CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 020895

PHARMACOLOGY REVIEWS

TOXICOLOGY PAGES 49-65

Incidence of mortality
(number of animals found dead or sacrificed as moribund)

	Cause of death	Dose (mg/kg)									
		Control		10		50		100		200	
		M	F	M	F	M	F	M	F	M	F
Main groups (n=10)	gavage accident	0	1	0	1	0	0	1	0	1	0
	gastro-intestinal dilation	0	0	0	0	3	0	2	1	2	1
	unknown	0	0	0	0	0	0	0	0	0	1
Pharmacokinetic groups (n=12)	not determined*	-	-	0	1	2	1	0	1	1	2

n : number of animals for each dose level and each sex.
* : the cause of the death in the pharmacokinetic groups is not routinely determined.

Noteworthy signs of toxicity at 50 mg/kg and above included prostration/decreased activity, dyspnea/noisy respiration and swollen abdomen; these signs were also noted in animals prior to death.

Bodyweight/bodyweight gain of drug treated mice were reduced compared controls.

Mean body weight and body weight gain in male mice: differences (%) in treated animals relative to controls at the end of the study (day 91)

Dose (mg/kg)	body weight gain	body weight
10	-10	-2
50	-40*	-9
100	-17	-5
200	-24	-5

* = statistically significant at p=0.05

The most remarkable sign of toxicity reported in the animals that died was g.i. dilatation at 50 mg/kg and above. Mortality was the consequence of marked g.i. dilatation. A few mice showed colonies of Gram-positive cocci within the lumen of dilated g.i. segments. Other remarkable signs included mild to marked hemoconcentration in moribund mice, fatty change in liver, and atrophy of adipose tissues, decrease in body weight gain (M at the 3 highest doses; not dose-related), dose-related decrease in plasma triglycerides, and increases in plasma cholesterol.

On day 63 of study, the range of maximal UK-92,480/UK 103,320 and $AUC_{1\text{-}5hr}$ were dose-related.

Changes in plasma lipids (% from controls)

Dose (mg/kg)	Triglycerides (males)	Cholesterol (females)
10	+4	+11
50	-9	+46 **
100	-48 **	+37 *
200	-33 **	+32

*, ** = statistically significant at p=0.05 and 0.01, respectively.
Figures in bold denote mean values outside the laboratory range for untreated animals.

Range of maximal UK-103,320 concentrations and mean $AUC_{(1-5h)}$

Dose (UK-92,480-10) (mg/kg)	Concentrations (µg/ml)	Mean AUC (µg.h/ml)
10		not calculated
50		1.07
100		3.20
200		4.68

Range of maximal UK-92,480 concentrations and mean $AUC_{(1-5h)}$

Dose (UK-92,480-10) (mg/kg)	Concentrations (µg/ml)	Mean AUC (µg.h/ml)
10		not calculated
50		3.02
100		9.43
200		13.82

In the drug sponsor conclusions, there were no statements regarding what was considered the a MTD of UK-92,480-10 or doses that might have been selected for the toxicity/carcinogenicity study in mouse. The NOAEL appears to < the LD-10 mg/kg.

Drug sponsor conducted a 2nd study 3-mo mouse repeat dose study which is summarized below (Study No. 94101).

2.3.3.2. 3-month oral (gavage) exploratory toxicity study in CD1 mice (study No. 94101; Vol. 1.30 pp. 7704-7929):

(Sprague-Dawley albino mice, CD-1 [Crl:COBS-VAF-CD1(ICR)BR) (GLP Study No. 94101 conducted in Pfizer Centre de Recherche, Amboise, France, Study starting date: 05-10-94 and ended Feb./Mar. 1995)

The aim of this 2nd study was to obtain further information to aid in the estimate the maximum non lethal dose of UK-92,480-10 so to select doses for the 2-year toxicity/carcinogenicity study in mice. Further, drug sponsor stated that the HD (100 mg/kg/day) was used to confirm the findings of the previous mouse study.

Material and methods were described in the study report. Briefly, the main study consisted of 4 treatment groups of 10 mice/sex/group given 0, 20, 40, and 100 UK-92,480-10 mg/kg/day by gavage for 90 or 91 days. As in the previous 3-mo study, the drug was suspended in a 0.5% sol. of methylcellulose containing 0.1% Tween 80 and controls received the vehicle.

For plasma drug or metabolite levels determination, a supplemental group of 3 mice/sex/dose were treated concurrently with similar doses of UK-92,480 used in the main study. The mice were 6 weeks old and weighed ~25 to 30 g.

During the study, mice were observed daily for signs of toxicity and clinical signs, body weight/food consumption, and mortality. In the main study, hematology, and clinical chemistry were performed at the end of the study. Mice were then sacrificed, necropsied and a number of organs weighed. Plasma drug/metabolite plasma concentrations were determined on day 63 of study at 1, 3, 5 and 8 hrs postdosing. Necropsy was performed on all drug treated mice in the main study. A number of organs were weighed and histopathological examinations were carried out on a range of tissues from mice found dead, sacrificed moribund or at scheduled sacrifice.

RESULTS

Drug related mortality occurred in 1 MD F (sacrificed moribund on day 48 of study); remarkable signs of toxicity before sacrifice included prostration, swollen abdomen, dyspnea. One HD F was found dead on day 89; post mortem signs of toxicity were g.i. dilation. Two other deaths recorded were no considered drug related (Control 1 F sacrificed moribund on day 57 of study with leukemia, 1 LD-M sacrificed moribund on day 17 showed hepatic abscess), and 1 HD M from the supplemental group showed g.i. dilatation, but was not considered drug related by drug sponsor.

There were no remarkable changes reported for hematology, body weight, and food consumption.

Plasma drug/demethylated metabolite determinations showed that the Cmax occurred 1 hr after dosing (determined on day 63); the concentrations of these compounds decreased thereafter to values below the limit of the assay (0.04µg/ml) after 3 hrs for the LD, and 5 hrs for the MD and HD groups.

The $AUC_{0\text{-}8hr}$ values of both UK-92,480 and the demethylated metabolite of the parent drug- UK-103,320 increased superproportionally with doses of the parent drug.

Since UK-103,320, is pharmacologically equipotent to the parent compound, the systemic exposure to these two compounds after oral administration of UK-92,480 is of importance.

Mean plasma concentration of the metabolite were highest a 1 hr after dosing and decreased rapidly. No sex difference was noted in plasma levels of the metabolite, thus data were of both sexes were combined for analysis.

Range of highest UK-92,480 concentrations and mean $AUC_{(0\text{-}8h)}$ values on day 63

Dose (UK-92,480-10) (mg/kg)	Concentrations (µg/ml)	Mean $AUC_{(0\text{-}8h)}$ (µg.h/ml)
20		0.46
40		1.97
100		7.26

Range of highest UK-103,320 concentrations and mean $AUC_{(0\text{-}8h)}$ values on day 63

Dose (UK-92,480-10) (mg/kg)	Concentrations (µg/ml)	Mean $AUC_{(0\text{-}8h)}$ (µg.h/ml)
20		NC
40		0.74
100		2.60

NC : not calculated

Postmortem Observations

The only remarkable effect noted was an increase in both absolute/relative liver weights when compared to control. However, drug sponsor asserted that these increase in values were within the level of their historical control values.

In the mice unscheduled deaths, the most remarkable findings reported were g.i. dilation in some MD and HD F. This findings was also reported in the previous 3-mo oral toxicity study in mice. Two other mice dying of causes unrelated to treatment showed macroscopic/microscopic abnormalities (1 LD M with nodules in liver, spleen, thymus and kidney sacrificed moribund; histologic correlates of macroscopic findings were described. One control F showed enlarged spleen consistent with lymphoblastic leukemia diagnosed cytologically; this pathologic condition was reported by drug sponsor to occur occasionally in young mice.)

Terminal sacrifice animals showed no treatment related findings.

Drug sponsor concluded that the findings in this study confirmed those of the previous mouse study in that the only treatment related effects were mortality and g.i. dilation at doses of 40 mg/kg/day and above.

2.3. Carcinogenicity

2.3.1. Rats

2.3.1.1. Twenty-four month oral toxicity and carcinogenicity study in Sprague Dawley rats (Study No. 94092; Vol. 1.19-1.25 pp. 2620-5147):

Testing Facility: Pfizer, Centre de Recherche, Amboise Cedex, France
Study Number: 94092
Study Date(s): 10/11/94 to 10/10/96
GLP Compliance: Yes

RAT STUDY DURATION: 104 weeks
RAT STRAIN: Sprague-Dawley albino rats, Crl:COBS-VAF-CD(SD)BR
ROUTE: Orally by esophageal intubation (gavage)
DOSING COMMENTS: Drug administered at 5 ml/kg body weight

NUMBER OF RATS:
- Main study:
  - Control 1 (C1): 60 males and 60 females
  - Control 2 (C2): 60 males and 60 females
  - Low Dose (LD): 60 males and 60 females
  - Middle Dose (MD): 60 males and 60 females
  - High Dose (HD): 60 males and 60 females

- Groups for plasma drug level determinations:
  - Low Dose (LD): 7 males and 7 females
  - Middle Dose (MD): 7 males and 7 females
  - High Dose (HD): 7 males and 7 females

RAT DOSE LEVELS* (mg/kg/day):
Rat Low Dose: 1.5
Rat Middle Dose: 5.0
Rat High Dose: 60.0
- *Dose adjusted during study

BASIS FOR DOSES SELECTED:
- MTD: The dose of 60 mg/kg/day chosen for the two year rat study was based on data from several toxicity and pharmacokinetic studies: (1) doses above 60 mg/kg resulted in mortality and hypertrophy of several organs, (2) a dose of 60 mg/kg for 6 months resulted in similar

adaptive responses and a moderate decrease in body weight gain (-9% in males and -7% in females), and (3) the sums of the AUC levels for free parent and metabolite in rats given 60 mg/kg for 14 days were 27X and 40X for male and female rats, respectively, the human exposure at the maximum recommended dose of 100 mg/day. It should be noted that after two years of treatment in the rat, the multiple of the human exposure was reduced to 18X and 21X for males and females, respectively. This may been due to liver enzyme induction and hypertrophy resulting in increased metabolism of the drug.

PRIOR FDA DOSE CONCURRENCE: No

RAT CARCINOGENICITY: Negative (males and females)

RAT TUMOR FINDINGS:

Tumors were analyzed using the Peto's death rate method for fatal tumors and prevalence analysis for incidental tumors (Peto *et al.*, 1980). According to the sponsor, the only statistically significant finding was an increased proliferation in thyroid follicular cells in male rats treated at the high dose of 60 mg/kg/day (combined incidence of hyperplasia, adenoma, and carcinoma; $P = 0.0056$ for positive trend using the Peto analysis; Table 14). A combined statistical analysis was performed as recommended for a multistage model of carcinogenesis in which thyroid follicular hyperplasia, adenoma, and carcinoma represent a morphological progression from hyperplasia to neoplasia (McConnell *et al.*, 1986). Other proliferative and neoplastic changes in males and females were observed with similar frequencies in the treated and untreated groups.

Table 14

Percent Incidence of Proliferative Changes
in Thyroid Follicular Cells of Male Rats
(n = 60)

	Dose (mg/kg/day)				
	C1	**C2**	**1.5**	**5.0**	**60.0**
Hyperplasia	0	1.7	5.0	1.7	8.3
Adenoma	6.7	0	0	3.3	8.3
Carcinoma	1.7	1.7	0	3.3	0
Combined	**8.4**	**3.4**	**5.0**	**8.3**	**16.6**

In a separate study to assess the relationship between liver enzyme induction and thyroxin clearance, female rats were given either vehicle or UK-92,480 orally at 200 mg/kg for 29 days. Results showed that treatment produced an increase in liver and thyroid weights, thyroid follicular cell hypertrophy, increased hepatic UDP-glucuronyl transferase (UDPGT) activity, increased TSH, decreased T3 and T4 hormones, and an increased clearance of exogenous thyroxin. These results were thought to be consistent with the view that the thyroid hypertrophy found in treated rats was due to induction of hepatic UDPGT which increased the clearance of thyroid hormone and caused a compensatory increase in plasma TSH which, in turn, stimulated the thyroid gland.

Evidence for such a mechanism at the 60 mg/kg dose was not presented, however. Additional experiments assessing induction of genes coding for specific hepatic enzymes, such as UDPGT-specific mRNA levels, would have been able to detect gene induction at the 60 mg/kg dose if such a mechanism were responsible for the thyroid hypertrophy observed in treated rats.

RAT STUDY COMMENTS:

Mortality: No drug-related increase in mortality was found (Table 15). Survival in the treated male groups appeared to be higher when compared to the untreated male controls and to all female groups.

Table 15

Percent Mortality and Percent Survival

	Males			
	Found Dead	**Sacrificed as Moribund**	**Total Unscheduled Deaths**	**Survival at the End of Study**
Control 1+2	56.7	25.0	81.7	18.3
1.5 mg/kg	43.3	15.0	58.3	**41.7**
5 mg/kg	30.0	35.0	65.0	**35.0**
60 mg/kg	48.3	21.7	70.0	**30.0**
	Females			
Control 1+2	34.2	45.0	79.2	20.8
1.5 mg/kg	33.3	41.7	75.0	25.0
5 mg/kg	30.0	48.3	78.3	21.7
60 mg/kg	55.0	30.0	85.0	15.0

Body Weights: Mean body weights are shown in Figure 14A (males) and Figure 14B (females). Percent changes in mean body weight gains in male and female rats are shown in Table 16 (Day 1 and Day 723). Results showed that high dose males (60 mg/kg/day) gained 11.0% less weight than controls, while mid- and high dose females gained 17.0% and 15.7% less weight, respectively than controls.

Figure 14A (Sponsor's Figure 8)

Effect of UK-92,480 on Group Mean Body Weight in Male Rats

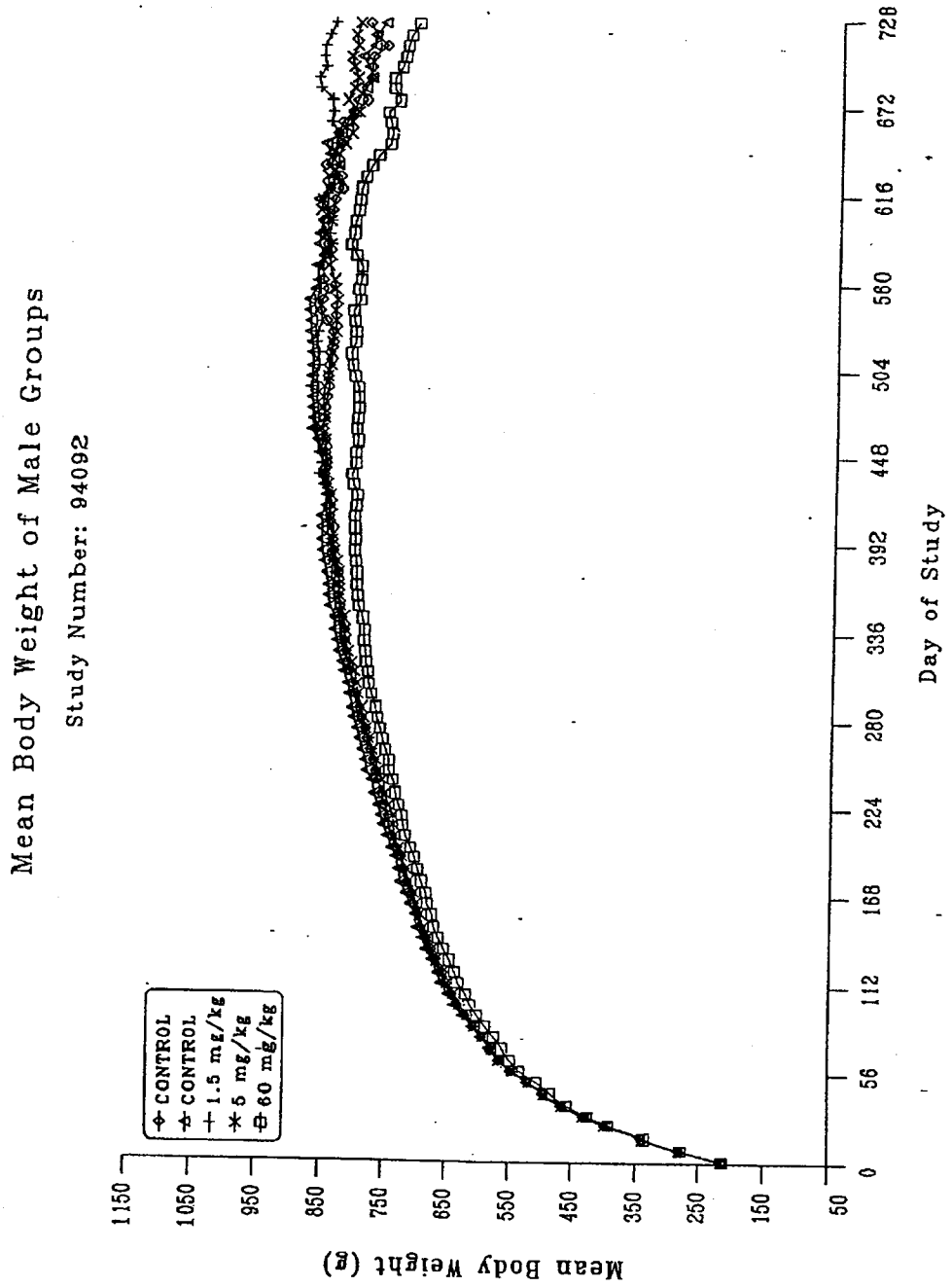


Figure 14B (Sponsor's Figure 9)

Effect of UK-92,480 on Group Mean Body Weight in Female Rats

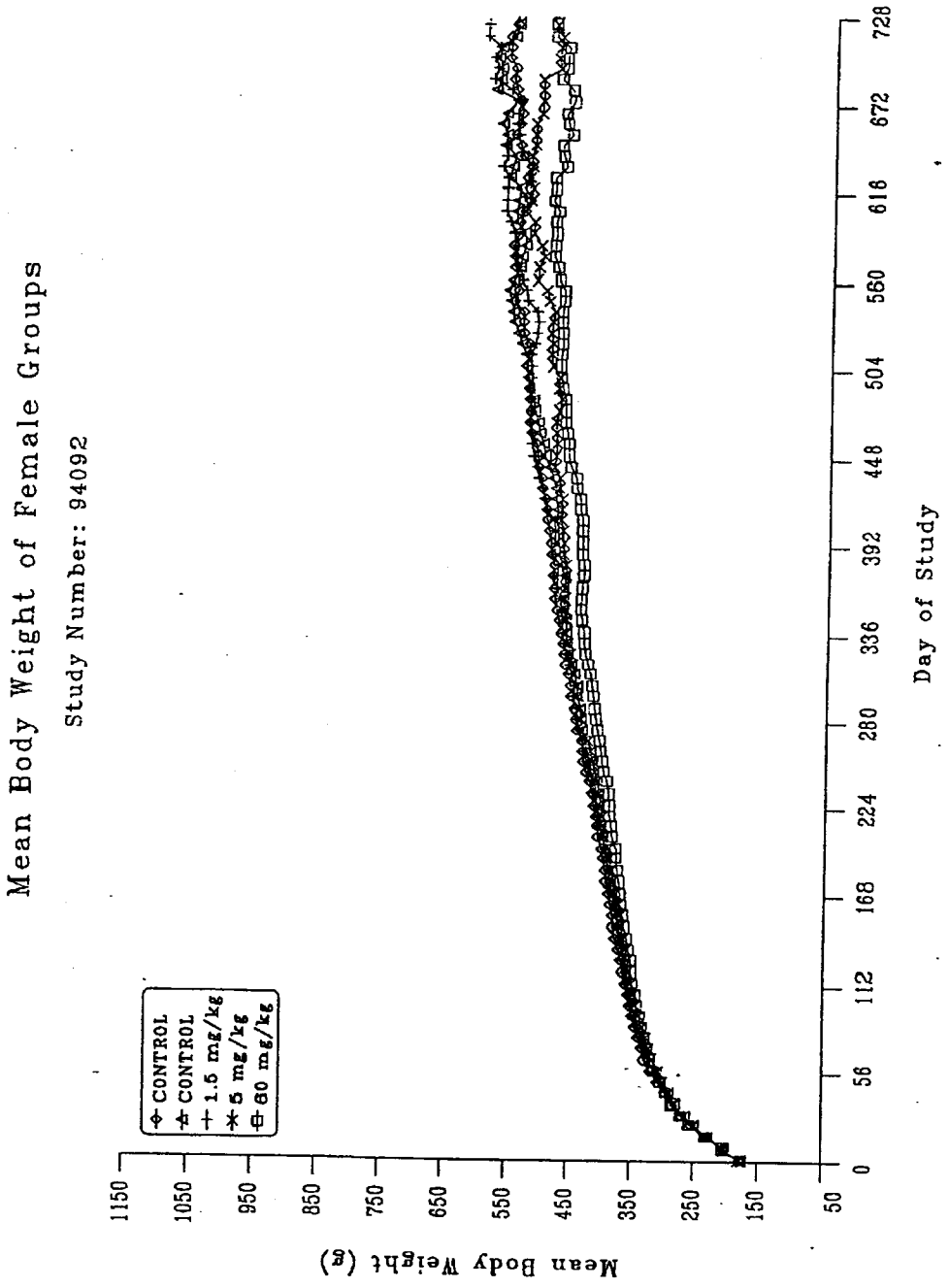


Table 16

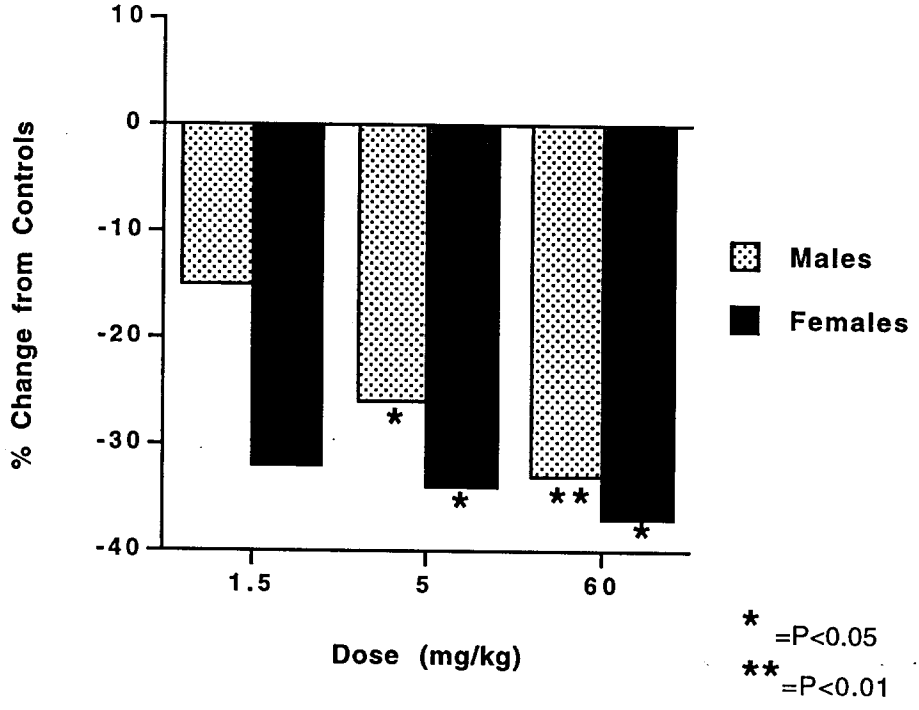
Effect of UK-92,480 on Mean Body Weight Gain in Rats

Sex	Dose (mg/kg/day)	Weight Day 1 (gms)	Weight Day 723 (gms)	Weight Gain (gms)	% Change in Wt. Gain from Controls
M	0	214.6	777.4	562.8	--
	1.5	216.1	845.4	629.3	+11.8
	5	214.7	807.5	592.8	+5.3
	60	213.0	713.8	500.8	**-11.0**
F	0	176.8	552.2	375.4	--
	1.5	177.4	598.8	421.4	+12.3
	5	178.0	489.5	311.5	**-17.0**
	60	174.9	491.3	316.4	**-15.7**

Non-Neoplastic Pathology: The only consistent change that was reported was a dose-related decrease in plasma bilirubin in both sexes which was statistically significant ($P < 0.01$ and 0.05) at the mid and high doses (Figure 15).

Figure 15

Percent Decrease in Plasma Bilirubin
in UK-92,480-Treated Rats



This effect on decreasing plasma bilirubin was thought to be due to the ability of UK-92,480 to increase hepatic uptake and conjugation of bilirubin through increased liver enzyme induction, although there was no evidence of liver enzyme induction, hepatic hypertrophy, or increased liver weight. It was postulated that the mechanism may operate chronically at a low level where liver changes would be undetectable.

Pharmacokinetics: UK-92,480 forms two pharmacologically active metabolites, one major and one minor. UK-103,320 is the major pharmacologically active metabolite and has about 50% of the potency of the parent drug. It represents 11% and 3% of the administered dose in rat and man, respectively. A minor pharmacologically active metabolite, UK-150,564, has only about 10% of the potency of the parent drug, and represents 16% and 22% of the administered dose in rat and man, respectively. The terminal elimination half-life was 0.3, 1.9, and 4.0 hours for male rat, female rat, and man, respectively.

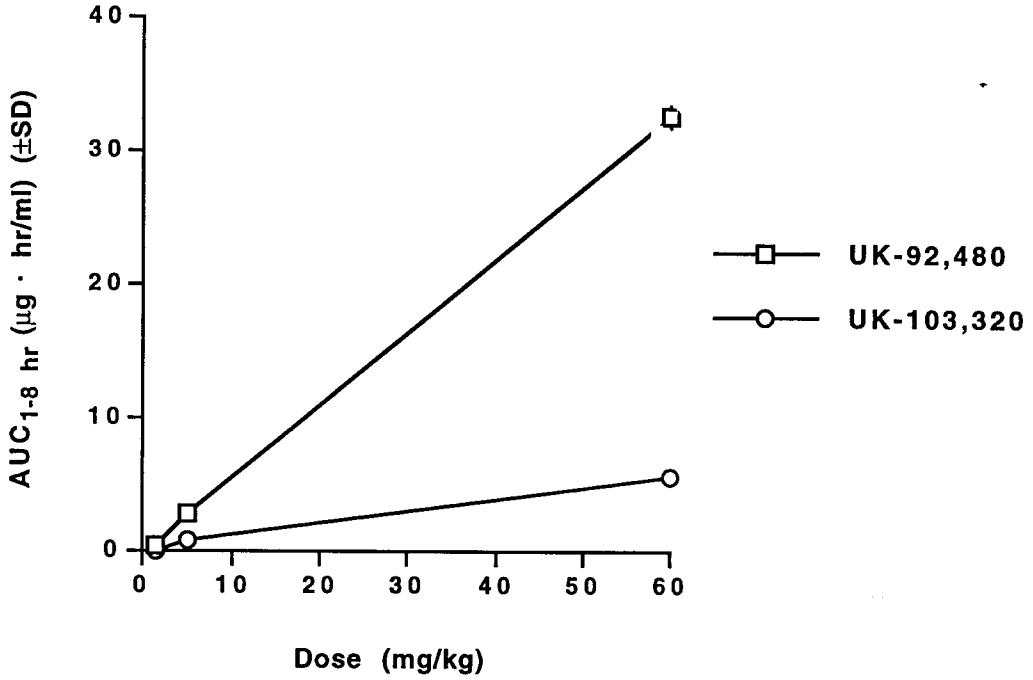
Plasma drug levels (AUCs) for UK-92,480 (parent drug) and UK-103,320 (major metabolite) were determined from supplementary rats on Day 366. Mean systemic exposures ($AUC_{1\text{-}8\ hr}$) to UK-92,480 and UK-103,320 are shown in Figure 16A (males) and Figure 16B (females). As can be seen, exposure to UK-92,480 and UK-103,320 was dose-proportional in both sexes. However, males were exposed mostly to the metabolite UK-103,320, whereas females were exposed mostly to the parent drug UK-92,480.

Figure 16A

Mean Exposure ($AUC_{1\text{-}8\ hr}$) to UK-92,480 and UK-103,320 in Male Rats

Figure 16B

Mean Exposure ($AUC_{1-8\ hr}$) to UK-92,480 and UK-103,320 in Female Rats



Comparative $AUCs_{(1-24\ hr)}$ for UK-92,480 and UK-103,320 between normal male human volunteers given the maximum recommended human dose (MRHD) of 100 mg (=1.43 mg/kg based on a 70 kg man) and male and female rats given 60 mg/kg/day are shown in Table 17 (values represent total drug, bound and unbound). [Note: Since the human study (#148-228) used pharmacokinetic sampling times up to 24 hours post-dose, the rat $AUCs_{(1-8\ hr)}$ were recalculated by this reviewer (T. Papoian) using the linear trapezoidal rule also to 24 hours post-dose which was past the last quantifiable plasma drug concentration.]

Table 17

Comparative Total $AUCs_{(1-24\ hr)}$ (Total Bound and Unbound) for UK-92,480 and UK-103,320 Between Male Humans and Male and Female Rats

Species	Dose	UK-92,480 $AUC_{(1-24hr)}$ (µg·hr/ml)	UK-103,320 $AUC_{(1-24hr)}$ (µg·hr/ml)
Man	100 mg/70 kg	1.667	0.756
Rat (male)	60 mg/kg/day	6.621	29.385
Rat (female)	60 mg/kg/day	54.25	11.379

Since pharmacologic activity for sildenafil (UK-92,480) and its active metabolite (UK-103,320) is represented by the unbound fraction, the percentage of plasma protein binding for both human and rat is shown in Table 18.

Table 18

Human and Rat Plasma Protein Binding

Species	UK-92,480		UK-103,320	
	% Bound	Fraction Unbound	% Bound	Fraction Unbound
Man	96	0.04	95	0.05
Rat	95	0.05	89	0.11

Comparison of the male and female rat $AUCs_{(1\text{-}24\ hr)}$ for total drug exposure (sum of unbound UK-92,480 and UK-103,320 AUCs) as a multiple of the maximum recommended human dose (MRHD) of 100 mg is shown in Table 19. The unbound AUCs were calculated by multiplying the total bound and unbound AUC (Table 17) by the fraction unbound (Table 18). As shown, the total of unbound $AUCs_{(1\text{-}24\ hr)}$ in male and female rats given 60 mg/kg/day was ~34X and ~38X, respectively the $AUC_{(1\text{-}24\ hr)}$ of men given a single dose of 100 mg.

Table 19

Rat Multiple of MRHD as a Function of Total Drug Exposure
(Sum of Unbound AUCs of UK-92,480 and UK-103,320)

Species	Unbound UK-92,480 AUC (μg·hr/ml)	Unbound UK-103,320 AUC (μg·hr/ml)	Total of Unbound AUCs (μg·hr/ml)	Multiple of MRHD
Man	0.067	0.038	0.105	--
Rat (male)	0.331	3.232	3.563	**33.9X**
Rat (female)	2.713	1.252	3.965	**37.8X**

Conclusions: The only statistically significant finding was an increased proliferation in thyroid follicular cells in male rats treated at the high dose of 60 mg/kg/day. This was expressed as the combined incidence of hyperplasia, adenoma, and carcinoma as recommended for a multistage model of carcinogenesis. Evidence from another study was presented to suggest that the mechanism for this effect was due to induction of hepatic UDPGT which increased the clearance of thyroid hormone and caused a compensatory increase in plasma TSH which, in turn, stimulated the thyroid gland. Evidence for such a mechanism at the 60 mg/kg dose was not presented.

No drug-related increase in mortality was found. Percent changes in mean body weight gains in male and female rats showed that high dose males (60 mg/kg/day) gained 11.0% less weight than controls, while mid and high dose females gained 17.0% and 15.7% less weight, respectively than controls. These values are an acceptable MTD according to ICH-S1C guidelines ("no more than 10% decrease in body weight gain relative to controls").

Systemic exposure to total unbound drug (sum of the parent drug UK-92,480 and the principle pharmacologically active metabolite UK-103,320) was calculated to be 34X and 38X the maximum recommended human dose of 100 mg in male and female rats, respectively. These results suggest that the lack of a carcinogenic effect in rats was not due to inadequate systemic exposure to sildenafil. A statistical review of tumor incidence in the rat study by the Division of Biometrics is pending.

2.3.1.2. 104-week oral (gavage) carcinogenicity study in the rat (aborted) (Study No. 911/002; Vol. 1.25 pp. 5148-5235):

Testing Facility: Pfizer, Centre de Recherche, Amboise Cedex, France
Study Number: 911/002
Study Date(s): 7/12/94 to 9/5/94
GLP Compliance: Yes (?)

Between days 18 and 25 after initiation of treatment, 46/61 of the high dose males died. Autopsy revealed necrotizing and inflammatory changes with hemorrhage in the GI tract suggesting a necrotizing event about two days before death. The drug formulations were analyzed and pharmacokinetics determined in the surviving animals. Although low levels of UK-92,480 were found, high levels of another substance with a MW of 270 containing fluorine but no nitrogen was detected (MW of UK-92,480 free base is 475 and contains nitrogen but no fluorine).

Discussions with the technician revealed that a highly cytotoxic compound from another client was mistakenly issued by the pharmacy for the week 3 preparation. It is not clear why only the high dose males died and not the high dose females, although an explanation was offered: "The cytotoxic compound did not suspend well in the vehicle used in the present study and the heterogenicity in the different dosing portions explain why only males of the high dose were affected." The study was invalidated and terminated at week 8 on 8/31/94.

2.3.1.3. One-month exploratory study in rats (Study No. 94085; Vol. 1.30 pp. 7658-7703):

Testing Facility: Pfizer, Centre de Recherche, Amboise Cedex, France
Study Number: 94085
Study Date(s): 8/9/94 to 9/5/94
GLP Compliance: Not mentioned

This study was initiated to determine the cause of death seen in male rats in an ongoing carcinogenicity study (Study No. 911/002). It was subsequently determined that the cause of death in the previous study was due to dosing of the animals with a cytotoxic compound from another company, and not with UK-92,480.

Male Sprague-Dawley rats (10/group; 209 gms) were given UK-92,480 (batch no. R108) orally by gavage at 60 or 120 mg/kg/day for 28 days. Controls received vehicle (0.5% methylcellulose with 0.1% Tween 80). Rats were observed for mortality and clinical signs. Body weights and food consumption were recorded. Blood was taken on Day 9 for plasma drug concentrations. After the last dose, a necropsy was performed which consisted of a gross exam, and weights of several organs.

No deaths were reported. Significant organ weight changes were seen in the livers and kidneys only at the high dose of 120 mg/kg/day (+16% and +10%, respectively). No other effects were noted.

Mean plasma concentrations (μg/ml) for the parent UK-92,480 and the active metabolite UK-103,320 one hour after dosing are shown in Table 20.

Table 20

Mean Plasma Concentrations (µg/ml) of UK-92,480 and UK-103,320 in Male Rats

Dose (mg/kg/day)	UK-92,480	UK-103,320
60	0.21	2.01
120	1.05	3.29

It was concluded that UK-92,480 when given orally to rats at doses up to 120 mg/kg/day for 28 days produced minimal adverse effects in male rats. These results were consistent with other toxicity studies in male rats.

2.3.1.4. Pharmacokinetic study in rats (Study No. 94067; Vol. 1.31 pp. 7930-7938):

(GLP Study No. 94067 conducted in Pfizer Centre de Recherche, Amboise, France. Study dates: 6/9/94 to 6/23/94.)

5 rats (8 wks old, 208-419 g)/sex/group were given repeated single dose of 60 mg/kg/day of UK-92,480-10 (dissolved in vehicle- 0.5% aq. sol. of methylcellulose/0.1% Tween 80), p.o. (by gavage) for 14 days. Drug sol. was given in a volume of 10 mg/kg.

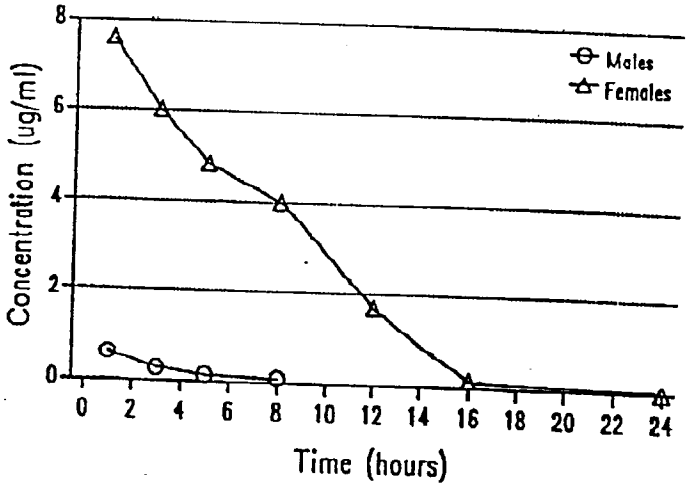
Observations and Measurements: Drug plasma levels of the drug/demethyl metabolite were determined on day 14 of study on all rats at 1, 3, 5, 8, 12, 16 and 24 hours post-dosing. Different volumes of blood were obtained from anesthetized rats from orbital sinus or aorta for clinical chemistry determination; samples were kept on ice until centrifuged to obtain plasma. Plasma analysis for UK-92,480 and metabolite UK-103,320 were done by an HPLC assay.

RESULTS

Clinical observations: No rats died, and no adverse clinical signs were reported.

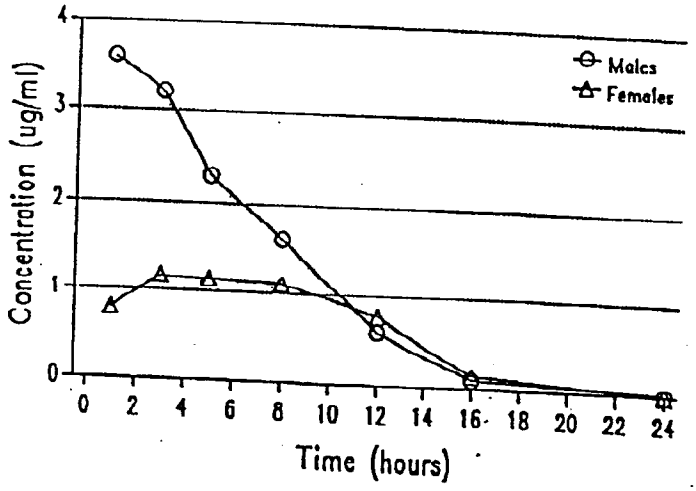
Plasma concentrations of UK-90,480: In F, plasma UK-92,480 levels were much higher in M; the highest individual concentrations were reported at 1-3 hours post-dosing. Levels of the drug in plasma ranged from 0.36 to 1.18 µg/ml in M, and from 5.81 to 9.98 µg/ml in F.

Variations of mean plasma UK-92,480 concentrations with time on day 14



UK-103,320 (Demethylated Metabolite of UK-92,480): Maximal plasma UK-103,320 levels were noted at 1-3 hours in M and 3-5 hours in F; the values reported ranged from 3.25-3.89 µg/ml in M, and 1.04-1.57 µg/ml for F. Mean conc. of the metabolite declined rapidly thereafter in M, and remained sustained during the first 8 hrs after treatment in F.

Variations of mean plasma UK-103,320 concentrations with time on day 14



In the drug sponsor conclusions, there were no statements regarding what was considered the a MTD of UK-92,480-10 or doses that might have been selected for the toxicity/carcinogenicity study in mouse. The NOAEL appears to be the LD-10 mg/kg.