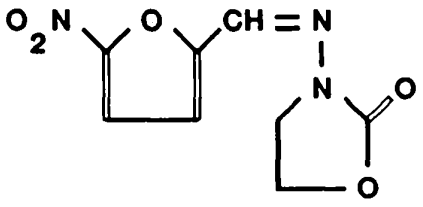
FURAZOLIDONE

IDENTITY

Chemical name: 3-[[(5-nitro-2-furanyl)methylene]-amino]-2-oxazolidinone

CAS number: 67-45-8

Structural formula:



Molecular formula: $C_8H_7N_3O_5$

Molecular weight: 225.2

OTHER INFORMATION ON IDENTITY AND PROPERTIES

Pure active ingredient: Furazolidone

Appearance: Yellow crystalline powder

Melting point: 275°C

Solubility: Slightly soluble in water, c. 40 mg per L.
Slightly soluble in 95% ethanol, c. 90 mg per L
Slightly soluble in chloroform, c. 200 mg per L.
Sparingly soluble in dimethylformamide
Insoluble in ether

UV maxima: 262 nm and 356 nm

Stability: Unstable in alkali and light

RESIDUES IN FOOD AND THEIR EVALUATION

CONDITIONS OF USE

The nitrofurans are most commonly administered by the oral route in both animal and human medicine. Solutions, suspensions, capsules, tablets, powders for reconstitution and veterinary feed premixes are available. Topical ointments, aerosol powders, soluble dressings, urethral and vaginal suppositories, and ophthalmic, nasal and ear solutions have also been developed to accommodate other routes of administration.

Furazolidone is a broad spectrum antibiotic and also has some antiprotozoal activity. It is often used as a second line antibiotic particulary when bacteria are found to be resistant to other first line antibiotics. It is used a feed additive for pigs and poultry both therapeutically and as a prophylactic for gastrointestinal and respiratory disorders.

The length of administration of the drug varies between very short periods for some therapeutic uses and almost continuous administration as an in-feed additive.

METABOLISM

Pharmacokinetics

In rats 50% of the administered dose was absorbed from the gastrointestinal tract and is mainly excreted in the urine. In pigs in a 48 hour period after oral dosing with formyl-labelled ^{14}C-Furazolidone up to 70% of the label is excreted in the urine with 12-19% excreted in the faeces and c. 3% in the expired air. The excretion in the faeces may be due to metabolism in the GI tract or entero-hepatic recirculation of the metabolites. Vroomen et al. (1986a) fed pigs with methylene-labelled ^{14}C-furazolidone and found 61% of the label excreted in the urine and 18% in the faeces over the treatment period and a 14 day withdrawal period. No label was found in the expired air. In piglets a plasma half-life of about 0.45 hours was calculated. (Yamamoto et al., 1978).

Metabolism in Food Animals.

The metabolism of the nitrofurans is extensive and complex. There is evidence of rapid degradation of the molecule yielding numerous and mostly unidentified polar metabolites. Some of the metabolites have been identified in pig urine or following *in vitro* studies with liver microsomes Vroomen, 1886). An unknown fraction of the metabolites enter the endogenous pool. There is also a substantial fraction of unidentified residues which are in the bound fraction. So far it is not possible to select either the parent drug nor any metabolite as a marker substance to indicate the level of total residues.

Dried liver, liver isolate and urine samples from treated pigs have been tested for mutagenic potential. None exhibited genetic activity in the Ames Salmonella/microsomal mutagenesis assay (Jaganath and Brusick, 1981).

A major route of metabolism in pigs and poultry is via the reduction of the 5-nitro group. The sponsors indicate that aerobic metabolism would predominate in the live animal and that further rapid metabolism occurs post-mortem and at low temperatures (-30°C). This would be mostly anaerobic metabolism. In a pig study Furazolidone was labelled with ^{15}N in the 5-nitro position and the urine examined. Only one minor component was identified with the ^{15}N still attached to the furan ring, suggesting that the nitro-group is removed before excretion into the urine.

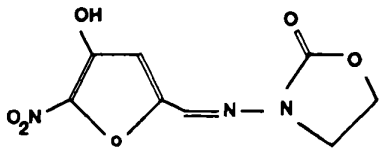
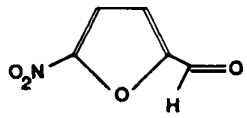
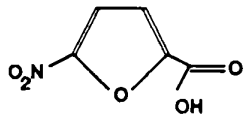
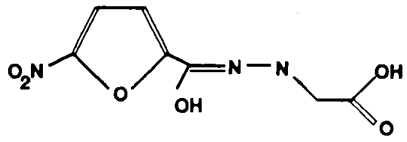
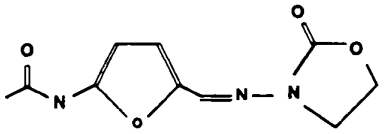
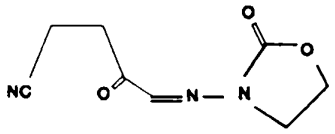
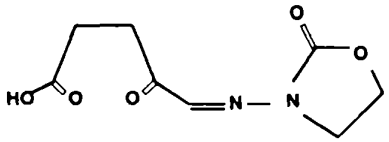
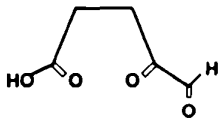
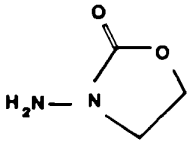
By contrast more of the nitrogen in the 5-nitro group is identified in the residues in rat and rabbit urine and in rat tissues. The open chain cyano-derivative is the major metabolite in rats and is also formed during incubation studies with pig liver microsomes. (Vroomen et al., 1987) or pig hepatocytes (Hoogenboom, 1991). However it is a very minor metabolite *in vivo* in pigs as it appears to be rapidly metabolised to polar metabolites.

α-Ketoglutaric acid is a metabolite in rat urine and it might occur in pigs and poultry as an intermediate for endogenous incorporation of residues.

The bound residues in pig tissues at 0, 14, 21 and 45 days withdrawal time contain measurable amounts of the 3-amino-2-oxazolidone (3AZO) side chain. This compound is released after mild acid hydrolysis by cleavage of the azomethine bond. The amount of 3-amino-2-oxazolidone as a percentage of the bound residues in pig liver lies between 15% and 25%.

The metabolites identified in *in vivo* studies are shown on the next page.

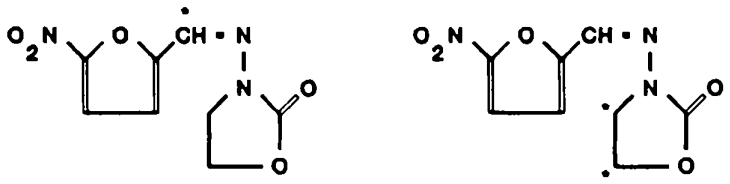
Urinary Metabolites of Furazolidone

	SPECIES
	pig, chicken, rat, rabbit, dog, human
	rat, pig
	pig
	pig
	pig, rat
	pig, rat, rabbit
	rat
	rat
	pig (after reduction of bound residues in liver and possibly formed in GI tract)

TISSUE RESIDUE DEPLETION STUDIES

Radiolabeled Residue Depletion Studies

The studies were carried out using ^{14}C-furazolidone labelled in either the formyl or methylene groups.



formyl label(*) methylene label(*)

Pigs

Several radiometric studies were done in pigs. The common results were;

(i) Residues of parent drug were extremely low or absent.
(ii) Most of the residues were polar metabolites.
(iii) A significant portion of the residues were nonextractable.

Two male pigs (5.9 kg) were administered 75 mg ^{14}C-Furazolidone (formyl label) in two doses per day via a stomach tube as equivalent to 300 mg per kg in feed for 10 days or equivalent to 12 mg per kg live weight per day. Tissues were collected in one pig at 2 hours after the last dose and from the other pig 14 days after dosing. The mean levels of radioactivity (total residues) expressed as mg per kg (ppm) equivalents of Furazolidone are shown in table 1. Between 40 and 90% of the total residues can be extracted with water as polar metabolites and most of the remaining residues are nonextractable bound residues (Vroomen et al, 1986a).

Table 1. Total residues of ^{14}C-Furazolidone in pigs

Tissue	Total residue (ppm) 2 hours	Total residue (ppm) 14 days
Skin	7.3 - 9.1	2.9 - 3.5
Subcut fat	6.0	4.3
Liver	32.9 (4.8)	3.1 (0.8)
Kidney	30.1 (2.9)	3.0 (0.9)
Muscles	5.7 - 7.2 (2.3)	2.0 - 2.1 (1.2)
Lung	10.9	2.3
Heart	8.3	1.9
Testes	11.5	2.3
Bile	81.1	1.1

The values in parenthesis are the concentrations of the nonextractable portion of the residues which remain after extraction with polar and non-polar solvents and 1M urea.

The samples of muscle, fat, kidney and liver were analyzed by GC-EC and shown to contain no detectable parent drug (limit of detection; 2 μg per kg).

In two studies by Craine (1977, 1978) two female pigs weighing 5.4 kg and 7.7 kg, were fed for five days 5 mg per kg body weight of ^{14}C-furazolidone labelled in either the formyl or methylene position. The pigs were slaughtered 1 day after the last dose and the total residues, expressed as mg per kg parent drug equivalents, are shown in table 2. In another study (Tennent and Ray, 1971) a male pig weighing 26 kg was dosed with 300 mg per kg in feed for 21 days and 1.25 mg ^{14}C-Furazolidone (formyl label) on the last day. The pig was slaughtered 2 days after the last dose and the results for total residues are also shown in table 2.

Table 2. Total residues in pigs as mg per kg (ppm) parent drug equivalents

Study (Label) TISSUE	Craine 1978 (formyl) 1 day	Craine 1978 (methylene) 1 day	Tennent & Ray (formyl) 2 days
Muscle	1.00	1.02	4.5
Liver	5.15	7.80	21
Kidney	3.30	4.33	30
Fat	NA	NA	1.95

In the most recent study (Sponsor, 1991) pigs were fed ^{14}C-Furazolidone at a dose equivalent to 300 mg per kg feed for 14 days and slaughtered at 0, 21 and 45 days withdrawal time. The total residues and the residues containing the 3-amino-2-oxazolidone ring were measured. The results are shown in table 3.

Table 3. Total residues and 3-amino-2-oxazolidone in mg per kg in pig tissues

WT (days)	Liver Total	Liver AOZ	Kidney Total	Kidney AOZ	Muscle Total	Muscle AOZ
0	42.1	3.71 (8.8%)	34.7	2.10 (6.1%)	12.2	1.40 (11.5%)
0	40.0	3.08 (7.7%)	34.0	1.71 (5.0%)	14.1	1.18 (8.4%)
21	3.7	0.268 (7.2%)	2.8	0.084 (3.0%)	2.7	0.135 (5.0%)
21	5.0	0.227 (4.5%)	3.9	0.115 (2.9%)	3.8	0.085 (2.2%)
45	1.9	0.085 (4.5%)	1.6	0.035 (2.2%)	2.0	0.050 (2.5%)
45	2.4	0.075 (3.1%)	2.4	0.028 (1.2%)	2.8	0.074 (2.6%)

AOZ is 3-amino-2-oxazolidone; the figures in parenthesis are the percentage of 3-amino-2-oxazolidone of the total residues.

Chickens

Chickens were fed 220 mg ^{14}C-Furazolidone (methylene label) per kg feed for 4 days. The chickens were slaughtered and the total residues determined; the results are in table 4. Chickens were also slaughtered during a 21 day period of radiolabeled drug administration and tissue residues determined. The residues reached a maximum after eight days of Furazolidone administration and then plateaued. (Buzard et al., 1961)

Table 4. Total residues in chickens expressed as mg per kg (ppm) parent drug

WT (days)	Muscles	Liver	Kidney	Fat
0	3.40-6.08	18.6/21.1	22.1/20.8	3.53
1.5	1.58-1.89	20.8/22.1	4.06	1.11
3	0.73-1.16	3.34/3.64	2.31/2.82	1.09/1.16
5	0.70-0.87	2.32	1.39	NA
8	0.54-0.68	1.08	0.90	1.23
11	0.44-0.48	0.87	0.58	1.46

The values for muscle are the range for the residues in three different muscles determined in two chickens per time point. All other value are for individual samples.

Hens were fed ^{14}C-Furazolidone labelled in the formyl group at three levels (25, 100 and 200 mg per kg feed) for 14 days. Tissues were collected at 0, 3 and 5 days withdrawal and analyzed for Furazolidone by reverse isotope dilution. One of two samples of skin with fat at 0 days withdrawal time from hens fed 200 mg per kg contained 13 μg per kg Furazolidone. None of the other tissues exceeded 10 μg per kg the lower limit of detection of the method. No other metabolites were investigated. (Heotis et al;1969, Nº185)

Cattle

There are no radiometric studies.

OTHER RESIDUE DEPLETION STUDIES

Pigs

After medicated feed (300 mg per kg) was fed to pigs for eight days residues of Furazolidone as parent drug declined from 61 μg per kg at 0.5 hours withdrawal time to control values in less than 6.5 hours after drug withdrawal. The study also showed that the residues degraded in deep frozen tissue but not in plasma samples (Carignan et al., 1990).

Pigs were fed 300 mg Furazolidone per kg of feed for 24 days. Residues of the parent drug and metabolites with the 5-nitro-furan ring structure in tact were found in muscle (11 μg per kg), kidney (<2 to 3.1 μg per kg), skin (8.7 μg per kg) at zero withdrawal time and not detected in liver or fat tissues; the skin of 1 of 3 pigs also contained residues at 1 day withdrawal time (Hobson, 1976).

Fourteen pigs were fed 14 mg Furazolidone per kg body weight for 7 days. The pigs were slaughtered at 0, 1, 2, 4, 5, 7, 14, 21 and 28 days after drug withdrawal. Piglets were fed 6 mg Furazolidone per kg body weight for 4 days and then slaughtered at 0, 1, 2, 4, 5 and 7 days after dosing. No residues of Furazolidone (limit of detection 1 μg per kg) were found in muscle, liver, kidney, fat or heart (Shaw, 1990).

Cattle

The half life of the parent drug is short and the drug rapidly degrades at temperatures down to -30°C in tissues of calves (Nouws and Laurensen, 1990).

Six calves were dosed orally with 16 mg Furazolidone per kg body weight per day for five days. The calves were sacrificed at 0, 1, 2, 4, 5 and 7 days after the last dose. Residues of Furazolidone in muscle tissue were analyzed by HPLC. Residues of Furazolidone (33 μg per kg) were found in muscle immediately after withdrawal (day 0) of the drug although these had disappeared after storage at -20°C for three weeks (Shaw, 1990). Residues were not detected at other withdrawal times.

Female calves were fed 10 or 20 mg Furazolidone per kg body per day for ? days. They were slaughtered 17 days after the last dose. No residues were detected in muscle, liver, kidney or fat (Kalim, 1990).

Poultry

No residues of Furazolidone were found in tissues of turkeys and chickens fed 400 mg per kg feed for 14 days and 200 mg per kg feed for 7 weeks respectively except in the skin of chickens, (Winterlin et al, 1982, 1984). Residues of Furazolidone are found in eggs for up to five days after drug withdrawal (Petz, 1984) and in hen tissues in the order 3-13 μg per kg following oral doses of 10 mg per kg body weight per day for 1-10 days (Yadava et al 1986).

Day old chicks were administered 55 mg Furazolidone per kg feed for 42 days and residues of 5-nitro-furan compounds were detected in liver (0.5-1.1 μg per kg) and muscle (up to 2.9 μg per kg) at zero withdrawal time but no residues were detected at 2 days after withwrawal (Parks and Kubena, 1990).

Chickens were fed 440 mg Furazolidone per kg feed for 10 days. The chickens were killed at 0, 1, 2, 4, 5 and 7 days after dosing. The concentration of residues of Furazolidone in muscle were;

Days after dosing	0	1	2	3	4	5 & 7
Furazolidone (μg/kg)	0.8	1.8	0.5	1.0	2.4	ND

ND is not detected. Data from Shaw (1990).

Other species

Residues have also been reported in tissues of goats (Mustafa et al, 1985) and trout (Schmidt and Buning-Pfaue, 1985).

For the fluids, residues of Furazolidone were found in the urine of chickens (Craine and Ray, 1972) and goats and also in milk of goats (Pandey et al., 1980).

Bound Residues

There is evidence that a large portion of the total residues are in the bound fraction and the percentage although not the absolute amount of bound residues increases with the withdrawal time (see table 1).

Some further evidence (see table 5) of the amounts of free and bound residues became available in April 1992 from a recently completed bioavailability study. The pig muscle and liver samples are the same as those reported in table 3. The non-extractable radioactive residues were measured in the fraction remaining after extraction of the tissues with solvents (1. methanol : water, 1:1 v/v, ; 2. methanol; 3. ether; 4. ethyl acetate). The majority of the residues are in the bound fraction.

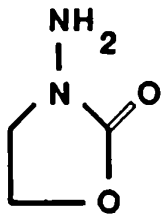
Table 5. Extractable (Free) and Bound residues in pig liver and muscle

Tissue	WT (days)	Total mg/kg	Free mg/kg	Bound mg/kg
Liver	0	41	18	23
Liver	45	2.15	0.18	1.97
Muscle	45	2.4	0.33	2.07

The bound residues can be divided into three types;

(i) Residues as metabolites which are of toxicological concern
(ii) Residues as metabolites which are of no toxicological concern
(iii) Residues which have entered the metabolic pool and become endogenously incorporated into cellular material and compounds

The bound residues in group (i) are the most important from a toxicology view, however the residues have not been identified or shown to be separate from those in group (ii). There is some evidence of minor mutagenic substances in rat urine and Hoogenboom (1991) showed that he could release 15-25% of the bound residues in pig liver as compounds with the 3-amino-2-oxazolidone side chain. 60% of the total residues in *in vitro* studies with pig hepatocytes also contained this side chain Hoogenboom 1991).



3-amino-2-oxazolidone

Metabolites with the 5-nitrofuran moiety intact may be present but have not been identified.

The fraction entering the endogenous pool is not known. In rats and chicks fed ^{14}C-Furazolidone there was expiration of radiolabeled CO_2 suggesting metabolism into the metabolic pool (via α-keto-glutarate). 3% of the label was expired in pigs administered ^{14}C-Furazolidone labelled in the formyl group but no radioactivity was expired if the label was in the methylene group. This might suggest that the oxazolidone ring does not become metabolised to form precursors for endogenous incorporation.

In summary; there is abundant evidence of bound residues and it might be assumed that much of the residue is of no toxicological concern, however more evidence is needed to apportion what fraction of the bound is toxic.

Bioavailability

The bioavailability of the bound residues was measured by refeeding lyophilized pig tissues to rats and measuring the amount of radioactivity absorbed and excreted (Sponsor study, HRC/SMI 125/911478, submitted in uncorrected final draft, April, 1992).

The incurred pig liver and muscle tissues were the same as those reported in tables 3 and 5. The bioavailability of free ^{14}C-furazolidone was also measured in three experiments in which ^{14}C-furazolidone was;

(i) Added direct to stomach of rat
(ii) Included in pelleted feed
(iii) Included as spike in lyophilised control (blank) liver and muscle.

The results are summarised in tables 6 and 7.

Table 6. Bioavailability of free ^{14}C-furazolidone

^{14}C-Furazolidone Administration	Vehicle	% absorbed
Direct to stomach	solvent	87
in pelleted feed	feed	90
Spike at 300 mg/kg	liver	73
Spike at 300 mg/kg	muscle	96

Table 7. Bioavailability of Residues in pig liver and muscle

Incurred Tissue	Residue Type	WT (days)	% absorbed	% total absorbed
Liver	Total	0	40	40
Liver	Total	45	19	19
Muscle	Total	0	37	37
Muscle	Total	45	41	41
Liver	Bound	0	31	17.4
Liver	Bound	45	16	14.7
Muscle	Bound	45	37	31.8

Combining the residue data in table 5 with the data in table 7, the amount of bioavailable residue in the free and bound fraction is calculated and shown in table 8.

Table 8. Bioavailability of free and bound residues in pig liver and muscle

Tissue	WT (days)	Free mg/kg	**Bioavailable** Free mg/kg	Bound mg/kg	**Bioavailable** Bound mg/kg
Liver	0	18	10.4	23	7.15
Liver	45	0.18	0.09	1.971	0.32
Muscle	45	0.33	0.22	2.07	0.77

The results indicate two main points;

1. The free residues are not all bioavailable, even for the parent drug added direct to the stomach.
2. The fraction of bound residues which are bioavailable is in the range 16% to 37%. In liver tissue this is equivalent to 7.15 mg/kg at day 0 withdrawal time and 0.32 mg/kg at day 45. In muscle the only measurements were made at 45 days withdrawal time and 0.77 mg/kg of bound residues are bioavailable.

In another study bioavailability was similary determined by feeding rats the nonextractable fraction of muscle tissues of piglets fed radiolabeled furazolidone for 10 days and slaughtered at zero withdrawal time. Approximately 41% of the residues were bioavailable (Vroomen et al, 1990).

Since the toxicology of the bioavailable bound residues is not known they will need to be equated with parent drug.

METHODS OF ANALYSIS FOR RESIDUES IN TISSUES

So far there is no recognised marker substance since the parent drug is rarely found as a residue. Nevertheless many countries regulate the drug by monitoring for Furazolidone. Investigations are proceeding into the possible conversion of residues into the 3-amino-2-oxazolidone molecule and it's use as a marker residue (Hoogenboom, 1991). Residues of 3-amino-2-oxazolidone were detected in pig liver at up to 45 days withdrawal time. The method for measuring 3-amino-2-oxazolidone has the following steps;

- Homogenate of liver containing 5-10 mg protein
- Incubate with 0.1*N* HCl and 0.5mM 2-nitro benzaldehyde for 20 hours at 37°C
- Extract with ethyl acetate
- Measure on HPLC with UV detection at 275 nm

This method is still in the development stage (Hoogenboom, 1991).

There are many, both old and recent, methods which are satisfactory for the routine screening or monitoring of residues of the parent drug. A review of methods for nitrofurans up to 1984 is provided by Kalim (1985). The methods are all based on a form of chromatography with various end-point detection systems. The most widely used methods have many of the following steps;

> Homogenise tissue → Solvent extraction with or without a gel → cartridge column chromatography → HPLC with UV, diodearray or electrochemical detection or GC with electron capture detection.

The methods have limits of determination of c. 0.2 to 2 μg per kg and are well validated for accuracy and precision. (e.g. Laurenson & Nouws, 1989; Aerts et al, 1990; Petz, 1982, 1983; Vroomen et al., 1986; Winterlin et al, 1981).

APPRAISAL

The metabolism and residue pattern of Furazolidone is not unlike that of the nitroimidazoles reviewed at the 34th meeting. The drug is well absorbed, extensively metabolised and excreted mainly in the urine. The parent drug has a short half life both *in vivo* and in post-mortem tissues, it is either not found as a residue or at very low concentrations at zero withdrawal time. The parent drug is occasionally found at slightly longer withdrawal times, although the results from the numerous studies are sometimes confused by treatment and assay method.

The most important point for discussion is the nature of the residues. The total residues are in the mg per kg range of which $\leq$1000th are parent drug. Most of the residues are polar compounds in either the free or bound form. Information is lacking on either the chemical nature or the toxicity of the majority of the residues although there is some indication that the residues in swine liver and urine do not possess genetic activity in the Ames Salmonella/microsomal mutagenesis assay. The half life of the parent drug is very short but the half-life of the total residues is very long because many of the metabolites are either bound or enter the endogenous pool.

Many metabolites resulting from *in vitro* studies in rats and pigs have been identified or at least postulated . The 5-nitro group is rapidly reduced in microsome preparations. Also both the furan and azolidone rings may be opened and cyano or keto end groups are among the possibilities. In *in vivo* studies there is evidence of extensive reduction of the 5-nitro group which continues in the post-mortem tissues. The nitrogen in the 5-nitro group and still attached to the furan ring is found in a significant fraction of the residues both excreted by the rat and rabbit and also in the incubation mixtures of the rat, chicken and pig microsomes, but it is only a very minor fraction of the residues in pigs. The ring structure of the oxazolidone is still present in some of the residues in pig tissues.

There is evidence for incorporation of the residues into the endogenous pool in rats, chickens and pigs. The fractions entering the endogenous pool are not known.

The percentage of residues in the bound fraction increases with withdrawal time. In pigs the 3-amino-2-oxazolidone group can be released from at least 15-25% of the bound residues in liver tissue. The bound residues constitute a significant amount (c. 1 mg per kg or higher) of the residues.

The bioavailability studies show that

1. The free residues are only 52% to 67% bioavailable, even the parent drug added direct to the stomach of rats was only 87% absorbed.

2. The fraction of bound residues which are bioavailable is in the range 16% to 37%. In liver tissue this is equivalent to 10 mg/kg at day 0 withdrawal time and 0.32 mg/kg at day 45. In muscle the only measuremnets were made at 45 days withdrawal time and 0.77 mg/kg of bound residues are bioavailable.

The toxicology of the bound residues is not known. In the absence of this information the potency of the bound residues will need to be considered.

Information is submitted on residues from cold studies in which only residues of the parent drug or the 5-nitro-furfurylaldehyde (after derivatisation) were measured. Residues were sometimes detected at short withdrawal times in pigs, poultry, goats and trout.

There are several well validated analytical methods for measuring and regulating residues of the parent drug. A technical problem is caused by the rapid degradation of Furazolidone in post-mortem tissues at temperatures down to -30°C.

Recent studies indicate that the measurement of residues of 3-amino-2-oxazolidone may offer a possible marker residue for pigs. Residues of this compound are detectable for at least a 45 day withdrawal period.

REFERENCES

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