MELENGESTROL ACETATE

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ADDENDUM
to the monograph and its addendum prepared by the 54th, 58th and 62nd meetings of the Committee and published in FAO Food and Nutrition Papers 41/13, 41/14 and 41/16, respectively.

Melengestrol acetate (MGA) is an orally active progestogen. It is used to improve feed conversion efficiency, promote growth and suppress estrus in female beef cattle fed for slaughter. The range of approved doses is 0.25 to 0.50 mg/heifer daily. MGA is fed for the duration of the fattening/finishing period, usually 90 to 150 days. The Committee previously evaluated MGA at the 54th, 58th and 62nd meetings (FAO, 2000; FAO, 2002; FAO, 2004, respectively). An ADI of 0-0.03 μg/kg of body weight was established based on hormonal activity. At the 62nd meeting of the Committee, MRLs of 8 μg/kg for fat and 5 μg/kg for liver in cattle were recommended, considering the new studies for which sufficient material could be isolated to identify and measure the relative progestational activity of all metabolites from treated animals compared to parent drug. The Secretariat was made aware of an error in the calculation of the MRLs and placed MGA on the agenda for the purpose of recalculating the MRLs.

The 62nd meeting reported the structure and progestogenic activity of the major metabolites of MGA. The progestogenic activity of the metabolites relative to MGA ranged from 0.09% to 12%. The percent of the total progestogenic activity attributable to MGA and to its metabolites was estimated from the percent of the total radioactive residue attributable to MGA and to its metabolites, and by assuming the relative progestogenic potency of all metabolites of MGA was 12%. The present Committee used percent median tritium-labelled MGA data from the 54th meeting when estimating the percent of total progestogenic activity attributable to MGA and to its metabolites in fat, liver, muscle and kidney (Table 1).

Table 1: Conversion of total radioactivity to progestogenic activity for MGA-related residues in tissues

Tissue	% of total radioactive residue attributable to:		% of total progestogenic activity attributable to[b]		
	MGA[a]	MGA metabolites	MGA	MGA metabolites	Sum of progestogenic residues (%)
Fat	**86**	14	$\frac{86 \times 1 \times 100}{86 + (0.12 \times 14)}$	**$\frac{14 \times 0.12 \times 100}{86 + (0.12 \times 14)}$**	98.08 + 1.92 = 100
Liver	30	70	$\frac{30 \times 1 \times 100}{30 + (0.12 \times 70)}$	$\frac{70 \times 0.12 \times 100}{30 + (0.12 \times 70)}$	78.12 + 21.88 = 100
Muscle	40	60	$\frac{40 \times 1 \times 100}{40 + (0.12 \times 60)}$	$\frac{60 \times 0.12 \times 100}{40 + (0.12 \times 60)}$	84.75 + 15.25 = 100
Kidney	34	66	$\frac{34 \times 1 \times 100}{34 + (0.12 \times 66)}$	$\frac{66 \times 0.12 \times 100}{34 + (0.12 \times 66)}$	81.11 + 18.89 = 100

[a] % Median ^{3}H-MGA data from 54th meeting of the Committee.

[b] The % of progestogenic activity of MGA-related residues is calculated by applying a weighting factor of 1 to MGA and of 0.12 (corresponding to the relative potency of the metabolite of MGA with the highest progestogenic activity) to all MGA metabolites in fat, liver, muscle and kidney, respectively.

The present Committee reconsidered data submitted to the 54th meeting. The Committee recommended that the MRLs should be derived from the 99th percentile of MGA concentrations in perirenal fat, collected either by biopsy or upon slaughter within short intervals after cessation of treatment, of feedlot animals treated with the highest recommended dose. The 54th meeting of the Committee had obtained this information by evaluating eight studies involving 370 animals treated at different doses (FAO, 2000). The majority of the animals (n=199) in two studies had been treated with the highest recommended dose of 0.5 mg MGA per heifer daily. The 99th percentile derived for MGA residues in perirenal fat for these animals was 18.5 µg/kg. There was relatively good agreement between this value and the 99th percentile value of 16.3 µg/kg for MGA residues in perirenal fat for all study animals derived by dose-response interpolations and dose extrapolations.

The median concentration of the marker residue obtained from a study with three animals treated with tritium-labelled MGA was 6.6 µg/kg for fat, 3.6 µg/kg for liver, 0.2 µg/kg for muscle and 0.6 µg/kg for kidney (Table 2). The proportion of the concentration found in the other three tissues, compared with perirenal fat that contains the highest residues, was derived from this study and was approximately 1:1.8 for liver, 1:33 for muscle and 1:11 for kidney.

MAXIMUM RESIDUE LIMITS

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

- The parent drug, MGA, is the marker residue.
- Fat, which contains the highest residue, is the most suitable target tissue for the purpose of monitoring the residues of MGA.
- The median concentrations of the marker residue were 6.6 µg/kg for fat, 3.6 µg/kg for liver, 0.2 µg/kg for muscle and 0.6 µg/kg for kidney.
- The conversion of marker residue to total residue was based on the fraction of the total progestogenic activity attributable to the marker residue; this fraction was 0.98 for fat, 0.78 for liver, 0.85 for muscle and 0.81 for kidney.
- A validated analytical method previously identified is available and suitable for routine monitoring.
- The established ADI is 0-0.03 µg/kg bw, equivalent to 0-1.8 µg for a 60 kg person.

On the basis of the above considerations, the Committee recommended MRLs in cattle of 18 µg/kg in fat, 10 µg/kg in liver, 1 µg/kg in muscle and 2 µg/kg in kidney, expressed as MGA. The TMDI corresponding to these MRLs is 2.7 µg or 150 % of the upper bound of the ADI. The Estimated Daily Intake (see Table 2) is 0.9 µg or 50% of the upper bound of the ADI.

Table 2: Estimated daily intake of MGA residues

Tissue	Median MGA[a] (µg/kg)	Fraction of total progestogenic activity attributable to marker residue	Total residue (µg/kg)	Standard Food Basket (kg)	Intake of residues (µg)
Fat	6.62	0.98	6.8	0.05	0.34
Liver	3.60	0.78	4.6	0.1	0.46
Muscle	0.20	0.85	0.24	0.3	0.07
Kidney	0.61	0.81	0.75	0.05	0.04
EDI					0.9

[a] Marker residue MGA

REFERENCES

FAO (2000). Melengestrol acetate. Residues of some veterinary drugs in animals and foods (Monograph prepared by the fifty-fourth meeting of the Joint FAO/WHO Expert Committee on Food Additives). FAO Food and Nutrition Paper 41/13, 75-86, Rome.

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