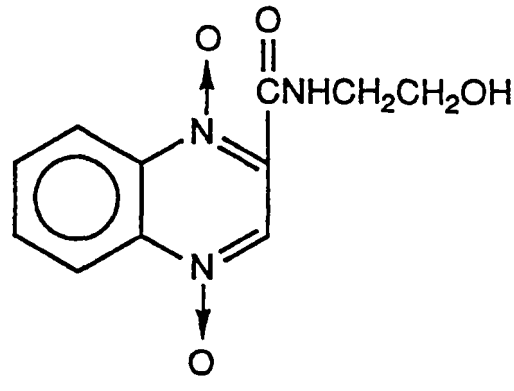
OLAQUINDOX

IDENTITY

Chemical name: N-(2-hydroxyethyl)-3-methyl-2-quinoxaline-carboxamide-1,4,-dioxide

Structural formula:



Molecular formula: $C_{12}H_{13}N_3O_4$

Molecular weight: 263.25

OTHER INFORMATION ON IDENTITIES AND PROPERTIES

Pure active ingredient:

Appearance: Pale yellow crystals

Melting point: 209° (decomp.)

Solubility: Slightly soluble in water, insoluble in most organic solvents. pKb = 11.3 at 25°. pH = 7.3 in water

Degradability:

Olaquindox is readily degraded by light. After an aqueous solution of Olaquindox was exposed to diffuse daylight for 2, 4 and 7 hours there remained respectively 69%, 15% and 3% of the drug. (Metzger, 1973, Bayer Pharm report, No. 73/7181)

In faeces

Olaquindox was incubated with fresh pig manure at 4°, 20° and 37° and determined microbiologically after separation by TLC. The starting concentration was 1024 ppm. At 4° and 20° detection of the drug was no longer possible on the fourth day; at 37° the

concentration fell below 2 ppm on the second day. (Otten, Foerster and Scheer, 1978, Bayer Pharm report, No. 7885).

In slurry

In the aerobic medium of activated sludge of a clearing plant more than 50% of the Olaquindox was degraded in 30 minutes. (Lemke, 1980, Bayer Pharm report, No. 80/10011).

In soil

Measurements of Olaquindox activity in soil shielded from the influence of light suggest that it is quantitatively degraded under normal practical conditions. The abnormally high concentrations of 100 ppm fall to <0.5 ppm in 2-10 days. (Metzger, 1973, Bayer Pharm report. No. 73/3882).

RESIDUES IN FOOD AND THEIR EVALUATION

CONDITIONS OF USE

Olaquindox is an in-feed growth stimulant for pigs. It has anti-bacterial properties, especially against gram-negative organisms. The normal inclusion rate in feed for pigs is 50 ppm. At 250 ppm negative effects on growth are observed.

METABOLISM STUDIES

PHARMACOKINETICS

Rat

A saline solution of 14C-labelled Olaquindox was administered either orally or into the duodenum at a dose of 10 mg/kg to about 40 rats (Duhm et al., 1973, Bayer, Pharma report-1939). About 90% of the drug was absorbed and approx. 85% of the radioactivity was excreted in the urine and the remaining 15% was excreted in the faeces. About 1% radioactivity remained in the animal two days after administration. 80% of the C14 in the urine was unchanged parent Olaquindox. Similar results were obtained after intravenous injection of radiolabelled Olaquindox.

Dog

In a short experiment in two dogs (Duhm et al, 1973, Bayer, Pharma report - 1939) 14C-Olaquindox was administered 10 mg/kg orally to two dogs as gelatin capsules. 65% of the activity was recovered in the urine within 3 days and 10% was recovered in the faeces.The peak concentration of radioactivity in the serum occurred at 2 hours after administration and goes down to about 1/500 of the maximal activity after 3 days.

Pig

Two studies using 14C-radiolabelled Olaquindox were reported by the sponsors. The drug was labelled in the 3-position with 14C in the quinoxaline ring.

In the first study (Bayer, Pharma report 4151) five female pigs aged 9-12 weeks and weighing 24-29 kg were administered 14C-Olaquindox at a dose of 2 mg/kg directly into the duodenum. The 14C-Olaquindox was dissolved in about 20 ml physiological saline.

More than 90% of the activity was excreted in the urine within 24 hours and 5% of the activity was excreted in the faeces, mostly within the first 48 hours.

The level of radioactivity in the plasma reached a maximum value of 2 ppm 1 hour after dosing. There was a rapid decline in the level to 5 ppb in about 48 hours with a biological half life value time of 4 hours. In one pig where measurements were continued for 28 days after dosing the level followed the above rapid decline for about 48 hours but then the rate of disappearance of the activity from the plasma fell more slowly and exponentionly but with a biological half time value of 9 days. The level in the plasma at 28 days after dosing was approx. 1 ppb.

The half life of the residues is similar in liver, kidney, muscle and adrenals and has a value of approx. 5 days.

In the second study, a 10 week old starved male pig, weighing 22.4 kg was given 2 mg/kg body weight 81.4 MBq 14C-Olaquindox in a gelatine capsule by means of a stomach tube (Maul et al., 1979, Bayer Pharma report 8114). Urine was collected at intervals throughout 48 hours.

95.4% of the radioactivity was excreted in the urine over the 48 hour collection period. The pattern of excretion was:-

Collection time hours after dosing	**% total radioactivity**
0 - 1.92	0.5
1.92 - 7	51.2
7 - 24	41.4
24 - 48	2.3

METABOLISM IN FOOD ANIMALS

Pig

Olaquindox metabolism was examined in urine in two studies using 14C-labelled Olaquindox. The first study (Duhm et al, 1973, Bayer Pharm. report 4151) used 5 female pigs dosed with 3-14C-Olaquindox and the second study (Maul et al, 1979, Bayer Pharm. report 8114) used one male pig dosed with Olaquindox uniformly labelled with 14C in the phenyl ring (U-14C-Olaquindox). The results of both studies are similar, although more detailed information was provided with the second study. Olaquindox is

rapidly absorbed from the gut of the pig and >90% of the dose is excreted in the urine within 48 hours after administration. Olaquindox is the major (>60% of original dose) excreted product and four other metabolites were identified and make up most of the remainder of the residues in urine. Less than 0.1% of the 14C-activity was excreted in the faeces of the male pig in the period 48 hours after dosing.

Olaquindox is metabolised either by oxidation of the alcohol to the carbonyl group on the side chain at position 2 on the quinoxaline ring or removal of one or both N-oxide groups at positions 1 and 4. No indication of the site or mechanism of metabolism are provided.

The residues were examined in the tissues and plasma of the one male pig. Tissues were collected at 48 hours after dosing with 2 mg/kg and plasma was collected at 2, 7, 24 and 48 hours post-dosing.

RADIOMETRIC STUDIES USING 14C-OLAQUINDOX

Five female pigs aged 9-12 weeks and weighing 24-29 kg were administered 3-14C-Olaquindox (s.a. 30 μCi/mg) at a dose of 2 mg/kg bodyweight directly into the duodenum as a solution in 20 ml physiological saline. The pigs were kept in metabolism cages. One 10 week old, starved male pig weighing 22.4 kg was given 44.8 mg, 2.2mCi (81.4 MBq) U-14C-Olaquindox in a gelatine capsule by means of a stomach tube. The animal was kept in a metabolic cage and fed and watered normally from 2 hours after dosing.

Urine was collected at 1.5, 3, 5 and 24 hours after dosing The female pigs. The metabolic profile was determined by spotting 10 μl urine onto paper and carrying out a two-dimensional separation first by high voltage electrophoresis (HVE) separation in one direction and then a simple paper chromatographic (PC) in the other direction.

The names and key to the metabolites is shown in table I. Five metabolites were found. The major product (I) (ca. 70% total activity in female pig urine) was identified as parent compound (Olaquindox) and the second major product (16% total activity in female pig urine) was a mono-N-oxide of Olaquindox (II). The other three metabolites were quantified but not identified.

The urine collected in the 24 hour period after dosing the male pig, was used for identification of the metabolites.The metabolites were separated by a combination of thin-layer chromatography (TLC) and HVE in the perpendicular direction to the TLC. They were identified by autoradiography and comparison and co-chromatography with authentic standards.The metabolites identified are shown in table I.

Table I. Metabolite profile of Olaquindox in male pig urine

Metabolite	side chain at the 2 position	position of -N-oxide	% total 14C
I(parent)	-CO-NH-CH_2-CH_2-OH	1 and 4	65
II	-CO-NH-CH_2-CH_2-OH	4	7
III	-CO-NH-CH_2-COOH	1 and 4	3
IV	-CO-NH-CH_2-COOH	4	6
V	-CO-NH-CH_2-COOH	1	1
VI	-CO-NH-CH_2-COOH	none	<1

(I and II were also identified in female pig urine).

A fraction of the urine was hydrolysed with the enzymes glucuronidase and sulphatase but subsequent analysis showed that there was no evidence of conjugated metabolites.

METABOLISM IN PLASMA AND TISSUES

Plasma from the male pig treated with U-14C-Olaquindox was collected at 2,4,7,24 and 48 hours after dosing. The concentrations of active compounds were low in all samples and it was only possible to identify metabolites in the samples collected at 2 and 7 hours after dosing. Two dimensional TLC was used to separate and identify the metabolites. The measurements were made close to the limits of detection for the method and only parent drug (I) and metabolite II were definitely identified. Metabolite IV was probably present in the 7 hour plasma sample.

Muscle, liver and kidney samples were collected at slaughter, 48 hours after dosing. After extraction and TLC it was not possible to identify any metabolites because the concentrations of the separated products were below the sensitivity of the method. Thus no information is provided on the metabolic profile in edible tissues, although the concentrations of total radioactivity are recorded.

METABOLISM IN RATS

Rats were administered intavenously 10 mg/kg B.W. 14C-Olaquindox and bile and urine were collected during the period 24 hours after dosing.

Most of the dose was eliminated through the kidneys into the urine. At least 80% activity in the urine is parent drug as measured by both inverted radioactive dilution analysis and TLC. Bile was examined by TLC and the activity was almost completely in the metabolised form (Duhm et al., 1970, Bayer Pharm. report, No. 1939).

RADIOLABELLED RESIDUE DEPLETION STUDIES.

Pigs were dosed with 14C-Olaquindox as described previously. The female pigs were slaughtered one on each of the days 2, 4, 8, 14 and 28 days after dosing. Tissues were collected at slaughter, homogenised and freeze dried. The radioactivity was determined in an aliquot by a standard incineration technique. The lower limit of sensitivity was

estimated to be 1-3 ppb. The results are shown in table II. (Duhm, B et al, 1973, Bayer Pharm report No. 4151).

Table II. Total 14C Residues in Pigs 2-28 Days after oral Administration of 2 mg/kg Body-weight 14C-Olaquindox (residues expressed as ppb equivalents of radio-labelled drug)

Withdrawal time (days)	Muscle	Liver	Kidney	Fat	Heart	Adrenals	Plasma
2	9	52	110	1	7	27	10
4	7	66	45	1	10	14	5
8	3	27	12	ND	5	4	3
14	2	13	6	ND	3	3	2
28	<1	2	1	ND	ND	ND	<1

(ND = not detectable)

The maximum residues were found in the kidneys (3.4 ppm) and the liver (1.4 ppm). Much lower concentrations were seen in the muscle and often not detected in fat. The concentrations in edible tissues of the individual metabolites are not recorded and thus the total residues will have to be considered as having the toxicological potency of Olaquindox.

RESIDUE DEPLETION STUDIES

The concentrations of total residues of Olaquindox in edible tissues of pigs administered 10-250 ppm Olaquindox in the feed were measured in five separate studies (see table III). The extraction methods were the same in all the studies and the metabolites were reduced with ferrous ions to form the (2-(N-2-hydroxyethyl-carbamoyl)-3-methyl-quinoxaline derivative, compound VII (side chain = -CO-NH-CH_2-CH_2-OH and N-oxide groups are absent). VII was measured by either TLC, HPLC or GC.

Table III. Summary of Studies for Determining Residues in Pigs fed Olaquindox

No. of Pigs(a)	Dose (ppm)	Time of Sampling hours after dose	Tissues (b)	Method	See Table
4M,4F	100	6,12,24,48	M,L,K	TLC	IV
5M,5F	160	6,12,24,48,96	M,L,K	TLC	IV
4M	250	17,41	M,L,K,F	TLC	V
6M,6F	20	6,12,24	M,L,K,F	TLC	VI
6M,6F	45	6,12,24	M,L,K,F	TLC	VI
13	10	4,8,12	M,L,K,	HPLC	VII
4	75	0.5,24	M,L,K,F+	TLC/GC	VIII
8	150	0.5,8,24,72	M,L,K,F+	TLC/GC	VIII
1M,1F	100	24,72	M,L,K,F+	TLC/GC	VIII
1M,1F	150	24,72	M,L,K,F+	TLC/GC	VIII

(a) M is male, F is female.
(b) M is muscle, L is liver, K is kidney, F is fat, + is other tissues.

The results of three pig studies using the TLC method are given in tables IV, V and VI.

Table IV. Total Residues (in ppm) of Olaquindox in Pigs Receiving 100 ppm and 160 ppm Olaquindox in the Feed (TLC Method)

The pigs were fed either 100 ppm or 160 ppm Olaquindox in the feed for 20 weeks. The animals were slaughtered in pairs, 1 female and 1 male, at intervals after the Olaquindox was withdrawn. (Medenwald, H and Gericke, H, 1974, Bayer Pharm report 4753).

Withdrawal Time (hours)	Muscle		Liver		Kidney	
	M	F	M	F	M	F
100 ppm in feed						
6	0.5	0.3	0.5	0.3	2.3	1.8
12	0.1	0.1	0.1	0.1	0.3	0.3
24	ND	ND	ND	ND	TR	TR
48			(All tissues ND)			
160 ppm in feed						
6	0.7	0.7	0.7	0.6	2.4	3.4
12	0.3	0.3	0.3	0.2	1.1	1.0
24	TR	TR	TR	TR	0.2	0.1
48 and 96			(All tissues ND)			

M is male, F is female, TR is trace amount (ca. 0.1 ppm), ND is not detectable (<0.1 ppm).

Table V. Total Residues (in ppm) of Olaquindox in Pigs Receiving 250 ppm Olaquindox in the Feed. (TLC Method)

Four pigs were fed 250 ppm Olaquindox in the feed for 30 days. The animals were slaughtered in pairs, at 17 and 41 hours after the Olaquindox was withdrawn. (Bories, G and Bourdon, D., 1977, Document 77/8813, Bayer)

Withdrawal Time (hours)	Muscle	Liver	Kidney	Fat
17	0.4, 0.6	1.4, 1.1	2.0, 2.4	0.1, 0.1
41	0.1, 0.1	0.1, 0.1	0.2, 0.3	0.1, 0.1

Table VI. Total Residues (in ppm) of Oliquindox in Pigs Receiving 20 ppm and 45 ppm Olaquindox in the Feed. (TLC Method)

Three groups of 6 male and 6 female pigs per group were fed either 0, 20 or 45 ppm Olaquindox in the feed per group for the whole fattening period. 2 females and 2 males from each group, were slaughtered and sampled at intervals of 6, 12 and 24 hours after the Olaquindox was withdrawn. (Liebetseder, J., 1980, Bayer Document 80/100225).

Withdrawal Time (hours)	Muscle		Liver		Kidney	
	M	F	M	F	M	F
20 ppm in feed						
6	0.16	0.13	0.14	0.14	0.30	0.25
12	ND	ND	ND	ND	0.1	0.1
24			(All tissues ND)			
45 ppm in feed						
6	0.23	0.25	0.18	0.18	0.31	0.26
12	0.09	0.09	0.11	0.10	0.19	0.17
24			(All tissues ND)			

Each value is the mean value for 2 pigs. M is male, F is female, ND is not detectable (<0.1 ppm). No residues were found in any fat sample.

The results of a study using 13 pigs fed 10 ppm Olaquindox in their feed and analysing the residues by an HPLC method are given in table VII.

Table VII. Total Residues (in ppm) of Olaquindox in Pigs Receiving 10 ppm Olaquindox in the Feed. (HPLC Method).

Pigs were fed 10 ppm Olaquindox in the feed for the whole fattening period. The animals were slaughtered in threes at 4, 8 and 12 hours after the Olaquindox was withdrawn. (Andersson, B. and Szabo, A. 1982, Bayer Document 82/10585, Report SLL 20).

Withdrawal Time (hours)	Muscle	Liver	Kidney
4	0.03;0.03;0.03	0.03;0.03;0.03	0.17;0.17;0.16
8	0.02;0.03; NM	0.01;0.01;0.02	0.19; NM ; NM
12	All <0.01	0.01;<0.01;<0.01	NM ; NM ; NM

NM = not measured. The limit of detection was 0.01 ppm.

The results of two studies in pigs with analysis of the residues by a GC/TLC method are shown in table VIII.

Table VIII. Total Residues (in ppm) of Olaquindox in Pigs Recieving 75 or 150 ppm Olaquindox in the Feed. (TLC/GC METHOD).

Pigs were fed 75 or 150 ppm Olaquindox in the feed for 12-13 weeks. The animals were slaughtered at different intervals, 0.5-72 hours, after the Olaquindox was withdrawn.

Withdrawal Time (hours)	Number Pigs	Muscle	Liver	Kidney	Fat	Blood
75 ppm in feed for 13 weeks						
0.5	1	ND	0.05	0.04	ND	ND
24	1	ND	ND	ND	ND	ND
150 ppm in feed for 12 weeks						
0.5	2	0.15	0.13	0.41	ND	0.12
8	2	ND	ND	0.07	ND	ND
24 & 72	2+2	ND	ND	ND	ND	ND

ND is not detectable (<0.02 ppm).

In a third study, 2 male and 2 female pigs were fed 100 and 150 ppm Olaquindox in the feed for 30 weeks and slaughtered 24 and 72 hours after the withdrawal of the Olaquindox. No residues were detected (detection limit 0.02 ppm) in muscle, liver, kidney, fat, heart, small intestine and blood. (Takase, I and Komachi, S., 1976, Bayer document 76/8508)

Summary of Results

In these studies the residues were extracted and reduced to compound VII which contains the -CO-NH-CH2-CH2-OH side chain, thus the small amount of residues, <5%, with the carboxyl group ending would not be measured. The residues are in general agreement between the studies using either the TLC method or the HPLC method. The results from the TLC/GC method give values much lower than the others. This is difficult to explain as the TLC/GC method is more sensitive and claims very high recoveries.

It was not possible to measure residues in the tissues at withdrawal times longer than 48 hours. This is because the chromatographic methods were not sensitive enough. Unfortunately the earliest withdrawal time measured for pigs in the radiometric study was 48 hours and so it is not possible to directly compare the results of the two studies.

Bound Residues/Bioavailability

No bioavailability studies were carried out by the sponsor. It must be assumed until proved otherwise that all the residues of Olaquindox are bioavailable. Since the residues are likely to contain Olaquindox as a major component and also several closely related metabolites there is good reason to believe that most of the residues are bioavailable.

METHODS OF RESIDUE ANALYSIS

Analysis after in-feed Administration of Olaquindox

The methods for measuring residues in pigs were either a radiometric method using 14C-Olaquindox or chromatographic methods. All the methods measured only the total residues and no data are provided for the concentrations of the individual metabolites.

Thin-Layer Chromatography (TLC) Analysis

A method was developed for the determination of Olaquindox and it's metabolites in aqueous extracts of pig tissues. Pig tissues were homogenised and extracted with water. The water phase was washed with a lipophilic solvent, hexane, and reduced with ferrous sulphate. The product, VII, was formed from Olaquindox and those metabolites containing the -CO-NH-CH_2-CH_2-OH side chain. VII was separated on two dimensional TLC and the spot containing VII was scraped from the plate, eluted with methanol and the extinction measured at 240 nm (Medenwald, 1974, Bayer Pharm. report 4751).

The method is sensitive to about 100 ppb (100 μg/kg). The recoveries are variable and depend on the metabolite profile. The recovery of Olaquindox is about 40-60% with the widest variation in kidneys, e.g. the recovery of 100 ppb added to pig kidneys was 34-59%

High Performance Liquid Chromatography (HPLC) Analysis

The HPLC method was developed in Sweden (Bayer Report. SLL 20) in 1981. Extraction from tissues followed by reduction with ferrous ions was carried out acording to the Medenwald method but instead of purification by TLC the extract was purified on a minicolumn and the amount of VII determined by HPLC.

The dried reduced extract from the tissues was disolved in 2 ml water and the solution put on SepPak C18 Waters minicolumn. The water eluates were discarded and the fraction containing VII was eluted from the column with 3 ml methanol:water, 1:1. An aliquot of the eluate was run on a 250 x 3.2 mm Spherisorb column. The eluting solvent is not named but thought to be methanol:water, 1:1. The peak at 240 nm corresponding to VII was identified and the amounts of VII determined from the area of the peak.

The method is claimed to be more reliable than the TLC method although the recoveries were much lower (30-37% with CV 20-24%). The lower limit of sensitivity was 10 ppb.

TLC/Gas Chromatography (GC) Analysis

The method was developed in Japan in 1975 by Takase and Kimosho at the Agric. Chem. Institute, Nihon Tokushu Noyaku Seizo K.K. (report NTN-045). Potassium carbonate was added to tissues and the mixture macerated and extracted with acetonitrile. The acetonitrile was evaporated and the residue disolved in n-hexane. The parent compound and metabolites were extracted with water and reduced with ferrous sulphate. Product VII was extracted with chloroform and cleaned up by TLC. The spot corresponding to VII was scraped from the plate, extracted with methanol, silylated and

the VII silyl ether determined on GC. The column was 100 cm x 3 mm packed with 10% silicone DC-200 on Gas-Chrom Q and the detector was an alkali flame ionisation detector. The amounts of VII-derivative were determined from the peak area compared with that of external standards. The lower limit of sensitivity of the method was claimed to be 20 ppb but under standard operaring procedures was 40 ppb. Recoveries were determined up to the end of the TLC procedure. When 200 ppb was added as a spike the recoveries were 84% in blood, 70% in liver, 81% in kidney and 57% in muscle. Three pig studies were carried out (see table III) and the results are reported in table VIII.

APPRAISAL

The total residues were measured using radiolabelled drug and following the residues during a 2-28 day withdrawal period. However none of the metabolites were identified and it was not possible to determine a marker compound for the residues. The residues were determined in many studies using chromatographic methods of analysis; but these methods did not measure all the residues and were not sensitive enough to measure residues in tissues sampled more than 48 hours after withdrawal of the drug when it can seen from the radiometric study that residues persisted for at least two weeks in most tissues.

No MRL can be recommended until a tissue depletion study is carried out to characterise the nature and amount of the residues in tissues and to identify a suitable marker substance.

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