Bromoxynil Residues Assessment

Summary

1. Background

The Australian Pesticides and Veterinary Medicines Authority (APVMA) has evaluated an application from Nufarm Australia Limited to approve a label for Nufarm Bromicide 200 Selective Herbicide (APVMA Product Number 31614) to include a use in sorghum to control a range of weeds. The application also provided information to enable the establishment of an entry to Table 4 of the MRL Standard for bromoxynil on cereal fodder and forage and pasture. The application was the subject of a Trade Advice Notice in June 2008. Comment received during the Trade Consultation Process resulted in the APVMA reconsidering the recommendations proposed in the TAN relating to grazing withholding periods and Maximum Residue Limits in both animal feed commodities and animal commodities. Those changes are outlined here. Further consideration of the use in regard to sorghum grain was not required.

2. Results from residues trials presented to the APVMA

Maximum label rates for use of bromoxynil on pastures and crops likely to produce animal feeds are:

Pastures	560 g ai/ha
Winter cereals	560 g ai/ha
Sorghum	400 g ai/ha

3. Results from residues trials presented to the APVMA

Animal feed commodities

Forage and fodder residue data relevant to the decision are summarised below.

Table 1. Summary of relevant bromoxynil residue data in forage and fodder. Sampling times varied between treatments. The half life of bromoxynil residues in pasture was estimated to be 6 to 8 days. Dry matter content of winter cereals and pastures was not reported. The pasture trials at 300-313 g ai/ha were undertaken on rye grass and the other trials on mixed grass pastures.

Crop	Rate (g ai/ha)	WHP	Sample	Residues (mg/kg as received)
Sorghum (AUS)	420	14	forage	2.0, 2.1, 3.4, **4.9** (DW)
		84	fodder	0.02 (DW)
		95	fodder	0.06 (DW)
Winter Cereals (Europe)	400	86-95	fodder	<0.1 ×5
		96-105	fodder	<0.1, **0.1**
		>105	fodder	<0.1 ×4
	415-470	46-75	fodder	<0.02,<0.05×5, <0.1
		76-85	fodder	<0.05×7
		86-89	fodder	<0.05

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Crop	Rate (g ai/ha)	WHP	Sample	Residues (mg/kg as received)
		96-105	fodder	<0.05×2, <0.1
		>105	fodder	<0.05×2, <0.1
	500	>105	fodder	<0.01×2, <0.1
	800	60-75	fodder	<0.1×2
		76-85	fodder	<0.1×2
		86-95	fodder	<0.1×3
Pasture	300-313	14	forage	<0.1×2
(Europe)	300-314	35-42	forage	<0.05, <0.1
	300-315	>56	forage	<0.01, <0.05
	400	12-14	forage	0.2, 2.3, 2.7, 2.9, 3
	400	35-42	forage	<0.08, 0.1, 0.19, 0.3
	800	12-14	forage	1.7, 5.9, **12.5**
	800	35-42	forage	<0.08, <0.08, **0.4**

Animal Commodities

Results of three animal transfer studies undertaken with bromoxynil (as the phenol or octanoate) are available to the APVMA and indicate that residues are present in animal commodities and milk products following exposure to bromoxynil at low levels in the diet. Two of the transfer studies addressed residues in milk.

4. Residues at the currently established grazing withholding period of 14 days

Based on the information in Table 1 the highest residue observed in sorghum forage following a 14 day withholding period was 4.9 mg/kg (DW). In the pasture trials the highest residue was at 800 g ai/ha. Applying a linear correction for application rate the pasture residue observation is estimated to be 8.75 mg/kg (12.5×560/800).

Dry matter content of the pasture was not reported. Based on an observed high residue of 8.75 mg/kg the dietary burden for cattle is estimated below assuming a dry matter content of 20%.

Cattle- 500 kg bw, 20 kg DM/day

Commodity	% in diet	Feed intake	Residue, mg/kg (HR)	% DM	Livestock dietary exposure		
					mg/animal	ppm	mg/kg bw
Grass Pasture	100	20	8.75	20	875	44	1.75

The highest bromoxynil residue (expressed as bromoxynil phenol) in tissues and milk after dosing at 42 ppm (bromoxynil phenol) for 34 days and required MRLs for the estimated dietary burden of 44 ppm are summarised below.

Sample	Bromoxynil residues after dosing at 42 ppm (mg/kg)	Required MRL (mg/kg)
Liver	11.7	25
Kidney	18.7	
Muscle	3.2	5
Fat	9.8	15
Milk	0.58	1

Chronic dietary exposure to bromoxynil with a 14 day grazing withholding period

The following health standards have been recommended by the Office of Chemical Safety, Department of Health and Ageing (ADI and ARfD lists, 31 December 2008).

Compound	Dietary Standard, mg/kg bw		No Observable Effect Level (NOEL), mg/kg bw	Safety Factor	Reference
Bromoxynil	ADI[1]	0.003	0.3	100	OCS, 19/02/93
	ARfD[2]	Not established			

The chronic dietary exposure to bromoxynil is estimated by the National Estimated Daily Intake (NEDI) calculation encompassing all registered/temporary uses of the chemical and the mean daily dietary consumption data derived from the 1995 National Nutrition Survey of Australia. The NEDI calculation is made in accordance with WHO Guidelines[3] and is a conservative estimate of dietary exposure to chemical residues in food. The results of the NEDI calculation are summarised below.

Compound	ADI mg/kg bw	NEDI (%ADI)
Bromoxynil	0.003	417%

The NEDI for bromoxynil is equivalent to 417% of the ADI and is not acceptable.

Trade risk associated with a 14 day grazing withholding period

Codex MRLs have not been established for bromoxynil.

The following relevant overseas residue MRLs/ tolerances have been established for bromoxynil residues in animal feeds:

Country/status	Commodity	Tolerance, mg/kg
USA	Sorghum, grain, forage	0.5
	Sorghum, grain, stover	0.2
Japan	Hay (includes hay, fodder, straw & silage)	0.1*
	Sorghum grain	0.2

*Established under the Amendment to the Enforcement Ordinance of the Standards of Feed and Feed Additives, Ministry of Agriculture, Forestry and Fisheries, Japan.

1 http://www.health.gov.au/internet/main/Publishing.nsf/Content/ocs-adi-list.htm
2 http://www.health.gov.au/internet/main/Publishing.nsf/Content/ocs-arfd-list.htm
3 Guidelines for predicting dietary intake of pesticide residues, WHO, 1997.

The following relevant overseas animal commodity MRLs /tolerances have been established for bromoxynil:

Country	Commodity	Tolerance, mg/kg
Australia – required for a 14 day grazing WHP (bromoxynil)	Meat (mammalian) [in the fat]	15
	Edible offal (mammalian)	30
	Milks	1
USA (bromoxynil (3,5-dibromo-4-hydroxybenzonitrile) and its metabolite 3,5-dibromo-4-hydroxybenzoic acid (DBHA))	Cattle, fat	1
	Cattle, meat	0.5
	Cattle, meat by-products	3.5
	Milk	0.1
Japan (bromoxynil)	Cattle, muscle	0.07 (provisional)
	Cattle, fat	0.1 (provisional)
	Cattle, liver	0.07 (provisional)
	Cattle kidney	0.07 (provisional)
	Cattle, edible offal	0.07 (provisional)
	Milk	0.07 (provisional)
EU (for bromoxynil including its esters expressed as bromoxynil – fat soluble)	Meat, fat, liver, kidney	0.05
	edible offal	0.2
	Others	0.05
	Milk	*0.01

No MRLs for bromoxynil are established for animal commodities by Codex, Korea or Taiwan. The critical bromoxynil residue concentration for trade purposes is a reasonable Limit of Quantitation of 0.01 mg/kg for all tissues and milk and 0.1 mg/kg for export fodder. Residues likely to arise following observance of a 14 day grazing and cutting for stockfood withholding period constitute an undue prejudice to trade and are not acceptable.

5. Residues at a grazing withholding period of 8 weeks (56 days)

Based on the information in Table 1 the residues observed in sorghum forage after an 8 week withholding period were 0.02 mg/kg in (DW) at 84 days and 0.06 mg/kg (DW) after 95 days.

In the European pasture trials the highest residue at 8 weeks after application was <0.05 mg/kg at an application rate of 315 g ai/ha (315/560=0.56X). The longest withholding period examined at the higher application rates was 35 - 42 days where residues of 0.4 mg/kg (800 g ai/ha) were observed. Applying a linear correction for application rate the highest pasture residue observation is estimated to be 0.28 mg/kg (0.4×560/800). Based on an estimated half life of residues in pasture of 6 to 8 days, approximately 2 additional half lives would elapse prior to the withholding period of 56 days and estimated residues would be 0.07 mg/kg (FW) or 0.35 mg/kg on a dry weight basis (assuming 20% DM).

In the cereal trials the shortest fodder withholding period examined was 60 days. Only 1 detectable residue was observed of 0.1 mg/kg in grain and straw at approximately 100 days after treatment, which was assumed to be at commercial maturity.

Based on the above data and analysis it is appropriate to establish a Primary Feed Commodity MRL for bromoxynil of T1 mg/kg pending provision of Australian data. The dietary burden for cattle is estimated below.

Cattle- 500 kg bw, 20 kg DM/day

Commodity	% in diet	Feed intake	Residue, mg/kg (HR)	% DM	Livestock dietary exposure		
					mg/animal	ppm	mg/kg bw
Grass Pasture	100	20	0.07	20	7	0.35	0.014

The bromoxynil residue (expressed as bromoxynil phenol) in tissues and milk after dosing at 0.7 ppm (as bromoxynil phenol – dosed as bromoxynil octanoate at 1 ppm) for 29 days (mean of 2 observations for tissues, 3 for milk) and required MRLs for the estimated dietary burden of 0.35 ppm and proposed Primary Feed Commodities MRL of T1 mg/kg are given below.

Sample	Bromoxynil residues after dosing at 0.7 ppm (mg/kg)	Required MRLs (mg/kg)
Liver	0.98	T3
Kidney	0.46	
Muscle	<0.05	-
Fat	0.31	T1
Milk	0.04	T0.1

Chronic dietary exposure to bromoxynil with an 8 week (56 day) grazing withholding period

The results of the NEDI calculation are summarised below.

Compound	ADI mg/kg bw	NEDI (%ADI)
Bromoxynil	0.003	56%

The NEDI for bromoxynil is equivalent to 56% of the ADI and is acceptable.

Trade risk associated with a 56 day (8 week) grazing withholding period

Required Australian MRLs and relevant overseas MRLs are summarised below.

Country/status	Commodity	Tolerance, mg/kg
Australia – required for 8 week grazing and cutting for stock food withholding period	Primary Feed Commodities	T1
USA	Sorghum, grain, forage	0.5
	Sorghum, grain, stover	0.2
Japan	Hay (includes hay, fodder, straw & silage)	0.1
	Sorghum grain	0.2

Country	Commodity	Tolerance, mg/kg
Australia – required for an 8 week grazing WHP (bromoxynil)	Meat (mammalian) [in the fat]	T1
	Edible offal (mammalian)	T3
	Milks	T0.1
USA (bromoxynil (3,5-dibromo-4-hydroxybenzonitrile) and its metabolite 3,5-dibromo-4-hydroxybenzoic acid (DBHA))	Cattle, fat	1
	Cattle, meat	0.5
	Cattle, meat by-products	3.5
	Milk	0.1
Japan (bromoxynil)	Cattle, muscle	0.07 (provisional)
	Cattle, fat	0.1 (provisional)
	Cattle, liver	0.07 (provisional)
	Cattle kidney	0.07 (provisional)
	Cattle, edible offal	0.07 (provisional)
	Milk	0.07 (provisional)
EU (for bromoxynil including its esters expressed as bromoxynil – fat soluble)	Meat, fat, liver, kidney	0.05
	edible offal	0.2
	Others	0.05
	Milk	*0.01

Export hay

On the basis of residue data from Australian sorghum and European cereal and pasture trials finite residues may be present in forages and fodders following an 8 week withholding period. The potential for undue prejudice to trade in export hay exists as residues may occur above the established MRL in Japan. Australian residue data are required to refine this assessment.

Animal Commodities

Following an 8 week grazing withholding period finite residues may still occur in animal commodities. The proposed Australian MRLs are at similar levels to those of the USA (noting the complex residue definition), are higher than those of Japan and the EU, and no MRLs are established in Korea, Taiwan, or by Codex. Residues in milk are also possible above the EU MRL of *0.01 mg/kg. Thus with an 8 week grazing withholding period, the potential for undue prejudice to trade in meat, offals, milk and milk products exists. Australian residue data for forages and fodders, along with full reports of all existing animal transfer studies are required to refine this assessment.

6. Further data

Further residue data and animal transfer studies would allow refinement of the MRLs and WHPs.

The following residue data from decline trials undertaken in Australia would be required for further label amendments.

- Cereal forage, fodder and straw residue trials (560 g ai/ha):
  - 6 on oats, covering both varieties used for fodder and grain production
  - 4 on wheat
  - 2 on barley
- Pasture (560 g ai/ha):
  - 6 on grass based pastures
  - 2 on lucerne
  - 2 on clover.

Trials should be undertaken in accordance with APVMA guidelines and include sampling of:

- Forage
- Fodder, at maturity corresponding to commercial cutting for hay production
- Straw and grain (individually), for the cereal trials

Residue data should be expressed on a dry weight basis and standing plant biomass should be estimated at time of application and a key times throughout the trial (e.g. estimated peak biomass, commercial hay cut, harvest).

7. Conclusions

The following changes to the APVMA MRL standard are recommended:

Table 1

Compound	Food			MRL (mg/kg)
Bromoxynil				
DELETE:	MO	0105	Edible offal (mammalian)	*0.02
	MM	0095	Meat [mammalian]	*0.02
	ML	0106	Milks	*0.02
ADD**:**				
	MO	0105	Edible offal (mammalian)	T3
	MM	0095	Meat (mammalian) [in the fat]	T1
	ML	0106	Milks	T0.1

Table 4

Compound	Animal feed commodity	MRL (mg/kg)
ADD: Bromoxynil	Primary feed commodities	T1

The following Withholding Periods are associated with the MRLs:

Harvest (cereal grains): Not required when used as directed.
Grazing: Do not graze or cut for stock food for 8 weeks after application.

The establishment of an 8 week grazing and cutting for stock food withholding period for bromoxynil will ensure acceptable dietary exposure to bromoxynil residues and significantly, but not totally, mitigate prejudice to trade in animal commodities, milk and milk products and export hay. Residue data, in accordance with section 6 (above) should be provided to allow refinement of the trade risk assessment.