LEVEL 1

Pyraflufen-ethyl

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

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

This monograph is submitted to support the application for the first inclusion of the new active substance pyraflufen-ethyl in Annex I to Directive 91/414/EEC.

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

Not applicable as pyraflufen-ethyl is a new active substance with only one applicant.

1.3 Identity of the active substance (Annex IIA 1)

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

Applicant : Nihon Nohyaku Co., Ltd.
2-5, 1-Chome, Nihonbashi, Chuo-ku
Tokyo 103, Japan

Tel. No. : (81) 3-3274-3383
Tfx. No. : (81) 3-3281-2443

Community address : Nihon Nohyaku London Office
3rd Floor, 8 Cork Street
Mayfair
London W1X 1PB, UK

Contact persons :

Nihon Nohyaku Co., Ltd.		**Rhône-Poulenc Agro**	
Nihon Nohyaku London Office **3rd Floor, 8 Cork Street** **Mayfair** **London W1X 1PB, UK**		**Rhône-Poulenc Agro** **14-20, rue Pierre Baizet** **69009 Lyon, France**	
Hiroshi Suzuki **Assistant Manager**		**P.E.Th. van der Kouwe** **Registration Manager**	
Tel. No. :	**(44) 171-434-0033**	**Tel. No. :**	**(33) 4 72 85 28 39**
Tfx. No. :	**(44) 171-287-1335**	**Tfx. No. :**	**(33) 4 72 85 29 64**

1.3.2 Manufacturer of the active substance (Annex IIA 1.2)

Manufacturer : Ihara Chemical Industry Co., Ltd.
1-4-26, Ikenohara, Taito-ku
Tokyo 110, Japan

Tel. No. : (81) 3-3822-5241

Location of plant : Ihara Chemical Industry Co., Ltd.
Shizuoka Plant
1800, Nakanogo, Fujikawa-cho, Ihara-gun
Shizuoka 421-33, Japan

Contact persons :

Nihon Nohyaku Co., Ltd.	**Rhône-Poulenc Agro**
Nihon Nohyaku London Office **3rd Floor, 8 Cork Street** **Mayfair** **London W1X 1PB, UK**	**Rhône-Poulenc Agro** **14-20, rue Pierre Baizet** **69009 Lyon, France**
Hiroshi Suzuki **Assistant Manager**	**P.E.Th. van der Kouwe** **Registration Manager**
Tel. No. : (44) 171-434-0033 **Tfx. No. : (44) 171-287-1335**	**Tel. No. : (33) 4 72 85 28 39** **Tfx. No. : (33) 4 72 85 29 64**

1.3.3 ISO common name and synonyms (Annex IIA 1.3)

Common name : Pyraflufen-ethyl (ISO-proposed), no synonyms

1.3.4 Chemical name (Annex IIA 1.4)

IUPAC nomenclature : ethyl 2-chloro-5-(4-chloro-5-difluoromethoxy-1-methylpyrazol-3-yl)-4-fluorophenoxyacetate

CA nomenclature : ethyl 2-chloro-5-[4-chloro-(5-difluoromethoxy)-1-methyl-1*H*-pyrazol-3-yl]-4-fluorophenoxyacetate

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

Code number : ET-751

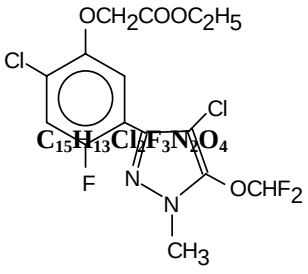
1.3.6 CAS, EEC and CIPAC numbers (Annex IIA 1.6)

CAS number : 129630-19-9
EEC number : not allocated
CIPAC number : not allocated

1.3.7 Molecular formula, molecular mass and structural formula (Annex IIA 1.7)

Molecular formula : $C_{15}H_{13}Cl_2F_3N_2O_4$

Structural formula :



Molecular mass : 413.18

1.3.8 Method or methods of manufacture (Annex IIA 1.8)

Confidential information, see Annex C

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

Minimum purity of pyraflufen-ethyl technical : 956 g/kg (certified limit)

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

Confidential information, see Annex C

1.3.11 Analytical profile of batches (Annex IIA 1.11)

Confidential information, see Annex C

1.4 Identity of the plant protection product MILAN™(Annex IIA 3.1; Annex IIIA 1)

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

Trade name : MILAN™
Code number : EXP 31279A

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

Applicant : Nihon Nohyaku Co., Ltd.
2-5, 1-Chome, Nihonbashi, Chuo-ku
Tokyo 103, Japan

Tel. No. : (81) 3-3274-3383
Tfx. No. : (81) 3-3281-2443

Community address : Nihon Nohyaku London Office
3rd Floor, 8 Cork Street
Mayfair
London W1X 1PB, UK

Contact person : Hiroshi Suzuki
Assistant Manager
Tel. No. : (44) 171-434-0033
Tfx. No. : (44) 171-287-1335

Manufacturer of the preparation : Rhône-Poulenc Agro
14-20, rue Pierre Baizet
69009 Lyon Cedex 09, France

Tel. No. : (33) 4 72 29 25 25 (general)
Tfx. No. : (33) 4 72 29 27 99 (general)

Location of plant : Rhône-Poulenc Agrochimie
1, Avenue Edouard-Herriot
B.P. 442, Limas
69656 Villefranche s/Saone, France

Tel. No. : (33) 4 74 62 76 76 (general)

Contact person : P.E.Th. van der Kouwe
Registration Manager
Tel. No. : (33) 4 72 85 28 39
Tfx. No. : (33) 4 72 85 29 64

Manufacturers of the active substances :

***Pyraflufen-ethyl* : Ihara Chemical Industry Co., Ltd.**
1-4-26, Ikenohara, Taito-ku
Tokyo 110, Japan

***Bifenox* : Rhône-Poulenc**
B.P. 17
38800 Le Pont de Claix, France

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

Preparation type and code : Suspension concentrate (SC)

1.4.4 Function (Annex IIIA 1.6)

Herbicide

1.4.5 Composition of the preparation (Annex IIIA 1.4)

Table 1.4.5-1 : Composition of MILAN™

Component	Content (g/L)	Function
Pyraflufen-ethyl **- pure a.s.** **- TC (average purity 97.9%)**	 **(9)** **9.2**	**Active substance**
Bifenox **- pure a.s.** **- TC (average purity 98%)**	 **(500)** **510**	**Active substance**
Other components	**Confidential information, see Annex C**	

1.5.1 Fields 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)

‘ Pyraflufen-ethyl is a novel inhibitor of protoporphyrinogen IX oxidase. Inhibition of this enzyme in chloroplast causes accumulation of protoporphyrinogen IX, which results in peroxidation of foliar cell membrane lipid under the light and finally cell death.

This herbicidal mode of action of pyraflufen-ethyl is similar to that of other peroxidizing herbicides containing of diphenyl ether moiety. Herbicidal effects of pyraflufen-ethyl are revealed as yellowing and browning in the foliate portion, and then death of whole plant with leaf burn.’

1.5.3 Summary of intended uses (Annex IIA 3.4; Annex IIIA 3.3 to 3.7)

Pyraflufen-ethyl is effective against broad-leaved weeds. The active substance applied in early post-emergence at 13.5 g a.s./ha provides excellent control of important weeds such as *Anthemis arvensis, Lamium purpureum, Sinapis arvensis* and a good suppression of *Matricaria chamomilla, Stellaria media, Veronica persica* and *Viola* spp.

Pyraflufen-ethyl is used in combination with bifenox which provides complement of activity against *Capsella bursa-pastoris, Papaver rhoeas, Veronica* spp and *Viola.* Both straight products present a moderate activity on *Galium aparine*

SUMMARY OF PROPOSED GOOD AGRICULTURAL PRACTICES FOR PESTICIDES USES
(Application on agricultural crops)

Responsible body by reporting : Nihon Nohyaku
Pesticide(s) (Common name) : pyraflufen-ethyl + bifenox
CAS No. : [*129630-19-9], [42576-02-3]*, resp.
Trade name(s) : MILAN®
Main uses : Herbicide

Date :May 1997
Page : 1
Country : The Netherlands, Germany, Belgium & Luxembourg

Crop and/or situation (a)	Member State or Country	F, G or I (b)	Pests or Group of pest controlled (c)	Formulation		Application			Application rate per treatment			PHI (days) (k)	Remarks (l)
				Type (d-f)	Conc. of (i)	Method kind (f-g)	Growth stage (j)	Number min max	kg a.s./hl min max	water l/ha min max	kg a.s./ha min max		
Winter and spring cereals	NL	F	Annual weeds	SC	ET-751: 9 g/l Bifenox: 500 g/l	Conventional spray	3 leaves to end of tillering	1	ET-751: 2.25-2.93 Bifenox: 125-162.5	400	ET-751: 9-11.7 Bifenox: 500-650	NA	Dose: 1-1.3 l/ha
Winter cereals	D	F	Annual weeds	SC	ET-751: 9 g/l Bifenox: 500 g/l	Conventional spray	BBCH 13-29	1	ET-751: 3.38 Bifenox: 1.87	400	ET-751: 13.5 Bifenox: 750	NA	Dose: 1.5 l/ha
Summer	D	F	Annual	SC	ET-	Conventio	BBCH	1	ET-751:	400	ET-751:	NA	Dose:

barley			weeds		751: 9 g/l Bifenox: 500 g/l	nal spray	13-29		2.25 Bifenox: 1.25		9 Bifenox: 500		1 l/ha
Winter barley and winter wheat	B & L	F	Annual weeds	SC	ET-751: 9 g/l Bifenox: 500 g/l	Conventional spray	BBCH 21->29	1	ET-751: 2.25-3 Bifenox: 125-444	150 - 400	ET-751: 9-12 Bifenox: 500-665	NA	Dose: 1-1.33 l/ha

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

See Annex B, Appendix A - Authorizations and registrations

LEVEL 2

Pyraflufen-ethyl

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

2.1.1 Identity

The minimum purity of the a.s. as manufactured, as stated by the notifier, is 956 g/kg . This purity value, as well as the proposed impurity profile, was confirmed by an acceptable analytical profile of batches.

2.1.2 Physical and chemical properties

Active substance :

The physico-chemical properties of the active substance can be summarized as follows :

Appearance :	**purified a.s. : fine white powder with no significant odour** **a.s. as manufactured (TC) : fine cream coloured powder (some claying present) with no significant odour**
Melting point :	**126.4 to 127.2°C (melting point range)**
Boiling point :	**not determinable due to thermal decomposition above its melting point**
Temperature of decomposition :	**approx. 240°C**
Relative density (24°C) :	**1.565**
Vapour pressure :	**$1.6\ 10^{-8}$ Pa (25°C)** **$4.3\ 10^{-9}$ Pa (20°C)**
Henry's law constant (20°C) :	**$2.2\ 10^{-5}$ Pa.m^3/mol**
UV/VIS absorption (λ_{max}) :	**203 nm (ε = 28700 L.mol^{-1}.cm^{-1})** **243 nm (ε = 12800 L.mol^{-1}.cm^{-1})** **291 nm (ε = 5900 L.mol^{-1}.cm^{-1})**
Solubility in water (20°C) :	**0.082 mg/L (neutral range)**
Solubility in organic solvents (TC) (25°C) :	**n-heptane : 234 mg/L** **p-xylene : 41.7 to 43.5 g/L** **1,2-dichloromethane : 100 to 111 g/L** **methanol : 7.39 g/L** **acetone : 167 to 182 g/** **ethyl acetate : 105 to 111 g/L**
Partition coefficient (log P_{ow}) (ambient temperature) :	**3.49 (neutral range)**
Hydrolysis (25°C) :	**pH 4 : hydrolytical stability** **pH 7 : DT_{50} = 13 d** **pH 9 : rapid hydrolysis**
Direct phototransformation (20°C) :	**DT_{50} = 30 h**
Quantum yield :	**Φ = 10.7%**
Dissociation constant :	**no acid or alkaline properties**
Stability in air :	**estimated DT_{50} in the troposphere = 11.3 h**
Flammability (TC) :	**not highly flammable**
Auto-flammability (TC) :	**not a self-heating substance**

Explosive properties (TC) :	**not explosive**
Oxidizing properties (TC) :	**test should be reported**

Pyraflufen-ethyl is very slightly soluble in water and moderately to readily soluble in a range of organic solvents. Its octanol/water partition coefficient indicates a potential for bioaccumulation.
Pyraflufen-ethyl is very slightly volatile, meaning that exposure of users through volatilization is not expected to present a significant problem but nevertheless needs to be taken into consideration, as well as off-target movement by transport in air.

Pyraflufen-ethyl is hydrolytically stable at pH4, moderately hydrolyzing at pH 7 and rapidly hydrolyzing under basic conditions, indicating that hydrolysis should play a role in the environmental dissipation of the molecule. Pyraflufen-ethyl is readily photodegradable; direct photodegradation thus is a significant.

The a.s. exhibits no explosive properties and is not highly flammable nor self-heating. Conclusive information with regard to its oxidizing properties is expected to be reported.

Formulation :

A suspension concentrate (SC) containing 9 g/L pyraflufen-ethyl and 500 g/L bifenox (MILAN^{TM}) was selected by the notifier as the representative formulated product
A summary table of the physico-chemical properties of MILAN^{TM} is given in Annex B, point 2.2.

All data requirements have been met, with the exception of <u>oxidizing properties</u>. The formulated product was found to be not explosive and its auto-ignition temperature is not critical.

The technical properties of the formulation indicate that no particular problems are to be expected when it is used as recommended and its stability allows storage under practical conditions.

2.1.3 Details of uses and further information

Field of uses :

Crops : winter and spring cereals (wheat, barley)

Pyraflufen-ethyl is effective against broad-leaved weeds. The active substance applied in early post-emergence at 13.5 g a.s./ha provides excellent control of important weeds such as *Anthemis arvensis, Lamium purpureum, Sinapis arvensis* and a good suppression of *Matricaria chamomilla, Stellaria media, Veronica persica* and *Viola* spp.

Pyraflufen-ethyl is used in combination with bifenox which provides complement of activity against *Capsella bursa-pastoris, Papaver rhoeas, Veronica* spp and *Viola.* Both straight products present a moderate activity on *Galium aparine*

Packaging :

The available packaging material was described and stated to have been approved according to ADR-methods 3552 to 3555. <u>Reports describing the results of aforementioned tests</u> were not submitted.

<u>Report demonstrating the resistance of the packaging material to its contents</u> was not submitted.

Procedures for cleaning application equipment and protective clothing :

The spray equipment is cleaned immediately after use by draining the system completely and rinsing spray

tank, boom and nozzles 2 to 3 times with clean water. The effectiveness of the cleaning procedure was demonstrated.

No specific recommendations were given regarding the cleaning of protective clothing.

Re-entry intervals, waiting periods and other precautions to protect man, livestock and the environment

Pre-harvest intervals
PHI is not applicable. Application timing is determined by the crop growth stage (BBCH 13-29).

Re-entry period for livestock
Not required.

Re-entry period for man to treated crops
Not required.

Withholding period for animal feedingstuffs
As there are no expected residues in animal feedingstuffs, a withholding period before milking and slaughter is not necessary.

Waiting period between last application and handling treated products
Not required.

Waiting period between last application and sowing or planting succeeding crops
A waiting period of 1 month between the application of pyraflufen-ethyl and sowing/planting of the succeeding crops should be observed.

Recommended methods, precautions and handling procedures to minimize the risks relating to warehouse storage, user level storage, transport, fire :

Hazards identification : Very toxic to algae and aquatic plants

Handling : When using, do not eat, drink or smoke.
Handle and open container with care. Do not breathe dust or vapor. Use with adequate ventilation. Avoid handling near open flame, source of heat. Prevent build-up of electrostatic charge.
Wash thoroughly with soap and water after handling. Do not contaminate water by cleaning of equipment or disposal of waste.
Personal protection :Dust mask and goggles should be used when handling. Appropriate protective clothing and gloves made of rubber or other suitable impervious materials should be worn to prevent skin contact. These must be changed and washed after use or after contamination. When removing, caution should be taken to avoid generation of dust or contact with spilled material resulting from earlier use.

Storage : Keep out of reach of children.
Keep away from food, drink and animal feeding stuffs.
Store in an authorized and dry place where only authorized persons have access.
Keep container closed, under room temperature and avoid exposure to sunlight.

Transport : · Classification Rail / Road RID / ADR : not regulated
· Classification Maritime : not regulated
· Classification Air : not regulated

Fire : *Extinguishing media* : Sprayed water jet, foam, extinguishing powder, CO_2 and sand.

Combustion gases : In the event of fire, the formation of hydrogen chloride, hydrogen fluoride, carbon monoxide and nitrogen oxides must be anticipated.

Special hazards : Avoid the escape of extinguishing media, such as fire-fighting water, to the environment (especially pond, river and lake).

Protective equipment : Fire fighters and others that may be exposed should wear full protective clothing and a self-contained breathing apparatus.

Not subject to the Regulation on Flammable liquids (VbF)

Procedures for use in the event of an accident during transport, storage or use :

Accidental release measures : Prevent entry intro drains, waters or soil. Recover the product by damping then sweeping or suction. Shovel up and place into a labelled tightly closed container. To clean contaminated floors and objects, wipe with a damp cloth. All contaminated cleaning materials should be placed in closable receptacles. Dispose of safely in accordance with local regulations (see B.3.5.5).

First aid measures : In case of *contact with skin*, remove contaminated clothes and carefully wash affected areas of skin with water.
In case of *contact with eyes*, rinse immediately with plenty of water for 20 minutes.
If *swallowed*, seek medical advice immediately and show this container or label.
If you feel unwell, seek medical advice (show the label where possible).
Keep the victim under medical control.

Procedures for destruction or decontamination of the formulations and their packaging :

- Neutralization procedures for use in the event of accidental spillages are not considered to be suitable.

- 'Controlled incineration is the preferred means to safely dispose of the preparation as well as plant protection products containing it, contaminated materials or packaging. Incineration must be done under controlled conditions according to the EEC Directive 94/67 : since EXP31279A contains more than 1% of halogens, following criteria are requested :
- temperature above 1100 °C
- residence time greater than 2 seconds
- presence of more than 6% of oxygen
In case of wastes containing less than 1% of chlorine, a temperature of 850 °C is requested.
Exhaust gases should not exceed : 10 mg/m³ hydrochloric acid as an average on 24 hours
1 mg/m³ hydrofluoric acid as an average on 24 hours.'

2.1.4 Classification and labelling

Classification and labelling of pyraflufen-ethyl made by the Rapporteur

Classification	N, R50/53	
Labelling:		
Hazard symbol:	N	
Indication of danger:	dangerous for the environment	
Risk phrases:	R50/53	very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
Safety phrases	S60	this material and its container must be disposed as hazardous waste
	S61	avoid release to the environment. Refer to special instructions/safety data sheets
	The RMS proposes to add a safety phrase such as:	Pyraflufen-ethyl may induce prophyria. Porphyria are inherited as Mendelian autosomal dominants, some types are recessive and other acquired through exposure to porphyrogenic compounds. Simultaneous or successive exposure to such compounds may be deleterious for people who carry a latent hereditary trait.

Justification for the proposal made by the Rapporteur concerning the classification and labelling of pyraflufen-ethyl.

Proposed classification	**Justification**
N, R50	EC50 (*Selenastrum capricornutum*) = 0.23 µg a.s./l
R53	The a.s. is not ready biodegradable. No mineralization occured in the water/sediment study.

2.2 Methods of analysis

2.2.1 Analytical methods for analysis of the active substance as manufactured

The validated GC and HPLC methods which were submitted allow to determine the purity and the impurities of the technical

However, with respect to the determination of pure pyraflufen-ethyl in pyraflufen-ethyl technical, accuracy of the HPLC-method remains to be addressed. No actual validation data were provided with regard to the methods for sulfate (turbidimetry) and moisture (coulometric moisture tester) analysis.

2.2.2 Analytical methods for formulation analysis

An HPLC method allowing the determination of the active substances (pyraflufen-ethyl and bifenox) in the representative formulation was submitted.

2.2.3 Analytical methods for residue analysis

Feed and food :

The GC-method submitted allows determination of parent Pyraflufen-ethyl and its main metabolite E-1 (as E-15) in *food matrices of plant origin* with a LOQ of 0.01 mg/kg for wheat grain and 0.02 mg/kg for wheat straw and shoot.

The modified multi-residue enforcement method DFG-S19 was found to be not applicable to the analysis of Pyraflufen-ethyl and E-1 in cereals.

Methods for the determination of residues in *food matrices of animal origin* are not required since residues of pyraflufen-ethyl are not expected in animal products for human consumption.

Soil, water, air :

The LC/MS-MS method submitted for *soil analysis* allows determination of parent Pyraflufen-ethyl and its main metabolites E-1, E-2 and E-3 in different soil types with a LOQ of 0.01 mg/kg.
Although LC/MS-MS is currently not considered to be a commonly available technique, the method can be accepted taking into account the justification stated by the notifier. According to Nihon Nohyaku there was a degree of uncertainty as to the GC/NPD method supplied (cfr. B.4.2.1) being able to achieve the required LOQ for all soil types.

The GC-ECD method provided for *water analysis* allows determination of parent Pyraflufen-ethyl and its metabolite E-1 (as E-15) in drinking water and surface water with a LOQ of resp. 0.1 µg/L and 1.0 µg/L.

The GC-ECD method submitted for *air analysis* allows to determine parent Pyraflufen-ethyl in ambient and warm, humid air with a LOQ of » 6 µg/m³.

Body fluids :

The HPLC method submitted allows determination of parent pyraflufen-ethyl and its main metabolites E-1 and E-9 in dog *plasma* with a LOQ of 0.3 mg/L.
Further analytical methodology for residue analysis in *tissues* is not required as pyraflufen-ethyl is not classified as toxic or highly toxic.

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 their transformation products.

Metabolism :

After oral administration, pyraflufen-ethyl showed a rapid, dose-dependent and saturable absorption from the gastro-intestinal tract.
An absorption rate of 56% was extrapolated from urinary and biliary excretion (36.09% in bile + 19.66% in urine) for low dose. Increasing the dose, increased fecal excretion (± 90%) and reduced simultaneously urinary excretion to 3.6%. Absorption after oral high dose represents ± 20% of the dose.
Pyraflufen-ethyl has a limited distribution in organs and tissues, and 96 h after dosing, there were no tissues or organs exhibiting specifically retained radioactivity. At 3, 6 or 9 h postdose, the highest radioactivity was associated with the gastro-intestinal tract and the organs of metabolism and elimination, i.e. liver and kidney. There was no evidence of accumulation.
Metabolism in rats as well as in plants, involves ester hydrolysis, O-dealkylation of the ether, N-demethylation on the pyrazole ring and further transformations of the phenoxyacetate into more polar metabolites. These metabolic pathways produce essentially 2 metabolites identified as E-1 and E-9 and other metabolites present at very low levels.
Excretion after oral administration was mainly fecal, representing ± 66% of a low dose, reaching 90% after high dose from which ± 78% was unchanged pyraflufen-ethyl. Urinary excretion represented 29-33% of the low dose and decreased to 2.5-5% after high dose. There was no evidence of accumulation.

Acute toxicity :

In rats and mice, acute oral toxicity was low and no mortality occurred after oral administration of 5000 mg/kg bw pyraflufen-ethyl. Moreover, no particular symptoms were recorded in rats. Male mice appeared more sensitive and some symptoms suggestive of an autonomic nervous sytem toxicity were observed.
Dermal toxicity was low but at the dose of 2000 mg/kg bw, male rats showed a significant reduced body weight at the 14th day.
A single oral dose of 5000 mg/kg bw is without significant effect on the mice liver weight, on the cytochrome P450 content and on the enzyme activities cytochrome P450 dependent. At 10000 mg/kg bw, decrease of CYP isoenzymes possibly reflecting a relative deficiency of heme for the responsible cytochromes isoforms occurred.

Pyraflufen-ethyl is not an eye and skin irritant, and is not a sensitizer.

Table 2.3.1-1 : Summary of acute toxicity of pyraflufen-ethyl

Type of test; test species	Test substance purity	Results	Classification	References
Acute oral, rat	97.5% batch n°.4 AM0021D	_ _ >5000 mg/kg bw	-	Amanuma, 1995a
Acute oral, mice	97.5% batch n°.4 AM0021D	_ _ >5000 mg/kg bw	-	Amanuma, 1995b
Rat, dermal, semi-occluded	97.6% batch n°.4 AM0021D	_ _ >2000 mg/kg	-	Amanuma, 1995c
Rat, nose only inhalation, 4 hours (dust)	97.0% B.n°. 4AM0024D	_ _ > 5.03 mg/l (423 mg/kg bw)	-	Cracknell, 1995
Rabbit, skin irritation	97.6% B.n°.4AM0021D	_: not irritant	-	Komatsu, 1995a
Rabbit, eye irritation	97.6% B.n°. 4AM0021D	_: not irritant	-	Komatsu, 1995b
Maximisation test	97.0%;	not sensitizer	-	Rees, 1995

	B.n°. 4AM0024D			

***Genotoxicity*:**

Genotoxicity of pyraflufen-ethyl was tested in a variety of different tests covering both, eukaryotes and prokaryotes *in vivo* and *in vitro*.
The aspect of mutagenicity is considered to be adequatly investigated.
While no point mutations were observed in bacterial cells, positive results were obtained in mouse lymphoma cells in the presence of metabolic activation. As the forward mutation study showed a slight positive evidence in the presence of metabolic activation, it was required from the notifier to confirm these results in a new study. A second test was conducted using lymphoma cells in which a clear negative response was observed.
Pyraflufen-ethyl was negative in the DNA repair test using the *Bacillus subtilis* rec assay as indicator, and did not cause DNA damage in rat liver *in vivo*. Pyraflufen-ethyl did not induce clastogenic or other damage *in vivo* in mice.
In conclusion, pyraflufen-ethyl is not genotoxic.

Table 2.3.1-2 : Summary of genotoxicity of pyraflufen-ethyl

Type of test Cell/Test species	**Test substance; purity**	**Conditions**	**Results**	**References**
***In vitro* gene mutation test**				
Salmonella and *Escherichia coli* / mammalian microsome test	pyraflufen-ethyl: 97.6%; b.n°.4AM0021D	TA98, 100, 1535, 1537, 1538 and WP2uvrA +/- S9 mix, DMSO; 156.3, 312.5, 625, 1250, 2500 and 5000 µg/plate	negative	May, 1994
mouse lymphoma cells L5178Y TK+/-	pyraflufen-ethyl: 97.6%; b.n°4AM0021D	- S9mix:10, 20, 40, 60 and 80 µg/ml +S9mix: 20, 40, 80, 120 and 160 µg/ml ; DMSO	-S9mix: negative + S9mix: positive	Lloyd, 1994
mouse lymphoma cells L5178Y TK+/-	pyraflufen-ethyl: 97.0%; b.n°4AM0021D	- S9mix:10, 20, 40, 50 µg/ml +S9mix: 150,200, 250, 300 and 350 µg/ml ; DMSO	negative	Tanaka, 1998
***In vitro* chromosome assays**				
chromosome aberrations in human lymphocytes	pyraflufen-ethyl: 97.6% b.n°4AM0021D	+/- S9mix : 650, 1300 and 2600 µg/ml	negative	Dance, 1994
***In vitro* DNA repair assays**				
rec assay, *Bacillus subtilis*	pyraflufen-ethyl: 98.1% b.n°4AM0021D	+/- S9 mix; 343, 687, 1375, 2750, 5500 µg/disk	negative	Inagaki, 1994
***In vivo* genotoxicity test**				
UDS in rat liver	pyraflufen-ethyl: 99% b.n°.6AM00381	600 or 2000 mg/kg bw	negative	Gant and Proudlock, 1998
micronucleus assay	pyraflufen-ethyl: 97.6% b.n°4AM0021D	mouse bone marrow : 1250, 2500, 5000 mg/kg bw, by gavage in corn oil	negative	Edwards, 1994

***Short-term toxicity* :**

Oral administration of pyraflufen-ethyl to rats or mice for 4 weeks resulted in the expression of diminished availability of vital hemoproteins : males were more sensitive and showed reduced body weight, reduced erythrocyte characteristics, increased plasma bilirubin indicative of mild hemolytic anemia associated with a compensatory response from the bone marrow (in rats) and from the spleen (extramedullary haematopoieisis in rats; increased weight in mice). Liver weight increase was associated with increase in AP, ALT, AST, suggesting liver dysfunction and necrosis. (See supplementary studies).
Oral administration to rats of pyraflufen-ethyl for 13 weeks confirmed the erythrocytes and liver as targets of toxicity. Minor renal effects were also reported. The NOAEL in this study was 5000 ppm (455 mg/kg bw/d).
Mice seems to be the most sensitive species : at 523.7 mg/kg bw/day, anemia and liver toxicity was reported. In this study a NOAEL of 20 mg/kg bw /d was retained. This value was also the lowest NOAEL in short-term toxicity studies and therefore used for the calculation of the AOEL.
Dogs did not shown any toxic effect after 13 or 52 week administration.

Table 2.3.1-3 : **Summary of short term-toxicity of pyraflufen-ethyl :**

Type of test	Compound and test substance purity	Results			References
		NOAEL (mg/kg bw /day)	LOAEL (mg/kg bw/day)	Critical endpoints	
Rat, oral, 28 day	B.n°.3AM0011N 96.8 %	223.2	2296.4	bwî; liver weight ì; AP and ALT ì; ì bilirubin and cholesterol ; extramedullary hematopoieisis; symptoms of haemolytic anemia	Broadmedow, 1994a
Mice, oral, 28 day	B.n°.3AM0019P 97.6 %	<441.8	441.8	bwî; î RBC; îHb; î triglycerides	Takahashi, 1994
Rat, oral, 90 day	B.n°.3AM0011N 96.8 %	455.5	1489.4	bwî; altered blood parameters; ì spleen and kidney weight; liver hepatocytic hypertrophy; ìserum AP, ALT, AST,β-glob, îα-glob, albumin, glucose	Broadmeadow , 1994b
Mice, oral, 90 day	b.n°.4AM0021D : 97.6%; b.n°. 4 AM0023D, 98%	20	98	histopathological liver alterations	Kuwahara, 1996
Dog, oral, 90 day	97%; b. n° 4AM0024D	>1000	-	-	Broadmeadow , 1996a
Dog, oral,1 year	97.3%; b. n°. EN31653 ; 5AM0025D, 97.7% used up to week 51 and b.n°.5AM0026D	> 1000	-	-	Broadmeadow , 1996b
Rabbit, dermal, 21 day	no data				

Long-term toxicity studies :

In both long-term studies, target organs were blood, liver and kidney as also observed in the short-term toxicity studies.
In rats, chronic oral administration induced microcytic anemia. In kidneys, renal papilla were affected. Cytotoxicity observed in liver was probably consecutive to the oxidative stress induced by an increase in liver porphyrin which is characterized in rats, at 10000 ppm, by bile duct hyperplasia, electron-lucent vacuoles in hepatocytic mitochondria wtihout impairment of mitochondrial function and in mice, at 1000 ppm, by liver swelling, cytoplasmic vacuolation, pigment accumulation in Kupfer cells, foci of cellular alterations, liver hyperplasia (PCNA) and benign hepatocellular adenomas (at 5000 ppm). The NOAEL for proliferative activity of hepatocytes is 200 ppm (= 20 mg/kg bw/d). Porphyrin acccumulation in liver were not measured after long-term exposure.
Pyraflufen-ethyl was not carcinogenic in the rat study.
From both rat and mice studies, a NOAEL of 20 mg/kg bw/day is provisionally acceptable waiting for a NOAEL for porphyrin accumulation in liver in mice.
It is concluded that the increased hepatocellular adenomas in the high dose group of the mouse carcinogenicity study might be induced through the non genotoxic/cytotoxic mode of action of pyraflufen-ethyl.
From the open literature, two retrospective studies and one case-control study have suggested an association between primary liver cancer and acute hepatic porphyrias and according to the authors, acute hepatic porphyria shoulde be considered as a rare cause of hepatocellular carcinoma (Andant et al., 1998).

Table 2.3.1-4 : **Summary of long-term toxicity and carcinogenicity of pyraflufen-ethyl**

Type of test Test species	Test substance purity	Results			References
		NOAEL (mg/kg bw/ day)	LOAEL (mg/kg bw/day)	Critical endpoints	
Rat, 104 week	From week 1-17 : 97.6%, b.n°.3AM0019P: week 18-75 ; 97.6%, b.n°.4AM0021D; from week 76 onwards : b.n° 5AM0026D; 97.7%	20	87	slight anisocytosis, ì kidney weight; electron lucent vacuoles in hepatocytic mitochondria	Patel, 1996
Mice, diet, 78 week	b.n°.4AM0021D: 97.6%; b.n°. 4 AM0023D, 98%	20	98	liver: histopahtological lesions	Kuwahara, 1996

Reproductive toxicity:

In the two generation study, parental animals receiving pyraflufen-ethyl at the highest dose revealed a decreased body weight gain and pathological changes in liver and kidneys, and their offspring showed a decreased body weight gain during lactation period. However there were no abnormalities in the reproductive performance of parental animals and the reproductive index of offspring. Rats did not show any treatment-related changes in the teratology study.
Rabbits appeared to be strongly sensitive to the toxic effects of pyraflufen-ethyl. Due to the high mortality and insufficient number of pregnant rabbits at the 2 top doses, the study was not accepted by the RMS. This point is adressed to the notifier.

Table 2.3.1-5 : Summary of reproductive toxicity and teratogenicity of pyraflufen-ethyl

Type of test **Test species**	**Test substance purity**	**Results**			**References**
		NOAEL (mg/kg b w/ day)	**LOAEL (mg/kg b w /day)**	**Critical endpoints**	
rat, 2 generation study	b.n°. 4AM0023D, 97.6%	-reproduction tox > 721 mg/kg bw/d. -syst.tox.= 70.8 mg/kg bw/d	- -721mg/kg bw/d	- -îbw, kidney and liver toxicity	**Fujii, 1996**
rat, developmental	b.n°4AM0024 D; 97.0%	-maternal tox ≥1000 mg/kg bw/d - foetal toxicity, development ≥1 000 mg/kg bw/d.	-	-	**Burns, 1995a**
Rabbit, developmental	b.n°4AM0024 D	The study is not accepted by the RMS; a NOAEL is proposed by the notifier = 20 mg/kg bw/d			**Burns, 1996**

Supplementary studies :

Supplementary studies were performed in male mice or rats, after short-term exposure.
Feeding to male mice produced, at high doses, a clear evidence of liver cell damage and cell death (necrosis) consecutive to an oxidative stress and/or cytotoxicity resulting probably from the accumulation of porphyrins known to induce liver cell necrosis and inflammation followed by regenerative liver growth :

- Porphyrin accumulation, during a 4 week exposure period, was mainly observed in liver and kidneys of male rats (200 mg/kg bw/d) and mice (600 mg/kg bw/d). No porphyrin accumulation was observed in skin. This may be explained by the fact that photosensitivity and related dermopathy are the prominent problems caused by deficiency of uroporphyrinogen decarboxylase, or uroporphyrinogen III synthase or ferrochelatase. Photosensitivity is also characteristic of protoporphyrinogen oxidase deficiency, known as *Variegate porphyria* but this type of porphyria is preferentially classified as hepatic porphyria, because biochemical expressions are especially prominent in liver (Ellefson and Ford, 1996). The presently available data strongly suggest a species sensitivity.
No NOAEL was defined in the mice study for porphyrin accumulation. This point is adressed to the notifier as mice being the most sensitive species, it is necessary to define a NOAEL for this specific effect in liver before final ADI and AOEL can be proposed.
The lowest NOAEL reported in these further toxicological studies is reported in the rat study, at 40 mg/kg bw/d. At this dose, no significant increase in hepatic porphyrin was reported.
- At 1000 mg/kg bw/d a significant reduction of E.R.O.D., P.R.O.D., E.C.O.D, aniline hydroxylase and aminopyrine demethylase activities was observed. NOAEL = 200 mg/kg bw/d is acceptable.
- After 2 week exposure, single cell hepatocellular necrosis rarely accompanied with cell inflammation was reported in mice. While this effect recovered completely at 600 mg/kg bw/d after 2 week withdrawal, at 1000 mg/kg bw/d, some small liver necrosis were still present in 1 animal. It is assumed that the enhanced mitotic activity is of regenerative nature, serving to replace lost cells. The hepatocellular necrosis, cell inflammatory foci, mitosis and hepatocellular hypertrophy recovered after 2 week pyraflufen-ethyl withdrawal, but not completely. This sustained induction of both adaptative and regenerative liver growth is associated with the formation of liver adenoma, reaching statistical significance at 5000 ppm in mice after 2 year exposure. If there is a link between porphyria and hepatocellular adenoma formation is not clear.
- After 7 days oral administration of 1000 mg/kg bw/d pyraflufen-ethyl to mice, liver catalase activity was strongly reduced and lipid peroxidation and beta-oxidation activity were increased suggesting proliferation of liver peroxisomes. At the top dose of 2 000 mg/kg bw/d, formation of 8-OH-dG was increased in liver DNA. NOAEL = 200 mg/kg bw/d is acceptable.

Overall, extrapolation from these experiments to man is difficult, however, certain human porphyrias are clearly associated with an increased risk for hepatocellular carcinoma. Peroxisome proliferators are well known rodent hepatocarcinogens and the relevance of hepatocarcinogenic effects of known peroxisome proliferators is often considered to be negligible for human hazard assessment.

Table 2.3.1-6 : **Summary of mechanistic studies of pyraflufen-ethyl**

Type of test	Compound and test substance purity	Results			References
		NOAEL (mg/kg bw /day)	LOAEL (mg/kg bw/day)	Critical endpoints	
mice, 28 day, oral	B.n°.4AM0021 D 97.6 %	<600	600	ì porphyrin in tissues	Nakatani, 1998
rat, 28 day, oral	B.n°.4AM0021 D 97.6 %	40	200	ì porphyrin in tissues	“
Mice, oral, 28 day	B.n°.4AM0021 D 97.5 %	200	1000	liver weight ì;îlevel cyt.P450 and associated enzyme activities	Amanuma, 1996
Mice,	94-T-0055			ì peroxisomal proliferation, ì	

oral, 7 day	**97.5%**	**200**	**1000**	**lipid peroxides, ìcatalase activity**	**Inagaki, 1998**
Mice, oral, 28 day	**B.n°.4AM0021 D 98.6 %**	**<600**	**600**	**ìALT, ìLiver weight; single cell necrosis, mitosis, pigments in Kupffer cells**	**Nakatani, 1994**

2.3.2 Establishment of an Acceptable Daily Intake (ADI)

A provisional ADI can be calculated from a NOAEL of 20 mg/kg bw/d (lowest NOAEL), identified in the 2 year rat and mice studies. Applying an assessment factor of 100 (10 for interspecies variation x 10 for intraspecies variation), the acceptable daily intake becomes :

ADI = 0.2 mg/kg bw/day

This value is a provisional proposal, waiting for futher information and NOAEL for porphyrin accumulation in mice liver.
An increase in benign hepatocellular adenoma was reported in the 78 week mouse study, at 540 mg/kg bw/day. Using an assessment factor of 100 is sufficient as the safety margin between the proposed ADI and the LOAEL is 2700.

2.3.3 Establishment of an Acute Reference Dose (ARfD)

Not applicable.

2.3.4 Establishment of an Acceptable Operator Exposure Level (AOEL)

The AOEL short-term for man is calculated on the basis of an internal NOAEL from a sub-chronic animal experiment, taking into account the apparent degree of absorption, and applying an assessment factor, chosen in function of the critical effect observed in the animal experiments.

It appears from the animal experiment that a subchronic exposure to 20 mg/kg bw/d (lowest NOAEL, taken from the 90 day, mice study) of pyraflufen-ethyl will not result in any toxic effect. This value is a provisional proposal, waiting for futher information and NOAEL for porphyrin accumulation in mice liver. The oral absorption seems to be 56 %. Applying an assessment factor of 100 for extrapolation to man. The acceptable operator exposure level, expressed as an internal, systemic dose becomes:

AOEL systemic = 0.112 mg/kg bw/d

The notifier proposed a AOEL based on the 28-day oral rat study in which a NOEL of 230 mg/kg bw/day was obtained. Taking a factor of 25, this gives an AOEL = 9.2 mg/kg bw/d.

2.3.5 Establishment of the drinking water limit

On the basis that exposure through drinking water should not account for more than 10% of the ADI, assuming an average consumption of 2 l of water per day and an average body weight of 70 kg, a limit of 0.7 mg/l is proposed.

$$\mathbf{MAC = \frac{ADI \times bw \times P}{C} = \frac{0.2 \times 70 \times 0.1}{2} = 0.7\ mg/l}$$

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

Health risk for humans:
Any effects would not be expected to occur at doses at which human exposure can occur. Realistic handling of pyraflufen-ethyl does not represent a significant risk to human.
From open literature, porphyria are enzymatic defects which could be acquired after chronic exposure to chemicals interfering with human porphyrin biosynthesis (Rio et al., 1997). Photosensitive skin diseases , recurring abdominal colic, episodes of psychiatric distress, nausea and vomiting, fever, paresthesia, numbness, dysesthesia, hypertension, tachycardia and seizures are characteristics of porphyrias (Ellefson and Ford, 1996).
Health risk for animals :
The acute toxicity of pyraflufen-ethyl is extremely low. In the acute rat test, there were no clinical symptoms even at a dose of 5000 mg/kg bw. Male mice appeared more sensitive and some symptoms suggestive of an autonomic nervous sytem toxicity were observed.
Short-term oral exposure in the rat has revealed the development of reversible hematological changes (anemia) and reversible effects on the liver (resulting from an oxidative stress probably induced by an increased accumulation of porphyrins) and kidneys. Rabbits presented gastro-intestinal tract disturbances**.**
Pyraflufen-ethyl is not genotoxic.
After long term exposure, benign liver adenoma were reported in mice.

Exposure resulting from the application of formulations containing pyraflufen-ethyl :

The formulation Milan SC (pyraflufen-ethyl (9g/l) and bifenox (500g/l) is designed for ground spray application (tractor mounted boom with hydraulic nozzles). Use rates are 1.5l/ha for late applications on developped weeds. In case of earlier applications, a reduced dose rate of 1.33l/ha can be applied. Tha maximum dose rate of 1.5l/ha correspond to 13.5 g pyraflufen-ethyl and 750 g active ingredient bifenox /ha. It is recommended to apply a preparation with 150 to 400 l water/ha.
Model calculations were made on the basis of UK-POEM and German model, foliar application in post-emergence of cereals, tractor mounted boom sprayers.

- *Operator exposure:*
The operator exposure (% AOEL, degree of exposure E) with or without protective equipment is acceptable.
This evaluation is however based on a provisional AOEL.

- *Bystander exposure:*
It can be assumed that bystanders may be present during the field use of Milan SC and can therefore be considered to be exposed mainly by the airborne route. If exposure of a bystander compared with an operator is proportional to the airborne material it is likely that a bystander, outside the treatment area will not be exposed to a dose greater than the AOEL.(Inhalation exposure of the operator during spraying is 0.00405 mg/day which represents 3.6% of the AOEL).

- *Worker exposure:*
Milan SC is applied on cereals crops. The product will be quickly absorbed into the top surface soil and will therefore not be readily transferred to workers. Also it is unnecessary to re-enter the field for further work following treatment. As there is no risk for the applicator, there are no risk during re-entry in the field.

Human exposure resulting from ingestion of residues:

Residue data covering the intended uses in cereals and in conformity with the proposed residue definition in plants were submitted. These data allow an estimation of the intake of residues by the consumer of treated crops to be carried out. TMDI and IEDI calculations were made using FAO guidelines and resulted in an acceptable exposure level for average consumers.

2.4 Definition of the residues

2.4.1 Definition of the residues relevant to MRLs

Plant products :

Based on the residue data in immature wheat plants and in straw at maturity, the sum of the parent compound and its metabolite E1 is proposed as the residue definition for monitoring in commodities of plant origin.
Moreover, these two metabolites exhibit the highest herbicidal activity . The contribution of metabolites E2 and E3 to that effect is considered as insignificant since the herbicidal reaction can be observed rapidly after the foliage application of pyraflufen-ethyl.

Animal products :

Neither metabolism studies nor livestock feeding studies have been performed as no significant residues occurred at a level > 0.1 mg/kg of the total diet. **Residue definition is not required for commodities of animal origin.**

2.4.2 Residues relevant to consumer safety

Pyraflufen-ethyl is used as post-emergence herbicide in cereals. (see point 1.5.3)
Assessment of the consumer safety indicated that the intake of pyraflufen-ethyl residues is well below the maximum acceptable level for the different consumer exposure models. (TMDI = 0.106% ADI)

2.4.3 Residues relevant to worker safety

See point 2.3.6

2.4.4 Proposed EU MRLs and compliance with existing MRLs

There are currently no existing EC MRLs.

Residue definition	Products	MRL (mg/kg)
sum of pyraflufen-ethyl and metabolite E-1 expressed as pyraflufen-ethyl	**cereal grain**	**0.02***

2.4.5 Proposed EU import tolerances and compliance with existing import tolerances

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2.5 Fate and behaviour in the environment

2.5.1 Definition of the residues relevant to the environment

Residue in soil : pyraflufen-ethyl and the major metabolites E-1, E-2, E-3 recovered in the soil metabolism studies.

Residue in water : pyraflufen-ethyl and the metabolite E-1

2.5.2 Fate and behaviour in soil

***Route of degradation* :**

In soil under *aerobic conditions*, pyraflufen-ethyl is rapidly degraded by hydrolysis to E-1. (DT_{50} a.s. <0.5 d, DT_{90} a.s. = 0.83 - 2.1 days).
The primary metabolite E-1 is further degraded to E-2 (DT_{50} E-1 = 16-20 d, DT_{90} E-1 = 52-67 d) (E-2 : maximum of 14-19% of applied radioactivity after 14-28 days then declining) and E-3 (56-69% applied radioactivity after 178 days), respectively. Small quantities of E-9 are also formed along with other minor/insignificant unidentified degradation products.
Soil 'bound' residues increased with time (up to 17% of the applied radioactivity after 100 days). The mineralization is low (1.18 - 2.53% of the applied radioactivity after 100 days)
The unknown 2 metabolite reaching 10% of the applied radioactivity was partially identified by MS. This substance would contain in its structure the phenyl group and the pyrazole group.

Hydrolysis of pyraflufen-ethyl to E-1 was also observed under sterile conditions indicating that the initial degradation process included chemical decomposition. However, no E-2 was found under sterile conditions indicating that micro-organisms were necessary for this hydrolysis reaction.

In soil under *anaerobic conditions* pyraflufen-ethyl is rapidly degraded to its major degradation product E-1 (DT_{50} a.s. and DT_{90} a.s. < 1d). The major degradation product E-1 was found in both the water and soil (DT_{50} E-1 = 125-191 d, DT_{90} E-1 = 414-634 d). E-2 was a major degradation product in soil but was not found at significant levels in the aqueous phase. Degradation products E-3, E-11 or E-8, E-9 were found at very low levels (N.D. to 1.5% of the applied radioactivity) in either the soil or aqueous phase.
The mineralization is very low (up to 0.2% of the applied radioactivity after 101 days). The bound residue level is very low (up to 2.04% of the applied radioactivity after 101 days).

No *photodegradation* of pyraflufen-ethyl occurred under the conditions of the test. The DT_{50} and DT_{90} values for photodegradation of pyraflufen-ethyl on a soil surface were calculated to be 299 and 993 days, respectively.

Rate of degradation :

Pyraflufen-ethyl is rapidly degraded under aerobic as well as anaerobic conditions at 20°Cwith DT_{50} of < 1 day .
Determination of the degradation rates of the 3 main soil metabolites were performed at 20°C under aerobic conditions:
DT_{50} (E-1) = 16-53 d
DT_{50} (E-2) = 6-11 d
DT_{50} (E-3) = 153-496 d

Some studies under anaerobic conditions or at lower temperature revealed lower degradation rates.

Field dissipation rate :

Pyraflufen-ethyl is rapidly degraded in soil under field conditions (Northern Europe) following spring or autumn

application with DT_{50} values in the range 1 - 7 days. Its major metabolite E-1 is also readily degraded with DT_{50} values of 11-71 days. No significant movement of residues down the soil profile was observed. Only low levels of degradation products E-2 and E-3 were detected (E-2 : £ 0.01 - 0.02 mg/kg soil; E-3 : < 0.01- 0.07 mg/kg soil)

Adsorption :

Pyraflufen-ethyl has low mobility according to its adsorption/desorption coefficient with a K_{oc} value of greater than 1000 (HPLC method).

The Koc of the 3 major soil metabolites were determined in series of 3 soils :
Koc (E-1) = 81-197
Koc (E-2) = 1424-2179
Koc (E-3) = 3098-4354

Mobility :
Fresh residue and aged residue column leaching studies revealed that the active substance and its metabolites had no tendency to leaching (0.2 to 0.5% RR in the leachate)

PEC soil
The formulation EXP31279A is a post-emergence herbicide in cereals (SC containing 9 g/l pyraflufen-ethyl and 500 g/l bifenox) which will be applied at an application rate of 1-1.5 l/ha at stage BBCH 13-29 (9-**13.5** g pyraflufen-ethyl/ha).

The estimations of the PECs were calculated assuming that :

- DT_{50} pyraflufen-ethyl = 7 days (maximum field DT_{50})
- DT_{50} E-1 = 71 days (maximum field DT_{50}). The a.s. is rapidly degraded to the metabolite E-1 (DT_{50} <1-7 days under field conditions). It was assumed that degradation of the a.s. to E-1 was complete and instantaneous.

- Equal distribution in the top 5 cm of the soil with a bulk density of 1.5 g/cm^3
- The substance is applied at the maximum application rate of 13.5 g a.s./ha at stage BBCH 13-29 (no interception of the spray by the crop)

PEC soil of the active substance and metabolite E-1

Time after applications (days)	Cereals 13.5 g a.s./ha 1 application 100% of applied dose reaching the soil			
	pyraflufen-ethyl		metabolite E-1	
	Actual concentration (mg/kg soil)	TWA concentration (mg/kg soil)	Actual concentration (mg/kg soil)	TWA concentration (mg/kg soil)
0	0.018	0.018	0.018	0.018
1	0.016	0.017	0.018	0.018
2	0.015	0.016	0.018	0.018
4	0.012	0.015	0.017	0.018
7	0.009	0.013	0.017	0.017
14	0.004	0.010	0.016	0.017
21	0.002	0.008	0.015	0.016
28	0.001	0.006	0.014	0.016

50	0	0.003	0.011	0.014
100	0	0.002	0.007	0.011

Metabolites E-2 and E-3 were found at low concentrations in the field dissipations studies. Maximum concentrations expected in the soil after an application at rate of 13.5 g a.s. could be estimated to be 0.001 and 0.005 mg/kg respectively for metabolites E-2 and E-3.

Predicted Environmental Concentrations in groundwater

To assess potential concentrations in ground water, simulations were performed with the computer model PELMO 2.01 using standard German scenarios (Wicks, 1997). Parameters used in these calculations were consistent with those used to calculate predicted environmental concentrations in soil. Annual applications of pyraflufen-ethyl to winter wheat at the maximum rate of 13.5 g a.i./ha were assumed on November 25 for autumn applications and April 25 for spring applications.

Simulations for metabolites assumed an application equivalent to the amount of parent (corrected for molecular rate on the application days already described for pyraflufen-ethyl. This is a very conservative assumption, especially for E-2 and E-3. The simulations were performed using a Borstel soil and standard weather scenarios (low: Hamburg 1971; average: Hamburg 1961; high: Hamburg 1978; with total annual rainfall of 542, 778, and 872 mm, respectively).

Since all simulations were run with conservative input parameters, residues of pyraflufen-ethyl, E-1, E-2, or E-3 in ground water resulting from classical leaching through the soil profile under normal agricultural conditions are unlikely to exceed the drinking water limit of 0.1 µg/l

2.5.3 Fate and behaviour in water

Hydrolysis
Hydrolysis rate (t½) of pyraflufen ethyl is = 13.1 d at pH 7, 25°C. The only hydrolysis product is E-1.
The active substance is hydrolytically stable at pH 4.
Metabolite E-1 is hydrolytically stable at pH 4-7-9.

Photodegradation
The main photodegradation product of pyraflufen-ethyl is PD-1 (ethyl 2-hydroxy-5-(4-chloro-5-difluoromethoxy-1-methylpyrazol-3-yl)-4-fluorophenoxyacetate).

The major water metabolite E-1 has a photodegradation half-life of 17.2-22.1 hours. Its degradation products (PD-2, PD-3, PD-4 and PD-5) were determined but not identified. These degradates would be more polar than E-1.

Ready biodegradability
Pyraflufen-ethyl is not ready biodegrable.

Water sediment study
The a.s. and the metabolites E-1, E-2 E-3 were observed in the water/sediment study.

- Pyraflufen-ethyl is rapidly degraded with a DT_{50} water of 1-2 hours .

- The metabolite E-1 reaches rapidly a maximum after a few days. It is mainly present in the water phase. Its DT_{50} can be estimated at 50-100 days. Its log Pow is 2.90.

- The metabolite E-2 is present at high level in sediment. The degradation rate of this compound cannot be estimated.

Its log Pow is 2.88.

- The metabolite E-3 is mainly found in sediment at relatively low level (6-7% after 100 days). Its log Pow is 3.66.

PEC surface water

The estimations of the PECsw were calculated assuming that :

- Drift scenarios according to Ganzelmeier (1992) is applied.
- The waterbody is 30 cm deep
- The application rate is 13.5 g a.s./ha
- Calculations according to a first order kinetics

- For the a.s. only initial PEC was calculated. Due to its very short DT_{50}, short and long term PEC are not relevant.
- For E-1, it is assumed that the a.s. is completely and almost instantaneously degraded to E-1. The DT_{50} of E-1 is 100 days
- For E-2 and E-3 no accurate PEC can be calculated. However, as both compounds degraded slowly, it can be assumed that the concentrations will remain at the level of the calculated initial PEC. TER are calculated with comparison against the initial PEC (assuming complete degradation of the a.s. into its metabolites)

PEC surface water of the active substance and metabolite E-1

Time after applications (days)	Cereals 13.5 g a.s./ha 1 application, 1m drift 4% of applied dose reaching the water body		
	pyraflufen-ethyl	metabolite E-1	
	Actual concentration (mg/l)	Actual concentration (mg/l)	TWA concentration (mg/l)
0	0.00018	0.00018	0.00018
1	-	0.00018	0.00018
2	-	0.00018	0.00018
4	-	0.00018	0.00018
7	-	0.00017	0.00018
14	-	0.00017	0.00017
21	-	0.00016	0.00017
28	-	0.00015	0.00016
50	-	0.00013	0.00015
100	-	0.00009	0.00013

2.5.4 Fate and behaviour in air

vapour pressure = $1.6\ 10^{-8}$ Pa
water solubility = 0.082 mg/L

Þ H = $8.1\ 10^{-5}$ Pa.m³/mol (Russell, 1996a)

Pyraflufen-ethyl is very slightly volatile. It is therefore not relevant to calculate PECa

2.6 Effects on non-target species

2.6.1 Effects on terrestrial vertebrates

Toxicity to birds :

LD50 > 2000 mg/kg bw
LC50 > 5000 mg/kg food
NOEC < 50 mg a.s./kg food

TER birds :

The risk assessment for birds is based on the following assumptions :
- Food consumption of 30% bw for small birds
- The initial residue is estimated according to Hoerger and Kenaga (1972)
- the maximum application rate is 13.5 g a.s./ha

The TER reveal that the acute (15930-17029), short-term (11947-12771) and long-term risk (119-128) to birds is negligible.

TER small mammals :

The risk assessment for mammals is based on the following assumptions **:**

- Toxicological data taken into consideration :
LD_{50} (rat) > 5000 mg a.s./kg bw
NOAEL (rat, 28 d) = 2000 mg a.s./kg food
NOAEL (rabbit, teratogenicity) = 20 mg/kg bw/d (provisional information)
- Food consumption of 30% bw for small mammals
- The initial residue is estimated according to Hoerger and Kenaga (1972)
- the maximum application rate is 13.5 g a.s./ha

The TER reveal that the acute (42571, 39825), short-term (5109, 4779) and long-term (150, 179) risk to mammals is negligible .
In absence of clear guidance provisional long-term TER was calculated. These long-term TER are probably superfluous for pyraflufen-ethyl

2.6.2 Effects on aquatic species

Toxicity to aquatic organisms :

LC_{50} (a.s., fish) > 100 μg/l
EC_{50} (a.s., daphnia) > 100 μg/l
EC_{50} (a.s., algae) = 0.23 μg/l

LC_{50} (E-1, fish) > 100000 μg/l
EC_{50} (E-1, daphnia) > 120000 μg/l
EC_{50} (E-1, algae) = 2.2 μg/l
NOEC (E-1, fish, chronic) = 10000 μg/l
NOEC (E-1, daphnia, chronic) = 100000 μg/l

EC_{50} (E-2, algae) = 0.16 μg/l

TER aquatic organisms :

The following assumptions were made to assess the risks for water organisms :

- the DT50 of the a.s. in water is very short (1-2h) : Only acute TER calculation is necessary
- the metabolite E-1 reached rapidly a maximum level in the water phase. Its DT50 is 50-100 days : TER acute and chronic were determined for fish, daphnia and algae.
- the metabolite E-2 is mainly present in sediment. However the TER for the most sensitive organism (alga) was determined.
- the metabolite E-3 is found at low level only in the sediment phase : No TER was calculated for the water organisms.
- 30 cm water depth,
- spray drift according to Ganzelmeir (1992),

We considered for the calculations of the TERmetabolites that metabolites E-1 and E-2 had the same molecular weight as the a.s., that the transformation of the a.s. into its metabolites was complete and instantaneous.

The TER calculations reveal that
- fish and aquatic invertebrates are not at risk :
- the a.s. and metabolite E-2 present a similar toxicity to algae. Mitigation techniques such as buffer zones should be applied in order to reduce the risk to algae and aquatic plants.

Table2.6.2-1 : Toxicity/Exposure Ratios for the most sensitive aquatic organisms exposed to pyraflufen-ethyl

Application rate (kg a.s./ha)	Crop	Organism	Time-scale	Distance (m)	TER	Annex VI trigger
pyraflufen-ethyl						
0.0135	Cereals	*Oncorhynchus mykiss*	acute	1	556	100
		Daphnia magna	acute	1	556	100
		Selenastrum capricornutum	acute	1	**1**	10
				5	**9**	10
				10	13	10
Metabolite E-1						
0.0135	Cereals	*Lepomis macrochirus*	acute	1	556000	100
		Daphnia magna	acute	1	667000	100
		Selenastrum capricornutum	acute	1	12	10
		Pimephales promelas	chronic (36 d)	1	55500	10
		Daphnia magna	chronic (21 d)	1	555000	10
Metabolite E-2						
0.0135	Cereals	*Selenastrum capricornutum*	acute	1	**1**	10
				5	**6**	10
				10	**9**	10
				15	18	10

2.6.3 Effects on bees and other arthropods

Honeybees :

LD_{50} (oral, contact) > 100 µg a.s./bee.
Hazard quotients (0.12-0.13) reveal that the bees are not at risk. As the formulation is applied on cereals crop up to tillering it is unlikely that bees will be exposed (no flowering plants in the field).

Other non-target arthropods :

The formulation (EXP 31279A, SC containing 9.57 g/l pyraflufen-ethyl and 519 g/l bifenox) is harmful to *Typhlodromus pyri* and slightly harmful to both plant dwelling organisms (*Chrysoperla carnea, Coccinella septempunctata*). No further testing was required as the exposure of these arthropods is very limited under the conditions of use (herbicide sprayed at tillering of the cereals).
The formulation is harmless to soil dwelling organisms (*Pardosa amentata, Poecilus cupreus*)

2.6.4 Effects on earthworms and other soil macro-organisms

Toxicity to earthworms :

LC_{50} (*Eisenia foetida,* 14 d) > 1000 mg a.s./kg

TER earthworms :

The following assumptions were made to assess the acute risk for earthworms :
- 100% of the spray reaches the soil surface.
- The substance (or formulation) is distributed in a 5 cm soil layer with a soil density of 1.5 g/cm^3

Due to the very high margin of safety observed with the acute TER for the a.s. (> 55556) and the formulation EXP31279A (564) , further testing of metabolites and/or sublethal effects is not required.

2.6.5 Effects on soil micro-organisms

The impact on the soil nitrogen turnover and on the respiration rate is negligible at the application rates of 20 and 100 g a.s./ha. These rates are equivalent to 1.5 and 7.4 the GAP rate of 13.5 g a.s./ha. The test should have been performed at 1 and 10 times the GAP rate. Nevertheless, We consider that the test is sufficient to assess the effects of pyraflufen-ethyl on soil micro-organisms

The test with the representative formulation presents numerous deviations. A new test should be provided.

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

The notifier submitted a summary of the screening tests performed on a wide range of organisms.

2.6.7 Effects on biological methods of sewage treatment

Under the normal conditions of practical use (herbicide in cereals) it is not expected that pyraflufen-ethyl will contaminate sewage treatment plant**.**

LEVEL 2

Pyraflufen-ethyl

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 or detection
A/G	albumin/globulin ratio
ai	active ingredient
ALD_{50}	approximate median lethal dose, 50%
AOEL	acceptable operator exposure level
AMD	automatic multiple development
approx.	approximate
as	active substance
at. wt.	atomic weight
ATP	adenosine triphosphate
BCF	bioconcentration factor
bfa	body fluid assay
BOD	biological oxygen demand
b.p.	boiling point
BSP	bromosulfophthalein
BUN	blood urea nitrogen
bw	body weight
c	centi- (x 10^{-2})
°C	degree celsius (centigrade)
CAD	computer aided design
cd	candela
CDA	controlled drop(let) application
CEC	cation exchange capacity
cf	confer, compare to
ChE	cholinesterase
cm	centimetre
CNS	central nervous system
CoC	code of conduct
COD	chemical oxygen demand
cu	cubic

cv	coefficient of variation
Cv	ceiling value
cyt	cytogenetic analysis
d	day
DL	racemic (optical configuration, a mixture of dextro- and laevo-; preceding a
dlt	dominant lethal test
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic Acid
dnd	DNA-damage
dni	DNA-inhibition
dnr	DNA-repair
dns	unscheduled DNA-synthesis
DO	dissolved oxygen
DOC	dissolved organic carbon
DT	disappearance time
DTH	delayed-type hypersensitivity
EC	effective concentration
ECD	electron capture detector
ELISA	enzyme linked immunosorbent assay
EMDI	estimated maximum daily intake
EP	end-use product
ERL	extraneous residue limit
F_0	parental generation
F_1	filial generation, first
F_2	filial generation, second
FID	flame ionization detector
f.p.	freezing point
FPD	flame photometric detector
FPLC	fast protein liquid chromatography
g	gram
GAP	good agricultural practice
GC-EC	gas chromatography with electron capture detector
GC-MS	gas chromatography-mass spectrometry
GC-MSD	gas chromatography with mass-selective detection
GEP	good experimental practice

GFP	good field practice
G.I.	gastro-intestinal
GIT	gastro-intestinal tract
GL	guideline level
GLC	gas liquid chromatography
GLP	good laboratory practice
GPC	gel-permeation chromatography
GPPP	good plant protection practice
h	hour(s)
ha	hectare
Hb	haemoglobin
HCG	human chorionic gonadotropin
hl	hectolitre
hma	host-mediated assay
HPLC	high pressure liquid chromatography or high performance liquid
HPPLC	high pressure planar liquid chromatography
HPTLC	high performance thin layer chromatography
HRGC	high resolution gas chromatography
Ht	haematocrit
I_{50}	inhibitory dose, 50%
IC_{50}	median immobilization concentration
i.d.	internal diameter
ID	ionization detector
i.m.	intramuscular
inh	inhalation
i.p.	intraperitoneal
IPM	integrated pest management
IR	infrared
i.v.	intravenous
k	kilo
K	Kelvin
kg	kilogram
l	litre
LBC	loosely bound capacity
LC	lethal concentration

LC	liquid chromatography
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
LOAEL	lowest observable adverse effect level
LOD	limit of determination
LOEC	lowest observable effect concentration
LOEL	lowest observable effect level
LPLC	low pressure liquid chromatography
LSC	liquid scintillation counting or counter
LT	lethal threshold
m	metre
M	molar
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
µg	microgram
mg	milligram
min	minute(s)
ml	millilitre
MLD	minimum lethal dose
mm	millimetre
mma	microsomal mutagenicity test
mmo	mutation in microorganisms
mnt	micronucleus test
mo	month(s)
mol	Mol
m.p.	melting point
MP	manufacturing-use product
mrc	gene conversion and mitotic recombination
MRE	maximum residue expected
MRL	maximum residue level
msc	mutation in mammalian somatic cells
MSDS	material safety data sheet
MTD	maximum tolerated dose

n	normal (defining isomeric configuration)
NAEL	no adverse effect level
n.d.r.	not dose-related
NEDI	no effect daily intake (mg/kg body wt/day)
NEL	no effect level
NERL	no effect residue level
NMR	nuclear magnetic resonance
no.	number
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 or detection
nse	non standard exposure
o	ortho (indicating position in a chemical name)
ODP	ozone-depleting potential
OP	organophosphorous pesticide
otr	oncogenic transformation
p	para (indicating position in a chemical name)
Pa	pascal
2-PAM	2-pralidoxime
PC	paper chromatography
PCV	haematocrit (packed corpuscular volume)
PD	position document
PEC	predicted environmental concentration
PED	plasma-emissions-detector
pH	pH-value
PHI	pre-harvest interval
pic	phage inhibition capacity
PNEC	predicted no effect concentration
p.o.	by mouth
P_{ow}	partition coefficient between n-octanol and water
ppb	parts per billion
ppm	parts per million
ppq	parts per quadrillion
ppt	parts per trillion

PSP	phenolsulfophthalein
PrT	prothrombin time
PRL	practical residue limit
PT	prothrombin time
PTT	partial thromboplastin time
RAC	raw agriculture commodity
RBC	red blood cell
Rf	ratio of fronts
RL_{50}	residual lifetime
RNA	ribonucleic acid
rns	rinsed
RPM	reversed phase material
RRT	relative retention time
s.c.	subcutaneous
SAC	strong adsorption capacity
SAP	serum alkaline phosphatase
SBLC	shallow bed liquid chromatography
sce	sister chromatid exchange
SD	standard deviation
SE	standard error
SEP	standard evaluation procedure
SF	safety factor
SFC	supercritical fluid chromatography
SFE	supercritical fluid extraction
SIMS	secondary ion mass spectroscopy
sin	sex chromosome loss and nondisjunction
slt	specific locus test
sp/spp.	species (only after a generic name)
SPE	solid phase extraction
SPF	specific pathogen free
sp gr	specific gravity
spm	sperm morphology
sq	square
SSD	sulphur specific detector
SSMS	spark source mass spectrometry
STEL	short term exposure limit
SVAT	soil-vegetation-atmosphere transfer

t	tonne (metric ton)
TADI	temporary acceptable daily intake
TBC	tightly bound capacity
TCD	thermal conductivity detector
TC_{Lo}	toxic concentration, low
TD	thermionic detector, alkali flame detector
TD_{Lo}	toxic dose low
tert	tertiary (in a chemical name)
TEP	typical end-use product
TGAI	technical grade of the active ingredient
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
trn	heritable translocation test
TWA	time weighted average
UDS	unscheduled DNA synthesis
ULV	ultra low volume
UV	ultraviolet
v/v	volume ratio (volume per volume)
WBC	white blood cell
wk	week
wt	weight
wt/vol	weight per volume
w/w	weight per weight
yr	year
<	less than
£	less than or equal to
>	greater than
³	greater than or equal to

Part 2 Organisations and Publications

BA	Biological Abstracts (Philadelphia)
CA	Chemical Abstracts
CAC	Codex Alimentarius Commission
CAS	Chemical Abstracts Service
CCPR	Codex Committee on Pesticide Residues
CIPAC	Collaborative International Pesticides Analytical Council Ltd
COREPER	Comite des Representants Permanents
EC	European Commission
ECCA	European Crop Care Association
ECPA	European Crop Protection Association
EHCD	Environmental Health Criteria Document
EINECS	European Inventory of Existing Commercial Chemical Substances
EPPO	European and Mediterranean Plant Protection Organization
EU	European Union
FAO	Food and Agriculture Organization of the UN
FJCMP	Joint FAO/WHO Food and Animal Feed Contamination Monitoring Programme
GATT	General Agreement on Tariffs and Trade
GIFAP	Groupement International des Associations Nationales de Fabricants de Produits Agrochimiques
IARC	International Agency for Research on Cancer
IBT	Industrial Bio-Test Laboratories
IMO	International Maritime Organisation
IOBC	International Organization for Biological Control of Noxious Animals and Plants
IPCS	International Programme on Chemical Safety
IR-4	Interregional Research Project No 4
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
JECFA	FAO/WHO Joint Expert Committee on Food Additives
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)

NATO	North Atlantic Treaty Organisation
NCI	National Cancer Institute (USA)
NCTR	National Center for Toxicological Research (USA)
NGO	non-governmental organization
OECD	Organization for Economic Cooperation and Development
PAN	Pesticide Action Network
RNN	Re-registration Notification Network
SCPH	Standing Committee on Plant Health
SI	Systeme International d'Unites
SITC	Standard International Trade Classification
UN	United Nations
UNEP	United Nations Environment Programme
WHO	World Health Organization
WTO	World Trade Organization
WWF	World Wildlife Fund

LEVEL 2

Pyraflufen-ethyl

Appendix 2 : Preparation (Formulation) Types and Codes

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 substance 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, homogeneous 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.
FG	Fine granule	A granule in the particle size range from 300 to 2500 µ.
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 ignition releases the active substances in the form of a smoke.

Code	Description	Definition
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 in an 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.
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	A stable suspension of active substance(s) in a fluid (= flowable concentrate) 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

Code	Description	Definition
		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 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 granule	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	

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

LEVEL 2

Pyraflufen-ethyl

Appendix 3 : Listing of endpoints

LEVEL 3

Pyraflufen-ethyl

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

3.1 Background to the proposed decision

-

3.2 Proposed decision concerning inclusion in Annex I

The postponement of the inclusion of the active substance in Annex I is proposed.

3.3 Rational for the postponement of the decision to include the active substance in Annex I, or for the conditions and restrictions to be associated with a proposed inclusion in Annex I, as appropriate

1) The mode of action of the active substance and the supplementary studies on mice and rats showed that the determination of the NOAELs should be based on the porphyrin accumulation :
- Pyraflufen-ethyl acts as an inhibitor of protoporphyrinogen IX oxidase (PPO).
PPO is one of the key enzymes in porphyrin biosynthesis, common to both plants and animals, as part of chlorophyll and heme synthesis.

- Supplementary studies which were performed in male mice or rats showed that feeding to male mice produced, at high doses, a clear evidence of liver cell damage and cell death (necrosis) consecutive to an oxidative stress and/or cytotoxicity resulting probably from the accumulation of porphyrins known to induce liver cell necrosis and inflammation followed by regenerative liver growth :

As the accumulation of porphyrin was not determined in the studies used for the AOEL and ADI definition, these endpoints should be considered as provisional.

A provisional AOEL systemic of 0.112 mg/kg bw/d can be calculated from a NOAEL of 20 mg/kg bw /d (lowest NOAEL) identified in the 90 day mice study. The oral absorption seems to be 56 %. The assessment factor of 100 was taken for extrapolation to man.

A provisional ADI of 0.2 mg/kg bw/day can be calculated from a NOAEL of 20 mg/kg bw/d (lowest NOAEL), identified in the 2 year rat and mice studies. The assessment factor of 100 (10 for interspecies variation x 10 for intraspecies variation) was taken for the extrapolation to man.

The Rapporteur Member State proposes to address this point to the notifier. As mice being the most sensitive species, it is necessary to define a NOAEL for porphyrin accumulation in liver before final ADI and AOEL can be proposed. However the consumer and operator exposure calculations which were made on the basis of these provisional endpoints show sufficient margin of safety. The Rapporteur Member State considers therefore that provisional authorizations could be granted for formulations containing the active substance.

2) In the teratogenicity study, rabbits appeared to be strongly sensitive to the toxic effects of pyraflufen-ethyl. Due to the high mortality and insufficient number of pregnant rabbits at the 2 top doses, the Rapporteur Member State did not accepted this study and required a new one at lower dosages.

LEVEL 4

Pyraflufen-ethyl

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 the Annex I

4.1 Identity of the active substance

-

4.2 Physical and chemical properties

Point addressed	Information or study required	Deadline
IIA 2.15	**Oxidizing properties of the a.s. : Information of the maximum burning rate of the barium nitrate/cellulose reference is required**	

4.3 Data on application and further information

Point addressed	Information or study required	Deadline
IIIA 4.1.2	The available packaging material was described and stated to have been approved according to ADR-methods 3552 to 3555. Reports describing the results of aforementioned tests were not submitted.	
IIIA4.1.3	**Report demonstrating the resistance of the packaging material to its contents**	

4.4 Methods of analysis

Point addressed	Information or study required	Deadline
IIA 4.1.1	Determination of pure a.s. in a.s. technical, accuracy of the HPLC-method remains to be addressed. No actual validation data were provided with regard to the methods for sulfate (turbidimetry) and moisture (coulometric moisture tester) analysis. **(Gladdines, 1995)**	

4.5 Toxicology and metabolism

Point addressed	Information or study required	Deadline
IIA 5.5	**- Information on the dose at which no porphyrin accumulation is observed in liver cells before definitive ADI and AOEL can be proposed.**	
IIA 5.6.2	**Rabbit teratogenicity study**	

4.6 Residue data

-

4.7 Environmental fate and behaviour

-

4.8 Ecotoxicology

Point addressed	Information or study required	Deadline
IIIA 10.7.1	**Impact of the formulation** EXP31279A **on soil microbial activity (laboratory)**	

4.9 Classification, packaging and labelling

Point addressed	Information or study required	Deadline
IIA 7.2.1.3.1	**The active substance is not readily biodegradable. A study for confirmation is ongoing.**	