ABAMECTIN (177)

EXPLANATION

Abamectin was placed on the agenda of the 2000 JMPR at the request of the CCPR at its thirty-second session in 2000 for reconsideration of the residue definition for animal commodities with a view to removing avermectin B_{1b} and 8,9-*Z*-avermectin B_{1b} from the definition for residues in animal commodities.

APPRAISAL

Abamectin is used both as a pesticide and as an anthelminthic drug in animals. It was evaluated toxicologically by the Meeting in 1992 and 1994, and an ADI of 0-0.0002 mg/kg bw was established on the basis of a NOAEL of 0.12 mg/kg bw per day for toxicity in pups in a study of reproductive toxicity in rats. A safety factor of 500 was applied because of concern about the teratogenicity of the 8,9-*Z*-isomer, a photodegradation product that has been detected as a residue in plants. MRLs were recommended for commodities of cattle (edible offal, 0.05 mg/kg; meat, 0.01* mg/kg; milk, 0.005 mg/kg) and goats (edible offal, 0.1 mg/kg; meat, 0.01* mg/kg; milk, 0.005 mg/kg). The residues were defined in 1992 as the sum of avermectin B_{1a}, 8,9-*Z*-avermectin B_{1a}, and avermectin B_{1b}. The 1992 Meeting was unaware of the existence of a photoisomer of avermectin B_{1b}.

In the analytical method, avermectin B_{1a} is derivatized to a fluorescent compound for analysis by HPLC. As avermectin B_{1a} and its 8,9-*Z*-isomer form an identical fluorescent derivative, they are not separated or distinguished in the analysis for residues. The method gives a single HPLC peak for the sum of avermectin B_{1a} and its 8,9-*Z*-isomer. Avermectin B_{1b} and its photoisomer behave analogously to produce a second, but smaller, peak. In 1992, the LOQ (known at that time as the limit of determination) for meat was 0.01 mg/kg.

The use of abamectin as a veterinary drug was considered by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) at its forty-fifth meeting, in 1995. The Committee had intended to rely on the toxicological evaluation of the 1994 JMPR, but, on reviewing the data on the residues found when abamectin is used as a veterinary drug, it learned that the 8,9-*Z*-isomer is not present in animal tissues and that the major residue in cattle liver and fat is avermectin B_{1a}, accounting for 50% of the total residue 7 days after treatment. 24-Hydroxymethyl-B_{1a} is a major part of a polar residue fraction that accounts for 22% of the total residue in liver 14 days after treatment and a major part of a fraction that accounts for 51% of the total residue in fat 21 days after treatment. Avermectin B_{1b}, which represents about 5% of the total residue in liver and fat 7 days after treatment, is a minor residue. Therefore, JECFA concluded that avermectin B_{1a} is a suitable marker residue and recommended that consultations be held between representatives of JECFA and JMPR. At that meeting, held in September 1995, it was recognized that consideration should be given to establishing different ADIs for abamectin when it is used as a pesticide and as a veterinary drug.

As a consequence, the 1995 JMPR agreed that the ADI of 0-0.0002 mg/kg bw was not appropriate for abamectin residues that do not contain the 8,9-*Z*-isomer, and it allocated an ADI of 0-

0.001 mg/kg bw to abamectin, on the basis of a NOAEL of 0.12 mg/kg bw per day observed in the study of reproductive toxicity in rats, with a safety factor of 100.

JECFA at its forty-seventh meeting, in 1996, established MRLs of 0.1 mg/kg for cattle liver and fat, and 0.05 mg/kg for cattle kidney. The marker residue was avermectin B_{1a}. A validated analytical method (HPLC with fluorescence detection) for avermectin B_{1a} is available. The residue defined for estimation of dietary intake is the total residue.

New toxicological data were evaluated by the JMPR in 1997. In view of the finding that rats are hypersusceptible postnatally, the Meeting agreed to reduce the interspecies safety factor in establishing an ADI. A safety factor of 50 was therefore applied to the NOAEL of 0.12 mg/kg bw in the multigeneration study in rats, which is corroborated by a NOEL of 0.24 mg/kg bw per day in a 1-year study in dogs, with a safety factor of 100. It was considered appropriate to establish a single ADI for abamectin and its 8,9-*Z*-isomer, since the potential teratogenicity of the isomer had been satisfactorily explained. An ADI of 0-0.002 mg/kg bw was established for the sum of abamectin and its 8,9-*Z*-isomer. In order to harmonize the MRLs with those proposed by JECFA, the Meeting suggested that the MRLs be modified as follows: cattle edible offal to be removed; cattle liver and cattle fat, 0.1 mg/kg; and cattle kidney, 0.05 mg/kg. These numerical values are the same as those proposed by JECFA, but the residue definition differs by including avermectin B_{1a}, avermectin B_{1b}, 8,9-*Z*-avermectin B_{1a}, and 8,9-*Z*-avermectin B_{1b}. The proposed MRLs for goat commodities remained unchanged.

The Meeting noted the large margin of safety between the estimated dietary intake of residues resulting from the accepted uses and the newly established ADI and concluded that the residue definition is not a matter of concern to public health but a question of analytical method and national enforcement measures for compliance with MRLs.

At a meeting to facilitate harmonization between JECFA and JMPR, held on 1-2 February 1999, the different definitions of the CCPR and the CCRVDF for residues of abamectin were noted, and the CCRVDF and JECFA were asked to consider expanding their residue definitions to include other isomers, such as the photodegradation isomer of avermectin B_{1a}.

JECFA at its fifty-fourth meeting, in February 2000, carefully considered the toxicological and chemical assessments of abamectin made by JMPR and concluded that inclusion of the photodegradation isomer in the residue definition would not be consistent with the assessment by JECFA of abamectin as a veterinary drug. Inclusion of other possible residues of abamectin will be reviewed at a future JECFA meeting.

The CCPR at its thirty-second session, in May 2000, noted that the CCRVDF at its 12th meeting had retained all draft MRLs at step 7 because of the different residue definitions for animal products proposed by JECFA and JMPR. The CCPR therefore decided to refer the question of the residue definition for animal products to the 2000 JMPR with the suggestion that avermectin B_{1b} and 8,9-*Z*-avermectin B_{1b} be removed from the definition for the sake of harmonization. In the meantime, the CCPR returned all draft MRLs for animal commodities to step 6 and advanced all draft MRLs for plant commodities to Step 8.

The following Table summarizes the residue definitions and MRLs currently recommended by the JMPR and JECFA.

Commodity	Residue definition		
	JMPR 1992	JMPR 1997	JECFA 1996
	Sum of avermectin B_{1a}, B_{1b} and 8,9-Z-avermectin B_{1a}	Sum of avermectin B_{1a}, B_{1b}, 8,9-Z-avermectin B_{1a} and B_{1b}	Avermectin B_{1a}
	MRL, mg/kg	MRL, mg/kg	MRL, mg/kg
Cattle edible offal	0.1	W	--
Cattle meat	0.01*		--
Cattle milk	0.005		--
Cattle liver		0.1	0.1
Cattle fat		0.1	0.1
Cattle kidney		0.05	0.05
Goat edible offal	0.1		--
Goat meat	0.01*		--
Goat milk	0.005		--

W: the previous recommendation is withdrawn

RECOMMENDATIONS

The Meeting recommended harmonizing the JMPR and JECFA proposals for abamectin in animal commodities by maintaining the recommended MRLs of 0.1 mg/kg for cattle liver and fat and 0.05 mg/kg for kidney, and simplifying the definition of the residue in animal commodities to include only avermectin B_{1a} and 8,9-*Z*-avermectin B_{1a} (i.e. eliminating avermectin B_{1b} and 8,9-*Z*-avermectin B_{1b}).

Definition of the residue for compliance with MRLs for animal commodities: sum of avermectin B_{1a} and 8,9-*Z*-avermectin B_{1a}.

Definition of the residue for compliance with MRLs for plant commodities and for estimating dietary intake: sum of avermectin B_{1a}, avermectin $B_{1b,}$ 8,9-*Z*-avermectin B_{1a} and 8-9-Z-avermectin B_{1b}.

CCN	Commodity	Recommended MRL, mg/kg[1]
MF 0812	Cattle fat	0.1
MO 1289	Cattle, kidney	0.05
MO 1281	Cattle, liver	0.1
MM 0812	Cattle meat	0.01*
ML 0812	Cattle milk	0.005
MO 0814	Goat, Edible offal of	0.1
MM 0814	Goat meat	0.01*
ML 0814	Goat milk	0.005

[1] The numerical values remain unchanged but with a revised residue definition

The present Meeting recommended that the JMPR and JECFA continue to meet to harmonize recommendations for MRLs, definitions of residues and marker residues, and commodity descriptions for substances used both as pesticides and veterinary drugs.