FLUCYTHRINATE (152)

EXPLANATION

Flucythrinate was first reviewed for residues by the 1985 JMPR, at which a number of MRLs were recommended. Additional data for a number of crops and more information on likely residues in animal products were desirable. New data were reviewed in 1987 and additional MRLs recommended. The 1988 and 1989 Meetings addressed issues relevant to MRLs for cabbage. The 1990 JMPR considered summary data submitted by the government of Spain from residue trials on citrus fruit, cucumbers, green beans and peppers and a separate submission of summary information on animal transfer studies. Full detials of the trials and transfer studies were required by 1992 so that maximum residue levels could be estimated.

Submissions to the 1992 JMPR in response to these requirements could not be reviewed at that Meeting. Much of the same, as well as other, information was submitted to the present Meeting, either by the manufacturer or the Spanish government, and other government comments were provided on animal MRLs. Some of the same data had been reviewed by the 1985 JMPR.

USE PATTERNS

New or updated information on relevant crops is summarized in Table 1. Where conflicting information was provided, the most recent is given preference.

Table 1. Nationally approved or registered uses of flucythrinate on selected crops.

Country/ crop	Application			PHI (days)	Notes
	Form.	Rate g ai/ha (g ai/hl)	No.		
Spain					
cabbages	EC	(4-6)*	**	3	* Except for maize, a separate submission on "registered uses to be considered by the EEC" lists 4-6 and 8-10 g ai/hl as the uses.
cotton seed	EC	40-60*** (4-6)	-	7	
cucurbits	EC ~	32-80 (4-10)	-	3	** Number was not indicated. "Each at 15-20 days" implies multiple applications at this interval.
green beans	EC	32-80 (4-10)	-	3	
lemons	EC	40 (4)	-	7	*** A separate submission indicated 20-30 g ai/ha.
maize	EC	1000-1200 (30-40)	-	7	
peppers	EC	32-80 (4-10)	-	3	
tomatoes	EC	32-80 (4-10)	-	3	
Japan					
Citrus fruits	EC	(3-4.4)*	4	21	* to run off
	WP	(3.3-5)*	4	21	

RESIDUES RESULTING FROM SUPERVISED TRIALS

Plants

The 1990 JMPR required detailed reports of trials on citrus fruits, cucumbers, green beans and peppers for which summary data had been provided. As indicated below, examination of the detailed reports by the Meeting revealed that most of them were the same as those reviewed by the 1985 JMPR. Although not requested, studies were also provided for brassicas, cotton seed and tomatoes. The trials on tomatoes, but apparently not those on brassicas and cotton seed, had been previously reviewed by the JMPR.

Beans, green. The trial details (Report Carse R-007, Spain, 1993; Cyanamid, 1993) revealed that these are the 1981 Egyptian trials reviewed by the 1985 JMPR. The Meeting was informed that the use is not GAP in Egypt, but is covered by Spanish GAP. Maximum residues were 0.14 and 0.22 mg/kg after three days from treatments within Spanish GAP.

Brassicas. The 0.2 mg/kg CXL for flowerhead brassicas (broccoli, Chinese broccoli, cauliflower) was recommended by the 1985 JMPR and the 0.5 mg/kg CXL for head cabbages (cabbage, green or red cabbage, oxhead cabbage, white cabbage, Savoy cabbage, yellow cabbage) by the 1987 JMPR. One national delegation had proposed higher limits on the basis of the data provided, but the relevant national uses were subsequently withdrawn and the current limits adopted. Although there appear to be no outstanding issues, data were submitted (Spain, 1993) on Brussels sprouts (two 1980 Netherlands trials, $\leq$0.06 mg/kg from treatments according to Spanish GAP, Reports TI-80-4 and TI-80-8/1414), broccoli (one 1982 German trial, $\leq$0.14 mg/kg, Report 1622), red cabbage (Report 1601), white cabbage (three 1981 German trials, 0.05 mg/kg from Spanish GAP, Report 1605) and Savoy cabbage (ten 1981 German trials, $\leq$0.37 mg/kg from Spanish GAP, Report 1549).

The trials on Brussels sprouts and broccoli appear to be the same as those reviewed by the 1985 JMPR.

Savoy cabbages. Data from ten 1981 supervised trials in Germany appear not to have been previously reviewed. Maximum residues were $\leq$0.29 mg/kg 3 to 5 days or more after 3 applications of an EC formulation at 30 g ai/ha (5 g ai/hl), except in one trial with residues of 0.28, 0.37, and 0.33 mg/kg after 4, 7, and 14 days respectively. All the trials were according to Spanish GAP and the residues are within the current 0.5 mg/kg limit for head cabbages.

Red and white cabbages. Three supervised trials in Germany in 1981 on each variety resulted in residues of 0.05 mg/kg 0 to 21 days after three EC applications at 30 g ai/ha (5-7 g ai/hl).

Citrus fruit. No new results were provided. Data from 4 Japanese trials (two on limes and 2 on mandarins) and 2 Egyptian trials on oranges (Report R-020) had been reviewed by the 1985 JMPR, but the Meeting was informed that the use is not GAP in Egypt. The Egyptian data on oranges included residues at 7 days, which is the Spanish PHI for lemons but from treatment at twice the Spanish GAP rate. The maximum residue was 1 mg/kg after 7 or 56 days. Residues in the Japanese trials from treatment in accordance with Japanese GAP were 0.2 to 1.5 mg/kg after 21 days, 0.2 to 1.7 mg/kg after 30 days and 0.2 to 1.5 mg/kg after 42/45 days. The required additional details of the trials reviewed in 1990 and details of the analytical method JT-001 used in the Japanese trials were also provided (Cyanamid, 1993).

Cotton seed. Summary data from supervised trials in 1978 in six States in the USA were submitted, which appear not to have been reviewed by the 1985 or 1987 Meetings (Spain, 1993). Reported residues were <0.05 mg/kg 29-166 days after 9 to 15 treatments at 60-120 g ai/ha. The current CXL is 0.1 mg/kg.

Cucumbers. The 1990 JMPR required the detailed reports which were summarized. The detailed report (Carse 003, Cyanamid, 1993) is of the

Egyptian trials reviewed by the 1985 JMPR.

Maize, maize forage and fodder. Residues in these crops are discussed below in the context of feed items relevant to MRLs for animal products.

Peppers. The detailed report required by the 1990 Meeting refers to the Italian trials reviewed by the 1985 JMPR (Report 1370/IT/GR/80, Spain, 1993, Cyanamid, 1993).

Tomatoes. The current 0.2 mg/kg CXL was recommended by the 1985 JMPR on the basis of data from Egypt, Finland, Italy, New Zealand and the United States and a 3-day PHI. Reports R-004-C/2 411/81, (1981 Egyptian trials) and 1290-IT/5R/80 (1980 Italian trials) were provided to the Meeting. These were reviewed by the 1985 JMPR (Spain, 1993).

Animals

The 1985 JMPR estimated temporary maximum residue levels at 0.5 mg/kg in the fat of meat for cattle and goats, 0.1 mg/kg in milk, and 0.05 mg/kg in eggs, although the basis for those estimates was not explained (the estimate for eggs was withdrawn by the 1990 Meeting). Of the animal feed items most relevant to these estimates, the 1985 JMPR recommended limits of 0.2 mg/kg for barley, oats and wheat, 5 mg/kg for their dry fodders, 0.2 mg/kg for green maize forage on the basis of European data, 0.5 mg/kg for pome fruit and 2 mg/kg for sugar beet tops. No limit was recommended for maize grain or fodder but the 1987 Meeting recommended 0.05 mg/kg for maize grain and 1 mg/kg for maize fodder on the basis of US data. All US uses have since been withdrawn.

The 1985 JMPR reviewed two goat metabolism studies and a cattle feeding study. In the first goat study goats fed for 7 days with [^{14}C]-alcohol- or [^{14}C]-acid-labelled flucythrinate up to 0.5 mg/kg in the feed showed flucythrinate equivalents of <0.01 mg/kg in the milk and <0.05 mg/kg in the tissues. In the second study, goats were fed for 7 days with both labels at 30 or 100 ppm in the diet. Milk and blood residues reached a plateau after 2 to 3 days. Maximum residues of flucythrinate equivalent from the 30 ppm feeding (alcohol label) in fat and milk were 1 mg/kg and 0.25 mg/kg respectively. The parent compound was the predominant residue in fat, muscle and blood, but hydrolysis products, lactones and conjugates predominated in kidney and liver.

In the cattle feeding study, with 13 and 39 ppm in the diet, residues in milk became steady after 4 days, a similar time to that found in goats. The 1985 JMPR did not record tissue residues, but cited average milk residues of 0.22 mg/kg for the lower feeding level. It was not indicated whether tissue residues had been provided.

The 1985 JMPR listed as desirable "information on actual residues found in meat, fat, milk and eggs after feeding treated animal feed crops or other crops of which wastes are used as animal feeds, e.g., straws of cereal grains, vines and/or straws of legume vegetables, etc." Over several years some delegations to the CCPR have questioned the temporary limits for cattle and goats, believing that adequate data on the residues in animals arising from feeding crops with expected residue levels were needed. Maize forage and fodder limits have been held at step 7B since 1989, awaiting reconsideration on the basis of storage stability studies. They were made temporary by the 1991 CCPR pending the submission of animal feeding studies. The 1990 JMPR received summary information on animal transfer studies, but did not evaluate it in the absence of the full reports.

The Meeting was provided with country comments on the issue, as well as comments from one of the two producers of flucythrinate. The Netherlands did not consider the relatively high feeding levels (30 or 13 mg/kg) to be suitable for estimating the maximum residue levels expected from the feeding of 5 mg/kg in cereal straws or 2 mg/kg in sugar beet leaves (Netherlands, 1992). Similar objections were raised by France (France, 1992).

One of the producers of flucythrinate repeated an argument already put forward in 1989 and 1990 in support of limits in animal products on the basis of information previously provided (Cyanamid, 1992). The 1990 JMPR had considered this information and had required submission of the detailed reports from which it was summarized by 1992.

As in 1989 and 1990, the latest submission did not consist in the detailed reports of the transfer studies, but extractions therefrom and a discussion of the issues. The data seemed to be from the studies reviewed by the 1985 JMPR, but included more detail than was given in the 1985 monograph. The Meeting did not have the original reports for reference. Although a full assessment is not possible in their absence, the Meeting noted the following points. The comments explain that the higher feeding levels were intended to accommodate worse-case levels expected at the time for proposed US uses (since withdrawn) and to provide sufficiently high levels of residues for metabolite identification. The producer points out that flucythrinate residues are fat-soluble, that residues increase linearly according to the dose and that residues are much higher in milk and fat than in other tissues. Tables 2 and 3 below were provided to support this view and, by pooling the data to support linear extrapolation formulas for fat of $y = 0.037x - 0.11$ ($r^2=0.98$) and for milk $y = 0.0075x + 0.06$ ($r^2=0.98$).

Table 2. Residues of [^{14}C]flucythrinate in goat tissues (quoted from Cyanamid, 1992).

Tissue	Mean residue levels		Residue ratio
	30 ppm feeding	100 ppm feeding	
Tenderloin muscle	0.041	0.085	2.1
Leg muscle	<0.05	0.075	
Kidney	0.013	0.057	4.4
Fat	0.86	3.63	4.2
Liver	0.021	0.079	3.8
Milk (4-7) days)	0.28	0.8	2.9
Blood (4-7 days)	0.07	0.28	4
Dose ratio: 30:100 = 1:3.3		Mean residue ratio 1:3.6	

Table 3. Residues of flucythrinate in cattle tissues (quoted from Cyanamid, 1992).

Tissue	Mean residue level		Residue ratio
	13 ppm feeding	39 ppm feeding	
Tenderloin muscle	<0.05-0.06	<0.05-0.075	
Omental fat	0.5	1.5	3
Back fat	0.3	0.99	3.3
Liver	<0.05	<0.05-0.052	
Kidney	<0.05-0.054	<0.05-0.086	
Milk (4-8 days)	0.22	0.37	1.7
Dose ratio: 13:39 = 1.3		Mean residue ratio 1:2.7	

NATIONAL MAXIMUM RESIDUE LIMITS

National MRLs for Spain were reported as 0.5 mg/kg for pome fruit, stone fruit, lemon, tomato, pepper, cucurbits, green beans, artichokes and cabbages.

APPRAISAL

Flucythrinate was reviewed for residues by the 1985, 1987, 1988, 1989 and 1990 Meetings. The 1985 JMPR listed additional data for a number of crops and information regarding likely residues in animal products as desirable. MRLs for these commodities have been retained at step 7, as have limits for maize forage and fodder. The 1990 JMPR required full documentation of data which were submitted only in summary form for citrus, cucumber, green beans and peppers. That Meeting did not evaluate summary information submitted on residues in animal products in the absence of the full reports. The present Meeting reviewed submissions made in response to the 1990 requirements, additional data for crops with and without current or proposed MRLs, and a re-submission of summary information on animal residues.

Green beans. Submission, as requested, of detailed reports on green bean trials provided only in summary to the 1990 JMPR reveals that the data are the same as the Egyptian data reviewed by the 1985 JMPR. The two values of 0.14 and 0.22 mg/kg after 3 days are consistent with reported Spanish GAP, but the Meeting concluded (as apparently did the 1985 JMPR) that the data were insufficient to support an MRL for green beans.

Brassica vegetables. There are no outstanding issues concerning the CXLs of 0.5 mg/kg for head cabbages and 0.2 mg/kg for flowerhead brassicas (broccoli, cauliflower). The Meeting received data on broccoli and Brussels sprouts which were reviewed by the 1985 JMPR and which did not need further review. New data were also received for red, white and Savoy cabbages. With maximum residues of 0.37 mg/kg from applications within Spanish GAP, no change in the current limits was required.

Citrus. Data reviewed by the 1985 JMPR from trials in Egypt (not GAP) and Japan were re-submitted, together with additional detail and GAP information for Japan and Spain. While the data suggest that residues are unlikely to exceed 2 mg/kg from GAP, the Meeting concluded (as implicitly did the 1985 JMPR) that data reflecting GAP in additional countries are needed to support an MRL for a major crop such as citrus. Processing studies would also be needed.

Cotton seed. Summary data reported from supervised trials in the United States and apparently not previously reviewed by the JMPR indicate residues well below the 0.1 mg/kg CXL. The Meeting concluded that there was no need to request the complete studies nor to revise previous estimates.

Cucumber. Submission of detailed reports as requested by the 1990 Meeting reveals that the data are the same as the Egyptian data reviewed by the 1985 JMPR. While the detailed reports indicate that the maximum residues of <0.05 mg/kg are consistent with reported Spanish GAP (3-day PHI) for cucurbits, the manufacturer could not confirm that the use is GAP on cucumbers anywhere. The Meeting concluded (as apparently did the 1985 JMPR) that the data were too limited to support an MRL.

Peppers. Submission, as requested by the 1990 JMPR, of detailed reports indicate that the summary data provided to that Meeting are the same as the Italian data reviewed by the 1985 JMPR. While the detailed reports indicate that the 0.14 and 0.13 mg/kg values after 4 days should be within Spanish GAP, the Meeting concluded (as apparently did the 1985 JMPR) that the data were too limited for estimating MRLs.

Tomatoes. There were no questions on the 0.2 mg/kg CXL recommended by the 1985 JMPR. The re-submitted studies had been previously reviewed.

Cattle meat and milk; goat meat. The current 0.5 mg/kg limits for the meat of cattle and goats and the 0.1 mg/kg limit for cattle milk have been retained at Step 7 by the CCPR pending submission of adequate animal feeding studies representative of feeding levels likely to occur in practice. Government comments provided to the Meeting proposed deletion of these limits with the view that available information was based on feeding levels irrelevant to actual animal intakes. The manufacturers again submitted discussion points and summary information previously provided to the 1990 JMPR, which required submission of the detailed reports from which

the summary information was taken. This information was not available to the Meeting.

The Meeting considered likely levels in commodities which could be used as animal feed items and agreed that the maximum dietary intake for cattle was unlikely to exceed 5 mg/kg, and in practice would probably be lower. Assuming this level, using the available feeding data summary, and assuming that residues in the animal products vary linearly with their levels in the feed from the 13 to 100 ppm levels fed experimentally down to the postulated 5 ppm, maximum residues of the order of 0.08 mg/kg in the fat of meat of cattle and goats and 0.1 mg/kg in milk could be estimated. This would suggest that the previously estimated levels of 0.5 mg/kg in the fat of meat and 0.1 mg/kg in milk would be adequate.

The summary information and comments provided to the Meeting provide greater insight into likely residues in animal products. However in the absence of the detailed reports from which the transfer data were summarized, and in view of the fact that the fat-solubility of flucythrinate leaves the potential for residues in animal tissues and milk, the Meeting recommended that the temporary limits for the meat and milk of cattle and goat meat should be withdrawn.

RECOMMENDATIONS

On the basis of the data on residues from supervised trials the Meeting concluded that the residue levels listed below are suitable for establishing maximum residue limits or should be withdrawn.

Definition of residue: flucythrinate

Commodity		Recommended MRL (mg/kg)	
CCN	Name	New	Previous
MM 0812	Cattle meat	W[1]	0.5 (fat) T
ML 0812	Cattle milk	W	0.1 F T
MM 0814	Goat meat	W	0.5 (fat) T

[1] Withdrawn

REFERENCES

Cyanamid, 1992. Flucythrinate Residue Tolerances (discussion on MRLs for animal products); Appendix I, Supplementary Flucythrinate Residue Data; Appendix II, Summary of Flucythrinate Residue Data; Table 1 (Exhibits 17 and 18).

Cyanamid, 1993. Submissions of American Cyanamid Company for a variety of crops and animal product issues, analytical methods and GAP:

Citrus - Japanese supervised trials reports TTR-83-011 and TTR-83-012 and information on Japanese GAP.

Method JT-001 used in the Japanese supervised field trials and further details of the trials.

Citrus	1 -	Report Carse R-20, Egyptian trials.
Citrus	2 -	Report TTR-83-011 (corrected submission), Japanese data.
Citrus	3 -	Report TTR-83-012 (corrected submission), Japanese data.
GAP	4-6	Japanese labels (translated)
Cucumber	7 -	Report Carse 003, 1981 Egyptian trials
Green beans	8 -	Report Carse R-007, 1982 Egyptian trials.
GAP	9 -	Spanish labels (translated)
Peppers	10 -	Report 1370, 1981 Italian trials.

GAP 11 - Italian label (translated)

France, 1992. Comments from France. Flucythrinate (re: residues in animal products). Fax to FAO August 25, 1992.

Netherlands, 1992. Information of The Netherlands on pesticides to be considered by the 1992 JMPR, Flucythrinate, June 1992 (Ministerie van WVC, Directoraat Generaal van de Volksgezondheid.

Spain, 1993. Spanish government submission of GAP information and supervised trials data for a number of crops:

Peppers - Report 1370/ IT/GR/80
Tomato - Report R-004/ C/2 411/81 Egypt; Report 1290/ IT/5R/80 Italy
Brussels sprouts - Report 1414/ TI-80-4
White Cabbage - Report 1605
Green Beans - Report Carse R-007
Broccoli - Report 1622
Red Cabbage - Report 1601
Cotton seed - summary of data from 1978 trials in the USA (California, Louisiana, South Carolina, Georgia, North Carolina and Arizona).
Ministerio de Agricultura, Pesca y Alimentación. 1993.