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DATA EVALUATION RECORD

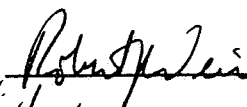
Vinclozolin

Metabolism in Rats

STUDY IDENTIFICATION: (a) Hawkins, D.R., Kirkpatrick, D., Dean, G.M., et al. The Biokinetics of ^{14}C -Vinclozolin in the Rat. (Unpublished study No. 90/0544, performed by Huntingdon Research Centre, Ltd., Cambridgeshire, England for BASF Aktiengesellschaft, Ludwigschafen, Germany; dated November 28, 1990.) MRID No. 418243-08.✓ (b) Hawkins, D.R., Kirkpatrick, D., Dean, G.M. et al. The Biotransformation of ^{14}C -Vinclozolin in the Rat. (Unpublished study No. 90/0514, performed by Huntingdon Research Centre, Ltd., Cambridgeshire, England, for BASF Aktiengesellschaft, Ludwigschafen, Germany; dated November 29, 1990.) MRID No. 418243-07.✓

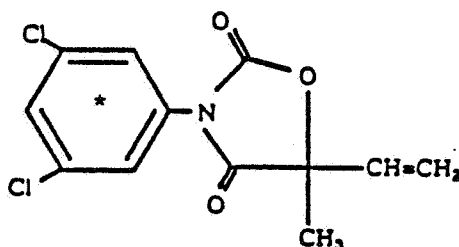
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1. CHEMICAL: Vinclozolin; 3-(3,5 dichlorophenyl)-5 methyl-5-vinyl-1,3-oxazolidin-2,4 dione.
2. TEST MATERIAL: A white solid, uniformly labeled with ^{14}C in the phenyl ring; lot 36/38 with a specific activity of 58 mCi/mmol (202.16 Ci/mg); radiochemical purity of >97%. Nonradiolabeled batch No. N183, Lot No. 88/375; 99.2% purity.



3. STUDY/ACTION TYPE: Metabolism/pharmacokinetics-balance.
4. STUDY IDENTIFICATION: (a) Hawkins, D.R., Kirkpatrick, D., Dean, G.M., et al. The Biokinetics of ^{14}C -Vinclozolin in the Rat. (Unpublished study No. 90/0544, performed by Huntingdon Research Centre, Ltd., Cambridgeshire, England, for BASF Aktiengesellschaft, Ludwigschafen, Germany; dated November 28, 1990.) MRID No. 418243-08. (b) Hawkins, D.R., Kirkpatrick, D., Dean, G.M., et al. The biotransformation of ^{14}C -Vinclozolin in the Rat. (Unpublished study No. 90/0514, performed by Huntingdon Research Centre, Ltd., Cambridgeshire, England, for BASF Aktiengesellschaft, Ludwigschafen, Germany; dated November 29, 1990.) MRID No. 418243-07.
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7. CONCLUSIONS:

- A. Absorption, distribution, and excretion of radioactivity were studied after oral or intravenous administration of [^{14}C -3,5-dichlorophenyl]Vinclozolin to groups of male and female Wistar rats. Single oral doses were administered at nominal levels of 10 and 100 mg/kg, and a single intravenous dose was administered at a level of 1 mg/kg. Non-radiolabeled material was also administered daily for 14 days at 10 mg/kg, followed by a single oral dose of ^{14}C material at 10 mg/kg. For additional pharmacokinetic studies, oral dosing was conducted at 200 mg/kg or by dietary administration of 5000 ppm ^{14}C -Vinclozolin-containing diets.

After single oral doses of 10 or 100 mg/kg, urinary and fecal excretion of radioactivity by both sexes in 5 days ranged between 48 and 54% and 38 and 49% of the dose, respectively. After intravenous dosing at 1 mg/kg, urinary and fecal excretion accounted for 72 and 23% of the dose, respectively. In rats with cannulated bile ducts, excretion of radioactivity in bile accounted for 73.2 and 63.5% of the 10 mg/kg oral dose in males and females, respectively (48 hours), and 62.0 (males) and 38.8% (females) of the 100 mg/kg dose. No radioactivity was excreted in expired air (pilot study). Retained radioactivity 120 hours after dosing accounted for less than 2% of any dose. Excretion of radioactivity in urine and feces was rapid with most of the administered dose (75 to 80%) eliminated by 48 hours for the 100-mg/kg oral dose. Biliary excretion was also rapid with 50% of a 10-mg/kg dose excreted within 12 hours for males and 18 hours for females.

Plasma levels of radioactivity were plotted against time after single oral doses of 10, 100, or 200 mg/kg ^{14}C -Vinclozolin, and pharmacokinetic parameters were determined. The same parameters were determined for rats ingesting diets containing 5000 ppm ^{14}C -Vinclozolin for 24 hours. In the oral gavage studies T_{max} , the time to maximum plasma level, increased with dose from 3.6 to 9.6 hours in males and from 1.8 to 13.2 hours in females with C_{max} values (peak concentration as μg equivalents/mL) between 2.8 and 23.2 in males and 2.0 to 15.6 in females. The areas under the curve (AUC) (μg equivalents/mL $\cdot$ hr) were similar in males and females and increased with dose (averaging approximately 74, 483, and 900 at 10, 100, and 200 mg/kg). After peak levels had been reached, concentrations in plasma declined in a biphasic manner with overall half-lives of 23 and 36 hours for males and females, respectively. Systemic availability of radioactivity appeared equivalent following gavage or dietary dosing.

The dietary doses were equivalent to 439 and 345 mg/kg in males and females, respectively; after withdrawal of diets, plasma levels declined with a half-life of about 40 hours.

Tissue concentrations of ^{14}C were higher in females than in males, with peak levels occurring 2 or 6 hours after dosing. The levels in liver, kidneys, fat, adrenals and Harderian glands were highest, 4 to 10 μg equivalents/g at peak, but the levels declined in a linear manner to about 0.02 to 0.2 μg eq/g by 5 days. After multiple dosing, concentrations in tissues were mainly in the range of 0.1 to 1.2 μg eq/g at 5 days after the ^{14}C dose.

Vinclozolin was extensively metabolized in the rat. HPLC (high performance liquid chromatography) analysis of urine indicated at least 15 metabolites in addition to small amounts of unchanged Vinclozolin. The major urinary metabolite was identified as a glucuronide conjugate of N-(3,5-dichlorophenyl)-2-methyl-2,3,4-trihydroxybutyramide (compound 25). This metabolite is derived from Vinclozolin by both cleavage of the 2,3 bond in the oxazolidine ring and epoxidation and subsequent hydration of the vinyl group. Another metabolite identified in urine had an intact oxazolidine ring but the vinyl group was modified to an ethylene glycol moiety; this compound was excreted as a glucuronide. Cleavage of Vinclozolin to dichloroaniline was a very minor pathway and accounted for less than 1% of the ^{14}C label. Cleavage of the 3,4 bond of the heterocyclic ring also occurred followed by loss of the vinyl group; the two resulting metabolites (12 and 11) accounted for less than 2% of the dose in the urine or feces and about 10% of the biliary metabolites. In the fecal extracts, unchanged Vinclozolin and the butyramide (compound 25) were the major radioactive components. Analysis of extracts of liver also showed that the same compounds were major radioactive components.

- B. Both studies are acceptable. The two studies combined fulfill the Guideline Requirements 85-1 for Metabolism studies.

Items 8-10--see footnote 1.

¹Only the items appropriate to this DER have been included.

11. MATERIALS AND METHODS (PROTOCOL):

I. Study I, Biokinetics of ^{14}C Vinclozolin in the Rat

- A. ^{14}C -Vinclozolin had a specific activity of 58 mCi/mmol (202.16 $\mu\text{Ci}/\text{mg}$) and a radiochemical purity of >97%. The non-radiolabeled test substance (lot N 183) had a purity of 99.8%. Both were supplied by BASF AG, Ludwigshafen, W. Germany. ^{14}C -Vinclozolin was diluted with non-radiolabeled Vinclozolin in a solution of either acetone or dichloromethane, the solvent removed under reduced pressure, and the substance dried to constant weight. The required amount was weighed out and suspended in the gavage dose vehicle (1% w/v aqueous carboxymethyl cellulose) using a Potter homogenizer. The suspension was stored at 4°C for up to four days. Aliquots were diluted for radioassay. For intravenous dosing, 4.87 mg ^{14}C -Vinclozolin was dissolved in polyethylene glycol 400 using ultrasonic mixing. Aliquots (0.2 mL) were drawn into preweighed 1-mL syringes for dosing and reweighed. For dietary administration, 7.8 g ^{14}C -material was mixed with 100 g powdered diet with a mortar and pestle and portions further diluted with diet and mixed manually by tumbling in a sealed pot. Ten aliquots were taken and combusted and radioassayed to check for homogeneity.
- B. Male and female Wistar rats (Charles River, Margate, UK, and Charles River, Portage, MI) were used and weighed approximately 200 g at dosing. The animals received food (LAD 1 pellet or LAD 2 powdered diet) and tap water ad libitum except for those with cannulated bile ducts.
- C. Fourteen studies were conducted as outlined in Table 1. ^{14}C -Vinclozolin was administered orally, intravenously, or via the diet. Excretion-balance studies were conducted after low or high oral gavage doses or after intravenous administration. Biliary excretion was also studied after a low or high oral dose and plasma kinetics were determined at 3 oral gavage dose levels as well as during dietary administration. Tissue distribution was studied after a single low oral dose or after repeated administration of unlabeled Vinclozolin followed by a single ^{14}C dose.
- D. Single oral dose studies--Urine was collected (5 rats/sex) at 0-6 and 6-24 hours and then at 24-hour intervals for 5 days. Feces were collected every 24 hours. Blood samples were collected prior to sacrifice, and following tissues taken after sacrifice (5 days): stomach, GI-tract, liver, kidneys, heart,

TABLE 1. Study Design

Study type	Dose route	Nominal dose level (mg/kg)	Number of animals		Actual Doses (mg/kg)
			Males	Females	
Excretion balance (pilot)	oral	10	2	2	10.4
Excretion balance	oral	10	5	5	8.5
Excretion balance	oral	100	5	5	85.3
Excretion balance ^b	oral	10	5	5	11.3
Excretion balance	intravenous	1	5	5	1.0
Plasma kinetics	oral	10	5	5	9.6
Plasma kinetics	oral	100	5	5	85.2
Plasma kinetics	dietary	200	5	5	169
Plasma kinetics	oral	5000 ^a	21	21	8
Biliary excretion	oral	10	3	3	8.5, 11.5
Biliary excretion	oral	100	3	3	91.8, 89.8
Whole-body autoradiography	oral	7 x 10 ^c	5	5	12.6, 12.5
Tissue distribution	oral	10	12	12	9.7, 10.7
Tissue distribution	oral	7 x 10 ^c	15	15	10.9, 11.1

^appm in diet.

^bRats were pretreated for 14 days with non-radiolabeled Vinclozolin at 10 mg/kg/day.

^cSingle daily dose of ¹⁴C-Vinclozolin for 7 days.

lungs, brains, spleen, eyes, adrenals, thyroid, gonads, muscle, fat, bone marrow, and remaining carcass.

Biliary excretion--Urine and feces were collected at 0-24 and 24-48 hours (3 rats/sex) and bile samples were collected at 1.5 hour intervals to 48 hours.

Blood kinetics--Following administration by oral gavage at 10, 100, or 200 mg/kg, blood samples were withdrawn from the tail vein into heparinized tubes at pretest, 0.5, 1, 2, 4, 6, 12, and 24 hours and 2, 3, 4, 5, 7, and 10 days. Cells were separated by centrifugation and aliquots of plasma were radioassayed.

Dietary exposure--Seven groups of three rats/sex were housed in a cage and after an eight-hour fast offered food containing 5000 ppm ^{14}C -Vinclozolin. At 24 hours, treated diet was replaced with normal diet. Groups of 3 rats/sex were removed at 2, 4, 6, 9, 12, and 18 hours, blood was removed by cardiac puncture and the animals sacrificed. From the seventh group, blood samples were collected from the tail vein at 24, 43, 67, 91, 120, 168, and 240 hours post initiation.

Tissue distribution--Groups of 3 rats/sex were given a single oral dose of 10 mg/kg ^{14}C -Vinclozolin and sacrificed at 2, 6, 12, and 48 hours. Similar groups were dosed daily with 10 mg/kg unlabeled compound followed by a single ^{14}C -dose and sacrificed at 2, 6, 24, 48, or 120 hours. Rats were bled by cardiac puncture after halothane anesthesia, sacrificed, and tissues collected for radioassay. An additional rat/sex dosed similarly (repeated dose) were sacrificed for whole body radioautography at 2, 6, 24, 48, and 120 hours.

- E. Radioassay--Weights of whole organs were recorded. Adrenals, ovaries, prostate, eyes, Harderian glands, thyroid and bone marrow were combusted whole (M2-TriCarb®); samples of other organs were minced and triplicate aliquots combusted. Urine, cagewash, bile, and plasma aliquots were radioassayed in duplicate (MI-31 scintillation cocktail). Feces were homogenized in water and triplicate aliquots radioassayed. Expired air trap aliquots were diluted with methanol (1 mL aliquots plus 1 mL methanol) for radioassay. Carcasses were solubilized for 24 hours at 55°C in $\text{NaOH}/\text{CH}_3\text{OH}/\text{Triton X405}$ (6/3/1), aliquots neutralized with nitric acid, and radioassayed.
- F. Whole-body autoradiography--After asphyxiation with CO_2 , whole rats were frozen at -80°C and trimmed.

After setting in a block of carboxymethylcellulose (2% w/v) at -80°C they were sectioned in a cryostat (-20°C) and sagittal sections of 30 μ m cut at several levels were mounted on cellux tape. The sections were exposed to x-ray film at -20°C for 35 days.

- G. Pharmacokinetic analysis-- C_{max} and T_{max} were determined from radioactivity vs. time plots. Total area under the curve (AUC) used a log-linear trapezoidal method. The AUC curves were adjusted to infinite time based on the concentration (C) at the last sampling time and λZ (the terminal rate constant) determined by linear regression. Half-lives were similarly adjusted. Predicted plasma concentrations during ingestion of 14 C-Vinclozolin were derived values assuming a constant rate of input of test compound (zero order) and equivalent bioavailability after dietary or gavage administration.

I. Study II, Biotransformation of 14 C-Vinclozolin in the Rat

- A. Biotransformation products of 14 C-Vinclozolin were analyzed from the following six studies described above (Study I):

Study type	Dose route	Nominal dose level mg/kg	Number of animals	
			Males	Females
Excretion balance	oral	10	5	5
Excretion balance	oral	100	5	5
Excretion balance	oral, repeated	10	5	5
Excretion balance	intravenous	1	5	5
Tissue distribution	oral	10	12	12
Tissue distribution	oral	7 x 10 ⁶	15	15

Samples from the following additional studies with one rat/sex were analyzed:

- Urine and feces collected at 24, 48, and 72 hours after a single oral dose of 200 mg/kg.
- Urine and feces collected at 6-24, 24-48, and 48-72 hour intervals after dietary dosing for 6 hours at 5000 ppm.

- Bile collected 24 hours after oral doses of 10 or 100 mg/kg to bile duct-cannulated rats.

B. Preparation of biological samples--Urine from male and female rats was analyzed separately. Urine samples (0-24 and 24-48 hours separately) were pooled and processed by absorption on a 500-mg C18 sorbent column. The column was washed with phosphate buffer (0.1 M) and then hexane, followed by elution with acetonitrile/methanol (1/1 by volume).

Urine samples were mixed with pH 5 acetate buffer and incubated at 37°C with β -glucuronidase for 46 hours or sulfatase for 24 hours. Untreated controls were also incubated. Bile samples were also treated with β -glucuronidase and sulfatase. Enzyme-treated samples of urine and bile were cleaned up as above on the sorbent column.

Urine samples from male rats 0-24 hours after a single dose of 100 mg/kg ^{14}C -Vinclozolin were also fractionated for metabolites. Urine was extracted with ethylacetate (2 times), acidified to pH 2, and further extracted with ethylacetate. The aqueous phase was adjusted to pH 7, placed on a column of Amberlite XAD 2, washed with water and eluted sequentially with acetonitrile and methanol. All organic fractions were concentrated to dryness and reconstituted to 5 mL.

Fecal samples collected up to 48 hours after dosing were grouped separately by sex and were extracted three times with 10 mL of acetonitrile and the organic phase concentrated.

Tissues (liver and kidney) aliquots were extracted three times with acetonitrile followed by methanol. The separate organic phases were concentrated and an aliquot of the residual tissue was combusted for ^{14}C analysis. Plasma was treated similarly to urine by sorbent extraction.

C. Chromatography and Mass Spectrometry: High performance liquid chromatography (HPLC) was carried out on Spherisorb 5 μm OD52 columns with Waters equipment and gradient elution with acetonitrile/methanol/0.1% formic acid. Radioactivity was measured with a Ramona detector cell and a u.v. detector was included in the eluate line. Samples were collected in scintillation vials. Samples for mass spectral analysis were converted to their trimethylsilyl derivatives and processed by gas chromatography on a fused silica capillary column using a programmed temperature

gradient. The column was interfaced to the ion source for electron impact mass spectrometry. Samples were also analyzed by direct injection into the ion source for liquid secondary mass spectrometry.

13. REPORTED RESULTS:

- A. The pilot study showed that more than 95% of the radioactivity was excreted in the urine and feces in 5 days and no detectable radioactivity was eliminated in expired air.

Table 2 summarizes radioactivity retained in the carcass or excreted in urine and feces 5 days after a single oral dose of 10 or 100 mg/kg, repeated oral dosing (14 daily doses of unlabeled Vinclozolin at 10 μ g/kg followed by a single 14 C-dose), or single intravenous dose (1 mg/kg). Urine and feces accounted for more than 90% of the administered dose. There was no essential difference between males and females. Residue retained in the carcasses after oral dosing ranged from 0.6 to 1.4% of the dose. Most of the dose was excreted within 48 hours (accounting for 86.9 and 81.8% in males and females, respectively, receiving 10 mg/kg orally). After an oral dose of 100 mg/kg, 84.7 and 74.7% were excreted within 48 hours in males and females, respectively. Pretreatment with unlabeled Vinclozolin for 14 days followed by a single labeled 10-mg/kg dose resulted in slightly less excretion of 14 C in the urine (5 days--Table 2). At 48 hours, total excretion of radioactivity was 71.8% and 73.4% of the administered dose in males and females, respectively.

- B. After an intravenous dose of 1 mg/kg, about 23% of the 14 C dose was excreted in the feces by 5 days indicating biliary excretion (Table 2). Total excretion at 48 hours in urine and feces was 80.6 and 78.0% of the administered radioactivity in males and females, respectively.

Table 3 summarizes results of excretion in bile urine and fgfeces 48 hours after administering single oral doses of 10 or 100 mg/kg 14 C-Vinclozolin to bile duct cannulated rats (3/sex). Biliary excretion was rapid with about 50% of the administered 10 mg/kg dose excreted by 12 hours in males and 18 hours in females (Figure 1). At the high dose, 50% of the administered 14 C in males was excreted in bile in 30 hours whereas in females the rate and amount (as percent of dose) excreted was less than in males, with only about 39% excreted in the bile at 48 hours. Total recovery of radioactivity ranged from 91 to 102% (Table 3). The retained dose at the high level was 4.9 and 10.6% in males

TABLE 2. Mean Excretion and Retention of Radioactivity
by Rats at Five Days After Various Single
Doses of ^{14}C -Vinclozolin

Results are expressed as % dose

Dose	Urine	Faeces	Carcass	Total
Oral 10mg/kg				
Male	52.0	46.2	0.9	99.0
Female	52.6	38.3	0.7	91.6
Oral 10mg/kg*				
Male	54.3	35.8	1.4	91.5
Female	55.5	33.8	1.1	90.4
Oral 100mg/kg				
Male	48.1	48.7	0.6	97.4
Female	54.3	39.7	1.1	95.1
I.V 1mg/kg				
Male	72.7	23.1	1.7	97.5
Female	70.5	22.8	1.1	94.5

For results in detail see Tables 3 - 10

* Pretreated with non-radiolabelled vinclozolin for 14 days

Source: Study No. 90/0544, CBI p. 43.

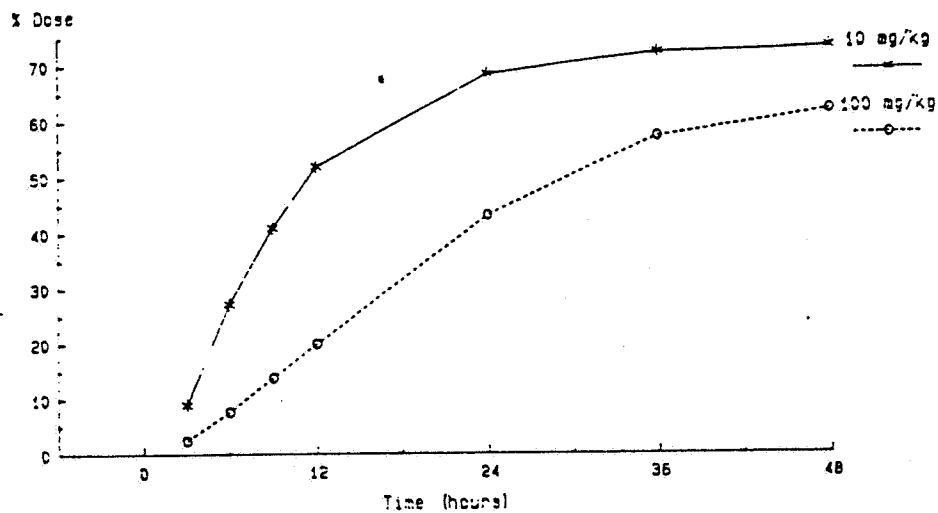
TABLE 3. Excretion and Retention of Radioactivity 48 Hours After a Single Oral Dose in Bile Duct Cannulated Rats

	Mean Percent of Radioactivity ($\pm$ S.D.) ^a			
	10-mg/kg dose		100-mg/kg dose	
Bile	73.2 $\pm$ 4.8	63.5 $\pm$ 7.5	62.0 $\pm$ 2.3	38.8 $\pm$ 3.9
Urine ^b	18.3 $\pm$ 1.8	24.1 $\pm$ 7.3	14.6 $\pm$ 0.5	17.6 $\pm$ 2.5
Feces	6.04 $\pm$ 1.0	10.8 $\pm$ 0.4	16.2 $\pm$ 4.1	23.9 $\pm$ 1.9
Carcass	1.61 $\pm$ 0.2	3.25 $\pm$ 1.3	4.85 $\pm$ 0.9	10.6 $\pm$ 3.4
Total	99.2 $\pm$ 4.2	102.0 $\pm$ 4.0	97.8 $\pm$ 2.0	90.9 $\pm$ 2.1

^aMean for 3 rats.

^bIncludes cage wash.

(a) Male rats



(b) Female rats

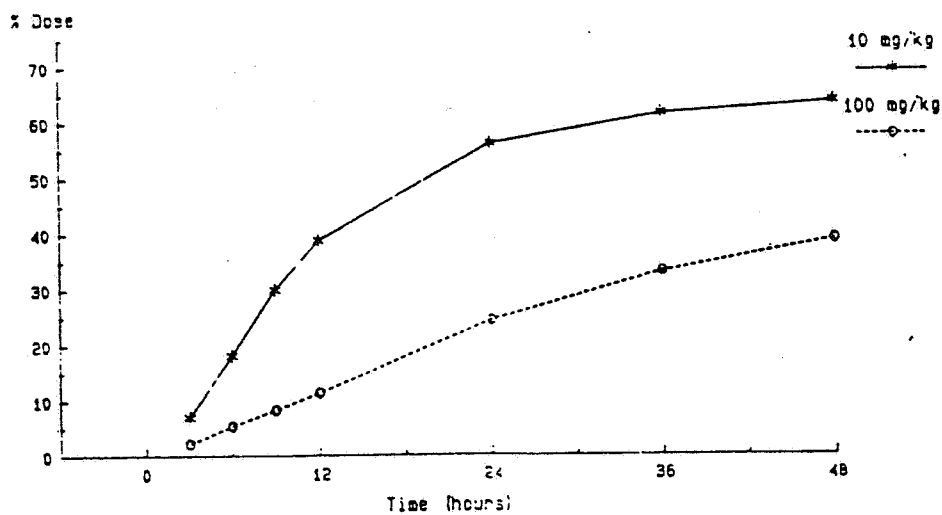


Figure 1. Cumulative excretion of radioactivity in bile by cannulated rats after single oral doses of ^{14}C -Vinclozolin at nominal levels of 10 mg/kg and 100 mg/kg.

Source: Study No. 90/0544, CBI Figure 5, CBI p. 107.

and females, respectively, compared to 1.6 and 3.3% at the low level.

Pharmacokinetics--Plasma concentrations versus time curves (linear scale) are shown in Figures 2 and 3. Expanded time scale curves are presented in Appendix A. The time to reach peak plasma concentrations of ^{14}C ($T_{\max}$) increased as the dose level was increased (single gavage doses). Radioactivity levels in plasma decreased with an apparent biphasic manner and the half-lives for the terminal portion of the curve were longer in females than in males. Table 4 summarizes data for pharmacokinetics parameters with increasing single oral doses.

The increase in $C_{\max}$ and AUC in both sexes were less than proportional with dose. Both parameters were higher in males than females. This indicates a lower clearance or greater volume of distribution in females and is consistent with the observed longer half-life in females.

In the dietary study, a diurnal pattern of input was observed as is expected (Table 36 of CBI; data not shown); the doses were equivalent to 439 and 345 mg/kg in males and females. For the first 12 hours, the predicted plasma concentrations based on the rate of ingestion were close to the observed (Table 5). The half-lives of plasma clearance after cessation of feeding labeled material was approximately 40 hours (41.0 and 38.9 in males and females, respectively). Based on AUC x dose, the bioavailability was similar in gavage and dietary studies, the relative bioavailability ratio was approximately 1 (Table 35 of CBI, data not shown). Figure 4 shows that when values for AUC are plotted against dose (mg/kg) for both oral gavage and the dietary route, a straight line relationship was observed up to 400 mg/kg (highest dose; dietary route).

Table 6 shows mean tissue levels of selected tissues in females 2 hours after a single oral 10-mg/kg dose or following repeated dosing for 7 days with labeled compound. After multiple dosing (7 days), tissue levels are approximately double those after a single oral dose. Figure 5 shows the decrease in tissue levels with time (females, multiple dose). The tissue/plasma ratios generally do not change as radioactivity is cleared from tissues (Table 6). This indicates essentially the same half-life for clearance from each tissue as for plasma clearance. Similar data were observed in males, except that tissue levels were slightly lower.

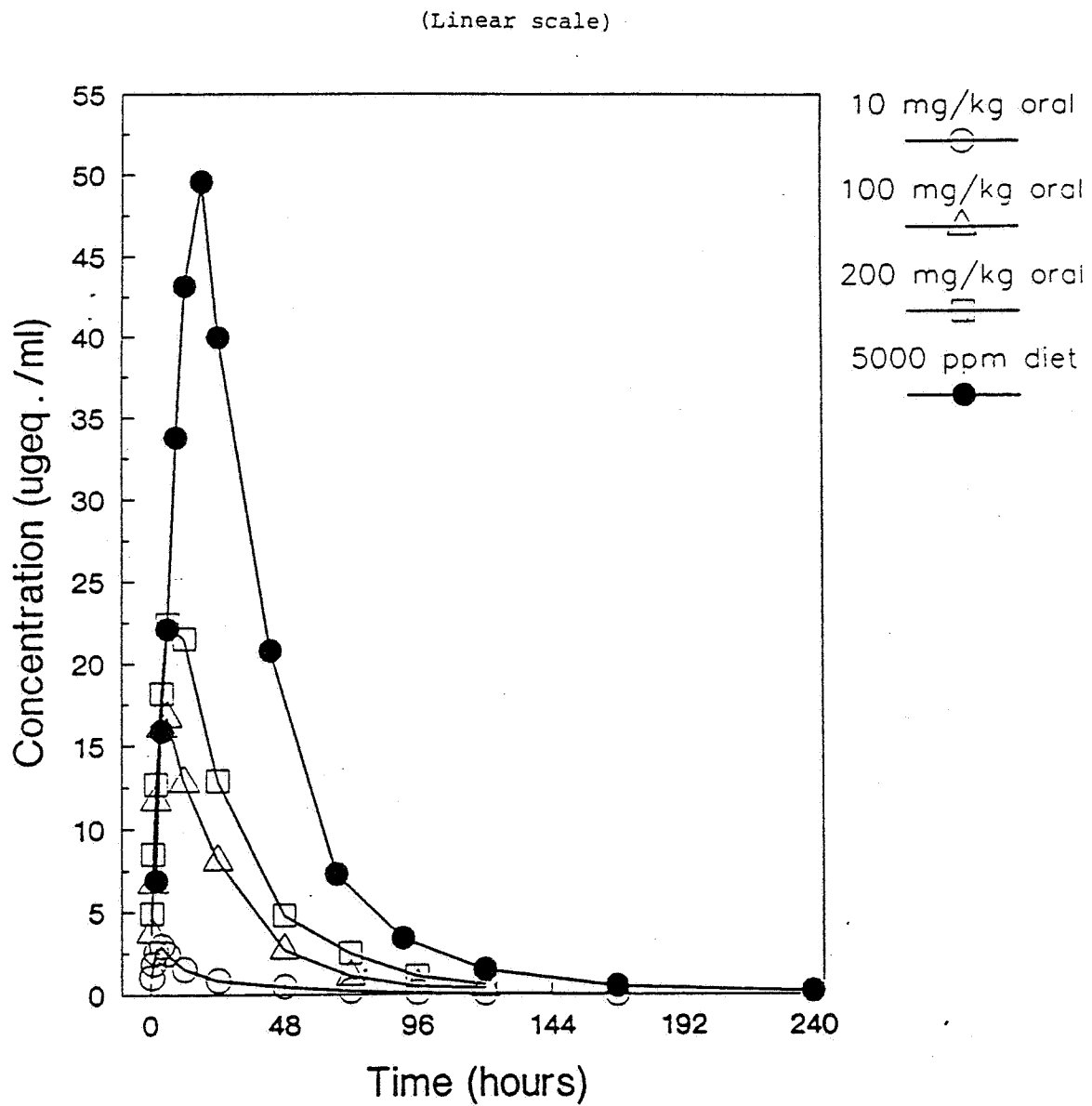


Figure 2. Mean plasma concentrations of radioactivity after various doses of ^{14}C -Vinclozolin administered to male rats.

Source: Study No. 90/0544, CBI Figure 7, CBI p. 109.

(Linear scale)

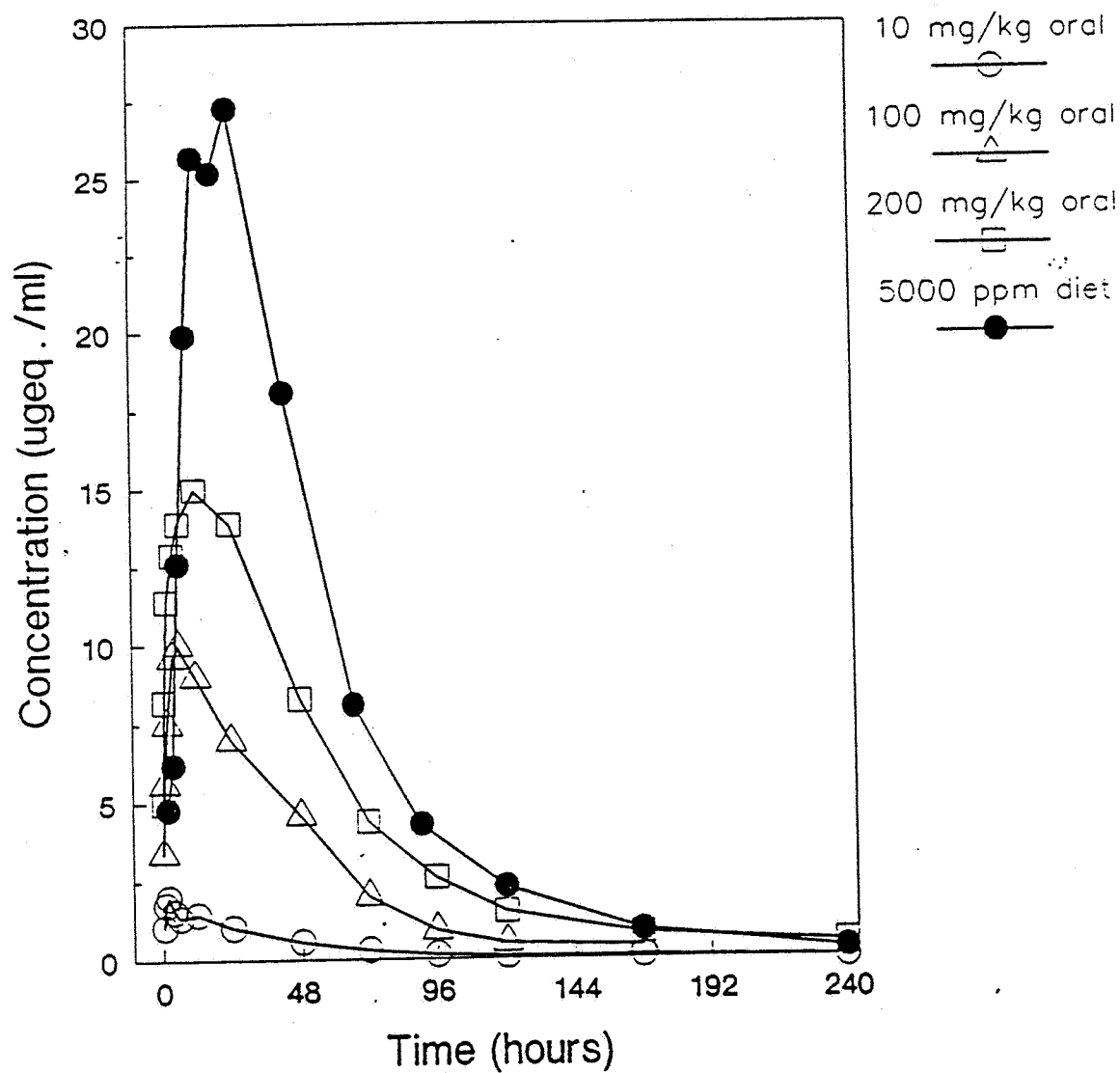


Figure 3. Mean plasma concentrations of radioactivity after various doses of ^{14}C -Vinclozolin administered to female rats.

Source: Study No. 90/0544, CBI Figure 9, CBI p. 111.

TABLE 4. Pharmacokinetic Parameters for Single Oral Doses

Dose		C _{max} (μg eq/mL)	T _{max} (hours)	AUC (μg eq/mL·hr)	t½ (hours)
mg/kg	mg/rat				
Males					
10	2.0	2.8 ± 0.5	3.6 ± 1.7	72.7 ± 55	27.3
100	17.9	16.8 ± 2.5	5.2 ± 1.1	482 ± 105	18.0
200	33.8	23.2 ± 3.1	9.6 ± 3.3	788 ± 54	22.6 (21.7) ^a
Females					
10	2.0	2.0 ± 0.1	1.8 ± 0.4	74.9 ± 9.2	64.4
100	17.9	10.3 ± 2.7	4.8 ± 1.1	485.0 ± 68	26.5
200	33.8	15.6 ± 1.8	13.2 ± 6.6	997.0 ± 90	45.2 (36.1) ^a

^aThe values in parentheses are the mean values for the three dose levels.

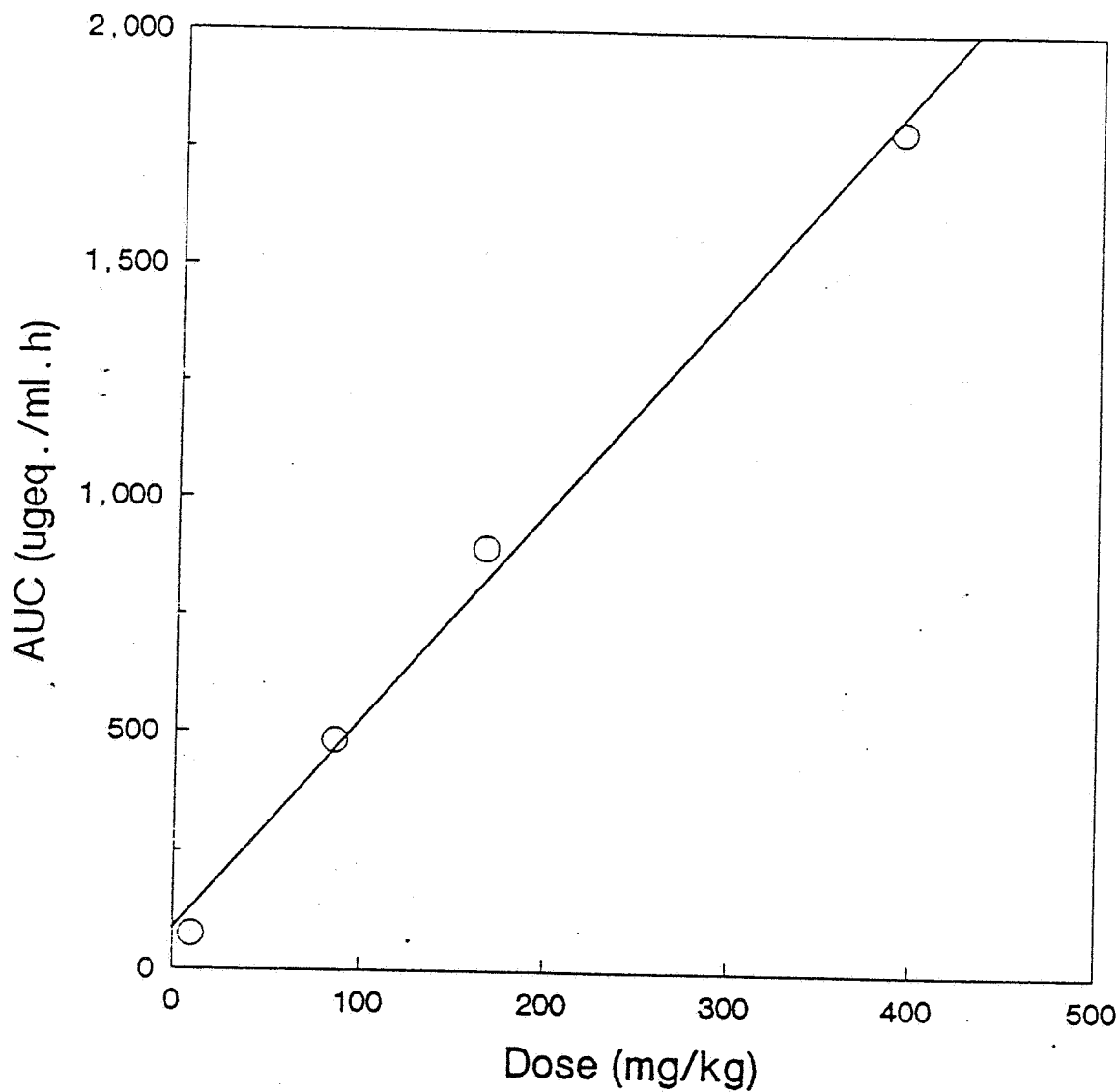
TABLE 5. Plasma Concentrations of Radioactivity During Ingestion of ^{14}C -Vinclozolin With the Diet

Time (hours)	Values expressed as ug eq./ml			
	Males		Females	
	Observed mean plasma concentration	^a Prediction concentration (Ct)	Observed mean plasma concentration	^a predicted concentration (Ct)
2	6.9	8.4	4.8	4.4
4	15.9	16.3	6.2	8.7
6	22.1	23.7	12.6	12.8
9	33.8	34.0	19.9	18.8
12	43.2	43.4	25.7	24.5
18	49.6	-	25.2	-
24	40.0	-	27.3	-

$$^a C_t = \frac{R_o}{CL} \cdot (1 - e^{-\lambda_z t})$$

where C_t is the plasma concentration at time t and R_o is the rate of ingestion of ^{14}C -vinclozolin taken as 6.1 and 5.0 mg/h for males and females respectively (Table 36). λ_z is the terminal (elimination) rate constant and CL is the (oral) clearance estimated from dose/AUC (Tables 31 and 32)

Source: Study No. 90/0544, CBI Table 37, CBI p. 78.



Highest dose of approximately 400 mg/kg administered with the diet

Figure 4. Relationship between dose of ^{14}C -Vinclozolin and AUC of radioactivity after single oral doses administered to male and female rats.

Source: Study No. 90/0544, CBI Figure 16, CBI p. 118.

TABLE 6. Radioactivity Levels in Selected Tissues of Female Rats 2 Hours After an Oral Dose of 10 mg/kg ¹⁴C-Vinclozolin

Tissue	$\mu\text{g eq./g}$		Ratio tissue/plasma ^c		
	2h ^a	2h ^b	2h	24h	48h
Plasma	2.12	3.91	1 (2.12) ^d	1 (1.10) ^d	1 (0.57) ^d
Harderian gland	6.94	12.3	3.1	2.1	1.9
Adrenal gland	5.77	10.6	2.7	2.3	2.1
Kidney	5.65	10.6	2.7	2.6	2.9
Liver	8.57	16.9	4.3	4.1	4.7
Lung	3.51	6.27	1.6	1.6	1.7
Heart	2.73	5.72	1.4	1.2	1.2
Pancreas	4.28	7.52	1.9	1.8	1.3
Muscle	1.40	2.94	0.75	0.71	0.70

^aRats received a single oral dose of 10 mg/kg ¹⁴C-Vinclozolin (CBI Table 39).

^bRats received 7 daily oral doses of 10 mg/kg ¹⁴C-Vinclozolin (CBI Table 55).

^cRats received 7 daily oral doses of 10 mg/kg ¹⁴C-Vinclozolin (CBI Table 61).

^dThe levels in μg equivalents/mL of plasma are given in parentheses.

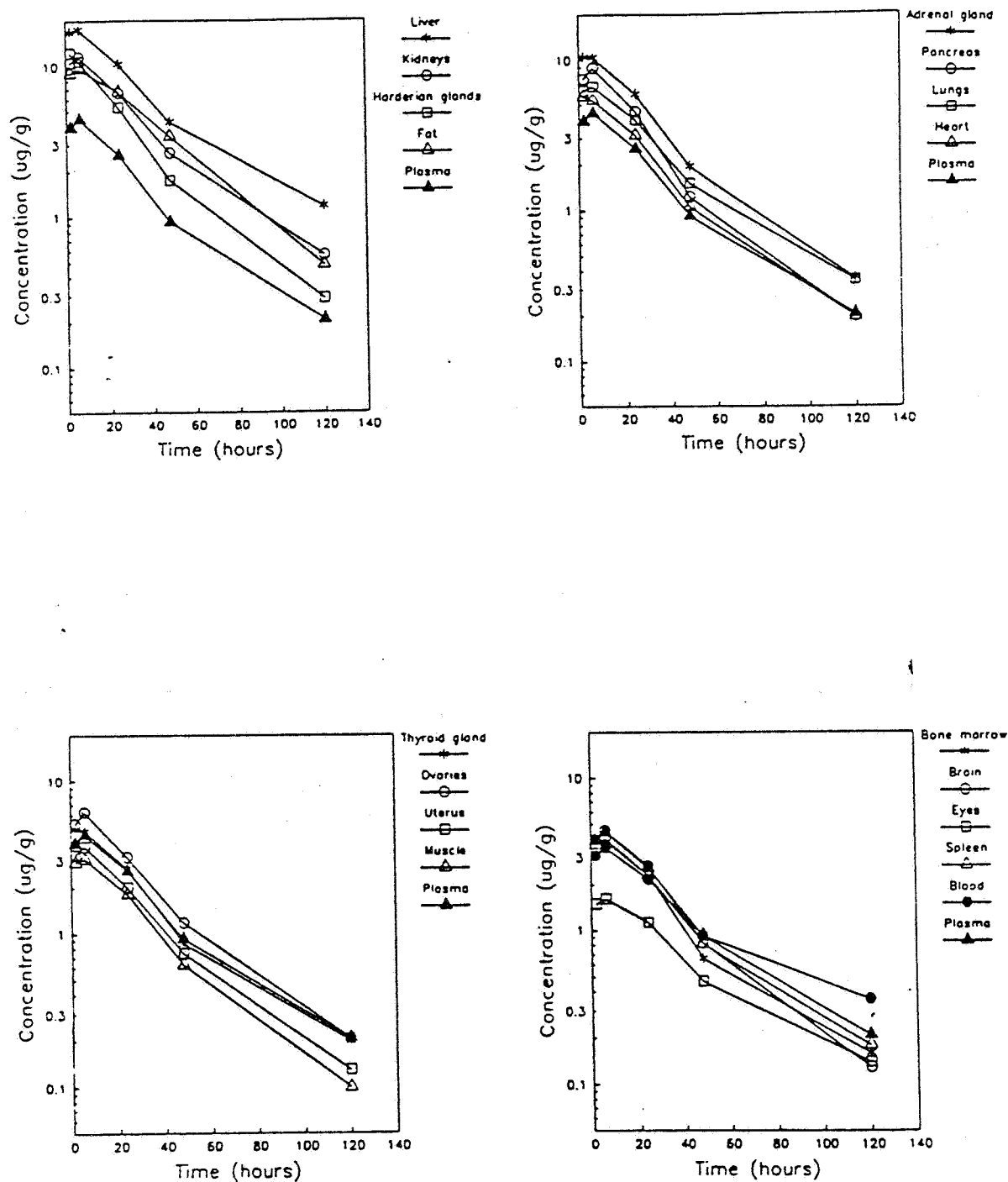


Figure 5. Changes in the mean ($n = 3$) concentrations of radioactivity with time in tissues of female rats after the last of seven daily oral doses of ^{14}C -Vinclozolin at a nominal level of 10 mg/kg/day.

Source: Study No. 90/0544, CBI Figure 25, CBI p. 127.

Tissue levels declined in a generally linear manner with time. After five days levels were mostly in the range of 0.1-3 µg/g with the highest levels present in the liver, kidney, and female fat.

Autoradiography: Whole body autoradiographs from animals dosed for 7 days with ¹⁴C-Vinclozolin showed that radioactivity was distributed in all tissues except bone at 48 hours postdosing. There was little variation in distribution with time or between sexes. The highest concentrations were in liver, gastrointestinal tract, kidneys and urinary bladder. Radioactivity in the adrenal was evenly distributed in the cortex. Lacrymal and Harderian glands had relatively high concentrations as well as nasal mucosa, salivary glands, and adrenal glands. The results of radioautography support the quantitative findings of tissue distribution.

II. Biotransformation of ¹⁴C-Vinclozolin in the Rat

Table 7 outlines the different groups of animals used, the urinary excretion, extraction efficiency, and percent of dose analyzed by HPLC. Urinary radioactivity extraction efficiency ranged from 93 to 98% for all samples. HPLC separated up to 13 components. Appendix B shows the reference compounds and their structural formulas. In general there were no marked differences in metabolite profiles in urine related to sex, route of administration, low or high dose, or single dose compared to repeated dosing (Table 8). Regardless of route, no more than 0.5% of the dose was unchanged Vinclozolin (component R13). The major radioactive component was R7 which constituted 4 to 23% of the administered dose after oral or dietary doses and up to 32% of the dose after intravenous administration. Component R7 was a conjugate since its level decreased after glucuronidase/sulfatase treatment of urine. For a 10 mg/kg oral dose in male rats, R7 and R8 constituted 14.3 and 2.6% of the dose. After deconjugation, the percent of R7 in urine decreased to 6.1% and R8 increased to 10.9% of the dose. Polar components R1, R2, and R3 decreased and R4, R5, R6 and R9 increased after enzyme treatment indicating that they were conjugates. Components R1, R2, and R3 also decreased after treatment of urine with a specific sulfatase enzyme.

Urinary samples (males 100 mg/kg dose) were pooled and extracted with ethylacetate at pH 7 and at pH 2 and the resulting aqueous phase extracted with methanol. Preparative HPLC on the three fractions (EA1, EA2, and MEL) yielded 10, 12, and 4 fractions, respectively, each of which underwent mass spectral analysis if sufficient material was isolated. Samples were analyzed after

TABLE 7. Excretion of Radioactivity in the Urine of Male and Female Rats After Various Doses of ^{14}C -Vinclozolin and the Proportion of the the Dose Analyzed by HPLC

Nominal dose level (mg/kg)	Dose route	Animal numbers	Time after dosing (hours)	Mean urinary excretion (% dose)	% urinary radioactivity extracted	Mean % dose analysed
10	Oral gavage	21-25♂	0-24	32.2	96.1	30.9
			24-48	12.1	95.4	11.5
		26-30♀	0-24	34.2	95.5	32.7
			24-48	12.2	95.0	11.6
100	Oral gavage	41-45♂	0-24	26.1	95.8	25.0
			24-48	13.8	96.9	13.4
		46-50♀	0-24	19.8	97.5	19.3
			24-48	20.6	98.0	20.2
10*	Oral gavage	61-65♂	0-24	27.5	94.6	26.0
			24-48	14.9	97.1	14.5
		66-70♀	0-24	29.5	97.5	28.8
			24-48	15.1	97.5	14.7
200	Oral gavage	171♂	0-24	14.9	95.0	14.2
			24-48	9.0	97.0	8.7
		172♀	0-24	9.7	95.0	9.2
			24-48	8.7	98.2	8.5
163	Dietary+	215♂	6-24	7.3	95.6	7.0
			24-48	6.8	92.8	6.3
170		216♀	6-24	7.2	95.9	6.9
			24-48	7.7	96.7	7.4
1	Intravenous	71-75♂	0-24	47.2	98.3	46.4
			24-48	15.1	97.8	14.8
		76-80♀	0-24	44.2	95.8	42.3
			24-48	15.4	97.2	15.0

* Rats received 14 consecutive daily oral doses of non-radiolabelled vinclozolin followed by a single oral dose of ^{14}C -vinclozolin at a nominal level of 10 mg/kg

+ Rats were offered diet for 6 hours containing ^{14}C -vinclozolin at a nominal concentration of 5000 ppm. Urine was collected after the withdrawal of treated diet

Source: Study No. 90/0514, CBI Table 2, CBI p. 38.

TABLE 8. Proportions of Radioactive Components in the Urine (0 - 48 hours) of Rats After Administration of Various Doses of ^{14}C -Vinclozolin

Results are expressed as % dose

Males

Radioactive component	Typical retention time (min)	10 mg/kg oral (21-25°)	10 mg/kg* oral (61-65°)	100 mg/kg oral (41-45°)	200 mg/kg oral (171°)	163 mg/kg diet+ (215°)	1 mg/kg intravenous (71-75°)
R1	6.3	1.0	1.0	1.1	1.0	1.7	5.5
R2	17.8	2.8	4.1	2.7	2.2	1.6	1.0
R3	20.3	2.5	2.9	2.1	1.8	1.0	1.8
R4	22.7	1.5	1.1	0.8	1.0	0.5	1.8
R5	25.7	0.9	1.1	1.0	0.4	0.3	4.3
R6	28.5	1.5	1.7	1.2	0.6	0.5	
R7	32.0	21.2	17.4	20.5	10.1	4.3	32.2
R8	36.3	3.2	2.9	1.9	1.3	1.1	3.7
R9	40.0	3.8	4.2	3.1	2.0	1.4	5.3
R10	43.7	1.3	0.8	0.6	0.4	0.2	1.1
R11	46.2	1.1	1.1	0.8	0.6	0.3	1.6
R12	49.8	0.4	0.5	0.4	0.3	<0.1	0.7
R13	53.2	0.2	0.1	0.2	0.1	<0.1	0.2
Others	-	1.0	1.5	1.8	1.3	0.5	2.2

Females

Radioactive component	Typical retention time (min)	10 mg/kg oral (26-30°)	10 mg/kg* oral (66-70°)	100 mg/kg oral (46-50°)	200 mg/kg oral (172°)	170 mg/kg diet+ (216°)	1 mg/kg intravenous (76-80°)
R1	6.3	0.7	0.8	0.6	0.4	0.6	5.2
R2	17.8	1.7	2.5	1.9	1.2	0.7	0.5
R3	20.3	1.9	2.2	1.3	0.9	0.6	1.4
R4	22.7	1.6	1.5	2.0	1.1	0.4	1.8
R5	25.7	0.7	1.0	0.4	0.2	0.4	4.5
R6	28.5	1.5	1.5	1.3	0.5	0.5	
R7	32.0	21.8	22.2	21.1	8.2	5.9	27.9
R8	36.3	3.3	3.2	2.4	1.0	0.8	3.6
R9	40.0	4.2	3.8	2.6	1.3	1.1	4.0
R10	43.7	1.7	0.8	0.5	0.2	0.2	2.2
R11	46.2	1.4	0.9	0.6	0.2	0.2	1.4
R12	49.8	1.6	1.7	3.2	2.0	2.5	2.2
R13	53.2	0.5	0.3	0.1	<0.1	0.1	0.4
Others	-	1.8	1.0	1.3	0.6	0.6	2.3

Results are the sum of data from separate 0 - 24 and 24 - 48 hour time periods which are shown in Tables 7(a) and 8

- * Rats received 14 consecutive daily oral doses of non-radiolabelled vinclozolin followed by a single oral dose of ^{14}C -vinclozolin at a nominal level of 10 mg/kg
- + Rats were offered diet for 6 hours containing ^{14}C -vinclozolin at a nominal concentration of 5000 ppm. Urine was collected after the withdrawal of treated diet

Source: CBI pp. 36 and 37.

derivatization by GC-MS or underivatized samples were directly injected into the electron impactor. Spectra of reference compounds similarly derivatized were used for comparisons.

Some compounds appeared in more than one fraction. The identity of R4, R5, R7, R8, R9, R11 and R12 were confirmed. Table 9 summarizes the data on characterization.

Fecal and Biliary Metabolites

Extraction efficiencies for fecal samples were generally lower than those for urinary samples, ranging from 73.5 to 97.3% for 12 samples (Table 10). Table 11 summarizes data for HPLC of feces extracts. Following oral dosing (48 hours) at 10, 100 or 200 mg/kg, unchanged ¹⁴C-Vinclozolin (R13) accounted for 21.1, 25.5, and 30.3% of the dose in males and 14.7, 21.3, and 42.1% of the dose in females (HPLC); 21.5 and 27.9% of the dietary dose in males and females cochromatographed with Vinclozolin. Only 0.1-0.2 of a 1 mg/kg intravenous dose chromatographed as Vinclozolin. Major metabolites were the N-(3,5-dichlorophenyl)-2-methyl-2,3,4-trihydroxybutyramide (R8) and its intermediate in which the vinyl group underwent epoxidation and hydration and the heterocyclic ring remained intact (R9).

Biliary excretion accounted for 70 and 40% of the administered radioactivity at low or high doses, respectively. Chromatography was not successful prior to glucuronidase/sulfatase digestion. Recovery of ¹⁴C was greater than 90% after enzymatic digestion followed by sorbent treatment and elution with acetonitrile/methanol (1/1). The major component was the glucuronide of R8 (the trihydroxybutyramide derivative) which represented about 41% of the low dose and 20% of the high dose. Resolution of other metabolites was poor.

Tissue metabolites--Liver and kidney samples 6 hours after the last of seven daily oral doses of ¹⁴C-Vinclozolin (10 mg/kg dose) were analyzed by HPLC after extraction with acetonitrile/methanol (87 and 91% extraction efficiency, liver and kidney, respectively). R8 was the major metabolite in both tissues and accounted for about 26 and 46% of the tissue radioactivity. Some unchanged Vinclozolin was detected (less in kidneys than liver) and variable amounts of more polar metabolites (R1 to R6). R8 was also the major metabolite found in chromatograms of acetonitrile/methanol extracts of plasma. However, only 55 to 72% of the radioactivity of plasma was extracted, suggesting binding of metabolites to plasma proteins.

TABLE 9. Summary of the Characterization of Vinclozolin Biotransformation Products in Rat Urine

Radioactive component	Typical retention time (min)	Characterisation	Corresponding isolated fraction	Supporting evidence for characterisation
R1	6.3	Sulphate conjugate	Me1/F1	Hydrolysis of urine by sulphatase enzyme.
R2	17.8	Sulphate conjugate		Hydrolysis of urine by sulphatase enzyme.
R3	20.3	Sulphate conjugate		Hydrolysis of urine by sulphatase enzyme.
R4	22.7	Reference compound 5	EA2/F2 EA1/F1	Identical mass spectrum to reference compound 5. Co-chromatography of 5 with R4 in rat urine. Co-chromatography of 5 with fraction EA1/F1.
R5	25.7	Ring hydroxylated analogue of reference compound 37	EA2/F4 EA1/F2	Interpretation of mass spectrum.
R6	28.5	Not complete	EA1/F3	Formed by enzyme hydrolysis of urine. Mass spectrum obtained.
R7	32.0	Glucuronic acid conjugate of reference compound 25 Glucuronic acid conjugate of reference compound 37	EA2/F6 EA2/F7 EA1/F4 EA1/F5 Me1/F3 Me1/F4 EA2/F8	Interpretation of mass spectra of EA2/F6 and EA2/F7. Hydrolysed by β -glucuronidase to yield reference compound 25. Interpretation of mass spectra.

Source: Study No. 90/0514, CBI Table 11, CBI pp. 47 and 48.

TABLE 9. Summary of the Characterization of Vinclozolin Biotransformation Products in Rat Urine (continued)

Radioactive component	Typical retention time (min)	Characterisation	Corresponding isolated fraction	Supporting evidence for characterisation
R8	36.3	Reference compound 25	EA1/F6	Identical mass spectrum to reference compound 25. Co-chromatography of 25 with R8 in rat urine. Co-chromatography of 25 with EA1/F6. Formed on hydrolysis of the glucuronic acid conjugate R7 by β -glucuronidase enzyme.
R9	40.0	Reference compound 37	EA2/F10	Identical mass spectrum to reference compound 37. Co-chromatography of 37 with R9. Co-chromatography of EA2/F10 with R9.
R10	43.7	None	-	
R11	46.2	Reference compound 31	EA1/F7	Identical mass spectrum to reference compound 31. Co-chromatography of 31 and EA1/F7.
		Reference compound 42	EA1/F8	Identical mass spectrum to reference compound 42. Co-chromatography of 42 with EA1/F8. Co-chromatography of 42 with R11 in rat urine.
R12	49.8	Reference compound 22	EA1/F9	Identical mass spectrum to reference compound 22. Co-chromatography of 22 with EA1/F9. Co-chromatography of 22 with R12 in rat urine.
R13	53.2	Unchanged vinclozolin	EA1/F10	Same HPLC retention time as vinclozolin.

Source: Study No. 90/0514, CBI Table 11, CBI pp. 47 and 48.

TABLE 10. Excretion of Radioactivity in the Feces of Male and Female Rats Up to 48 Hours After Various Doses of ^{14}C -Vinclozolin and the Proportion of the Dose Extracted and Analyzed by HPLC

Nominal dose level mg/kg	Dose route	Animal nos.	Mean faecal excretion (% dose)	% faecal radioactivity extracted	Mean % dose analysed
10	Oral	21-25♂	42.6	90.5	38.6
		26-30♀	35.4	93.8	33.2
10*	Oral	61-65♂	29.4	73.5	21.6
		66-70♀	28.8	81.5	23.5
100	Oral	41-45♂	44.9	90.6	40.7
		46-50♀	34.4	93.8	32.3
200	Oral	171♂	50.0	82.7	41.4
		172♀	49.7	97.3	48.4
163	Diet+	215♂	35.6	88.0	31.3
170		216♀	39.8	89.9	35.8
1	Intravenous	71-75♂	18.4	83.9	15.4
		76-80♀	18.5	79.0	14.6

* Rats received 14 consecutive daily oral doses of non-radiolabelled vinclozolin followed by a single oral dose of ^{14}C -vinclozolin at a nominal level of 10 mg/kg

+ Rats were offered diet for 6 hours containing ^{14}C -vinclozolin at a nominal concentration of 5000 ppm. Faeces were collected after withdrawal of treated diet

Source: Study No. 90/0514, CBI p. 50.

TABLE 11. Proportions of Radioactive Components in the Feces (0 - 48 Hours) of Rats After Administration of Various Doses of ^{14}C -Vinclozolin

Results are expressed as % dose

Males

Radioactive component	Typical retention time (min)	10 mg/kg oral (21-25 $^{\circ}$)	10 mg/kg* oral (61-65 $^{\circ}$)	100 mg/kg oral (41-45 $^{\circ}$)	200 mg/kg oral (171 $^{\circ}$)	163 mg/kg diet+ (215 $^{\circ}$)	1 mg/kg intravenous (71-75 $^{\circ}$)
R1-R7	-	2.6	1.7	2.3	1.8	1.6	2.1
R8	36.3	9.0	8.9	8.4	6.2	5.4	8.5
R9-R10	-	3.6	3.6	2.6	1.8	1.2	3.5
R11	46.2	1.5	1.4	1.0	0.7	0.9	1.1
R12	49.8	0.5	0.2	0.6	0.3	0.2	0.2
R13	53.2	21.1	5.4	25.5	30.3	21.5	0.2
Others	-	0.3	0.4	0.2	0.2	0.4	-

Females

Radioactive component	Typical retention time (min)	10 mg/kg oral (26-30 $^{\circ}$)	10 mg/kg* oral (66-70 $^{\circ}$)	100 mg/kg oral (46-50 $^{\circ}$)	200 mg/kg oral (172 $^{\circ}$)	170 mg/kg diet+ (216 $^{\circ}$)	1 mg/kg intravenous (76-80 $^{\circ}$)
R1-R7	-	3.2	2.4	2.2	1.7	0.5	3.0
R8	36.3	10.9	9.3	5.9	3.3	3.6	8.9
R9-R10	-	2.1	2.0	1.1	0.7	0.7	1.8
R11	46.2	1.7	1.3	0.7	0.6	0.5	0.9
R12	49.8	0.6	0.5	0.6	0.2	0.2	0.1
R13	53.2	14.7	7.3	21.3	42.1	27.9	<0.1
Others	-	<0.1	0.8	0.6	<0.1	2.3	0.1

* Rats received 14 consecutive daily oral doses of non-radiolabelled vinclozolin followed by a single oral dose of ^{14}C -vinclozolin at a nominal level of 10 mg/kg

+ Rats were offered diet for 6 hours containing ^{14}C -vinclozolin at a nominal concentration of 5000 ppm. Faeces were collected after the withdrawal of treated diet

Radiochromatograms are shown in Figures 19 - 21

Source: Study No. 90/0514, CBI Tables 14 and 15, CBI pp. 51 and 52.

13. STUDY AUTHORS CONCLUSIONS/QUALITY ASSURANCE MEASURES:

- A. Biokinetics of [U-¹⁴C-phenyl]Vinclozolin were studied in male and female Wistar rats. After administration of single oral doses at nominal levels of 10 mg/kg and 100 mg/kg, mean urinary and fecal excretion of radioactivity by both sexes lay in the ranges 48 to 54% and 38 to 49% of the dose, respectively. Retention of radioactivity after 5 days amounted to 0.6 to 1.4% of the dose with similar retention both doses but slightly lower retention in males than in females. After a single intravenous dose of 1 mg/kg excretion (mean of both sexes) after 5 days accounted for 71.6 and 23.0% of the dose in urine and feces respectively. In rats with cannulated bile ducts, biliary excretion accounted for 73.2 and 63.5% of an oral dose of 10 mg/kg and 62.0 and 38.8% of an oral dose of 100 mg/kg in males and females, respectively. Pronounced enterohepatic recirculation of radioactivity occurs. After single oral doses of 10, 100, or 200 mg/kg, peak plasma concentrations (c_{max}) linearly increased with dose level and time to peak also tended to increase c_{max} values were higher in males than females. Plasma concentration decline in an apparent biphasic manner with terminal half-lives of 23 and 36 hours for males and females, respectively.

During dietary ingestion of 5000 ppm ¹⁴C-Vinclozolin for 24 hours, the plasma concentrations increased with an apparent zero order absorption model and half lives of decline after removal of labeled diet were apparently 40 hours. Systemic availability of radioactivity appeared equivalent by gavage or dietary administration. ¹⁴C-label was generally widely distributed to tissues with peak levels in liver, kidneys, fat, and adrenals and Harderian gland (4-10 µg eq/g at 10 mg/kg) and declined to levels in the range of 0.02 to 0.2 µg eq/g after 5 days.

Vinclozolin was extensively metabolized in the rat; Figure 6 shows the proposed metabolic pathway. Urine contained at least 15 metabolites in addition to low levels of unchanged ¹⁴C-Vinclozolin. Metabolic transformation proceeds by epoxidation and hydration of the vinyl side chain and hydrolytic cleavage of the 2,3 bond of the oxazolidine ring to give N-(3,5-dichlorophenyl)-2-methyl-2,3,4-trihydroxybutyramide (R8). This product is conjugated as a glucuronide and excreted in the urine. An intermediate in this pathway with an intact heterocyclic ring is also conjugated as a glucuronide and excreted in the urine. Other metabolites result from aromatic hydroxylation. Minor metabolites result from cleavage of the 3,4 bond of the heterocyclic ring and loss of the vinyl group. 3,5-Dichloroaniline was detected in urine but accounted for only about 1% of the dose. The major urinary metabolite

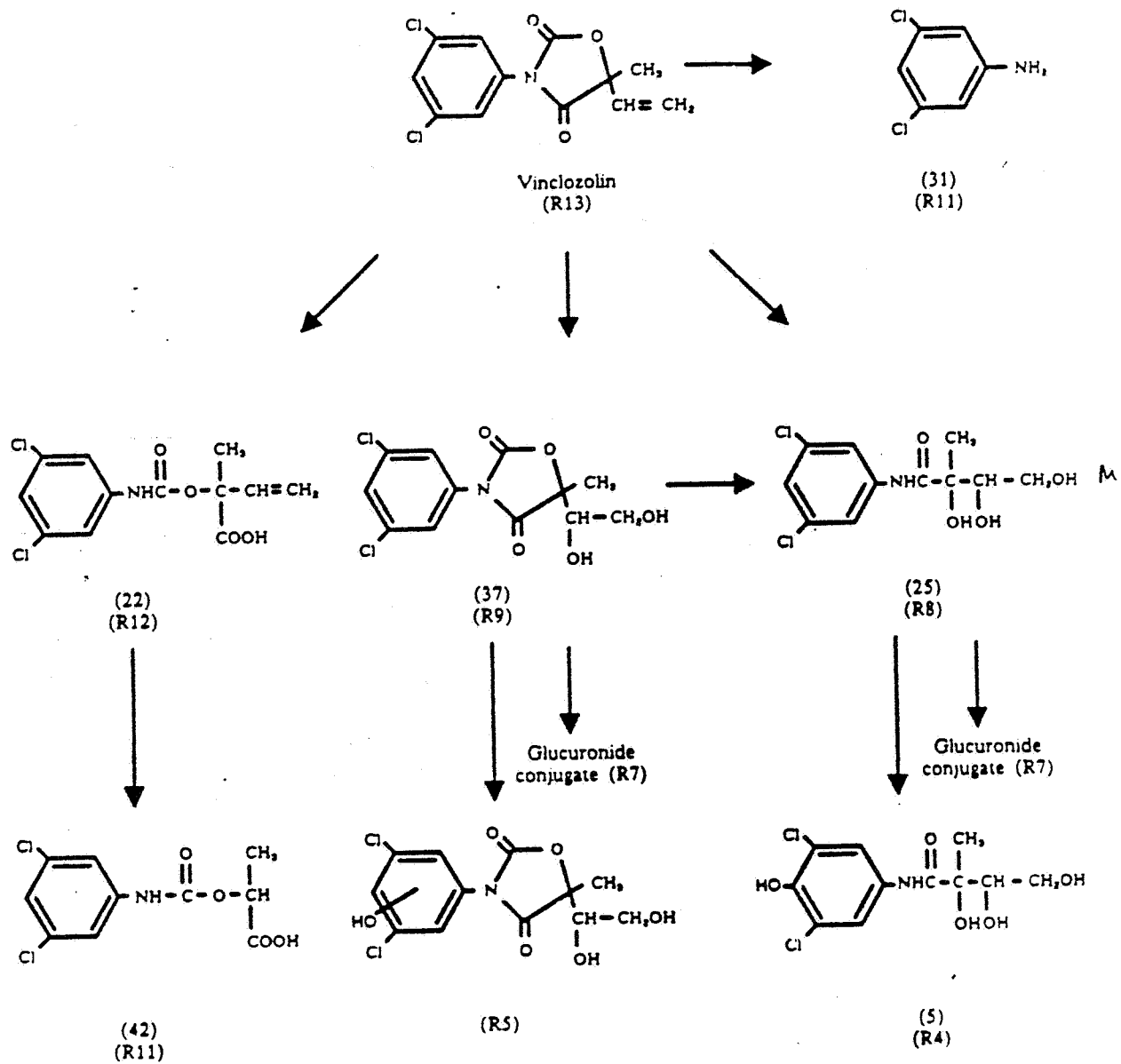


Figure 6. Postulated biotransformation pathway of ^{14}C -Vinclozolin in the rat.
Source: Study No. 90/0514, CBI p. 93.

(R8) was also conjugated with glucuronide and excreted in the bile: The major ¹⁴C-compound in feces was unchanged Vinclozolin.

- B. Quality Assurance: Quality Assurance statements were present, signed and dated November 28, 1990, for the Biokinetic study and March 4, 1991, for the Biotransformation study.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF RESULTS:

The design, conduct, and reporting of the two studies were excellent. There were no toxic effects at the high dose. However, the use of a dose approaching the LD₅₀ (6400 mg/kg) would have been impractical since the resulting specific activity would have been too low and compromised sensitivity of detection of radioactivity. The reviewers agree with the study authors conclusions. Chromatographic scans and mass spectral data were well presented and all techniques were adequate. Sample calculations were provided and efficiency of counting was well documented.

Items 15-16--see footnote 1.

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Pages 24 through 40 are not included.

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 - ☐ Identity of product impurities.
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