DORAMECTIN

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ADDENDUM
to the doramectin residue monograph prepared by the 45th meeting of the Committee and published in FAO Food and Nutrition Paper 41/8, Rome 1996

INTRODUCTION

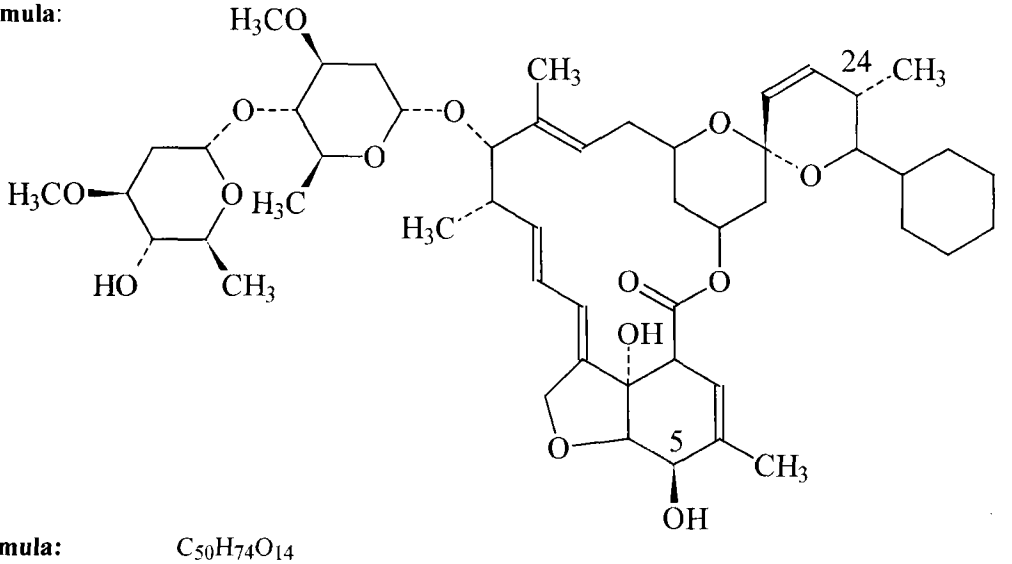
The use of doramectin as an ecto- and endoparasiticide for cattle was assessed at the 45th JECFA in 1995 (JECFA 1996a, 1996b, 1996c). An ADI and MRL were established. This review assesses the use of doramectin in pigs.

IDENTITY

Chemical name: 25-cyclohexyl-5-O-demethyl-25-de(1-methylpropyl)avermectin A_{1a}

Synonyms: Doramectin; Dectomax; UK-67,994®

Structural formula:



Molecular formula: $C_{50}H_{74}O_{14}$

Molecular weight: 899.14

OTHER INFORMATION ON IDENTITY AND PROPERTIES

Pure active ingredient: Doramectin

Appearance: White to light tan powder

Melting point (average): 160.5 - 162.2°C

Solubility:

water	0.0003 g/L at 22°C -25°C
acetonitrile	33 g/L
methylene chloride	530 g/L

Optical Rotation: + 12.2°C (anhydrous)

UV_{max}: 244 nm

RESIDUES IN FOOD AND THEIR EVALUATION

CONDITIONS OF USE

General

Doramectin is a parasiticide for use in cattle and pigs.

Dosage

Doramectin is administered to pigs for the treatment of endo and ectoparasitic infections as a single intramuscular (IM) dose of 0.3 mg/kg BW. Doramectin is not intended for use in dairy cattle producing milk for human consumption.

METABOLISM AND PHARMACOKINETIC STUDIES

Pharmacokinetics

The plasma kinetics of doramectin were determined in eight pigs (4 male castrates and 4 females, each weighing approximately 40 kg) dosed IM with [^{3}H]-doramectin at 0.3 mg/kg BW using a prototype commercial formulation (75% sesame oil/25% ethyl oleate). The plasma concentrations were determined using liquid scintillation for quantification of total residues and chromatographic techniques for the quantification of unchanged doramectin. Data from this study are presented in Table 1.

Table 1 **Plasma concentration of total radio-labelled material and of doramectin in pigs treated IM with [^{3}H]-doramectin at 0.3 mg/kg BW.**

	Equivalents of Doramectin (µg/L)							
Day	0.5	1	3	5	7	10	14	21
Total [^{3}H] residues	16	21	26	25	21	16	11	6
Doramectin residues	12	17	17	14	13	9	6	<3

The apparent terminal half-lives of elimination from plasma of total [^{3}H]-labelled materials and unchanged doramectin were 7.7 and 6.4 days, respectively.

The drug dispersed from the injection site (see below) (Pfizer Inc, 1995a) and the main route of excretion in pigs was the faeces. After IM dosing, with [^{3}H]-doramectin at 0.3 mg/kg BW, 61 ± 20% of the dose was excreted in the faeces within 21 days and <1% of the dose was excreted into the urine (Pfizer, 1995a). The faeces are also the major route of excretion in cattle, dog and rat.

Metabolism in animals

The biotransformation of doramectin was investigated in rats, dogs, pigs and cattle. Tissue distribution studies, discussed in detail below, showed that the highest concentrations of total residues were in liver and fat of treated cattle and pigs, with only traces detectable in muscle and kidney. For this reason, metabolite identification studies in pigs were limited to liver. The identity of doramectin metabolites was previously reviewed by the 45th JECFA in association with the use of doramectin in cattle. The methods employed for metabolite identification included gradient liquid chromatography with radiochemical

detection and fast atom bombardment mass spectrometry. A tritium label (^3H) was introduced into the doramectin molecule at the 5-position with high specificity (minimum 14.1 mCi/mg). The material used ranged in radiopurity from 95 to ~99.8%. The label was metabolically stable, since less than 1% was recovered as tritiated water from cattle faeces containing 87% of the dose (Pfizer Inc, 1994a).

The products of doramectin metabolism were similar in all species investigated. The metabolites were more polar than doramectin and were the result of O-demethylation in the distal saccharide ring (component C), of hydroxylation of the 24-methyl group (component B) and a combination of both of these biotransformations (component A). Table 2 shows the distribution of the metabolites (as a percentage of total radioactivity of the major radiolabelled component) in the liver and faeces of pigs, cattle, rats and dogs at 2, 3, 7 or 21 days post dose. Rats and dogs were dosed orally with 5 and 3.5 mg/kg BW respectively. Pigs were administered an IM dose at 0.3 mg/kg BW, cattle received a SC injection of 0.2 mg/kg BW.

Table 2. Percentage of total radioactivity of the major radio-labelled components in the liver and faeces of pigs, cattle, rats and dogs at 2, 3, 7 or 21 days post dose

Tissue	Species	Day	% ^3H recovered	Component*			
				A	B	C	UD
Liver	Pigs	3[a]	39	ND	ND	9	28
Liver	Pigs	7[aa]	89 ± 8	ND	ND	20 ± 2	71 ± 4
Liver	Cattle	3[b]	95	7	ND	9	70
Liver	Cattle	21[c]	82	8	4.4	6.8	57.8
Liver	Rat		37	2	3	12	18
Liver	Dog		51	ND	ND	12	28
Fat	Cattle	21	74-91	ND	ND	ND	91[e]
Faeces	Pigs		72	ND	8	14	10
Faeces	Cattle		75-82	4	5	14	24
Faeces	Rat		NC[d]	16	14	19	22
Faeces	Dog		46	4	5	8	6

* As identified above and in equivalents of [^3H]-doramectin. [a] Study CM-93-02, Pfizer Inc, 1994b;

[aa] Study using different extraction of liver tissue from Study CM-93-02, Pfizer 1994b;

[b] Study CM-92-01, Pfizer Inc, 1992a; [c] Study CM-93-01, Pfizer Inc, 1993

[d] NC = not calculated since this sample was used as a reference standard.

[e] 4.8-10.9% (mean 7.4%) of total residues were epi-doramectin. UD = unchanged doramectin; ND = not detected

Pigs

The metabolite profile of doramectin in pigs treated with [^3H]-doramectin was initially determined using subcutaneous (SC) administration of a 0.3 mg/kg BW dose in an aqueous micelle formulation to four male castrate pigs. One male was killed three days after dose administration and the liver collected for metabolite identification. The remaining animals were placed in metabolism cages and the faeces and urine collected at 24 hour intervals for 7 days. The samples containing the highest concentrations of radioactivity were selected for metabolite identification. In this study, 39% of the total radioactivity was extracted from liver (Pfizer, 1994b). The concentrations of the major radiolabelled components were confirmed by examination of liver and faeces samples collected from four animals (2 male and 2 female) weighing approximately 40 kg dosed with [^3H]-doramectin in the prototype commercial formulation (75:25 sesame oil:ethyl oleate) as an IM dose of 0.3 mg/kg BW. Animals were sacrificed seven days after treatment. Faeces were collected at 24-hour intervals until day 7 post-dose. The extraction of residues from the liver was improved over the earlier experiment, resulting in extraction of 89% of the label of which 71% of total residues (TR) was doramectin. Drug and metabolites were quantified using radiochemical

detection after separation by HPLC chromatography. The major drug-related component in pigs was unchanged doramectin, as in all species studied, (see Table 2) and bound residues constitute, at most, only a small fraction of the total. One metabolite (component C) was detected in porcine liver and faeces and component B was only detected in faeces. Component A was not detected in any pig sample, although this metabolite is found in treated cattle. The unchanged drug was the main component in pig faeces (Pfizer Inc, 1994b). In summary, the metabolism of doramectin is generally similar between the four species examined.

Radiolabelled residue depletion studies

General Comments

The studies were done in compliance with GLP. Total drug-related residues were measured by the use of tritium labelled doramectin. The radiochemical purity of [^{3}H]-doramectin used in these studies was ~ 99.8%. The [^{3}H] label was found to be metabolically stable in cattle since less than 1% of faecal radioactivity was recovered as tritiated water (Pfizer Inc, 1990, 1992a, 1994a).

Pigs

In the total residue depletion study, pigs weighing approximately 40 kg received a single IM dose of 0.3 mg/kg BW [^{3}H]-doramectin in the commercial prototype formulation described above. Two pigs of each sex were sacrificed at 7, 14, 21 and 28 days after dose administration and samples of muscle, liver, kidney and fat collected for analysis of total radioactivity and unchanged doramectin (Pfizer 1995b). Injection site samples were collected from these animals under a separate protocol and reported separately (Pfizer, 1995a). The concentrations of total doramectin residues, unchanged doramectin and the calculated unchanged drug to total residue ratios are presented in Table 3.

Table 3. Radiolabelled residues and unchanged drug (µg/kg) in pig tissues after a single IM dose of 0.3 mg/kg BW [^{3}H]-doramectin[a]

Tissue	Mean Residue Concentration	Day 7	Day 14	Day 21	Day 28
Muscle	Total [^{3}H] residues (µg/kg)[b] Unchanged drug[c](µg/kg) Unchanged drug (%)	35 ± 7 7 ± 1 (20)	19 ± 6 <4 (<24)	6 ± 1 <3 n.e.	4 ± 3 <3 n.e.
Liver	Total [^{3}H] residues (µg/kg))[b] Unchanged drug[c] (µg/kg) Unchanged drug (%)	186 ± 47 66 ± 15 (36)	111 ± 20 37 ± 11 (34)	46 ± 10 11 ± 3 (24)	37 ± 20 <7 (<229)
Kidney	Total [^{3}H] residues (µg/kg))[b] Unchanged drug[c] (µg/kg) Unchanged drug (%)	79 ± 19 23 ± 7 (30)	46 ± 7 11 ± 3 (23)	17 ± 4 6 ± 2 (35)	8 ± 3[d] 3 ± 1[d] (45)[d]
Fat	Total [^{3}H] residues (µg/kg))[b] Unchanged drug[c] (µg/kg) Unchanged drug (%)	412 ± 54 242 ± 22 (59)	255 ± 42 113 ± 26 (44)	90 ± 18 42 ± 14 (45)	8 ± 33 30 ± 20 (49)
Injection Site (250 g)	Total [^{3}H] residues (µg/kg))[b] Unchanged drug[c] (µg/kg) Unchanged drug (%)	5130 3660 (74)	2510 2550 (102)	1080 1030 (92)	118* 35* (32)*

a = Study 1525N-60-90-011/012 (Pfizer, 1992b and 1995a) ; data are means ± SD from four animals at each time.
b = Expressed as doramectin equivalents
c =For calculations of the means 2.5 or 5 µg/kg, as appropriate, was substituted for those unchanged drug concentrations falling below the LOQ. A "less than" symbol (<) indicates that some data were below the LOQ (limit of quantification).
d - One sample of pig kidney on day 28 was apparently mislabelled and was actually an injection site sample. Therefore, this sample is not included in the mean calculations for kidney day 28. Individual data are provided in the study report.

n.e.= Not estimated because two or more individual samples were below the LOQ.
The results of the total residue depletion study presented in Table 3 clearly indicate that the liver and fat are most appropriate for selection as target tissues since the concentrations are the highest and the depletion from both tissues is slowest. Residues in kidney and muscle are low and close to the limit of quantification by day 28.

The ratio of unchanged drug to total residues was found to be generally constant over the measured withdrawal periods for each tissue. Combining the data from all measured withdrawal times (days 7, 14, 21 and 28) for each tissue, the approximate mean percentages of unchanged drug to total residues were calculated as follows: liver - 30%; fat - 50%; muscle - 20 %; kidney - 30%.

The calculated ratio of 30% for liver is considered by the sponsors to be inappropriately low. They argued that the assay methodology in place at the time this study was conducted was subsequently found to have deficiencies related to the variable extraction of unchanged drug from the liver and maybe from the other edible tissues. The liver samples from this study were not re-analysed after the method was improved. Evidence to support that the ratios of unchanged drug to total residues in liver were disproportionately low in this study are provided by inspection of the metabolic profile data generated in pig liver using radiochemical detection (Table 2, day 7). Using this methodology, it is clear that unchanged doramectin represents a much greater proportion of total residues than was detectable using the earlier, less robust HPLC method where incomplete residue extraction is probable.

Residues at the Injection Site

The injection site, consisting of fascia and underlying tissue, was removed and trimmed to approximately 250g (Pfizer, 1995a). The concentrations of total residues and unchanged drug were measured by similar methods used for the edible tissues. The results are shown in Table 4.

Table 4. Residues (µg/kg) at the injection site of pigs.

Residue	7 days	14 days	21 days	28 days
Total Residues (TR)	5100 ± 4400	2500 ± 1800	1100 ± 720	120± 38
Doramectin (UD)	3600 ± 3000	2600 ± 1900	1000 ± 850	35 ± 6
% Doramectin in TR	71%	102%	96%	30%

The residues at the injection site persist for at least 21 days but by day 28 they have fallen to much lower levels. In a study (see below) using non-radiolabelled doramectin, the results for the residues at the injection site yield much higher concentrations of doramectin and they are evenly distributed throughout a 500g sample. Thus the amount of residues in the tissue around the injection site in this labelled study could be double the amount found in the 250g sample taken for this work. The percentage of doramectin in the residue remaining at the injection is down to 30% and it is probable that the unidentified part of the residue is less active than doramectin.

Depletion studies with unlabelled drug

The depletion of the marker residue, doramectin, from edible tissues was evaluated in a depletion study conducted in pigs with a mean weight of 62 kg. Each pig received a single IM dose of doramectin in a commercial prototype formulation at a dosage of 375 µg/kg, which was 1.25x the recommended dose (Pfizer Inc, 1995b). Six animals, three of each sex, were evaluated at each time point. The injection site, consisting of a cylinder approximately 10 cm in diameter and 6 cm in depth, was removed and trimmed to approximately 500g, equivalent to the U.S. (500 g) requirement. The inner 300g portion, equivalent to the EU requirement, containing the injection site was trimmed from the 500g sample and homogenised; the outer portion was homogenised separately. One-half of the homogenised 300g sample was re-homogenised with one-half of the outer portion to yield a sample representing the 500g sample of the injection site. Two sub-samples were taken from each homogenate. The results of this study are presented in Table 5.

Table 5. **Depletion of doramectin (in µg/kg) from specified tissues of pigs treated with a single IM dose of 0.375 mg/kg BW of doramectin[a]**

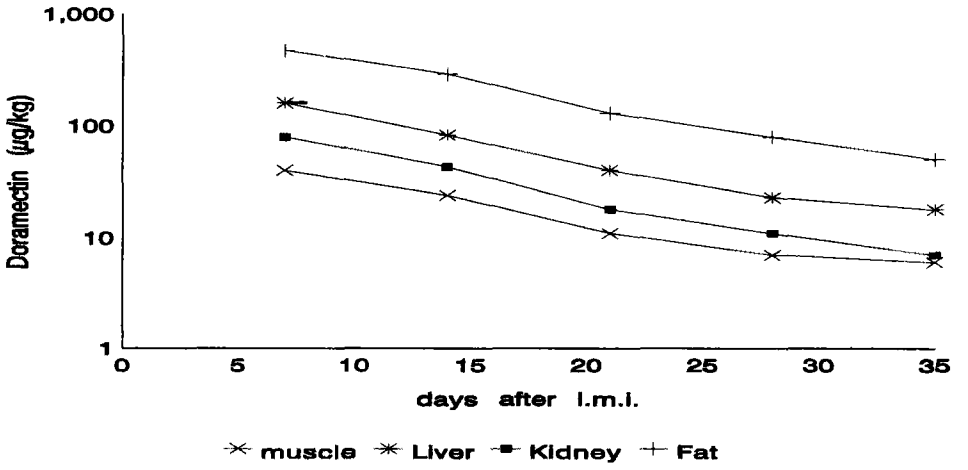
Tissue	7 days	14 days	21 days	28 days	35 days
Muscle	40 ± 9	24 ± 8	11 ± 5	<7	<6
Liver	160 ± 30	83 ± 8	40 ± 20	23 ± 13	18 ± 8
Kidney	80 ± 20	43 ± 7	18 ± 7	<13	<7
Fat	470 ± 120	290 ± 40	130 ± 50	80 ± 50	50 ± 20
I. Site (500g)	9000 ± 6000	5000 ± 6000	900 ± 500	800 ± 600	70 ± 70
I. Site (300g)	7000 ± 4000	5000 ± 3000	900 ± 500	700 ± 500	160 ± 150

[a] Study 1521N-60-94-007. Data are means ± SD from 6 animals (3of each sex) at each time point.

[b] For calculation of the means, concentrations falling below the LLOQ of 2.5 µg/kg were included in the mean using a value of 2.5 µg/kg, and the mean value was preceded with a less than (<) symbol.

Concentrations of doramectin were highest in the liver, fat and injection sites. Although injection site samples showed a high degree of variability, this is not unexpected for this class of compounds. It is noteworthy that there was close agreement between the mean concentrations of residue in the 300 and 500 g sample, indicating that the drug was dispersed evenly throughout the 500g sample. Therefore it is probable that the residues at the injection site are spread over a larger volume than the sample collected in this study. Also the mean concentration of residues of doramectin (ca. 750 µg/kg) at 28 days are much higher than those observed in the radiolabelled study, in which 35µg/kg µg/kg doramectin and 118 µg/kg total residues, respectively, where found in a 250g core sample. This difference is not due to the 25% higher dose used in the cold study, particularly because the depletion of drug from the cold injection site was linear and relatively rapid, with a mean depletion half-life of approximately 4 days. Doramectin was shown to also deplete in a linear fashion from liver, fat, kidney and muscle, a shown in Figure 1, with depletion half-lives of 7.6 - 9.5 days.

Figure 1. **Depletion of doramectin from edible pig tissues following a 0.375 mg/kg BW IM dose.**



It is concluded, from both the total and marker residue depletion studies in pigs, that unchanged drug is the appropriate marker residue and liver and fat are the appropriate target tissues for the evaluation of doramectin residues in the edible tissues of pigs. Muscle and kidney are not considered to be suitable target tissues since concentrations of both total and unchanged residues are much lower and are, in fact, near the limit of quantification by 28 days post-treatment.

Bound Residues/Bioavailability

The results of the metabolism and total residue depletion studies conducted with [^{3}H]-doramectin indicate that doramectin residues are not tightly bound to tissues. The extractability of the total residues was measured in a pig liver, collected 7 days after dosing IM with radiolabelled doramectin. The liver was extracted using the proposed regulatory method and 93 ± 3% of the radioactivity was extracted with 9 ± 0.5% remaining in the pellet (Pfizer, 1997a). Unchanged doramectin comprises the majority (up to 71%) of doramectin related residues in liver (Pfizer Inc, 1994b)

Choice of marker residue

Examination of the results for the radiolabelled depletion studies indicates clearly that the parent drug, doramectin, is the best choice as the marker residue. However there are some minor difficulties in allocating the ratios of parent drug to total residues in tissues because the HPLC method used in the radiolabelled depletion study may not have recovered a significant proportion of the unchanged drug. This is addressed in detail in the later section on MRL.

METHODS OF ANALYSIS FOR RESIDUES IN TISSUES

General

Doramectin concentration in pig tissues was determined by a validated HPLC method. The detection and quantification of doramectin at the µg/kg level was based on the extraction from tissue homogenate or fat and subsequent conversion to a chemically stable aromatic fluorescent derivative. The methods used for analysis of doramectin in pig tissues were substantially the same as those used for the quantification and confirmation of doramectin residues in cattle tissues and previously reviewed by JECFA (JECFA, 1996a). The HPLC method was specific for doramectin and showed good chromatographic separation from other avermectins and milbemycins, including ivermectin, abamectin and moxidectin. The proposed regulatory method was different from those used for determining residues of unchanged drug in the radiolabelled depletion studies. In particular the regulatory method used a much more exhaustive extraction procedure, whereas the mild extraction used in the radiolabelled studies was thought to only partially extract unchanged drug from liver tissue.

High Performance Liquid Chromatography (HPLC)

Liver, kidney, muscle and injection site samples were extracted by incubation at 55°C followed by re-homogenisation in the presence of extraction solvent. Fat samples were extracted using incubation at 55°C in hexane followed by homogenisation and re-partitioning into acetonitrile. The residues were derivatised by treatment with trifluoroacetic anhydride and triethylamine (minimising exposure to moisture), followed by treatment with methanolic ammonia to yield a fluorescent derivative that was stable to moisture. It was necessary to protect the derivative from light using amber coloured glass vials. Separation was effected using a reverse-phase C_{18} HPLC column using acetonitrile, tetrahydrofuran and water in the mobile phase. The amount of doramectin in each sample was quantified with or without the use of an internal standard (UK-71,647). The assay, which was very similar to assays for related substances such as the avermectins, showed good sensitivity with a limit of quantification (LOQ) of 2.5 µg/kg in liver, kidney, muscle and injection site, and of 5 µg/kg in fat. Recoveries of doramectin from liver and fat were in excess of 80%. The coefficient of variation, was approximately10% (Pfizer Inc, 1995b, 1997b, 1998a and b)

High Performance Liquid Chromatography - Mass Spectrometry (LC-MS)

The presence of doramectin in pig liver and fat can be confirmed at trace (µg/kg) levels using LC-MS techniques. Doramectin was extracted from liver or fat using the same methods employed in the determinative HPLC method. Extracts from both tissues were then subjected to clean up by partitioning and re-partitioning of the analyte into acetonitrile and hexane or by elution from a solid phase extraction (SPE) column. The extract was then analysed by LC-MS/MS, using a

triple quadrupole mass spectrometer equipped with an ion spray HPLC interface. Daughter ions (m/z 145, 331, 593, and 899) of the doramectin ammonium adduct (m/z 916) generated by collision activated dissociation (CAD) were monitored. The analyses of tissues fortified with approximately 200 µg/kg doramectin were successfully carried out as was the analysis of tissues incurred with doramectin residues at concentrations programmed to be in the range of 81 and 184 µg/kg. The method was specific for the confirmatory identification of doramectin in tissue. No interference was found when ivermectin was analysed by this method (Pfizer Inc, 1997b).

Prior to the assay of study samples, a one-day mini-validation was performed of the existing pig tissue assay on the HPLC system to be used. For these tests, the batch (M03B) consisted of a duplicate curve, triplicate process standards, triplicate quality assurance standards, and control tissue. For the calibration standards, a 1/C weighted linear least squares regression provided absolute errors of the mean back-calculated concentration of 14.2% or less at any level. The precision (for duplicate assays of the standards) ranged from ± 0.2% at the 50.3 µg/kg level to ± 3.6% at the 2.52 µg/kg level. For the quality assurance samples, the errors of the mean concentration found ranged from 1.7% for the 201 µg/kg pool to 5.1% for the 50.3 µg/kg samples. Intra-assay precision for the Quality Assurance samples (n = 3) varied from ± 0.5% to ± 1.4%. There were no peaks in the blank tissue pool samples co-eluting at the retention times of either the drug or the internal standard. The correlation coefficient, r, was 0.99888 for this batch. Though not stated the internal standard was probably UK-71,647.

HPLC Method used in Radiolabelled Depletion Studies.

A different method was used for the determination of the amount of unchanged drug in the radiolabelled depletion study (Pfizer, 1992b). The method used twice the amount of tissue and a much milder extraction procedure. Five gram muscle, liver or kidney samples were vortexed at room temperature with acetone/water and partitioned with isooctane. The isooctane layer was chromatographed on florisil. After elution, the analyte was derivatised and further purified on a silica column before HPLC. This method was assumed to have failed to extract the majority of the doramectin residue in liver. The sponsor's claim that the recovery of doramectin from muscle, kidney and fat was the same for both analytical methods was not substantiated by submission of experimental data. The sponsor did not analyse the incurred tissues by both methods and thus it is difficult to give an accurate figure for the true ratio of unchanged drug to total residues that are found in liver.

Maximum residue limits (MRLs)

The ADI established by the Committee was 0 - 0.5 µg/kg and is equivalent to 30 µg per day for a 60 kg person.

The values for the mean + 3SD for total residues (see table 3) and the theoretical maximum daily intake (TMDI) at day 28 are calculated in Table 6. There is no correction for the ratio of MR:TR. The theoretical maximum daily intake of residues is 22.4 µg, which is 70% of the ADI. Thus there is reassurance from the radio-depletion study that the total residues do not exceed the ADI at day 28. The main problem in the calculation of MRL is placing a value on the ratio of MR to TR. In the radiolabelled studies, the ratio is almost certainly too low because of the incomplete extraction of doramectin (the marker residue). However, whereas the regulatory method for MRL would appear to extract a much higher proportion of doramectin from the tissues, this method has not been applied to the radiolabelled study.

Table 6. Theoretical maximum daily intake (TMDI) calculated on the total residues (TR) found 28 days after an IM dose of 0.3 mg/kg BW of [^{3}H]-Doramectin . Data from Table 3.

Tissue	TR Mean ± SD (µg/kg)	TR + 3SD (µg/kg)	Tissue consumed (kg)	TMDI (µg)
Muscle	4 ± 3	13	0.3	4
Liver	37 ± 20	97	0.1	9.7
Kidney	8 ± 3	17	0.05	0.9
Fat	58 ± 33	157	0.05	7.8
			Total	22.4 µg

In recommending MRLs the Committee took account of the following factors;

1 The drug is only intended for use in non-lactating cattle and pigs.
2. The marker residue (MR) is the parent drug doramectin.
3. The target tissues are fat and liver.
4. The total residues do not exceed the ADI at 28 days after dosing.
5. The Committee agreed to use the same estimated ratio MR:TR for residues as were used by the 45th Committee. The percentage of residues of parent drug to total residues in each tissue are 70% for muscle, 55% for liver, 75% for kidney and 80% for fat.
6. There are <10% bound residues.
7. No multiple or repeat doses are administered.
8. The LOQs of the analytical methods are 2.5 µg/kg for muscle, liver and kidney and 5 µg/kg for fat.
9. The possibility of harmonising the MRL for cattle and pigs.

The Committee recommended MRLs for pigs of 5 µg/kg in muscle, 100 µg/kg in liver, 30 µg/kg for kidney and 150 µg/kg in fat expressed as parent drug. Incorporating the factors given above the TMDI for each tissue and the total TMDI is calculated as shown in Table 7.

Table7. Calculation of TMDI for pigs based on recommended MRL

Tissue (Wt)	**MRL (µg/kg)**	**µg**
Muscle (300 g)	5	2.1 (0.7)
Liver (100 g)	100	18 (0.55)
Kidney (50 g)	30	2 (0.75)
Fat (50 g)	150	9.4 (0.8)
Total TMDI		**29.5 µg**

- the figure in paretheses indicate the % of MR to TR adopted at the 45Th JECFA

Repeat dosing has not been considered. The Committee also notes the high concentrations of residues at the injection sites.

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