3. Derquantel

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Identity

International Non-proprietary Name (INN): derquantel

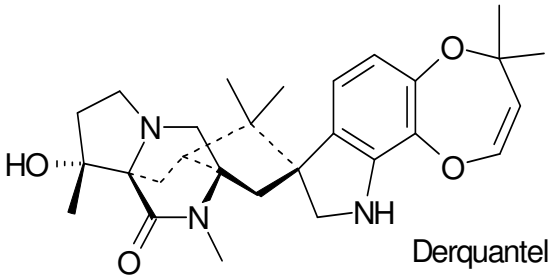
Synonyms: PF-00520904, PNU-141962, 2-DOPH, 2-desoxyparaherquamide, 2-deoxyparaherquamide, Startect® (derquantel + abamectin)

IUPAC Name: (1*R*,3*S*,5*R*,7*S*,12*R*)-12-Hydroxy-4,4,4',4',12,14-hexamethyl-9',10'-dihydro-4'*H*spiro[9,14-diazatetracyclo [5.5.2.01,9.03,7]tetradecane-5,8'-[1,4]dioxepino[2,3-*g*]indol]-13-one

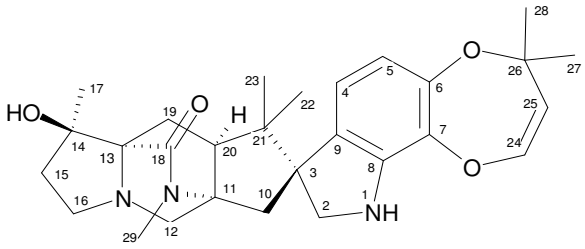
Chemical Abstract Service Number: 187865-22-1

Molecular formula: $C_{28}H_{37}N_3O_4$

Molecular weight: 479.6



Derquantel



Chiral

Background

Derquantel, a spiroindole, is an oral anthelmintic registered for use, in combination with abamectin, to treat and control a broad range of adult and immature gastrointestinal nematodes of sheep. Derquantel is available only as a combination product with abamectin.

Derquantel was previously reviewed by the Committee at its 75th meeting (FAO, 2012), which assigned an ADI of 0–0.3 µg/kg corresponding to an upper bound of acceptable intakes of 18 µg/day for a 60 kg person. Although deficiencies were identified in the residue dossier, MRLs were recommended, expressed as derquantel parent compound, in sheep tissue at 0.2 µg/kg in muscle, 0.2 µg/kg in kidney and 0.7 µg/kg in fat. In addition, a MRL of 0.2 µg/kg in liver was estimated by the Committee; however, due to an error, this MRL was presented in the report as 2 µg/kg. There were not sufficient data to calculate an estimated daily intake (EDI). Using the model diet and mean marker to total ratios of 6% for muscle, 3% for liver, 7% for kidney and 15% for fat, a theoretical maximum daily intake (TMDI) was calculated of 8 µg/person per day, which represents 45% of the upper bound of the ADI.

At the 20th meeting of the Codex Committee for Residues of Veterinary Drugs in Food (CCRVDF), concern was expressed regarding the basis for the ADI assignment (FAO/WHO, 2013). One Observer proposed an alternative approach to the derivation of the MRLs. A Member State expressed concern as to the ratio of the marker residue to total radioactive residues used by JECFA in the calculation of the dietary intake, specifically that the ratio involved time-points for the marker residue and total residue that differed from the time-point used for assignment of MRLs. The Member State and an Observer proposed that the CCRVDF consider lower MRLs for derquantel.

In the light of the above discussion, the CCRVDF agreed to include derquantel on the priority list for re-evaluation by JECFA to: (i) review the ADI in the light of a possible different interpretation of the toxicological database; (ii) review the calculation of the marker to total radiolabel residue ratio; and (iii) revise the recommended MRLs, if appropriate.

Current evaluation

No new data or studies were provided for the current evaluation. A Member State provided written concerns, including exposure scenarios, associated with the concerns that had been expressed during the 20th Meeting of the CCRVDF (Concerns from a Member State, 2012). Additionally, an alternative approach to determining the ratio of marker residue to total radioactive residues was presented by the sponsor (Zoetis, 2013).

Concern from Member State

The concern identified by the Member State was that the ratios of marker residue to total radioactive residue (MR:TRR[3]) used by JECFA were not appropriate, given the time-point selected for recommending MRLs. As a result, the selected MR:TRR ratios may lead to an underestimation of exposure. The request for clarification by the Member State included an outline of concerns over the interpretation of the MR:TRR ratios used in the risk assessment and an interpretation of the total radioresidue data. The conclusion reached in the suggested exposure scenarios is that the JECFA MRL proposals would lead to a TMDI estimate that exceeds the assigned ADI. Two questions were posed to JECFA:

[3] MR:TRR as used in this monograph is consistent with the terminology used by the Member State and the sponsor, where MR is marker residue and TRR is total radioactive (radiolabelled) residues. In the Appraisal and Maximum Residue Limits sections of this monograph, the preferred JECFA terminology, MR:TR, is used, where TR is total residues.

Question 1. Did JECFA take into consideration the fact that the only MR:TRR data available are for the rapid phase of elimination (≤6 days) and that no data are available for MR:TRR for the terminal slow phase of elimination, the period relevant to the MRL proposals?

Question 2. Did JECFA look at other evidence, such as TRR studies, to determine whether or not exposure would be acceptable for the proposed MRLs?

The concern identified by the Member State also suggested that these MR:TRR ratios will be much lower during the slow terminal phase of elimination. Supporting scenarios for MR:TRR ratio interpretation were provided.

Using the data in Table 3.19 of JECFA Monograph 12 (FAO, 2012), the Member State noted that there is a clear decline in MR:TRR ratios over time post-dosing, especially for liver, moving from the fast rate of elimination phase to the slow rate of elimination phase (Figure 3.1).

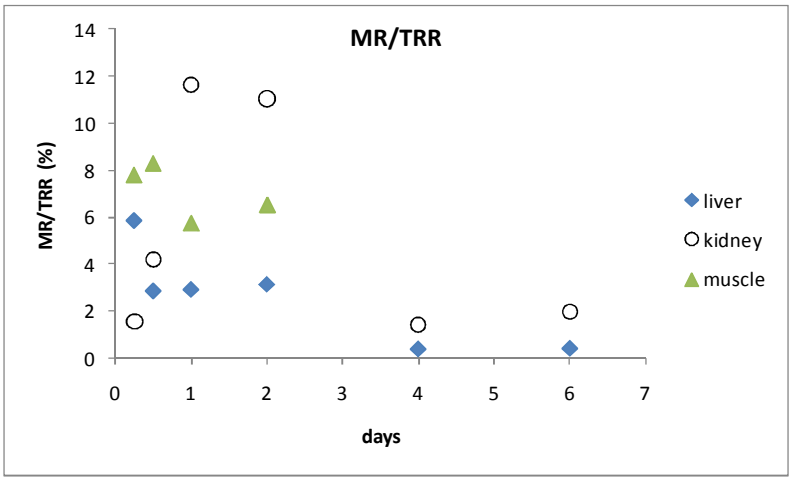


Figure 3.1. Summary of MR:TRR data reported by JECFA for liver, kidney and muscle

The Member State noted that the change in MR:TRR ratios was illustrated also in the marker residue study (Chambers, 2009) and the TRR study of Byrd and Liu (2008) (Figure 3.2). The Member State suggested that the study of Byrd and Liu (2008) (TRR; not commercial formulation) might reflect the expected TRR when using the commercial formulation, i.e. same kinetics. The Member State provided plots of the ratios of derquantel from Chambers (2009) and TRR from Byrd and Liu (2008) and noted that the ratio of mean MR and TRR concentrations (with data corrected to same dose rates) are similar to those derived using MR reported by Byrd and Liu (2008). The Member State noted that the presentations were intended to illustrate the decline and were not suggested to be used for MRL estimation or dietary exposure calculation. They were intended to illustrate the trend with time post-dosing.

Additionally, the concern identified by the Member State noted that the samples may have been stored at -20°C for differing periods, which could have resulted in a 50% reduction in derquantel residues (Table 3.1). Even if this were the case, the MR:TRR ratio at 6 days (144 hours) corrected for reduction on storage would be less than 0.01 (<1%) and would be expected to be even lower by 8 days, the time-point relevant to the JECFA MRL recommendations.

Table 3.1. Ratio of marker residue to total radioactive residues (%) for liver

Slaughter interval post-dosing	Byrd and Liu, 2006 [2]	Byrd and Liu, 2008 [2]	Byrd, 2008 [3]
3	19.9 (26.2)		
6	—	5.86	
12	7.32 (9.21)	2.09	4.36
24	1.07 (1.83)	3.25	2.23
48		4.43	0.73
96			0.44
144		0.2 [1]	

NOTES: (1) derquantel reported as 0 µg/kg is assumed to be present at ½ LOD of 0.5 µg/kg; (2) samples stored at ≤-10°C prior to analysis; (3) samples stored at -20 and -70°C prior to analysis; (3) samples stored at -20°C prior to analysis.

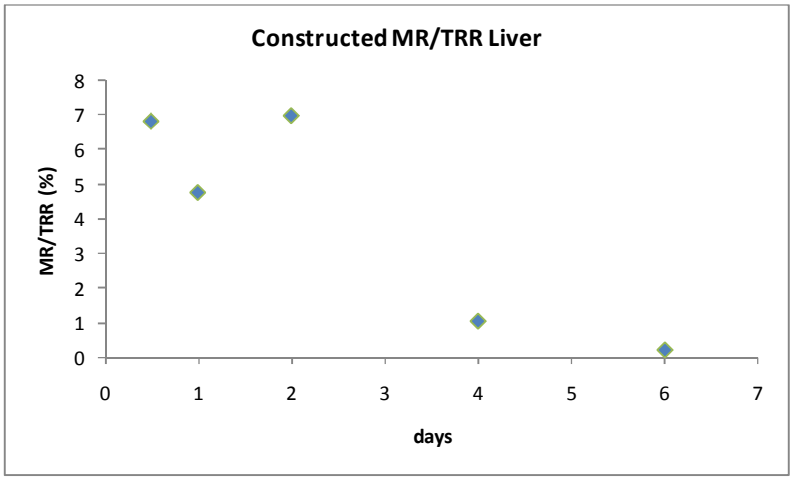


Figure 3.2. Summary of MR:TRR ratios constructed using data reported in Chambers (2009) for MR and Byrd and Liu (2008) for TRR

The conclusion from the Member State was that the MR:TRR ratio for liver exhibited a significant decline of the MR:TRR ratio with time after dosing. The MR:TRR ratio for liver relevant to the MRL proposal (8 days) is much lower than the 0.03 (or 3%) used by JECFA for liver and is likely to be <0.3 (0.003%). The plot of the data from Chambers (2009) showed an initial rapid decline phase followed by a longer slow terminal elimination phase (Figure 3.3).

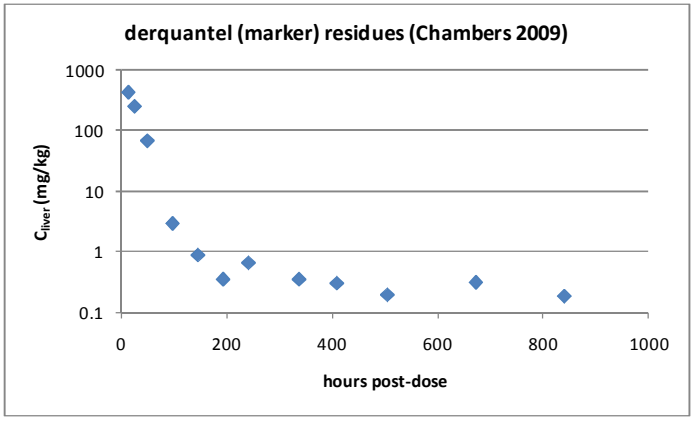


Figure 3.3. Plot of Marker residue (derquantel) residues with time after dosing

The Member State noted that the choice of MR:TRR ratio has a large impact on the resulting exposure assessment using the standard food basket and, if the MR:TRR ratio for liver is 0.003, this would give rise to a TMDI (liver only) that is 370% of the upper bound of the ADI established by JECFA. The Member State therefore proposed that an appropriate MR:TRR ratio for liver was less than 0.03 (3%) but more likely greater than 0.003 (0.3%). TRR in a single animal dosed at 2 mg/kg bw were 17.4 µg/kg at 28 days after dosing (Byrd, 2008, as stated in *FAO JECFA Monographs* 12, Table 3.16 (FAO, 2012), while derquantel residues at 28 days reported by Chambers (2009) were 0.32 ±0.19 µg/kg (or 0.21 ±0.13 µg/kg when corrected to the same dose). Overall TRR (single animal per time) in Byrd (2008) were lower than those in Byrd and Liu (2008), also suggesting lower MR concentrations. The Member State concluded that the liver MR:TRR ratio was anticipated to be about (0.21 ±0.13)/17.4 = 0.005–0.02.

Alternative approach proposed by the sponsor to determine the M:T ratio

The alternative approach proposed by the sponsor (Zoetis, 2013) utilized the residue depletion data determined by Chambers (2009) and the combined TRR data of Byrd and Liu (2008) and Byrd (2008). The focus was on residues from Day 4 and Day 6. To facilitate the comparison of residue concentrations from disparate studies, the TRR concentrations (dose of 2 mg/kg) were "arithmetically normalized" to the higher dose employed in the Chambers study (dose of 3 mg/kg) (i.e. the residue values from the 2 mg/kg TRR study dosing were multiplied by 1.5 to correspond to a 3 mg/kg residue depletion study dosing). The combined TRR data, including "arithmetically normalized" values, are shown in Tables 3.2–3.5.

Table 3.2. Total radioactive residue data – Day 4.

Tissue	TRR Data at 4 days (Studies 171+186)	Adjust for 3/2×dose	Mean TRR (µg/kg)	Std Dev Std Error	T Value (97.5%; 0.05/2.3)	Upper 95% CI Mean + T*SE (µg/kg)
Liver	122.1	183.15	292.05	85.3 42.7	3.1825	427.8
	178.3	267.45				
	249.3	373.95				
	229.1	343.65				
Kidney	20.5	30.75	58.725	25.3 12.6	3.1825	98.9
	29.3	43.95				
	53.1	79.65				
	53.7	80.55				
Muscle	1.7	2.55	4.6875	1.68 0.838	3.1825	7.4
	3.0	4.5				
	4.4	6.6				
	3.4	5.1				
Fat	1.8	2.7	9.525	7.43 3.72	3.1825	21.4
	6.1	9.15				
	4.2	6.3				
	13.3	19.95				

NOTES: CI = Confidence interval; T = total residue; T*SE = T-value × standard error of the mean. Studies 171 and 186 are sponsor study numbers and correspond to the combined TRR data of Bird and Liu, 2008, and Bird, 2008.

Table 3.3 Derquantel Marker Residue data – Day 4

Marker Residues (Chambers, 2009) (µg/kg)					Marker to Total Ratio [1]	Exposure at 4 Days	
Tissue	VHR [3]	PAH [4]	Mean	Group Mean		Consumption (kg)	Total [2] Intake (µg)
Liver	3.51	2.94	3.225	2.806	1.0%	0.1	42.8
	1.2	1.55	1.375				
	5.41	4.36	4.885				
	0.95	1.13	1.04				
	0.6	1.06	0.83				
	6.19	4.77	5.48				
Kidney	2.27	1.07	1.67	1.536	2.6%	0.05	4.9
	0.77	0.5	0.635				
	2.34	1.38	1.86				
	0.48	0.251	0.3655				
	0.51	0.317	0.4135				
	4.42	4.12	4.27				
Muscle	0.39	0.307	0.3485	0.514	11%	0.3	2.2
	0.28	0.124	0.202				
	0.45	0.576	0.513				
	0.39	0.108	0.249				
	0.37	0.118	0.244				
	1.61	1.44	1.525				
Fat SC/PR	3.55/2.36	3.26/3.14	2.96/3.20	4.17 (all PR and SC values)	44%	0.05	1.1
	0.15/0.78	0.958/0.984	0.47/0.97				
	0.13/4.87	7.8/3.75	2.50/5.78				
	2.11/0.95	1.8/0.815	1.53/1.31				
	0.72/0.81	1.03/0.804	0.77/0.92				
	21.8/14.2	11.9/11.5	18.0/11.7				
						TOTAL CONSUMPTION (µg) =	**51.0**

NOTES: (1) Group Mean (Table 3.3) divided by Mean TRR (Table 3.2); (2) Consumption Factor (Table 3.3) × Upper 95% Confidence interval (Table 3.2); (3) Analyses by VHR (Veterinary Health Research, Pty, Ltd); (4) Analyses by PAH (Pfizer Animal Health); CI = Confidence interval; PR = perirenal; SC = subcutaneous

Table 3.4. Total Radioactive Residue data – Day 6

Tissue	TRR Data at 6 days (Study 171)	Adjust for 3/2× dose	Mean TRR (µg/kg)	Std Dev Std Error	T Value (97.5%; 0.05/2.2)	95% Upper CI Mean + T*SE (µg/kg)
Liver	185.1	277.65	207.3	72.22	4.3027	386.7
	140.6	210.9				
	88.9	133.35		41.69		
Kidney	32.5	48.75	38.05	10.65	4.3027	64.5
	25.3	37.95				
	18.3	27.45		6.15		
Muscle	2.8	4.2	3.25	1.17	4.3027	6.1
	2.4	3.6				
	1.3	1.95		0.67		
Fat	1.9	2.85	2.3	0.95	4.3027	4.7
	1.9	2.85				
	0.8	1.2		0.55		

NOTES: CI = Confidence interval; T = total residue; T*SE = T-value × standard error of the mean.
SOURCE: Data provided by the sponsor.

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Table 3.5. Derquantel Marker Residue data – Day 6

Marker Residues (Chambers, 2009) (µg/kg)					Marker to Total Ratio [1]	Exposure at 6 Days	
Tissue	VHR [3]	PAH [4]	Mean	Group Mean		Consumption (kg)	Total [2] Intake (µg)
Liver	0.56	1.06	0.81	0.692	0.33%	0.1	38.7
	0.42	1.34	0.88				
	0.53	0.962	0.746				
	0.39	0.356	0.373				
	0.42	0.537	0.4785				
	0.56	1.17	0.865				
Kidney	0.15	0.123	0.1365	0.083	0.22%	0.05	3.2
	0.08	0.0606	0.0703				
	0.09	0.0776	0.0838				
	0.05	0.0477	0.04885				
	0.09	0.04	0.065				
	0.1	0.0834	0.0917				
Muscle	0.04	0.0436	0.0418	0.033	1.0%	0.3	1.8
	0.04	0.022	0.031				
	0.04	0.0257	0.03285				
	0.04	0.022	0.031				
	0.04	0.022	0.031				
	0.04	0.0236	0.0318				
Fat SC/PR	1.93/0.35	1.22/0.398	1.14/0.81	0.398 (all PR and SC values)	17%	0.05	0.2
	0.52/0.17	0.302/0.233	0.35/0.27				
	0.48/0.46	0.288/0.596	0.47/0.44				
	0.48/0.17	0.149/0.226	0.33/0.19				
	0.35/0.17	0.106/0.236	0.26/0.17				
	0.32/0.13	0.128/0.151	0.23/0.14				
					TOTAL CONSUMPTION (µg) =		**44.0**

NOTES: (1) Group Mean (Table 3.5) divided by Mean TRR (Table 3.4); (2) Consumption Factor (Table 3.5) × Upper 95% Confidence interval (Table 3.4); (3) Analyses by VHR (Veterinary Health Research, Pty, Ltd); (4) Analyses by PAH (Pfizer Animal Health). SC= subcutaneous; PR = perirenal.

Appraisal

As part of the current assessment, the concerns raised by the Member State, the alternative approach proposed by the sponsor, and the original assessment by the 75th Meeting of the JECFA (FAO, 2012) were all considered.

The Committee reviewed the comments provided by the Member State. A re-assessment of the residue depletion data indicated that residues at Day 6 are consistent with a total exposure below the TMDI. Thus, the Day 6 time-point can be used for the recommendation of MRLs, rather than the Day 8 time-point used for the original assessment. Data through Day 6 were used to determine the MR:TR ratios.

Regarding the alternative approach, the Committee concluded that determining the MR:TR ratio from a radiolabel study was the customary and preferred practice. This customary approach is compatible with MR:TR ratios through Day 6.

Maximum Residue Limits

In recommending MRLs for derquantel, the Committee considered the following factors:

- An ADI of 0–0.3 µg/kg bw was established previously by the Committee and confirmed at this meeting, based on an acute toxicological end-point. The upper bound of this ADI is equivalent to 18 µg/day for a 60 kg person.
- Derquantel is extensively metabolized; derquantel represents 6% of total residues in muscle, 3% in liver, 7% in kidney and 15% in fat. Derquantel, although constituting a small percentage of total residues, is suitable as the marker residue in tissues. No data are provided for residues in sheep milk.
- Liver contains the highest concentration of total radiolabelled residues at all sampling times. Fat contains the highest concentrations of derquantel residues in the unlabelled residue depletion study at early sampling points. At times beyond the Day 4 sampling time, derquantel residues are highest in liver. Derquantel residue concentrations are variable. The highest concentration of the proposed marker residue, derquantel, at the time-point relevant to recommending MRLs is found in liver, followed by fat, then kidney and then muscle. Liver and fat can serve as the target tissues.
- A validated analytical procedure for the determination of derquantel in edible sheep tissues (liver, kidney, muscle and fat) is available and may be used for monitoring purposes.
- The MRLs recommended for sheep tissues are based on the upper limit of the one-sided 95% confidence interval over the 95th percentile (the "upper tolerance limit 95/95" or UTL 95/95) for the Day 6 post-treatment data from the unlabelled residue depletion study.

Based on these new assessments, the Committee proposed the following revised MRLs in sheep tissues: 0.3 µg/kg in muscle, 0.4 µg/kg in kidney, 0.8 µg/kg in liver and 7.0 µg/kg in fat. There were insufficient data to calculate an EDI, and the TMDI approach was used.

Using the model diet and the MT:TR approach, these MRLs result in an estimated dietary exposure of 6.8 µg/person, which represents approximately 38% of the upper bound of the ADI.

Table 3.6. Calculation of the Theoretical Maximum Daily Intake (TMDI)

Tissue	MRL (µg/kg)	Standard Food Basket (kg)	MR:TR ratio	TMDI (µg)
Liver	0.8	0.1	0.03	2.7
Kidney	0.4	0.05	0.07	0.3
Muscle	0.3	0.3	0.06	1.5
Fat	7	0.05	0.15	2.3
			TMDI	**6.8**
			As % of ADI	38%

NOTES: MR:TR ratio is the ratio of marker residue to total residues.

References

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Byrd, J. & Liu, D. 2006. Pfizer Reference Number: 1545R-60-05-169. Southwest Bio-Labs Study Number: 205-0832. Xenobiotics Laboratories Reference Number: XBL05795. Pilot total residue depletion study in sheep: Generation and TRR determination of ovine excreta and tissue samples containing [^{14}C] PF-520904 residues.

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Concerns from a Member State. 2012. Submitted by the Delegation of Australia, includes one attachment with TMDI scenarios.

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