 rats), 0.2 neoplastic nodule/liver; and 2-AAF plus oxazepam (10 rats), 0.2 neoplastic nodule/liver (Mazue *et al.*, 1982; Remandet *et al.*, 1984). [The Working Group noted the small numbers of animals and the single dose level of oxazepam.]

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

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

The pharmacokinetics of oxazepam have been reviewed (Greenblatt, 1981). Oxazepam is absorbed fairly rapidly, reaching peak plasma concentrations within 1–4 h, with a mean of about 2 h in most studies. Greenblatt *et al.* (1980) found that the time of maximum absorption of 30 mg oxazepam was 2.2 h (range, 0.75–4.25 h) in 18 men and 3.1 h (range, 0.5–8.0 h) in 20 women. The maximal plasma concentrations in this study were 622 ± 37 ng/mL in men and 837 ± 51 ng/mL in women. In volunteers given multiple doses (5 mg/day for 10 days), Alván *et al.* (1977) found evidence of only minimal accumulation. The bioavailability is believed to be essentially complete (93%) (Alván & Odar-Cederlöf, 1978; Sonne *et al.*, 1988). The drug is extensively (97%) bound to plasma proteins (Boudinot *et al.*, 1985). Considerable variation in the elimination half-life has been reported, with mean values ranging from about 5 to about 15 h (Greenblatt, 1981). Sonne *et al.* (1988) found values of 6.7 h (range, 5.5–9.2 h) and 5.8 h (range, 5.4–8.4 h) following intravenous and oral administration, respectively. A sex difference has been reported, with a value of 7.8 ± 0.4 h (range, 4.9–10.8 h) in men and 9.7 ± 0.8 h (range, 6.3–19.4 h) in women (Greenblatt *et al.*, 1980). In this study, the elimination half-life was not age-associated in men (r = –0.085), but tended to increase, although not significantly, with age in women (r = 0.45). Other factors which have been suggested to modify the pharmacokinetics of oxazepam are renal insufficiency (Greenblatt *et al.*, 1983) and hypothyroidism (Sonne *et al.*, 1990), which reduce clearance, while hyperthyroidism increases the rate of glucuronidation and consequently increases clearance (Scott *et al.*, 1984). However, liver disease characterized by cirrhosis or viral hepatitis has no significant effect (Shull *et al.*, 1976; Sellers *et al.*, 1979).

The percentage of dose recovered in urine as glucuronides has varied widely, which may reflect in part methodological differences (Greenblatt, 1981), but at least 60–80%

seems generally agreed. Sonne *et al.* (1988) found that, 48 h after administration of a 15-mg dose, no more than 1% was excreted in the urine as oxazepam, whereas about 70% was recovered as oxazepam glucuronide. Alván *et al.* (1977) found that the urinary recovery of conjugates was 67 ± 15% of the administered dose, with only 2.4 ± 2.4% appearing in the faeces as the parent compound. The glucuronide exists as a pair of diastereoisomers (Ruelius *et al.*, 1979), since oxazepam, like all 3-hydroxybenzodiazepines, is used clinically as a racemic mixture. In a study of these diastereoisomers, Seideman *et al.* (1981) recovered a mean of 54.6 ± 6.6 μmol total glucuronides in 24 h from the urine of six volunteers given a single oral dose of 15 mg oxazepam. The ratio of (+)/(−) isomers [(3*S*)/(3*R*) configurations] was 2.1 ± 0.8. Trace amounts of six other metabolites have been reported (Sisenwine *et al.*, 1972) (see Figure 1). It has been calculated that less than 0.1% of 10 mg given three times daily for three days would be excreted in one litre of milk of a breast-feeding mother (Wretlind, 1987). The excretion of oxazepam in breast milk has been confirmed (Dusci *et al.*, 1990).

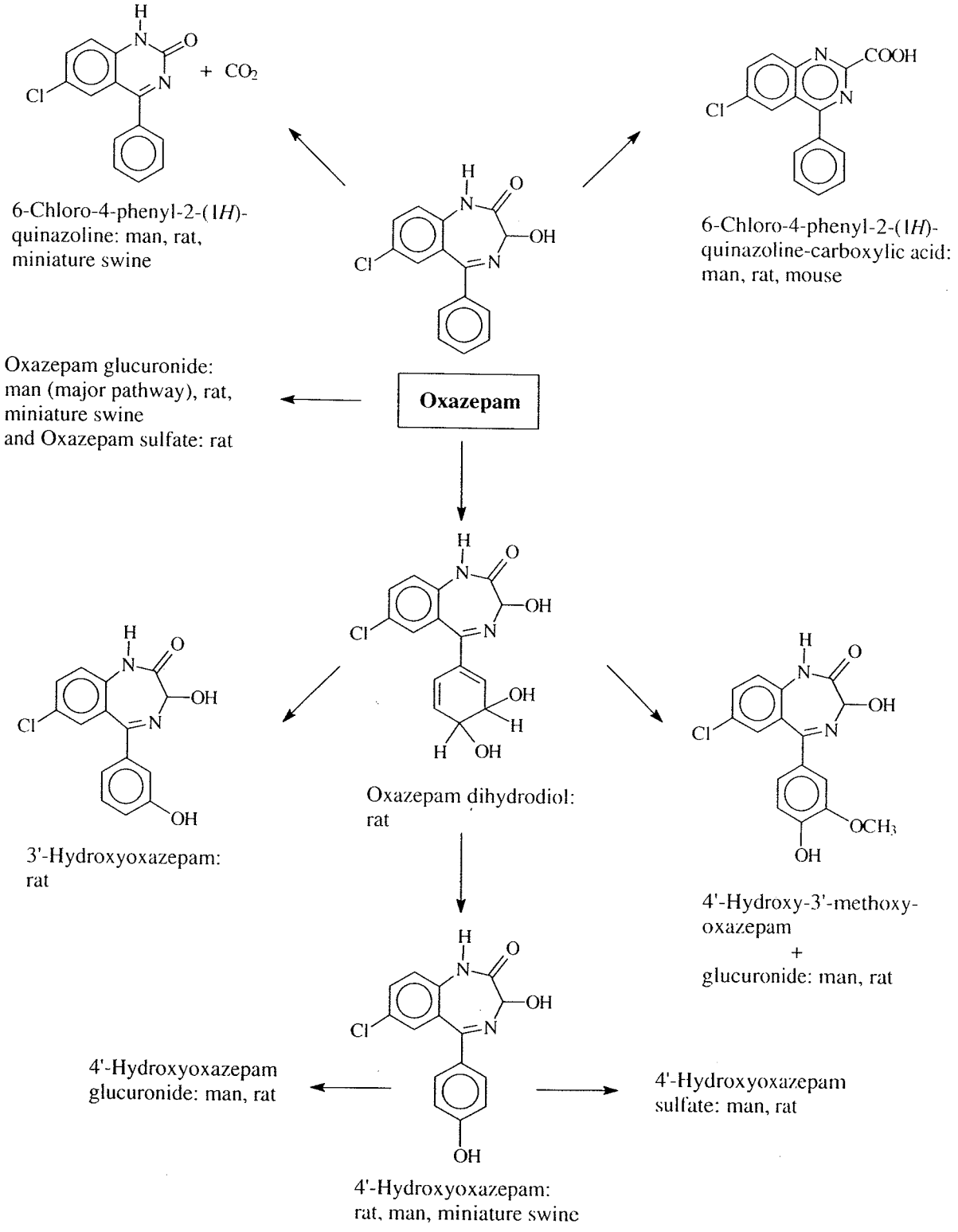
Tomson *et al.* (1979) showed the rapid placental passage of oxazepam and the minimal capacity of the fetus to glucuronidate oxazepam even in late pregnancy. Thus, conjugated oxazepam found in fetal compartments was produced by neither the placenta nor the fetus, but was probably of maternal origin. Newborns are able to conjugate oxazepam. In early and late pregnancy, the mean ratios of the plasma concentration of total oxazepam (free and glucuronide conjugate forms) in the umbilical cord to that in a maternal vein were 0.6 and 1.1, respectively (Kangas *et al.*, 1980). The penetration of oxazepam from maternal serum to placental tissue in a 4-h period after drug administration was 49%, indicating rapid transfer (Jørgensen *et al.*, 1988).

4.1.2 *Experimental systems*

Garattini *et al.* (1973) gave rats, mice and guinea-pigs 5 mg/kg bw oxazepam by intravenous injection and measured blood levels of the drug at times from 1 min up to 10 h. Maximal oxazepam concentrations were found at the earliest sampling time in all species, the values being 1.63 ± 0.09 μg/mL at 1 min in rats, 3.16 ± 0.05 μg/mL at 1 min in mice and 1.81 ± 0.12 μg/mL at 5 min in guinea-pigs. Blood levels were < 0.05 μg/mL at 5 h in rats and 0.07 ± 0.01 μg/mL at 10 h in guinea-pigs, but were still 0.20 ± 0.01 μg/mL at 10 h in the mice. Biliary excretion of conjugated hydroxylated metabolites, expressed as percentages of the dose 3 h after administration, were 5.3 ± 0.4% in rats, 34.7 ± 3.4% in guinea-pigs and 49.7 ± 5.3% in mice. [The Working Group considered that the 'conjugated hydroxylated benzodiazepines' in this study were the glucuronides of oxazepam and not the phenolic metabolites measured in the studies of Sisenwine and Tio (1986) described below. The low recovery of the oxazepam conjugate in the rat after administration of oxazepam (5.3 ± 0.4%) is therefore consistent with the claim of Sisenwine and Tio that aromatic hydroxylation products predominate in rats.]

The plasma concentrations of oxazepam in male B6C3F1 mice fed diet containing 125 and 2500 mg/kg (ppm) oxazepam appeared to reach steady-state levels by one week of feeding. These levels were 1 μg/mL for the low-dose group and 5–10 μg/mL for the high-dose group (Yuan *et al.*, 1994).

Figure 1. Metabolism of oxazepam in man, miniature swine, rat and mouse



From Sisenwine *et al.* (1972); Griffin & Burka (1993, 1995)

Oxazepam accumulates in adipose tissue. Garattini *et al.* (1973) found that adipose tissue/blood ratios of the drug in mice given 5 mg/kg bw intravenously varied from 1.7 (at 5 min) to 4.9 (at 30 min). Accumulation also occurred in the brain. Maximal concentrations of oxazepam in the brain were 14.3 ± 0.17 μg/g in mice, 4.5 ± 0.03 μg/g in rats and 3.5 ± 0.47 μg/g in guinea-pigs, all at 5 min. Brain/blood drug level ratios in these species varied from 1.1 (at 1 min) to 11.3 (at 10 h) in mice, from 1.9 (at 1 min) to 6.2 (at 1 h) in rats and from 1.9 (at 5 min) to 8.9 (at 5 h) in guinea-pigs.

The disposition of oxazepam in rats and miniature swine was studied by Sisenwine *et al.* (1972). The miniature swine (like humans) eliminated oxazepam primarily as the glucuronides, while aromatic hydroxylation predominated in the rat. In rats, 70.7 ± 6.0% of a single oral dose of 20 mg/kg bw was eliminated in faeces following biliary secretion, while 18.9 ± 2.4% of the dose was found in the urine (Sisenwine & Tio, 1986). In CD-1 mice given an oral dose of 22 mg/kg bw oxazepam, 57.8% was recovered from the faeces and 27.3% was recovered from urine over five days (Sisenwine *et al.*, 1987). Reinvestigation of the metabolism of oxazepam in Swiss-Webster and B6C3F1 mice (Griffin & Burka, 1993) and in Fischer 344 rats (Griffin & Burka, 1995) confirmed the results of the earlier studies. Treatment with 2500 mg/kg diet (ppm) oxazepam in the diet for 14 days before administration of oxazepam by gastric instillation led to a shift from faecal to urinary excretion in mice, but not rats, so that the urinary excretion almost doubled.

There are three major pathways of oxazepam metabolism in mice and rats (as in humans): direct conjugation, phenyl ring oxidation and diazepine ring contraction (Sisenwine & Tio, 1986; Sisenwine *et al.*, 1987; Griffin & Burka, 1993, 1995). In mice, conjugation is mainly with glucuronide, predominantly excreted in the urine; in rats, conjugation is mainly with sulfate, which is almost entirely eliminated in the faeces. The sulfate conjugate of oxazepam, which is unstable in acidic media, may be the source of the faecal oxazepam reported by Sisenwine and Tio (1986). It has not been detected in mice. Studies with recirculating, perfused male Swiss (CD-1) mouse liver preparations showed that oxazepam glucuronides are the dominant liver metabolites in this species (St-Pierre *et al.*, 1990). Oxazepam can also be conjugated with glucuronide by the placenta of rabbits (Berte *et al.*, 1969), apparently in contrast to the human organ (Tomson *et al.*, 1979). Phenyl ring oxidation is more important in rats than in mice (or humans) and Griffin and Burka (1995) found that a dihydrodiol (probably the 3′,4′-dihydrodiol, since 2'-hydroxy derivatives are not known) accounts for about 30% of the 72-h urinary metabolites in Fischer 344 rats. This metabolite, which probably forms via an arene oxide intermediate and has not been found in mice, holds implications for the toxicological properties of oxazepam. In rats, ring contraction to 6-chloro-4-phenyl-2(1*H*)-quinazoline carboxylic acid occurs to roughly one half of the extent seen in mice.

4.2 Toxic effects

4.2.1 *Humans*

(*a*) *Acute toxicity*

Fifteen cases of fatal poisoning due to suicidal or accidental ingestion of large doses of oxazepam, either alone or in combination with alcohol and/or other drugs, have been reported. In a review of fatal poisonings attributed to benzodiazepines in the United Kingdom during the 1980s, oxazepam had a comparatively low fatal toxicity index; that is, it caused fewer deaths per million prescriptions than temazepam, diazepam or prazepam (Serfaty & Masterton, 1993).

(*b*) *Chronic toxicity*

In addition to effects associated with psychological and physical dependence and withdrawal phenomena, chronic oxazepam administration has been associated in very rare cases with jaundice (both hepatocellular and cholestatic), nausea, skin rashes, lowering of blood pressure and, in isolated cases, with the enhancement of parkinsonism or arthritic symptoms (reviewed by Dollery *et al.*, 1991).

4.2.2 *Experimental systems*

(*a*) *Acute toxicity*

Oral and intraperitoneal LD_{50} values for oxazepam in carboxymethyl cellulose have been reported to range from about 1500 mg/kg bw to > 5000 mg/kg bw in various strains of mice and were greater than 5000 mg/kg bw in Wistar and Charles River CD rats (Owen *et al.*, 1970; United States National Toxicology Program, 1993). Owen *et al.* (1970) reported that oxazepam was only one third as toxic as diazepam when given by the oral route and six times less toxic after intraperitoneal administration.

Unusually high mortality rates (about 20%) were observed in Swiss albino mice within seven days after intraperitoneal injection of 60 mg/kg bw oxazepam (a hypnotic dose causing loss of righting reflex in approximately 70% of the animals) dissolved in dimethyl sulfoxide (Wong & Teo, 1992). In a diazepam-sensitive strain of Swiss albino mice developed by the same group, the mortality rate was 37.5% when 60 mg/kg bw oxazepam was administered intraperitoneally. In neither strain was there mortality among dimethyl sulfoxide-treated control animals. Gross post-mortem examination did not reveal any consistent cause of death. In contrast, with the same oxazepam treatment regimen, mortality was only 7% in BALB/c mice. [The authors did not offer any explanation for the high mortality rates in the two Swiss mouse strains; there are no other reports in the literature of such high mortality rates due to benzodiazepine administration.]

(*b*) *Subacute and chronic toxicity*

Owen *et al.* (1970) administered oxazepam in the diet to male and female Charles River CD rats at concentrations of 600, 1250, 2500 or 5000 mg/kg diet (ppm) for six weeks (20 animals per group). After six weeks, two of the high-dose rats had died, and

weight gain was impaired in the males given 2500 ppm concentration. Liver, adrenal gland and kidney weights were significantly greater in the two highest-concentration groups of both sexes. The only treatment-related histopathological change was a mild to moderate increase in liver parenchymal fat; no liver necrosis or fibrosis was found. There was no increase in liver fat in animals maintained on drug-free diet for four weeks after administration of 5000 ppm oxazepam in the diet for six weeks.

Groups of 30 male and 30 female Charles River CD rats were fed diets containing 0, 150, 300, 600 or 1200 mg/kg diet (ppm) oxazepam for 55 weeks. There was no clearly treatment-related death. Except at the lowest dose, liver weights were higher compared with the controls. Kidney weights were higher at the two highest doses in oxazepam-treated males, and ventral prostate and uterine weights were lower at the highest dose level. There was no effect on body weight or haematological parameters and no significant histopathological sign of toxicity (Owen *et al.*, 1970).

In a 14-week study, oxazepam was given to Swiss-Webster mice in the diet at concentrations of 0, 625, 1250, 2500, 5000 or 10 000 mg/kg (ppm). Consumption of these diets resulted in average daily intakes of 80, 170, 330, 680 or 1400 mg/kg bw in males and 100, 220, 440, 830 and 1620 mg/kg bw in females. The mean body weights of all groups of exposed females were greater than those of the control group. In addition to sedative effects, decreased locomotor activity and muscle strength were observed, especially at the beginning of the study. Except for the lowest-intake groups, absolute and relative liver weights were significantly greater than those of the controls; the increases were dose-related. Heart and kidney weights were increased in some male and female groups. Dose-dependent hepatocellular hypertrophy was observed in all treated animals. Foci of hepatocellular necrosis were also detected in some animals; however, the low incidence and the lack of a dose-related increase suggested that these lesions were not causally linked to oxazepam administration. In a parallel 14-week assay, the effects of oxazepam were investigated in B6C3F1 mice under similar conditions, yielding practically identical results, notably those concerning body and liver weights and liver histopathology (United States National Toxicology Program, 1993).

Groups of 10 male B6C3F1 mice were fed diet containing 0, 25, 125, 2500 or 5000 mg/kg diet (ppm) oxazepam [approximately between 2 and 400 mg/kg bw per day] for 15, 30, 45 or 90 days. The two highest doses were selected to parallel those used in the United States National Toxicology Program bioassay of oxazepam (United States National Toxicology Program, 1993) and the two lowest doses to achieve blood concentrations similar to those reported in the literature for humans at therapeutic dose levels (1.1 μg/mL) or in the course of intoxications (up to 8.0 μg/mL). During the final seven days before they were killed, the animals were exposed to bromodeoxyuridine delivered by osmotic minipumps for quantification of hepatocellular replicative DNA synthesis. Liver/body weight ratios, serum clinical chemistry and histopathology of the liver were also monitored to provide data that would permit the distinction of cytotoxic from mitogenic mechanisms of cell proliferation. The liver/body weight ratios were significantly increased in a dose-dependent manner and the major histopathological feature was dose-dependent hypertrophy of hepatocytes; neither histopathology nor serum clinical chemistry revealed clear signs of hepatotoxicity. There was a dose-related

increase in replicative DNA synthesis at 15 days in the 125-, 2500- and 5000-ppm treatment groups (up to five-fold at the highest dose), but this returned to control levels in all groups by 30 days (Cunningham *et al.*, 1994). The transient mitogenic response observed might arise from initial activation followed by down-regulation of peripheral benzodiazepine receptors in the liver (Verma & Snyder, 1989). In addition to the benzodiazepine receptors in the central nervous system, there are also peripheral receptors in many organs, such as the liver, pituitary and adrenal glands, testes, heart and kidney (Ferrarese *et al.*, 1993).

Groups of male B6C3F1 mice were fed diets containing 125 mg/kg diet (ppm) (a non-carcinogenic dose in chronic studies) or 2500 mg/kg diet (ppm) (a carcinogenic dose in chronic studies [see Section 3]) oxazepam for 3, 7, 10 or 21 days. At the end of dosing, increased specific activities of various hepatic enzymes were observed, including cytochrome P450s (such as aminopyrine *N*-demethylase and aniline hydroxylase), cytochrome b5, glucuronyl transferase and glutathione *S*-transferase. At the low dose, only aminopyrine *N*-demethylase and glutathione *S*-transferase activities were significantly increased (Griffin *et al.*, 1995). The time pattern of induction was generally an early increase in the specific activities followed by a gradual decline until, by day 21, the specific activities were equivalent to or even below the control levels. The liver/body weight ratios continued to increase up to day 21.

In a continuation of these studies, labelling of hepatic cell nuclei with bromodeoxyuridine delivered by an implanted osmotic mini-pump over seven days indicated increased levels of cell proliferation by seven days on the low dose and by 10 days on the high dose. The delay observed at the higher dietary concentration probably reflects a sedative effect leading to reduced food consumption. Labelling was lower, but still above control values, after 21 days at this dose level. Hepatic cytochrome P450 and b5 protein levels and glucuronyl transferase activity were increased two-fold after 10 days of treatment with 2500 ppm oxazepam. Plasma thyroid-stimulating hormone levels were unaffected by the 125-ppm diet, but, in the mice exposed to the 2500-ppm oxazepam diet, thyroid-stimulating hormone levels increased three-fold after 10 days' treatment and returned to control levels by 21 days (Griffin *et al.*, 1996).

4.3 Reproductive and prenatal effects

4.3.1 *Humans*

Oxazepam, together with diazepam, nitrazepam and chlordiazepoxide, was included in the benzodiazepine category in a case–control study of oral clefts in Finland (Saxén & Saxén, 1975), but was not analysed as a separate category. The study is reviewed in detail in the monograph on diazepam (p. 66).

Laegreid *et al.* (1987a) reported seven cases with intra- and extrauterine growth retardation, facial dysmorphism and central nervous system dysfunction from 36 mothers (37 infants) who took benzodiazepines regularly during pregnancy. Of the seven children, two were exposed to oxazepam (75 mg daily) throughout pregnancy. One case had Moebius syndrome, including facial dysmorphism, convulsions and severe mental

retardation, while another child was affected with lissencephaly, distortion of neuronal migration with cerebral pachygyria and Dandy-Walker malformation, facial dysmorphism and polycystic kidney. Later, the second case was diagnosed, following the suggestion of Winter (1987), as Zellweger syndrome (Laegreid *et al.*, 1987b). [The Working Group noted that both Moebius and Zellweger syndromes may have a Mendelian mode of inheritance.]

The association between maternal psychotropic drug use and perinatal deaths was investigated in a case–control study in Gothenburg, Sweden (Laegreid *et al.*, 1992a). Too few women had used oxazepam to permit analysis of the specific association with this drug. The study is reviewed in more detail in the monograph on diazepam (p. 68).

Laegreid *et al.* (1992b,c) examined the neurodevelopment of 17 children born to 16 mothers who used benzodiazepines throughout pregnancy: 15 used oxazepam (15–60 mg daily) or diazepam (5–30 mg daily) alone or in combination and one mother used lorazepam. The results were compared with those for 29 children born to mothers without any known use of psychotropic drugs. Significant differences in the frequency of pre- and perinatal complications, for example, intrauterine asphyxia, instrumental delivery and respiratory disturbances, and in neurobehaviour between the benzodiazepine and control groups were found.

The 17 cases studied by Laegreid *et al.* (1992b,c) were followed up prospectively into late infancy (Viggedal *et al.*, 1993). A general delay in mental development up to 18 months of age associated with prenatal exposure to benzodiazepines was found. [The Working Group noted that maternal depression itself has an important negative effect on children's development (Cox, 1988). In addition, neuropsychological symptoms are frequent among children of abusers of psychoactive substances (Deren, 1986; Van Baar *et al.*, 1989).]

A case of floppy-infant syndrome (namely muscular relaxation, respiratory depression and limpness) following treatment of pre-eclampsia with oxazepam has been reported (Drury *et al.*, 1977).

4.3.2 *Experimental systems*

Oxazepam did not cause congenital abnormalities in mice (300 mg/kg diet (ppm)), rats (300 or 600 mg/kg diet (ppm)) or rabbits (25 or 50 mg/kg bw orally) (Owen *et al.*, 1970). An oral dose of 400 mg/kg bw induced resorption in Swiss-Webster mice, but no increase in the frequency of malformations (Miller & Becker, 1973). However, Simon and Sulik (1992, abstract) found craniofacial malformations (agnathia, an- or microphthalmia, coloboma, exencephaly, encephalocele, holoprosencephaly) when doses of 375 mg/kg bw or 1000 mg/kg bw oxazepam were administered by gastric instillation to C57Bl/6J mice on gestational day 7 at 0 h and 4 h. However, the authors noted that human exposure to the dose range examined is unlikely.

Chronic administration of 500 or 1500 mg/kg diet (ppm) oxazepam in the diet to breeding pairs of Swiss-Webster mice resulted in a significant decrease in mating performance and in body weights at birth (Guerriero & Fox, 1976). Female mice that received oxazepam (500 mg/kg diet (ppm)) prenatally had delay in the age of vaginal opening;

however, the age of first oestrus was generally lower than that of controls due to disruption of normal hypothalamic-pituitary relations (Fox & Guerriero, 1978). Oxazepam treatment (5, 15 or 50 mg/kg bw, twice daily, orally) on days 12–16 of pregnancy also resulted in postnatal growth retardation in CD-1 mice (Alleva *et al.*, 1985). Oxazepam (100 mg/kg bw orally) showed no noteworthy fetal toxicity in Sprague-Dawley rats (Saito *et al.*, 1984).

The long-term postnatal developmental (including behavioural) effects of oxazepam have been studied. Male Swiss-Webster mice that received oxazepam (500 mg/kg diet (ppm)) prenatally and during early infancy showed enhanced performance of a Y-maze task as adults. The drug produced its greatest effect (enhanced learning) when given prenatally (Fox *et al.*, 1977). The main effect of prenatal oxazepam treatment (5, 15 or 50 mg/kg bw, twice daily, orally) in CD-1 mice on days 12–16 of pregnancy was an impairment of active avoidance response, while effects on overall discrimination performance were less marked and limited to later stages of training (Alleva *et al.*, 1985).

CD-1 mice were exposed to oxazepam (15 mg/kg bw, twice daily, orally) on days 12–16 of fetal life (at a critical ontogenetic stage of type II benzodiazepine receptor increase) or to vehicle alone. Reduced locomotor activity on postnatal day 14 and modified profiles of muscimol effects (faster recovery from the initial depression) at 21 and 28 days were observed. These effects might be explained either by accelerated development of a GABAergic regulatory mechanism or by changes in the monoaminergic system — changes which may account for other effects of prenatal benzodiazepine exposure (Laviola *et al.*, 1992a). The eight-arm maze performance and neophobia were studied in prenatally exposed mice at 7–8 weeks of age. Overall, the oxazepam-exposed mice were much less efficient in the radial arm maze task than the vehicle-exposed animals. In addition, the latency of first approach to a novel stimulus object was considerably increased and a deficit of habituation in the course of the subsequent exploratory period was found (Laviola *et al.*, 1992b).

This mouse model was used to study typical responses of lactating dams; oxazepam enhanced maternal aggression towards the offspring (Laviola *et al.*, 1991).

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see also Table 4 for references and Appendices 1 and 2)

Oxazepam does not cause mutations in either *Salmonella typhimurium* or *Saccharomyces cerevisiae*. Furthermore, it does not cause mitotic recombination in *S. cerevisiae* or either non-disjunction or crossing-over in *Aspergillus nidulans*. No chromosomal damage was observed in *Nigella damascena*.

In cultured mammalian cells, oxazepam did not cause unscheduled DNA synthesis (in primary hepatocyte cultures) or mutation at either the *tk* or the *hprt* locus. Consistently positive responses have been observed in cultured mammalian (including human) cell

Table 4. Genetic and related effects of oxazepam

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	2500	Balbi *et al.* (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	NG	Matula & Downie (1983) (abstract)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	2500	Balbi *et al.* (1980)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	2500	Balbi *et al.* (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	2500	Balbi *et al.* (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	NG	Matula & Downie (1983) (abstract)
SCH, *Saccharomyces cerevisiae*, mitotic recombination	–	NT	NG	Matula & Downie (1983) (abstract)
SCR, *Saccharomyces cerevisiae*, reverse mutation	–	NT	NG	Matula & Downie (1983) (abstract)
ANG, *Aspergillus nidulans*, non-disjunction and crossing-over	–	NT	NG	Bignami *et al.* (1974)
PLC, *Nigella damascena*, chromosomal aberrations	–	NT	50	Moutschen *et al.* (1987)
URP, Unscheduled DNA synthesis, rat primary hepatocytes	–	NT	0.5	Swierenga *et al.* (1983) (abstract)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	–	NT	250	Stopper *et al.* (1993)
GIA, Gene mutation, rat primary hepatocytes, *hprt* locus *in vitro*	–	–	50	Swierenga *et al.* (1983) (abstract)
MIA, Micronucleus test, Syrian hamster embryo fibroblast (SHE) cells *in vitro*	+[c]	NT	75	Stopper *et al.* (1993)
MIA, Micronucleus test, mouse lymphoma L5178Y cells *in vitro*	+[c]	NT	50	Stopper *et al.* (1993)
MIH, Micronucleus test, human amniotic fluid fibroblast-like (AFFL) cells *in vitro*	+[c]	NT	75	Stopper *et al.* (1993)
DVA, DNA strand breaks, rat liver *in vivo*	–		287 po × 1	Carlo *et al.* (1989)

Table 4 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
DVA, DNA strand breaks, rat liver *in vivo*	–		57 po × 15	Carlo *et al.* (1989)
GVA, Gene mutation (H-*ras*), mouse liver tumours *in vivo*	–		600 diet 2 yrs	Devereux *et al.* (1994)
ICH, Inhibition of gap-junctional intercellular communication, human hepatoma cells (SK-HEP-1) *in vitro*	+	NT	10	Rolin-Limbosch *et al.* (1987)

[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

[c] Kinetochore-positive; L5178Y cells *in situ* also positive for centromeric DNA

assays for the induction of micronuclei and aneuploidy (as indicated by micronucleus tests with kinetochore staining).

Gap-junctional intercellular communication was inhibited by oxazepam in a human cell line.

No increase in DNA single-strand breaks and/or alkali-labile sites was observed in the liver of rats given single or multiple oral doses of oxazepam. Hepatocellular adenomas and carcinomas which developed in male and female B6C3F1 mice fed 0, 125, 2500 or 5000 mg/kg diet (ppm) oxazepam for up to two years (see Section 3.1.1) were examined for activated *ras* proto-oncogenes (Devereux *et al.*, 1994). Thirteen of 37 (35%) adenomas and carcinomas from the 125-ppm group carried codon 61 mutations in H-*ras*, while mutations were detected in two of 25 (8%) of the liver tumours from the 2500-ppm group and in none of 22 liver tumours in the 5000-ppm group. These figures compare with 80/126 (63%) historical controls and 11/20 (55%) concurrent control tumours. In addition, 12 hepatoblastomas from the two highest-dose groups were examined for codon 61 mutations, but none was found. These data imply that H-*ras* mutations in codon 61 do not appear to be involved in the formation of hepatocellular tumours or hepatoblastomas induced by oxazepam. This further suggests that promotion of hepatic tumours by oxazepam in mice involves a mechanism independent of that for spontaneous hepatic tumour formation. No tumour in the exposed groups had a mutation in codons 12, 13 or 117 of H-*ras* or in codons 12 or 13 of K-*ras* genes.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Oxazepam is a benzodiazepine used extensively since the 1960s for the treatment of anxiety and insomnia and in the control of symptoms of alcohol withdrawal. It is a metabolite of diazepam, prazepam and temazepam, among the benzodiazepines considered in this volume.

5.2 Human carcinogenicity data

In one case–control study evaluating benzodiazepine use, subjects using oxazepam were included, but were too few to analyse as a separate category.

5.3 Animal carcinogenicity data

Oxazepam was tested for carcinogenicity in three experiments in two strains of mice by oral administration in the diet. Significant increases in the incidence of benign and malignant liver tumours were found in two of the studies. The incidence of an uncommon malignant liver tumour, hepatoblastoma, was also increased in one strain of mice. In the third study, an increased incidence of liver adenomas was found. In one of

the studies, a small increase in the incidence of thyroid gland adenomas was observed in females of one strain of mice.

Oxazepam promoted liver tumour development in one two-stage model in mice and in one of three studies in rats.

5.4 Other relevant data

Oxazepam is rapidly and completely absorbed in humans and is largely eliminated in urine conjugated with glucuronic acid. The half-life averages 5–6 h.

Oxazepam is also extensively metabolized in animals. In some species (miniature swine), conjugation predominates, while in others (rats) oxidative metabolism is the major route.

Oxazepam has low acute and chronic toxicity for humans at therapeutic concentrations. The main adverse effects of chronic administration are psychological and physical dependence and withdrawal phenomena; specific organ toxicity of oxazepam to humans has not been observed.

The acute toxicity of oxazepam to experimental animals is also low. Short-term, high-dose administration of oxazepam to mice and rats resulted in increased liver weights. A transient increase in cell proliferation was observed in oxazepam-treated mice.

Perinatal death and neurodevelopmental retardation have been reported in the offspring of women who were exposed to oxazepam during pregnancy (see the monograph on diazepam for further discussion relating to cleft palate). However, confounding factors could not be controlled adequately in these studies.

Malformations have been observed following high doses of oxazepam in mice, but not at moderate doses in this species or in rats or rabbits.

Oxazepam is inactive in most genetic toxicity assays, although it has been shown to cause micronuclei and aneuploidy *in vitro* and to inhibit gap-junctional intercellular communication in human hepatoma cells *in vitro*. No data were available on humans.

Mechanistic considerations

There is no evidence that oxazepam interacts with DNA. Evidence of mutagenic activity is limited to aneuploidy in cell culture systems.

The induction of hepatocellular proliferation and hepatic cytochrome P450s by oxazepam was observed in mice at doses that were carcinogenic following long-term exposure. These adaptive effects are typical of several non-genotoxic compounds with promoting activity that are carcinogenic in mouse liver. Oxazepam has demonstrated promoting activity. Furthermore, the formation of hepatocellular tumours and hepatoblastomas by oxazepam does not involve the H-*ras* codon 61 pathway. Similarities have been observed between the hepatic effects of oxazepam and those of phenobarbital, which also promotes development of hepatocellular tumours in mice. Taken together, these data support the conclusion that liver tumours are produced in mice by a promoting mechanism.

The implications of these findings with respect to potential cancer risk of oxazepam exposure in humans are unclear. Specifically, information on the relevant effects of oxazepam in human groups or systems is not available. In general, the sensitivity of human liver to tumour formation, even if induction of cytochrome P450s and hepatocellular proliferation at levels comparable to those in mice were to occur, has not been established.

Levels of thyroid-stimulating hormone were increased in mice fed oxazepam at doses that induced adenomas and hyperplasia following long-term exposure. Sustained thyroid stimulation has been implicated as a mechanism of thyroid tumorigenesis in rodents.

5.5 Evaluation[1]

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

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

Overall evaluation

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

In making the overall evaluation, the Working Group took into account that:

(i) uncertainty exists regarding the formation of mouse liver tumours by oxazepam as a relevant end-point for evaluation of carcinogenic risks to humans.

(ii) appropriate mechanistic information in humans is lacking.

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

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