IVERMECTIN

RESIDUE DEPLETION STUDY

Background

Ivermectin residues, greater than expected after a withdrawal period of 35 days, were observed in livers of heavy cattle (~ 450 kg) treated with ivermectin injectable in New Zealand. The original cattle residue study summarized by the 36th JECFA Meeting was conducted with cattle weighing ~ 260 kg. In view of these new data, a definitive tissue residue study with ivermectin injectable was conducted using cattle weighing 300-400 kg. Cattle in this weight range were considered the most appropriate population in which to assess tissue residue depletion of anthelmintics based upon their use pattern in the cattle industry.

Cattle

Seventy eight crossbred beef cattle aged 12 to 14 months and weighing 297 to 401 kg were used. Seventy two of the animals were given IVOMEC Injection (1% w/v ivermectin) at 1 ml/50 kg, and six animals were used as untreated controls. The allocation of animals is detailed below.

Group	Treatment	Day of Slaughter	Number of Cattle[a]
1	Untreated controls	--[b]	6
2	IVOMEC Injection	21	12
3	IVOMEC Injection	28	12
4	IVOMEC Injection	35	12
5	IVOMEC Injection	42	12
6	IVOMEC Injection	49	12
7	IVOMEC Injection	56	12

[a] Equal number of steers and heifers
[b] One steer and heifer slaughtered on each of days 21, 35 and 56

At slaughter, samples of perirenal fat, both kidneys, the whole liver, skeletal muscle and injection site were collected, homogenized, then measured using HPLC assays developed and validated by the Company. The limit of detection of the assay is 1 ng/g.

Ivermectin (H_2B_{1a}) residue data from tissues of cattle slaughtered on Days 21-49 are summarized below in Table 1. Because tissues at day 49 contained ivermectin residues that were nearly undetectable, tissues from cattle slaughtered on Day 56 post-treatment were not assayed. Ivermectin residues were higher in liver than in fat and lowest in muscle and kidney. On Day 42, all residue values for liver and fat were $\leq$ 10 ng/g. Ivermectin residues for muscle and kidney were low relative to those of liver and fat and by Day 35 all values for muscle and kidney were near or below the level of detection of the assay. Concentrations of H_2B_{1a} in injection sites of some cattle are ~2500 ng/g at 35 (1/12), 42 (2/12) and 49 (1/12) days post-treatment. Metabolism of ivermectin is not expected in the injection site; therefore, the majority of the total residue is probably parent ivermectin. (Wallace et al., 1992)

Table 1. Concentration (ng/g) of Ivermectin (H_2B_{1a}) in Tissues of Cattle Treated with a Single SC Injection of 0.3 mg/kg

Withdrawal Time (days)	Muscle	Liver	Kidney	Fat	Inj. Site
21	4	46	4	29	NA
28	1	27	2	11	1280
35	1	10	1	6	576
42	0	3	0	2	570
49	0	3	0	1	231

NA - Not assayed

APPRAISAL

JECFA used the residue chemistry data in the monograph developed for the 36th Session of JECFA to recommend MRLs in cattle as follows:

Cattle

Based on the ADI of 0-1 μg/kg established by the 40th JECFA, the permitted maximum daily intake of ivermectin is 60 μg of total drug-related residue contributed by 500 g of food animal meat in the diet of a 60-kg person. At 28 days of withdrawal, the intake of residues of ivermectin is well below the ADI. Based on the data from the metabolism and residue studies, JECFA recommended MRLs of 100 μg/kg for liver and 40 μg/kg for fat (see Table 2).

Table 2. Recommended MRLs for Ivermectin in Cattle

Tissue	Observed Concentration at Day 28 Withdrawal, μg/kg 0.3 mg/kg SC	μg Ivermectin Consumed	μg/kg Recommended MRL (parent)	μg(a) Consumed (Theory)
Muscle	1(1.5)b	0.45	2(3)b	0.9
Liver	27(73)c	7.30	100(270)c	27.0
Kidney	2(3.7)d	0.19	4(7.4)d	1.4
Fat	11(61)e	3.05	40(222)e	11.1
Total		10.99		40.4

a) Based on a daily intake of 0.3 kg muscle, 0.1 kg liver, 0.05 kg kidney and fat.
b) Adjusted observed value by 67% to estimate total residues at 28 days withdrawal.
c) Adjusted observed value by 37% to estimate total residues at 28 days withdrawal.
d) Adjusted observed value by 54% to estimate total residues at 28 days withdrawal.
e) Adjusted observed value by 18% to estimate total residues at 28 days withdrawal.

The concentrations of ivermectin at the injection site were considered significant in regards to their quantity; however, the human toxicological data summarized in the WHO monograph established that the extremely rare consumption of an injection site would not result in an adverse health effect.

REFERENCES

Wallace, D.H., Kunkle, B.N., Maddox, R., Wooden, J.W., Malinski, T.J., Fox, A. and Wehner, T.A. 1992. Unpublished report ASR 13527. Submitted to FAO by Merck, Sharp and Dohme Research Laboratories, Rahway, NJ.