

RACTOPAMINE HYDROCHLORIDE

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ADDENDUM

**to the Ractopamine Hydrochloride residue monograph prepared by the 62nd meeting
of the Committee and published in FAO Food and Nutrition Paper 41/16, Rome 2004**

The 62nd meeting of the Committee reviewed ractopamine hydrochloride and established an ADI of 0-1.0 µg per kg of body weight, equivalent to 0-60 µg for a 60 kg person, and recommended MRLs for edible tissues of pigs and cattle, expressed as ractopamine base: muscle, 10 µg/kg; liver, 40 µg/kg; kidney, 90 µg/kg; and fat, 10 µg/kg. The recommended MRLs result in a theoretical daily maximum intake of 50 µg, or 84% of the upper bound of the ADI, based on the JECFA model diet of 300 g of muscle, 100 g of liver and 50 g each of kidney and fat.

In considering these recommendations at its 15th Session in 2004, CCRVDF noted that the ADI recommended by JECFA had been rounded down resulting in a lower ADI than had been established by some member states (CAC, 2005). After further discussion concerning the JECFA policy on rounding the ADI to one significant figure, the CCRVDF agreed that JECFA should be requested to consider setting the MRLs using the calculated value obtained by dividing the NOEL by the safety factor and to recommend MRLs for ractopamine hydrochloride based on this result, not the one significant figure rounded value (0-1 µg per kg b.w.). The present Committee confirmed that the rounding practices used in expressing the ADI are scientifically and mathematically sound (see General considerations, page 2).

The present Committee reviewed the MRLs recommended at the 62nd meeting. The MRLs recommended for liver and kidney of pigs and cattle by the 62nd Committee were based primarily on the large set of available data from the pig studies, supported by the smaller number of studies and data for cattle. While these MRLs should accommodate the majority of situations involving slaughter within 12 hours of last treatment for both pigs and cattle, the available data for cattle suggest that the residue distribution between liver and kidney of cattle may not be the same as that in pigs.

The relationship between marker and total residues in cattle liver and kidney appears to be dose-dependent, so that the amount of marker residue in cattle liver may be as high as 80-85% of the marker residue found in kidney from the same animal. In one study (Study ABC-0408, 1989), conducted to assess relationships between marker and total residues, the mean residues found in livers and kidneys from 3 animals sacrificed 12 hours after the last treatment were 36 µg/kg and 43 µg/kg, respectively. This is higher than the residues ratio found in the cattle liver and kidney in other studies, where residues in liver varied from 32% of those found in kidney (Smith and Shelver, 2002) to 45% at 12 hours post-treatment (Study T4V739301, 1995). These studies were summarized in the FAO monograph prepared by the 62nd meeting of the Committee (FAO, 2004). No new data were provided for consideration at the present meeting of the Committee.

The study conducted at a dose equivalent to 45 mg/kg in feed by rumen insertion of a capsule containing the drug (Dalidowicz et al, 1987) was the only study where ractopamine parent

residues were detected in muscle and fat (0.02 and 0.01 mg/kg, respectively). Residues of parent ractopamine were not detected in the other studies where tissues were tested. Total radiolabelled residues were 0.01 to 0.05 mg/kg in muscle and fat at 12 hrs post-administration and depleted rapidly to non-detectable within a few days, even with administration above the recommended dose. Therefore, the recommendation of MRLs for muscle and fat of cattle based on the limit of quantitation (LOQ) was considered appropriate. The studies conducted at the recommended dose did not provide evidence that residues in liver and kidney of cattle would exceed the recommended MRLs for those tissues.

Pooled data from the depletion studies in pigs reviewed by the 62nd meeting of the Committee were evaluated using an Excel[®]-based worksheet. The data covering the time span from 12 to 120 hours after the last exposure used by the 62nd Committee in recommending the MRLs, were subjected to further statistical evaluations. Figures 1 and 2 show the data points, the linear regression line and a dotted line of the tolerance limits¹.

The Committee considered that the data available for residue depletion in cattle were not suitable for evaluation using the Excel[®] worksheet, due to the various dose rates and modes of administration used in the studies. A residue depletion study with unlabelled ractopamine administered in feed at the recommended maximum dose is required for the Committee to conduct this evaluation to reconsider the MRLs for cattle.

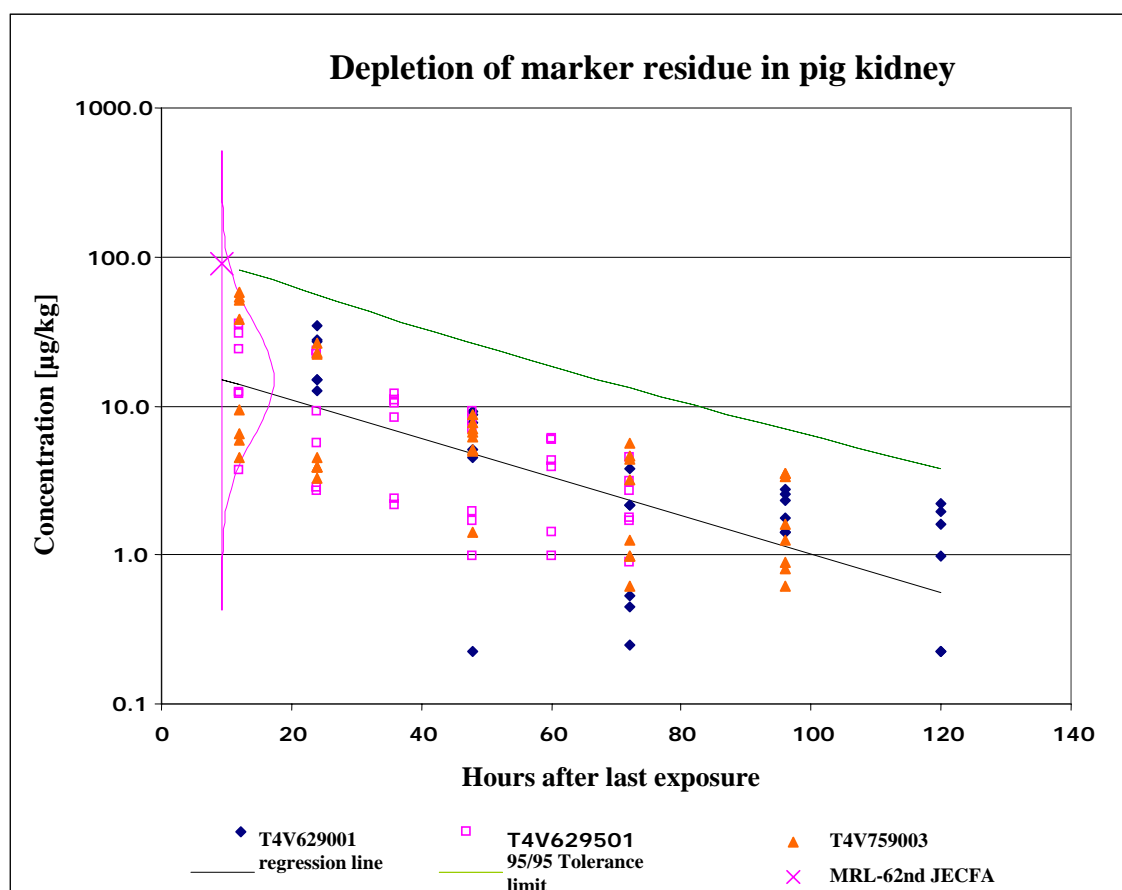


Figure 1: Depletion of marker residue in kidneys of ractopamine-treated pigs

¹ The upper limit of the one-sided 95 % confidence interval over the 95th percentiles is used throughout and referred to as “tolerance limit”.

The MRLs recommended by the 62nd JECFA are shown as a point “×” on the line showing the tolerance limits. The MRL for kidney is 90 µg/kg. The exact depletion time to reach this point is 9.324 hours. At this time point the distribution of marker residue concentrations between -4 and +4 standard deviations is shown in Figure 1. It has a median value of 14.97 µg/kg. The residue content corresponding to +4 standard deviations is 520 µg/kg; the content corresponding to -4 standard deviations is 0.431 µg/kg, indicating that the residue contents in kidney show a high variability. The MRL for liver is 40 µg/kg. The exact time to reach this value is 2.39 hours. Figure 2 shows the distribution of residue contents at this time point. The median concentration is 9.8 µg/kg. The numerical value corresponding to +4 standard deviations is 151 µg/kg; the content corresponding to -4 standard deviations is 0.640 µg/kg. The concentrations in liver are lower than those measured in kidney and show a slightly smaller variability. The MRL in kidney determines the minimum depletion time to comply with both MRLs. The statistical approach using the Excel[®]-based worksheet would lead to approximately the same MRL recommendations made by the 62nd meeting of the Committee.

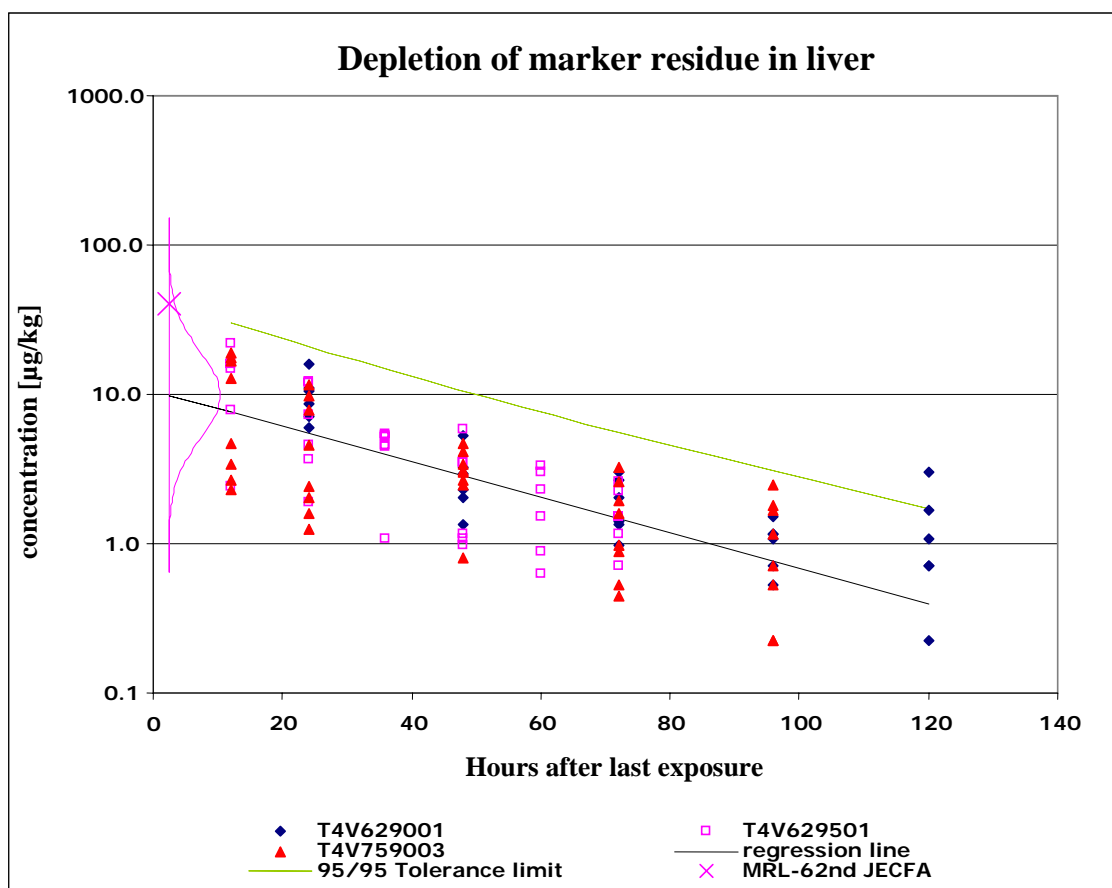


Figure 2: Depletion of marker residue in liver of pigs treated with ractopamine

The distribution of residue contents at time point “×” were used by the present Committee for testing different approaches to intake estimation. Based on one of the recommendations of the *Workshop on MRLs for Pesticides and Veterinary Drugs* held 7-10 November, 2005, in Bilthoven, The Netherlands, in the framework of the ongoing project “*Updating the Principles and Methods of Risk Assessment*”, the Committee considered the median value of the distribution of ractopamine residue concentrations (from which the MRL is derived) for

the calculation of conservative estimates of long-term (chronic) intakes. Different approaches were tested to investigate the variability of the estimate, taking account of the variability of the ratio between the marker residue and the total residue as functions of animal species, dose and time. After review of the results, the median value of the distribution of residue concentrations (from which the MRL is recommended) was used as a new point estimate instead of the recommended MRL. The calculations are based on the time (9.3 h) estimated to obtain 95% of ractopamine residues in kidney below the MRL of 90 µg/kg recommended for this tissue (Figure 1). The median residue concentrations calculated at this time were: liver, 8 µg/kg, kidney, 15 µg/kg, muscle, 5.0 µg/kg and fat 2.5 µg/kg. Using this approach, the data-derived factors for the transformation of marker residue concentrations to total residue concentrations were: muscle, 1.0; liver, 6.3; kidney, 3.1; fat, 1.0.

Applying this analysis to recommended MRLs, the Committee concluded that based on the available data the MRLs recommended by the 62nd Committee for liver and kidney of pigs and cattle remained appropriate. The Committee affirmed the MRLs recommended at the 62nd meeting of the Committee. Based on the median values and the data-derived factors, the corresponding daily intake estimate is 9.0 µg (see Table 1).

Table 1: Estimated Daily Intake of Ractopamine Residues from median value obtained from data for tissues from pigs

Food Item	Median (µg/kg)	Standard Food Basket (kg)	MR/TR ¹	EDI (µg)
Muscle	5.00	0.300	1.00	1.5
Liver	8.14	0.100	6.29	5.1
Kidney	14.97	0.050	3.05	2.3
Fat	2.50	0.050	1.00	0.1
Total:				9.0

¹ MR = marker residue (parent drug); TR = total residues

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