IPRONIDAZOLE

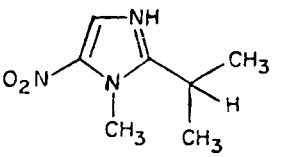
IDENTITY

Chemical name: 2-isopropyl-1-methyl-5-nitroimidazole

1-methyl-2-(1-methylethyl)-5-nitro-1H-imidazole

Synonyms: Ipropran

Structural formula:



Molecular formula: $C_7H_{11}N_3O_2$

Molecular weight: 169.18

OTHER INFORMATION ON IDENTITY AND PROPERTIES

Pure active ingredient:

Appearance: white plates

Melting point: 60°C

(Windholz, 1983)

RESIDUES IN FOOD AND THEIR EVALUATION

CONDITIONS OF USE

General

Ipronidazole is used in turkeys (1) for the prevention and treatment of blackhead (histomoniasis) and (2) for increased rate of weight gain and improved feed efficiency.

The use of the drug for controlling and treating swine dysentery has also been reported. (Messersmith, et al., 1973)

Dosages

Ipronidazole is administered through the feed at levels of approximately 0.00625% (prevention) to 0.025% (treatment). In addition, the drug may be given via the drinking water at 0.0125% to turkeys already receiving 0.00625% in the feed for treatment purposes.

Continuous feeding of ipronidazole at a concentration of 100 g/ton in feed has been shown to prevent swine dysentery. Administration of ipronidazole at 200 to 800 mg/gal of drinking water for seven days was claimed to be effective in treating swine dysentery. (Messersmith, et al., 1973)

RADIOLABELED RESIDUE DEPLETION STUDIES

Turkeys

Two 14-week-old turkeys were pretreated from 1 day of age to 14 weeks of age with a medicated feed containing 0.00625% ipronidazole. A single oral capsule of 20 mg of ipronidazole-2-14C (equivalent to 0.00625% in the feed) was administered to each turkey at 14 weeks of age. The turkeys were sacrificed at 5 days of withdrawal. The average concentration of total radioactivity (ppb) in the edible tissues of treated birds were: breast muscle, 64.85; leg and wing muscle, 71.21; liver 285.40; kidney, 257.72; fat, 24.81; and skin/fat, 92.18. (Laurencot, et al., 1977)

Bioavailability of Turkey Tissue Residue in Rat

The liver or the muscle tissue from the birds of the study described above was lyophilized and pelleted and fed to rats. The liver tissue had a concentration of total residue expressed as ipronidazole equivalents of 0.96 ppm and the muscle, 0.22 ppm. Rat urine, bile, and feces were collected for 24 before treatment, during the 24-hour treatment period on turkey tissue, and for 24 hours after treatment. The rats were killed 24 hours after treatment and the carcass, liver, GI tract, and GI tract contents were taken for assay of total radioactivity.

For rats treated with lyophilized and pelleted turkey liver tissue, an average of 56% of the radioactivity was found in the feces and 0.36% in the contents of the GI tract, for a total of 56.36% as non-absorbed radioactivity. An average of 2.77% was found in the bile, 3.11% in the carcass, 0.25% in the GI tract tissue, 0.42% in the liver and 42.8% in the urine, for a total of 49.35% as absorbed radioactivity from liver tissue. Total recovery averaged 105.71%. (Laurencot, et al., 1977)

For rats treated with lyophilized and pelleted muscle tissue, an average of 23.3% of the radioactivity was found in the feces and 0.38% in the contents of the GI tract, for a total of 23.68% as non-absorbed radioactivity. An average of 5.96% was found in the bile, 8.23% in the carcass, 0.51% in the GI tract tissue, 0.73% in the liver and 52.35% in the urine, for a total of 67.78% as absorbed radioactivity from muscle tissue. Total recovery averaged 91.46%. (Laurencot, et al., 1977)

Swine

A 4-week-old, 7 kg male pig was treated with a single oral capsule of ipronidazole-2-14C at 43.11 mg (equivalent to 0.0126% in the feed). The pig was sacrificed at 5 days of withdrawal and tissue samples were taken for radioassay by combustion analysis. Total residue concentrations (ppb) in the edible tissues were: muscle, 41.1; liver, 192.7; kidney, 189.5; fat, 20.6; and skin, 36.3. (Laurencot, et al., 1978)

Bioavailability of Swine Tissue Residue in Rat

The liver tissue from the pig of the study described above was lyophilized and fed to 4 rats. The liver tissue had a concentration of total residue expressed as ipronidazole equivalents of 0.62 ppm. Over the collection period of the experiment, an average of 45.61% of the radioactivity was found in the feces and 0.09% in the GI tract contents, for a total of 45.70% as non-absorbed radioactivity. An average of 1.72% was found in the bile, 0.13% in the GI tract tissue, 0.52% in the liver and 42.54% in the urine, for a total of 44.91% as absorbed radioactivity from liver tissue. Total recovery averaged 90.61%. (MacDonald, 1977a)

RESIDUE DEPLETION STUDIES

Turkeys

Nine-week-old turkeys were placed on feed medicated with ipronidazole at the 0.00625% level for 12 weeks. Birds were sacrificed after a withdrawal period of 0, 1, 2, 3, 4, 5 or 6 days. The concentration of ipronidazole and the hydroxy metabolite, 1-methyl-2-

(2'-hydroxyisopropyl)-5-nitroimidazole (HIP), was determined in the tissues of ten birds at each withdrawal period. Assays were done using gas chromatography (GC) with electron capture detection specific for each compound to 2 ppb. No ipronidazole was detectable in tissues of the treated turkeys. The concentrations of HIP (ppb) are given in Table I. No HIP was detected in any edible tissue beyond 4 days post dosing. (Kaykaty, 1969; MacDonald, et al., 1971)

Table I. Concentration of HIP in Turkeys Dosed with 0.00625% Ipronidazole in the Feed (ppb)

Withdrawal Time (days)	Muscle	Liver	Kidney	Skin/Fat
0	64.2	ND	ND	90
1	21.5	ND	ND	8.5
2	1.2	ND	ND	3.6
3	ND	ND	ND	2.0
4	ND	ND	ND	ND

ND = not detected

Male turkeys which were 24-weeks old received ipronidazole in the drinking water at a dose of 0.0125% for seven days. Birds were sacrificed at zero withdrawal and at days 1 through 9 of withdrawal. The concentration of ipronidazole and HIP was determined in the tissues of five birds at each withdrawal time. The concentrations of ipronidazole and HIP (ppb) are shown in Table II. No residues of ipronidazole were observed beyond the 1-day withdrawal and none of HIP beyond the fourth day of withdrawal. Analyses were done with the GC procedure sensitive to 2 ppb. (Fellig, et al., 1971)

Table II. Concentrations of Ipronidazole and HIP in Turkeys Treated With 0.0125% Ipronidazole in the Drinking Water (ppb)

		Ipronidazole		
Withdrawal Time (days)	Muscle	Liver	Kidney	Skin/Fat
0	0.9	ND	ND	52.0
1	ND	ND	ND	0.8

		HIP		
Withdrawal Time (days)	Muscle	Liver	Kidney	Skin/Fat
0	24.5	ND	ND	35.5
1	8.0	ND	ND	22.1
2	0.6	ND	ND	5.5
3	0.4	ND	ND	4.2
4	ND	ND	ND	0.4

ND = not detected

Male turkeys, 24 weeks of age, received ipronidazole at a dose of 0.025% (therapeutic level) in the feed for seven days. Birds were sacrificed at zero withdrawal and at days 1 through 9 of withdrawal. The concentration of ipronidazole and HIP was determined in the tissues of five birds at each withdrawal time. The concentrations of ipronidazole and HIP (ppb) are shown in Table III. No residues of ipronidazole were observed beyond the 1-day withdrawal and none of HIP beyond the second day of withdrawal. Analyses were done with the GC procedure sensitive to 2 ppb. (Fellig, et al., 1972a)

Table III. Concentrations of Ipronidazole and HIP in Turkeys Treated With 0.025% Ipronidazole in the Feed (ppb)

	Ipronidazole			
Withdrawal Time (days)	Muscle	Liver	Kidney	Skin/Fat
0	1.4	ND	ND	115.0
1	ND	ND	ND	0.5
	HIP			
Withdrawal Time (days)	Muscle	Liver	Kidney	Skin/Fat
0	106.8	ND	ND	66.2
1	17.7	ND	ND	19.9
2	ND	ND	ND	0.6

ND = not detected

Fifty-four 18-week-old turkeys, mixed as to sex, received ipronidazole at 0.00625% in the feed for four weeks, followed by drug at 0.0625% (10 times the recommended use level) for two days. Birds were sacrificed at zero withdrawal and at days 1 through 6 of withdrawal. The concentration of ipronidazole and HIP was determined in the tissues of five birds at each withdrawal time. The concentrations of ipronidazole and HIP (ppb) are shown in Table IV. No residues of ipronidazole were observed beyond the 1-day withdrawal and none of HIP beyond the third day of withdrawal. Analyses were done with the GC procedure sensitive to 2 ppb. (Fellig, et al., 1972b)

Table IV. Concentrations of Ipronidazole and HIP in Turkeys Treated With Ipronidazole at 0.0625% in the Feed (ppb)

	Ipronidazole			
Withdrawal Time (days)	Muscle	Liver	Kidney	Skin/Fat
0	10.2	ND	ND	8.2
1	ND	ND	ND	1.6
	HIP			
Withdrawal Time (days)	Muscle	Liver	Kidney	Skin/Fat
0	1185.5	ND	ND	957.3
1	113.0	ND	ND	152.4
2	0.8	ND	ND	2.2
3	ND	ND	ND	0.8

ND = not detected

Fifty 18-week-old male and female turkeys were administered 0.00625% ipronidazole via the feed for seven weeks and 0.0125% ipronidazole via the drinking water for the last seven days of the seven-week period. Birds were sacrificed at zero withdrawal and at days 1 through 7 of withdrawal. The concentration of ipronidazole and HIP was determined in the tissues of five birds at each withdrawal period. The concentrations of ipronidazole and HIP (ppb) are given in Table V. No residues of ipronidazole were observed beyond 1 day of withdrawal and none of HIP beyond the second day of withdrawal. Analyses were done with the GC procedure sensitive to 2 ppb. (Fellig, et al., 1972c)

Table V. Concentrations of Ipronidazole and HIP in Turkeys Treated With Ipronidazole in the Feed and Drinking Water (ppb)

	Ipronidazole			
Withdrawal Time (days)	Muscle	Liver	Kidney	Skin/Fat
0	0.6	ND	ND	96.9
1	ND	ND	ND	0.3

	HIP			
Withdrawal Time (days)	Muscle	Liver	Kidney	Skin/Fat
0	141.5	ND	ND	172.4
1	0.9	ND	ND	3.3
2	ND	ND	ND	0.6

ND = not detected

Swine

Eighteen 5-week-old pigs received 200 g/ton ipronidazole through the feed for 6 weeks. Three animals were sacrificed at 0, 3, 4, 5, 6 and 7 days of withdrawal. Samples of muscle, liver, kidney and fat were collected and assayed for ipronidazole and HIP with a GC procedure sensitive to 50 ppb for each compound. No residues of ipronidazole were found in any of the edible tissues. Residues of HIP averaged 327 ppb in muscle and 47 ppb in fat at 0 withdrawal; otherwise, no residues of HIP were observed in any edible tissue at any withdrawal time. (MacDonald, 1969)

Eighteen 5-week-old pigs received 100 g/ton ipronidazole through the feed for 6 weeks. Three animals were sacrificed at 0, 2, 3, 4, 5 and 6 days of withdrawal. Samples of muscle, liver, kidney and skin/fat were collected and assayed for ipronidazole and HIP with a GC method sensitive to 2 ppb for each compound. Residues of ipronidazole averaged 1.6 ppb in skin/fat and 0.5 ppb in muscle at 0 withdrawal; otherwise, none was detected in any tissue sample at any withdrawal time. Residues of HIP averaged 77 ppb in skin/fat and 167.5 ppb in muscle at 0 withdrawal; otherwise, none was detected in any sample at any withdrawal time. (Kaykaty, 1970)

Twenty 7-week-old pigs, equally mixed as to sex, were placed on feed containing 100 g/ton ipronidazole for 14 weeks. Three animals were sacrificed on each of days 0 through 5 of withdrawal. Samples of liver, kidney, internal fat, subcutaneous fat, thigh muscle and loin muscle were collected for analysis with the GC procedure having a sensitivity of 2 ppb. At 0 withdrawal, residues of ipronidazole averaged 2.8 ppb in loin muscle, 1.4 ppb in thigh muscle, 1.9 ppb in subcutaneous fat and 3.4 ppb in internal fat. At zero withdrawal, residues of HIP were 43.2 ppb in loin muscle, 29.8 ppb in thigh muscle, 15.5 ppb in subcutaneous fat and 7.1 ppb in internal fat. No other samples at any withdrawal time contained detectable residues of ipronidazole or HIP. (Fellig, et al., 1973a) (Fellig, et al., 1975)

Twenty-three pigs, mixed as to sex and averaging 77.6 kg, were treated with ipronidazole through an oral aqueous solution at 44 mg/kg body weight for 7 consecutive days (equivalent to 7 to 15 times the dose expected via 100 g/ton in the feed). Three animals were sacrificed on each of withdrawal days 0 through 6 and two were killed on day 7 of withdrawal. Samples of liver, kidney, skin/fat, internal fat, thigh muscle and loin muscle were taken for analysis with the GC procedure sensitive to 2 ppb. The results of the analyses are shown in Table VI. No residues of ipronidazole or HIP were found in any tissues beyond 5 days of withdrawal. (Fellig, et al., 1973b) (Fellig, et al., 1975)

Table VI. Concentrations of Ipronidazole and HIP in Swine Treated With Ipronidazole Via An Oral Aqueous Solution (ppb)

Ipronidazole

Withdrawal Time (days)	Thigh Muscle	Loin Muscle	Liver	Kidney	Skin Fat	Int. Fat
0	448.1	433.4	ND	5.4	545.9	843.5
1	98.9	69.0	ND	1.7	20.3	55.1
2	9.3	5.6	ND	0.9	10.3	32.0
3	1.2	ND	ND	ND	2.4	3.6
4	7.5	ND	ND	ND	2.4	1.7
5	ND	ND	ND	ND	ND	2.0

HIP

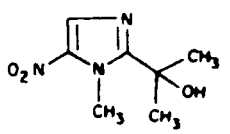
Withdrawal Time (days)	Thigh Muscle	Loin Muscle	Liver	Kidney	Skin Fat	Int. Fat
0	4913.3	3296.0	ND	2.1	934.4	2064.0
1	72.0	196.0	ND	ND	64.6	74.4
2	4.4	11.4	ND	ND	19.1	5.6
3	1.1	ND	ND	ND	1.3	ND
4	0.5	ND	ND	ND	1.2	ND

ND = not detected

METABOLISM STUDIES

Turkeys

The only two drug-related compounds identified in the tissues of turkeys administered ipronidazole are parent ipronidazole and the hydroxy-isopropyl metabolite (1-methyl-2-(2'-hydroxyisopropyl)-5-nitroimidazole, HIP) formed by oxidation of the alkyl group at the 2-position of ipronidazole. The structure of HIP, shown below, was reported to be deduced from infrared spectroscopy, nuclear magnetic resonance, ultraviolet spectroscopy and mass spectrometry, and confirmed by comparison to a synthesized standard. Unchanged drug and HIP account for about 40% of the excreted dose. The remaining metabolites are highly water-soluble and cannot be extracted into organic solvents before or after enzymic hydrolysis. (Fellig, et al., 1969) (Weiss, et al., 1981)



1-methyl-2-(2'-hydroxyisopropyl)-5-nitroimidazole, HIP

Swine

A 4-week-old, 7 kg male pig was treated with a single oral dose of ipronidazole-2-14C at 43.11 mg (equivalent to 0.0126% in the feed). Five days following treatment 97.9% of the radioactivity had been recovered in the urine, feces and tissues. A breakdown of the total residue in edible tissues by extractability is given in Table VII. Approximately 31 to 71% of the residue in edible tissues is water soluble. Moreover, none of the radioactivity of gut contents, which comprised 53.3% of the total recovered radioactivity, was benzene extractable, indicating that ipronidazole and HIP were not present. Of interest also, approximately 29 to 68% of the residue in edible tissues was unextractable. The unextractable residue may reflect covalent binding (bound residue) or incorporation of fragments from ipronidazole into natural components. No metabolites were identified in this study. (Laurencot, et al., 1978)

Table VII. The Concentration and Distribution of Radioactivity of RO 7-1554-2^{14}C and Its Possible Metabolites in the Benzene Soluble, Water Soluble and Insoluble Residue Fractions of the Edible Tissues of a Four Week Old Male Cross Bred Chester White Swine Five Days after Treatment

	Treated Tissues		Control Tissues	
	µg	ppb	Minimal Detectable ppb	Background Count Error ppb
Fat				
Benzene soluble	0.5473	2.9518	0.0287	0.0197
H_2O soluble	1.4274	7.6989	0.9741	0.6703
Insoluble residue	1.8456	9.9547	0.0480	0.0330
Kidney				
Benzene soluble	0.0020	0.0512	0.1320	0.0906
H_2O soluble	5.1104	129.4420	2.3255	1.5874
Insoluble residue	2.3706	60.0448	0.0750	0.0515
Liver				
Benzene soluble	0.0291	0.1046	0.0486	0.0335
H_2O soluble	38.0718	136.9489	1.0541	0.7244
Insoluble residue	15.4623	55.6198	0.0304	0.0209
Muscle				
Benzene soluble	0.9032	0.4756	0.0508	0.0349
H_2O soluble	24.0375	12.6580	1.6148	1.0956
Insoluble residue	53.1060	27.9652	0.1187	0.0816
Skin				
Benzene soluble	2.3392	2.0934	0.0512	0.0351
H_2O soluble	15.4286	13.8076	2.0257	1.3920
Insoluble residue	22.7530	20.3624	0.1110	0.0763
Blood				
Benzene soluble	0.0180	0.0704	-	-
H_2O soluble	12.1249	47.5487	-	-
Insoluble residue	1.1192	4.3890	-	-

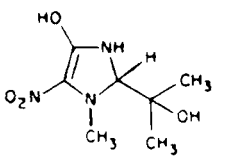
Ipronidazole-2-14C was incubated with a fortified swine liver microsome preparation under aerobic and anaerobic conditions. The benzene soluble metabolites, both before and after glusulase (a preparation of beta-glucuronidase and sulfatase) incubation, were separated by paper chromatography, identified by radiochromatogram scanning, and quantified by

sample oxidation and liquid scintillation counting. The only metabolite found in the benzene extracts of the aerobic incubation was HIP, with 31.2% being free and 3.8% conjugated. Neither ipronidazole nor HIP was found in the benzene extracts of the anaerobic system containing FAD (a nitro-reduction enhancer) either before or after glusulase incubation. (Laurencot, et al., 1975)

Rats

In two separate studies, it was observed that following a single intraperitoneal dose of 20.5 mg/kg ipronidazole-2-14C, the urine of treated rats contained about 30% of the administered radioactivity, the feces, approximately 58%, and expired air, about 3% of $14CO_2$. Only 0.5% of the treatment radioactivity was benzene extractable from the urine and 1.0% benzene extractable from the feces before and after glusulase incubation. Paper and thin layer chromatography of the whole urine, and water and benzene extracts of the feces indicated that neither ipronidazole nor HIP was present. It was concluded that the radioactivity remaining at the origin in the chromatograms indicates the polar nature of the components and that the production of $14CO_2$ demonstrated the opening of the imidazole ring structure. (MacDonald, 1977b)

A novel metabolite was identified in the water soluble extract of feces of bile-cannulated rats. Fasted female rats with stomach cannulae were treated with ipronidazole-2-14C at 20 mg/kg for 4 days. The results show that 71% of the radioactivity in feces (the feces comprise 31% of the total administered activity) was water soluble. By a number of analytical techniques, including nuclear magnetic resonance, infrared spectroscopy, and mass spectrometry, about 34% of the water extractable fecal metabolites was identified as 2,3-dihydro-2-(2'-hydroxyisopropyl)-3-methyl-4-nitro-1H-imidazol-5-ol (see structure below). Approximately 15% of the total dose in cannulated rats was isolated as this water soluble metabolite. (Weiss, et al., 1978) (Weiss, et al., 1981)



2,3-dihydro-2-(2'-hydroxyisopropyl)-3-methyl-
4-nitro-1H-imidazol-5-ol

METHODS OF RESIDUE ANALYSIS

The earliest procedure for the residue analysis of ipronidazole in edible tissues relied on pulse polarography and gas chromatography. The method had a sensitivity of 50 ppb for unchanged ipronidazole and the hydroxy metabolite, HIP. (MacDonald, et al., 1969)

An improved gas chromatographic procedure lowered the level of sensitivity for each of the analytes in edible tissues of treated swine and turkeys to 2 ppb. The initial tissue extraction with benzene is followed by silica gel column clean-up and concentration. The column eluate is divided for individual extraction procedures followed by a gas chromatographic assay using electron capture detection specific for each compound. This method is accepted as the approved regulatory assay by the United States Food and Drug Administration. (MacDonald, et al., 1971) (FDA, 1988)

Subsequently, two procedures relying on mass spectrometric (MS) techniques were put forth to confirm the identity of ipronidazole and HIP in edible tissues of turkeys. In the first method, tissue is processed according to the procedures outlined for the electron capture-GC regulatory assay. Portions of the resulting benzene extracts are then analyzed by GC-MS using selective ion detection. For ipronidazole the m/e 169 molecular ion and the m/e 123 fragment ion are monitored, while for HIP the mass spectrometer is set to collect the m/e 185 molecular ion and the m/e 128 fragment ion. (Garland and Gonzales, 1975)

In the second method, portions of the benzene extract from the tissue work-up are also analyzed using selective ion monitoring. Methane is used both as the GC carrier gas and negative chemical ionization reagent gas. For the determination of ipronidazole and HIP, molecular ions at m/e 169 and 185, respectively, are monitored in the GC effluent. Deuterated analogues of ipronidazole and HIP are added at the 2 ppb level to tissue before

processing as described in the paragraph above to establish the retention times, extraction efficiencies, mass spectral responses and chromatographic peak shapes of both ipronidazole and HIP. (Garland, et al., 1980)

For a variety of reasons, including lack of sufficient recovery data, severe interferences, and inadequacy of single ion monitoring, neither of the above methods was found acceptable

APPRAISAL

The use of ipronidazole at permitted concentrations in the feed and drinking water of turkeys produces residues that deplete below detectable levels at 3 to 4 days post dosing. The assay used in the depletion studies had a sensitivity of 2 ppb for ipronidazole and the hydroxy metabolite, HIP.

Tissues of swine treated with ipronidazole through the feed at the recommended level of 100 g/ton were free of detectable residues at one day of withdrawal. Tissues of swine treated with a therapeutic dose of ipronidazole via an aqueous oral solution were free of residues at 6 days of withdrawal. The assay used in these studies was also sensitive to 2 ppb for ipronidazole and HIP.

Although the residue depletion studies in turkeys show that residues in edible tissues fall below 2 ppb in 3 to 4 days, the radiotracer work demonstrates that at 5 days of withdrawal the total residue ranges from 24.8 ppb in fat to 285.4 ppb in liver and to 257.7 ppb in kidney . Likewise, the total residue in swine at 5 days of withdrawal ranges from 20.6 ppb in fat to 192.7 ppb in liver and to 189.5 ppb in kidney. The residue depletion data taken as a whole are insufficient for establishing a relationship between the total residue and a compound (ipronidazole and/or HIP) measured with a chemical assay.

The metabolism work that has been done supports the proposed pathways that characterize the 5-nitroimidazoles. In particular, oxidation occurs at the 2-alkyl group; reduction can take place in the 5-nitro group; scission of the molecule occurs, with fragmentation of the imidazole ring; and incorporation of the fission products into natural tissue components proceeds to some degree. It is also possible that bound residues form, and this must be taken into account during the safety evaluation.

REFERENCES

Fellig, J., MacDonald, A., Meseck, E. and Laurencot, H. (1969). The metabolism of ipronidazole in the turkey. Poultry Sci., 48, 1806.

Fellig, J., Kaykaty, M., Gonzales, L., Duke, M.J. and Hecht, B.R. (1971). Clearance of ipronidazole in the turkey following administration at therapeutic levels in the drinking water. Unpublished report submitted to FAO by Hoffmann-LaRoche, Inc., Nutley, New Jersey.

Fellig, J., Kaykaty, M., Gonzales, L., Duke, M.J. and Hecht, B.R. (1972a). Clearance of ipronidazole in the turkey following administration at therapeutic levels in the feed. Unpublished report submitted to FAO by Hoffmann-LaRoche, Inc., Nutley, New Jersey.

Fellig, J., Kaykaty, M., Gonzales, L. and Eisenbeis, H.G. (1972b). Clearance of ipronidazole in the turkey following administration at 0.0625% in a premix concentrate. Unpublished report submitted to FAO by Hoffmann-LaRoche, Inc., Nutley, New Jersey.

Fellig, J., Kaykaty, M., Gonzales, L., Duke, M.J. and Hecht, B.R. (1972c). Clearance of ipronidazole in the turkey following administration in feed and drinking water. Unpublished report submitted to FAO by Hoffmann-LaRoche, Inc., Nutley, New Jersey.

Fellig, J., Kaykaty, M., Gonzales, L. and Eisenbeis, H.G. (1973a). Clearance of ipronidazole in swine following administration in feed at 100 g/ton. Unpublished report submitted to FAO by Hoffmann-LaRoche, Inc., Nutley, New Jersey.

Fellig, J., Kaykaty, M., Gonzales, L. and Eisenbeis, H.G. (1973b). Clearance of ipronidazole soluble powder in swine. Unpublished report submitted to FAO by Hoffmann-LaRoche, Inc., Nutley, New Jersey.

Fellig, J., Kaykaty, M., Gonzales, L., Eisenbeis, H.G. and Messersmith, R.E. (1975). Elimination of ipronidazole from the tissues of swine. Vet. Med./Small Animal Clinician, 70, 31-34.

Food and Drug Administration (1988). Code of Federal Regulations, 21, 477-481.

Garland, W.A. and Gonzales, L. (1975). Determination of ipronidazole (Ro 7-1554) and its metabolite (Ro 7-7916) in turkey tissue utilizing combined gas chromatography, mass spectrometry, and selective ion detection. Unpublished report submitted to FAO by Hoffmann-LaRoche, Inc., Nutley, New Jersey.

Garland, W.A., Hodshon, B.J., Chen, G., Weiss, G., Felicito, N.R. and MacDonald, A. (1980). Determination of ipronidazole and its principal metabolite in turkey skin and muscle by combined gas chromatography-negative chemical ionization mass spectrometry-stable isotope dilution. J. Agric. Food Chem., 28, 273-277.

Kaykaty, M. (1969). Tissue clearance of ipronidazole in turkeys. Unpublished report submitted to FAO by Hoffmann-LaRoche, Inc., Nutley, New Jersey.

Kaykaty, M. (1970). Tissue clearance of Ro 7-1554 and its metabolite Ro 7-7916 in swine. Unpublished report submitted to FAO by Hoffmann-LaRoche, Inc., Nutley, New Jersey.

Laurencot, H.J., Rose, N.K. and Kohut, J. III. (1975). In vitro metabolism of ipronidazole-2-14C by swine liver microsomes. Unpublished report submitted to FAO by Hoffmann-LaRoche, Inc., Nutley, New Jersey.

Laurencot, H.J., Crowley, C.A., Gonzales, L. and Campbell, J.S. (1977). The disposition and bioavailability of ipronidazole-2-14C-derived radioactivity in turkeys. Unpublished report submitted to FAO by Hoffmann-LaRoche, Inc., Nutley, New Jersey.

Laurencot, H., Kohut, J. III and Rose, N. (1978). The disposition of ipronidazole-derived radioactivity in swine. Unpublished report submitted to FAO by Hoffmann-LaRoche, Inc., Nutley, New Jersey.

MacDonald, A. (1969). Tissue clearance of Ro 7-1554 and its metabolite Ro 7-7916 in swine. Unpublished report submitted to FAO by Hoffmann-LaRoche, Inc., Nutley, New Jersey.

MacDonald, A., Castro, E., Chen, G. and Hopkins, P. (1969). Residue methodology and tissue clearance of histomonastat ipronidazole in turkeys. Poultry Sci., 48, 1837.

MacDonald, A., Chen, G., Kaykaty, M. and Fellig, J. (1971). Residue analysis of ipronidazole and its metabolite at the 2 ppb level in turkey tissue. J. Agric. Food Chem., 19, 1222-1227.

MacDonald, A. (1977a). August 17,1977, Status report: studies involving the elucidation of ipronidazole metabolism and disposition. Unpublished report submitted to FAO by Hoffmann-LaRoche, Inc., Nutley, New Jersey.

MacDonald, A. (1977b). March 10, 1977, Status report: studies involving the elucidation of ipronidazole metabolism and disposition. Unpublished report submitted to FAO by Hoffmann-LaRoche, Inc., Nutley, New Jersey.

Messersmith, R.E., Oetjen, K.B., Hussey, F.J. and Kanning, H.H. (1973). Effect of ipronidazole on swine dysentery. Vet. Med./Small Animal Clinician, 68, 1021-1033.

Weiss, G., Rose, N. and Duke, P. (1978). Isolation and identification of a major water soluble rat fecal metabolite of ipronidazole. Unpublished report submitted to FAO by Hoffmann-LaRoche, Inc., Nutley, New Jersey.

Weiss, G., Rose, N., Duke, P. and Williams, T.H. (1981). A major rat faecal metabolite of ipronidazole. Xenobiotica, 11, 207-215.