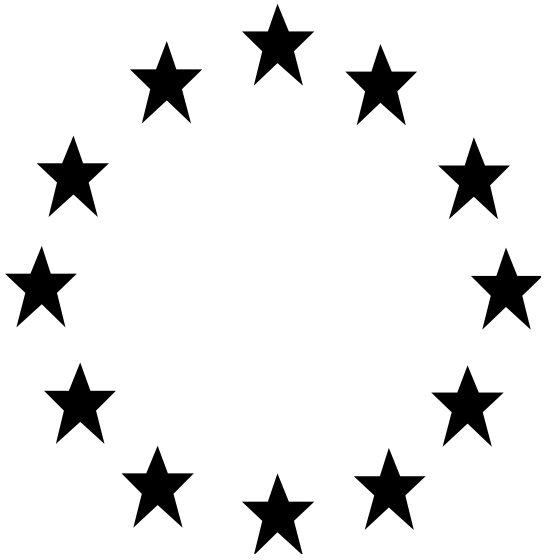

Draft Assessment Report (DAR)

- public version -

Initial risk assessment provided by the rapporteur Member State Austria for the existing active substance

FLUAZINAM

of the third stage (part A) of the review programme referred to in Article 8(2) of Council Directive 91/414/EEC

Volume 1

July 2006

Federal Office for Food Safety

Spargelfeldstraße 191
1226 Vienna
Austria

Monograph prepared in the context of inclusion of following active substance in Annex I of the Council Directive 91/414/EEC

Fluazinam

Volume 1

Report and Proposed Decision

Draft: December 2005

The monograph was prepared under the responsibility of:

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Toxicology and metabolism:

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Residue data:

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Level 1

Fluazinam

Statement of Subject Matter and Purpose of Monograph

1. Statement of subject matter and purpose for which the monograph was prepared

1.1 Purpose for which the monograph was prepared (Dossier Document A)

This monograph has been prepared to support the first inclusion of the existing active substance Fluazinam in Annex I of the Council Directive 91/414/EEC, according to Commission Regulations (EC) No 451/00 and (EC) No 1490/02.

1.2. Summary and assessment of information relating to the collective assessment of dossiers (Dossier Document B)

ISK Biosciences Europe S.A. is the sole notifier for Fluazinam.

1.3 Identity of the active substance (Annex IIA 1, Dossier Documents J, K-II and L-II)

1.3.1 Name and address of applicant(s) for inclusion of the active substance in Annex I (Annex IIA 1.1)

Company:
ISK Biosciences Europe S.A.
Avenue Louise 480, B.12
B-1050 Brussels
BELGIUM

Contact person:
[redacted]

1.3.2 Common name and synonyms (Annex IIA 1.3)

Fluazinam is the approved ISO common name.

1.3.3 Chemical name (Annex IIA 1.4)

IUPAC: 3-chloro-N-(3-chloro-5-trifluoromethyl-2-pyridyl)- α,α,α- trifluoro-2, 6-dinitro-p-toluidine

CA: 3-chloro-N-[3-chloro-2, 6-dinitro-4-trifluoromethyl) phenyl]-5-(trifluoromethyl)-2-pyridinamine

1.3.4 Manufacturer's development code number (Annex IIA 1.5)

Code number: IKF-1216, B-1216, PP192

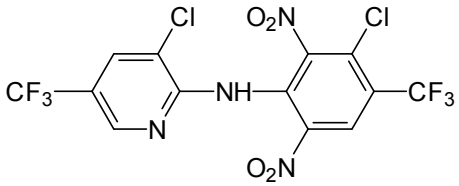
1.3.5 CAS, EEC and CIPAC numbers (Annex IIA 1.6)

CAS: 79622-59-6
EEC: Not allocated
CIPAC: 521

1.3.6 Molecular formula, structural formula, molecular mass (Annex IIA 1.7)

Molecular formula: $C_{13}H_4Cl_2F_6N_4O_4$

Structural formula:



Molecular mass: 465.1 g mol^{-1}

1.3.7 Manufacturer or manufacturers of the active substance (Annex IIA 1.2)

Confidential information, see Volume 4, Annex C.

1.3.8 Method or methods of manufacture (Annex IIA 1.8)

Confidential information, see Volume 4, Annex C.

1.3.9 Specification of purity of the active substance (Annex IIA 1.9)

The minimum content of fluazinam technical material is: 960 g/kg

1.3.10 Identity of isomers, impurities and additives (Annex IIA 1.10)

Confidential information, see Volume 4, Annex C.

1.3.11 Analytical profile of batches (Annex IIA 1.11)

Confidential information, see Volume 4, Annex C.

1.4 Identity of the plant protection product

1.4.1 Current, former and proposed trade names and development code numbers (Annex IIIA 1.3)

Ohayo (Belgium, Denmark, France, Germany, Greece, Italy and the Netherlands); Legacy (UK); Shirlan (Belgium, Denmark, Estonia, Finland, France, Germany, Ireland, Latvia, Lithuania, Portugal, Sweden, the Netherlands and UK); Shirlan Programme (UK); Altima (Eastern European countries) Sagiterre (France); Salvo (UK); Frowncide (France and Ireland); Winner (Austria)

Code:

Fluazinam 500SC

1.4.2 Manufacturer or manufacturers of the plant protection product (Annex IIIA 1.2)

Confidential information, see Volume 4, Annex C.

1.4.3 Type of the preparation and code (Annex IIIA 1.5)

Suspension concentrate (SC)

1.4.4 Function (Annex IIA 3.1, Annex IIIA 1.6)

Fungicide

1.4.5 Composition of the preparation (Annex IIIA 1.4)

Content of fluazinam (IKF-1216): 500.0 g/L

Information with respect to formulants is contained with all other confidential information in Volume 4, Annex C (C1.3.2).

1.5 Use of the plant protection product

1.5.1 Field of use (Annex IIA 3.3, Annex IIIA 3.1)

Agriculture

1.5.2 Effects on harmful organisms (Annex IIA 3.2, Annex IIIA 3.2)

Fluazinam acts as a fungicide with activity against fungus from the class of *Oomycetes*, especially against *Phytophthora infestans*, both potato late blight and tuber blight. It works protectively and needs to be applied before the disease attack. Depending on the disease pressure, good protection against the disease can be expected over a period of 7 to 10 days. Protection is also observed for tubers after harvest.

1.5.3 Summary of representative uses evaluated (Fluazinam) (Annex IIA 3.4)

Crop and/ or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Preparation		Application				Application rate per treatment			PHI (days) (m)	Remarks:
					Type (d-f)	Conc. of as (i)	method kind (f-h)	growth stage & season (j)	number min/ max (k)	interval between applications (min)	g as/hL (l) min – max	water L/ha min – max	g as/ha (l) min – max		
Potatoes	Europe	Fluazinam 500SC	F	*Phytophtora infestans* (late blight and tuber blight)	SC	500 g/L	Field boom sprayer with hydraulic boom and nozzles	first application when warning systems forecast indicates significant disease attack last treatment BBCH 95-97	10	7 to 10 day intervals depending on the disease pressure	40 - 100	200 - 500	max. 200	7	

(a) For crops, the EU and Codex classifications (both) should be taken into account; where relevant, the use situation should be described (*e.g.* fumigation of a structure)

(b) Outdoor or field use (F), greenhouse application (G) or indoor application (I)

(c) *e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds

(d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)

(e) GCPF Codes - GIFAP Technical Monograph No 2, 1989

(f) All abbreviations used must be explained

(g) Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench

(h) Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plant- type of equipment used must be indicated

(i) g/kg or g/L. Normally the rate should be given for the active substance (according to ISO) and not for the variant in order to compare the rate for same active substances used in different variants (e.g. fluoroxypyr). **certain cases, where only one variant is synthesised, it is more appropriate to give the rate for the variant (e.g. benthiavalicarb-isopropyl).**

(j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application

(k) Indicate the minimum and maximum number of application possible under practical conditions of use

(l) The values should be given in g or kg whatever gives the more manageable number (e.g. 200 kg/ha instead of 200 000 g/ha or 12.5 g/ha instead of 0.0125 kg/ha

(m) PHI - minimum pre-harvest interval

1.5.4 Information on authorisation in EU Member States (Annex IIIA 12.1)

Information given by the notifier:

Fungicides containing the active substance fluazinam are currently authorised under different trade names in the following EU Member States:

Ohayo (Belgium, Denmark, France, Germany, Greece, Italy and the Netherlands); Legacy (UK); Shirlan (Belgium, Denmark, Estonia, Finland, France, Germany, Ireland, Latvia, Lithuania, Portugal, Sweden, the Netherlands and UK); Shirlan Programme (UK); Altima (Eastern European countries) Sagiterre (France); Salvo (UK); Frowncide (France and Ireland); Winner (Austria)

Level 2

Fluazinam

Overall Conclusions

2. Reasoned statement of the overall conclusions drawn by the Rapporteur Member State

2.1 General information

2.1.1 Identity

Most of the points of Annex IIA and Annex IIIA section 1 have been addressed and most of the information supplied is acceptable.

2.1.2 Physical and chemical properties, including a listing of end points relating to physical and chemical properties

Fluazinam pure and technical active substance is a yellow solid.
The melting point is 117 °C for the purified substance. The relative density determined at 20 °C is 1.81. The vapour pressure of the active substance is (7.5 ± 0.8) x 10^{-3} Pa at 20°C. The Henry´s constant is calculated to be 25.9 Pa.m³.mol^{-1} at pH 7 and 20°C. The IR-, MS and NMR spectra are in agreement with the chemical structure. Solubility values in water are 0.106 mg/L at pH 5, 0.135 mg/L at pH 7 and 2.72 mg/L at pH 9, all measured at 20 °C. The test substance is readily soluble in all organic solvents. The log P_{ow} is 4.03 (neutral range and 25 °C) and the pKa value is 7.34 at 20 °C. The active substance is not highly flammable, auto-flammable or explosive. The oxidizing properties are required. The decadic molar extinction coefficient for neutral and acidic media > 290 nm must be reported.

Fluazinam 500SC is a suspension concentrate containing 500 g/L active ingredient. The homogeneous suspension is light-yellow with no characteristic odour. The formulation is not explosive or flammable. Its pH is within the range that occurs naturally, e.g., in soil. Its technical properties indicate that no particular problems are to be expected, when it is used as recommended. Storage stability data indicate that its stability allows storage under practical and normal commercial conditions. The determination of pourability and content of relevant impurities before and after storage are required just as the determination of the oxidizing properties.

2.1.3 Details of uses and further information

2.1.3.1 Details of uses

Fluazinam acts as a foliar (contact, protective) fungicide for the control of *Phytophtora infestans* (late blight and tuber blight) in potatoes.

2.1.3.2 Further information

Information on handling, storage, transport or fire, destruction or decontamination, and emergency measures for the active substance as manufactured and information on packaging, cleaning procedures, handling, storage, transport or fire, emergency measures, and procedures for destruction or decontamination for the suspension concentrate have been supplied and are acceptable.

2.1.4 Classification and labelling

Active Substance

On the basis of the available data the following classification and labelling is proposed according to Directive 67/548/EEC in combination with Directive 93/21/EEC:

Hazard symbols:		Skull over crossed bones
		
		Dead fish, dead tree
Indication of danger:	T Xi N	Toxic Irritant Dangerous for the environment
Risk phrases:	R 23	Toxic by inhalation
	R 41	Risk of serious damage to eyes
	R 43	May cause sensitisation by skin contact
	R 50/53	Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
	R 63	Possible risk of harm to the unborn child
Safety phrases:	S 1	Keep locked up
	S 2	Keep out of the reach of children
	S 13	Keep away from food, drink and animal feeding stuffs
	S 20/21	When using do not eat, drink or smoke
	S 24/25	Avoid contact with skin and eyes
	S 26	In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
	S 27/28	After contact with skin, take off immediately all contaminated clothing and wash immediately with plenty of water
	S 36/37/39	Wear suitable protective clothing, gloves and eye/face protection
	S 38	In case of insufficient ventilation, wear suitable respiratory equipment
	S 45	In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible)
	S 56	Dispose of this material and its container to hazardous or special waste collection point.
	S 57	Use appropriate container to avoid environmental contamination.
	S 60	This material and its container must be disposed of as hazardous waste.
	S 61	Avoid release to the environment. Refer to special

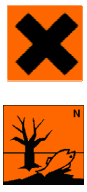
		instructions/safety data sheets.
	S 63	In case of accident by inhalation: remove casualty to fresh air and keep at rest

Justification for the proposal:

T	Follows from R 23
Xi	Follows from R 41 and R 43
N	Follows from R 50/53
R 23	Acute inhalative LC_{50} in rats (4h, whole body exposure) 0.46 mg/l (Tobeta Y., 1988)
R 41	Corneal, iridal and conjunctival effects which persisted partly through day 21 of the study (Shults S. K., 1992)
R 43	Sensitization in the Magnusson and Kligman maximization study and in the method of Buehler (Cummins H. A.., 1984; Pritchard V. A., 1986)
R 50/53	Follows from the toxicity to fish (*Oncorhynchus mykiss* LC_{50} = 0.036 mg/L, Gelin & Laveglia 1992), the Log_{POW} of active substance is 4.03 (Sanders, 1992) and the active substance is not ready biodegradable (Grützner, 2000).
R 63	Gross morphological fetal abnormalities (cleft palate, diaphragmatic hernia) at maternal toxic doses (Willoughby C. R., 1985)
S 1, S 2, S 13, S 20/21, S 36/37/39, S 45	Proposed because fluazinam is toxic by inhalation, has risk of serious damage to eyes, may cause sensitization by skin contact and is teratogenic
S 24/25	Proposed because fluazinam has risk of serious damage to eyes and may cause sensitization by skin contact
S 26	Proposed because fluazinam has risk of serious damage to eyes
S 27/28	Proposed because fluazinam may cause sensitization by skin contact
S 38, S 63	Proposed because fluazinam is toxic by inhalation
S 56, S 57, S 60, S 61	Proposed because the toxicity of fluazinam to aquatic organisms and potential long term adverse effects to the aquatic environment

Formulation

On the basis of the available data the following classification and labelling is proposed according to Directive 67/548/EEC in combination with Directive 93/21/EEC:

Hazard symbols:		Dead fish, dead tree
Indication of danger:	Xn	Harmful

	Xi N	Irritant Dangerous for the environment
Risk phrases:	R 43	May cause sensitisation by skin contact
	R 50/53	Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
	R 63	Possible risk of harm to the unborn child
Safety phrases:	S 1	Keep locked up
	S 2	Keep out of the reach of children
	S 13	Keep away from food, drink and animal feeding stuffs
	S 20/21	When using do not eat, drink or smoke
	S 24	Avoid contact with skin
	S 27/28	After contact with skin, take off immediately all contaminated clothing and wash immediately with plenty of water
	S 36/37/39	Wear suitable protective clothing, gloves and eye/face protection
	S 45	In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible)
	S 56	Dispose of this material and its container to hazardous or special waste collection point.
	S 57	Use appropriate container to avoid environmental contamination.
	S 60	This material and its container must be disposed of as hazardous waste.
	S 61	Avoid release to the environment. Refer to special instructions/safety data sheets.

Justification for the proposal:

Xn	Follows from R 63
Xi	Follows from R 43
N	Follows from R50/53
R 43	Sensitization in the Magnusson and Kligman maximization study and in the method of Buehler (Smith K. D., 1992; Lees D., 1991)
R 50/53	Follows from the toxicity to fish (*Oncorhynchus mykiss* LC_{50} = 0.0611 mg/L, Sankey et al 1991), the Log_{POW} of active substance is 4.03 (Sanders, 1992) and the active substance is not ready biodegradable (Grützner, 2000).
R 63	Gross morphological fetal abnormalities (cleft palate, diaphragmatic hernia) at maternal toxic doses (Willoughby C. R., 1985)
S 1, S 2, S 13, S 20/21, S 24, S 27/28, S 36/37/39, S 45	Proposed because fluazinam 500 SC may cause sensitization by skin contact and is teratogenic
S 56, S 57, S 60, S 61	Proposed because the toxicity of fluazinam 500 SC to aquatic organisms and potential long term adverse effects to the aquatic environment

2.2 Methods of analysis

2.2.1 Analytical methods for analysis of the active substance as manufactured

The submitted method is suitable for the determination of Fluazinam and for the impurities in the technical material [HPLC-UV].

No CIPAC methods exist at the moment of evaluation.

2.2.2 Analytical methods for formulation analysis

The submitted method is sufficiently validated for the determination of the active substance in the formulation [HPLC-UV]. Also a method for impurity 5 is provided and suitable for the determination in Fluazinam 500SC.

Impurity ■ is also considered relevant by Section Toxicology. Therefore a method is required.

No CIPAC methods exist at the moment of evaluation for fluazinam in the formulation.

2.2.3 Analytical methods for residue analysis

The analytical method for residues in food/feed of plant origin is successfully validated since the LOQs enable the enforcement of the relevant residue limits (at the time of evaluation). Mean recovery rates at each fortification level are in the range of 70 to 110 % with a relative standard deviation of ≤ 20 %. The analytical calibration extend over a range appropriate to the lowest and highest nominal concentration of the analyte ± at least 20% for this analytical method. No interfering blanks (< 30 % of the LOQ) occurred. The linearity range of the ILV needs clarification.

Readily available equipment and reagents are used.

Matrix	LOQ	Relevant residue limit	Principle of the method
Plant and plant products	Potatoes (grape and wine) 0.01 mg/kg	Potatoes 0.01 mg/kg	GC-ECD
Soil (fluazinam)	0.05 mg/kg*)	0.05 mg/kg general upper limit	GC-ECD
Soil (HYPA)	0.01 mg/kg	6.1 mg/kg (most sensitive organism: Collembola)	HPLC-UV
Drinking water	0.1 µg/L*)	0.1 µg/L EU drinking water limit	GC-ECD
Surface water (fluazinam)	10 µg/L	2.9 µg/L NOEC (fish)	HPLC-UV
Air	a new validation is required	1.1 µg/m3 based on an AOELsystemic of 0.0035 mg/kg b.w./d	HPLC-UV

*) For the determination of residues in soil and drinking water the LOQs are set by RMS since validation data are not acceptable on all points for the lower LOQs, proposed by the notifier.

Methods for the determination of residues in soil and drinking water need additional confirmatory techniques and a new validation for the determination of residues in air is required the same as for the analytical methods (residue) for body fluids and tissues.
According to Section Residue, a method for monitoring TFAA (trifluoro acetic acid) is necessary, if a residue definition is set for TFAA in rotational crops.
Due to the fact that the relevant residue limit is 2.9 µg/L for fluazinam in surface water, a valid method with an adequate LOQ is required.
The submitted methods for the determination of residues of fluazinam in body fluids and tissues are not sufficiently validated due to the lack of linearity data and therefore a validation is required.

2.3 Impact on human and animal health

2.3.1 Effects having relevance to human and animal health arising from exposure to the active substance or to impurities contained in the active substance or to their transformation products

Adsorption, distribution, metabolism, excretion

Metabolic and kinetic studies were conducted with radiolabeled fluazinam, following oral administration at a low dose of 0.5 mg/kg bw, a high dose of 50 mg/kg bw and 14 daily oral doses of unlabeled fluazinam followed by ^{14}C-fluazinam (labelled in the phenyl position) of 0.5 mg/kg bw. The majority of radiolabeled material was detected in the feces (> 88 %). Urine was a minor excretory route (2 - 4 %). Less than 1 % of the administered dose was found in the carcass. The highest concentration was detected in the liver. There were no major differences related to sex or dose level. The median peak time for blood concentration of radiolabel activity for both sexes was 6 hours. At the time of peak concentration, the radioactivity in the blood represented 0.4 % - 0.6 % of the administered dose for 0.5 and 50 mg/kg bw dose groups. By 72 hours, about 0.1 % of the administered dose was found in the blood of both sexes at both dose levels. Approximately 30 % (high dose) – 40 % (low dose) of fluazinam was considered to be absorbed based on excretion rates in bile and urine. The predominant route of excretion of the absorbed dose was the bile, which contained approximately 87 % of the absorbed dose. 24 hours after dose administration, biliary excretion of the absorbed dose was 80 % complete at the high dose level and 92 % complete at the low dose level.

Metabolites were identified using several techniques including HPLC coelution with standards, direct identification by mass spectrometry and comparison with standards, NMR, and degradation experiments. The distribution of these metabolites, as a function of dosing regimen, position of radiolabel, and sex, was determined. Major metabolites isolated and identified from feces, urine and bile were the parent compound, DAPA, AMPA, AMPA mercapturate, DAPA glucuronide and DAPA cysteine conjugate. The major metabolites of the organic fraction of feces were parent compound, AMPA and DAPA and the major metabolite in the aqueous fraction of feces was DAPA cysteine conjugate. The feces were the major route of excretion of fluazinam and its metabolites. AMPA

mercapturate, DAPA glucuronide and DAPA were found in the urine at low levels (≤ 2 % of administered dose) and AMPA mercapturate and DAPA glucuronide were found in the bile (≤ 5 % of administered dose). Fluazinam was also metabolized by the intestine microflora to form AMPA and DAPA. The identified metabolites were the same in samples from both phenyl and pyridyl labels, indicating that metabolic cleavage of the two rings did not occur. The metabolism of fluazinam was similar between male and female rats within a dose group. It can be concluded that fluazinam is metabolized by both reduction and glutathione conjugation and further metabolism.

Acute toxicity

After oral application to mice and rats of both sex, fluazinam is of low acute toxicity with LD_{50} values ≥ 4100 mg/kg bw.

After acute dermal application of fluazinam to rats of both sex, the acute dermal LD_{50} was > 2000 mg/kg bw. The inhalative LC_{50} of fluazinam in rats (whole-body exposure) was 0.46 mg/l.

Fluazinam is mildly irritating to the skin and severely irritating to the eyes of New Zealand White rabbits. In the Magnusson and Kligman dermal maximization study and in the Buehler-Test fluazinam caused evidence of delayed contact hypersensitivity in guinea pigs. A summary of the results from the acute toxicity studies is presented in table 6.2.7-1.

According to Annex VI of the EC Council Directive 67/548/EEC, fluazinam has to be classified as toxic by inhalation, severely irritating to the eyes (risk of serious damage to eyes) and as a sensitizer (hazard symbols T, Xi, risk phrases R 23, 41, 43).

Table 2.3.1-1 Summarised results of the acute toxicity studies with fluazinam

Type of study	Species	Vehicle	Results	Reference
Acute oral toxicity	CD-1 mice	Maize oil	m/f > 5000 mg/kg bw	*Cummins, 1988*
Acute oral toxicity	Sprague Dawley - Rat	Maize oil	m/f > 5000 mg/kg bw	*Cummins, 1988*
Acute oral toxicity	Sprague Dawley Rat	Methylcellulose	m 4500 mg/ kg bw f 4100 mg/ kg bw	*Liggett, 1988*
Acute dermal toxicity	Sprague Dawley Rat	-	m/f > 2000 mg/kg bw	*Cummins, 1988*
Acute inhalation toxicity	Sprague Dawley Rat	Polyethylen glycol 400	m 0.463 mg/L air f 0.476 mg/L air (4h, whole body exposure)	*Tobeta, 1988*
Dermal irritation study	Rabbit (NZW)	Moistened with deionized water	Mildly irritating	*Shults, 1992*
Eye irritation study	Rabbit (NZW)	-	severely irritating	*Shults, 1992*
Dermal sensitization M & K-test	Guinea pig (Dunkin Hartley)	Paraffin oil	Sensitizing	*Cummins, 1984*
Dermal sensitization Buehler –test	Guinea pig (Dunkin Hartley)	Polysorbate 80	Sensitizing	*Pritchard, 1986*

Short term toxicity

Subacute and subchronic administration of fluazinam to rats, mice and dogs caused reduced food consumption and body weight gain. Changes of hematological parameters such as lower haemoglobin concentrations, lower erythrocyte counts and lower platelet counts were also observed. Clinical chemistry parameters showed low ALT activity, higher cholesterol, phospholipid and glucose concentrations. Higher absolute and relative liver weights and histopathological changes in the liver such as periacinar hepatocytic hypertrophy were observed in all species. In mice and dogs, vacuolation of white matter in brain and spinal cord was observed. High dosed dogs of the 4- and 13-week oral toxicity studies (150 and 100 mg/kg bw/d resp.) showed retinal hyperreflection and grey pigmentation of the tapetal fundus of the retina. At histopathologic examination, a dystrophy of the pigment epithelium of the retina was observed in the majority of dogs, including controls. The toxicological significance of the ophthalmic observations and the possible interrelationships between these and the retinal findings observed histopathologically were unknown. Oral administration of 200/150 mg/kg bw/d fluazinam to beagle dogs for 11 weeks revealed ERG-abnormalities which can be accounted for by functional changes in the pigment epithelium of the retina. The results show recovery of response amplitude after withdrawal of fluazinam, but it is not possible to say if recovery would be complete.

Dermal administration of fluazinam to rats for 3 weeks revealed changes in clinical chemistry parameters such as higher AST activity and higher cholesterol levels in all dose groups (10, 100 and 1000 mg/kg bw). A toxic effect was also observed histopathologically in the liver in both sexes of the high dose and in males of the mid dose groups (periacinar hepatocytic hypertrophy). Dermatitis and acanthosis of the skin were seen in all dose groups compared to controls.

Table 2.3.1-2: Summarised results of subacute/subchronic toxicity studies with fluazinam

Study; Reference	Dose levels	NOAEL	Relevant effects
CD rats 4 weeks oral *Broadmeadow A. et al; 1983*	0, 10, 50, 250 and 3000 ppm/diet (equivalent to 0, 1.26, 5.21, 26.1 and 305.4 mg/kg bw)	1.26 mg/kg bw/d	-reduced food consumption and body weight gain -hematological and clinical chemical findings -higher absolute and relative liver weights -histopathological changes in the liver
CD rats 13 weeks oral *Broadmeadow A. et al; 1985*	0 and 500 ppm/diet (equivalent to 0 and ≈ 40 mg/kg bw/d)	Cannot be determined	-reduced body weight gain -higher relative liver weights -histopathological changes in the liver
CD rats 13 weeks oral *Broadmeadow A. et al; 1984*	0, 2, 10, 50 and 500 ppm/diet (equivalent to 0, 0.16, 0.82, 4.1 and 41 mg/kg bw)	4.1 mg/kg bw/d	-hematological findings -higher relative liver weights -higher absolute and relative lung and uterus weights -histopathological changes in the liver

Study; Reference	Dose levels	NOAEL	Relevant effects
CD rats 21 days dermal *Cummins H. A. et al; 1985*	0, 10,100 and 1000 mg/kg bw)	Cannot be determined	-reduced body weight gain -clinical chemical findings -higher absolute and relative liver weights -encrustations or staining of the skin -histopathological changes in the liver and skin
CD-1 mice 4 weeks oral *Amyes S. J. et al; 1983*	0, 10, 50, 250 and 3000 ppm/diet (equivalent to 0, 1.6, 7.9, 39.5 and 455 mg/kg bw)	1.6 mg/kg bw/d	-reduced food consumption and body weight gain -clinical chemical findings -higher absolute and relative liver and kidney weights -histopathological changes in the liver
CD-1 mice 4 weeks oral *Chambers P. R. et al; 1994*	0, 3000, 5000 and 7000 ppm/diet (equivalent to 0, 607, 994 and 1302 mg/kg bw)	Cannot be determined	-clinical chemical findings -higher absolute and relative liver and kidney weights -histopathological changes in liver and kidneys -vacuolation of white matter in brain and spinal cord
CD-1 mice 13 weeks oral *Dawe S. et al; 1985*	0, 1, 10, 100 and 1000 ppm/diet (equivalent to 0, 0.13, 1.23, 14.4 and 135.28 mg/kg bw for males and 0, 0.15, 1.58, 15.07 and 152.45 mg/kg bw for females)	Cannot be determined	-higher absolute and relative liver and kidney weights
Beagle dogs 4 weeks oral *Broadmeadow A. et al; 1984*	0, 1, 5, 25 and 150 mg/kg bw, gelatine capsules)	5 mg/kg bw/d	-reduced food consumption and body weight gain -grey pigmentation of the tapetal fundus of the retina -higher relative liver weights
Beagle dogs 13 weeks oral *Broadmeadow A. et al; 1985*	0, 1,10 and 100 mg/kg bw, gelatine capsules)	10 mg/kg bw/d	-reduced food consumption and body weight gain -grey pigmentation of the tapetal fundus of the retina -clinical chemical findings -higher absolute and relative liver weights -histopathological changes in the liver
Beagle dogs 11 weeks oral *Hull R. M. et al; 1986*	0 and 200/150 mg/kg bw, gelatine capsules)	Not determined	-reduced food consumption and body weight gain -clinical chemical findings -brown granularity of the tapetal fundus of the retina -ERG-abnormalities
Beagle dogs 52 weeks oral *Broadmeadow A. et al; 1987*	0, 1, 10 and 50 mg/kg bw, gelatine capsules)	1 mg/kg bw/d	-reduced food consumption and body weight gain -hematological and clinical chemical findings -higher absolute and relative liver weights -histopathological changes in the stomach -vacuolation of white matter in brain and spinal cord

Genotoxicity

Mutagenicity assays performed with fluazinam *in vitro* included gene mutation tests in bacteria (*S. typhimurium and E.coli*) and in mammalian cells (*mouse lymphoma*), a chromosomal aberration test in mammalian cells (Chinese hamster lung fibroblasts) and a DNA repair test in bacteria (Bacillus subtilis). Results from these studies showed that fluazinam did not induce gene mutation in any of the bacterial tester strains of *S. typhimurium* and *E.coli,* or gene mutation in mammalian cells in culture (mouse lymphoma). No potential for clastogenicity was observed in the in vitro chromosome aberration test in chinese hamster lung fibroblasts (CHL). There was also no induction for DNA damage observed in the DNA repair test with B.subtilis.

In the *in vivo micronucleus test* no induction of micronuclei by fluazinam in mouse bone marrow cells could be observed (table 6.4.3 -1).

Table 2.3.1-3: Summarised results of genotoxicity studies with fluazinam

Type of study	Test system	Dose range	Results	Reference
In vitro-studies				
Bacterial mutation assay	S. typhimurium (TA1535, TA1537, TA98 and TA100) and E. coli WP2uvrA/pKM101 (CM891)	0.005, 0.015, 0.050, 0.15, 0.5, 1.5, 5, 15, 50, 150, 500, 1500 and 5000 µg/plate	Negative	*Kitching J.;2000*
Bacterial reverse mutation test	*S. typhimurium* (TA100, TA1535, TA98 and TA1537) *E. coli* (WP2 uvr A)	0.0625 - 2 µg/plate (without S-9 mix), 3.13 - 100 µg/plate (with S-9 mix) 15.6 - 250 µg/plate (without S-9 mix), 31.3 – 500 µg/plate (with S-9 mix)	Negative	*Ohtsuka M.; 1988*
Bacterial reverse mutation test	*S. typhimurium* (TA100, TA1535, TA98 and TA1537) *E. coli* (WP2 uvr A)	0.0313 - 1µg/plate (without S-9 mix), 3.13 - 100 µg/plate (with S-9 mix) 15.6 - 250 µg/plate (without S-9 mix), 31.3 - 500 µg/plate ((with S-9 mix)	Negative	*Ohtsuka M.; 1989*
Mammalian cell mutation assay	mouse lymphoma L5178Y cells	First test: 0.05 - 5 µg/ml (without S-9 mix); 0.5 - 20 µg/ml (with S-9 mix) Second test: 0.005 - 0.5 µg/ml (without S-9 mix); 0.5 – 10 µg/ml (with S-9 mix)	Negative	*Ransome S.; 2000*
Chromosomal aberration test	CHL	1 - 4 µg/ml (with S-9 mix); 2.375 - 9.5 µg/ml (without S-9 mix)	Negative	*Kajiwara Y.; 1988*
DNA repair test	bacillus subtilis	0.003 - 0.3 µg/disk (without S-9 mix), 0.3 – 30 µg/disk (with S-9 mix)	negative	*Ohtsuka M.; 1988*
In vivo-studies				
Micronucleus test	mouse bone marrow	single oral doses of 0, 500, 1000 and 2000 mg/kg bw	negative	*Matsumoto K.; 1999*

Long term toxicity/carcinogenicity

In the two long term toxicity/carcinogenicity studies in rats, treatment-related non-neoplastic effects were manifest at 100 ppm especially in the liver and testes. No treatment-related effects were seen on the spontaneous tumor profile at any dose level. Taking the two long term toxicity/carcinogenicity studies in rats together, an overall NOAEL for fluazinam can be obtained at 50 ppm, equivalent to 1.9 mg/kg bw/d for males and 2.4 mg/kg bw/d for females.

In two carcinogenicity studies in mice, liver cell tumours (adenomas and carcinomas) were observed in a greater number of male mice after dietary administration of 1000, 3000 and 7000 ppm fluazinam, reaching statistical significance for adenomas at dose levels of 1000 (33 %) and 3000 ppm (40 %) only. The historical control data for liver tumours carried out at Huntingdon Research Centre Ltd. in the years 1981 – 1983 and 1991 – 1993 showed incidences of adenomas in the range of 3.8 to 34 %. Thus the incidence of liver tumours at 1000 and 3000 ppm were within or slightly above the range of the historical control data. However, hepatocellular adenomas in the highest dose group of 7000 ppm reached an incidence of 28 % and were within the range of the historical controls.

A statistically significant increase of vacuolation of white matter in the brain and cervical spinal cord was observed in both sexes at dose levels of 1000 ppm fluazinam and above. 10 ppm, equivalent to 1.12 mg/kg TG/d for males and 1.16 mg/kg TG/d for females, were considered to be the NOAEL in carcinogenicity studies in mice.

Table 2.3.1-4: Summarised results of long term toxicity studies with fluazinam

Study; Reference	Dose levels	NOAEL	Main effects/target organs
Sprague-Dawley rats 104 weeks oral *Mayfield R. et al; 1988*	0, 1, 10, 100 and 1000 ppm/diet (equivalent to 0, 0.04, 0.38, 3.82 and 40 mg/kg bw males, 0, 0.05, 0.47, 4.87 and 53 mg/kg bw females)	10 ppm (0.38 mg/kg bw males, 0.47 mg/kg bw females)	-hematological and clinical chemical findings -higher liver and thyroid weights -histopathological changes in liver, pancreas, lungs and testes
Sprague-Dawley rats 104 weeks oral *Chambers P. R. et al; 1993*	0, 25, 50 and 100 ppm/diet (equivalent to 0, 1.0, 1.9 and 3.9 mg/kg bw males, 0, 1.2, 2.4 and 4.9 mg/kg bw females)	50 ppm (1.9 mg/kg bw males, 2.4 mg/kg bw females)	-higher liver, testes and epididymides weights -histopathological changes in liver, pancreas, lungs and testes
CD-1 mice 104 weeks oral *Mayfield R. et al; 1988*	0, 1, 10, 100 and 1000 ppm/diet (equivalent to 0, 0.12, 1.12, 10.72 and 107 mg/kg bw males, 0, 0.11, 1.16, 11.72 and 117 mg/kg bw females)	10 ppm (1.12 mg/kg bw males, 1.16 mg/kg bw females)	-higher liver weights -histopathological changes in liver, liver cell tumours -vacuolation of white matter in brain and spinal cord
CD-1 mice 104 weeks oral *Chambers P. R. et al; 1998*	0, 1000, 3000 and 7000 ppm/diet (equivalent to 0, 126, 377 and 964 mg/kg bw males, 0, 162, 453 and 1185 mg/kg bw females)	Cannot be determined	-higher liver, brain and adrenal weights -histopathological changes in liver, liver cell tumours -vacuolation of white matter in brain and spinal cord

Reproductive toxicity:

In a two generation reproduction study, rats fed a diet containing fluazinam in the highest concentration of 500 ppm showed statistically significant reductions in body weight and body weight gain and reduced food intake. Relative liver weights were significantly increased in both sexes of the highest dose group and also in females of the intermediate and low dose group of the F0 generation, but a clear dose response was not observed. High dose males of the F1 generation showed also an increase of relative liver weight. Histopathologically, an statistically significant increase of periacinar hepatocytic fatty changes were detected in high dose males of F0 and F1 animals and also in F1 males of the 100 ppm group. The NOAEL for systemic toxicity was considered to be 20 ppm, equivalent to approximately 1 mg/kg bw/d for males and 1.4 mg/kg bw/d for females.

Reproductive performance of F0 animals was unaffected by treatment. In the F1 generation, conception rate and fertility index were slightly reduced in the 500 ppm group. Gestation length was slightly increased in the high and intermediate dose groups. Numbers of implantation sites and mean litter sizes to day 4 post partum were slightly reduced for F1 animals of the high dose group and marginally lower in the intermediate group (100 ppm). The NOAEL for reproductive parameters was considered to be 20 ppm, equivalent to approximately 1 mg/kg bw/d for males and 1.4 mg/kg bw/d for females.

Two teratology studies in rabbits had been performed. In the first study, dose levels of 0.3, 1 and 3 mg/kg bw fluazinam from day 6 to 19 of gestation had been chosen. There was no evidence of a teratogenic potential up to the highest dose tested (3 mg/kg bw/d). In the high dose group of 3 mg/kg bw fluazinam, reduced food intake and incomplete ossification were observed. Based on these results, the NOAEL for maternal toxicity and fetal toxicity was obtained at 1 mg/kg bw/d.
In the second study, oral administration of fluazinam to pregnant rabbits during the period of organogenesis was associated with reduced maternal weight gain and food intake in the highest dose group of 12 mg/kg bw/d. Macroscopic and microscopic lung and liver changes were observed at a dose level of 4 mg/kg bw/d and above. So the maternal NOAEL was considered at 2 mg/kg/day. Increased incidences of fetal abnormalities (placental abnormalities, some skeletal abnormalities including kinked tail tip, fused or incompletely ossified sternebrae and abnormalities of the head bones) were seen at the top dose. At all dose levels, increased incidences of preimplantation losses were observed, however, the values fell within the recorded background control range of the laboratory. Based on increased abortion and postimplantation loss from 4 mg/kg bw/d upwards, the NOAEL for developmental effects was set at 2 mg/kg bw/d.
Taking the two teratology studies in rabbits together, an overall NOAEL for maternal and fetal toxicity can be obtained at 2 mg/kg bw/d.

In a teratology study in rats, oral administration of fluazinam at the high dose level of 250 mg/kg bw/d to pregnant rats during the period of organogenesis was associated with reduced mean food consumption and weight loss, followed by a slight reduced rate of weight gain compared to controls. Weight gain in the 50 mg/kg bw/d group was marginally, but not statistically significant, reduced. So

the maternal NOAEL was considered at 10 mg/kg/day.

Fetal and placental weights were significantly reduced in the high dose group and there were indications of fetal immaturity. In the 50 mg/kg bw/d group, fetal and placental weights were reduced, but not significantly, compared to controls. An increased incidence of gross morphological fetal abnormalities were recorded at the top dose, values were outside the range of the concurrent controls and the recorded background controls of the laboratory. So the NOAEL for developmental effects was considered at 10 mg/kg bw/d. According to Annex VI of the EC Council Directive 67/548/EEC, fluazinam should be classified to "category 3 of reproductive substances" and labelled with the risk phrase "R 63 – Possible risk of harm to the unborn child".

Table 2.3.1-5: Summarised results of reproductive toxicity/teratogenicity studies with fluazinam

Study Reference	Dose levels	NOAEL	Main effects/target organs
Two generation reproduction, rats *Tesh J. M. et al; 1987*	0, 20, 100 or 500 ppm, equivalent to 0, 1, 5 and 26 mg/kg bw/d males; 0, 1.4, 6.7 and 34 mg/kg bw/d females (lowest value of the range)	Parental and Reproductive NOAEL 20 ppm (1 mg/kg bw/d males, 1.4 mg/kg bw/d females)	Parental: body weight and body weight gain ↓; relative liver weight ↑ Offsprings: gestation length ↑; implantation sites and litter sizes ↓
Teratology in the rabbit *Tesh J. M. et al; 1985*	0, 0.3, 1 and 3 mg/kg bw/d (oral application by gavage)	Maternal NOAEL 1 mg/kg bw/d Developmental NOAEL 1 mg/kg bw/d	Maternal: food consumption ↓ Developmental: ossification incomplete
Teratology in the rabbit *Tesh J. M. et al; 1988*	0, 2, 4, 7 and 12 mg/kg bw/d (oral application by gavage)	Maternal NOAEL 2 mg/kg bw/d Developmental NOAEL 2 mg/kg bw/d	Maternal: food consumption ↓; weight gain ↓; histopathological liver changes Developmental: abortion ↑; postimplantation loss ↑
Teratology in the rat *Willoughby C. R. et al; 1985*	0, 10, 50 and 250 mg/kg bw/d (oral application by gavage)	Maternal NOAEL 10 mg/kg bw/d Developmental NOAEL 10 mg/kg bw/d	Maternal: food consumption ↓; weight gain ↓ Developmental: fetal and placental weight ↓; ossification incomplete; gross morphological fetal abnormalities

Neurotoxicity:

Single oral doses (gavage) of 1000 and 2000 mg/kg bw fluazinam produced statistically significantly lower motor activity in female rats compared to controls. No pathological findings were observed at gross necropsy examination and no histopathological findings were seen in the sections of nervous tissues examined. The NOAEL based on systemic toxicity was considered to be 50 mg/kg bw. After 13 weeks of treatment with fluazinam in the diet, no evidence of neurotoxicity and neuropathology during the course of the study was observed. Reduced locomotor activity observed in males during week 8 of treatment compared to controls was not considered to be treatment related as there were no statistically significant differences during week 13. The NOAEL for neurotoxicity was established at 1000 ppm (69 mg/kg bw). The NOAEL for systemic toxicity was established at 300 ppm (21 mg/kg bw/d), based on statistically significantly lower body weight gains among females treated with 1000 ppm fluazinam.

Further toxicological studies:

Metabolites:

The metabolite G-450, HYPA, chemical name 5-((3-chloro-5-(trifluoromethyl)-2-pyridyl)amino)-α,α,α- trifluoro-4,6-dinitro-o-cresol, detected in liver, kidney, muscle, fat and eggs of Laying hens but not in rat metabolism studies, was found to be more toxic than fluazinam after oral administration. The acute oral median lethal dose (LD_{50}) of HYPA in mice was 331 mg/kg bw (fluazinam is of low acute toxicity with LD50 values ≥ 4100mg/kg bw in mice and rats).

In an Ames- test, HYPA showed slight reverse mutagenicity against S. typhimurium TA98 without S-9 mix. The other bacteria tester strains (S. typhimurium TA100, TA1535, TA1537 and E.coli WP2uvrA) showed no increase in the number of revertant colonies at any dose level. In a second Ames-test, carried out with the same tester strains, HYPA showed no evidence of mutagenic activity, either in the presence or absence of metabolic activation. Micronucleus tests showed that HYPA does not induce micronuclei in the bone marrow cells of male and female mice.

Metabolite G-525, MAPA, chemical name 2-(2-amino-3-chloro-α,α,α-trifluoro-6-nitro-*p*-toluidino)-3-chloro-5-(trifluoromethyl)pyridine was found in liver, kidney, muscle, fat and eggs of Laying hens but not in rat metabolism studies and showed only low acute toxicity with a LD_{50} > 5000 mg/kg bw in mice.

In a bacterial reverse mutation test, MAPA showed no increase in the number of revertant colonies at any dose level.

Impurities:

Impurity G-624, chemical name [redacted] showed low acute oral toxicity in rats of both sexes with a median lethal dose (LD_{50}) of > 5000 mg/kg bw.

In a bacterial reverse mutation test, G-624 showed reverse mutagenicity against S. typhimurium TA98, TA100, TA1535 and TA1537 with and without S-9 mix and also against *E. coli* (WP2 uvr A) in the absence of S-9 mix. However, G-624 is included in toxicity studies with the active ingredient. There was no potential of genotoxicity seen with fluazinam technical, so no further studies with G-624 are required.

Dietary administration of Impurity-[redacted], chemical name [redacted] to male mice at a concentration of 5 mg/kg bw caused clinical signs, decreased body weights, increased brain weights, edema of the brain and vacuolation of white matter in the brain. The oral administration of [redacted] at a single oral dose of 50 mg/kg bw or higher caused no adverse effects on mortality, clinical signs, body and brain weight, macroscopic pathology or histopathology of the brain.

The neurotoxic effect of Impurity 5 in mice and rats was comparable in quality and strength. In dogs, the magnitude and extent were only trace and focal. The lower susceptibility in dogs might be imputed to that further older dogs were not utilized. Adult mice and rats are more sensitive to neurotoxicity of Impurity 5 than pubescent ones. The two-divided administration method used for

dogs to prevent vomiting might be another reason for the minor appearance of the brain histopathological alteration in dogs.

Based on the results obtained in the study, the effects of Impurity-5 on the brain and optic nerves of mice were considered to increase with animal age until about ten weeks and then remain at a constant level until at least 24 weeks.

After 14 days of treatment with Impurity-5, female rats and mice showed similar sensitivity to the vacuolation of the white matter of the brain.

The incidence and severity of white matter vacuolation of the brain is similar in male mice and rats, but ten-week old animals were more sensitive in both rats and mice as compared to the three-week old animals.

General Pharmacology:

At intraperitoneal doses of 80 mg/kg bw fluazinam technical and less, there were no changes in the condition of male or female mice. Though no death was caused in the groups of 160 mg/kg bw, a descent of body temperature was seen. Mice of the highest dose group (320 mg/kg bw) died without showing special symptoms expect the descent of body temperature.

After administration of 0.5 mg/kg bw fluazinam i.v., a decrease of the number of pulse was observed. There were no effects on brain waves following i.v. administration of 0.5 mg/kg bw fluazinam. Following administration of 1.0 mg/kg bw, both cortical and deep brain waves declined but recovery was seen after 30 minutes. A dose dependent temporary rise in blood pressure and a decrease in pulse were observed in rabbits at a dose of 1.0 mg/kg bw fluazinam i.v., with recovery after 30 minutes. No change in the electrocardiogram and no effect on the pupils nor the contraction of tibialis anterior muscle of rabbits was observed. Suppression in carbon powder transportability in the small intestine was observed following subcutaneous administration of a high dose of 5000 mg/kg bw fluazinam. Doses of 2500 mg/kg and less caused no observable changes. Slight hemolysis was observed in erythrocytes of rabbits by adding fluazinam at a concentration of 1 mg/ml.

The reversibility of vacuolation of white matter in the brain was tested after dietary administration of fluazinam at high concentrations (714 and 1743 mg/kg bw in rats; 1043, 1173 and 1871 mg/kg bw mice). The affected animals recovered nearly completely after a 25 day or 56 day recovery period respectively, indicating that the histopathological change is reversible.

Representative electron-microscopic photographs of the cerebellum white matter indicated that the effect of treatment appeared to be confined to the myelin sheaths, that the nucleus and mitochondria in oligodendroglia were kept intact and that myelin sheaths had recovered during the recovery period.

In studies in which high doses of Fluazinam technical failed to induce white matter vacuolation in the CNS, the batch contained very low levels of Impurity-5 (< 0.005 %).The threshold dose was independent of the Impurity-5 level in fluazinam technical. The CNS effect depends on the dose of Impurity-5 received by experimental animals. No white matter vacuolation was observed in rats, mice and dogs at dose levels of Impurity-5 below approximately 0.1 mg/kg bw/d.

Medical data:

No reports on exposure of general population and epidemiological studies have been submitted. In the reported cases on manufacturing plant personnel and farmers, there appeared to be a delayed type hypersensitivity reaction (type IV allergic reaction) including itching, skin rash, swollen eyes and face, burning and mucous membrane irritation. Symptoms typically develop over a few hours to several days following exposure. Affected individuals make a full recovery, with no long term adverse consequences, within a short period of time.

Table 2.3.1-6: Summary of repeat oral dose studies with fluazinam for setting the ADI/AOEL/ARfD

Study	Dose levels	NOAEL	LOAEL	Effects observed at the LOAEL
CD rats 4 weeks oral *Broadmeadow A. et al; 1983*	0, 10, 50, 250 and 3000 ppm/diet (equivalent to 0, 1.26, 5.21, 26.1 and 305.4 mg/kg bw)	10 ppm (1.26 mg/kg bw/d)	50 ppm (5.21 mg/kg bw/d)	-higher relative liver weights
CD rats 13 weeks oral *Broadmeadow A. et al; 1984*	0, 2, 10, 50 and 500 ppm/diet (equivalent to 0, 0.16, 0.82, 4.1 and 41 mg/kg bw)	50 ppm (4.1 mg/kg bw/d)	500 ppm (41 mg/kg bw/d)	-hematological findings -higher relative liver weights -higher absolute and relative lung and uterus weights -histopathological changes in the liver
CD-1 mice 4 weeks oral *Amyes S. J. et al; 1983*	0, 10, 50, 250 and 3000 ppm/diet (equivalent to 0, 1.6, 7.9, 39.5 and 455 mg/kg bw)	10 ppm (1.6 mg/kg bw/d)	50 ppm (7.9 mg/kg bw/d)	-clinical chemical findings
Beagle dogs 4 weeks oral *Broadmeadow A. et al; 1984*	0, 1, 5, 25 and 150 mg/kg bw, gelatine capsules)	5 mg/kg bw/d	25 mg/kg bw/d	-higher relative liver weights
Beagle dogs 13 weeks oral *Broadmeadow A. et al; 1985*	0, 1,10 and 100 mg/kg bw, gelatine capsules)	10mg/kg bw/d	100 mg/kg bw	-reduced food consumption and body weight gain -grey pigmentation of the tapetal fundus of the retina -clinical chemical findings -higher absolute and relative liver weights -histopathological changes in the liver
Beagle dogs 52 weeks oral *Broadmeadow A. et al; 1987*	0, 1, 10 and 50 mg/kg bw, gelatine capsules)	1mg/kg bw/d	10 mg/kg bw	-hematological findings -higher absolute and relative liver weights -histopathological changes in the stomach
Sprague-Dawley rats 104 weeks oral *Chambers P. R. et al; 1993*	0, 25, 50 and 100 ppm/diet (equivalent to 0, 1.0, 1.9 and 3.9 mg/kg bw males, 0, 1.2, 2.4 and 4.9 mg/kg bw females)	50 ppm (1.9 mg/kg bw males, 2.4 mg/kg bw females)	100 ppm (3.9 mg/kg bw males, 4.9 mg/kg bw females)	-higher liver, testes and epididymides weights -histopathological changes in liver, pancreas, lungs and testes

Study	Dose levels	NOAEL	LOAEL	Effects observed at the LOAEL
CD-1 mice 104 weeks oral *Mayfield R. et al; 1988*	0, 1, 10, 100 and 1000 ppm/diet (equivalent to 0, 0.12, 1.12, 10.72 and 107 mg/kg bw males, 0, 0.11, 1.16, 11.72 and 117 mg/kg bw females)	10 ppm (1.12 mg/kg bw males, 1.16 mg/kg bw females)	100 ppm (10.72 mg/kg bw males, 11.72 mg/kg bw females)	-higher liver weights -histopathological changes in liver
Two generation reproduction, rats *Tesh J. M. et al; 1987*	0, 20, 100 or 500 ppm, equivalent to 0, 1, 5 and 26 mg/kg bw/d males; 0, 1.4, 6.7 and 34 mg/kg bw/d females (lowest value of the range)	Parental and Reproductive NOAEL 20 ppm (1 mg/kg bw/d males, 1.4 mg/kg bw/d females)	100 ppm (5 mg/kg bw/d males, 6.7 mg/kg bw/d females)	Parental: relative liver weight ↑ Offsprings: gestation length ↑; implantation sites and litter sizes↓
Teratology in the rabbit *Tesh J. M. et al; 1985*	0, 0.3, 1 and 3 mg/kg bw/d (oral application by gavage)	Maternal NOAEL 1 mg/kg bw/d Developmental NOAEL 1 mg/kg bw/d	Maternal LOAEL 3 mg/kg bw Developmental LOAEL 3 mg/kg bw/d	Maternal: food consumption ↓ Developmental: ossification incomplete
Teratology in the rabbit *Tesh J. M. et al; 1988*	0, 2, 4, 7 and 12 mg/kg bw/d (oral application by gavage)	Maternal NOAEL 2 mg/kg bw/d Developmental NOAEL 2 mg/kg bw/d	Maternal NOAEL 4 mg/kg bw/d Developmental NOAEL 4 mg/kg bw/d	Maternal: histopathological liver changes Developmental: abortion ↑; postimplantation loss ↑
Teratology in the rat *Willoughby C. R. et al; 1985*	0, 10, 50 and 250 mg/kg bw/d (oral application by gavage)	Maternal NOAEL 10 mg/kg bw/d Developmental NOAEL 10 mg/kg bw/d	Maternal LOAEL 50 mg/kg bw/d Developmental LOAEL 50 mg/kg bw/d	Maternal: food consumption ↓; weight gain ↓ Developmental: fetal and placental weight ↓
CD rats Acute neurotoxicity *Serrone D. M. 1995*	0, 50, 1000 and 2000 mg/kg bw (oral application by gavage)	Systemic toxicity: 50 mg/kg bw Neurotoxicity: 2000 mg/kg bw	1000 mg/kg bw	-soft stool -lower motor activity
CD rats 13 weeks neurotoxicity *Hughes E. W. 1998*	0, 300 and 1000 ppm/diet (equivalent to 0, 21 and 69 mg/kg bw)	Systemic toxicity: 300 ppm (21 mg/kg bw) Neurotoxicity: 1000 ppm (69 mg/kg bw)	1000 ppm (69 mg/kg bw/d)	-reduced body weight gains

2.3.2 ADI

The estimation of the Acceptable Daily Intake (ADI) is based on the lowest no-observed adverse effect level (NOAEL) observed in subchronic and chronic toxicity, carcinogenicity, reproduction and neurotoxicity studies with fluazinam. Given the results from all relevant studies (see table 6.10.1-6), the lowest NOAELs of 1.12 mg/kg bw/d and 1.0 mg/kg bw/d respectively were found in the 104-week chronic toxicity/cancerogenicity study in mice, the subchronic toxicity study (52 weeks) in dogs and the two generation study in rats. It can be concluded that fluazinam exhibits no mutagenic,

neurotoxic or oncogenic potential. In the rat teratology study, an increased incidence of gross morphological fetal abnormalities was recorded at the top dose of 250 mg/kg bw/d, values were outside the range of the concurrent controls and the recorded background controls of the laboratory. 10 mg/kg bw/d was considered as a clear NOAEL for developmental effects. Applying the standard uncertainty factor of 100 to account for intraspecies and interspecies variability to the NOAELs of 1.12 mg/kg bw/d and 1.0 mg/kg bw/d respectively from the mouse, rat and dog studies mentioned, results in an ADI of 0.01 mg/kg bw/d. This provided a 1000 fold safety factor over the NOAEL of 10 mg/kg bw/d in the teratology study in rats.

Remark: The notifier proposed an ADI of 0.01 mg/kg bw/d based upon the NOAEL of 1 mg/kg bw/d established in the dog subchronic toxicity study also.

2.3.3 ARfD (acute reference dose)

For the determination of the Acute Reference Dose (ARfD), results from oral studies that used acute or short term exposure are considered to be the most relevant. Fluazinam is of low acute oral toxicity but there was evidence of teratogenicity seen in a rat developmental study at the high dose level of 250 mg/kg bw/d.

The most appropriate study for selection of an ARfD seems to be the teratogenicity study in rabbits, with a NOAEL of 2 mg/kg bw/d for maternal and developmental effects. The standard uncertainty factor of 100-fold is applied to account for intraspecies and interspecies variability.

So an ARfD of 0.02 mg/kg bw/day is proposed for fluazinam.

Remark: The notifier proposed no ARfD due to the low acute oral toxicity of fluazinam.

2.3.4 AOEL

According to the principles of Annex VI to Directive 91/414 EEC, the proposed acceptable operator exposure level should be established on the basis of the highest dose at which no adverse effect is observed in relevant studies in the most sensitive species. The setting of an AOEL is usually based on mid-term studies (i.e. subacute/ subchronic and reproduction or developmental toxicity studies) since these studies in most cases can be considered a more appropriate model for the actual operator exposure to be expected.

The lowest NOAEL of all relevant studies were found in the 52-week dog study, which is considered a mid-term study. This NOAEL of 1 mg/kg bw/d was based on haematological findings, higher absolute and relative liver weights and histopathological changes in the stomach at the next higher dose level of 10 mg/kg bw/d. This NOAEL was also supported by the NOAELs of 1.6 mg/kg bw/d and 1.2 mg/kg bw in the 4-week and 104-week toxicity study in mice and the NOAEL of 1.0 mg/kg bw/d in the 2-generation study in rats, respectively. Using an absorption of 35 % (between 30 – 40 % of an oral dose of fluazinam is absorbed), the systemic equivalent of the 1 mg/kg bw/d NOAEL would be approximately 0.35 mg/kg bw/d. If a 100 fold safety factor is applied to the systemic NOAEL, an AOEL of 0.0035 mg/kg bw/d is established. Therefore a systemic AOEL of 0.0035 mg/kg bw/d is proposed.

Remark: The notifier proposed an systemic AOEL of 0.014 mg/kg bw/d based on the NOAEL of 4.1 mg/kg bw/d derived in the 13-week feeding study in rats.

2.3.5 Drinking water limit

The determination of a maximum allowable concentration (MAC) value in drinking water is not necessary, because according to Directive 91/414/EC only the ADI, ARfD and AOEL values have to be determined. According to Directive 98/83/EC a drinking water limit of 0.1 µg fluazinam/L is established.

2.3.6 Impact on human or animal health arising from exposure to the active substance or to impurities contained in it

Fluazinam is toxic by inhalation, has risk of serious damage to eyes and may cause sensitisation by skin contact. The available data for fluazinam do not support evidence of mutagenic, oncogenic, neurotoxic and fertility damaging properties of the active substance. Gross morphological fetal abnormalities have been observed in one developmental study in rats so according to Annex VI of the EC Council Directive 67/548/EEC, fluazinam should be classified to "category 3 of reproductive substances" and labelled with the risk phrase "R 63 – Possible risk of harm to the unborn child".
In a bacterial reverse mutation test, impurity G-624, chemical name [redacted] showed reverse mutagenicity against S. typhimurium TA98, TA100, TA1535 and TA1537 with and without S-9 mix and also against *E. coli* (WP2 uvr A) in the absence of S-9 mix. However, G-624 is included in toxicity studies with the active ingredient and there was no potential of genotoxicity seen with fluazinam technical.
Dietary administration of impurity-5, chemical name [redacted] caused vacuolation of white matter in the brain of mice, rats and dogs. Different Lot Numbers of fluazinam technical used in toxicological studies were analyzed by HPLC for its concentration of Impurity-5. The results of the analyses showed that in those studies in which high doses of fluazinam technical failed to induce white matter vacuolation in the CNS, the batch contained very low levels of Impurity-5 (< 0.005 %). In order to investigate the threshold value for white matter vacuolation in the CNS induced by Impurity-5, the available studies were reanalyzed to calculate the achieved daily intake of Impurity-5 using its content in fluazinam technical and the fluazinam intake in each study of the mouse, rat and dog. 0.1 mg/kg bw/d of Impurity-5 was the lowest effect level for white matter vacuolation seen in the 52-week study in dogs. No vacuolation was seen in any spezies at lower dose levels.
The data support a non-linear dose-response for the production of white matter vacuolation in all of the 3 spezies with a threshold, below which no white matter vacuolation occurs, at approximately 0.1 mg/kg bw/d of Impurity-5.

The potential operator exposure was estimated for the intended uses using tractor mounted sprayers for application in potatoes. The operator exposure estimates were calculated using both the German model and the UK-POEM Model.
For the scenarios calculated (tractor mounted boom sprayer; 0.2 kg a.i./ha; 100 % absorption rate for inhalative exposure and a dermal absorption rate of 1.5 % for the concentrate and 7 % for the spray dilution), the results of the exposure estimations according to the POEM model exceed the proposed systemic AOEL of 0.0035 mg/kg bw/d even if personal protective equipment is used

(gloves). Exposure estimations with the German model exceed the proposed systemic AOEL only if no protective equipment is used. If gloves, hood + visor, boots and an overall are used, the systemic exposure will be 13 % of AOEL.
Short exposure of bystanders outside the treatment areas would be 6.2 % of AOEL and should therefore not give rise to concern.
Worker re-entry exposure following spraying on potato leaves does not exceed the AOEL if sprayed plants are handled with proper PPE (18 % of AOEL).

2.4 Residues

The **metabolism** of ^{14}C-fluazinam **in plants** was investigated in potatoes, peanuts, grape and apples. Chromatographic analyses of samples from both phenyl and pyridyl labels were used to determine if metabolic cleavage of the phenyl and pyridyl rings occurred.
Metabolites that were identified or characterized were classified into two types:
phase 1 metabolites still retaining the basic fluazinam structural two-ring moiety and
phase 2 secondary products resulting from degradation of either the phenyl or pyridyl ring resulting in conversion to carbon dioxide or other small molecules and subsequent reincorporation. So the following metabolic pathway can be proposed for fluazinam:
The phase 1 of the metabolic pathway of fluazinam in plants involves reduction of one or both nitro groups (to form AMPA or DAPA). This level also includes AMGT (replacement of the phenyl ring chlorine to form a glutathione conjugate) and SDS-67230 (replacement of one nitro group by a hydroxyl group). These and other metabolites that could result from reduction and/or displacement are now more activated toward oxidative degradation because one or more of the deactivating groups (NO_2, Cl) have been replaced by an activating group (NH_2, OH, SR). As aromatic rings with two adjacent activating groups are susceptible to ring opening, ring cleavage occurs.
The phase 2 products of ring fragmentation are TFAA and other small molecules (2-to3-carbon fragments) resulting from complete degradation of fluazinam, which enter the carbon pool and are finally incorporated in glucose, fructose and sucrose.
However, the secondary products of plant metabolism are numerous and complex due to the extensive metabolic processes that occur in plants. Fluazinam is the major residue on plant parts such as foliage or fruit that are exposed to the spray application. Since no residues of fluazinam are transported to the potato tubers or peanuts it can be concluded that the active substance is not systemic.
The metabolism studies for fluazinam in potatoes, peanuts, grapes and in apples demonstrated that the end products of metabolism involved re-incorporation of ^{14}C from fluazinam into natural products, including starch and fatty acids.
Extent and nature of residues in plant material after application of fluazinam were tested in potatoes at the normal maximum application rate of 2.02 kg phenyl labelled a.i./ha and 1.72 kg pyridyl labelled a.i./ha..
Overall levels of ^{14}C residue in potato tubers were extremely low. The highest residue levels were found in the pyridyl level treated potatoes (25 µg equ/kg). The two phenyl label treated samples had less than half of that amount of residue. The major fractions of the TRR were:

- the PES fraction, which mostly consisted of radioactivity that had been reincorporated into natural products such as starch,
- a polar fraction, which probably consisted of various extensively degraded fragments and soluble natural products containing re-incorporated radioactivity, and
- non polar residues in very low amounts: The total amount of non polar residue was less than 4 µg equ/kg and consisted of multiple components. The amount of parent fluazinam in all samples was less than 2 µg equ/kg.

The fact that radioactivity from both labelled fluazinam appeared in starch indicated that both rings were broken down into fragments that could enter the carbon pool.
The metabolism of ^{14}C-fluazinam was additionally investigated in peanuts, grapes and apples. Chromatographic analyses of samples from both phenyl and pyridyl labels were closely compared to determine if metabolic cleavage of the phenyl and pyridyl rings occurred.
Metabolites that were identified or characterized were classified into two types:
phase 1 metabolites still retaining the basic fluazinam structural two-ring moiety and
phase 2 secondary products resulting from degradation of either the phenyl or pyridyl ring resulting in conversion to carbon dioxide or other small molecules and subsequent reincorporation.
So the following metabolic pathway can be pointed out for fluazinam:
The phase 1 of the metabolic pathway of fluazinam in plants involves reduction of one or both nitro groups (to form AMPA or DAPA). This level also includes AMGT (replacement of the phenyl ring chlorine by glutathione conjugation) and SDS-67230 (replacement of one nitro group by a hydroxyl group). These and other metabolites that could result from reduction and/or displacement are now more activated towards oxidative degradation because one or more of the de-activating groups (NO_2, Cl) have been replaced by an activating group (NH_2, OH, SR). As aromatic rings with two adjacent activating groups are susceptible to ring opening, ring cleavage occurs.
The phase 2 products of ring fragmentation are TFAA, glucose, fructose and sucrose, resulting from complete degradation of fluazinam into $^{14}CO_2$and other small molecules (2-to 3-carbon fragments) that can enter the carbon pool.
However, the secondary products of plant metabolism are numerous and complex due to the extensive metabolic processes that occur in plants. Fluazinam is the major residue on plant parts such as foliage or fruit that are exposed to the spray application. Since fluazinam is not systemic, no residues of fluazinam are transported to the potato tubers or peanuts since they grow in the ground.
The metabolism studies for fluazinam in potatoes, peanuts, grapes and in apples demonstrated that the end products of metabolism involved reincorporation of ^{14}C from fluazinam into natural products, including starch and fatty acids.

Livestock metabolism studies were performed in ruminants and poultry:
Following oral administration of ^{14}C- Fluazinam (IKF-1216) to two lactating goats at a nominal dose level of 0.33 mg/kg body weight per day (phenyl label) and 0.36 mg/kg body weight per day (pyridyl label) once daily for four consecutive days, concentrations of radioactivity in milk were low, reaching a maximum of 0.071 mg equivalents/kg following the fourth dose. A plateau level in milk was reached within the run of the study. Concentrations of radioactivity in kidney and liver were 0.047

and 0.661 mg equivalents/kg, respectively. Levels of radioactivity in muscle and fat were 0.030 and 0.211 mg equivalents/kg respectively.
Although in this study the concentration in feed (average of both labels: 11.3 mg/kg feed as received) represented more than 30 times the calculated dietary burden basing on the highest residue found in potatoes, only little transfer into edible tissues and milk was observed; residues in meat and milk after uptake from fluazinam in animal feed will not exceed the LOQ if the active substance is used according to the supported GAP.
The nature of the residue studies in lactating goats show that the major residues were the reduction products AMPA and DAPA and their sulfamate conjugates. These residues were similar to residues identified after oral administration of fluazinam to rats (the AMPA and DAPA conjugates identified from rats were glucuronides). Parent fluazinam was not detected in any of the samples.
Following oral administration of ^{14}C- Fluazinam (IKF-1216) to laying hens at a nominal dose level of 0.76 mg/kg body weight per day (phenyl and pyridyl label each) once daily for four consecutive days, concentrations of radioactivity in eggs reached a maximum of 0.388 mg equivalents/kg following the fourth dose. A plateau level in eggs was not reached within the run of the study. Concentration of radioactivity in liver was 0.984 mg equivalents/kg. Levels of radioactivity in dark muscle and fat were 0.053 and 0.948 mg equivalents/kg respectively.
Although in this study the concentration in feed (average of both labels: 10.35 mg/kg feed as received) represented more than 800 times the calculated dietary burden basing on the highest residue found in potatoes, only little transfer into edible tissues and eggs was observed; it is expected that residues in meat and eggs after uptake from fluazinam in animal feed will not exceed the LOQ if the active substance is used according to the supported GAP.
In laying hens, the major metabolites were reduction products, primarily AMPA, DAPA, MAPA and HYPA, as well as measurable amounts of fluazinam parent molecule. Other metabolites found also included a mixture of conjugates representing the products of glutathione conjugation and subsequent metabolism.
In the metabolism studies in lactating goat and laying hens it was demonstrated that fluazinam does not accumulate in tissues, milk or eggs.

In 16 **supervised residue field trials** no levels at or above the LOQ of 0.01 mg/kg have been determined in the potato tubers at harvest. This is consistent with the results obtained in the potato plant metabolism study.
In total 13 trials have been performed at the critical Northern European GAP ± 25%. The number of applications ranged from 8 to 11 and the PHI ranged from 6 – 7 days. These trials were conducted in Germany (8) and the UK (5) during 1989 – 1996. Eight of these residue trials were decline studies with sampling times between 0 and 14 days. Fluazinam residues were below the LOQ at all sampling points in these decline studies.
Only three trials were available for Southern Europe. These trials were conducted in Greece; using a PHI of 14 - 15 days and including 6 applications. The trials spanned a two year period. Although the PHI in the trials was not at the GAP, the lack of residues even at 0 day PHI intervals observed in the residue decline studies described above as well as the results of the plant metabolism study in

potatoes demonstrate that no residues of fluazinam above the LOQ of 0.01 mg/kg in potatoes should be expected in any planting situation.

Table 2.4-1: Key results of crop residue trials conducted with fluazinam (with relevance to MRL-estimation)

Crop	Application [kg a.i./ha]	Region[1)]	No. of trials	PHI [days]	Lowest residue at harvest [mg/kg][2)]	Highest residue at harvest [mg/kg][2)]
potatoes	11 x 0.200	N	13	0-7-14	<0.01	<0.01
potatoes	6 x 250	S	3	14-15	<0.01	<0.01

1) N: Northern Region of Europe; S: Southern Region of Europe
2) Residues expressed as fluazinam

Livestock feeding studies are not required for fluazinam as the results of both plant metabolism studies and residue trials demonstrate that fluazinam residues in or on potatoes are expected to be below 0.01 mg/kg, the limit of quantitation (LOQ) for the residue method. In addition, animal metabolism testing using goats and hens show that fluazinam is extensively metabolized in both animals and that it is not accumulated in tissues, milk or eggs. Little to no fluazinam was found in any edible fractions, even at an extremely high dose level of 10 mg/kg in feed.

No studies on the effects of **industrial processing and/or household preparation** have been submitted; due to the residue situation (no residues above the LOQ are to be expected based on the application regime and on the results of the residue trials provided), these studies are not regarded as necessary.

The possible intake of soil derived fluazinam residues via **succeeding crops** was investigated by 3 studies using radio-labelled fluazinam, the test substance was applied to bare soil at the maximum field rate. Accumulation of fluazinam related residues in rotational crops after uptake from treated soil was not observed. Residues represented fragments from either the phenyl or pyridine ring structure resulting from extensive metabolic degradation. In organo-extractable residues no fluazinam-related compounds (metabolites still retaining the basic fluazinam structural two-ring moiety) ≥0.01 mg/kg were detected. Characterization of the non-extractable residue demonstrated that ^{14}C from fragmentation of the pyridine ring had been reincorporated into natural products such as starch.

In the aqueous fractions significant radioactive residues in edible parts of plants were found. These residues were identified as trifluoroacetic acid TFAA amounting >0.1 mg-equ/kg in lettuce (0.27 mg-equ/kg at DAT 30; 0.16 mg-equ/kg at DAT 120) and in barley grain (0.12 mg-equ/kg at DAT 120; 0.18 mg-equ/kg at DAT 365; amount increasing with planting interval).

TFAA was not found in soil metabolism and it was neither determined in livestock nor in laboratory animal metabolism.

2.4.1 Definition of the residues relevant to MRLs

For definition of the relevant residues of fluazinam in raw agricultural commodities the following facts were taken into account:

Based on the chemical composition of identifiable residues in the metabolism study in potatoes (on which the use of fluazinam is intended), as well as on the supporting metabolism studies on peanut, apple and grape metabolism, the residue in these crops can be defined by quantification of the parent molecule, fluazinam (IKF-1216). The phase 1 of the metabolic pathway of fluazinam in plants involves reduction of one or both nitro groups (to form AMPA or DAPA), replacement of the phenyl ring chlorine by glutathione conjugation (forming AMGT in plants) and then further metabolism or conjugation. This general pathway for formation of phase I metabolites is the same in animals and plants.

Parent fluazinam is rapidly degraded and is either **not found** or barely detectable **in peanuts and potatoes**. Fluazinam parent was the **major identifiable residue in** a **grape** metabolism study. Identifiable residues in very low amounts either closely resemble fluazinam in structure or are the result of re-incorporation of the fluazinam carbon pool into natural products.

The residue in the supported crop can be defined only by quantification of the parent molecule fluazinam.

Therefore the proposed residue definition in plants for risk assessment and monitoring purposes is **fluazinam**.

Residues in rotational crops represent fragments from either the phenyl or pyridine ring structure resulting from extensive metabolic degradation. In organo-extractable residues no fluazinam-related compounds (metabolites still retaining the basic fluazinam structural two-ring moiety) ≥0.01 mg/kg were detected. Parent fluazinam was not detected in any organic extract from any crop sample. Characterization of the non-extractable residue demonstrated that ^{14}C from fragmentation of the pyridine ring had been reincorporated into natural products such as starch.

In the aqueous fractions significant radioactive residues in edible parts of plants were found. These residues were identified as trifluoroacetic acid TFAA amounting >0.1 mg-equ/kg in lettuce (0.27 mg-equ/kg at DAT 30; 0.16 mg-equ/kg at DAT 120) and in barley grain (0.12 mg-equ/kg at DAT 120; 0.18 mg-equ/kg at DAT 365; amount increasing with planting interval). TFAA was not found in soil metabolism and it was neither determined in livestock nor in laboratory animal metabolism. Therefore further information is needed on the toxicological significance of TFAA to decide whether this compound has to be included in the residue definition for rotational crops. Provided an inclusion of TFAA in the residue definition, either supervised field trials in succeeding crops should be required or restrictions with regard to appropriate plant-back intervals for rotational crops should be considered.

Metabolism studies in livestock showed only little transfer of fluazinam into edible tissues, milk and eggs. No accumulation of the active substance was observed in livestock animals. Only low residues of fluazinam are expected in potential feeding stuffs (<0.01 mg/kg in potatoes); the

calculations for dietary burdens for livestock animals demonstrated that no residues above the LOQ of 0.01 mg/kg are to be expected in edible tissues, milk and eggs. Therefore a residue definition for food of animal origin is not proposed.

2.4.2 Residues relevant to consumer safety

The estimation of the chronic exposure through diet shows a Theoretical Maximum Daily Intake (TMDI) to be 0.002408 mg fluazinam/person/day for an adult person and 0.000711 mg fluazinam/person/day for a 4-6 year old girl. These results are equivalent to 0.000040 mg/kg bw/day (adult person, 60 kg bw) and 0.000053 mg/kg bw/day (girl, 13.5 kg bw). The Acceptable Daily Intake (ADI) of fluazinam based on the results of a 52 week study in dogs, was set to 0.01 mg/kg bw/d.
Therefore, the TMDI of fluazinam-derived residues through the relevant food items accounts for 0.4 % of the ADI (adult, 60 kg bw) and 0.5 % (4-6 year old girl, 13.5 kg bw), respectively.

The estimation of the acute exposure through diet shows a International Estimated Short Term Intake (IESTI) to be 0.000259 mg/kg bw/day for an adult person (71.1 kg bw, 16-64 years) and 0.0010503 mg/kg bw/day for toddlers (14.5 kg bw, 1.5-4.5 years). The Acute Reference Dose (ARfD) of fluazinam based on the results of a rabbit developmental study, was set to 0.02 mg/kg bw/d.
Therefore, the IESTI of fluazinam-derived residues through the relevant food items accounts for 1.3 % of the ARfD for the adult general population and 5.3 % for children, respectively.

2.4.3 Residues relevant to worker safety

Worker re-entry exposure following spraying on potato leaves does not exceed the AOEL even if sprayed plants are handled without proper PPE (73 % of AOEL). With PPE, the estimated exposure will be 3.65 % of AOEL.

2.4.4 Proposed EU MRLs and compliance with existing MRLs

According to the intended uses, MRLs as summarised in table 2.4.4-1 can be proposed:

Table 2.4.4-1: MRL proposals for fluazinam (based on the intended use)

Commodity	Proposed EU-MRLs according to the intended uses [mg/kg][1)]	Comments
potatoes	0.01*	---

1) Residues expressed in mg fluazinam /kg

2.4.5 Proposed EU import tolerances and compliance with existing MRLs

Currently no EU-MRLs are set for this compound. The notifier did not request to set import tolerances.

2.4.6 Basis for differences, if any, in conclusion reached having regard to established or proposed CAC MRLs

There are no CAC MRLs existing for fluazinam.

2.5 Fate and behaviour in the environment

2.5.1 Definition of the residues relevant to the environment

Soil:	Fluazinam, HYPA
Groundwater:	Fluazinam
Surface water:	Fluazinam, G-504 (from aqueous photolysis)
Sediment:	Fluazinam, AMPA
Air:	Fluazinam

2.5.2 Fate and behaviour in soil

Metabolism

Fluazinam is metabolised by microbial activity. The main metabolic pathway is the formation of bound residues, which were found in amounts of up to 47.2 % of applied radioactivity after 180 days in laboratory studies under **standard conditions**. Metabolites which would indicate cleavage of the bridging amino group were not observed. Mineralization (formation of CO_2) amounted for up to 6 % applied radioactivity after one year under standard conditions. Under aerobic conditions HYPA was the major metabolite which is formed by hydrolysis of the phenyl ring chlorine of fluazinam to a hydroxyl group. The maximum amount found in laboratory studies under standard conditions was 13.9 % AR, after 48 days of incubation. MAPA and DAPA, which are formed by reduction of one or both NO_2 groups, respectively, on the phenyl ring of fluazinam, were found in minor amounts. Under **anaerobic conditions** MAPA and DAPA were the major metabolites, whereas HYPA was found only in minor amounts. Degradation of fluazinam is accelerated and formation of NER is enhanced under anaerobic conditions but mineralization (CO_2 formation) seems lower.

Degradation

The degradation of ^{14}C-fluazinam (label position on the phenyl or the pyridyl ring) in soil under **aerobic conditions** was investigated in two studies, including two sandy loam soils and one loamy sand. A third study with unlabelled fluazinam included a sandy soil. In the first study the half lives of fluazinam under standard conditions, recalculated separately for the two label positions by the RMS on the basis of single 1st order kinetics, were in the range of 96 and 263 days for the phenyl labelled fluazinam and between 63 and 189 days for the pyridyl labelled fluazinam. The corresponding DT_{90} values were in the range of 320 – 873 days and 210 – 628 days, respectively. In the second study a DT_{50} value of 17 days was calculated for a mixture of the two label positions. In the third study the calculated DT_{50} value for unlabelled fluazinam was 62 days (single 1st order kinetics).

The data derived from the test at 10° C were not sufficient to calculated reliable degradation rates. However, it was possible to conclude from the data available that **low temperatures** as well as exaggerated application rate reduced the metabolism of fluazinam.
Under **anaerobic conditions** degradation of fluazinam is fast. Flooding the soil on day 0 of incubation yielded DT_{50} values of 3.8 days, for both, the phenyl labelled and the pyridyl labelled fluazinam. DT_{90} values were 12.6 and 12.8 days for the two label positions, respectively.
Degradation rates for the main soil metabolite HYPA were investigated in one study including three different soils. Calculated DT_{50} and DT_{90} values were in the range of 54 to 148 days (arithm. mean: 95 d) and 179 to 490 days (arithm. mean: 305 d), respectively (single 1st order kinetics).

Photolysis
Under the influence of light degradation of fluazinam on soil is significantly increased. Degradation rates were recalculated by the RMS on the basis of single 1st order kinetics for the two label positions separately. The DT_{50} values for the phenyl ring label were 72 days (dark control) versus 22 days (light condition) and for the pyridyl label 68 days (dark) versus 17 days (light). The corresponding DT_{90} values were 238 days (phenyl label) and 226 days (pyridyl label) for the dark control and 72 days (phenyl label) and 65 days (pyridyl label) for the light exposed samples. The light intensity was comparable to southern European conditions. Under both, light and dark conditions conversion to bound residues was the main pathway. Conversion to bound residues was more extensive for the light-exposed samples. In general, photolysis appears to accelerate reactions that occur in soil under dark conditions. The presence of HYPA at comparable levels in the dark controls and the light samples suggests it is a product of soil metabolism. AMPA, however, is found in the light-exposed samples at levels slightly higher than in the dark controls (5 % AR versus <1 % AR).

Field studies
Two European field studies and four field studies conducted in the USA were submitted. The risk assessment of fluazinam is based on the data from the European field studies. The studies from the USA were not considered relevant by the RMS.
Two soil degradation trials were carried out with fluazinam (formulation Shirlan 50 SC) in the UK over a period of 15 and 16 months. The test substance was applied either on potatoes or on bare soil on ten occasions (7 – 10 day interval) at a rate of 0.3 kg ai/ha each. Fluazinam residues in the upper soil layer (10 cm) taken from bare ground plots declined throughout the trial at both sites from initial residues of 0.61 mg/kg and 0.38 mg/kg to 0.02 mg/kg and 0.01 mg/kg after 370 days. Concentrations in soil from the planted plots were significantly lower. No quantifiable residues of fluazinam (LOQ = 0.01 mg/kg) were found in deeper soil layers with only very few exceptions. Concentrations of soil metabolite HYPA were in the range of 0.03 and 0.09 mg/kg in the upper soil layer. No measurable amounts of HYPA were found in all the 10 – 20 cm soil samples.
Four soil degradation trials were carried out with fluazinam (50 % w/v SC formulation) in Germany over a period of 12 months. The test substance was applied on bare ground at a rate of 1.35 kg ai/ha. Initial concentrations of fluazinam in the upper soil layer were in the range of 0.7 to 1.0 mg/kg

soil, which declined to <0.01 to 0.08 mg/kg after 306 days. In deeper soil layers no measurable residues of fluazinam were found. The residues of the metabolite HYPA were below the LOD (= 0.01 mg/kg) in the upper soil layer, with very few exceptions. HYPA was not detected in deeper soil layers.

The calculated dissipation rates of fluazinam under field conditions (UK and Germany) were in the range of 8.3 and 40.8 days (single 1st order kinetics), with a geometric mean of 20.4 days. For FOCUS ground water modelling temperature normalised (20 °C) DT_{50} values were used. These were in the range of 8.4 and 25 .7 days, with a geometric mean of 16.4 days.

PEC_{SOIL}

For calculation of the predicted environmental concentration in soil the highest DT_{50} for fluazinam from European soil dissipation studies was used. Plant interception values between 50 % and 80 % were applied. Calculations for soil metabolite HYPA were done on the basis of 13.9 % maximum formation and the worst case laboratory DT_{50} from studies with the metabolite.

Table 2.5.2-1: PEC values used for the risk assessment (soil organisms and bioaccumulation)

10 x 200 g ai/ha on potatoes		
	Fluazinam	HYPA
PECi after last application (= peak value)	0.54 mg/kg	0.114 mg/kg
TWA 21 days after last application	0.454 mg/kg	--

For soil metabolite HYPA an environmental plateau concentration in soil was calculated by the RMS. Assuming a worst case DT_{50} of 148 days, incorporation into 5 cm soil, a soil density of 1.5 g/cm^3 and ten applications per year a plateau level of 0.107 mg/kg soil is reached after 3 years.

Adsorption and leaching behaviour

Fluazinam showed low mobility in a batch equilibrium study with four different soils. The calculated K_{OC} values were in the range of 1 705 to 2 316 mL/g, with an arithmetic mean of 1958 mL/g. The results obtained indicate that a large percentage of fluazinam is irreversibly adsorbed onto soils with different properties. Increasing adsorption (K_f) was observed with increasing organic matter content. For soil metabolite HYPA the calculated K_{OC} values from a study conducted with six different soils, were in the range of 450 and 1 700 mL/g, with an arithmetic mean of 920 mL/g. From this batch equilibrium study medium to low mobility for HYPA can be concluded. In acidic soils higher K_{OC} values were observed compared to alkaline soils. When excluding the two acidic soils, which are considered not representative for potato growing areas by the RMS the arithmetic mean K_{OC} value for the four remaining soils is 630 mL7g.

According to the results of a column leaching study it is unlikely that normal agricultural use of fluazinam will result in significant contamination of ground water. After application of fluazinam at a rate equivalent to 750 g ai/ha on sand, loamy sand and sandy loam soils, less than 2 % of the applied amount leached through the soil columns.

PEC_{GW} Modelling

For FOCUS groundwater modelling the geometric mean of temperature normalised (20 °C) field DT_{50} values of fluazinam from European field dissipation studies was used. 50 % plant interception was assumed. Two calculations for soil metabolite HYPA were carried out: on the basis of an average occurrence in laboratory studies (9.7 %; modelling by the NF) as well as on the basis of a maximum formation factor of 0.193 (modelling by RMS). The arithmetic mean DT_{50} from laboratory studies with HYPA, without moisture correction, was used (i.e. 95 days; modelling by the NF) as well as a DT_{50} of 105 days from the study with the highest formation of HYPA as a worst case (modelling by the RMS).

According to FOCUS PELMO modelling the predicted 80th percentile annual average concentrations at 1 m depth of fluazinam and its main soil metabolite HYPA are predicted to be < 0.001 µg/L. In case of HYPA the results of the two modelling approaches were the same.

Unacceptable contamination of groundwater is not expected to occur if fluazinam is applied according to good agricultural practice and according to the proposed use (10 x 200 g ai/ha on potatoes).

2.5.3 Fate and behaviour in water

Under acidic conditions fluazinam is stable to **hydrolysis**. Under sterile neutral and alkaline conditions fluazinam is rapidly hydrolysed with DT_{50} values between 2.7 and 4.5 days (pH 7) and 3.5 and 3.9 days (pH 9) to form CAPA. CAPA was identified as major metabolite which accounts for up to 94 % AR at pH 7 and up to 99 % AR at pH 9 (study termination, day 29). Under high temperatures (50 °C) CAPA was shown to metabolise itself to metabolite DCPA. DCPA was shown to be stable to hydrolysis. Half lives of CAPA were estimated to be 31.7 days (pH 7) and 7.7 days (pH 9) at 50 °C.

^{14}C-phenyl labelled and ^{14}C-pyridyl labelled fluazinam degraded rapidly during aqueous **photolysis** at pH 5 (sterile buffer solution) at 25° C. The half life was calculated to be 2.5 days for both labels. The major metabolites are G-504 (max. 17.1 % AR after 10 days) and CO_2 (max. 17.7 % AR after 30 days). A large number of minor degradation products was found, which results from a complex degradation pathway with reduction and hydrolysis of NO_2, Cl and CF_3 substituents, the cleavage between the two ring systems of fluazinam, ring opening leading to complex mixtures of polar compounds, and oxidative fragmentation with CO_2 production.

According to the results of a 28-day Manometric Respirometry test fluazinam is **not readily biodegradable**.

In **water/sediment systems** fluazinam disappeared from the water phase with DT_{50} values (single 1st order kinetics; calculated by the RMS) between 1.93 days (phenyl label) and 2.85 days (pyridyl label) in one system and between 1.84 days (phenyl) and 4.25 days (pyridyl) in the other water/sediment system. The calculated DT_{50} values in the sediment were 2.42 days (phenyl label) and 3.35 days (pyridyl label) in one system and 6.41 (phenyl) and 9.5 days (pyridyl) in the other. With the compartment model ModelMaker DT_{50} values in sediment of 3.0 days and 12.1 days were

calculated by the notifier. On the basis of single 1st order kinetics the RMS calculated DT_{50} values for the whole systems between 3.3 days (phenyl label) and 2.9 days (pyridyl label) in one system and between 5.2 days (phenyl) and 6.2 days (pyridyl) in the other system. Residues partitioned rapidly from the water phase into the sediment. Extractable residues in the sediment reached their maxima after 2 days in both systems and amounted for 50 % AR and 48.5 % AR. They declined to 27.4 % and 21.9 % AR after 100 days in the two systems, respectively. At day 0 of incubation 30.6 % and 27.4 % AR were found as extractable residues in the sediment. Non extractable residues in the sediment amounted for up to 55 % AR and 54 % AR at study termination (100 days). Several minor metabolites and a mixture of polar compounds were detected in the water phase and in the sediment. Degradation of fluazinam is via hydrolysis of the phenyl ring chlorine to a hydroxyl group or reduction of one or both nitro groups of the phenyl ring. Identified minor metabolites were HYPA, DAPA and MAPA. AMPA was identified as the major metabolite, which was detected in the sediment in amounts up to 26.7 % AR (phenyl label; day 14) and 20.2 % AR (pyridyl label; day 2) in one system and up to 12.7 % AR (phenyl; day 14) and 18.9 % AR (pyridyl; day 7) in the other system. In the water phase AMPA amounted only up to 2.5 % AR as maximum.
The two water/sediment systems used did not differ significantly from each other with regard to texture, organic carbon content and microbial biomass. As the organic carbon content was rather high in both systems (3.3 % and 4.3 %) a worst case situation with regard to the dissipation of fluazinam from the water phase is not represented. From the batch equilibrium studies it was concluded that a clear correlation between the adsorption of fluazinam to soils (K_f) and the C_{org} content of soils does exist. A statement was submitted by the notifier explaining that due to rapid hydrolysis of fluazinam it is expected that lower organic carbon content of sediments will not effect the dissipation of fluazinam from the water phase significantly.

PEC_{SW}

Predicted environmental concentrations of fluazinam and metabolite AMPA in water and sediment were calculated by $FOCUS_{SW}$ Step 1, Step 2 and Step 3 (only parent) modelling. For fluazinam a DT_{50} of 3.1 days in the water phase was assumed.

Table 2.5.3-1: Summary of maximum PEC values (FOCUS Steps 1, 2 and 3)

Region	Scenario	Water body	compound	PEC_{SW} (max)
Step 1 (10 x 200 g ai/ha on potatoes)				
N & S EU	-	-	Fluazinam	203 µg/L
	-	-	AMPA	10.2 µg/L
Step 2 (10 x 200 g ai/ha on potatoes)				
S EU	-	-	Fluazinam	9.02 µg/L
	-	-	AMPA	1.35 µg/L
Step 3 (values from single application)*				
-	D3	Ditch	Fluazinam	1.045 µg/L
-	D4	Pond		0.042 µg/L
-		Stream		0.866 µg/L
-	D6	Ditch		1.028 µg/L
-	R1	Pond		0.042 µg/L
		Pond		0.058 µg/L **
-		Stream		0.726 µg/L
-	R2	Stream		0.958 µg/L
-	R3	Stream		1.023 µg/L

* assuming single application resulted in the highest PEC values, except for scenario R1 pond
** multiple application calculation

Predicted environmental concentrations of fluazinam were also calculated with FOCUS Step 4 modelling in order to determine the drift and runoff mitigation provided by 5 m unsprayed buffers. With the exception of drift and runoff mitigation measures all input parameters used in the Step 4 calculations were the same as those used in the Step 3 calculations.

Table 2.5.3-1: Summary of maximum PEC values (FOCUS Step 4): 5 m buffer zone

Sce-nario	Water Body	PEC_{sw} (µg L^{-1})				PEC_{sed} (µg kg^{-1})			
		Max	1d TWA	2d TWA	28d TWA	Max	1d TWA	2d TWA	28d TWA
D3	Ditch	0.342*	0.112*	0.057*	0.009	0.077*	0.075*	0.072	0.050
D4	Pond	0.038*	0.027*	0.020*	0.003	0.032	0.032	0.032	0.022
	Stream	0.364*	0.022*	0.011*	0.002	0.022	0.021	0.020	0.010
D6	Ditch	0.337*	0.067*	0.034*	0.007	0.062	0.060	0.057	0.035
R1	Pond	0.038*	0.027	0.020	0.006	0.055	0.055	0.054	0.040
	Stream	0.305*	0.155	0.087	0.021	0.500	0.489	0.474	0.318
R2	Stream	0.403*	0.080	0.042	0.007	0.140	0.135	0.129	0.064
R3	Stream	0.431*	0.098*	0.049*	0.012	0.091	0.088	0.083	0.062

Note: values are maximum results from either single or multiple applications
*assuming single application resulted in the highest PEC values

2.5.4 Fate and behaviour in air

According to the phys./chem. parameters of fluazinam this substance is expected to have medium to high potential for volatilisation. With a vapour pressure of 7.5 ± 0.8 x 10^{-3} Pa (20° C), a water solubility of 0.135 mg/L and a resulting Henry's law constant of 25.9 Pa x m³ x mol^{-1} (20°C) fluazinam has a rather high potential for being available in air. On the basis of the available data it can be concluded that the half-life of fluazinam by photochemical oxidative degradation in air most probably is > 2 days. Absorption of light above 290 nm was shown for fluazinam with a molar extinction coefficient (**ε**) > 10. The quantum yield (Φ) of fluazinam was stated to be 1.7 x 10^{-5} mole/Einstein (pH 6 distilled water).

Hydrolytic (pH 7 and 9; 25 °C) and aqueous photolytic degradation of fluazinam was observed, with DT_{50} values <4 days.

For the time being no harmonised model/method to calculate concentrations in air is available.

2.5.5 Additional information

Two studies were submitted with the aim to compare **impurity-5** with fluazinam with regard to environmental behaviour. In three Japanese soils under laboratory conditions (25 °C) it was shown that imprurity-5 degrades much faster than the active substance fluazinam. Half-lives were calculated by linear regression analysis (Microsoft Excel for Windows 98, vers. 7). DT_{50} values for the impurity were calculated to be 1.3 – 2.7 days.

In the second study the dissipation behaviour of fluazinam and impurity-5 from glass and plant surface with and without irradiation with light was compared. It was shown that from glass surface, which was irradiated with a xenon lamp (approx. 100 000 lux; 20 °C) after the formulation Omega 500 F (SC) was allowed to dry, impurity-5 (8 % left on the glass plate after 24 hours) dissipated much faster than fluazinam (71 % left on the glass plate after 24 hours). Further, the formulation was sprayed to kidney beans, potato plants and peanut plants at a rate equivalent to 2.24 kg ai/ha. After drying the spraying solution, plants were kept in the green house where temperature was kept at 25 °C (day, 14 hours) and 20 °C (night, 10 hours) for 14 days. After 1 day 100 % of fluazinam was still left on kidney bean leaves compared to 82 % on potato leaves and 75 % on peanut leaves. 28 %, 26 % and 42 % of impurity-5 were left after 24 hours, respectively. After 14 days the respective values were 41 %, 39 % and 45 % for fluazinam, and 6 %, 5 % and 8.6 % for impurity-5. Similar results were obtained with peanut plants kept outdoor. Without addition of an adjuvant dissipation was slower or even stopped in case of fluazinam.

Impurity-5 was considered not relevant from an environmental point of view.

2.6 Effects on non-target organisms

2.6.1 Effects on terrestrial vertebrates

2.6.1.1 Birds:

Fluazinam is of low toxicity to birds, the relevant toxicity endpoints are as follows:

Acute toxicity: LD50 = 1782 mg/kg bw (bobwhite quail)

Short-term dietary toxicity: LC50 > 10600 ppm (mallard duck) ≅ > 1230 mg/kg bw

Reproductive toxicity: NOEC = 500 ppm ≅ 60.4 mg/kg bw (bobwhite quail)

The exposure assessment is based on recommendations in the Guidance Document for Risk Assessment of Birds and Mammals (SANCO/4145/2000, Sept. 2002). The major exposure route of fluazinam to wild birds is assumed to be via intake of foliage and arthropods contaminated after spray treatment. In the first tier of the assessment, realistic worst case exposure scenarios are selected with regard to the intended application rate and relevant bird indicator species. The estimated tier 1 TER-figures are presented in the table below. Estimations relate to the intended use of ten applications of 200 g ai/ha in potatoes for medium herbivores and insectivores.

	TER_a	**TER_{st}**	**TER_{lt}**
medium herbivorous bird	67	> 78	7.2
insectivorous bird	165	> 205	10

The exposure via drinking water was also assessed and revealed acceptable TERs. No metabolites of ecotoxicological concern were identified.

Because the $logP_{ow}$ > 3 a potential for bioaccumulation of fluazinam is indicated and this route of exposure is addressed according to SANCO/4145/2000. The estimated $TER_{long\text{-}term}$ for earthworm-eating birds is 43.8 and for fish-eating birds 6.5.

All resulting TER figures are above the respective trigger values given in Annex VI of directive 91/414 and indicate that the risk for wild birds after application of fluazinam is low.

2.6.1.2 Mammals:

The ecotoxicologically relevant toxicity endpoints for fluazinam are as follows:

Acute toxicity: LD50 = 4100 mg/kg bw (fluazinam techn., female rat)

LD50 = > 2000 mg/kg bw (Fluazinam 500 SC, rat)

Reproductive toxicity: NOAEL = 5 mg/kg bw (male rat, two-generation)

The NOAEL from the two-generation reproduction study in rats of 5 / 6.7 mg/kg bw is the next higher dosage level compared to the NOEC identified in the toxicology section (1 mg/kg). Effects observed at the dosage level of 100 ppm (5 / 6.7 mg/kg bw for males/females) were slightly reduced bodyweights of females and slightly reduced conception rates and fertility indices only in F_1. These slight effects are considered as not ecologically relevant at population level and the next higher level was chosen as NOAEL of ecological relevance.

The exposure assessment is based on recommendations of the Guidance Document for Risk Assessment of Birds and Mammals (SANCO/4145/2000, Sept. 2002). The major exposure route of fluazinam to wild mammals is assumed to be via intake of foliage and arthropods contaminated after spray treatment. In the first tier of the assessment, realistic worst case exposure scenarios are selected with regard to the intended application rate and relevant mammalian indicator species. TER-figures were calculated for small herbivores and for insectivores. For TERlt / Tier 1 estimations, a default half-life of fluazinam of 10 days was assumed. The estimated tier 1 TER-

figures for medium herbivores and insectivores are presented in the table below. Estimations relate to the intended use of 10 applications of 200 g ai/ha in potatoes.

	TER_a (ai)	TER_a (form.)	TER_{lt}
medium herbivorous mammal	421	> 103	1.6*
insectivorous mammal	2324	> 556	7.8

*as potato foliage is unpalatable to mammals, this scenario is considered not relevant

The exposure via drinking water was also assessed and revealed acceptable TERs. No metabolites of ecotoxicological concern were identified.

Because the $logP_{ow}$ > 3 a potential for bioaccumulation of fluazinam is indicated and this route of exposure is addressed according to SANCO/4145/2000. The estimated $TER_{long\text{-}term}$ (tier 1) for earthworm-eating mammals is 2.9 and for fish-eating mammals 35 (calculated with a FOCUS step 2 PEC). Because fluazinam is extensively metabolised and excreted, and because potato fields are not an attractive habitat for wild mammals (PT will be < 1), the risk based on more realistic assumptions is considered low also for earthworm-eating mammals.

The risk for wild mammals after the use of fluazinam according to GAP appears low.

2.6.2 Effects on aquatic species

Acute risk assessment:

Active substance and formulation

The active substance fluazinam and the formulation (Fluazinam 500 SC containing 50 % active substance) are acutely very toxic to fish, aquatic invertebrates and algae. The relevant endpoints of the most sensitive organisms are: LC50 (96 h) of 36 µg ai/L for fish, EC50 (48 h) of 119 µg ai/L for daphnids and EC_b50 (72 h) of 160 µg ai/L for green algae.

The risk assessment was performed assuming the intended application scenarios in potatoes (10 x 200 g ai/ha, spring) with concentrations calculated by FOCUS Step 1, 2 and 3. The results of calculations with FOCUS Step 1 (TER ≤ 1 for all species) indicate a high risk for all tested organisms because trigger values for the safety factors established in Annex VI to EEC Directive 91/414 were not met. For fish a TER of 10 was applied in accordance with the HARAP guidance document (1999), since five fish species were tested and the data confirmed a very narrow range of sensitivities (EC50 ranged from 36 µg ai/L to 120 µg ai/L).

The TER values calculated with FOCUS Step 2 resulted in acceptable safety factors for algae (TER = 17), however TER values for fish (TER = 4) and daphnids (TER = 21) were not sufficient. Thus FOCUS Step 3 calculations were performed for these two species. For all scenarios the calculated TER values were above the relevant trigger values (TER ≥ 35 for fish and TER ≥ 114 for daphnids). Therefore the acute risk to aquatic organism regarding the application of the active substance fluazinam with the intended uses in potatoes is acceptable.

Metabolites:

The major metabolite in water phase was **AMPA**. This metabolite is rather insoluble in water and the solubility limit is < 40 µg/L. Acute test with the standard species were performed and no effects

were observed at concentrations higher than the solubility limit. TER values calculated with Focus Step 2 provided a sufficient margin of safety and the risk to aquatic organisms is acceptable.
G-504 is a major metabolite in aqueous photolysis study, therefore this metabolite could be relevant for the aquatic ecosystem. Aquatic toxicity data of G-504 were calculated by "Syracus Research Cooperation ECOWIN software" for fish, daphnids and green algae. The EC50 were estimated to be 36.5 mg/l for fish, 3.6 mg/L for daphnids and 14.8 mg/L for green algae. These toxicity data are indicated that G-504 is much less toxic than the active substance. Therefore the risk can be concluded as very low.
The major soil metabolite **HYPA** could reach surface water via run-off and drainage, however no data on the effects on aquatic organisms are available.

Long term risk assessment

Fluazinam is very toxic for all tested organisms (fish and aquatic invertebrates) in chronic studies. In general the chronic NOEC was ≤ 0.0125 mg/L. The most sensitive organisms were fish (fathead minnow) with a NOEC of 2.9 µg/L from a full life cycle test.
TER calculations with FOCUS Step 1 and 2 indicated a high chronic risk to the aquatic biocenosis, since no TER value met the relevant safety factor. Therefore for all organisms calculations with FOCUS Step 3 were performed: TER values calculated for daphnids and zooplankton (microcosm) met the trigger values of 10 (aquatic invertebrates) and 5 (microcosm) in all scenarios. However the TER values for the most sensitive fish species as well as for the sediment dwelling midge larvae were below the relevant trigger value of 10 for all scenarios. Therefore the chronic risk for fish and sediment dwelling organisms were refined with $FOCUS_{sw}$ Step 4 calculations based on risk mitigation measures (5 m buffer zone). Furthermore for fish the "ETC" (environmental trigger concentration)[1], which describes the actual measured concentrations over the 278 day exposure period divided by an safety factor of 10, of the FLC was compared to the PECs of $FOCUS_{sw}$ scenarios. Since the ETC was shown always higher concentrations levels than the PECs of the respective $FOCUS_{sw}$ scenarios (Step 4, 5 m buffer zone) it can be concluded that the risk is acceptable.

Bioaccumulation

The BCF values of 960 and 1090 of fluazinam in whole fish and the incomplete depuration (after 14 days 22 – 24 % of total ^{14}C-tissue residues remained in fish) indicate a risk of bioaccumulation. However, fluazinam was extensively metabolised in fish organisms to AMPA, DAPA, MAPA and numerous non identified degradation products. Neither the active substance nor the identified or non-identified metabolites were found in amounts > 10 %. Furthermore the calculated BCF values could not only be attributed to active substance alone, since the determination is based on total ^{14}C-residues amounts. Thus, the potential of bioaccumulation in fish is considered to be low.
Furthermore the risk of secondary poisoning to fish eating-birds and mammals was already considered in the long term risk assessment for birds and mammals (see 2.6.1) and no unacceptable risk was identified.

[1] Term introduced by the PPR Panel, The EFSA Journal (2005), 178 1 – 45

No data on the bioaccumulation potential for AMPA, the major metabolite in surface water, is available.

2.6.3 Effects on bees and other arthropod species

Honey-bees:

Honey-bees may be exposed to formulated fluazinam through contact with fresh or dry residues or by oral uptake of contaminated pollen, nectar and honey dew.

Fluazinam is practically non-toxic to bees, the LD_{50}-value for the active substance for contact toxicity is > 200 µg ai/bee and for oral toxicity > 100 µg ai/bee. Fluazinam 500 SC also proved to be non-toxic to bees by contact, oral and inhalatory route.

Based on these data hazard quotients (HQ`s) have been calculated for oral and for contact exposure and these are < 3.5 and < 7 and therefore below the relevant trigger, which indicates a low risk to honeybees. Hence, it is concluded that after application under conditions of the intended representative use the risk to honey-bees is low.

Non-target arthropods:

Laboratory studies with five species of non-target arthropods, among them the two indicator species, have been used for the risk assessment.

A LR_{50} of > 200 g ai/ha is indicated for *Aphidius rhopalosiphi*. Based on this value a HQ is calculated as follows (according to ESCORT 2 procedure) for the intended use in potatos:

species	application rate (g ai/ha)	LR_{50} [g ai/ha]	HQ in-field	HQ off-field
A. rhopalosiphi	10 x 200	> 200	< 3.5	< 0.1

The HQ in-field possibly exceeds the critical value of 2, whereas the HQ off-field indicates a low risk for non-target arthropods in the off-crop area.

In an extended lab study with detached potato leaves mortality rates of *A. rhopalosiphi* were below 50 % and in consequence the risk to parasitoids is considered acceptable when fluazinam is applied according to GAP.

Typhlodromus pyri and *Chrysoperla carnea* were not significantly affected by Fluazinam 500 SC in extended laboratory studies when applied according to GAP. Hence, the product does not pose an unacceptable risk to predatory mites and other foliage dwelling arthropods.

Pterostichus melanarius and lycosid spiders were also not affected by Fluazinam 500 SC in the laboratory. Hence, the product does not pose an unacceptable risk to ground dwelling arthropods.

It is concluded that both in- and off-field exposure to Fluazinam 500 EC from the intended use does not cause unacceptable effects to populations of terrestrial non-target arthropods.

2.6.4 Effects on earthworms and other soil macro-organisms

2.6.4.1 Effects on earthworms

Active substance and formulation

To assess the acute toxicity to earthworms two 14 days acute toxicity studies with fluazinam and the lead formulation (Fluazinam 500 SC) were submitted. In both cases the estimated EC50 values were > 1000 mg/kg dw. At lower concentration levels significant effects on the body weight were observed and resulted in NOEC values of 10 mg/kg dw (fluazinam) and < 138 mg product/kg dw (Fluazinam 500 SC). However calculated TER values were well above the trigger value of 10 and the acute risk to earthworms is acceptable.

A long-term study was triggered due to the repeated application of fluazinam in potatoes (10 x 200 g as/ha). A reproduction toxicity study in laboratory and a field study, each with the formulation were submitted. Significant effects on the reproduction were noted (NOEC < 0.35 mg/kg dw) and the corresponding long term TER (< 0.325) indicates a long-term risk. However no significant effects were observed in the field study with a realistic exposure scenario (10 x 200 g as/ha) and finally the long term risk to earthworms is considered to be acceptable.

Metabolite:

A 14 day acute toxicity test with the metabolite HYPA was submitted. The EC50 was > 1000 mg/kg dw and the NOEC (bodyweight) was 269 mg/kg dw. The calculated TERa was > 10. The potential long-term exposure to the metabolite is covered by the field study with the formulation. Thus the metabolite HYPA posses no unacceptable risk to earthworms.

2.6.4.2 Effects on other soil macro-organisms

Active substance and formulation:

A test with collembola was triggered because the worst case DT90 value of fluazinam is > 1 year under laboratory conditions. Furthermore the long term TER for earthworms was calculated to be < 5. Therefore a study on the effects on the reproduction of collembola (*Folsemia candida*) with the formulation (Fluazinam 500SC) was submitted. Effects on mortality were observed at all tested concentrations, therefore a NOEC could not be determined and was fixed with < 1.57 mg ai/kg (lowest tested concentration). The long term TER was calculated to be < 1.45 and is below the relevant trigger value of 5. Thus, the risk is not acceptable and a litter bag test under field conditions is required.

Metabolite:

One collembola reproduction study with the metabolite HYPA was submitted. No effects on the reproduction rate and mortality were reported at concentration until 6.08 mg HYPA/kg (highest tested concentration). The TERlt value was calculated to be 26.5 and is above the relevant safety factor. Thus, the risk of the metabolite is considered acceptable.

2.6.5 Effects on soil micro-organisms

Active substance and formulation:

Fluazinam did not significantly effected the activity of the soil micro-flora under test conditions in laboratory. The test was performed with the lead formulation Fluazinam 500 SC at two doses:

0.684 mg formulation/kg soil dw (corresponding to 0.27 mg fluazinam/kg) and 5.748 mg formulation/kg soil dw (corresponding to 2.27 mg fluazinam/kg). It can be concluded, that fluazinam when applied according to GAP did not significantly effected soil microflora respiration and soil nitrogen transformation.

Metabolites:

The metabolite HYPA had no unacceptable impact on soil micro-flora up to a concentration of 0.38 mg/kg dw. Therefore, after the use of fluazinam according to GAP no unacceptable long-term adverse effects of HYPA on the soil micro-flora are expected.

2.6.6 Effects on other non-target organisms (flora and fauna)

Non-target plants:

Terrestrial non-target plants may be exposed to fluazinam by spray drift.

Only one of 10 species tested exhibited an inhibition > 25 % in biomass in the vegetative vigour screening test at a rate of 1.5 kg ai/ha, cucumber (*Cucumis sativus*). However, this effect of a 28 % reduction of fresh weight was not confirmed in a subsequent multi-dose test on cucumber. The EC_{50} for all species tested is therefore > 1.5 kg ai/ha. As the maximum single rate is 0.2 kg/ha, no significant effects on non-target terrestrial plants in- or off-field are expected.

2.6.7 Effects on biological methods of sewage treatment

In a test with activated sludge from a wastewater treatment system an EC_{50} of 118 mg ai/L was observed. The inhibitory effect of fluazinam on *Pseudomonas putida* was low, with an observed EC_{50} of > 1.53 mg ai/L. The water solubility of fluazinam is 0.135 mg/L at pH 7. It is considered very unlikely that fluazinam will enter water treatment plants in amounts that will lead to effects on water treatment procedures, when fluazinam is applied according to the GAP.

Overall Conclusions, including a listing of critical end points

recommended restrictions/conditions with regard to physical and chemical properties and analytical methods	none
recommended restrictions/conditions with regard to toxicity and metabolism findings	none
recommended restrictions/conditions with regard to residues and risks for consumers	none
recommended restrictions/conditions with regard to fate and behaviour in the environment	none
recommended restrictions/conditions with regard to ecotoxicological findings	risk mitigation measures for aquatic organisms (e.g. buffer zones) are necessary

Appendix 1

Standard Terms and Abbreviations

Part 1 Technical Terms

A	Ampere
Ach	Acetylcholine
AchE	Acetylcholinesterase
ADI	acceptable daily intake
ADP	adenosine diphosphate
AFID	alkali flame-ionization detector of detection
A/G	albumin/globulin ratio
ai	active ingredient
ALD_{50}	approximate median lethal dose, 50 %
ALT	alanine aminotransferase (SGPT)
AMD	automatic multiple development
ANOVA	analysis of variance
AOEL	acceptable operator exposure level
AP	alkaline phosphatase
approx.	Approximate
as	active substance
AST	aspartate aminotransferase (SGOT)
ASV	air saturation value
ATP	adenosine triphosphate
BCF	bioconcentration factor
bfa	body fluid assay
BOD	biological oxygen demand
bp	boiling point
BSAF	biota-sediment accumulation factor
BSE	bovine spongiform encephalopathy
BSP	Bromosulfophthalein
Bt	bacillus thuringiensis
Bti	bacillus thuringiensis israelensis
Btk	bacillus thuringiensis kurstaki
Btt	bacillus thuringiensis tenebrionis
BUN	blood urea nitrogen
bw	body weight
c	centi- (x 10^{-2})
°C	degree Celsius (centigrade)
CA	controlled atmosphere
CAD	computer aided design
CBI	confidential business information
cd	Candela
CDA	controlled drop(let) application
cDNA	complementary DNA
CEC	cation exchange capacity
cf	confer, compare to
CFU	colony forming units
ChE	Cholinesterase
CI	confidence interval
CL	confidence limits
cm	centimetre
CNS	central nervous system
COD	chemical oxygen demand
CPK	creatine phosphatase
cv	coefficient of variation

Cv	ceiling value
CXL	Codex Maximum Residue Limit (Codex MRL)
d	day
DES	diethylstilboestrol
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic Acid
dna	designated national authority
DO	dissolved oxygen
DOC	dissolved organic carbon
dpi	days pot inoculation
DT_{50}	period required for 50 percent dissipation (define method of estimation)
DT_{90}	period required for 50 percent dissipation (define method of estimation)
dw	dry weight
DWQG	drinking water quality guidelines
ε	decadic molar extinction coefficient
EC_{50}	median effective concentration
ECD	electron capture detector
ECU	European currency unit
ED_{50}	median effective dose
EDI	estimated daily intake
ELISA	enzyme linked immunosorbent assay
e-mail	electronic mail
EMDI	estimated maximum daily intake
EPMA	electron probe micro analysis
ERC	environmentally relevant concentration
ERL	extraneous residue limit
F_0	parental generation
F_1	filial generation, first
F_2	filial generation, second
FIA	fluorescence immunoassay
FID	flame ionization detector
FOB	functional observation battery
fp	freezing point
FPD	flame photometric detector
FPLC	fast protein liquid chromatography
g	gram
GAP	good agricultural practice
GC	gas chromatography
GC-EC	gas chromatography with electron capture detector
GC-FID	gas chromatography with flame ionization detector
GC-MS	gas chromatography-mass spectrometry
GC-MSD	gas chromatography with mass-selective detection
GEP	good experimental practice
GFP	good field practice
GGT	gamma glutamyl transferase
GI	gastro-intestinal
GIT	gastro-intestinal tract
GL	guideline level
GLC	gas liquid chromatography
GLP	good laboratory practice
GMM	genetically modified micro-organism
GMO	genetically modified organism
GPC	gel-permeation chromatography
GPPP	good plant protection practice
GPS	global positioning system
GSH	glutathion
GV	granulosevirus

h	hour(s)
H	Henry's Law constant (calculated as a unitless value), (see also K)
ha	hectare
Hb	haemoglobin
HCG	human chorionic gonadotropin
Hct	haemocrit
HEED	high energy electron diffraction
HID	helium ionization detector
hl	hectolitre
hma	host-mediated assay
HPAEC	high performance anion exchange chromatography
HPLC	high pressure liquid chromatography or high performance liquid chromatography
HPLC-MS	high pressure liquid chromatography –mass spectroscopy
HPPLC	high pressure planar liquid chromatography
HPTLC	high performance thin layer chromatography
HQ	hazard quotient
HRGC	high resolution gas chromatography
H_s	Shannon-Weaver index
Ht	haematocrit
I_{50}	inhibitory dose, 50 %
IC_{50}	median immobilization concentration
ICM	integrated crop management
ID	ionization detector
IEDI	international estimated daily intake
IGR	insect growth regulator
im	intramuscular
inh	inhalation
ip	intraperitoneal
IPM	integrated pest management
IR	infrared
ISBN	international standard book number
ISSN	international standard serial number
iv	intravenous
IVF	in vitro fertilization
k	kilo
K	Kelvin or Henry's Law constant (in atmospheres per cubic meter per mole) (see also H)
K_{ads}	adsorption constant
K_{des}	apparent desorption coefficient
kg	kilogram
K_{oc}	organic carbon adsorption coefficient
K_{om}	organic matter adsorption coefficient
kg	kilogram
L	litre
LAN	local area network
LASER	light amplification by stimulated emission of radiation
LBC	loosely bound capacity
LC	liquid chromatography
LC-MS	liquid chromatography-mass spectrometry
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LC_{50}	lethal concentration, median
LCA	life cycle analysis
LC_{Lo}	lethal concentration low
LD_{50}	lethal dose, median; dosis letalis media
LD_{Lo}	lethal dose low
LDH	lactate dehydrogenase
LOAEC	lowest observable adverse effect concentration
LOAEL	lowest observable adverse effect level
LOD	limit of detection

LOEC	lowest observable effect concentration
LOEL	lowest observable effect level
LOQ	limit of quantification (determination)
LPLC	low pressure liquid chromatography
LSC	liquid scintillation counting or counter
LSD	least squared denominator multiple range test
LSS	liquid scintillation spectrometry
LT	lethal threshold
m	metre
M	molar
µm	micrometer (micron)
MAF	multiple application factor
MC	moisture content
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
MDL	method detection limit
MFO	mixed function oxidase
mg	milligram
µg	microgram
MHC	moisture holding capacity
min	minute(s)
mL	millilitre
MLD	minimum lethal dose
MLT	median lethal time
mm	millimetre
mo	month(s)
mol	Mole(s)
MOS	margin of safety
mp	melting point
MRE	maximum residue expected
MRL	maximum residue level
mRNA	messenger ribonucleic acid
MS	mass spectrometry
MSDS	material safety data sheet
MTD	maximum tolerated dose
n	normal (defining isomeric configuration) or number of observations
NAEL	no adverse effect level
nd	not detected
NEDI	no effect daily intake (mg/kg body wt/day)
NEL	no effect level
NERL	no effect residue level
ng	nanogram
nm	nanometer
NMR	nuclear magnetic resonance
no	number
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOED	no observed effect dose
NOEL	no observed effect level
NOIS	notice of intent to suspend
NPD	nitrogen-phosphorus detector of detection
NPV	nuclear polyhedrosis virus
NR	not reported
nse	non standard exposure
NTE	neurotoxic target esterase
OC	organic carbon content
ODP	ozone-depleting potential

ODS	ozone depleting substances
OM	organic matter content
op	organophosphorous pesticide
Pa	Pascal
PAD	pulsed amperometric detection
2-PAM	2-pralidoxime
pc	paper chromatography
PCV	haematocrit (packed corpuscular volume)
PEC	predicted environmental concentration
PEC_A	predicted environmental concentration in air
PEC_{GW}	predicted environmental concentration in ground water
PEC_s	predicted environmental concentration in soil
PEC_{SW}	predicted environmental concentration in surface water
PED	plasma-emissions-detector
pH	pH-value
PHI	pre-harvest interval
PIC	prior informed consent
pic	phage inhibition capacity
pic	phage inhibitory capacity
PIXE	proton induced X-ray emission
pKa	negative logarithm (to the base 10) of the dissociation constant
PNEC	predicted no effect concentration
po	by mouth
P_{OW}	partition coefficient between n-octanol and water
POP	persistent organic pollutants
ppb	parts per billion (10^{-9})
ppm	parts per million (10^{-6})
ppp	plant protection products
ppq	parts per quadrillion (10^{-24})
ppt	parts per trillion (10^{-12})
PSP	phenolsulfophthalein
PrT	prothrombin time
PRL	practical residue limit
PT	prothrombin time
PTDI	provisional tolerable daily intake
PTT	partial thromboplastin time
QSAR	quantitative structure-activity relationship
r	correlation coefficient
r^2	coefficient of determination
RBC	red blood cell
REI	restricted entry interval
Rf	ratio of fronts
RfD	reference dose
RH	relative humidity
RL_{50}	residual lifetime
RNA	ribonucleic acid
RP	reversed phase
rpm	rotations per minute
rRNA	ribosomal ribonucleic acid
RRT	relative retention time
RT	Retention time
RUD	residue unit dose
s	seconds
SAC	strong adsorption capacity
SAP	serum alkaline phosphatase
SAR	structure/activity relationship
SBLC	shallow bed liquid chromatography
sc	subcutaneous

sce	sister chromatid exchange
SD	standard deviation
SE	standard error
se	standard error
SEM	standard error of the mean
SEP	standard evaluation procedure
SF	safety factor
SFC	supercritical fluid chromatography
SFE	supercritical fluid extraction
SIMS	secondary ion mass spectroscopy
SOP	standard operating procedures
sp	species (only after a generic name)
SPE	solid phase extraction
SPF	specific pathogen free
spp	subspecies
sq	square
SSD	sulphur specific detector
SSMS	spark source mass spectrometry
STEL	short term exposure limit
STMR	supervised trials median residue
t	tonne (metric ton)
$t_{1/2}$	half-life (define method of estimation)
T_3	tri-iodothyroxine
T_4	thyroxine
TADI	temporary acceptable daily intake
TBC	tightly bound capacity
TCD	thermal conductivity detector
TC_{Lo}	toxic concentration, low
TD_{Lo}	toxic dose low
TDR	time domain reflectrometry
TER	Toxicity Exposure Ratio
TER_I	toxicity exposure ratio for initial exposure
TER_{LT}	toxicity exposure ratio following chronic exposure
TER_{ST}	toxicity exposure ratio following repeated exposure
tert	tertiary (in a chemical name)
TEP	typical end-use product
TGGE	temperature gradient gel electrophoresis
TID	thermionic detector, alkali flame detector
TLC	thin layer chromatography
Tlm	median tolerance limit
TLV	threshold limit value
TMDI	theoretical maximum daily intake
TMRC	theoretical maximum residue contribution
TMRL	temporary maximum residue limit
TOC	total organic carbon
Tremcard	transport emergency card
tRNA	transfer ribonucleic acid
TSH	thuroid stimulating hormone (thyrotropin)
TWA	time weighted average
UDS	unscheduled DNA synthesis
UF	uncertainty factor (safety factor)
ULV	ultra low volume
UV	ultraviolet
v/v	volume ratio (volume per volume)
WBC	white blood cell
wk	week
wt	weight

w/v	weight per volume
w/w	weight per weight
ww	wet weight
XRFA	X-ray fluorescence analysis
yr	year
≤	less than or equal to
≥	greater than or equal to
<	less than
>	greater than

Part 2 Organisations and Publications

ASTM	American Society for Testing and Materials
BA	Biological Abstracts (Philadelphia)
BART	Beneficial Arthropod Registration Testing Group
CA	Chemical Abstracts
CAB	Centre for Agriculture and Biosciences International
CAC	Codex Alimentarius Commission
CAS	Chemical Abstracts Service
CCFAC	Codex Committee on Food Additives and Contaminants
CCGP	Codex Committee on General Principles
CCPR	Codex Committee on Pesticide Residues
CE	Council of Europe
CIPAC	Collaborative International Pesticides Analytical Council Ltd
COREPER	Comite des Representants Permanents
EC	European Commission
ECB	European Chemical Bureau
ECCA	European Crop Care Association
ECDIN	Environmental Chemicals Data and Information Network of the European Communities
ECDIS	European Environmental Chemicals Data and Information System
ECE	Economic Commission for Europe
ECETOC	European Chemical Industry Ecology and Toxicology Centre
ECLO	Emergency Centre for Locust Operations
ECMWF	European Centre for Medium Range Weather Forecasting
ECPA	European Crop Protection Association
EDEXIM	European Database on Export and Import of Dangerous Chemicals
EHC (number)	Environmental Health Criteria (number)
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EMIC	Environmental Mutagens Information Centre
EPA	Environmental Protection Agency
EPO	European Patent Office
EPPO	European and Mediterranean Plant Protection Organization
ESCORT	European Standard Characteristics of Beneficials Regulatory Testing
EU	European Union
EUPHIDS	European Pesticide Hazard Information and Decision Support System
EUROPOEM	European Predictive Operator Exposure Model
FAO	Food and Agriculture Organization of the UN
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
GATT	General Agreement on Tariffs and Trade
GAW	Global Atmosphere Watch

GCOS	Global Climate Observing System
GCPF	Global Crop Protection Federation (formerly known as GIFAP)
GEDD	Global Environmental Data Directory
GEMS	Global Environmental Monitoring System
GIEWS	Global Information and Early Warning System for Food and Agriculture
GIFAP	Groupement International des Associations Nationales de Fabricants de Produits Agrochimiques
GRIN	Germplasm Resources Information Network
HRAC	Herbicide Resistance Action Committee
IARC	International Agency for Research on Cancer
IATS	International Academy of Toxicological Science
IBT	Industrial Bio-Test Laboratories
ICBB	International Commission of Bee Botany
ICBP	International Council for Bird Preservation
ICES	International Council for the Exploration of the Seas
ICPBR	International Commission for Plant-Bee Relationships
ILO	International Labour Organisation
IMO	International Maritime Organisation
IOBC	International Organization for Biological Control of Noxious Animals and Plants
IPCS	International Programme on Chemical Safety
IRAC	Insecticide Resistance Action Committee
IRC	International Rice Commission
ISCO	International Soil Conservation Organization
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
JECFA	FAO/WHO Joint Expert Committee on Food Additives
JFCMP	Joint FAO/WHO Food and Animal Feed Contamination Monitoring Programme
JMP	Joint Meeting on Pesticides (WHO/FAO)
JMPR	Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
NAFTA	North American Free Trade Agreement
NATO	North Atlantic Treaty Organisation
NCI	National Cancer Institute (USA)
NCTR	National Center for Toxicological Research (USA)
NGO	non-governmental organization
NTP	National Toxicology Programme (USA)
OECD	Organization for Economic Cooperation and Development
OLIS	On-line Information Service of OECD
PAN	Pesticide Action Network
RNN	Re-registration Notification Network
RTECS	Registry of Toxic Effects of Chemical Substances (USA)
SCPH	Standing Committee on Plant Health
SETAC	Society of Environmental Toxicology and Chemistry
SI	Systeme International d'Unites
SITC	Standard International Trade Classification
Toxline	Toxicology Information On-line
UN	United Nations
UNEP	United Nations Environment Programme
WCDP	World Climate Data Programme
WCP	World Climate Programme
WCRP	World Climate Research Programme
WFP	World Food Programme

WHO	World Health Organization
WTO	World Trade Organization
WWF	World Wildlife Fund

Part 3 Preparation (Formulation) Types and Codes *

Code	Description	Definition
AB	Grain bait	Special forms of bait.
AE	Aerosol dispenser	A container-held preparation which is dispersed generally by a propellant as fine droplets/particles upon actuation of a valve.
AL	Other liquids to be applied undiluted	Self defining.
BB	Block baits	Special forms of bait.
BR	Briquette	Solid block designed for controlled release of active ingredient into water.
CB	Bait concentrate	A solid or liquid intended for dilution before use as a bait.
CG	Encapsulated granule	A granule with a protective or release controlling coating.
CS	Capsule suspension	A stable suspension of capsules in a fluid normally intended for dilution with water before use.
DC	Dispersible concentrate	A liquid homogeneous preparation to be applied as a solid dispersion after dilution in water.
DP	Dustable powder	A free-flowing powder suitable for dusting.
DS	Powder for dry seed treatment	A powder for application in the dry state directly to seed.
EC	Emulsifiable concentrate	A liquid, homogenous preparation to be applied as an emulsion after dilution in water.
ED	Electrochargeable liquid	Special liquid preparation for electrostatic (electrodynamic) spraying.
EO	Emulsion, water in oil	A fluid, heterogeneous preparation consisting of a dispersion of fine globules of pesticide in water in a continuous organic liquid phase.
ES	Emulsion for seed treatment	A stable emulsion for application to the seed either directly or after dilution.
EW	Emulsion, oil in water	A fluid, heterogeneous preparation consisting of a dispersion of fine globules of pesticide in an organic liquid in a continuous water phase.
FD	Smoke tin	Special form of smoke generator.

* based upon the catalogue of Pesticide Formulation types and International Coding Systems, developed by GIFAP in co-operation with the German working group on documentaion questions (Arbeitsgruppe EDV Pflanzenschutz Versuchswesen). GIFAP Technical Monograph No 2, 1989.

Code	Description	Definition
FG	Fine granule	A granule in the particle size range from 300 to 2500µ.
FK	Smoke candle	A smoke generator in the form of a candle.
FP	Smoke cartridge	Special form of smoke generator.
FR	Smoke rodlet	Special form of smoke generator.
FS	Flowable concentrate for seed treatment	A stable suspension for application to the seed either directly or after dilution.
FT	Smoke tablet	Special form of smoke generator.
FU	Smoke generator	A combustible preparation generally solid, which upon ignitionreleases the active substances in the form of a smoke.
FW	Smoke pellet	Special form of smoke generator.
GA	Gas	A gas packed in pressure bottle or pressure tank.
GB	Granular bait	Special forms of bait.
GE	Gas generating product	A preparation which generates a gas by chemical reaction.
GG	Macrogranule	A granule in the particle size range from 2000 to 6000 µ.
GP	Flo-dust	Very fine dustable powder for pneumatic application in glass-houses.
GR	Granule	A free-flowing solid preparation of a defined granule size range ready for use.
GS	Grease	Very viscous preparation based on oil or fat.
HN	Hot fogging concentrate	A preparation suitable for application by fogging equipment either directly or after dilution.
KN	Cold fogging concentrate	A preparation suitable for application by cold fogging equipment, either directly or after dilution.
LA	Lacquer	A solvent based film-forming preparation.
LS	Solution for seed treatment	A solution for application to the seed either directly or after dilution.
MG	Microgranule	A granule in the particle size range from 100 to 600 µ.
OF	Oil miscible flowable (=oil active substances in a miscible suspension)	A stable suspension of concentrate fluid intended for dilution inan organic liquid before use.
OL	Oil miscible liquid	A liquid, homogenous preparation to be applied as a homogenous liquid after dilution in an organic liquid.

Code	Description	Definition
OP	Oil dispersible powder	A powder preparation to be applied as a suspension after dispersion in an organic liquid.
PA	Paste	A water based film forming preparation.
PB	Plate bait	Special forms of bait.
PC	Gel or paste concentrate	A solid preparation to be applied as a gel or a paste after dilution with water.
PR	Plant rodlet	A small rodlet, usually a few centimetres in length and a few millimetres in diameter containing active substance.
PS	Seed coated with a pesticide	Self defining.
RB	Bait (ready for use)	A preparation designed to attract and be eaten by the target species.
SB	Scrap bait	Special forms of bait.
SC	Suspension concentrate (= flowable concentrate)	A stable suspension of active substance(s) in a fluid intended for dilution with water before use.
SE	Suspo-emulsion	A fluid, heterogeneous preparation consisting of a stable dispersion of active substance(s) in the form of solid particles and of fine globules in a continuous water phase.
SG	Water soluble granules	A preparation consisting of granules to be applied as a true solution of active substance after dissolution in water but may contain insoluble inert ingredients.
SL	Soluble concentrate	A liquid homogenous preparation to be applied as a true solution of the active substance after dilution with water.
SO	Spreading oil	A preparation designed to form a surface layer on application to water.
SP	Water soluble powder	A powder preparation to be applied as a true solution of the active substance after solution in water but which may contain insoluble inert ingredients.
SS	Water soluble powder for seed treatment	A powder to be dissolved in water before application to the seed.
SU	Ultra low volume (ULV) suspension	A suspension ready for use through ULV equipment.
TB	Tablet	Solid preparation in the form of small, flat plates for dissolution in water.
TP	Tracking powder	A rodenticidal contact preparation in powder form.
UL	Ultra low volume (ULV) liquid	A homogenous liquid ready for use through ULV

Code	Description	Definition
		equipment.
VP	Vapour releasing product	A preparation containing one or more volatile ingredients, the vapours of which are released into the air. Evaporation rate normally is controlled by using suitable preparations and/or dispensers.
WG	Water dispersible	A preparation granule consisting of granules to be applied after disintegration and dispersion in water.
WP	Wettable powder	A powder preparation to be applied as a suspension after dispersion in water.
WS	Water dispersible powder for slurry seed treatment	A powder to be dispersed at high concentration in water before application as a slurry to the seed.
XX	Others	

Appendix 2

Specific Terms and Abbreviations

ILV	Independent laboratory validation
RSD	Relative standard deviation
PES	Post extraction solid
TFAA	Trifluoro acetic acid
TIC	Total ion current or total ion chromatogram

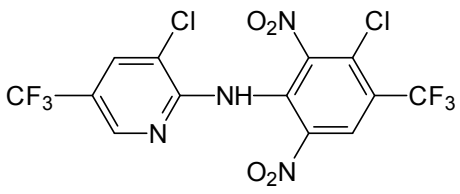
Appendix 3

Listing of end points

Chapter: Identity, Physical and Chemical Properties, Details of Uses, Further Information

Active substance (ISO Common Name)	Fluazinam
Function (*e.g.* fungicide)	Fungicide
Rapporteur Member State	Austria

Identity (Annex IIA, point 1)

Chemical name (IUPAC)	3-chloro-N-(3-chloro-5-trifluoromethyl-2-pyridyl)- α,α,α-trifluoro-2, 6-dinitro-p-toluidine
Chemical name (CA)	3-chloro-N-[3-chloro-2, 6-dinitro-4-trifluoromethyl) phenyl]-5-(trifluoromethyl)-2-pyridinamine
CIPAC No	521
CAS No	79622-59-6
EC No (EINECS or ELINCS)	not available
FAO Specification (including year of publication)	no FAO specification is available at the time of evaluation
Minimum purity of the active substance as manufactured	960 g/kg
Identity of relevant impurities (of toxicological, environmental and/or other significance) in the active substance as manufactured	Impurity 5 and 6 is considered to be relevant by section toxicology. After confirmation the chemical name and specified max. content will be added
Molecular formula	$C_{13}H_4Cl_2F_6N_4O_4$
Molecular mass	465.1
Structural formula	

Physical and chemical properties (Annex IIA, point 2)

Melting point (state purity)	117 °C	(99.8% w/w)
Boiling point (state purity)	not applicable	
Temperature of decomposition (state purity)	not applicable	
Appearance (state purity)	PGAI: yellow, crystalline solid odorless	(100% w/w) at 20 – 22 °C
	TGAI: yellow, solid weak aromatic hydrocarbon-like	(97.7% w/w) at 23 – 24 °C
Relative density (state purity)	D_4^{20} = 1.81 at 20 ± 1.0 °C	(99.8% w/w)
Vapour pressure (state temperature, state purity)	(7.5 ± 0.8) x 10^{-3} Pa at 20 °C	(99.8% w/w)
Henry's law constant	25.9 Pa.m³.mol^{-1} at 20 °C	
Solubility in water (state temperature, state purity and pH)	at 20 ± 1 °C 1.06 x 10^{-4} g/L in buffered solution (at pH 5) 1.35 x 10^{-4} g/L in buffered solution (at pH 7) 2.72 x 10^{-3} g/L in buffered solution (at pH 9)	(99.8% w/w)
Solubility in organic solvents (state temperature, state purity)	at 25 °C [g/L]	(96.8% w/w)
	acetone 853 dichloromethane 675 ethyl acetate 722 ethyl ether 231 hexane 8 methanol 192 octanol 41 toluene 451	
Surface tension (state concentration and temperature, state purity)	66.3 mN/m at 20 °C (90% saturated solution)	(95.5% w/w)
Partition co-efficient (state temperature, pH and purity)	log $P_{O/W}$ = 4.03 at 25 °C neutral range	(96.8% w/w)
	Calculation: 4.19 at pH 4 to 7 3.5 at pH 8 2.5 at pH 9	
Hydrolytic stability (DT_{50}) (state pH and temperature)	[^{14}C-phenyl] Fluazinam (2.33 GBq mmol^{-1} 100% radiopurity) DT_{50} (25 °C): stable at pH 4 DT_{50} (25 °C): 4.5 d at pH 7 DT_{50} (25 °C): 3.5 d at pH 9 [^{14}C-pyridyl] Fluazinam (2.37 GBq mmol^{-1} 97.7% radiopurity) DT_{50} (25 °C): stable at pH 4 DT_{50} (25 °C): 2.7 d at pH 7 DT_{50} (25 °C): 3.9 d at pH 9	
Dissociation constant (state purity)	pK_A = 7.34 (20 ± 1 °C)	(99.9% w/w)
UV/VIS absorption (max.) (if absorption > 290 nm	c = 4.66 x 10^{-5} mol/L	(99.8% w/w)

state ε at wavelength) (state purity, pH)	Solvent	$\lambda_{max\ [nm]}$	ε_{max} [$L \cdot mol^{-1} \cdot cm^{-1}$]
	MeOH/HCl 90/10 (0.1 N) v/v	238	21900
	MeOH	238	21200
	MeOH/NaOH 90/10 (0.1 N) v/v	260 341 479	18100 20100 3710
	ε above 290 nm in alkaline solution > 10 Data requirement as the spectra show in neutral and acidic media additional absorbance at approx. 340 nm, which is not reported		
Photostability (DT_{50}) (aqueous, sunlight, state pH)	[^{14}C-phenyl] IKF-1216 (57.3 mCi/ mmol, >99%) [^{14}C-pyridyl] IKF-1216 (66.2 mCi/ mmol, >99%) DT_{50} = 2.5 days in sterile buffer (pH 5 ± 0.05) for both labels at 25 ± 1 °C		
Quantum yield of direct phototransformation in water at Σ > 290 nm	$\Phi = 5.1 \times 10^{-5}$ (pH 5 buffer) $\Phi = 1.7 \times 10^{-5}$ (pH 6 distilled water) $\Phi = 2.1 \times 10^{-6}$ (pH 9 buffer) in molecules degraded per Einstein^{-}		
Flammability	Not highly flammable (96.7% w/w)		
Explosive properties	No explosive properties (97.8% w/w)		
Oxidising properties (state purity)	Data requirement		

Identity, Physical and Chemical Properties, Details of Uses, Further Information

Summary of representative uses evaluated (*Fluazinam*)

Crop and/ or situation	Member State or Country	Product name	F G or I	Pests or Group of pests controlled	Preparation		Application				Application rate per treatment			PHI (days)	Remarks:
					Type	Conc. of as	method kind	growth stage & season	number min/ max	interval between applications (min)	g as/hL (l)	water L/ha	g as/ha (l)		
(a)			(b)	l	(d-f)	(i)	(f-h)	(j)	(k)		min – max	min – max	min – max	(m)	
Potatoes	Europe	Fluazinam 500SC	F	*Phytophtora infestans* (late blight and tuber blight)	SC	500 g/L	Field boom sprayer with hydraulic boom and nozzles	first application when warning systems forecast indicates significant disease attack last treatment BBCH 95-97	10	7 to 10 day intervals depending on the disease pressure	40 – 100	200 – 500	max. 200	7	

(a)	For crops, the EU and Codex classifications (both) should be taken into account; where relevant, the use situation should be described (*e.g.* fumigation of a structure)	(i)	g/kg or g/L. Normally the rate should be given for the active substance (according to ISO) and not for the variant in order to compare the rate for same active substances used in different variants (e.g. fluoroxypyr). **Certain cases, where only one variant is synthesised, it is more appropriate to give the rate for the variant (e.g. benthiavalicarb-isopropyl).**
(b)	Outdoor or field use (F), greenhouse application (G) or indoor application (I)	(j)	Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
l	*e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds	(k)	Indicate the minimum and maximum number of application possible under practical conditions of use
(d)	*e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)	(l)	The values should be given in g or kg whatever gives the more manageable number (e.g. 200 kg/ha instead of 200 000 g/ha or 12.5 g/ha instead of 0.0125 kg/ha
(e)	GCPF Codes – GIFAP Technical Monograph No 2, 1989	(m)	PHI – minimum pre-harvest interval
(f)	All abbreviations used must be explained		
(g)	Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench		
(h)	Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plant- type of equipment used must be indicated		

Chapter: Methods of analysis

Analytical methods for the active substance (Annex IIA, point 4.1)

Technical as (analytical technique)	HPLC-UV
Impurities in technical as (analytical technique)	HPLC-UV
Plant protection product (analytical technique)	HPLC-UV

Analytical methods for residues (Annex IIA, point 4.2)

Food/feed of plant origin (analytical technique and LOQ for methods for monitoring purposes)	GC-ECD LOQ = 0.01 mg/kg (potato, grape and wine)
Food/feed of animal origin (analytical technique and LOQ for methods for monitoring purposes)	No residue definition is proposed therefore no analytical method is required
Soil (analytical technique and LOQ)	GC-ECD LOQ = 0.05 mg/kg (Fluazinam) HPLC-UV LOQ = 0.01 mg/kg (HYPA)
Water (analytical technique and LOQ)	Drinking water: GC-ECD LOQ = 0.1 µg/L Surface water: HPLC-UV LOQ = 10.0 µg/L
Air (analytical technique and LOQ)	UV-Vis Method is insufficiently validated (data requirement)
Body fluids and tissues (analytical technique and LOQ)	Tissues: GC-ECD Method is insufficiently validated (data requirement) Body fluids: (Fluazinam is classified as toxic) No method has been submitted (data requirement)

Classification and proposed labelling with regard to physical and chemical data (Annex IIA, point 10)

	RMS/EPCO proposal	ECB decision
Active substance or variant	RMS: none	

Chapter: Impact on Human and Animal Health

Absorption, distribution, excretion and metabolism in mammals (Annex IIA, point 5.1)	
Rate and extent of absorption:	30 % - 40 % absorbed based on excretion rates in bile and urine (rat studies, 0.5 and 50 mg fluazinam/kg bw/d)
Distribution:	Highest levels found in liver
Potential for accumulation:	No evidence for accumulation
Rate and extent of excretion:	Rapid, mainly via feces (> 84 % within 24 h, > 93 % after 7 days)
Metabolism in animals	Almost completely metabolized by hydroxylation, followed by conjugation
Toxicologically significant compounds (animals, plants and environment)	Parent compound and Impurities 5 and 6

Acute toxicity (Annex IIA, point 5.2)		
Rat LD_{50} oral	$\geq$ 4100 mg/kg bw	
Rat LD_{50} dermal	> 2000 mg/kg bw	
Rat LC_{50} inhalation	0.46 mg/l air /4h	**T, R 23**
Skin irritation	mildly irritating	
Eye irritation	severely irritating	**Xi, R 41**
Skin sensitisation	Sensitising (M & K, Buehler)	**Xi, R 43**

Short term toxicity (Annex IIA, point 5.3)	
Target / critical effect	reduced body weight gain, histopathological changes in the liver (rat, mouse and dog), histopathological changes in the stomach (dog)
Lowest relevant oral NOAEL	52 weeks dog 1 mg/kg bw/d
Lowest relevant dermal NOAEL	21 days rat, NOAEL could not be determined
Lowest relevant inhalation NOAEL	No data – not required

Genotoxicity (Annex IIA, point 5.4)	
	No genotoxic potential

Long term toxicity and carcinogenicity (Annex IIA, point 5.5)	
Target/critical effect	liver weight ↑; histopathological changes in the liver
Lowest relevant NOAEL	104 weeks mouse: 10 ppm (1.12 mg/kg bw/d males, 1.16 mg/kg bw/d females)

Carcinogenicity	No carcinogenic potential

Reproductive toxicity (Annex IIA, point 5.6)	
Reproduction target / critical effect	Parental: body weight and body weight gain ↓; relative liver weight ↑ gestation length ↑; implantation sites and litter sizes ↓
Lowest relevant reproductive, parental NOAEL	20 ppm (1 mg/kg bw/d males, 1.4 mg/kg bw/d females)
Lowest relevant reproductive, offspring NOAEL	20 ppm (1 mg/kg bw/d males, 1.4 mg/kg bw/d females)
Developmental target / critical effect	rabbits: postimplantation loss↑, abortion ↑, ossification incomplete; rats: fetal and placental weight ↓, gross morphological fetal abnormalities at maternal toxic doses **Xn, R 63**
Lowest relevant developmental NOAEL	Rabbit: 2 mg/kg bw/d

Neurotoxicity (Annex IIA, point 5.7)	
Acute neurotoxicity target / critical effect	locomotor activity ↓
Lowest relevant NOAEL	50 mg/kg bw
Repeated neurotoxicity target / critical effect (13 weeks rat)	body weight gain ↓
Lowest relevant NOAEL	69 mg/kg bw (neurotoxic), 21 mg/kg bw (systemic)

Other toxicological studies (Annex IIA, point 5.8)	
Metabolites	G-450, HYPA: more toxic than fluazinam after oral administration. LD_{50} oral mouse 331 mg/kg bw 1. Ames-test: slight reverse mutagenicity against S. typhimurium TA98 without S-9 mix. 2. Ames-test: no evidence of mutagenic activity, either in the presence or absence of metabolic activation. Micronucleus test: negative Metabolite G-525, MAPA: low acute oral toxicity with a LD_{50} > 5000 mg/kg bw in mice. Bacterial reverse mutation test: negative
Impurities	Impurity G-624: low acute oral toxicity with a LD_{50} > 5000 mg/kg bw in rats. B acterial reverse mutation test: reverse mutagenicity against S. typhimurium TA98, TA100, TA1535 and TA1537 with and without S-9 mix and against *E. coli* (WP2 uvr A) in the absence of S-9 mix. However, G-624 is included in toxicity studies with the active ingredient. There was no potential of genotoxicity seen with fluazinam technical, so no further studies with G-624 are required. Impurity-5: neurotoxic effect with a non-linear dose-response for the production of white matter vacuolation in the brain in rats, mice and dogs with a threshold, below which no white matter vacuolation occurs, at approximately 0.1 mg/kg bw/d of Impurity-5.

Medical data (Annex IIA, point 5.9)	
	Studies on worker exposure indicate allergic contact dermatitis

Summary (Annex IIA, point 5.10)	**Value**	**Study**	**Safety factor**
ADI	0.01 mg/kg bw/d	dog, 52-week study	100
AOEL	0.0035 mg/kg bw/d	dog, 52-week study	100 (35%*)
ArfD (acute reference dose)	0.02 mg/kg bw/d	rabbit, developmental study	100

¬ Correction for oral absorption

Dermal absorption (Annex IIIA, point 7.3)	
Product information: Fluazinam 500 SC, 50 % of a.s.	Concentrate: 1.5% Spray dilutions: 7% Rat *in vivo* and comparative *in vitro* (human/rat skin)

Acceptable exposure scenarios (including method of calculation)	
Operator	Acceptable with PPE (German model, tractor application 13 % of AOEL)
Workers	Acceptable for proposed uses with PPE 18 % of AOEL
Bystanders	Acceptable for proposed uses (6.2 % of AOEL)

Classification and proposed labelling with regard to toxicological data (Annex IIA, point 10)

Active substance	T, R 23; Xi; R 41, R43; R 63
Preparation	Xn, R 63; Xi; R43

Chapter: Residues

Metabolism in plants (Annex IIA, point 6.1 and 6.7, Annex IIIA, point 8.1 and 8.6)

Plant groups covered	Root vegetables (potatoes) pulses/oilseeds (peanuts) fruits (grapes, apples)
Rotational crops	Lettuce, carrots, barley
Metabolism in rotational crops similar to metabolism in primary crops	To a large extent comparable; two exceptions: - TFAA occurred in significant amounts in all rotational crops; in primary crops (potatoes, peanut foliage and apples) it was observed in trace amounts only. - Parent fluazinam was not detected in any extract from any rotational crop sample..
Processed commodities	No processing studies required.
Residue pattern in processed commodities similar to residue pattern in raw commodities	No processing studies required.
Plant residue definition for monitoring	Fluazinam
Plant residue definition for risk assessment	Fluazinam
Conversion factor (monitoring to risk assessment)	None.

Metabolism in livestock (Annex IIA, point 6.2 and 6.7, Annex IIIA, point 8.1 and 8.6)

Animals covered	Lactating goat Laying hen
Time needed to reach a plateau concentration in milk and eggs	Milk: plateau level reached during the run of the study (4 days). Eggs: plateau level not reached during the run of the study (4 days).
Animal residue definition for monitoring	Not necessary.
Animal residue definition for risk assessment	Not necessary.
Conversion factor (monitoring to risk assessment)	Not necessary.
Metabolism in rat and ruminant similar (yes/no)	Yes.
Fat soluble residue: (yes/no)	Yes (log $P_{O/W}$ = 4.03 at 25 °C), but no accumulation of active substance or metabolites in animal tissues, milk and eggs was observed.

Residues in succeeding crops (Annex IIA, point 6.6, Annex IIIA, point 8.5)

Total radioactive residues declined with the last planting interval; fluazinam was not accumulated by plants after uptake from soil. Parent fluazinam was not detected in any extract from any crop sample. Related residues still retaining the basic fluazinam structural two ring moiety remained below any relevant level in edible parts of the crops. The main part of the radioactivity recovered was found to be TFAA (trifluoro-acetic acid) at a significant level up to 0.27 mg/kg. Fluazinam was not translocated into deeper soil layers but it could be observed that fluazinam or related residues were persistent in the upper soil layer.

Stability of residues (Annex IIA, point 6 introduction, Annex IIIA, point 8 Introduction)

Potato tubers: 26 months

Residues from livestock feeding studies (Annex IIA, point 6.4, Annex IIIA, point 8.3)

	Ruminant:	Poultry:	Pig:
	Conditions of requirement of feeding studies		
Intakes by livestock ≥ 0.1 mg/kg diet (dry weight basis) (yes/no – If yes, specify the level)	no	no	Not required.
Potential for accumulation (yes/no):	no	no	Not required.
Metabolism studies indicate potential level of residues ≥ 0.01 mg/kg in edible tissues	no	no	Not required.
	Feeding studies: <u>not required</u>. Residue levels in matrices : Mean (max) mg/kg		
Muscle Liver Kidney Fat Milk Eggs	Not relevant.		

Summary of critical residues data (Annex IIA, point 6.3, Annex IIIA, point 8.2)

Crop	Northern or Mediterranean Region	Trials results relevant to the representative uses (a)	Recommendation/comments	MRL estimated from trials according to the intended use	HR I	STMR (b)
Potatoes (tubers)	Northern Region	PHI = 7 days: 13 x <0.01	Within the 13 residue trials 8 decline/degradation studies resulted in residues <0.01 mg/kg at PHI = 0.	0.01 *	<0.01	<0.01
Potatoes (tubers)	Southern Region	PHI = 14 – 15 days: 3 x <0.01	Only three trials have been performed in the Southern Region including 6 applications at the critical rate + 25% (250 g/ha). Although the PHI was not at the GAP, the lack of residues even at 0 day PHI intervals observed in the residue decline studies described above as well as the results of the plant metabolism study in potatoes demonstrate that no residues of fluazinam above the LOQ of 0.01 mg/kg in potatoes are expected.	0.01 *	<0.01	<0.01

(a) Numbers of trials in which particular residue levels were reported *e.g.* 3 x <0.01, 1 x 0.01, 6 x 0.02, 1 x 0.04, 1 x 0.08, 2 x 0.1, 2 x 0.15, 1 x 0.17

(b) Supervised Trials Median Residue *i.e.* the median residue level estimated on the basis of supervised trials relating to the representative use

I Highest residue

Consumer risk assessment (Annex IIA, point 6.9, Annex IIIA, point 8.8)

ADI	0.01 mg/kg bw/d		
TMDI (% ADI)	TMDI (European diet; adult of 60 kg): 0.4 % of ADI		
TMDI (% ADI) according to national (to be specified) diets	TMDI (German diet; girl of 13.5 kg body weight): 0.5 % of ADI.		
IEDI (European Diet) (% ADI)	Not relevant.		
NEDI (specify diet) (% ADI)	Not relevant.		
Factors included in IEDI and NEDI	Not relevant.		
ArfD	0.02 mg/kg bw/d		
IESTI (% ArfD)	potatoes	adult aged 16 – 64 years: 1.3 %	Toddlers aged 1 ½ - 4 ½ years: 5.3 %
NESTI (% ArfD) according to national (to be specified) large portion consumption data	Not relevant.		
Factors included in I(N)ESTI	Not relevant.		

Processing factors (Annex IIA, point 6.5, Annex IIIA, point 8.4)

Crop/process/processed crop	Number of studies	Transfer factor
Not necessary.	---	---

[6] See separate example at the beginning of part B, section residues

Proposed MRLs (Annex IIA, point 6.7, Annex IIIA, point 8.6)

Potatoes	0.01* mg fluazinam/kg

Chapter: Fate and Behaviour in the Environment

Route of degradation (aerobic) in soil (Annex IIA, point 7.1.1.1.1)

Mineralization after 100 days	1.2-2.2 % after 90 d, [^{14}C-phenyl]-label (n = 2) 0.4-1.2 % after 90 d, [^{14}C-pyridyl]-label (n = 2) 2.7 % after 120 d, mixture of the two label positions (n=1) Sterile conditions: <0.1 % after 30 d (n = 1, only phenyl label measured)
Non-extractable residues after 100 days	16.7-37.1 % after 90 d, [^{14}C-phenyl]-label (n = 2) 15.8-35.5 % after 90 d, [^{14}C-pyridyl]-label (n = 2) 46.6 % after 120 d, mixture of the two label pos. (n = 1) Sterile conditions: 6.2 % after 30 d (n= 1, only phenyl label measured)
Metabolites requiring further consideration – name and/or code, % of applied (range and maximum)	HYPA [^{14}C-phenyl]-label: 8.2 % (day 14) and 5.9 % (day 7) [^{14}C-pyridyl]-label: 9.3 % (day 180) and 5.6 % (day 14) Mixture of the two label positions: 13.9 % (day 48) Sterile conditions: <0.5 % after 30 d

Route of degradation in soil – Supplemental studies (Annex IIA, point 7.1.1.1.2)

Anaerobic degradation

Mineralization after 100 days	0.8 % after 90 d, [^{14}C-phenyl]-label 0.2 % after 90 d, [^{14}C-pyridyl]-label
Non-extractable residues after 100 days	46.9 % after 90 d, [^{14}C-phenyl]-label 41.6 % after 90 d, [^{14}C-pyridyl]-label
Metabolites that may require further consideration for risk assessment – name and/or code, % of applied (range and maximum)	MAPA [^{14}C-phenyl]-label: 31.2 % (day 14) [^{14}C-pyridyl]-label: 27.4 % (day 14) DAPA [^{14}C-phenyl]-label: 12.0 % (day 90) [^{14}C-pyridyl]-label: 11.6 % (day 90)

Soil photolysis

Metabolites that may require further consideration for risk assessment – name and/or code, % of applied (range and maximum)	[^{14}C-phenyl]-label and [^{14}C-pyridyl]-label: Photolysis significantly increases degradation of fluazinam on soil. Conversion to bound residues even more extensive under light conditions. HYPA as a product of soil metabolism, whereas AMPA slightly higher under light: up to 5 % AR (light)

versus <1 % AR (dark)

Rate of degradation in soil (Annex IIA, point 7.1.1.2, Annex IIIA, point 9.1.1)

Laboratory studies (Labelling at phenyl- or pyridyl-ring of fluazinam possible)

Fluazinam	Aerobic conditions						
Soil type	Applic. Rate	pH	T °C / % MWHC	DT_{50} / DT_{90} (d)	DT_{50} (d) 20°C pF2/10kPa	St. (r^2)	Method of calculation
Sandy loam	1 kg/ha	6.9	20 °C / 40 %	Phenyl: 96 / 320 Pyridyl: 63 /210	n.c.	0.91 0.81	SFO
Sandy loam	5 kg/ha	6.9	20 °C / 40 %	Phenyl: 174 /578 Pyridyl: 171 /568	n.c.	0.62 0.56	SFO
Loamy sand	1 kg/ha	6.4	20 °C/ 40 %	Phenyl: 263 / 873 Pyridyl: 189 / 628	n.c.	0.89 0.95	SFO
Sandy loam	0.74 kg/ha	7.1	20 °C/ 40 %	Mixture: 17 / n.c.	n.c.	0.99	SFO
Sandy soil	0.56 kg/ha	5.4	20 °C/ 40 %	Unlabelled: 62 / n.c.	n.c.	0.96	SFO
Sandy loam	1 kg/ha	6.9	10 °C/ 40 %	Phenyl: 212 Pyridyl: 139	-	-	Arrhenius equ. Q_{10}: 2.2
Geometric mean / arithmetic mean / median DT_{50} of 20 °C and <5 kg/ha samples (both labels): 66 / 95 / 71 days							

HYPA	Aerobic conditions							
Soil type	Applic. Rate	pH	T °C / % MWHC	DT_{50}/DT_{90} (d)	Label position	DT_{50} (d) 20°C pF2/10kPa	St. (r^2)	Method of calculation
Sand	0.16 mg/kg	5.2	20 °C / 40 %	148 / 490	Unlabelled	n.c.	0.99	SFO
Loamy sand	0.16 mg/kg	5.6	20 °C / 40 %	77 / 245	Unlabelled	n.c.	0.96	SFO
Clay loam	0.16 mg/kg	6.2	20 °C / 40 %	54 / 179	Unlabelled	n.c.	0.96	SFO
Geometric mean / arithmetic mean DT_{50}: 85 / 95 days								

n.c. = not calculated

Field studies

Fluazinam (formulated)	Aerobic conditions							
Soil type (inidicate if bare or cropped soil was used).	Location	Application kg ai/ha	pH	Depth (cm)	DT_{50} / DT_{50} NORM 20 °C (d)	DT_{90} (d) *	St. (r^2) DT_{50} / DT_{90}*	Method of calculation DT_{50}
Clay loam (bare soil)	UK	10 x 0.3	6.6	10	35 / 24	193 *	0.88 / 0.89*	SFO / 20 °C norm.
Sandy clay loam (bare)	UK	10 x 0.3	7.5	10	41 / 26	254 *	0.82 / 0.71*	SFO / 20 °C norm.

Loamy sand (bare)	Germany	1 x 1.35	6.1	10	28 / 21	161 *	0.97 / 0.97*	SFO / 20 °C norm.
Sandy loam (bare)	Germany	1 x 1.35	6.1	10	8.3 / 8.4	67 *	0.98 / 0.97*	SFO / 20 °C norm.
Clay (bare soil)	Germany	1 x 1.35	5.3	10	13.4 /13.5	144 *	0.97 / 0.94*	SFO / 20 °C norm.
Clay loam (bare soil)	Germany	1 x 1.35	6.8	10	16 / 13.6	127 *	0.98 / 0.90*	SFO / 20 °C norm.
Geom. Mean / arithmetic mean / median DT_{50}: 20.4 / 23.6 / 22.1 and DT_{50} normalised to 20 °C: 16.4 / 17.6 / 17.2								
HYPA	Aerobic conditions							
Soil type	Location	Depth (cm)	pH	Maximum concentration detected				
Clay loam (bare soil)	UK	10	6.6	0.09 mg/kg (dw)				
Sandy clay loam (bare)	UK	10	7.5	0.09 mg/kg (dw)				
Loamy sand (bare)	Germany	10	6.1	<0.01 mg/kg (dw)				
Sandy loam (bare)	Germany	10	6.1	0.01 mg/kg (dw)				
Clay (bare soil)	Germany	10	5.3	<0.01 mg/kg (dw)				
Clay loam (bare soil)	Germany	10	6.8	0.02 mg/kg (dw)				

¬ DT_{90}: Timme and Frehse best fit

pH dependence (yes / no) (if yes type of dependence)	no
Soil accumulation and plateau concentration	Fluazinam: No accumulation expected HYPA: Calculated environmental plateau concentration after 3 years: 0.107 mg/kg

Soil adsorption/desorption (Annex IIA, point 7.1.2)

Fluazinam							
Soil Type	OC %	Soil pH	Kd	Koc	Kf	Kfoc (mL/g)	1/n
Sand	0.48	6.0	126	26 250	11.12	2 316	0.6204
Loamy sand	2.55	6.0	261	10 245	43.48	1 705	0.6813
Silt loam	1.42	7.7	227	15 986	27.19	1 915	0.6504
Clay loam	2.0	7.1	264	13 237	37.88	1 894	0.6492
Geometric mean / arithmetic mean:					29.9 / 26.6	1 945 / 1 958	0.65 / 0.65
pH dependence:			no				

HYPA							
Soil Type	OC %	Soil pH	Kd	Koc	Kf	Kfoc (mL/g)	1/n
Sandy loam	3.1	7.7	20	640	14	450	Not stated
Sandy loam	1.9	8.1	18	950	13	700	0.84
Loamy sand	1.8	7.9	12	640	8.1	450	Not stated
Coarse sand	0.5	5.7	6.6	1 400	4.3	920	Not stated
Silty clay loam	1.5	5.0	35	2 400	19	1 300	0.75
Sandy loam	1.6	4.7	51	3 200	26	1 700	Not stated
Geometric mean / arithmetic mean / median:					14 / 12 / 13.5	813 / 920 / 810	
pH dependence:			in acidic soils higher Kfoc were observed				

Mobility in soil (Annex IIA, point 7.1.3, Annex IIIA, point 9.1.2)

Column leaching	Fluazinam formulated (SC): ¬ soils: sand, loamy sand, sandy loam Application rate: 750 g ai/ha Elution (mm): 200 mm Time period (d): 2 d
	Leachate: residues of fluazinam in the leachates below the LOD (i.e. <2 µg/L)
Aged residues leaching	Not submitted, not required
Lysimeter/ field leaching studies	Not submitted, not required

PEC (soil) (Annex IIIA, point 9.1.3)

Fluazinam	DT_{50} (d): 40.8 days (Worst case from field studies)
Method of calculation	Kinetics: 1st order
Application data	Crop: potatoes Depth of soil layer: 5 cm 50 % and 80 % plant interception Number of applications: 10 Interval (d): 7 Application rates: 200 g as/ha

$PEC_{(s)}$ (mg/kg)		Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial (after the last application)		0.133		0.540	
Short term	24h	0.131	0.132	0.531	0.536
	2d	0.129	0.131	0.522	0.531
	4d	0.125	0.129	0.505	0.522
Long term	7d	0.118	0.126	0.480	0.509
	21d	0.093	0.112	0.378	0.454
	28d	0.083	0.106	0.336	0.430
	50d	0.057	0.090	0.231	0.364
	100d	0.024	0.064	0.099	0.260
Plateau concentration		Not applicable			

HYPA		Molecular weight relative to the parent: 0.960			
Method of calculation		DT_{50} (d): 148 (Worst case from laboratory studies, no moisture correction) Kinetics: SFO			
Application data		Application rate assumed: 10 x 200 g as/ha (assumed HYPA is formed at a maximum of 13.9 % of the applied dose)			
$PEC_{(s)}$ (mg/kg)		Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial (after last application)		0.018		0.114	
Short term	24h	0.018	0.018	0.113	0.114
	2d	0.018	0.018	0.113	0.113
	4d	0.017	0.018	0.112	0.113
Long term	7d	0.017	0.018	0.110	0.112
	28d	0.016	0.017	0.100	0.107
	50d	0.014	0.016	0.090	0.102
	100d	0.011	0.014	0.071	0.091
Plateau concentration		0.107 mg/kg after 3 yr			

Route and rate of degradation in water (Annex IIA, point 7.2.1)

Hydrolytic degradation of the active substance and metabolites > 10%.	pH 4: stable (25 °C)
	Fluazinam: DT_{50} pH 7: (25 °C) 1st order: Phenyl-label: 4.5 d r^2=0.970 Pyridyl-label: 2.7 d r^2=0.996 CAPA: Phenyl-label: 92.3 % AR (day 29 = study termination) Pyridyl-label: 95.1 % AR (day 29 = study termination)
	Fluazinam: DT_{50} pH 9: (25 °C) 1st order: Phenyl-label: 3.5 d r^2=0.997 Pyridyl-label: 3.9 d r^2=0.998 CAPA: Phenyl-label: 94.0 % AR (day 29 = study termination) Pyridyl-label: 102.6 % AR (day 29 = study termination)
Photolytic degradation of active substance and metabolites above 10%	Fluazinam: DT_{50}: (25 °C) Light: 2.5 d for both label positions (linear regression, r^2=0.977-0.994) Dark: no significant degradation G-504: Phenyl-label: 17.1 % AR (day 10) Pyridyl-label: 14.0 % AR (day 7)
Quantum yield of direct phototransformation in water at Σ > 290 nm	1.7×10^{-5} mol · Einstein $^{-1}$
Readily biodegradable (yes/no)	Not ready biodegradable

Degradation in water / sediment

Parent	Phenyl: Max. in water 73.7 % after 0 hours ("Virginia") and 72.5 % after 0 hours ("Emperor") Pyridyl: Max. in water 65.3 % after 6 hours ("Virginia") and 63.5 % after 6 hours ("Emperor") Phenyl: Max. in sediment 34.7 % after 48 hrs ("Virginia") and 33.8 % after 24 hrs ("Emperor") Pyridyl: Max. in sediment 17.0 % after 0 hrs ("Virginia") and 31.5 % after 48 hrs ("Emperor")											
Water / sediment system	pH water	pH sed	% C_{org}	T °C	DT_{50} / DT_{90} whole sys. (days)	r^2	DT_{50} / DT_{90} water (days)	r^2	DT_{50} / DT_{90} sediment (days)	r^2	Method of calculation	
"Virginia Water"	6.9	6.6	3.3	20	Mean both labels: 2.9 / 32 ***** RMS: Phenyl: 3.3 / 10.9 Pyridyl: 2.9 / 9.7	 0.68 0.99 0.98	RMS: Phenyl: 1.93 / 6.41 Pyridyl: 2.85 / 9.47	 0.97 0.99	Mean both labels: DT_{50} 3.0 RMS: Phenyl: 2.42 / 8.03 Pyridyl: 3.35 / 11.1	 0.91 0.97 0.94	Single 1st order kinetics	
"Emperor Lake"	5.6	5.8	4.3	20	Mean both labels: 3.2 / 35.4 ***** RMS: Phenyl: 5.2 / 17.4 Pyridyl: 6.2 / 20.6	 0.96 0.97 0.98	RMS Phenyl: 1.84 / 6.12 Pyridyl: 4.25 / 14.1	 0.94 0.98	Mean both labels: DT_{50} 12.1 RMS: Phenyl: 6.41 / 21.3 Pyridyl: 9.5 / 31.5	 0.73 0.76 0.77	Single 1st order kinetics	
Arithmetic mean:					3.1 / 33.7 ***** RMS: Phenyl: 4.3 / 14.2 Pyridyl: 4.6 / 15.2		RMS: Phenyl: 1.9 / 6.3 Pyridyl: 3.5 / 11.8		RMS: Phenyl: 4.4 / 14.7 Pyridyl: 6.4 / 21.3			
***** Timme/Frehse (square root 1st order)!												
AMPA	Phenyl: Max. in water 2.5 % after 14 d ("Virginia") and 0.4 % after 14 d ("Emperor") Pyridyl: Max. in water 1.9 % after 7 d ("Virginia") and 0.9 % after 14 d ("Emperor") Phenyl: Max. in sediment 26.7 % after 14 d ("Virginia") and 18.9 % after 7 d ("Emperor") Pyridyl: Max. in sediment 20.2 % after 2 d ("Virginia") and 12.7 % after 14 d ("Emperor")											
Water / sediment system	pH water	pH sed	% C_{org}	T °C	DT_{50} / DT_{90} whole sys.	R^2	DT_{50} / DT_{90} water	r^2	DT_{50} / DT_{90} sed	r^2	Method of calculation	
"Virginia Water"	6.9	6.6	3.3	20	not possible	-	<1.7 % AR	-	not possible	-	-	
"Emperor Lake"	5.6	5.8	4.3	20	Mean both labels: DT_{50}: 32 Simple linear exponential decay	 0.95	<0.6 % AR	-	Phenyl: 24.0 / 79.8 Pyridyl: 43.7 / 145	 0.95 0.91	Single 1st order kinetics	

Arithmetic mean:			-		-		33.9 / 113		
Mineralization and non extractable residues									
Water / sediment system	pH water	pH sed	% C_{org}	Mineralisation after 100 d (end of the study)	Non-extractable residues in sediment : Max. % after n days		Non-extractable residues in sediment: % after 100 d (end of the study)		
"Virginia Water"	6.9	6.6	3.3	Phenyl: 2 % Pyridyl: 2 %	Phenyl: 59.2 (day 100) Pyridyl: 51.0 (day 100)		Phenyl: 59.2 Pyridyl: 51.0		
"Emperor Lake"	5.6	5.8	4.3	Phenyl: 3.0 % Pyridyl: 1.4 %	Phenyl: 57.8 (day 61) Pyridyl: 52.8 (day 61)		Phenyl: 57.9 Pyridyl: 50.6		

PEC (surface water) and PEC sediment (Annex IIIA, point 9.2.3)

Parent	Molecular weight (g/mol): 465.1
Parameters used in FOCUSsw Step 1 and 2	Water solubility (mg/L): 0.135 DT_{50} soil (d): 16.4 (□esoc. Mean of temperature normalised (20 °C) field half-lives. In accordance with FOCUS SFO) DT_{50} water (d): 3.1 DT_{50} sediment (d): 12.1 Crop interception (%): 50 % average
Parameters used in FOCUSsw Step 3	Vapour pressure : 7.5 x 10^{-3} Pa Koc (L/kg) : 1 985 1/n : 0.9 (FOCUS default)
$FOCUS_{SW}$ Step 4	5 m buffer zone : Reduction of drift : methodology of FOCUS 2003 Reduction of runoff: Stream: 50 % mass loadings 10.4 % runoff volume Pond: 50 % mass loadings 50 % runoff volume Reduction of drainage: none
Application rate	Crop: potatoes Crop interception: 50 % average Number of applications: max. number of applications possible in SWASH: 8, D6 and R2: 6 applications Interval (d): 7 Application rate(s): 200 g as/ha Depth of water body: 30 cm (FOCUS Step 1 + 2) Application window: FOCUS Step 1 + 2: June – September FOCUS Step 3: D3, D4: 14/6 – 1/9 D6: 3/5 – 7/7 (only 1st cultivation period) R1: 8/6 – 25/8 R2: 5/4 – 23/6 R3: 23/5 – 10/8

Main routes of entry | Spray drift (FOCUS Step 1-3)

FOCUS STEP 1 Scenario	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
	0	203		3 620	
	24	152	177	2 970	3 290
	2d	121	157	2 380	2 980
	4d	77.6	127	1 520	2 450
	7d	39.7	96.9	777	1 870
	14d	8.29	58.5	162	1 130
	21d	1.73	40.4	33.9	782
	28d	0.36	30.5	7.10	591
	42d	0.02	20.4	0.31	395

FOCUS STEP 2 Scenario	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
Northern EU	0	6.13		119	
	24	4.87	5.50	112	116
	2d	4.40	5.07	102	111
	4d	3.60	4.53	83.2	102
	7d	2.66	3.92	61.5	89.0
	14d	1.32	2.92	30.4	66.6
	21d	0.65	2.26	15.0	51.7
	28d	0.32	1.81	7.43	41.5
	42d	0.08	1.26	1.82	29.0
Southern EU	0	9.02		175	
	24	7.17	8.10	166	171
	2d	6.49	7.46	150	164
	4d	5.30	6.67	123	150
	7d	3.92	5.78	90.7	131
	14d	1.94	4.30	44.8	98.2
	21d	0.96	3.33	22.2	76.2
	28d	0.42	2.67	11.0	61.1
	42d	0.12	1.86	2.68	42.7

FOCUS STEP 3 Maximum concentrations Scenario	Water body	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
D3	Ditch *	1.045	0.342	0.234	0.228
D4	Pond *	0.042	0.029	0.030	0.030
	Stream *	0.866	0.053	0.038	0.036
D6	Ditch *	1.028	0.205	0.147	0.140
R1	Pond *	0.042	0.029	0.028	0.028
	Pond #	0.058	0.046	0.087	0.086
	Stream *	0.726	0.129	0.127	0.122
R2	Stream *	0.958	0.079	0.057	0.054
R3	Stream *	1.023	0.233	0.165	0.157

¬ maximum concentration derived by employing single application calculations

the only case, where multiple application calculations yielded in a higher max. concentration than single application calculations

FOCUS STEP 4 Maximum concentrations 5 m buffer zone	Water body	PEC_{SW} (µg/L)			
Scenario		Actual maximum	1 d TWA	2 d TWA	28 d TWA
D3	Ditch	0.342*	0.112*	0.057*	0.009*
D4	Pond	0.038*	0.027*	0.020*	0.003
	Stream	0.364*	0.022*	0.011*	0.002
D6	Ditch	0.337*	0.067*	0.034*	0.007
R1	Pond	0.038*	0.027	0.020	0.006
	Stream	0.305*	0.155	0.087	0.021
R2	Stream	0.403*	0.080	0.042	0.007
R3	Stream	0.431*	0.098*	0.049*	0.012

¬ maximum concentration derived by employing single application calculations

FOCUS STEP 4 Maximum concentrations 5 m buffer zone	Water body	PEC_{SED} (µg/kg)			
Scenario		Actual maximum	1 d TWA	2 d TWA	28 d TWA
D3	Ditch	0.077*	0.075*	0.072	0.050
D4	Pond	0.032	0.032	0.032	0.022
	Stream	0.022	0.021	0.020	0.010
D6	Ditch	0.062	0.060	0.057	0.035
R1	Pond	0.055	0.055	0.054	0.040
	Stream	0.500	0.489	0.474	0.318
R2	Stream	0.140	0.135	0.129	0.064
R3	Stream	0.091	0.088	0.083	0.062

¬ maximum concentration derived by employing single application calculations

AMPA

Parameters used in FOCUSsw step 1 and 2

Molecular weight (g/mol): 435.1

Water solubility (mg/L): 0.14

Soil or water metabolite: water metabolite

Koc (L/kg): 920

DT_{50} soil (d): 95 (arithm. Mean of HYPA laboratory half-lives)

DT_{50} water (d): 32

DT_{50} sediment (d): 32

Maximum occurrence observed:

Soil: 2.2 % AR

Water/Sediment: 23.7 % AR

FOCUS STEP 1 Scenario	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
	0h	10.2		56.7	
	24h	7.28	9.03	72.0	64.3
	2d	7.66	8.39	70.4	67.8
	4d	7.33	7.94	67.4	68.3
	7d	6.87	7.58	63.2	67.0
	14d	5.90	6.98	54.3	62.8
	21d	5.07	6.48	46.7	58.7
	28d	4.36	6.03	40.1	54.8
	42d	3.22	5.28	29.6	48.1

FOCUS STEP 2 Scenario	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
Northern EU	0h	1.11		8.92	
	24h	0.97	1.04	8.73	8.83
	2d	0.95	1.00	8.55	8.73
	4d	0.91	0.96	8.18	8.55
	7d	0.85	0.93	7.67	8.28
	14d	0.73	0.86	6.59	7.70
	21d	0.63	0.80	5.66	7.17
	28d	0.54	0.75	4.87	6.69
	42d	0.40	0.65	3.59	5.86
Southern EU	0h	1.35		11.1	
	24h	1.21	1.28	10.9	11.0
	2d	1.18	1.23	10.6	10.9
	4d	1.13	1.19	10.2	10.6
	7d	1.06	1.15	9.53	10.3
	14d	0.91	1.07	8.19	9.57
	21d	0.78	0.99	7.04	8.91
	28d	0.67	0.93	6.05	8.31
	42d	0.50	0.81	4.46	7.28

PEC (ground water) (Annex IIIA, point 9.2.1)

Method of calculation and type of study (*e.g.* modelling, field leaching, lysimeter)	Model(s) used: FOCUS PELMO 3.3.2 Scenarios (list of names): Châteaudun, Hamburg, Jokionen, Kremsmünster, Okehampton, Piacenza, Porto, Sevilla, Thiva Crop: Potatoes FLUAZINAM DT_{50}: 16.4 days (geometric mean of simple 1st order half-lives from field trials normalised to reference soil temperature, 20°C; n = 6) Depth factor for degradation: FOCUS default K_{oc}: 1 985 (arithmetic mean n = 4) 1/n: 0.9 (FOCUS default) HYPA DT_{50}: 95 days (arithmetic mean from 20°C laboratory study, without moisture correction; n = 3) DT_{50}: 105 days* Depth factor for degradation: FOCUS default K_{oc}: 920 (arithmetic mean n = 6) or K_{OC} 630 (arith. Mean excluding two acidic soils with high K_{OC} values, n=4)* 1/n: 0.9 (FOCUS default) Formation in soil: 9.7 % AR (average occurrence in laboratory studies with fluazinam) or Formation factor 0.193 (i.e. 19.3 %)* *Calculations done by the RMS: Results in identical PEC values
Application rate	Application rate: 200 g/ha. No. of applications: 10 Time of application: 4 weeks post emergence Plant uptake: 0 Interception: 50 % at each application

PEC(gw) – FOCUS modelling results (80th percentile annual average concentration at 1m)

For fluazinam and metabolite HYPA: <0.001 µg/L in all of the scenarios

Fate and behaviour in air (Annex IIA, point 7.2.2, Annex III, point 9.3)

Direct photolysis in air	Not studied – no data requested
Quantum yield of direct phototransformation (aqueous solution)	$\Phi = 5.1 \times 10^{-5}$ (pH 5 buffer) $\Phi = 1.7 \times 10^{-5}$ (pH 6 distilled water) $\Phi = 2.1 \times 10^{-6}$ (pH 9 buffer) in molecules degraded per Einstein
Photochemical oxidative degradation in air	DT_{50}: >2 days (Atkinson method)
Volatilisation	from plant surfaces: study not considered valid
	from soil surfaces: study not considered valid

PEC (air)

Method of calculation	According to the phys./chem. Properties (vapour pressure: 7.5 ±8 x 10^{-3} Pa, water solubility: 0.135 mg/L, Henry´s law constant: 25.9 Pa x m^3/mol) fluazinam shows medium to high volatility. Fluazinam is considered stable with regard to photochemical oxidative degradation in air (DT50: >2days, Atkinson method)
PEC	
Maximum concentration	No harmonised method available to calculate PECair

Residues requiring further assessment

Environmental occurring metabolite requiring further assessment by other disciplines (toxicology and ecotoxicology).	Soil:	fluazinam, HYPA
	Surface Water:	fluazinam, AMPA
	Ground water:	fluazinam
	Air:	fluazinam

Monitoring data, if available (Annex IIA, point 7.4)

Soil (indicate location and type of study)	None available – not requested
Surface water (indicate location and type of study)	None available – not requested
Ground water (indicate location and type of study)	None available – not requested
Air (indicate location and type of study)	Data should be reported if available

Points pertinent to the classification and proposed labelling with regard to fate and behaviour data

R 53 Not readily biodegradable

Chapter: Ecotoxicology

Effects on terrestrial vertebrates (Annex IIA, point 8.1, Annex IIIA, points 10.1 and 10.3)

Species	Test substance	Time scale	Endpoint (mg/kg bw/d)	Endpoint (mg/kg feed)
Birds				
Colinus virginianus	a.s.	Acute	1782	-
Anas platyrhynchus	a.s.	Short-term	> 1230	> 10600
Colinus virginianus	a.s.	Long-term	60.4	500
Mammals				
Rattus norvegicus, female	a.s.	Acute	4100	-
Rattus norvegicus	Fluazinam 500 SC	Acute	> 2000	-
Rattus norvegicus, male	a.s.	Long-term	5	100
Additional higher tier studies				
not relevant				

Toxicity/exposure ratios for terrestrial vertebrates (Annex IIIA, points 10.1 and 10.3)

potatoes 10 x 0.2 kg a.s./ha

Indicator species/Category	Time scale	ETE	TER	Annex VI Trigger
Tier 1 (Birds)				
medium herbivorous bird	Acute	26.5	67	10
	Short-term	15.7	> 78	10
	Long-term	8.4	7.2	5
insectivorous bird	Acute	10.8	165	10
	Short-term	6.0	> 205	10
	Long-term	6.0	10	5
earthworm-eating bird	Long-term	1.4	44	5
fish-eating bird	Long-term	9.2	6.5[1]	5
Tier 1 (Mammals)				
medium herbivorous mammal	Acute	16	421	10
	Long-term	3	1.6*	5
insectivorous mammal	Acute	2	2324	10
	Long-term	0.6	7.8	5
earthworm-eating mammal	Long-term	1.8	2.9[2]	5
fish-eating mammal	Long-term	0.14	35[3]	5

* as potato foliage is unpalatable to mammals, this scenario is considered not relevant

[1] based on FOCUS step 1 PEC

[2] refined with a weight-of-evidence approach (rapid metabolism and excretion, PT<1)

[3] based on FOCUS step 2 PEC

Toxicity data for aquatic species (most sensitive species of each group) (Annex IIA, point 8.2, Annex IIIA, point 10.2)

Group	Test substance	Time-scale (Test type)	Endpoint	Toxicity[a)] (mg/L)
Laboratory tests				
Fish				
Oncorhynchus mykiss	fluazinam	96 hr (flow-through)	Mortality, LC50	0.036 (mm)
Pimephales promelas (Full life cycle study)	fluazinam	278 d (flow through)	F_0 reproduction and F_0 growth	0.0029 (mm)
Oncorhynchus mykiss	Fluazinam 500SC	96 hr (flow-through)	Mortality, LC50	0.160 (mm) (0.0611 mg as/L)
Brachydanio rerio	AMPA	96 hr (static)	Mortality, LC50	> 0.09 (mm)
Aquatic invertebrate				
Daphnia magna	fluazinam	48 h (flow through)	Immobility, EC50	0.220 (mm)
Daphnia magna	fluazinam	21 d (static)	Growth, NOEC	0.0125 (nom)
Daphnia magna	Fluazinam 500SC	48 h (static)	Immobility, EC50	0.310 (nom) (0.119 mg as/L)
Daphnia magna	AMPA	48 h (static)	Immobility, EC50	> 0.260 (mm)
Sediment dwelling organisms				
Chironomus riparius	fluazinam	28 d (static)	Emergence, NOEC	0.00625 (im)
Algae				
Pseudokirch subcap.	Fluazinam	72 h (static)	Biomass: E_bC50 Growth rate: E_rC50	0.0160 (mm) > 0.020 (mm)
Pseudokirch subcap.	Fluazinam 500SC	72 h (static)	Biomass: E_bC50 Growth rate: E_rC50	1.4 (mm) (0.53 mg as/L) > 5.7 (mm) (> 2.2 mg as/L)
Scenedesmus subspicatus	AMPA	72 h (static)	Biomass: E_bC50 Growth rate: E_rC50	≥ 0.240 (mm) ≥ 0.240 (mm)
Microcosm or mesocosm tests				
Indoor microcosm study	Shirlan®	12 w (static)	NOEAC zooplankton community	0.01 mg as/L (nom)

¬ concentration based on nominal (nom), mean measured (mm), initial measured (im) concentrations.

Toxicity/exposure ratios for the most sensitive aquatic organisms (Annex IIIA, point 10.2)

FOCUS Step1
Potatoes (10 x 200 g a.s./ha, spring)

Test substance	Organism	Toxicity endpoint (mg a.s./L)	Time scale	PECmax (mg/L)	TER	Annex VI Trigger
fluazinam	Fish	0.036	Acute	0.203	0.18	10[a)]
fluazinam	Fish	0.0029	Chronic	0.203	0.014	10
fluazinam	Aquatic invertebrates	0.220	Acute	0.203	1.08	100
fluazinam	Aquatic invertebrates	0.0125	Chronic	0.203	0.062	10
fluazinam	Algae	0.160 > 0.220	Chronic	0.203	0.8 > 1.1	10
fluazinam	Sediment-dwelling organisms	0.00625	Chronic	0.203	0.031	10
AMPA	Fish	> 0.09	Acute	0.0102	>8.8	100
AMPA	Aquatic invertebrates	> 0.26	Acute	0.0102	>25.5	100
AMPA	Algae	> 0.24	Acute	0.0102	>23.5	10
Fluazinam 500 SC	Fish	0.0611	Acute	0.203	0.30	100
Fluazinam 500 SC	Aquatic invertebrates	0.119	Acute	0.203	0.59	100
Fluazinam 500 SC	Algae	0.53/> 2.2	Acute	0.203	2.6/11	10
Shirlan®	Indoor microcosm Zooplankton	0.01	Chronic	0.203	0.5	5[b)]

a) Five fish species were tested, therefore the TER was lowered according HARAP guidance document (1999)

b) Regarding the uncertainties of test conditions safety factor should not be lower than 5

FOCUS Step 2

Potatoes (10 x 200 g a.s./ha, spring), Southern Europe

Test substance	Organism	Toxicity endpoint (mg a.s./L)	Time scale	PECmax (mg/L)	TER	Annex VI Trigger
fluazinam	Fish	0.036	Acute	0.00902	3.99	10[a]
fluazinam	Fish	0.0029	Chronic	0.00902	0.062	10
fluazinam	Aquatic invertebrates	0.220	Acute	0.00902	21.1	100
fluazinam	Aquatic invertebrates	0.0125	Chronic	0.00902	1.4	10
fluazinam	Algae	0.160 > 0.220	Chronic	0.00902	17 24	10

Ecotoxicology

Test substance	Organism	Toxicity endpoint (mg a.s./L)	Time scale	PECmax (mg/L)	TER	Annex VI Trigger
fluazinam	Sediment-dwelling organisms	0.00625	Chronic	0.00902	0.7	10
AMPA	Fish	> 0.09	Acute	0.00135	>67	100
AMPA	Aquatic invertebrates	> 0.26	Acute	0.00135	>193	100
AMPA	Algae	> 0.24	Acute	0.00135	>178	10
Fluazinam 500 SC	Fish	0.0611	Acute	0.00902	6.8	100
Fluazinam 500 SC	Aquatic invertebrates	0.119	Acute	0.00902	13.2	100
Fluazinam 500 SC	Algae	0.53 > 2.2	Acute	0.00902	59 241	10
Shirlan®	Indoor microcosm Zooplankton	0.01	Chronic	0.00902	1.1	5[b)]

[a)] Five fish species were tested, therefore the TER was lowered according HARAP guidance document (1999)

[b)] Regarding the uncertainties of test conditions safety factor should not be lower than 5

Refined aquatic risk assessment using higher tier FOCUS modelling.

FOCUS Step 3
Potatoes (10 x 200 g a.s./ha, spring)

Test substance	Scenario	Water body type	Test organism	Time scale	Toxicity endpoint (µg/L)	PEC (µg/L)	TER	Annex VI trigger
Fluazinam	D3	ditch	Fish	Acute	36	1.045	35	10[a]
	D4	pond				0.042	857	10[a]
	D4	stream				0.866	42	10[a]
	D6	ditch				1.028	35	10[a]
	R1	pond				0.058	621	10[a]
	R1	stream				0.726	50	10[a]
	R2	stream				0.958	38	10[a]
	R3	stream				1.023	35	10[a]

Test substance	Scenario	Water body type	Test organism	Time scale	Toxicity endpoint (µg/L)	PEC (µg/L)	TER	Annex VI trigger
Fluazinam	D3	ditch	Fish	chronic	2.9	1.045	2.78	10
	D4	pond				0.042	96.1	10
	D4	stream				0.866	3.35	10
	D6	ditch				1.028	2.82	10
	R1	pond				0.058	50.0	10
	R1	stream				0.726	3.99	10
	R2	stream				0.958	3.03	10
	R3	stream				1.023	2.83	10
Fluazinam 500 SC	D3	ditch	Aquatic invertebrates	Acute	119	1.045	114	100
	D4	pond				0.042	2833	100
	D4	stream				0.866	137	100
	D6	ditch				1.028	116	100
	R1	pond				0.058	2052	100
	R1	stream				0.726	164	100
	R2	stream				0.958	124	100
	R3	stream				1.023	116	100
Fluazinam	D3	ditch	Aquatic invertebrates	Chronic	12.5	1.045	12	10
	D4	pond				0.042	298	10
	D4	stream				0.866	14	10
	D6	ditch				1.028	12	10
	R1	pond				0.058	216	10
	R1	stream				0.726	17	10
	R2	stream				0.958	13	10
	R3	stream				1.023	12	10
Fluazinam	D3	ditch	Sediment dwelling organism	Chronic	6.25	1.045	6.0	10
	D4	pond				0.042	148.8	10
	D4	stream				0.866	7.2	10
	D6	ditch				1.028	6.1	10
	R1	pond				0.058	107.8	10
	R1	stream				0.726	8.6	10
	R2	stream				0.958	6.5	10
	R3	stream				1.023	6.1	10

Test substance	Scenario	Water body type	Test organism	Time scale	Toxicity endpoint (µg/L)	PEC (µg/L)	TER	Annex VI trigger
Shirlan	D3	ditch	Indoor Microcosms Zooplankton	Chronic	10	1.045	9.6	5[b)]
	D4	pond				0.042	238.1	5[b)]
	D4	stream				0.866	11.5	5[b)]
	D6	ditch				1.028	9.7	5[b)]
	R1	pond				0.058	172.4	5[b)]
	R1	stream				0.726	13.8	5[b)]
	R2	stream				0.958	10.4	5[b)]
	R3	stream				1.023	9.8	5[b)]

[a)] Five fish species were tested, therefore the TER was lowered according HARAP guidance document (1999)

[b)] Regarding the uncertainties of test conditions safety factor should not be lower than 5

Refined aquatic risk assessment using higher tier FOCUS modelling.

FOCUS Step 4 (5 m bufferzone)
Potatoes (10 x 200 g a.s./ha, spring)

Test substance	Scenario	Water body type	Test organism	Time scale	Toxicity endpoint (µg/L)	PEC (µg/L)	TER	Annex VI trigger
Fluazinam	D3	ditch	Fish	chronic	2.9	0.342	8.5	10
	D4	pond				0.038	76.3	10
	D4	stream				0.364	8.0	10
	D6	ditch				0.337	8.6	10
	R1	pond				0.038	76.3	10
	R1	stream				0.305	9.5	10
	R2	stream				0.403	7.2	10
	R3	stream				0.431	6.7	10
Fluazinam	D3	ditch	Sediment dwelling organism	Chronic	6.25	0.342	18	10
	D4	pond				0.038	165	10
	D4	stream				0.364	17	10
	D6	ditch				0.337	19	10
	R1	pond				0.038	165	10
	R1	stream				0.305	21	10
	R2	stream				0.403	16	10
	R3	stream				0.431	15	10

Ecotoxicology

Bioconcentration		
	Active substance	
logPow	4.03	
	phenyl label	phyridyl label
Bioconcentration factor (BCFss)	1090*	960*
Annex VI Trigger for the bioconcentration factor	100	100
Clearance time (days) (CT_{50})	6.0 ± 0.4	5.0 ± 0.3
Level of residues (%) in organisms after the 14 day depuration phase	22*	24*

* based on total ^{14}C residues

Effects on honeybees (Annex IIA, point 8.3.1, Annex IIIA, point 10.4)

Test substance	Acute oral toxicity (LD50 µg/bee)	Acute contact toxicity (LD50 µg/bee)
a.s.	> 100	> 200
Fluazinam 500SC	> 101 µg a.s.	no effect after direct overspray at 0.2 % a.s.
Field or semi-field tests		
not required		

Hazard quotients for honey bees (Annex IIIA, point 10.4)

potatoes 10 x 0.2 kg a.s./ha

Test substance	Route	Hazard quotient[1]	Annex VI Trigger
a.s.	contact	< 3.5	50
a.s.	oral	< 7	50

[1] exposure calculated as single rate x MAF

Effects on other arthropod species (Annex IIA, point 8.3.2, Annex IIIA, point 10.5)
Laboratory tests with standard sensitive species

Species	Test Substance	Endpoint	Effect (LR_{50} g/ha[1])
Typhlodromus pyri	no lab study		
Aphidius rhopalosiphi	Fluazinam 500 EC	Mortality	> 200 g a.s./ha

potatoes 10 x 0.2 kg a.s./ha

Test substance	Species	Effect (LR_{50} g/ha)	HQ in-field	HQ off-field[1]	Trigger
Fluazinam 500 EC	*Aphidius rhopalosiphi*	> 200 g a.s.	< 3.5	< 0.11	2

[1] 1 m distance / 1.52 % drift rate

Ecotoxicology

Further laboratory and extended laboratory studies

Species	Life stage	Test substance, substrate and duration	Dose (g/ha)[1]	Endpoint	% adverse effect	Trigger
Aphidius rhopalosiphi	adult	Fluazinam 500 EC, potato leaves, 48 h	10 x 200 g a.s. (7-10 d)	mortality fecundity	3 / 78.1 / 40.6[a] -38 / -66 / -51	50 %
Typhlodromus pyri	proto-nymphs	Fluazinam 500 EC, potato leaves, 7 d	10 x 200 g a.s. (7-10 d)	mortality fecundity	- 5.5 / 6.1 / 0.3[a] 2.8 / -4.3 / -1[a]	50 %
Chrysoperla carnea	larvae - adult	Fluazinam 500 EC, potato leaves, 7 d	10 x 200 g a.s. (7-10 d)	mortality fecundity	18.8 / 11.8 / 15.2[a] 4.9 / -19 / -5.7[a]	50 %
Pterostichus melanarius	adults	Fluazinam 500 EC, overspray +soil appl., 6 d	200 g a.s.	mortality feeding act.	10 0	50 %
		Fluazinam 500 EC,soil appl.,6 d	2000 g a.s.	mortality feeding act.	0 0	50 %
lycosid spider	adults	Fluazinam 500 EC, overspray +soil appl., 6 d	200 g a.s.	mortality feeding act.	3.3 0	50 %
		Fluazinam 500 EC,soil appl.,6 d	2000 g a.s.	mortality feeding act.	0 0	50 %

[1] initial residues
[a] underside / upperside / both sides of leaves

Field or semi-field tests
not required

Effects on earthworms, other soil macro-organisms and soil micro-organisms (Annex IIA points 8.4 and 8.5. Annex IIIA, points, 10.6 and 10.7)

Test organism	Test substance	Time scale	Endpoint
Earthworms			
Eisenia fetida	Fluazinam	Acute 14 days	LC50 > 1000 mg/kg d.w.soil
Eisenia fetida	Fluazinam 500 SC	Acute 14 days	LC50 > 682 mg a.s./kg d.w.soil
Eisenia andrei	Fluazinam 500 SC	Chronic 28 days	NOEC < 0.35 mg a.s./kg d.w.soil
Eisenia fetida	HYPA	Acute 14 days	LC50 mg > 1000/kg d.w.soil
Collembola			
Folsomia candida	Fluazinam 500 SC	Chronic 28 days	NOEC < 1.57 mg a.s./kg d.w.soil
Folsomia candida	HYPA	Chronic 28 days	NOEC 6.08 mg/kg d.w.soil
Soil micro-organisms			
Nitrogen mineralisation	Fluazinam 500 SC	Chronic 28 days	13.2 % effect at day 28 at 2.27mg a.s./kg d.w.soil

Ecotoxicology

Test organism	Test substance	Time scale	Endpoint
Nitrogen mineralisation	HYPA	Chronic 28 days	8.41 % effect at day 28 at 0.38 mg a.s./kg d.w.soil
Carbon mineralisation	Fluazinam 500 SC	Chronic 28 days	2.89 % effect at day 28 at 2.27mg a.s./kg d.w.soil
Carbon mineralisation	HYPA	Chronic 28 days	14 % effect at day 28 at 0.38 mg a.s./kg d.w.soil
Field studies			
Lumbricus terrestis, Allobophora rosea, Stachellius mammalis	Fluazinam 500 SC	Chronic 12 month	no effects after application rate of 10 x 200 g a.s./ha (7 days interval) in potatoes

Toxicity/exposure ratios for soil organisms

Potatoes 10 x 200 g a.s./kg (7 days interval)

Test organism	Test substance	Time scale	initial PECs (mg/kg)	TER	TER corr.[1]	Trigger
Eisenia fetida	Fluazinam	Acute	0.54	>1852	>926	10
Eisenia fetida	Fluazinam 500 SC	Acute	0.54	>1263	>632	10
Eisenia andrei	Fluazinam 500 SC	Chronic	0.54	<0.65	<0.325	5
Eisenia fetida	HYPA	Acute	0.114	>8772	>4386	10
Collembola	Fluazinam 500 SC	Chronic	0.54	<2.9	<1.45	5
Collembola	HYPA	chronic	0.114	53	26.5	5

[1] corrected by a factor of 2 due to high Log_{POW} of 4.02 of fluazinam

Effects on non target plants (Annex IIA, point 8.6, Annex IIIA, point 10.8)

Preliminary screening data

10 species tested at 1.5 kg a.s./ha in screening seedling emergence and vegetative vigour tests: the only effect > 25 % was a 28 % reduction in biomass fresh weight in cucumber

Laboratory dose response tests

Most sensitive species	Test substance	ER50 (g/ha) vegetative vigour	ER50 (g/ha) emergence	Exposure[1] (g/ha)	TER	Trigger
cucumber	fluazinam techn.	> 1500 g a.s.	> 1500 g a.s.	not relevant		

Additional studies (e.g. semi-field or field studies)

not required

Effects on biological methods for sewage treatment (Annex IIA 8.7)

Test type/organism	endpoint
Activated sludge	EC50: 118 mg a.s./L
Pseudomonas putida	EC50: > 1.53 mg a.s./L

Residues definition (consider all relevant metabolites requiring further assessment from the fate section)

Compartment	Ecotoxicologically relevant residue
soil	fluazinam
water	fluazinam, HYPA (preliminary)
sediment	fluazinam
groundwater	fluazinam

Classification and proposed labelling with regard to ecotoxicological data (Annex IIA, point 10 and Annex IIIA, point 12.3)

	RMS/EPCO proposal
Active substance	R 50/53
Preparation	R 50/53

Level 3

Fluazinam

Proposed Decision with Respect to the Application for Inclusion of the Active Substance in Annex I

3 Proposed decision with respect to the application for inclusion of the active substance in Annex I

3.1 Background to the proposed decision

Concerning physical and chemical properties all studies required by Directive 91/414/EEC are available and were conducted according to Guideline requirements and GLP regulations. Amendments are required in some cases.

Fluazinam acts as a fungicide with activity against fungus from the class of *Oomycetes*, especially against *Phytophthora infestans*, both potato late blight and tuber blight. It works protectively and needs to be applied before the disease attack in a concentration of max. 200 g as/ha.
Fluazinam 500SC is registered in several European countries. A maximum number of 10 applications is recommended, the first treatment against potato late blight should take place when warning systems forecast indicates significant disease attack and the last at growth stage BBCH 95-97 using field boom sprayers with hydraulic boom and nozzles. The typical spray volumes are between 200 to 500 L/ha.

Analytical methodology is available for the determination of the active substance in the technical material as well as in the formulated product. The methods are sufficiently validated.
The analytical method for residues in food/feed of plant origin is successfully validated since the LOQs enable the enforcement of the relevant residue limits (at the time of evaluation).

Methods for the determination of residues in soil and drinking water needs additional confirmatory techniques. In addition a new validation for the determination of residues in air is required the same as for the analytical method (residue) for body fluids and tissues.

The available data on mammalian toxicology, mutagenicity and animal metabolism for the active substance are considered to adequately support the risk evaluation of fluazinam in humans.
Concerning toxicology and metabolism studies required by Directive 91/414/EEC are available and were conducted mainly according to Guideline requirements and GLP regulations.
Fluazinam was found to have a very high acute toxicity potential when tested by the inhalative route. It is minimal irritating to skin and severely irritating to eyes and has sensitising properties. In subchronic and chronic toxicity tests conducted in rats, mice and dogs, the main target organ was the liver. White matter vacuolation in the brain in rats, mice and dogs is not due to fluazinam itself, but rather to a manufactory impurity, called Impurity-5. All vacuolation effects were found to be reversible. There is a non-linear dose-response for the production of white matter vacuolation with a threshold, below which no white matter vacuolation occurs, at approximately 0.1 mg/kg bw/d of Impurity-5.
Further data for fluazinam do not support evidence of genotoxic, carcinogenic and the fertility disturbing properties of the active substance. Gross morphological fetal abnormalities have been observed in one developmental study in rats so according to Annex VI of the EC Council Directive 67/548/EEC, fluazinam should be classified to "category 3 of reproductive substances" and labelled with the risk phrase "R 63 – Possible risk of harm to the unborn child".

For operators the use of fluazinam with regard to the intended uses is acceptable if appropriate PPE is worn (German model, tractor application, 13 % of AOEL).
Worker exposure would be acceptable for the proposed uses if PPE is used (18 % of AOEL).
Short exposure of bystanders outside the treatment areas would be 6.2 % of AOEL.

The theoretical Maximum Daily Intake (TMDI) accounted for 0.4 % of the ADI for an adult of 60 kg bodyweight. The TMDI for a 4 –6- year old child accounted for 0.5 % of the ADI.
The large portion intake for potatoes does not exceed the Acute Reference Dose (ARfD) of 0.02 mg/kg bw/d; it accounted for 1.3 and 5.3 % of the ARfD for adults and toddlers, respectively.

A final evaluation of the residue data is only possible after evaluation of the toxicological relevance of the degradation product TFAA (trifluoro-acetic acid) formed in rotational crops. Depending on the outcome residue definition has to be reconsidered. Provided an inclusion of TFAA in the residue definition for rotational crops, either supervised field trials in succeeding crops or restrictions with regard to plant-back intervals for rotational crops would be appropriate.

The available data on fate and behaviour in the environment and on ecotoxicology are considered to adequately support the risk evaluation of Fluazinam and its metabolites with regard to the environment and non-target organisms. Accumulation of Fluazinam and its metabolites in soil and water is not expected under normal conditions of use. It is unlikely that Fluazinam and its soil metabolites will reach ground water in significant amounts when applied according to intended uses and Good Agricultural Practice. According to its physical/chemical properties Fluazinam has some tendency to volatilise. Fluazinam is considered relatively stable against reaction with OH-radicals in the troposphere.

No unacceptable effects on terrestrial vertebrates (birds and mammals), bees, non-target arthropods and aquatic organism are expected if the plant protection product is used in accordance with good plant protection practice and with regard to the intended use. However, in order to avoid unacceptable impact on aquatic organisms risk mitigation measures (e.g. buffer zones) are necessary to ensure a safe use in potatoes.
No unacceptable risk of Fluazinam and its soil metabolites was identified for earthworms and soil micro-organisms. However, for soil macro-organisms (collembola) an unacceptable risk is identified and a further study (litter bag) is required. Effects on non-target plants are low even at in-crop rates of fluazinam.

3.2 Proposed decision concerning inclusion in Annex I

[redacted]

The information in section 3.2 has been removed upon request by the EU Commission as it relates to risk management recommendations or proposals.

Level 4

Fluazinam

Demand for Further information

4 Further information to permit a decision to be made, or to support a review of the conditions and restrictions associated with the proposed inclusion in Annex I

4.1 Identity (B.1)

Detailed specification of the active substance:

- C.1.2.3 Analytical profile of batches: Weber, H.A. (2003): Report No. 310260.1.019 and Weber, H.A. (2004): Report No. 310260.1.027 the certificate of the GLP authority is missing.
- C.1.2.4 Methods of analysis for the determination of impurities: Lorence, P. J. (1999) Report No. 4039-98-0203-AS-001: % RSD for accuracy is missing

*) Confidential information, see volume 4, annex C.

4.2 Physical and chemical properties (B.2)

Active Substance:

Spectra of the active substance: UV-Vis:

van Rijsbergen, L.M. (2002)(Document 341167): The UV spectra in neutral and acidic media show additional absorbance at approximately 340 nm. The decadic molar extinction must be reported.

Spectra of relevant impurities:

Impurity 5: The UV spectrum shows an additional absorbance maximum at approx. 297 nm, which must be reported.

Impurity 6 is considered relevant, therefore UV/VIS, MS, IR and NMR spectra must be submitted.

Oxidising properties:

A test according to method EEC/A17 is required as the provided statement is not acceptable on all points.

Formulation:

Oxidising properties:

A test according to method EEC/A17 for the active substance is required therefore the situation on oxidising properties for the formulation is unclear.

Storage test:

The pourability of the preparation before and after storage is missing.

According to FAO-WHO specifications the content of relevant impurities (RMS is considering impurities 5 and 6 as relevant) before and after storage must be determined.

4.3 Data on application and further information

No further information requested.

4.4 Classification, packaging and labelling

No further information requested.

4.5 Methods of analysis

Analytical methods for the determination of active ingredient and impurities:

- Lorence, P. J. (1999) Report No. 4039-98-0203-AS-001:
  The RSD of accuracy for the impurities is missing.
- An analytical method for impurity 6, which is considered as relevant by RMS must be provided. If the preparation contains more than one relevant impurity according to SANCO 3030/99, the method must be capable of determining each in the presence of the other and in the presence of the active substance.

Analytical methods for the determination of the active ingredient in the formulation:

- Krainz, A. (2001) Report No 838923:
  Additional data to demonstrate linearity according to SANCO 825/00 should be documented.

Analytical methods (residue) for plants and plant products:

- Specht, W. (1992)
  The applicability (study plan) of a multiresidue method (e.g. according to DFG 19) is reported in German for residues of fluazinam in potatoes. It should be submitted in English and validated according to guidance document SANCO 825/00.
- Wais, A. (2002) Report No. 845972:
  A confirmatory technique is required.
- Brachet, A., Nésa, C. (2002) Report No. A22-02-04:
  The linearity range for the ILV method do not meet the requirements of SANCO 825/00 which should be at least ± 20% of the fortification levels . In this case the fortification level of 0.1 mg/kg is not covered by the linearity range. Clarification is required.
- Schulz H. (1992) Report No. 284670
  In the case that HYPA and MAPA will be covered by the residue definition the submitted method is not valid due to the fact that an insufficient number of samples are taken for the determination of the LOQ and fortification levels, respectively.
- According to Section Residues: in the case that a residue definition is set for TFAA (trifluoroacetic acid), which is included in rotational crops, an analytical method for the determination of residue for typical rotational crops (e.g. leafy vegetables, grain and carrots) must be provided.

Analytical methods (residue) for soil, water, air

Soil:

- A Ryan, J., Sapiets, A. (1992) Report No. ARAM 211:
  A confirmatory technique is required.
- Burke, S., Sapiets, A., Gentle, W. (1993) Report No RAM/218/01:
  A confirmatory technique is required and the correlation coefficient and equation of the calibration graph is missing.

Drinking water:

- Ryan, J., Sapiets, A. (1994) Report No RJ 1576B
  A confirmatory technique is required.

Surface water:

- Due to the fact that the relevant residue limit (NOEC fish) is 2.9 µg/L for fluazinam, a method with an adequate LOQ is required. The submitted method for freshwater (with a LOQ of 0.0954 µg/L, which cannot be verified) is not clear and not validated according to guidance document SANCO 825/00.

Air:

- Ryan, J., Sapiets, A. (1993) Report No RF1529B
  The method is not valid due to the fact that no linearity data are included..

Analytical methods (residue) for body fluids and tissues:

- Kenyon, R. G. (1994) Report No. 6068-94-0088-MD-001
  The method is not valid due to the fact that no linearity data are provided. A confirmatory technique is required.
- Tillkes, M. (1995) Report No. ZEN-9504V
  The method is not valid as insufficient linearity data (one point calibration) are included. No confirmatory method is reported.
- An analytical method for body fluids must be submitted due to Fluazinam is classified as toxic.

4.6 Toxicology and metabolism

No further information requested.

4.7 Residue data

- Annex IIA 6.7: Definition of the residue for rotational crops:
  The concentration of TFAA (trifluoro-acetic acid) reached up to 94.81% of the total radioactivity in extracts of lettuce, up to 82.37% of the total radioactivity in extracts of carrot roots and up to 74.21% of the total radioactivity in extracts of barley grain. As the toxicological relevance of TFAA is not investigated by the corresponding studies in laboratory animals, the relevance of TFAA should be addressed by the notifier. Provided toxicological significance, TFAA (trifluoro acetic acid) has to be included in the residue definition for rotational crops. In this case, supervised field studies in succeeding crops

and should be required. Alternatively restrictions with regard to plant-back intervals for rotational crops would be appropriate.

4.8 Environmental fate and behaviour

- PEC_{SW} – soil metabolite
  The entry into surface water of soil metabolite HYPA via run off and drainage has to be addressed.

4.9 Ecotoxicology

- Effects on aquatic organisms – risk assessment of metabolites
  The risk of the metabolite HYPA to aquatic organisms has to be addressed.
- Effects on aquatic organisms – bioaccumulation of metabolite
  The bioaccumulation potential of the metabolite AMPA has to be clarified
- Effects on soil non-target macro-organisms (IIA 8.6, IIIA 10.6.2):
  Litter bag study with the formulation (the study was already started in July 2005)