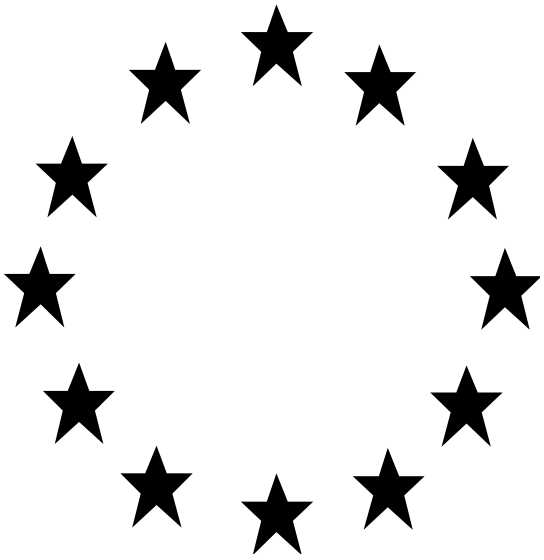


Final addendum to the

Draft Assessment Report (DAR)

- public version -

Initial risk assessment provided by the rapporteur Member State
The United Kingdom for the new active substance

CYFLUFENAMID

as referred to in Article 8(1) of Council Directive 91/414/EEC

January 2008

Table of contents

Council Directive 91/414/EEC

Cyflufenamid

Addendum 1

Volume 3

Annex B

to the Report and Proposed Decision of the United Kingdom made to the European Commission under Article 8(1) of 91/414/EEC

Prepared March 2007

PESTICIDES SAFETY DIRECTORATE
Mallard House, Kings Pool,
3 Peasholme Green,
York YO1 7PX, UK

Website: www.pesticides.gov.uk

Introduction

As a result of comments in the cyflufenamid Reporting table (Section 2) that the dermal absorption value for the spray solution should be increased from 1% to 8%, the recalculated exposure using 8% for the in use dilution are presented in this Addendum.

Content

B.6.14 Exposure data (IIIA 7.2)

B.6.14.1 Operator exposure (IIIA 7.2.1)

'NF 149 EW' is an oil in water emulsion containing 5% cyflufenamid. The proposed use is as an agricultural fungicide on cereals. Usage information pertinent to operator exposure is summarised in Table B.6.47. 'NF-149 EW' is to be applied *via* tractor-mounted hydraulic boom sprayer from the beginning of stem elongation stage (GS30) up to full emergence of the ear stage (GS59). The product is to be packaged in 0.5 or 1 litre HDPE co-extruded polypropylene containers. Water is the diluent/carrier in all situations.

Table B.6.47 Application parameters for 'NF-149EW'

Crops	**Application method**	**Max. ind. dose product** (l product/ha)	**Max. ind. dose a.s.** (g a.s./ha)	**Max. no. of applications** (per crop)	**Min. water volume** (litres/ha)
Winter and spring wheat, durum wheat, triticale, winter and spring barley, winter rye	FCS	0.5	25	2	200

FCS=Field crop sprayer

The applicant has proposed the product be classified as 'Harmful' with the associated risk phrases 'Harmful by inhalation' and 'Irritating to skin'. Evaluation of supporting toxicity data has confirmed that the product be unclassified (Section B.6.11.2) and therefore no PPE are required on the basis of this classification alone.

B.6.14.1.1. Estimation of operator exposure

Based on the dermal absorption data submitted, the applicant has proposed dermal absorption values for cyflufenamid of 5% for the concentrate and 12% for the in-use dilution. The dermal absorption values assumed for this evaluation are 1% for both the concentrate and 8% for the in-use dilution respectively (see Reporting table 2(50)).

A short term systemic AOEL for cyflufenamid of 0.065 mg/kg bw/day is proposed by the applicant based on a NOAEL of 6.5 mg/kg bw/day in a 90-day dog study, a correction factor of oral absorption of 1 and a safety factor of 100. The use of the 90-day dog study is considered appropriate but with a revised correction factor for oral absorption of 0.7 and a 1000 fold safety factor. A short term systemic AOEL of 0.016 mg/kg bw/day is proposed by this evaluation (DAR, Section B.6.10.3).

The applicant has provided estimates of operator exposure to cyflufenamid arising from the use of 'NF-149 EW' using the German model (geometric mean) and the UK Predictive Operator Exposure Model (POEM).

Estimation according to the German Model

The following assumptions have been used in calculating operator exposure:

The area treated in one day is: 20 ha/day for cereals
The application dose is: 25 g a.s./ha

Estimates of exposure for operators wearing no PPE are as follows;

Table B.6.48 Estimated exposure to cyflufenamid: German model

Use/ Method	Dermal exposure (mg a.s./person/day)			Inhalation exposure (mg a.s./person/day)			Systemic* exposure (mg/kg bw/day)		
	Mix/ load	Spray	Total	Mix/ load	Spray	Total	Mix/ load	Spray	Total
Cereals/ FCS	1.2	1.02	2.22	0.0003	0.0005	0.0008	0.0002	0.0012	0.0013
FCS = Field crop sprayer *Assumes a 70 kg operator, 1% (concentrate) and 8% (in-use dilution) absorption *via* the dermal route and 100% absorption *via* the inhalation route.									

On the basis of the above estimate of operator exposure, the proportion of the systemic AOEL accounted for is given in Table B.6.49.

Table B.6.49 Estimated exposure as a proportion of the AOEL: German model

Use / Method	PPE	Total *systemic exposure (mg/kg bw/day)	Systemic exposure as a % of AOEL
Cereals / FCS	No PPE	0.0013	8
FCS=Field crop sprayer *Assumes a 70 kg operator, 1% (concentrate) and 8% (in-use dilution) absorption *via* the dermal route and 100% absorption *via* the inhalation route.			

Estimation according to UK POEM

The applicant has proposed a work rate of 50 ha/day which is considered appropriate in the UK for application to cereals *via* vehicle mounted/drawn field crop sprayers. The minimum recommended spray volume is 200 l/ha. The applicant has estimated exposure arising from the use of 0.5 and 1 litre containers, however, there are no specific pouring data for 0.5 litre containers and the use of the larger 1 litre containers is considered more realistic based on the work rates proposed.

Table B.6.50 Estimated exposure to cyflufenamid: - UK POEM

Use/ Method	Dermal exposure (mg a.s./person/day)			Inhalation exposure (mg a.s./person/day)			Systemic* exposure (mg/kg bw/day)		
	Mix/load	Spray	Total	Mix/load	Spray	Total	Mix/load	Spray	Total
Cereals/ FCS	12.5	5.194	17.694	**neg.	0.008	0.008	0.002	0.007	0.009
FCS = Field crop sprayer *Assumes a 60 kg operator, 1% (concentrate) and 8% (in-use dilution) absorption *via* the dermal route and 100% absorption *via* the inhalation route. **neg. = assumed to be negligible									

On the basis of the above estimate of operator exposure, the proportion of the systemic AOEL accounted for is given in Table B.6.51

Table B.6.51 Estimated exposure as a proportion of the AOEL: UK POEM

Use / Method	PPE	Total *systemic exposure (mg/kg bw/day)	Systemic exposure as a % of AOEL
Cereals / FCS	No PPE	0.009	56
FCS=Field crop sprayer *Assumes a 60 kg operator, 1% (concentrate) and 8% (in-use dilution) absorption *via* the dermal route and 100% absorption *via* the inhalation route.			

6.14.1.2 Operator exposure Summary

The estimates of exposure detailed above suggest operator exposure to cyflufenamid is expected to be within the systemic AOEL for operators wearing no PPE (German model estimate is 8% of the systemic AOEL, UK POEM estimate is 56% of the systemic AOEL) . Evaluation of the supporting toxicity data has confirmed that the product be unclassified and therefore no PPE are required on the basis of hazard classification.

B.6.14.2 Bystander exposure (IIIA 7.2.2)

Bystanders may be subject to dermal and inhalation exposure to the spray solution at the time of application. As cyflufenamid is only very slightly volatile (vapour pressure 3.54 x 10^{-5} Pa at 20°C), exposure to vapour is likely to be of less significance to bystanders than exposure from drift. The applicant has submitted a case propounding that such exposure will be of short duration, is unlikely to be repeated, and is likely to be at a lower level than that affecting the sprayer operator considering the greater distance of a bystander from the application equipment.

Based on actual measurements of bystander exposure in the UK for boom spray applications (Lloyd and Bell, 1983[1]), in a typical case following a single pass of the sprayer, mean potential dermal exposure was measured as 0.1 ml of spray on a bystander positioned at 8 m from the edge of the treatment area. Typical mean potential inhalation exposure was measured as 0.02 ml spray/m^3. Maximum values were about five times these mean values.

In estimating bystander exposure the following additional assumptions have been made;

- Maximum spray concentration of cyflufenamid is 0.125 mg/ml.
- 8% dermal absorption and 100% absorption *via* inhalation.
- No exposure reduction from clothing.
- A respiratory rate of 1.2 m^3/hr (=0.02 m^3/min or 20 l/min).
- An exposure duration of 5 minutes.
- A body weight of 60 kg.

Bystander exposure is calculated as follows;

i. Systemic exposure (dermal) $= \frac{0.1 \text{ ml} \times 0.125 \text{ mg/ml} \times 0.08}{60 \text{ kg}}$

$= 1.7 \times 10^{-5}$ mg/kg bw/day

ii. Systemic exposure (inhalation) $= \frac{(5 \times 0.02 \text{ m}^3/\text{min}) \times 0.02 \text{ ml/m}^3 \times 0.125 \text{ mg/ml}}{60 \text{ kg}}$

$= 4.2 \times 10^{-6}$ mg/kg bw/day

Total systemic exposure of bystanders is estimated to be 0.00002 mg/kg bw/day which is ,1% of the proposed short term systemic AOEL of 0.016 mg/kg bw/day. It is therefore unlikely that exposure of bystanders outside the treatment area will exceed the short term systemic AOEL with regards to application to field crops.

B.6.14.3 Worker exposure (IIIA 7.2.3)

The harvesting of cereals is a predominantly mechanised process, however, some manual operations will result in direct contact with treated foliage. The applicant has predicted exposure using the German worker re-entry model (Hoernicke *et al*, 1998[2]). A work rate of 8 hours for 'field walking' (i.e. crop inspection) activities has been assumed by the applicant. This is considered conservative for crop inspection activities (2 hours/day is likely to be more realistic), however, for 'rogueing' activities a 6-8 hour working day is considered appropriate.

A transfer co-efficient of 5,000 cm^2/person/hr has been assumed by the applicant. No TC data specifically for cereal crops appear to be available, however, harvesting a crop such as carnations in terms of morphology, leaf area index and work task can be considered as a suitable surrogate for rogueing activities in cereal crops. Published data for workers harvesting glasshouse carnations which included cutting, sorting and bundling together (van Hemmen and Brouwer, 1997[3]) specify a transfer co-efficient of 4,500 cm^2/person/hour for this activity.

Residues on the foliage depend on application rate, extent of remaining residues from previous applications and the crop habitat [total size of foliage compared to surface area – Leaf Area Index (LAI)]. As DFR studies with cyflufenamid are not available, DFR is predicted from a conservative value of 1 μg/cm^2 per kg a.s./ha applied. Based

on an application rate of 1 kg a.s./ha and a LAI of 1, the theoretical initial concentration of residues on leaves is 10 µg/cm^2 or 5 µg/cm^2 per side assuming both sides of the leaf are sprayed. The LAI for most crops is in the range of 3 – 5 therefore the DFR is estimated to be in the range 1 – 1.66 µg/cm^2 (≈ 1 µg a.s./cm^2).

The approval holder has assumed a single application is made at the maximum approved rate of 0.025 kg a.s./ha, however, two applications can be made per crop. In the absence of foliar residues decline data, two applications at the maximum rate are assumed with no decline in foliar residues occurring between applications.

In accordance with this model, the following worst-case assumptions have been used:

Application rate (R)	2 x 0.025 kg a.s./ha
Initial dislodgeable foliar residue (DFR)	1 µg/cm^2 x R
Task related transfer coefficient (TC)	4,500 cm^2/person/h
Duration of task (A)	8 h/day

On this basis, potential dermal exposure (D) for an unprotected harvest worker has been estimated to be:

D = DFR x TC x A
D = (2 x 0.025) x 4,500 x 8 = 1800 µg a.s./person/day
D = 1.8 mg a.s./person/day

Assuming a worker body weight of 60 kg and a dermal absorption value of 8%, systemic worker exposure (highest of derived dermal absorption values is assumed as worse case) is estimated to be 0.0024 mg/kg bw/day which is 15% of the short term systemic AOEL.

B.6.14.4 Conclusions

Levels of systemic exposure for operators, bystanders, workers from the proposed use of 'NF-149 EW' are expected to be within acceptable levels.

Label amendments:

None

Data requirements

None

B.6.15 References relied on

Ref No.	Annex point	Author	Date	Title and Company reference	GLP	Pub.
1.	IIIA, 7.2.2.1/01	Lloyd G.A., Bell G.J.	1983	Hydraulic nozzles: a comparative spray drift study	no	yes
2.	IIIA, 7.2.3.1/01	Hoernicke, E., Nolting H. G., Westphal, D., Anwenderschutz, F.	1998	Hinweise in der Gebrauchsanleitung zum Schutz von Personen ben Nachfolgearbeiten in mit Pflanzenschutzmitteln behandelten Kulturen. Nachrichtenbl. Deut. Pflanzenschtzd. 50 (10) p. 267	no	yes
3.	IIIA, 7.2.3.1/01	Brouwer, R., Brouwer, D.H., Tijssen, S.C.A., van Hemmen, J.J.	1992	Pesticides in the Cultivation of Carnations in Greenhouses: Part II Relationship Between Foliar Residues and Exposures. Am Ind. Hyg. Assoc. J. 53 p 582-587	no	yes

Appendix 1

THE GERMAN MODEL (GEOMETRIC MEAN VALUES)

Application method	Tractor-mounted/trailed boom sprayer: hydraulic nozzles				
Product	NF 149 EW		Active substance	Cyflufenamid	
Formulation type	Liquid		a.s. concentration	50	g/l
Dermal absorption from product	1	%	Dermal absorption from spray	8	%
RPE during mix/loading	None		RPE during application	None	
PPE during mix/loading	None				
PPE during application: Head	None	Hands	None	Body	None
Dose	0.5	l product/ha	Work rate/day	20	ha

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	2.4	mg/kg a.s.
Hand contamination/day	1.2	mg/day
Protective clothing	none	
Transmission to skin	100	%
Dermal exposure to a.s.	1.2	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0.0006	mg/kg a.s.
Inhalation exposure/day	0.0003	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0.0003	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique: Tractor-mounted/trailed boom sprayer: hydraulic nozzles

	Head	Hands	Rest of body	
Dermal contamination/kg a.s.	0.06	0.38	1.6	
Dermal contamination/day	0.03	0.19	0.8	
Protective clothing	none	none	none	
Transmission to skin	100	100	100	%
Total dermal exposure to a.s.	1.02	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure/kg a.s.	0.001	mg/kg a.s.
Inhalation exposure/day	0.0005	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0.0005	mg/day

ABSORBED DOSE

	Mix/load		Application		
Dermal exposure to a.s.	1.2	mg/day	1.02	mg/day	
Percent absorbed	1	%	8	%	
Absorbed dose (dermal route)	0.012	mg/day	0.0816	mg/day	
Inhalation exposure to a.s.	0.0003	mg/day	0.0005	mg/day	
Total systemic exposure	0.0123	mg/day	0.0821	mg/day	

PREDICTED EXPOSURE

Total systemic exposure	0.0944	mg/day
Operator body weight	70	kg
Operator exposure	0.001348571	mg/kg bw/day

THE UK PREDICTIVE OPERATOR EXPOSURE MODEL (POEM)

Application method	Tractor-mounted/trailed boom sprayer: hydraulic nozzles				
Product	**NF 149EW**		Active substance	**Cyflufenamid**	
Formulation type	organic solvent-based		a.s. concentration	**50**	mg/ml
Dermal absorption from product	**1**	%	Dermal absorption from spray	**8**	%
Container	1 litre any closure				
PPE during mix/loading	None		PPE during application	None	
Dose	**0.5**	l/ha	Work rate/day	**50**	ha
Application volume	**200**	l/ha	Duration of spraying	**6**	h

EXPOSURE DURING MIXING AND LOADING

Container size	1	litres
Hand contamination/operation	0.01	ml
Application dose	0.5	litres product/ha
Work rate	50	ha/day
Number of operations	25	/day
Hand contamination	0.25	ml/day
Protective clothing	None	
Transmission to skin	100	%
Dermal exposure to formulation	0.25	ml/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique	Tractor-mounted/trailed boom sprayer: hydraulic nozzles			
Application volume	200	spray/ha		
Volume of surface contamination	10	ml/h		
Distribution	Hands	Trunk	Legs	
	65%	10%	25%	
Clothing	None	Permeable	Permeable	
Penetration	100%	5%	15%	
Dermal exposure	6.5	0.05	0.375	ml/h
Duration of exposure	6	h		
Total dermal exposure to spray	41.55	ml/day		

ABSORBED DERMAL DOSE

	Mix/load		Application	
Dermal exposure	0.25	ml/day	41.55	ml/day
Concen. of a.s. product or spray	50	mg/ml	0.125	mg/ml
Dermal exposure to a.s.	12.5	mg/day	5.19375	mg/day
Percent absorbed	1	%	8	%
Absorbed dose	0.125	mg/day	0.4155	mg/day

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure	0.01	ml/h
Duration of exposure	6	h
Concentration of a.s. in spray	0.125	mg/ml
Inhalation exposure to a.s.	0.0075	mg/day
Percent absorbed	100	%
Absorbed dose	0.0075	mg/day

PREDICTED EXPOSURE

Total absorbed dose	0.548	mg/day
Operator body weight	60	kg
Operator exposure	0.009133333	mg/kg bw/day

Council Directive 91/414/EEC

Cyflufenamid

Addendum 2

Volume 3

Annex B

to the Report and Proposed Decision of the United Kingdom made to the European Commission under Article 8(1) of 91/414/EEC

Prepared November 2007

PESTICIDES SAFETY DIRECTORATE
Mallard House, Kings Pool,
3 Peasholme Green,
York YO1 7PX, UK

Website: www.pesticides.gov.uk

Contents

B.5 METHODS OF ANALYSIS

B.5.1.1 Technical active substance

Corrected Table B.5.1 Summary of method validation cyflufenamid technical active substance

	linearity range demonstrated	precision	accuracy (%)	specificity	interference	Reference
NF-149	0.125-0.375mg/ml (corresponding to ~ 50 – 150 %w/w)	0.2% @ 97.89 % w/w (n=6)	Demonstrated. The detector response to the active substance was not affected by the presence of impurities at levels of 0.1 %w/w and 0.3 %w/w.	NMR spectral match HPLC-DAD spectral match	None	Unemoto, T 2001d RD-II02054 Unemoto, T 2000b RD-II02057

The LOQ column and the footnote at the bottom of the table have been removed as this was included in error.

B.5.3.3 Residues in air (IIA 4.2.4) –corrected as highlighted

Samples are extracted with acetone, filtered and concentrated prior to analysis by GC-MS (analytical column: DB-XLB) using ion m/z 412 for quantitation and ions m/z 294 and 321 for confirmation. Validation data were generated by spiking the front of the Tenax absorption tubes, then passing air through the tubes at 1 ml/min for 8 hours under ambient conditions and also under conditions of enhanced temperature and humidity.

Validation data are presented in Table B.5.3. of the DAR

The LOQ of 1µg/m^3 is acceptable with respect to concentration, C = 3 µg/m^3, as defined below:

$$C = \frac{\text{AOELsystemic} \times 0.1 \text{ (}\textit{safety factor}\text{)} \times 60 \text{ (}\textit{body weight in Kg}\text{)}}{20 \text{ (}\textit{air intake [volume per day in } m^3\textit{]}\text{)}}$$

Note: The long term systemic AOEL of 1 µg/m^3 day was used in this calculation as an inhalation AOEL has not been set.

B.6 TOXICOLOGY AND METABOLISM

B.6.8 Further toxicological studies (IIA 5.8)

B.6.8.1 Supplementary studies on the active substance

B.6.8.1.6 Supplementary information on neurotoxicity – Report of Expert Panel

During the UK national evaluation of cyflufenamid, concerns were raised regarding the toxicological significance of the vacuolation seen within the brain in dogs. In response to these concerns the Notifier commissioned an "Expert Panel" of neuropathologists and neurotoxicologists to review the studies performed with cyflufenamid and in particular to examine the histopathology slides and electron micrographs of the nervous system from these studies. The report of this Expert Panel is reproduced below.

The RMS response to this expert report was presented in the Reporting Table at Point 2(54) as follows.

Reporting Table rev. 1-1 (22.06.2007)

Other comments				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
2(54)	Vol. 3, Appendix 4, Mammalian toxicology references	NOT: In Vol. 3, page 443, Appendix 4, there is no summary of the independent report on the neurotoxicity of cyflufenamid prepared by an international panel of expert neurotoxicologists and neuropathologists. This is considered to be critical to the DAR and so needs to be included.	RMS: The "independent report" referred to was a panel of expert neuropathologists and neurotoxicologists which was convened by the Notifier to review the cyflufenamid data. The panel reviewed the toxicity and metabolism data, and also the histopathological slides and electron micrographs of the dog brains. The panel concluded that the dog brain lesions were unique in their experience, but there were clear NOELs in each study, no similar lesions in mice or rats and the panel considered that no further data were necessary. The experts for this panel were selected and paid by the Notifier. No new data or scientific arguments were introduced in this report. The report confirms the findings and NOAELs reported in the DAR for these lesions, but does not add anything further. Addressed.	Addressed.

CYFLUFENAMID

NF-149

Report of Expert Panel on Neurotoxicity

Meeting at HLS, 10th-12th December 2004

PANEL: WF Blakemore. Ph.D., Sc.D., M.R.C.V.S, F.R.C.Path. Professor of Neuropathology,
University of Cambridge
PS Spencer. Ph. D., F.R.C.Path. Professor and Senior Scientist, Center for Research on Occupational and Environmental Toxicology, Oregon Health Science University, Oregon, USA
RO Weller. Ph.D., M.D., F.R.C.Path. Emeritus Professor of Neuropathology, University of Southampton
AD Dayan [Convenor]. Ll.B., M.D., F.R.C.Path. Emeritus Professor of Toxicology, University of London

SUMMARY

1. The Expert Panel met at HLS from 10th – 12th December 2004 to review information and histopathological material about the neurotoxicity of cyflufenamid as seen in toxicity testing.

2. After careful review of the original reports and the microscope slides of the nervous system the Panel concluded that –

- High doses of cyflufenamid produce an unique pattern of toxic damage to oligodendrocytes and oedema of myelin in the white matter in certain areas of the brain of the dog.
- The effect was dose-related; it resolved slowly after cessation of dosing.
- The rat and mouse were not affected.
- There was a clear $NOEL_{neurotoxicity}$ for the lesion in the brain of the dog –

28-day dietary toxicity test [NOD 025/983491]

2000ppm – 97 [M] and 93 [F] mg/kg/d

13-week dietary test [NOD 039/983796]

500ppm – 23[M] and 24[F] mg/kg/d

13-week dietary test with 13-week recovery period [NOD 124/993983]

150ppm – 6.3mg/kg/d

13-week dietary test with 26 week recovery period [NOD 125/993984]

Reversibility of brain lesion demonstrated.

1-year dietary test [NOD 066/002463]

No neurotoxicity at top-dose of 480ppm - 17mg/kg/d

3. The available data on the nervous system represented an impressive database well suited to evaluation of the neurotoxicity of cyflufenamid,

4. The cause of the brain lesion in the dog is not known. Several approaches to exploring its pathogenesis are mentioned. They all represent academic research and do not affect the risk assessment of the compound.

5. The risk assessment for neurotoxicity for workers and consumers proposed in the EU Draft Assessment Report prepared by the UK PSD* is appropriate and has paid proper attention to the occurrence and nature of the neurotoxicity in a single species and its relation to dose.

The Panel did not consider other aspects of the toxicity of cyflufenamid.

[*Nippon Soda. EU Plant Protection Product Dossier. Annex IIa-Tier II. Summary Document M-II. Section 3. NF-149. November 2002

PSD Cyflufenamid. Vol I. Report and Proposed Decision of the United Kingdom. Draft: December 2003 (ACP Meeting)]

1. INTRODUCTION

a. Cyflufenamid is a novel fungicide. Its mode of action is not known.

Amongst the extensive conventional safety studies done to support its registration for agricultural use, there have been shorter and longer term oral toxicity tests in the mouse, rat and dog, and reproduction tests in the rat and rabbit.

The studies in the dog at particular dose levels were reported to show a pattern of microscopic vacuolation in certain regions of the cerebral white matter . Other areas of the CNS and PNS were said not to be affected. There was a clear NOEL at 23 [M] and 24 [F] mg/kg/d PO [500 ppm] for 13 weeks. The lesion appeared to be slowly reversible, being greatly diminished after recovery for 13 weeks after 13 weeks of dosing, and being virtually undetectable after a 26-week recovery period.

Electron microscopy of affected white matter from dogs in the 13-week dietary experiment had shown intramyelinic vacuoles and myelin oedema.

No brain damage was reported in the rat or mouse dosed, respectively, for up to 104 and 78 weeks with up to 5000 and 2000ppm.

b. The Expert Panel reviewed general information about the toxicity and metabolism of cyflufenamid and its metabolites in the study reports and the members examined relevant pathological material from those experiments, comprising microscope slides stained by HE and in some instances by specialised techniques [GFAP and solochrome cyanin], as well as a few electron micrographs from the brain of dogs in the 13-week dietary test. See Appendix 1 for details of the written materials and slides reviewed.

c. The Panel was asked for answers to specific questions [see below Sections 2 to 6] about the reported neurotoxicity and to consider whether it represented a risk to humans exposed

according to the standard models used to estimate doses to workers and consumers. They were also asked to advise on additional experiments likely to be helpful in understanding the pathogenesis of the lesion and useful in assessing its potential risk to humans. The likely value of the ARG study in the dog recently proposed in a letter from PSD was also discussed.

d. The Panel met in private at HLS on 10th-12th December 2004 when all the reports and slides etc were available. After examining the slides and reviewing the reports the Panel agreed its draft conclusions. A preliminary draft report was written and discussed at the time, which was subsequently circulated by email, finalised by agreement and signed by all the Experts.

QUESTIONS and RESPONSES of the EXPERTS

2. ***Were the Experiments Appropriate, was the Pathological Material Examined of Sufficient Quality and had the Necessary Areas of the Nervous System been Covered to Permit Evaluation of the Neurotoxicity of Cyflufenamid?***

2.1 The Panel considered that the availability of results and slides of the nervous system from three species given a wide range of doses over a broad range of times represented an impressive database well suited to evaluation of the neurotoxicity of cyflufenamid.

2.2 The microscope slides were of good quality and so were the small number of copies of electron micrographs. The routine and special stains employed were suitable for their intended purposes.

The Panel was impressed by the quality of the preparations of the eyes from dogs and of the large, matching half-sections of the basal ganglia and hypothalamus from dogs. The consistency of the sites sampled in different experiments was helpful.

2.3 The areas of the brain, spinal cord, dorsal root ganglia and peripheral nerves sampled for neuropathological examination in the present experiments were appropriate for study of the neurotoxicity of cyflufenamid.

2.4 In future studies of neurotoxicity the Panel suggested that additional value might be obtained from use of specialised staining techniques, but they agreed in the present instance that they were able to reach diagnoses and to draw clear conclusions from the available pathological preparations. The specialised stains they had in mind were greater use of GFAP staining for gliosis, and immunocytochemical markers for activated microglia and axons.

In the present instance, for example, GFAP staining of brain sections from dogs in the 4-week and 13-week experiments would have provided useful supplementation of findings made in the HE-stained sections by aiding determination of whether the initial lesion was associated with any astrocytic response. Similarly, use of GFAP and microglial staining of brain sections of rats from the 4- and 13-week tests would have added additional confirmation of the decision that there were no white matter changes in those animals.

Retention of semi-thin epoxy resin sections prepared prior to electron microscopy should also be considered in future because their examination can give invaluable information about the precise nature of lesions. More extensive ultrastructural examination would have been beneficial in specifying the nature and likely evolution of the neuropathological lesion.

From time to time consideration should be given to the use of positive control substances in investigating neurotoxicity so that there was recent familiarity with findings both in those and negative controls, and experience of lesions of differing appearances and severity. The small number of extra animals required for this purpose would be justified by the increased diagnostic acumen it would afford.

3. *What Were the Nature and Distribution of the Lesion seen in the Brain, Which Species were Affected and What Was its Relationship to Dose and Duration of Treatment? Was it Reversible?*

3.1 Lesions were only seen in the central nervous system of the dog, largely or exclusively in the brain. No treatment-related neuropathological changes were found in the CNS, PNS or muscle of the rat and mouse.

The general nature and distribution of the lesions in the brain of the dog had previously been described in Dr Gopinath's special neuropathological report.

3.2 The primary effect in the dog appeared to be severe vacuolation of oligodendrocyte cytoplasm followed by intramyelinic oedema. Ultimately in the most severely affected areas there was general pallor of myelin staining.

Use of the term 'Myelin vacuolation' in some reports was potentially misleading as it picked on only one later aspect of the pathological findings. 'Oligodendrocyte vacuolation in certain areas of the CNS' was more appropriate.

There was no indication that demyelination was the primary disorder. Neuronal and axonal degeneration were not seen.

In the recovery experiments the sequence of changes appeared to follow the reverse order of their development.

It is possible that a very few necrotic oligodendrocytes were present in some animals. Astrocytosis was seen in affected areas at the end of the recovery experiments.

There were no signs of infiltration of lymphocytes or polymorphonuclear leukocytes anywhere in the brain. Limited microglial activation was seen as well as the occasional macrophage. There were no vascular changes.

3.3 The most severely affected areas were in the thalamus and pillars of the fornix, subcortical white matter and cortex, and the area of the cerebellar roof nuclei.

The retina, optic and other cranial nerves sampled, the basal ganglia and brain stem, spinal roots and dorsal root ganglia, and peripheral nerve trunks were not affected. The spinal cord [corticospinal tracts] was possibly affected in one instance.

3.4 Prolonged administration of lower doses [1500ppm for 13 weeks] led to more marked changes of the same type and distribution as those seen in the shorter term high dose study [4000ppm for 4 weeks].

3.5 The distribution and histological nature of the brain lesion were similar in affected animals dosed for 4 and 13 weeks; there was clear inter-animal variation in its intensity.

In the recovery experiments the histological findings favoured slow resolution of the lesion.

Other than mild astrocytosis in affected areas, including the cerebral cortex, no permanent lesions were found. There was no detectable involvement of neurons or axons in the degenerative or recovery processes; these structures remained intact in all samples from all species.

3.6 The Panel agreed with the NOELneurotoxicity for the brain lesions in the dog established in the experiments performed by Nippon Soda and HLS: see Table I and list below

28-day dietary toxicity test [NOD 025/983491]
2000ppm – 97 [M] and 93 [F] mg/kg/d
13-week dietary test [NOD 039/983796]
500ppm – 23[M] and 24[F] mg/kg/d
13-week dietary test with 13-week recovery period [NOD 124/993983]
150ppm – 6.3mg/kg/d

13-week dietary test with 26 week recovery period [NOD 125/993984]
Reversibility of brain lesion demonstrated
1-year dietary test [NOD 066/002463]
No neurotoxicity at top-dose of 480ppm – 17mg/kg/d

3.7 In the experience of the Panel the lesion was probably unique.

It differed in its detailed nature and distribution from the toxic effects produced by hexachlorophene, cycloleucine, cuprizone, vigabatrin, monoamine oxidase inhibitors and triethyl tin.

There was some similarity between the vacuolation of oligodendrocytes and the changes described in the encephalopathy associated with liver disease in certain species. However, other changes associated with hepatic encephalopathy were not present.

4. ***What was the Opinion of the Expert Panel about the Risk Assessment for Humans Proposed by the Manufacturer and in the Draft Report to the EC by PSD*** [PSD Cyflufenamid. Vol I. Report and Proposed Decision of the United Kingdom. Draft: December 2003 (ACP Meeting)]

The Panel was asked only to consider the risk assessment, including the suggested ADI, ARfD and short and long term AOEL values, in relation to neurotoxicity.

They considered that in those calculations proper attention had been paid to the occurrence and the nature of the neurotoxicity in a single species and its relation to dose.

5. *How did the Panel Regard the Proposed ARG* *[autoradiography]* *Study in the Dog?*

The Panel was uncertain how the results of such a study would aid understanding of the pathogenesis of the lesion or would assist Risk Assessment.

Consideration of the dosimetry and the nature of ARG as a technique suggest it would be unlikely that a pathogenic metabolite unique to the brain of the dog could be detected.

Such a study was not recommended unless there were a clear question that it could help to answer.

6. *Did the Panel have Suggestions about Further Studies to Aid Understanding of the Brain Lesion and its Importance?*

6.1 The pathogenetic mechanism of the lesion is not known.

One approach to understanding it would be to consider the mode of action of cyflufenamid as a fungicide. Once that had been discovered, the possibility that the same mechanism might be important in the brain could be investigated.

6.2 From an academic viewpoint. investigation of energy metabolism in oligodendrocytes and of fluid transport by those cells might be considered. However, those represented basic research approaches and were unlikely to be of immediate help in evaluating the toxicity of the compound.

6.3 The Panel noted the clinical findings in the acute oral toxicity studies in the rat of cyflufenamid and its principal metabolites. There were broadly similar effects after very high doses of all the compounds, some of which appear to have persisted for a number of days. The clinical effects in the acute studies were not reproduced in the repeated dose experiments.

6.4 It might be worth finding out if cuflufenamid was a carbonic anhydrase inhibitor, since oligodendrocytes show high activity of that enzyme and certain experimental inhibitors have caused white matter damage.

Signed

WF Blakemore .....

P Spencer .....

RO Weller .....

AD Dayan .....

Table I Cyflufenamid: **$NOEL_{neurotoxicity}$** established in toxicity tests in the dog

Study	Dose levels	$NOEL_{neurotoxicity}$
28-day dietary toxicity test (NOD 025/983491)	0, 1000, 2000, 4000 ppm 0, 45, 97, 152 mg/kg/day (M) 0, 48, 93, 142 mg/kg/day (F)	2000 ppm 97 (M) and 93 (F) mg/kg/day
13 week dietary toxicity test (NOD 039/983796)	0, 150, 500, 1500 ppm 0, 6.5, 23, 76 mg/kg/day (M) 0, 7.5, 24, 71 mg/kg/day (F)	500 ppm 23 [M] and 24 [F] mg/kg/day
13 week dietary test with 13 week recovery period (NOD 124/993983)	0, 150, 1500 ppm 0, 6.3, 65 mg/kg/day	150 ppm 6.3 mg/kg/day
13 week dietary test with 26 week recovery period (NOD 125/993984)	0, 1500 ppm 0, 64 mg/kg/day	Reversibility demonstrated $NOEL_{neurotoxicity}$ not examined
1-year dietary toxicity test (NOD 066/002463	0, 30, 120, 480 ppm 0, 1.04, 4.14, 17 mg/kg/day 0, 1.08, 4.41, 17 mg/kg/day	No neurotoxicity at top dose level of 480 ppm 17 mg/kg/day

APPENDIX 1

DOCUMENTS and PATHOLOGICAL MATERIAL EXAMINED

1. DOCUMENTS

1.1 EU Plant Protection Product Dossier according to 91/414/EEC
Annex IIA-Chemical Substances. Tier II Summary – Document M-II. Section 3 Cyflufenamid.
November 2002

1.2 Cyflufenamid. Volume 1. Report and Proposed Decision of the United Kingdom made to the European Commission under Article 8(1) 0f 91/414/EEC. Draft: December 2003 (ACP Meeting).

1.3 22 January 2004. PSD COP2003/000059(PP): Application for the Use of 'NF-149 EW' as an Agricultural Fungicide on Cereals: Committee Procedure. Letter from PSD to Nippon Soda, 22 January 2004 plus Responses to ACP's comments of 15 January 2004 submitted by Nippon Soda Co Ltd (12 February 2004).

10 August 2004. PSD COP2003/000059(PP): Further Data on Distribution of Cyflufenamid and its Metabolites in Dog Brain.

1.4 Protocol Cyflufenamid Autoradiography of Dog Brain. HLS Enquiry 30874A.

1.5 Effect of NF-149 on Mitochondrial Function. Nippon Soda RD-II 02178
.. Dog Brain Monoamine Oxidase RD-II 02179
.. Dog GABA-Transaminase RD-II 02180

1.5 Cyflufenamid: Dog Brain Lesion ACP's Concerns/Interest and Nisso's Position. Copy of overheads used on September 27, 2004.

2. SLIDES etc AVAILABLE at MEETING

2.1 Sections of brain from all animals in the following studies

DOG
NOD 025/983491; 4-week dietary toxicity test
NOD 039/983796;13-week dietary toxicity test
NOD 124/993983;13-week+13-week recovery phase toxicity test
NOD 125/993984; 13-week+26 week recovery phase toxicity test
NOD 066/002463; 52-week dietary toxicity test

RAT
NOD 009/972496;4-week dietary toxicity test
H080 13 week dietary toxicity test
NOD 010/002653; 104-week combined chronic tox/carc test
NOD 174/012398;13-week dietary neurotoxicity test
NOD 067/002313; 2-generation dietary reproduction toxicity test
NOD 244(2004); 2-generation dietary reproduction toxicity test

MOUSE
NOD 014/980077; 4-week dietary toxicity test
H081 13 week dietary toxicity test
NOD 022/002230;78-week dietary toxicity test
NOD 054/002545; 78-week dietary carc test

3. Additional Material Examined

Full reports of Acute Oral Toxicity studies in the rat

B.6.10.1 Acceptable daily intake (ADI) – further consideration

In the DAR the ADI was proposed as follows:-

Draft Assessment Report B.6.10.1

The acceptable daily intake is derived using the most appropriate NOAEL from the most sensitive species, and an appropriate safety factor. Comparing the 90 day rat, dog and mouse studies, the dog is the most sensitive species. The lowest overall NOAELs were from the 2 year rat chronic toxicity / carcinogenicity study and the 1 year dog study, both *ca* 4 mg/kg bw/day. However, a potentially severe and irreversible effect, brain vacuolation, was seen in the 90 day dog study (NOAEL 23 mg/kg bw/day). The relevance to man of brain vacuolation in dogs cannot be discounted, even though it did not drive the NOAELs in the 90 day and 1 year dog studies. It is therefore proposed to use the NOAEL for brain vacuolation from the 1 year dog study (17 mg/kg bw/day – top dose tested; brain vacuolation was not observed in the study) with a 1000 fold safety factor to derive the ADI. An extra safety factor of 10 is included in addition to the 100 default factor as the exact mechanism and reversibility of brain vacuolation in dogs has not been elucidated.

An ADI of 0.017 mg/kg bw/day is proposed.

This ADI provides a margin of safety of 3700 of the NOAEL for the mouse liver tumours observed, 1350 over the NOAEL for brain vacuolation in the 90 day dog study, and >1000 over the top dose in the 1 year dog study in which brain vacuolation was not observed.

Further justification for the ADI proposal was presented in the Reporting Table at Point 2(41):-

Reporting Table Point 2(41)

RMS: The rationale for selecting the NOAEL for brain vacuolation and the higher safety factor for the ADI are presented in Section B.6.10.1. The main concerns are the potentially severe nature of this finding (if it is relevant for humans), and the fact that there is uncertainty over whether it is reversible. The reversibility of brain vacuolation was only demonstrated in animals maintained for a 26 week recovery period (not 13 weeks recovery), and the group size was small (3 females only). It is felt necessary to ensure at least a 1000-fold margin over the NOAEL for this effect. The size of the safety margin and the choice of NOAEL for the ADI should be confirmed at an Expert Meeting.

An alternative proposal from a Member State was to derive the ADI from the NOAEL from the carcinogenicity study in rats and the 1 year study in dogs (both ≈4 mg/kg bw/day) divided by the usual 100-fold assessment factor (i.e. 0.04 mg/kg bw/day). This ADI would be 575-fold lower than the NOAEL for brain vacuolation seen in the 90 day dog study.

Study	NOAEL	LOAEL	Effects at LOAEL
90 day dog (diet) 0, 150, 500, 1500 ppm 0, 6.5, 23, 76 mg/kg bw/d ♂ 0, 7.5, 24, 71 mg/kg bw/d ♀ [Bellringer, 1999c]	6.5 mg/kg bw/d [Other effects] 23 mg/kg bw/d [Brain vacuolation]	23 mg/kg bw/d [Other effects] 76 mg/kg bw/d [Brain vacuolation]	23: ↓ bodyweight gain, histo-pathology (liver and thymus) 76: brain vacuolation
1 year dog (diet) 0, 30, 120, 490 ppm 0, 1.04, 4.1, 17 mg/kg bw/d ♂ 0, 1.08, 4.4, 17 mg/kg bw/d ♀ [Bellringer, 2000]	4.1 mg/kg bw/d [Other effects] >17 mg/kg bw/d [Brain vacuolation]	17 mg/kg bw/d [Other effects] No brain vacuolation observed at high dose	17: liver effects (↑ liver-derived alkaline phosphatase in serum). No brain vacuolation observed up to the highest dose tested.

The critical issue in relation to the ADI is the size of the safety margin which is needed over the NOAEL for brain vacuolation. If it is considered that a larger than normal safety margin is not needed over this effect, then it is appropriate to apply the normal 100-fold assessment factor to the overall NOAEL in the 1 year dog study, supported by the NOAEL in the chronic rat study (4 mg/kg bw/day ÷ 100 = 0.04 mg/kg bw/day). This ADI would be 425-fold below the NOAEL for brain vacuolation in the 1 year dog study (highest dose tested), and 575-fold below the NOAEL for brain vacuolation in the 90 day dog study.

The RMS considers that at least a 1000-fold margin should be maintained over the NOAEL for brain vacuolation in a long term study (for the reasons given above), hence the proposed ADI of 17 mg/kg bw/day (NOAEL in 1 year dog study) ÷ 1000 = 0.017 mg/kg bw/day.

B.6.10.2 Acceptable operator exposure level (AOEL) – further consideration

For the AOEL the issues are:-

1) the size of the safety margin over the NOAEL for brain vacuolation, and hence the choice of NOAEL to derive the AOEL, and
2) the extent of oral absorption relevant to the AOEL, which in turn depends on which toxicological effect (liver toxicity or brain vacuolation) is used to derive the AOEL.

In the DAR the short-term systemic AOEL was proposed as follows:-

Draft Assessment Report B.6.10.2

The most appropriate study for setting the short term AOEL was the 90 day dog study (the most sensitive species at this study duration). This study was considered to be of sufficient duration to cover the effects of exposure up to 90 days of use per annum. There were no critical endpoints such as developmental toxicity that produced a lower NOAEL than the 90 day dog study. The NOAEL in this study was 6.5 mg/kg bw/day based on reduced bodyweight and histopathological lesions in the brain liver and thymus. A 100 fold safety factor on this value might have been appropriate in the absence of any other concerns. However a brain vacuolation specific NOAEL (23 mg/kg bw/day) from this study is used with a 1000 fold safety factor, because the brain vacuolation seen in dogs may be relevant to man and, and a mechanism was not established. Because the AOEL is a systemic dose as opposed to a dietary dose like the ADI, a correction factor for oral absorption must be applied. ADME studies showed oral absorption to be 70-85%, hence correction is applied for oral absorption is necessary.

A short-term systemic AOEL of 0.016 mg/kg bw/day is proposed.

The issues regarding the size of the safety margin over the NOAEL for brain vacuolation are the same as for the ADI (see above). However, as was pointed out by a Member State in the Reporting Table (Point 2(44)), the correction for oral absorption should not necessarily take into account absorption indicated by biliary excretion since the brain may not have been exposed to a large part of the biliary component.

If it is proposed to base the AOEL on the NOAEL for liver effects in the 13 week dog study (6.5 mg/kg bw/day) and hence the safety margin over the brain vacuolation effect is considered adequate, then the full 70% absorption (including all the biliary component) is appropriate and the AOEL would be 0.05 mg/kg bw/day [6.5 mg/kg bw/day ÷ 100 x 70%].

If it is proposed to base the AOEL on the NOAEL for brain vacuolation (23 mg/kg bw/day) then the RMS considers that there is evidence that at least some of the biliary component would have been systemically available and hence the entire biliary component should not be excluded. The RMS proposal is for 50% oral absorption (based on the amount excreted in bile from 6 hours after dosing onwards plus urine from cannulated rats). Justification for this value was presented in the Reporting Table (Point 2(44)) and is reproduced below. The revised AOEL proposal on this basis would be 0.012 mg/kg bw/day [23 mg/kg bw/day ÷ 1000 x 50%].

Reporting Table rev. 1-1 (22.06.2007)

Figure B.6.2 (low dose) and Table B.6.2 from the DAR are reproduced below.

Summary of mammalian toxicology and setting of ADI, AOEL and ARfD (B.6.10)			
No.	Column 1 Reference to DAR	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur
2(44)	Vol. 3, B.6.10.3, AOEL, pg 192	NL: The proposed AOEL is based on the NOAEL for brain vacuolisation in a 90 day oral study with the dog (23 mg/kg bw/day). A correction for oral absorption of 70% is applied. However, excretion in bile was 61-77%. Enterohapic cycling occurs, but urinary excretion in non cannulated rats was 31%(males) 18% (females). Therefore, the target organ (brain) will not have seen a large part of the biliary component and a greater reduction factor should be applied for calculating the AOEL based on brain vacuolisation. 18% systemic availability is proposed, based on urinary excretion, cage wash and carcas in females of the SOLD group.	RMS: It is agreed that the correction for oral absorption (when the NOAEL for brain vacuolation is used) should be considered further. The draft Guidance Document on Setting AOELs (rev.10, 7 July 2006) states that where the critical target organ is not the liver (or the GI tract) and the biliary component is unlikely to have reached the target organ due to rapid excretion, then exclusion of the biliary component should be considered. However, in this case there is evidence that at least some of the biliary component would have been systemically available to reach the brain and it is not considered appropriate to exclude the entire biliary component for the following reasons. The following assumes that ADME in rats is comparable to dogs (and humans) – without ADME data from dogs no other assumption is possible. The low dose ADME data for bile duct cannulated rats does not indicate "rapid excretion" via bile as referred to in the draft AOEL Guidance Document. Table B.6.2 in the DAR indicates ≈20-30% excretion via bile up to 6 hours, which could be described as reasonably rapidly excreted and could be excluded as suggested by the Guidance Document. However, excretion via bile continues in significant amounts such that ≈40-45% of the dose is excreted in the period 6-48 hours after dosing. The question arises where is this 40-45% of the dose located over the first 6 hours after dosing and beyond until it is eventually excreted over 24 to 48 hours? The plasma concentration curves (Figure B.6.2) suggest rapid absorption of a low dose from the stomach/GI tract (an early peak of absorption with T_{max} 1-4 hours) so this 40-45% does not appear to be lying unabsorbed in the stomach/GI tract for the first few hours. The tissue distribution data indicates a substantial amount of material in the liver after 4 hours (reflecting the ≈20-30% excreted via bile in the first few hours?). It is not known what proportion of the 40-45% is retained in the liver and never reaches the systemic circulation. The fact that <0.5% of the dose remains in the liver of cannulated rats after 48 hours (equivalent to the amount in the GI tract and less than the amount in the remaining carcass) argues against highly effective retention/accumulation of material in the liver and in favour of dose "passing through" the liver via bile. It is therefore possible that some proportion of the 40-45% of dose not rapidly excreted via bile (possibly all of it) will have been systemically available to a significant extent. Taking all bile excreted from 6 hours onwards plus urine from cannulated rats as representing systemically available material would give an oral absorption value of ≈50% for both sexes. Using the NOAEL of 23 mg/kg bw/day for brain vacuolation and the 1000-fold safety margin as proposed in Section B.10.3, then applying a revised oral absorption correction of 50% would give a revised short term AOEL of 0.012 mg/kg bw/day. If the proposal of the Netherlands to use 18% oral absorption was accepted, the AOEL would be 0.004 mg/kg bw/day. If the proposal to base the AOEL on the NOAEL for liver effects (point 2(42)) was accepted, then a 70% oral absorption correction (based on all

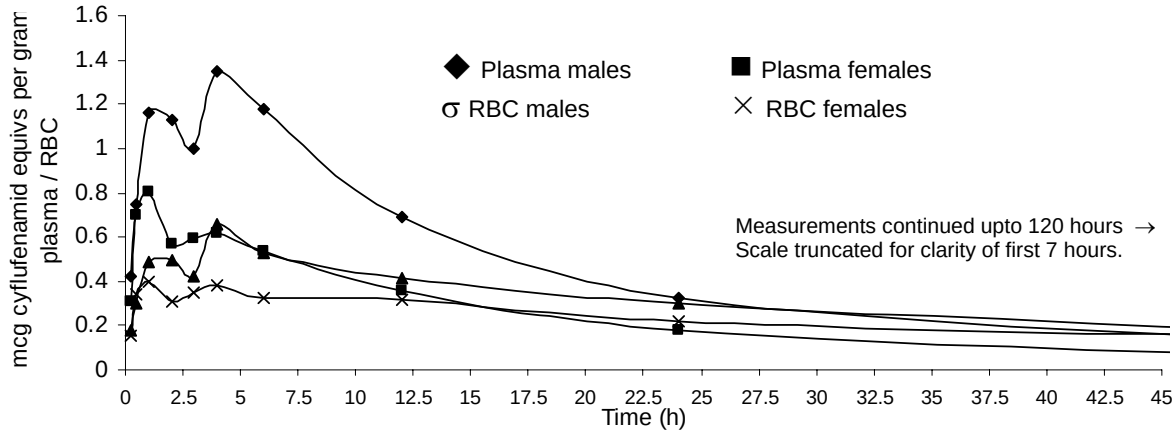
Summary of mammalian toxicology and setting of ADI, AOEL and ARfD (B.6.10)			
No.	Column 1 Reference to DAR	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur
			material excreted in bile) would be appropriate (which would give 0.05 mg/kg bw/day). The appropriate value to use for oral absorption (and the NOAEL) should be discussed in an Expert Meeting.

Table B.6.2 Mean excretion and retention of radioactivity in bile duct cannulated rats 48 hours after a single oral dose of either 10 mg/kg or 200 mg/kg of [^{14}C-fluorinated phenyl] cyflufenamid (% of administered dose)

Sample	10 mg/kg		200 mg/kg	
	Male	Female	Male	Female
Urine				
0-12h	2.54	2.41	0.86	0.65
0-24h	6.29	4.56	4.43	2.35
0-48h	8.31	5.43	5.75	3.40
Cagewash (0-48h)	0.17	0.13	0.20	0.18
Bile				
0-3h	10.1	17.7	1.33	3.61
0-6h	21.1	32.3	3.79	7.36
0-12h	42.1	54.5	9.43	14.1
0-24h	57.7	72.9	26.2	34.3
0-48h	60.6	77.4	33.5	43.2
Feces				
0-12h	3.94	2.52	2.34	0.73
0-24h	18.7	10.0	36.2	38.4
0-48h	24.2	15.6	61.5	54.3
Liver	0.47	0.50	0.26	0.27
Gastrointestinal tract	0.13	0.40	0.23	0.25
Carcass	0.91	1.86	0.84	3.76
Total	94.8	101	102	105
Extent of absorption	70.4	85.3	40.6	50.8

Figure B.6.2 Concentration of radioactivity (µg cyflufenamid equivs. per gram matrix) in plasma and RBC after single oral doses with fluorinated phenyl ring labelled ^{14}C cyflufenamid.

SOLD



B.6.10.3 Acute reference dose (ARfD) – further consideration

For the ARfD the key issue is the conflicting findings in the two rabbit developmental studies. The brain vacuolation in dogs is not relevant to setting the ARfD since other toxicological effects of cyflufenamid are more sensitive to a short-term or acute exposure.

In the DAR the ARfD was proposed as follows:-

Draft Assessment Report B.6.10.3

The acute reference dose is based on the NOAEL (5 mg/kg bw/day) for maternal toxicity in the two rabbit developmental toxicity studies. It was based on reduced food consumption which was apparent on or soon after the first day of dosing in this gavage study. As this is a dietary reference dose no adjustment for oral absorption is required. A 100 fold assessment factor is considered sufficient.

An acute reference dose of 0.05 mg/kg bw/day is proposed.
[NB if brain vacuolation were to be used to drive the ARfD, the 28 day dog brain vacuolation NOAEL (97 mg/kg bw/day) could be used. Using a 1000 fold safety factor this gives an ARfD of 0.097 mg/kg bw/day which is greater than that proposed above.]

In one rabbit developmental study there was an effect on bodyweight gain and food consumption at 10 mg/kg bw/day but this finding was not reproduced in a second near-identical study where doses of 5 or 10 mg/kg bw/day had no effect on food consumption or bodyweight gain. The studies are summarised below, along with the bodyweight and food consumption data from the two studies for comparison.

Study	NOAEL	LOAEL	Effects at LOAEL
Rabbit Developmental toxicity 0, 10, 60 and 300 mg/kg bw/d [Patten, 2000]	<10 mg/kg bw/d [maternal toxicity]	10 mg/kg bw/d [maternal toxicity]	10: Dose-related reductions in bodyweight gain and food consumption
	10 mg/kg bw/d [developmental toxicity]	60 mg/kg bw/d [developmental toxicity]	60: Reduced foetal weight, retarded ossification
Rabbit Developmental toxicity 0, 5 and 10 mg/kg bw/d [Patten, 2001]	10 mg/kg bw/d [maternal toxicity]	>10 mg/kg bw/d [maternal toxicity]	No effects on maternal toxicity up to the highest dose tested.
	10 mg/kg bw/d [litter parameters]	>10 mg/kg bw/d [litter parameters]	No effect on litter parameters (no foetal examination)

Summary of data from Patten, 2000				
Gavage dose of cyflufenamid (mg/kg bw/day)	**0**	**10**	**60**	**300**
:	**Disposition**			
Mated	26	26	26	26
Not pregnant	1	1	2	3
Aborted	0	0	0	7
Total litter death	0	0	1	0
Total with viable foetuses at Day 29	25	25	23	16
	Body weight change (kg)			
Days 0-6	0.07	0.05	0.07	0.05
Days 6-18	0.18	0.10**	0.10**	0.01**
Days 18-29	0.18	0.17	0.14	0.11
Days 6-29	0.36	0.26*	0.24*	0.12**
Days 0-29	0.43	0.31*	0.31*	0.17**

Summary of data from Patten, 2000				
Gavage dose of cyflufenamid (mg/kg bw/day)	**0**	**10**	**60**	**300**
Days 6-29 (adjusted for gravid uterine weight)	-0.14	-0.29**	-0.30**	-0.38**
	Food consumption (g/animal/day)			
Day 1	140	145	141	133
Day 8	144	135	123	104**
Day 15	140	108*	102**	86**
Day 18	137	126	109*	81**
Total food consumption	3816	3438	3314	2793
(% of control)	-	(90%)	(87%)	(73%)

Summary of data from Patten, 2001				
Gavage dose of cyflufenamid (mg/kg bw/day)	**0**	**5**	**10**	
:	**Disposition**			
Mated	24	24	24	
Not pregnant	1	0	1	
Aborted	0	1	1	
Humane sacrifice (not treatment-related)	2	0	1	
Total with viable foetuses at Day 29	21	23	21	
	Body weight change (kg)			
Days 0-6	0.12	0.08	0.11	
Days 6-18	0.10	0.17*	0.14*	
Days 18-29	0.24	0.23	0.25	
Days 6-29	0.34	0.40	0.39	
Days 0-29	0.46	0.48	0.50	
Days 6-29 (adjusted for gravid uterine weight)	-0.17	-0.16	-0.17	
	Food consumption (g/animal/day)			
Day 1	143	131	127	
Day 8	139	130	149	
Day 15	133	128	149	
Day 18	126	130	145	
Total food consumption	3713	3689	3836	
(% of control)	-	(99%)	(103%)	

The two studies were almost identical (same laboratory, same batch of test material and performed only a short time apart, almost identical methods used). The same strain of rabbits was used (NZ White) but the animal supplier was different.

The RMS proposal was to take the conservative approach in view of the uncertainty. This meant taking the clear NOAEL from these two studies (5 mg/kg bw/day), and applying the default assessment factor of 100 to derive an ARfD of 0.05 mg/kg bw/day.

An alternative proposal from a Member State was to use the NOAEL of 10 mg/kg bw/day since the effects in one study at this dose level were not reproducible in the other. Applying the default assessment factor of 100 would derive an ARfD of 0.1 mg/kg bw/day.

B.6.12 Dermal absorption – further consideration

As described in the Reporting Table at Point 2(50) the RMS considers it appropriate to re-calculate the dermal values from the *in vitro* study including the material within the skin as absorbed. A revised Table B.6.46 from the DAR is presented below. Since skin stripping of the outer layers of skin did not take place then including the entire proportion in the skin may represent a slight overestimate but this is unavoidable. Any overestimate should not be excessive since the material removed by swabbing again after 24 hours has been excluded as not absorbed.

Table B.6.46 Distribution of radioactivity following the application of [^{14}C]-cyflufenamid in a comparative *in vitro* dermal penetration study in rat and human skin.

	Units	**Low dose (spray dilution)**		**High dose (formulation concentrate)**	
		Rat skin	**Human skin**	**Rat skin**	**Human skin**
Non-absorbed Skin swab (6 hours)	(%) (µg)	40.82 0.591	47.67 0.670	65.29 207.71	82.64 252.78
Non-absorbed Skin swab (24 hours)	(%) (µg)	6.10 0.088	14.93 0.210	7.50 23.87	5.33 16.31
Absorbed Skin (24 hours)	(%) (µg)	28.40 0.411	28.68 0.403	17.25 54.90	3.80 11.63
Absorbed Receptor fluid (0 to 24 hours)	(%) (µg)	16.92 0.245	0.84 0.012	2.10 6.68	0.07 0.23
Total absorbed	**(%)**	**45.32%**	**29.52%**	**19.35%**	**3.87%**
Total recovery	(%)	94.63	95.55	94.29	92.43
Rat:human absorption ratio		**1.54**		**5.0**	

The *in vivo* skin penetration study in rats indicated values of 5% for undiluted formulation and 12% for the in-use dilution. Applying the revised rat:human correction factors of 5.0 and 1.54 derived from the *in vitro* study gives penetration values for human skin of 1% for the concentrate and 8% for the in-use dilution.

	In-use Dilution	Concentrate
Penetration through rat skin (from *in vivo* study)	12%	5%
Relative permeability rat:human (from *in vitro* study)	*45.32% ÷ 29.52%* = 1.54	*19.35% ÷ 3.87%* = 5.0
Dermal penetration value estimated for *in vivo* human skin	*12% ÷ 1.54* = 8%	*5% ÷ 5.0* = 1%

Operator, bystander and worker exposure estimates have been revised from the DAR using these values of 1% for concentrate and 8% for the in-use dilution. These revised estimates were presented in Addendum 1 (March 2007).

B.8 ENVIRONMENTAL FATE AND BEHAVIOUR

This Addendum provides the Rapporteur evaluation of additional data submitted by the Applicant in support of the EC review of the new active substance cyflufenamid following the finalisation of the Reporting Table (rev. 1-1 (22.06.2007)). The new information submitted by the Applicant specifically addresses the following key Open Points and Data Requirements identified in the Evaluation Table:-

- Date Requirement 4.1: Applicant to provide further details on the monitoring study on phenyl acetic acid (PAA) in soil performed in Japan

- Date Requirement 4.2: Applicant to provide further information to support the choice of field trial sites, specifically with regard %OC content, to cover the wide range of European conditions

- Open Point 4.2: MS to discuss the suitability of the approach used to model the metabolites for groundwater contamination in a meeting of experts

- Open Point 4.4: RMS to provide explanations on the inconsistency between the timing of application as indicated in the GAP table and the actual dates of application used in the assessment

In addition the List of Endpoints has been updated to reflect a number of other changes proposed by the remaining Open Points, and to update the format in agreement with the current harmonised version of the list of endpoints.

The Addendum is presented in separate sections as the Applicant has addressed each of the outstanding open points and data requirement that were identified in the Reporting Table and the subsequent Evaluation Table. Section numbering follows the numbering in the original DAR for consistency. Where reference is made to the original cyflufenamid DAR the page numbers refer to the January 2006 (Word version).

B.8.1 Route and rate of degradation in soil (IIA 7.1.1; IIIA 9.1.1)

Data requirement 4.1
Applicant to provide further details on the monitoring study on phenyl acetic acid (PAA) in soil performed in Japan, to support the reported natural background concentrations in soil.
In the comments received on the reporting table, the applicant stated that the study has been submitted to RMS on 6 June 2007.
Refer to reporting table 4(3)

In order to address this point the Applicant referred to the study report that investigated the analytical method for phenyl acetic acid (PAA) in Japanese soils. This brief study is evaluated below.

Report: Ryuichi Yamasaki, 2001. Investigation of Analytical Method for PAA in soil. Nippon Soda Co., Ltd. Study Number NSM 00-004NG

Guidelines: None
Document No.: RD-01176
GLP: No

Untreated control soil from Ibaragi, Japan was analysed for the determination of phenyl acetic acid (PAA). Soil properties are listed in Table B.8.1 below. The soil (2mm sieved) was weighed and shaken with 100ml acetone for 30 minutes. The sample was centrifuged and the acetone extract removed. The extraction procedure was repeated and extracts combined. Aliquots were dried, re-dissolved in acetone and filtered prior to analysis via GC/MS. Calibration curves were prepared using a standard solution of PAA. The LOQ of PAA was reported by the study authors to be 2 mg/l. The Rapporteur noted that it was not possible to validate this LOQ, or to relate it to an effective soil concentration (i.e. in mg/kg), on the basis of the information provided in the report. On the basis of the GC/MS chromatograms presented in the study report 2 ions with an m/z ratio of 91 and 136 were used for identification/quantification.

Table B.8.1 Properties of untreated Japanese control soil tested for the determination of PAA (Yamasaki, 2001)

Soil name/location	**Ibaragi, Japan**
Textural classification (SSLRC)	Clay
Particle size distribution: Sand (%) Silt (%) Clay (%)	 25 28 48
Organic carbon (%)	3.3
pH (H_2O)	7.0
Water content (%)	32.45

As a result of the analysis of the control soil PAA was determined to be present at a concentration of 0.076mg/kg. As reported in the original DAR (see pages 284-285) the maximum application rate of cyflufenamid is 50 g a.s./ha which corresponds to a worst case soil PEC of 0.067 mg/kg (assuming a homogenous distribution in the top 5cm soil layer and a soil density of 1.5 g/cm^3). If all the cyflufenamid were degraded to PAA and related compounds the expected soil concentration of PAA would be approximately 0.022 mg/kg. Therefore the concentration of naturally occurring PAA was observed to be greater in one Japanese soil than would be formed via degradation of cyflufenamid.

(Yamasaki, 2001)

In the opinion of the RMS the study of Yamasaki (2001) provided evidence of limited quality only on the determination of PAA in soil.

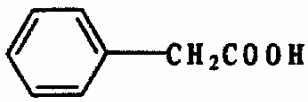
Ideally the method validation study should have been conducted to GLP. In the briefly reported study it was not possible to confirm whether the analytical method was suitable in accordance with the EU guidance for generating and reporting

methods of analysis in support of pre-registration data requirements (SANCO/3029/99 rev.4). For example, it was not possible confirm whether the method was suitable with regards to the specificity, linearity (over a suitable range), accuracy or precision. Soil storage details prior to analysis were also only briefly stated (e.g. it was reported that soils were stored at 0-10°C prior to analysis). Information on historical pesticide use at the site was also absent. The experimental determination of the LOQ was also not reported. Procedural recoveries were also not reported. In addition it would probably have been preferable to have tested a standard EU soil to determine the background levels of PAA representative of EU conditions.

However, despite the shortcomings of the study of Yamasaki (2001) the RMS considers it highly plausible that PAA is a naturally occurring compound and that the potential formation of such a substance from applied cyflufenamid would have an insignificant effect on the naturally occurring levels of this substance derived from alternative sources. The structure of the PAA metabolite is presented in Figure B.8.1 below. Appendix 4A of the original DAR (see page 436) confirmed that PAA was a constituent of rat urine in un-dosed control rats tested during metabolism studies. In the opinion of the RMS the Applicant could have provided a much more detailed case to support their position. A brief review of the World Health Organisation Food Additives Series: 50 (2003; ISBN 92 4 166050 3) has confirmed that PAA is a common food flavouring agent with no safety concerns. This document also indicated that most recent annual volumes of usage of phenyl acetic acid as a flavouring agent in Europe was approximately 2000 kg/year (based on data from 1999) as well as indicating that this substance is naturally present in many foods.

In the opinion of the RMS no further information is necessary and the data requirement should be considered addressed.

Figure B.8.2 Structure of phenyl acetic acid



B.8.1.1.2.2 Field studies (III 7.1.1.2.2; IIIA 9.1.1.1.2)

Data requirement 4.2
Applicant to provide further information to support the choice of field trial sites, specifically with regard %OC content, to cover the wide range of European conditions.
In the comments received on the reporting table, the applicant stated that the study has been submitted to RMS on 6 June 2007.
See reporting table 4(5)

The original comment in the Reporting Table concerned the observation that under laboratory conditions, degradation appeared to be dependent on soil organic matter content (much slower degradation observed in the higher organic matter soils). Field

studies were only tested with relatively low organic matter contents. A data requirement was set for the Applicant to provide further information and the Applicants response is presented below in italics.

The choice of the trial sites and soils used in the field dissipation trials (sand, loamy sand, clay loam and silty clay) was based on SETAC-Europe 1995 Procedures for assessing the environmental fate and ecotoxicity of pesticides recommendations. The trials were specifically located in areas of Northern and Southern Europe with soil types representative of crop production areas for intended uses of NF-149 EW, the representative EU formulation, as stated in the study reports for wheat and barley. Furthermore, information from field trials experts in the EU is that organic matter in typical cereal growing areas has a ***maximum*** *of 3-5% organic matter.*

Although in the laboratory studies, there was a tendency for a long DT_{50} to be associated with a high organic matter content, this was not supported by data in the field dissipation study. In this field dissipation study, no such correlation was found (Tables B.8.2 and B.8.3 below). The shortest DT_{50} value (10.2 days) was associated with an intermediate level of organic matter content (1.89%) and the longest DT_{50} corresponded with the lowest content (1.38%).

In conclusion, the soil types chosen for the field dissipation study were relevant to those used for cereal crops such as wheat and barley, the principal crops on which cyflufenamid is intended to be applied. The apparent dependency of the rate of degradation with organic matter content seen in the laboratory studies did not occur in the field dissipation studies under conditions representative of agricultural environmental conditions.

Table B.8.2 Field dissipation study with cyflufenamid (NF-149) – Organic matter content and DT_{50} values

Trial site	***Soil type***	***Organic matter content, % (Organic carbon content, %)***	***DT_{50} (days)[a]***
UK	*Sand*	*1.72 (1.0)*	*25.7*
Germany	*Loamy sand*	*1.38 (0.8)*	*91*
N. France	*Clay loam*	*1.89 (1.1)*	*10.2*
S. France	*Silty clay*	*2.92 (1.7)*	*17.3*

[a]: From Draft Assessment Report (see Table B.8.42, page 307)

Table B.8.3 Laboratory studies with cyflufenamid (NF-149) – Organic matter content and DT_{50} values

Study	***Soil type***	***Organic matter content, % (Organic carbon content, %)***	***DT_{50} (days)[a]***
Aerobic rate of degradation	*Bromsgrove* *Evesham 3* *Speyer 2.2*	*2.41 (1.4)* *3.27 (1.9)* *4.82 (2.8)*	*8.95* *20.6* *121*
Aerobic rate of degradation	*Abington* *Terling*	*3.61 (2.1)* *5.33 (3.1)*	*18.9* *412*
Aerobic route of degradation	*Arrow*	*3.10 (1.8)*	*40.5*

[a]: From Draft Assessment Report (see Table B.8.40, page 306)

As stated in the Reporting Table (see Point 4(5)) the RMS agreed with the observation that the slowest dissipation occurred in the two soils with the highest %OM content (e.g. SFO DT_{50} of 121 and 412d in the Speyer 2.2 and Terling soils with %OM of 4.82 and 5.33% respectively). In general there was noted to be a very wide range in the available DT_{50} values for the parent based on the laboratory data base (i.e. from 8.95 to 412 d, Table B.8.3 above) which may be considered somewhat unusual. It is possible that the degradation is partly influenced by the relatively strong sorption, which was also noted to correlate well with soil organic content (i.e. strongest sorption in soils with highest %OM) which may in turn reduce the fraction available for degradation.

With regard to the choice of field trial sites, the RMS accepted that a reasonable range of soil types had been selected (e.g. sand, loamy sand, clay loam and silty clay), covering both Northern EU and Southern EU conditions and covering a reasonable range of individual soil characteristics (e.g. pH 4.5 to 7.9; clay content 7.10 to 39.36%) and therefore accepted the original data submitted as being sufficient to meet the data requirements. The RMS notes the Applicants arguments that the tendency for increased DT_{50} with increasing soil OM% was not supported by data from the field dissipation study. However, given the relatively narrow range of %OM contents tested in the field (i.e. only 1.38 to 2.92%) the RMS does not consider it possible to make any definitive conclusions on the influence of individual soil properties on dissipation rate based on the available information from the field.

Given the relatively wide range of DT_{50} values observed in the laboratory soils, and the potential relationship between DT_{50} and soil OM%, the RMS considers it would have been useful to have tested soils with a wider range of OM% under field conditions. However as stated above the RMS considers that the submitted field dissipation data meets the data requirements and does not consider it necessary to request any further information.

For further reassurance the RMS has simply re-run the groundwater exposure assessment using a simple worst case laboratory DT50 of 412 d in place of the original value of 19.4 d used in the DAR. All other input parameters were as per the modelling in the DAR (see Section B.8.6.1 below for further details of input parameters). Even with this conservative value the cyflufenamid PECgw was 0.000µg/l according to FOCUS PELMO simulations. This simple worst case calculation is presented for illustrative purposes only and the DT50 of 412 d is not considered appropriate for routine groundwater exposure assessments.

The RMS considers that no further information is required.

B.8.6 Predicted environmental concentrations in surface water, sediment and groundwater (PEC_{SW} and PEC_{SED}, PEC_{GW}) (IIIA 9.2.1, 9.2.3)

B.8.6.1 Groundwater

A number of Open Points were raised concerning the presentation of the groundwater exposure assessment in the original DAR and these are addressed below.

Open point 4.2
MS to discuss the suitability of the approach used to model the metabolites for groundwater contamination in a meeting of experts.
EFSA note: the direct application of metabolites instead of using sequential degradation in the model would result in a best case as the amount of the leaching of metabolite during its formation from the parent is excluded in the modelling. Therefore this approach is not recommended.
Refer to reporting table 4(14).

As stated in the Reporting Table (see point 4(14)) the degradation pathway for cyflufenamid was relatively complex and it was not considered possible to perform full kinetic analyses that would result in the derivation of reliable formation fractions of all four metabolites in the degradation studies conducted with the parent. For example, a clear pattern of formation and decline was not always observed for all metabolites, particularly the later metabolites in the metabolic pathway. There would therefore be a degree of uncertainty around some of the formation fractions derived.

The four soil metabolites were therefore simulated as independent compounds in the groundwater exposure assessment. Inputs to soil were been calculated based on an instantaneous input of parent compound of a total of 20.0 g a.s./ha (the sum of 12.5 and 7.5 g a.s./ha taking into account crop interception) and considering the maximum occurrence of each metabolite in laboratory degradation studies and the ratio of molecular weights of parent and each respective metabolite. Maximum peak occurrences of the four metabolites occurred over a range of times in the laboratory. The 'applications' of metabolites were assumed to occur on the date of the second application of parent cyflufenamid. The metabolite 149-F1 showed an intermediate leaching potential. As the timing of peak occurrence in soil was uncertain, a second set of runs were carried out for this compound with input to soil assumed to occur 90 days after the date of maturation. The results of the original groundwater exposure assessment are presented in the DAR from page 327 onwards. Overall during the preparation of the DAR the RMS considered this to be an appropriate approach in the absence of further details on formation fraction etc.

However, it is accepted that this simplistic approach ignores the potential for metabolite leaching to occur during the individual formation phases that would be simulated if the formation fraction approach had been used. In addition, it is noted that the first metabolite in the metabolic pathway (i.e. 149-F11) has a much shorter DT50 than the precursor parent substance. Therefore the true formation fraction of this metabolite is likely to be much higher than the peak occurrence level, since significant degradation will occur during the formation phase (thus reducing the

peak observed relative to the formation fraction). The methodology used in the original DAR could therefore underestimate the leaching potential of such metabolites. For the later metabolites that are more persistent (e.g. 149-F1 and 149-F6) there is likely to be less of a difference between peak occurrence and true formation fraction, and therefore the impact of the exposure methodology is also likely to be somewhat less.

It is not easy to assess how big an impact the method of assessing metabolite leaching potential used in the original DAR has on the overall exposure assessment. For simplicity, the RMS has repeated the FOCUS groundwater assessment assuming a formation fraction of 100% for each stage of the metabolic pathway (i.e. parent → 149-F11 → 149-F → 149-F1 → 149-F6). The input parameters for each substance were identical to those used in the original DAR, and are provided below for completeness in Table B.8.4. Due to the complexity of the metabolic pathway, the FOCUS PELMO (version 3.3.2) was used as implementation of multiple metabolites is marginally easier in this model. Two applications of 25 g a.s./ha were simulated, either 35 or 7 d prior to maturation (as per the DAR). Crop interception was assumed to be 50% (1st application) and 70% (2nd application), again in accordance with the modelling in the DAR[1].

Results of the worst case simulation assuming 100% formation fraction for each stage of the metabolic pathway are presented in Table B.8.5.

[1] Note during the preparation of the original DAR the assessment was based on an assumed GAP of two applications of cyflufenamid at 25 g a.s./ha at GS 29-37 and GS 51-59. The final uses supported are 2 applications between GS 30 and 59. Therefore according to the latest version of the crop interception tables (FOCUS groundwater, version 1.1, 2002) 70% interception would be assumed for the elongation staged (GS 30-39) and 90% assumed for GS 40-89. Overall the crop interception values selected are considered worst case.

Table B.8.4 Input parameters for FOCUS PELMO (v3.3.2) modelling of cyflufenamid and metabolites

Parameter	Value	Further information
Cyflufenamid		
DT50 (d)	19.4	Arithmetic mean rate constant from field studies (non-normalised). Moisture and Temperature correction routines disabled. Vapour pressure set to zero
Kfoc (ml/g)	1595	Arithmetic mean of 4 values
1/n	0.93	Arithmetic mean of 4 values
149-F11		
DT50 (d)	2.3	Arithmetic mean rate constant from 3 laboratory soils, normalised to pF 2.
Kfoc (ml/g)	13.6	Arithmetic mean of 3 values
1/n	0.88	Arithmetic mean of 3 values
149-F		
DT50 (d)	8.5	Arithmetic mean rate constant from 3 laboratory soils, normalised to pF 2.
Kfoc (ml/g)	32	Arithmetic mean of 3 values
1/n	0.84	Arithmetic mean of 3 values
149-F1		
DT50 (d)	147	Arithmetic mean rate constant from 3 laboratory soils, normalised to pF 2.
Kfoc (ml/g)	79	Arithmetic mean of 3 values
1/n	0.94	Arithmetic mean of 3 values
149-F6		
DT50 (d)	1162	Arithmetic mean rate constant from 3 laboratory soils, normalised to pF 2.
Kfoc (ml/g)	8.5	Arithmetic mean of 3 values
1/n	0.99	Arithmetic mean of 3 values

Table B.8.5 80^{th} percentile annual average concentration in leachate below 1m depth (µg/l) for cyflufenamid and its four soil metabolites following application to winter cereals according to FOCUS PELMO v 3.3.2 and assuming 100% formation fractions for each metabolic step and parent DT50 of 19.4 days

Compound	C	H	J	K	N	P	O	S	T
Cyflufenamid	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
149-F11	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
149-F	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
149-F1	0.286	0.546	0.385	0.395	0.453	0.526	0.061	0.011	0.196
149-F6	3.743	2.385	3.652	2.208	1.566	2.491	2.000	5.623	4.043

C = Châteaudun, H = Hamburg, J = Jokioinen, K = Kremsmünster, N = Okehampton, P = Piacenza, O = Porto, S = Seville, T = Thiva

As can be seen from the results in Table B.8.5 above, neither parent cyflufenamid nor either of the first two metabolites in the metabolic pathway (149-F11 and 149-F) are predicted to occur in groundwater (all scenarios resulted in PECgw of 0.000µg/l). This is consistent with the conclusions of the original DAR.

The PECgw values for metabolite 149-F1 are noted to be approximately 5 times higher than reported in the original DAR (see Table B.8.69, page 330). This is consistent with the fact that the original method based the formation of 149-F1 on its peak occurrence in the laboratory studies of 22.9% (compared with the 100% formation assumed in Table B.8.5 above). Similarly, PECgw values of 149-F6 are

approximately 10 times higher than reported in the DAR (again due to the fact that the method used in the DAR assumed a formation of 149-F6 based on its peak occurrence of only 9.0% rather than the 100% assumed here). Clearly the assumption of 100% formation fraction for each step in the metabolic pathway results in the most conservative assessment possible, and these calculations are provided for illustrative purposes only. However it is also accepted that the use of peak occurrence levels to simulate metabolites in such exposure assessments results in a best case assessment with regards to groundwater leaching. The use of actual formation fractions would be predicted to result in an exposure assessment giving PECgw values between these two extremes, however as stated above the available laboratory degradation data for cyflufenamid and its metabolites would not allow accurate formation fractions to be determined.

As stated in section B.8.1.1.2.2 of this addendum, FOCUS groundwater modelling was also conducted by the RMS in FOCUS PELMO v 3.3.2 using the longest laboratory DT50 value of 412 days. All other parameterisation for simulated substances were as specified in Table B.8.4 above, and the application scenario was unchanged. Results of this modelling are presented in Table B.8.6.

Table B.8.6 80^{th} percentile annual average concentration in leachate below 1m depth (µg/l) for cyflufenamid and its four soil metabolites following application to winter cereals according to FOCUS PELMO v 3.3.2 and assuming 100% formation fractions for each metabolic step and parent DT50 of 412 days

Compound	C	H	J	K	N	P	O	S	T
Cyflufenamid	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
149-F11	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
149-F	0.000	0.000	0.000	0.000	0.000	0.001	0.000	0.000	0.000
149-F1	0.351	0.593	0.331	0.434	0.526	0.693	0.076	0.014	0.308
149-F6	3.550	2.204	3.364	2.100	1.537	2.383	1.764	5.286	3.976

C = Châteaudun, H = Hamburg, J = Jokioinen, K = Kremsmünster, N = Okehampton, P = Piacenza, O = Porto, S = Seville, T = Thiva

As can be seen, concentrations of metabolite 149-F1 are generally slightly higher when using a parent DT50 of 412 days compared to 19.4 days, but concentrations of metabolite 149-F6 are slightly lower. The peak PECgw of metabolite 149-F1 was 0.693µg/l (Piacenza scenario) and the peak PECgw of metabolite 149-F6 was 5.623µg/l (Seville scenario).

Since both 149-F1 and 149-F6 were predicted to occur above 0.1µg/l in the original DAR, they were subject to a relevance assessment according to SANCO/221/2000-rev.10, February, 2003 and were considered non-relevant. In Section B.6.10.3 of the original DAR (see page 193) a maximum allowable concentration (MAC) in drinking water for cyflufenamid was estimated to be 51µg/l. The concentrations of both potential groundwater metabolites are seen to be clearly below the MAC derived for the parent, even using relatively simple worst case input parameters in the exposure assessment.

Therefore in the opinion of the RMS the groundwater exposure assessment is considered acceptable.

Open point 4.3
MS to discuss the appropriate DT50 value to be used in FOCUSgw modelling in a meeting of experts.
Refer to reporting table 4(17)

The original DAR was prepared during 2003, prior to the release of the FOCUS degradation kinetics guidance document. The DAR was therefore prepared using the best available guidance at the time. As such the degradation input parameters used in the FOCUSgw modelling were based on the arithmetic mean of the individual rate constants. The RMS accepted this approach during the preparation of the DAR (rather then taking a mean of the DT50 values as was more usually the case in the past) since the groundwater models use the actual rate constant in the simulations (rather than the DT50). The approach of the Applicant appeared valid in the absence of further guidance.

It is now recognised that best practise would be to base the modelling input parameters on the geometric mean DT50 or rate constant (since the calculation of geometric mean values results in the same value for the mean of the DT50 or rate constant). To demonstrate the impact these different methods have on deriving input parameters for exposure modelling both approaches are presented in Table B.8.7 below.

Table B.8.7 Derivation of input parameters based on either arithmetic or geometric mean values of either the first order rate constant or the equivalent DT50 value

Compound	**Soil**	**Soil type**	**First-order rate constant at -10 kPa (1/d)[a]**	**First order DT50 at -10kPa (d)**
Cyflufenamid[b]	UK	Sand	0.026971	25.7
	Germany	Loamy sand	0.007617	91.0
	N. France	Clay loam	0.067956	10.2
	S. France	Silty clay	0.040066	17.3
	Arithmetic mean	-	**0.035652 (19.4 d)**	36.1
	Geometric mean	-	0.027348 (25.3 d)	25.3
149-F	Bromsgrove	Sandy loam	0.12000	5.78
	Evesham 3	Clay loam	0.06337	10.94
	Arrow	Sandy loam	0.06171	11.23
	Arithmetic mean	-	**0.08169 (8.5 d)**	9.32
	Geometric mean	-	0.07771 (8.91)	8.91
149-F1	Bromsgrove	Sandy loam	0.00211	328
	Evesham 3	Clay loam	0.00773	89.7
	Arrow	Sandy loam	0.00427	162.3
	Arithmetic mean	-	**0.00470 (147.5 d)**	193.5
	Geometric mean	-	0.004114 (168.5 d)	168.5
149-F6	Bromsgrove	Sandy loam	0.000818	847
	Evesham 3	Clay loam	0.000648	1070
	Arrow	Sandy loam	0.000324	2139
	Arithmetic mean	-	**0.000597 (1162 d)**	1352
	Geometric mean	-	0.000556 (1247 d)	1247
149-F11	Bromsgrove	Sandy loam	0.3735	1.9
	Evesham 3	Clay loam	0.2672	2.6
	Arrow	Sandy loam	0.2738	2.5
	Arithmetic mean	-	**0.3048 (2.3 d)**	2.3
	Geometric mean	-	0.301199 (2.3 d)	2.3

[a]values in brackets represent the effective 1st order DT50 based on the mean rate constants
[b]dissipation rates for cyflufenamid are based on un-normalised field values

In Table B.8.7 above the values in bold font represent the values used in the original groundwater exposure assessment in the DAR (i.e. based on arithmetic mean of the available rate constants). The shaded values represent the input parameters that would be selected using more modern decision making criteria (i.e. based on the geometric mean of either the rate constant or DT50).

Given the relatively high K_{foc} and large margin of safety on the parent PECgw simulations presented in the DAR (i.e. K_{foc} = 1595 ml/g and all PECgw = 0.000µg/l), the RMS does not consider that a revised FOCUSgw modelling assessment using a marginally longer DT50 (i.e. 25.3 d versus the current 19.4 d used in the DAR) would alter the conclusions of the DAR with respect groundwater leaching potential of cyflufenamid. (In fact in Section B.8.1.1.2.2 it has been shown that even using a worst case soil DT50 of 412 d from the laboratory data set the PECgw is still 0.000µg/l in all scenarios according to FOCUS PELMO simulations). Therefore no further assessment is proposed.

With respect to metabolites 149-F11 and 149-F, the RMS considers that the alternative DT50 based on geometric means would not significantly alter the conclusions of the DAR with respect groundwater leaching potential of these substances. In addition further groundwater modelling has been presented in this Addendum based on a conservative formation fraction of 100% for these metabolites, and exposure concentrations were still reported to be 0.000µg/l according to FOCUS PELMO (see Table B.8.5 above). Therefore no further assessment is proposed.

For metabolites 149-F1 and 149-F6, it is clear that using the marginally longer DT50 values based on geometric means would result in an increase in the PECgw values. However the additional assessment of potential groundwater exposure presented in this Addendum based on the assumption of 100% formation fractions is considered sufficiently precautionary and no further assessment is proposed. Both these metabolites have been subject to a relevance assessment in accordance with SANCO/221/2000-rev.10, February, 2003. Therefore no further assessment is proposed.

Open point 4.4
RMS to provide explanations on the inconsistency between the timing of application as indicated in the GAP table and the actual dates of application used in the assessment.
EFSA note: it is noted that in all field trials cyflufenamid was applied in late May or middle June. In addition, in FOCUS GW the crop interception factors were calculated based on applications to cereals at GS 20-39 and GS 40-89 (it was not possible to check the actual dates of application used in the modelling because the original report on FOCUS PECgw is not available).
Refer to reporting table 4(18)

The selection of application dates for cyflufenamid during the groundwater exposure assessment was based on the assumption that the date of maturation in FOCUS PELMO is equivalent to GS60 (start of flowering). The RMS considered this assumption to be acceptable since it is reasonable to assume that the green area of

canopy would be at its maximum at the start of flowering (and therefore equivalent to the point of 'maturation' in the FOCUS scenarios, as this point is also taken as the date of maximum leaf area index for the purposes of modelling). Accordingly, the two applications to winter cereals were assumed to occur 35 and 7 days before the date of maturation. The growth period specified for spring cereals by FOCUS (2000) is particularly short, so the two applications were set to worst-case timings of 21 and 0 days before maturation. These timings for applications to both winter and spring cereals are considered acceptable to match the proposed GAP of 2 applications between GS 30 and 59.

For completeness, the dates of maturation from FOCUS PELMO and the dates of the first and second applications to winter cereals used in the groundwater assessment for each scenario are presented in Table B.8.8 below.

Table B.8.8 Dates of maturation and application assumed during the FOCUS PELMO modelling of potential groundwater exposure following use of clyflufenamid on winter cereals

Sceanrio	**Date of maturation of winter cereals assumed in FOCUS PELMO (value in brackets represents the corresponding maturation date for spring cereals[a])**	**Date of first application to winter cereals (35 d prior to maturation)**	**Date of second application to winter cereals (7 d prior to maturation)**
Châteaudun	31-May (10-June)	26-Apr	24-May
Hamburg	1-June (5-June)	27-Apr	25-May
Jokioinen	25-June (30-June)	21-May	18-June
Kremsmünster	5-June (5-June)	1-May	29-May
Okehampton	15-May (22-May)	10-Apr	8-May
Piacenza	10-May	5-Apr	3-May
Porto	30-Apr (10-June)	26-Mar	23-Apr
Sevilla	28-Feb	26-Apr	24-May
Thiva	30-Mar	23-Feb	23-Mar

[a]Applications to spring cereals were assumed to take place 21 and 0 days before maturation

It is accepted that application date can be a sensitive parameter in groundwater exposure assessments, but in the opinion of the RMS this usually only results in significant differences when the difference in application date is large (i.e. weeks or months rather than days). For parent cyflufenamid and metabolites 149-F11 and 149-F there appear to be large margins of safety around the existing groundwater exposure assessment (all PECgw values were 0.000µg/l). Therefore the RMS does not consider that small changes to the application date would result in significantly different conclusions with respect groundwater leaching potential of these substances.

For metabolites 149-F1 and 149-F6, it is clear that using alternative application dates would result in a change in the PECgw values generated by the standard FOCUS models. However the RMS does not consider that small changes to the application date would result in significantly different conclusions with respect groundwater leaching potential of these substances either. This is because both are considered potential groundwater contaminants and have been assessed according to SANCO/221/2000-rev.10, February, 2003 and found to be non-relevant. In addition

the further assessment of potential groundwater exposure presented in this Addendum based on the assumption of 100% formation fractions is considered sufficiently precautionary and no further assessment is proposed to assess the impact of application date.

During the field dissipation study a single application of cyflufenamid at an application rate equivalent to the maximum proposed total dose (i.e. approximately 50 g a.s./ha) was made at each site. The timing of applications varied from 28-May (Germany site) up to 15-June (Northern France site) and were considered by the RMS to be reasonably representative of the likely timing of the second application under the proposed GAP. The application timings in the field are also noted to be broadly consistent with the timings used in the FOCUS groundwater assessment for applications to winter and spring cereals.

Overall the RMS considers that there is no significant inconsistency between the GAP and application dates used in the assessment (either during the field dissipation studies or during the FOCUSgw modelling). Therefore the RMS considers that no further information is required.

Council Directive 91/414/EEC

Cyflufenamid

Addendum 3

Volume 3

Annex B

to the Report and Proposed Decision of the United Kingdom made to the European Commission under Article 8(1) of 91/414/EEC

Prepared February 2008

PESTICIDES SAFETY DIRECTORATE
Mallard House, Kings Pool,
3 Peasholme Green,
York YO1 7PX, UK

Website: www.pesticides.gov.uk

Contents

Introduction

This Addendum presents further information on methods of analysis and revised risk assessment for residues and operators following discussions at the PRAPeR expert meetings, 36, 39 & 40, November/December 2007).

B.5 Methods of analysis

B.5.3 Analytical methods (residue) in soil, water and air (IIA 4.2.2 to 4.2.4, IIIA 5.2)

B.5.3.2 Residues in water (IIA 4.2.3)

The LC-MS method for the determination of cyflufenamid and metabolites in leachate water reported by Brewin, S.A., 2000, NOD 137/002147 (report no.RD-II2006) was considered by experts at PRAPeR 36 to address the requirement for a confirmatory method for the determination of cyflufenamid in water, since the proposed confirmatory method was validated at 100 times higher than the LOQ.

The analytes were extracted using tandem C18 and SCX solid phase extraction cartridges. Metabolite 149-F1 was eluted from the SCX cartridge, the other analytes were eluted from the C18 cartridge. The extracts were combined and the organic solvent was evaporated off before they were diluted for analysis by LC-MS. Cyflufenamid and metabolites 149-F6 and 149-F11 were chromatographed by gradient elution using a LUNA C8 analytical and ammonium acetate, acetic acid/acetonitriole mobile phase. Metabolites 149-F and149-F1 were chromatographed by gradient elution using a LUNA C8 analytical column and ammonium acetate/ammonia/acetic acid mobile phase. Acceptable validation data were presented for cyflufenamid and metabolites 149-F, 149-F1, 149-F6 and 149-F11 in leachate water with an LOQ of 0.05 µg/l. The experts considered the data and agreed that the method was an acceptable confirmatory method for cyflufenamid in water.

Brewin, S. A., 2000

B.5.6 References relied on

Active substance

Annex point	Author	Date	Title and Company reference	Data Protection claimed Y/N	Owner
IIA, 4.2.3/ 01	Brewin, S. A.	2000	Development and validation of methodology for the determination of residues in soils from three sites in Southern France, Northern France and Germany, and for the determination of residues in soil and water from a site in the United Kingdom Huntingdon Life Sciences Ltd., Laboratory no. NOD 137/002147 (RD-II02006)	Yes	Nippon Soda

B.6 TOXICOLOGY AND METABOLISM

B.6.14 Exposure data (IIIA 7.2)

B.6.14.1 Operator exposure (IIIA 7.2.1)

'NF 149 EW' is an oil in water emulsion containing 5% cyflufenamid. The proposed use is as an agricultural fungicide on cereals. Usage information pertinent to operator exposure is summarised in Table B.6.47. 'NF-149 EW' is to be applied *via* tractor-mounted hydraulic boom sprayer from the beginning of stem elongation stage (GS30) up to full emergence of the ear stage (GS59). The product is to be packaged in 0.5 or 1 litre HDPE co-extruded polypropylene containers. Water is the diluent/carrier in all situations.

Table B.6.47 Application parameters for 'NF-149EW'

Crops	Application method	Max. ind. dose product (l product/ha)	Max. ind. dose a.s. (g a.s./ha)	Max. no. of applications (per crop)	Min. water volume (litres/ha)
Winter and spring wheat, durum wheat, triticale, winter and spring barley, winter rye	FCS	0.5	25	2	200

FCS=Field crop sprayer

The applicant has proposed the product be classified as 'Harmful' with the associated risk phrases 'Harmful by inhalation' and 'Irritating to skin'. Evaluation of supporting toxicity data has confirmed that the product be unclassified (Section B.6.11.2) and therefore no PPE are required on the basis of this classification alone.

B.6.14.1.1. Estimation of operator exposure

Based on the dermal absorption data submitted, the applicant has proposed dermal absorption values for cyflufenamid of 5% for the concentrate and 12% for the in-use dilution. The dermal absorption values assumed for this evaluation are 1% for both the concentrate and 8% for the in-use dilution respectively (see Reporting table 2(50)).

A short term systemic AOEL for cyflufenamid of 0.065 mg/kg bw/day is proposed by the applicant based on a NOAEL of 6.5 mg/kg bw/day in a 90-day dog study, a correction factor of oral absorption of 1 and a safety factor of 100. The use of the 90-day dog study is considered appropriate but with a revised correction factor for oral absorption of 0.7 and a 1000 fold safety factor. Following consideration of cyflufenamid in the PRAPeR expert meetings a short term systemic AOEL of 0.03 mg/kg bw/day was agreed.

The applicant has provided estimates of operator exposure to cyflufenamid arising from the use of 'NF-149 EW' using the German model (geometric mean) and the UK Predictive Operator Exposure Model (POEM), see Appendix 1.

Estimation according to the German Model

The following assumptions have been used in calculating operator exposure:

The area treated in one day is: 20 ha/day for cereals
The application dose is: 25 g a.s./ha

Estimates of exposure for operators wearing no PPE are as follows;

Table B.6.48 Estimated exposure to cyflufenamid: German model

Use/ Method	Dermal exposure (mg a.s./person/day)			Inhalation exposure (mg a.s./person/day)			Systemic* exposure (mg/kg bw/day)		
	Mix/ load	Spray	Total	Mix/ load	Spray	Total	Mix/ load	Spray	Total
Cereals/ FCS	1.2	1.02	2.22	0.0003	0.0005	0.0008	0.0002	0.0012	0.0013
FCS = Field crop sprayer *Assumes a 70 kg operator, 1% (concentrate) and 8% (in-use dilution) absorption *via* the dermal route and 100% absorption *via* the inhalation route.									

On the basis of the above estimate of operator exposure, the proportion of the systemic AOEL accounted for is given in Table B.6.49.

Table B.6.49 Estimated exposure as a proportion of the AOEL: German model

Use / Method	PPE	Total *systemic exposure (mg/kg bw/day)	Systemic exposure as a % of AOEL
Cereals / FCS	No PPE	0.0013	4
FCS=Field crop sprayer *Assumes a 70 kg operator, 1% (concentrate) and 8% (in-use dilution) absorption *via* the dermal route and 100% absorption *via* the inhalation route.			

Estimation according to UK POEM

The applicant has proposed a work rate of 50 ha/day which is considered appropriate in the UK for application to cereals *via* vehicle mounted/drawn field crop sprayers. The minimum recommended spray volume is 200 l/ha. The applicant has estimated exposure arising from the use of 0.5 and 1 litre containers, however, there are no specific pouring data for 0.5 litre containers and the use of the larger 1 litre containers is considered more realistic based on the work rates proposed.

Table B.6.50 Estimated exposure to cyflufenamid: - UK POEM

Use/ Method	Dermal exposure (mg a.s./person/day)			Inhalation exposure (mg a.s./person/day)			Systemic* exposure (mg/kg bw/day)		
	Mix/load	Spray	Total	Mix/load	Spray	Total	Mix/load	Spray	Total
Cereals/ FCS	12.5	5.194	17.694	**neg.	0.008	0.008	0.002	0.007	0.009
FCS = Field crop sprayer *Assumes a 60 kg operator, 1% (concentrate) and 8% (in-use dilution) absorption *via* the dermal route and 100% absorption *via* the inhalation route. **neg. = assumed to be negligible									

On the basis of the above estimate of operator exposure, the proportion of the systemic AOEL accounted for is given in Table B.6.51

Table B.6.51 Estimated exposure as a proportion of the AOEL: UK POEM

Use / Method	PPE	Total *systemic exposure (mg/kg bw/day)	Systemic exposure as a % of AOEL
Cereals / FCS	No PPE	0.009	30
FCS=Field crop sprayer *Assumes a 60 kg operator, 1% (concentrate) and 8% (in-use dilution) absorption *via* the dermal route and 100% absorption *via* the inhalation route.			

B. 6.14.1.2 Operator exposure Summary

The estimates of exposure detailed above suggest operator exposure to cyflufenamid is expected to be within the systemic AOEL for operators wearing no PPE (German model estimate is 4% of the systemic AOEL, UK POEM estimate is 30% of the systemic AOEL). Evaluation of the supporting toxicity data has confirmed that the product be unclassified and therefore no PPE are required on the basis of hazard classification.

B.6.14.2 Bystander exposure (IIIA 7.2.2)

Bystanders may be subject to dermal and inhalation exposure to the spray solution at the time of application. As cyflufenamid is only very slightly volatile (vapour pressure 3.54 x 10^{-5} Pa at 20°C), exposure to vapour is likely to be of less significance to bystanders than exposure from drift. The applicant has submitted a case propounding that such exposure will be of short duration, is unlikely to be repeated, and is likely to be at a lower level than that affecting the sprayer operator considering the greater distance of a bystander from the application equipment.

Based on actual measurements of bystander exposure in the UK for boom spray applications (Lloyd and Bell, 1983[1]), in a typical case following a single pass of the sprayer, mean potential dermal exposure was measured as 0.1 ml of spray on a bystander positioned at 8 m from the edge of the treatment area. Typical mean potential inhalation exposure was measured as 0.02 ml spray/m^3. Maximum values were about five times these mean values.

In estimating bystander exposure the following additional assumptions have been made;

- Maximum spray concentration of cyflufenamid is 0.125 mg/ml.
- 8% dermal absorption and 100% absorption *via* inhalation.
- No exposure reduction from clothing.
- A respiratory rate of 1.2 m^3/hr (=0.02 m^3/min or 20 l/min).
- An exposure duration of 5 minutes.
- A body weight of 60 kg.

Bystander exposure is calculated as follows;

i. Systemic exposure (dermal) $= \frac{0.1 \text{ ml} \times 0.125 \text{ mg/ml} \times 0.08}{60 \text{ kg}}$

$= 1.7 \times 10^{-5}$ mg/kg bw/day

ii. Systemic exposure (inhalation) $= \frac{(5 \times 0.02 \text{ m}^3/\text{min}) \times 0.02 \text{ ml/m}^3 \times 0.125 \text{ mg/ml}}{60 \text{ kg}}$

$= 4.2 \times 10^{-6}$ mg/kg bw/day

Total systemic exposure of bystanders is estimated to be 0.00002 mg/kg bw/day which is <1% of the short term systemic AOEL of 0.03 mg/kg bw/day. It is therefore unlikely that exposure of bystanders outside the treatment area will exceed the short term systemic AOEL with regards to application to field crops.

B.6.14.3 Worker exposure (IIIA 7.2.3)

The harvesting of cereals is a predominantly mechanised process, however, some manual operations will result in direct contact with treated foliage. The applicant has predicted exposure using the German worker re-entry model (Hoernicke *et al*, 1998[2]). A work rate of 8 hours for 'field walking' (i.e. crop inspection) activities has been assumed by the applicant. This is considered conservative for crop inspection activities (2 hours/day is likely to be more realistic), however, for 'rogueing' activities a 6-8 hour working day is considered appropriate.

A transfer co-efficient of 5,000 cm^2/person/hr has been assumed by the applicant. No TC data specifically for cereal crops appear to be available, however, harvesting a crop such as carnations in terms of morphology, leaf area index and work task can be considered as a suitable surrogate for rogueing activities in cereal crops. Published data for workers harvesting glasshouse carnations which included cutting, sorting and bundling together (van Hemmen and Brouwer, 1997[3]) specify a transfer co-efficient of 4,500 cm^2/person/hour for this activity.

Residues on the foliage depend on application rate, extent of remaining residues from previous applications and the crop habitat [total size of foliage compared to surface area – Leaf Area Index (LAI)]. As DFR studies with cyflufenamid are not available, DFR is predicted from a conservative value of 1 $\mu g/cm^2$ per kg a.s./ha applied. Based on an application rate of 1 kg a.s./ha and a LAI of 1, the theoretical initial concentration of residues on leaves is 10 $\mu g/cm^2$ or 5 $\mu g/cm^2$ per side assuming both sides of the leaf are sprayed. The LAI for most crops is in the range of 3 – 5 therefore the DFR is estimated to be in the range 1 – 1.66 $\mu g/cm^2$ ($\approx$ 1 μg a.s./cm^2).

The approval holder has assumed a single application is made at the maximum approved rate of 0.025 kg a.s./ha, however, two applications can be made per crop. In the absence of foliar residues decline data, two applications at the maximum rate are assumed with no decline in foliar residues occurring between applications.

In accordance with this model, the following worst-case assumptions have been used:

Application rate (R)	2 x 0.025 kg a.s./ha
Initial dislodgeable foliar residue (DFR)	1 $\mu g/cm^2$ x R
Task related transfer coefficient (TC)	4,500 cm^2/person/h
Duration of task (A)	8 h/day

On this basis, potential dermal exposure (D) for an unprotected harvest worker has been estimated to be:

D = DFR x TC x A
D = (2 x 0.025) x 4,500 x 8 = 1800 µg a.s./person/day
D = 1.8 mg a.s./person/day

Assuming a worker body weight of 60 kg and a dermal absorption value of 8%, systemic worker exposure (highest of derived dermal absorption values is assumed as worse case) is estimated to be 0.0024 mg/kg bw/day which is 8% of the short term systemic AOEL.

B.6.14.4 Conclusions

Levels of systemic exposure for operators, bystanders, workers from the proposed use of 'NF-149 EW' are expected to be within acceptable levels.

Label amendments:

None

Data requirements

None

B.6.15 References relied on

Ref No.	Annex point	Author	Date	Title and Company reference	GLP	Pub.
1.	IIIA, 7.2.2.1/01	Lloyd G.A., Bell G.J.	1983	Hydraulic nozzles: a comparative spray drift study	no	yes
2.	IIIA, 7.2.3.1/01	Hoernicke, E., Nolting H. G., Westphal, D., Anwenderschutz, F.	1998	Hinweise in der Gebrauchsanleitung zum Schutz von Personen ben Nachfolgearbeiten in mit Pflanzenschutzmitteln behandelten Kulturen. Nachrichtenbl. Deut. Pflanzenschtzd. 50 (10) p. 267	no	yes
3.	IIIA, 7.2.3.1/01	Brouwer, R., Brouwer, D.H., Tijssen, S.C.A., van Hemmen, J.J.	1992	Pesticides in the Cultivation of Carnations in Greenhouses: Part II Relationship Between Foliar Residues and Exposures. Am Ind. Hyg. Assoc. J. 53 p 582-587	no	yes

B.7 Residues data

B.7.16.2 Intakes by humans

B.7.16.2.1 Long term dietary intakes

The NEDIs for cyflufenamid from the consumption of cereals has been calculated for adults, young people, toddlers, infants, vegetarians and elderly adults based on UK consumption surveys. The following assumptions have been made:

(i) upper range of normal (97.5th percentile) consumption of each individual crop which may have been treated.

(ii) all produce eaten which may have been treated, has been treated and contains residues at the contains residues at the median level (STMR) found in the trials considered to support GAP [cereal grain 0.02 mg/kg]

(iii) there is no loss of residue during transport, storage, processing or preparation of foods prior to consumption.

Table B.7.22 Long term intakes (NEDIs) of cyflufenamid from treated cereals [ADI for cyflufenamid is 0.04 mg/kg bw/day] and consumption data relevant to chronic exposure for cereals

	INTAKES (97.5th percentile) in mg/kg bw/day and Consumption Values (relevant to chronic exposure) in kg/day									
	ADULT	**INFANT (6-12 MONTHS)**	**TODDLER (1 ½ –4 ½ YEARS)**	**4-6 YEARS**	**7-10 YEARS**	**11-14 YEARS**	**15-18 YEARS**	**VEGETARIAN**	**ELDERLY (own home)**	**ELDERLY (residential)**
Intakes of cereal (based on residue 0.02 mg/kg)	0.000092	0.000169	0.000195	0.000185	0.000158	0.000119	0.000103	0.000108	0.000071	0.000072
%ADI	<1%	<1%	<1%	<1%	<1%	<1%	<1%	<1%	<1%	<1%
97.5th %le kg/day cereal	0.3218	0.0735	0.1411	0.1892	0.2442	0.2862	0.3278	0.3599	0.2513	0.2220
mean kg/day cereal	0.1483	0.0356	0.0664	0.1009	0.1276	0.1479	0.1678	0.1669	0.1225	0.1123

Calculations have also been carried out using the WHO Standard European diet and are shown in Table B.7.23.

Table B.7.23 Intake of cyflufenamid from treated cereals (WHO European diet)

crop	Adult intake	
	crop/food (kg/person/day)	[Adult] (mg/kg bw/day
Cereals (total)	0.2263	0.000065

WHO total intake for adults: 0.000065 mg/kg bw/day or 0.2 % of the ADI.

Long term intakes calculated for UK consumption data (adults, young people, toddlers, infants, vegetarians and elderly adults) and using adult intake data for the WHO European diet are all less than 1% of the ADI (0.04 mg/kg bw/day). The long term risks to consumers are acceptable.

B.7.18 References relied on

None

Appendix 1

Operator Exposure Estimates

THE GERMAN MODEL (GEOMETRIC MEAN VALUES)

Application method	Tractor-mounted/trailed boom sprayer: hydraulic nozzles					
Product	NF 149 EW		Active substance		Cyflufenamid	
Formulation type	Liquid		a.s. concentration		50	g/l
Dermal absorption from product	1	%	Dermal absorption from spray		8	%
RPE during mix/loading	None		RPE during application		None	
PPE during mix/loading	None					
PPE during application: Head	None	Hands	None	Body	None	
Dose	0.5	l product/ha	Work rate/day		20	ha

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	2.4	mg/kg a.s.
Hand contamination/day	1.2	mg/day
Protective clothing	none	
Transmission to skin	100	%
Dermal exposure to a.s.	1.2	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0.0006	mg/kg a.s.
Inhalation exposure/day	0.0003	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0.0003	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique: Tractor-mounted/trailed boom sprayer: hydraulic nozzles

	Head	Hands	Rest of body	
Dermal contamination/kg a.s.	0.06	0.38	1.6	
Dermal contamination/day	0.03	0.19	0.8	
Protective clothing	none	none	none	
Transmission to skin	100	100	100	%
Total dermal exposure to a.s.	1.02	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure/kg a.s.	0.001	mg/kg a.s.
Inhalation exposure/day	0.0005	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0.0005	mg/day

ABSORBED DOSE

	Mix/load		Application	
Dermal exposure to a.s.	1.2	mg/day	1.02	mg/day
Percent absorbed	1	%	8	%
Absorbed dose (dermal route)	0.012	mg/day	0.0816	mg/day
Inhalation exposure to a.s.	0.0003	mg/day	0.0005	mg/day
Total systemic exposure	0.0123	mg/day	0.0821	mg/day

PREDICTED EXPOSURE

Total systemic exposure	0.0944	mg/day
Operator body weight	70	kg
Operator exposure	0.001348571	mg/kg bw/day

THE UK PREDICTIVE OPERATOR EXPOSURE MODEL (POEM)

Application method	Tractor-mounted/trailed boom sprayer: hydraulic nozzles				
Product	**NF 149EW**		Active substance	**Cyflufenamid**	
Formulation type	organic solvent-based		a.s. concentration	**50**	mg/ml
Dermal absorption from product	**1**	%	Dermal absorption from spray	**8**	%
Container	1 litre any closure				
PPE during mix/loading	None		PPE during application	None	
Dose	**0.5**	l/ha	Work rate/day	**50**	ha
Application volume	**200**	l/ha	Duration of spraying	**6**	h

EXPOSURE DURING MIXING AND LOADING

Container size	1	litres
Hand contamination/operation	0.01	ml
Application dose	0.5	litres product/ha
Work rate	50	ha/day
Number of operations	25	/day
Hand contamination	0.25	ml/day
Protective clothing	None	
Transmission to skin	100	%
Dermal exposure to formulation	0.25	ml/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique	Tractor-mounted/trailed boom sprayer: hydraulic nozzles			
Application volume	200	spray/ha		
Volume of surface contamination	10	ml/h		
Distribution	Hands	Trunk	Legs	
	65%	10%	25%	
Clothing	None	Permeable	Permeable	
Penetration	100%	5%	15%	
Dermal exposure	6.5	0.05	0.375	ml/h
Duration of exposure	6	h		
Total dermal exposure to spray	41.55	ml/day		

ABSORBED DERMAL DOSE

	Mix/load		Application	
Dermal exposure	0.25	ml/day	41.55	ml/day
Concen. of a.s. product or spray	50	mg/ml	0.125	mg/ml
Dermal exposure to a.s.	12.5	mg/day	5.19375	mg/day
Percent absorbed	1	%	8	%
Absorbed dose	0.125	mg/day	0.4155	mg/day

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure	0.01	ml/h
Duration of exposure	6	h
Concentration of a.s. in spray	0.125	mg/ml
Inhalation exposure to a.s.	0.0075	mg/day
Percent absorbed	100	%
Absorbed dose	0.0075	mg/day

PREDICTED EXPOSURE

Total absorbed dose	0.548	mg/day
Operator body weight	60	kg
Operator exposure	0.009133333	mg/kg bw/day

Council Directive 91/414/EEC

Cyflufenamid

Addendum 4

Volume 4

Annex C
to the Report and Proposed Decision of the United Kingdom made to the European Commission under Article 8(1) of 91/414/EEC

Confidential Information

Prepared February 2008

PESTICIDES SAFETY DIRECTORATE
Mallard House, Kings Pool,
3 Peasholme Green,
York YO1 7PX, UK

Website: www.pesticides.gov.uk

CONFIDENTIAL BUSINESS INFORMATION:

available at RMS