LEVEL 1

Kresoxim-methyl

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

1.1 Purpose of the monograph (Document A)

- Evaluation of the dossier submitted as an application for the first inclusion of a new active substance in Annex I of the Council Directive 91/414/EEC. The annex III of the original dossier is dealing with the product MENTOR (Kresoxim-methyl + Fenpropimorph / fungicide used in cerealiculture)

- Two applications for provisional selling authorizations of products containing Kresoxim-methyl were submitted after the reception of the original dossier :
ALLEGRO (Kresoxim-methyl + Epoxiconazole / fungicide used in cereals)
CANDIT (Kresoxim-methyl / fungicide used in apple)

1.2 Identity of the active substance (Annex IIA 1)

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

Headquarter/Germany

BASF Aktiengesellschaft
Registrierung
Postfach 120
D-67114 Limburgerhof

Tel. No.: (0)6236/68-2603
Tfx. No.: (0)6236/68-2604
Contact person: Ms. Regina Baßler
Alternative person: Dr. Henning Regenstein
Tel. (0)6236/68-2413

1.2.2 Manufacturer of the active substance (Annex IIA 1.2)

Manufacturer and contact point: as applicant

1.2.3 ISO common name and synonyms (Annex IIA 1.3)

Common name (ISO, proposed): Kresoxim-methyl

1.2.4 Chemical name (Annex IIA 1.4)

IUPAC name: methyl (E)-2-methoxyimino-2-[2-(o-tolyloxymethyl)phenyl]acetate
CA name : a-(methoxyimino)-2-[(2-methylphenoxy)methyl]benzeneacetic acid methyl ester

Further information
Derivatives: Neither free acid nor different ester developed as active substance.
Chemical family: "Strobilurin analogue" according to those fungal products of fungicidal activity.

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

Code numbers of BASF for the a.s. : LAB 242 009, BASF Reg.-No. 242 009, BAS 490 F

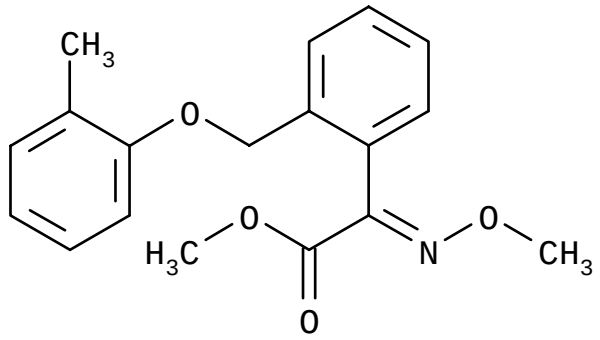
1.2.6 CAS, EEC and CIPAC numbers (Annex IIA 1.6)

CAS:	143390-89-0
CIPAC:	not assigned
EINECS:	not assigned

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

Molecular formula: $C_{18}H_{19}NO_4$

Structural formula:



Molecular mass: 313.3

1.2.8 Method or methods of manufacture (Annex IIA 1.8)

Confidential information, see Annex C

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

Minimum purity = 910 g a.s./kg technical product

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

Confidential information, see Annex C

1.2.11 Analytical profile of batches (Annex IIA 1.11)

Confidential information, see Annex C

1.3a Identity of the plant protection product MENTOR (Annex IIA 3.1; Annex IIIA 1)

1.3.1a Current, former and proposed trade names and development code numbers (Annex IIIA 1.3)

Trade name : MENTOR

Code number : BAS 492 01 F

1.3.2a Manufacturer or manufacturers of the plant protection product (Annex IIIA 1.2)

- Holder of the authorization of sale of MENTOR in Belgium :
BASF Belgium S.A.
Avenue Hamoir 14
B-1180 Bruxelles
Contact person: Mr. Defloor

- Contact point for Europe :
Headquarter/Germany
BASF Aktiengesellschaft
Registrierung
Postfach 120
D-67114 Limburgerhof
Tel. No.: (0)6236/68-2603
Tfx. No.: (0)6236/68-2604
Contact person: Ms. Regina Baßler
Alternative person: Dr. Henning Regenstein
Tel. (0)6236/68-2413

1.3.3a Type of the preparation and code (Annex IIIA 1.5)

Physical state : suspo-emulsion (SE)

1.3.4a Function (Annex IIIA 1.6)

fungicide

1.3.5a Composition of the preparation (Annex IIIA 1.4)

Table1.3.5a-1 : Composition of the preparation MENTOR

Component	Content at 20 °C		Function
	g/l	g/kg	
1- Fenpropimorph (pure a.s.)	300	288	Active substance
2- Kresoxim-methyl (pure a.s.)	150	144	Active substance
Other components	Confidential information, see Annex C		

1.4a Uses of the plant protection product MENTOR

1.4.1a Fields of use (Annex IIA 3.3; Annex IIIA 3.1)

Agriculture

1.4.2a Effects on harmful organisms (Annex IIA 3.2; Annex IIIA 3.2)

Kresoxim-methyl is a mitochondrial respiration inhibitor. Depending on pathogens and time of application the effects are protective, curative and/or eradicative

Fenpropimorph is particularly effective for the control of powdery mildew and rust diseases of cereals. In addition to prophylactic effects, its systemic activity allows the control of established infections by preventing the further growth of fungal structure within plant tissues. Diffusion in the gas phase may also be a factor in the protective effects of the compound on plant tissue not present at the time of spraying

1.4.3a Summary of intended uses (Annex IIA 3.4; Annex IIIA 3.3 to 3.7, 3.9)

Table 1.4.3-1 : Intended uses of kresoxim-methyl (formulation MENTOR) - Data in amount kresoxim-methyl

Crop Disease	Country : Europe	Maximum rate per application (kg a.s./ha)	Maximum rate per season (kg a.s./ha)	Spray concentration (g/l)	Maximum number of applications per season Timing	spray interval in days	Pre-harvest interval in days
Winter wheat, spring wheat, spelt *Erysiphe graminis sp. tritici* *Septoria tritici* *Septoria nodorum*	North	0.105	0.210	- (*)	1-2 between the stages last leave and ears forming	-	35
Winter barley, spring barley *Erysiphe graminis sp. hordei* *Puccinia hordei* *Pyrenophora teres*	North	0.105	0.210	- (*)	1-2 at the stage first node and/or stage last leave	-	35

(*) : depending upon spray technique : 200-400 l water/ha

1.4.4a Information on authorizations in EU Member States (Annex IIIA 12.1)

Table 1.4.4a-1 : Authorizations and Registrations in the EU

Country	Type of authorization	Crops/uses	Authorization details
Belgium	Commercial	- Winter wheat, spring wheat, spelt - Winter barley, spring barley	MENTOR SE Reg. N°. 8818/B Exp. Date : 14.03.1997

1.3b Identity of the plant protection product ALLEGRO (Annex IIA 3.1; Annex IIIA 1)

1.3.1b Current, former and proposed trade names and development code numbers (Annex IIIA 1.3)

Trade name : ALLEGRO
Code number : BAS 494 02 F

1.3.2b Manufacturer or manufacturers of the plant protection product (Annex IIIA 1.2)

- Holder of the authorization of sale of ALLEGRO in Belgium :
BASF Belgium S.A.
Avenue Hamoir 14
B-1180 Bruxelles
Contact person: Mr. Defloor

- Contact point for Europe :
Headquarter/Germany
BASF Aktiengesellschaft
Registrierung
Postfach 120
D-67114 Limburgerhof
Tel. No.: (0)6236/68-2603
Tfx. No.: (0)6236/68-2604
Contact person: Ms. Regina Baßler
Alternative person: Dr. Henning Regenstein
Tel. (0)6236/68-2413

1.3.3b Type of the preparation and code (Annex IIIA 1.5)

Physical state : SC (suspension concentrate)

1.3.4b Function (Annex IIIA 1.6)

Fungicide

1.3.5b Composition of the preparation (Annex IIIA 1.4)

Table1.3.5b-1 : Composition of the preparation ALLEGRO

Component	Content at 20 °C		Function
	g/l	g/kg	
1- Epoxiconazole (pure a.s.)	125	115	Active substance
2- Kresoxim-methyl (pure a.s.)	125	115	Active substance
Other components	Confidential information, see Annex C		

1.4b Uses of the plant protection product ALLEGRO

1.4.1b Fields of use (Annex IIA 3.3; Annex IIIA 3.1)

Agriculture

1.4.2b Effects on harmful organisms (Annex IIA 3.2; Annex IIIA 3.2)

Kresoxim-methyl is a mitochondrial respiration inhibitor. Depending on pathogens and time of application the effects are protective, curative and/or eradicative

Epoxiconazole has protective, curative and/or eradicative effects ; Systemic transport in phloem and xylem

1.4.3b Summary of intended uses (Annex IIA 3.4; Annex IIIA 3.3 to 3.7, 3.9)

Table 1.4.3b-1 : Intended uses of kresoxim-methyl (formulation ALLEGRO) - Data in amount kresoxim-methyl

Crop Disease	Country : Europe	Maximum rate per application (kg a.s./ha)	Maximum rate per season (kg a.s./ha)	Spray concentration (kg/100l)	Maximum number of applications per season Timing	spray interval in days	Pre-harvest interval in days
Wheat *Pseudocercosporella herpotrichoïdes*	North	0.150	0.150	- (*)	1 stage first node	-	35
Wheat *Erysiphe graminis sp. tritici* *Puccinia recondita* *Puccinia striiformis* *Septoria tritici* *Septoria nodorum* *Fusarium sp*	North	0.105	0.210	- (*)	1-2 between stages first node and ears forming	-	35
Barley *Erysiphe graminis sp. hordei* *Puccinia hordei* *Puccinia striiformis* *Pyrenophora teres* *Rhynchosporium secalis*	North	0.105	0.210	- (*)	1- 2 stages first node and/or last leave	-	35
Triticale, rye *Puccinia recondita* *Puccinia striiformis* *Septoria tritici*	North	0.105	0.105	- (*)	1 between stages last leave and ears emergence	-	35
Spelt *Erysiphe graminis* *Puccinia recondita* *Puccinia striiformis*	North	0.105	0.210	- (*)	1-2 between stages first node and ears forming	-	35

(*) : depending upon spray technique : 200-400 l water/ha

1.4.4b Information on authorizations in EU Member States (Annex IIIA 12.1)

Table 1.4.4b-1 : Authorizations and Registrations in the EU - ALLEGRO

Country	Type of authorization	Crops/uses	Authorization details
Belgium	Commercial	Winter wheat, spring wheat, winter barley, spring barley, triticale, rye, spelt	ALLEGRO SC Reg. N°. 8817/B Exp. Date : 14.03.1997

1.3c Identity of the plant protection product CANDIT (Annex IIA 3.1; Annex IIIA 1)

1.3.1c Current, former and proposed trade names and development code numbers (Annex IIIA 1.3)

Trade name : CANDIT
Code number : BAS 490 02 F

1.3.2c Manufacturer or manufacturers of the plant protection product (Annex IIIA 1.2)

- Holder of the authorization of sale of CANDIT in Belgium :
BASF Belgium S.A.
Avenue Hamoir 14
B-1180 Bruxelles
Contact person: Mr. Defloor

- Contact point for Europe :
Headquarter/Germany
BASF Aktiengesellschaft
Registrierung
Postfach 120
D-67114 Limburgerhof
Tel. No.: (0)6236/68-2603
Tfx. No.: (0)6236/68-2604
Contact person: Ms. Regina Baßler
Alternative person: Dr. Henning Regenstein
Tel. (0)6236/68-2413

1.3.3c Type of the preparation and code (Annex IIIA 1.5)

Physical state : WG

1.3.4c Function (Annex IIIA 1.6)

Fungicide

1.3.5c Composition of the preparation (Annex IIIA 1.4)

Table1.3.5c-1 : Composition of the preparation CANDIT

Component	Content at 20 °C g/kg	Function
1 - Kresoxim-methyl (pure a.s.)	500	Active substance
Other components	Confidential information : see Annex C	

1.4c Uses of the plant protection product CANDIT

Fungicide

1.4.1c Fields of use (Annex IIA 3.3; Annex IIIA 3.1)

Orchards (apples, pears)

1.4.2c Effects on harmful organisms (Annex IIA 3.2; Annex IIIA 3.2)

Kresoxim-methyl is a mitochondrial respiration inhibitor. Depending on pathogens and time of application the effects are protective, curative and/or eradicative

1.4.3c Summary of intended uses (Annex IIA 3.4; Annex IIIA 3.3 to 3.7, 3.9)

Table 1.4.3c : Intended uses of kresoxim-methyl (formulation CANDIT) - data in amount kresoxim-methyl

Crop Disease	Country : Europe	Maximum rate per application (kg a.s./ha)	Maximum rate per season (kg a.s./ha)	Spray concentration (kg/100l)	Maximum number of applications per season Timing	spray interval in days	Pre-harvest interval in days
Apples *Venturia inequalis*	All	100	800	- (*)	6-8 from the first 'warning' to the end of the ascospores release period; curative efficacy up to 96 hours after the infection	10-14	35
Apples *Podosphaera leucotricha*	All	100	800	- (*)	6-8 from the first 'warning' to the end of the ascospores release period; curative efficacy up to 96 hours after the infection	10-14	35

(*) : depending upon spray technique : 1000-1500 l water/ha

1.4.4c Information on authorizations in EU Member States (Annex IIIA 12.1)

Table 1.4.4c-1 : Authorizations and Registrations in the EU - CANDIT

Country	Type of authorization	Crops/uses	Authorization details
Belgium	Commercial	Apples (also in Integrated Pest Management)	CANDIT 50 % WG Reg. N°. 8829/B Exp. Date : 14.03.97

LEVEL 2

Kresoxim-methyl

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

2.1 Identity

The kresoxim-methyl technical has a minimal purity of 910 g/kg.

Studies do not reveal impurities of particular toxicological or environmental concern.
All the informations concerning the identity of the active substance and the method of manufacture are well documented.

2.2 Physical and chemical properties

Active substance :
Kresoxim-methyl is a strobilurin fungicide which can be formulated as suspo-emulsion, suspension concentrate, water dispersible granule.

The main physico-chemical properties of the a.s. are :

Molecular weight :	313.3
Water solubility :	2.00 mg/l at 20°C
Partition coefficient (Kow) :	2500 at 25°C
Vapour pressure :	2.3 10^{-6} Pa at 20°C
Dissociation in water :	no dissociation at pH 4.0 to 6.3
Photodegradation :	half-life under continuous irradiation : 40.41 hours
Hydrolysis rate in function of pH :	DT50 (pH 5) = 875 days DT50 (pH 7) = 34 days DT50 (pH 9) = 7 hours
Flammability - auto-flammability :	no burning no self-heating up to 400°C
Explosive properties :	not potentially explosive
Oxidizing properties :	not potentially oxidizing

Formulations :
No evidence of adverse physical or chemical properties of the formulation MENTOR.
MENTOR is non-explosive, non-oxidizing and non-flammable.
Summary tables of the physico-chemical properties of MENTOR are given in Annex B, point 2.1

No evidence of adverse physical or chemical properties of the formulations ALLEGRO and CANDIT. (The physico-chemical characteristics of these two products are not reported in the monograph.)

2.3 Details of uses and further information

Fields of use :
In cereals (wheat, barley, spelt, rye,triticale) 1 or 2 foliar applications are made at an application rate of 100-150 g a.s./ha during the growth of the plants (between stages first node and ears forming)

In orchard (apples, pears) a maximum of 8 applications are made during the growing season at an application rate of 100 g a.s.

Viticulture is another expected use (metabolism and residue information submitted in the notifier's dossier was taken into account in the monograph)

The notifier expects to extend the use of the a.s. to other crops in the near future (ornamentals, tomato, pepper, cucumber, leek, melon, onion, pea, sunflower, sugar beet)

Extent of the risk assessment :
The operator/ worker exposure risk assessment takes into account the uses in cereals (formulations MENTOR and ALLEGRO) and the use in orchard (formulation CANDIT). It can be considered that the risk to operator/worker in viticulture is intermediate between field uses and orchard uses.

The risk assessment due to exposure through the diet takes into account the uses in cereals (formulations MENTOR and ALLEGRO), the use in orchard (application of formulation CANDIT in apples and pears) and the uses in viticulture (expected use)

The calculations of PEC soil, ground water and surface water as well as the evaluation of the risk to non target organisms are performed taking account the uses in cereals (formulations MENTOR and ALLEGRO) and the use in orchard (formulation CANDIT).
It is considered that the risk assessment for orchard use also covers viticulture.

Packaging :
The description of the packagings of the formulation MENTOR (Annex III submitted in the scope of the inclusion of the a.s. in Annex I) was submitted.

According to ADR 2600, testing is not required for the formulations MENTOR, ALLEGRO and CANDIT (DL_{50} oral > trigger value of 500 mg/kg; LD_{50} dermal > trigger value of 1000 mg/kg; LC_{50} (1hour) > trigger value of 10 mg/l)
No study was submitted testing the suitability and the resistance of the packagings.

Security :
Hazards identification :
According to EU guidelines no classification

Handling and storage :
To maintain quality, store in a dry place and protect from temperatures below 0 and above 40 °C.
Store so that unauthorised persons do not have access.
Keep away from food, drink and animal feeding stuffs.
Keep container tightly closed and in a well-ventilated place.
Remainders of tank mixes are to be diluted with water by 1 : 10 and sprayed onto the previously treated area.

Transport information :
According to UN guidelines no classification
Fire-fighting measures :

Extinguishing media:-Sprayed water, foam, CO_2, extinguishing powder, sand
Fire-fighting water should be contained.
Combustion gases:-In the event of fire, the formation of CO_2/CO, H_2O, N_2/NO_x, SO_2/SO_3, SiO_2, Na_2CO_3 and other sodium salts is to be expected.

Emergency measures in the case of an accident :
During cleaning operations safety goggles, rubber gloves, mouth-and-nose-mask and protective clothing shall be worn as standard precaution.

Destruction and decontamination :
Neutralization :
Chemically speaking, the product and its aqueous dilutions are neutral. Chemical conversions are not advised.

Controlled incineration:
“Small as large quantities shall be disposed of by combustion in a licensed incinerator. Additional methods are described in the GIFAP monograph. "Disposal of unwanted pesticide stocks", 1991. Uncleaned empty containers shall be treated like full ones: tightly closed and clearly labelled.

Empty rinsed containers should be disposed of according to local regulations and best available practice. For up-to-date information consult your qualified adviser. Rinsing should comply with the "Guidelines for the rinsing of agrochemical containers" (published by ECPA, 1993)”

Pyrolytic behaviour :
Combustion of formulations (MENTOR, ALLEGRO, CANDIT) will produce CO_2/CO, H_2O, N_2/NO_x, SO_2, SiO_2 and Na_2CO_3 or other sodium salts. Approx. 1100 °C is advised as incineration temperature.

The formulations do not contain halogenated compounds which could lead to the formation of dioxins during incineration.

2.4 Impact on human and animal health

2.4.1 Effects having relevance to human and animal health arising from exposure to the active substance or to its transformation products

Metabolism :
After oral administration in the rat, kresoxim-methyl showed a rapid but saturable and low absorption from the GI tract.
Up to 71% of the parent compound was found in the feces, and biliary excretion accounted for only 14 to 43% of the dose. After parenteral administration, faecal excretion was considerably lower than after ingestion (23-48% versus 71%) and the fraction of the dose excreted via the urine was correspondingly increased. Moreover, when the results obtained at the low and high doses were compared, it became evident that the ratio of fecal versus urinary excretion increased with the dose.
In the rat, radioactive material was distributed in all tissues and organs throughout the body, and 96 h after dosing the total radioactivity in the organs was less than 2% of the dose administered. The highest radioactivity was associated with the gastro-intestinal tract and the organs of metabolism and elimination, liver and kidney.
After oral administration in the rat, the systemically available proportion of kresoxim-methyl was rapidly and completely metabolized. The ester cleavage, as indicated by the metabolites found in plasma, is the fastest and most important biotransformation step.
Due to the saturable absorption , excretion after oral administration mainly occurred, via feces (66-81% of the dose) . After intravenous application, equal amounts were excreted via urine (66%) and feces (48%). There was no evidence of accumulation of radioactive material after repeated dosing.
In vitro dermal absorption using human and rat skin was dose-dependent: after single application of the compound, the rate of penetration of kresoxim-methyl through rat skin was 3, 1.5 and 2.5 times greater than that observed in human skin at the low, intermediate and high dose levels, respectively.

The major metabolic pathways proposed for the active substance are similar in rats, goats and hens.
An additional minor pathway is , however, observed in hens. Unchanged parent compound was the predominant radioactive constituent in plants. Samples, however, from a rotational crop study did contain , if any, very low amounts of unchanged parent compound, and in these cases a high percentage of conjugated metabolites was identified.

Acute toxicity :
The acute toxicity of kresoxim-methyl is low. There were no treatment-related morphological alterations in kidneys and liver. After inhalation exposure, male rats presented signs of upper airway irritation (already at a concentration of 2.04 mg/l air) and systemic toxicity (at the concentration of 5.6 mg/l air).Local signs were discharged reddish nose, sounded and irregular respiration, crust formation and bloody nose, reddish and discharged eyes and reddish eyelids with crusts. Signs of systemic toxicity were : high stepping gait, reduced general state , squatting posture and piloerection. The fact that signs of systemic toxicity were seen upon inhalation of a dose of 475 mg/kg over 4 hours, i.e., a dose at least 10 times lower than the highest sign-free, oral dose tested, is in agreement with the partial absorption observed in the toxicokinetic studies after oral administration.

Kresoxim-methyl has no skin or eye irritant properties and is not a sensitiser. It should not be classified for acute toxicity.

Genotoxicity :
Kresoxim-methyl is not genotoxic under the conditions of the assays . It , however, induces some hepatocyte proliferation.

Short- and long-term toxicity:
After subchronic oral exposure at the MTD of kresoxim-methyl, rats showed increases in liver weight, serum albumin and GGT, decreases in the number and the content of fat containing vacuoles in the liver, decreases in serum AP , ALT and AST ,without overt signs of hepatotoxicity. At the 28 day MTD dose no alterations could be observed at the electron microscopic level in the liver peroxisomes or mitochondria. Although no clearcut changes

occurred in food intake, which would have explained a decrease in serum AP, additional information suggests that this might be due to a slight interference with fat absorption. Decreases in serum ALT and AST remain more difficult to explain, but being accompanied by an increase in GGT, suggest some metabolic stress.
An increase in TSH levels, without changes in T3 or T4 and without enzyme induction, an isolated finding in the 28 day rat test, is interpreted as a chance finding.

Negative results were obtained in a short term interaction study performed to assess whether inhibition of esterases that detoxify kresoxim-methyl by cholinesterase inhibitors may potentiate the toxicity of kresoxim-methyl.

Mice responded in a similar way, although the changes were less pronounced.

Dogs seemed to be more sensitive, especially regarding altered food intake, and reacted with vomiting and diarrhea, with impact on body weight and transient decreases in serum albumin and protein concentrations but without signs of organ toxicity.

Kresoxim-methyl has an oncogenic potential at the MTD (8000ppm) in rats and a significant increase in malignant liver tumours was reported . The primary epithelial neoplasms of the liver were cholangiomas, carcinomas, and cholangiocarcinomas. In both sexes, liver tumours occurred exclusively in old animals that survived until the scheduled termination of the study.
The non-neoplastic liver lesions-eosinophilic foci of hepatocellular alterations and hypertrophy of hepatocytes-further indicates metabolic stress on the liver parenchyma. The incidence and degree of severity of minimal to severe bile duct proliferation was increased in female of the high dose group (16000 ppm), while the incidence of fatty change was decreased. In male rats , significant and dose-dependent increase in GGT was found throughout the study at the MTD.

At doses of 200 and 800 ppm, no oncogenic or systemic toxic findings were noted.

As described above, kresoxim-methyl has no genotoxic properties and does not initiate the formation of liver foci as seen with the cancer initiator N-nitrosomorpholine. At carcinogenic doses it produced hepatic cell proliferation together with mild hepatic toxicity, both being reversible. On the basis of all data presented it can be concluded that kresoxim-methyl is a non-genotoxic carcinogen in the rat, acting as a promotor for which a threshold dose exists.

In C57BL-strain mice, the test article was not oncogenic under the conditions of this assay. Papillary necroses of the kidneys and increased number of females with amyloidosis of the liver associated with a higher degree of severity in females exposed to 8000ppm were considered as treatment related .

Reproductive toxicity and carcinogenicity :

Kresoxim-methyl had no adverse effects on reproductive parameters of rats , but produced some dose -dependent developmental toxicity in the pups, impaired body weight/body weight gain and some indications for delays in the morphological development at doses which produced clear parental toxicity. The overall and developmental NOAEL were 100 and 1500 mg/kg bw/d, respectively.

No substance related adverse effects were observed in pregnant rats and Himalayan rabbits and there were no indications of embryo-/fetotoxicity and especially no substance-induced signs of teratogenicity .

Table 2.4.1-1 : Summary of acute toxicity of kresoxim-methyl

Type of test Test species	Result	purity(%)	kresoxim-methyl batch n°.	reference
LD50 oral rat _+_	>5000 mg/kg bw	93.7	N 36	Kirsch et al.,1993
LD50 dermal rat	> 2000 mg/kg bw	93.7	N 36	Kirsch et al.,1993a
LC50 rat , 4 h dust _;_	>5.6 mg/l air = (475 mg/kg)	96.6	N 30	Gamer et al.,1992
Skin irritation rabbit 4 h	non irritant	93.7	N 36	Rossbacher and Kirsch,1992
Eye irritation rabbit	not irritant	93.7	N 36	Rossbacher and Kirsch,1992a
Skin sensitization guinea pig M&K	not a sensitizer	93.7	N 36	Rossbacher and Kirsch,1993

Table 2.4.1-2 : Summary of short-term toxicity of kresoxim-methyl

Type of test Test organism	Results			kresoxim-methyl, purity (%) batch number	References
	NOAEL mg/kg bw/d	LOAEL mg/kg bw/d	critical effects		
28 d , p.o., rat	_: 365 _: 375	1428 1481	ì serum GGT, albumin, TSH	96.5 % CP 5864	Schilling et al., 1992
28 d, p.o., mice	_: 485 _: 798	2141 3755	î triglycerides, cholesterol and lymphocytes	96.5 % CP 5864	Schilling et al., 1992a
90 d, p.o., rat	_: 146 _: 43	577 172	ì relative liver weight	98.7 % N 21	Mellert et al.,1994
90 d, p.o., mice	_: 230 _: 2583	909 -	altered weight parameters	98.7 % N 21	Mellert et al.,1994a
90 d, p.o. ,dog	_:150 _: 168	776 846	î serum albumin and protein; î body weight gain	94%, N 27; 96.6%, N 30	Mellert et al.,1994b
21 d, dermal, rat _+_	1000	-	no effect	94.3% N 36	Kirsch et al.,1994
1 yr, p.o. ,dog	_: 138 _ : 761	714 -	î body weight	93.7 % N 36	Hellwig et al.,1994

Table 2.4.1-3 : Summary of genotoxicity of kresoxim-methyl

Type of test	Result	kresoxim-methyl purity, batch number	References
In vitro genotoxicity tests:			
Ames test TA1535, TA1537, TA98 and TA100+/- S9+ E.coli WP2uvrA	negative	93.7%; B.n°:N27	Gelbke et al.,1993
Ames test TA1535, TA1537, TA98 and TA100 +/- S9	negative	94.3%; B.n°:N36	Gelbke et al.,1994
HPRT locus assay in CHO-K1 cells	negative	94.3%; B.n°:N36	Pôlloth and Hoffmann, 1994
chromosomes aberrations on human lymphocytes+/- S9	negative	98.7%; B.n°:N21	Engelhardt and Hoffmann,1993
UDS in mammalian cells	negative	94.3%; B.n°:N36	Pôlloth and Hoffmann, 1994a
In vivo genotoxicity tests:			
micronucleus assay in mice (i.p exposure)	negative	93.7%; B.n°:N36	Engelhardt and Hoffmann,1993a
rat hepatocytes(unic oral adm.) : UDS	negative	94.3%; B.n°:N36	Pôlloth at al.,1994b
: proliferating activity	positive after 200 mg/kg bw	94.3%; B.n°:N36	
UDS in rat hepatocytes(oral adm.:3 wks)	negative	94.3%; B.n°:N36	Pôlloth at al.,1994c

Table 2.4.1-4 : Summary of long-term oral toxicity of kresoxim-methyl

Type of test Test organism	Results			kresoxim-methyl, purity (%) batch number	References
	NOAEL mg/kg bw/d	LOAEL mg/kg bw/d	critical effects		
2 yr, p.o. rat	_ :36 _: 48	370 503	ìGGT, liver weight, îbody weight, hepatocellular carcinoma	N27, 94%; N30, 96.6%; N36, 93.7%	Mellert et al.,1994c
2 yr, p.o. rat	_ :36 _: 47	375 497	eosinophilic foci in liver and hepatocellular carcinoma	96.6% ; N30 93.7% ; N 36 94%; N 27	Mellert et al.,1994d
18 mth, p.o., mice	_: 304 _: 81	1308 400	îbody weight; papillary necroses (kidneys);ì number	92.7 %; N 36 95.4% ; N 30	Mellert et al.,1994e

			of females with amyloidosis (liver)		

Table 2.4.1-5 :Summary of reproductive toxicity and teratogenicity of kresoxim-methyl

Type of test Test organism	Results			kresoxim-methyl, purity (%) batch number	References
	NOAEL mg/kg bw/d	LOAEL mg/kg bw/d	critical effects		
2 gen., rat, p.o.	100	424	F0: îbody weight; ì serum GGT; î liver fat storing cells F1b pup: retarded morpho.devel.	93.7% ; N 36	Hellwig et al.,1994a
terato., rat, p.o.	1000 (maternal +fetal)	-	no effect	93.7% ; N 36	Hellwig and Hildebrand,1994
terato., rabbit, p.o.	1000 (maternal +fetal)	-	no effect	96.6% ; N 30	Hellwig and Hildebrand,1994a

2.4.2 Establishment of an Acceptable Daily Intake (ADI)

Consumer exposure to kresoxim-methyl will be mainly orally, with food intake.

It appears from the animal experiment that a chronic exposure to 36 mg/kg bw/day (lowest NOAEL, taken from the 2 year rat study) of kresoxim-methyl will not result in any toxic effect. At a higher dose hepatotoxic effects were seen. A lower NOAEL in the short term cell proliferation studies is not taken into account since the LOAEL in that study is higher than the NOAEL in the 2 year rat study.

The critical toxic effect in the rat is an hepatic toxicity resulting in an increased occurrence of hepatocarcinomas. Kresoxim-methyl is not genotoxic, the carcinogenic effect only occurs in old rats and seems to be mediated via induction of cell proliferation. It means that below an active dose, the potential to induce tumours is negligible. Therefore, but because of the tumour effect, an irreversible second end-point, an uncertainty factor of 250 is proposed for the extrapolation to man:

ADI = 0.15 mg/kg bw/day

This ADI is 2500 lower than the LOAEL producing liver tumours in the rat, which seems sufficient for a non genotoxic carcinogenic substance (1000 being a minimum).

2.4.3 Establishment of an Acceptable Operator Exposure Level (AOEL)

Operator exposure to kresoxim-methyl will be via several routes, by inhalation, via the skin and orally, each contributing to an internal dose. The exposure may occur during different time spans of their professional life. Therefore, we propose to calculate an Acceptable Exposure Level short-term (AELshort-term) and an Acceptable Exposure Level long-term (AEL long term), both internal doses.

Acceptable exposure level short-term in man, an internal dose (AELshort-term):

The AELshort-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 uncertainty factor, chosen in function of the critical effect observed in the animal experiments.

It appears from the animal experiment that a subchronic exposure to 140 mg/kg bw/day (lowest NOAEL, taken from the 1 year dog) of kresoxim-methyl will not result in any toxic effect. A lower NOAEL in the 90 day rat study is not taken into account since the LOAEL in that study is higher than the NOAEL in the 1 year dog. At higher dose hepatotoxic effects are seen.
It further appears from the ADME studies that only part of the kresoxim-methyl orally ingested is absorbed, a figure of about 50% at the dose of 140 mg/kg bw/day is proposed. The internal dose at that oral intake, therefore, equals 70 mg/kg bw/day. The critical toxic effect in the rat is an hepatic toxicity resulting, in the long term study, in an increased occurrence of hepatocarcinomas. Kresoxim-methyl is not genotoxic, the carcinogenic effect only occurs in old rats and seems to be mediated via induction of cell proliferation. It means that below an active dose, the potential to induce tumours is negligible. Therefore, but because of the tumour effect, an irreversible second end-point, an uncertainty factor of 250 is proposed for extrapolation to man.

This gives *:* *AELshort-term= 0.3 mg/kg bw/day.*

Acceptable Operator Exposure short-term (AOELshort-term)

The AOEL, being the sum total of the doses absorbed via different routes, equals the AEL short-term:

AOEL = 0.3 mg/kg bw/day

The AOEL is 600 lower than the LOAEL producing liver tumours in the rat, which seems not sufficient for a non genotoxic carcinogenic substance (1000 being a minimum). Therefore, a AOELlong term should be used for the risk assessment to ensure a sufficient safety margin :

Acceptable exposure level long-term in man, an internal dose (AEL long-term) :

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

It appears from the animal experiment that a chronic exposure to 36 mg/kg bw/day (lowest NOAEL, taken from the 2 year rat study) of kresoxim-methyl will not result in any toxic effect. At higher dose hepatotoxic effects are seen. A lower NOAEL in the short term cell proliferation studies is not taken into account since the LOAEL in that study is higher than the NOAEL in the 2 year rat study.
It further appears from the ADME studies that only part of the kresoxim-methyl, orally ingested, is absorbed, a figure of about 50% of the dose of 36 mg/kg bw/day can be accepted. The internal dose at that oral intake, therefore, equals 18 mg/kg bw/day.
The critical toxic effect in the rat is an hepatic toxicity resulting in an increased occurrence of hepatocarcinomas. Kresoxim-methyl is not genotoxic, the carcinogenic effect only occurs in old rats and seems to be mediated via induction of cell proliferation. It means that below an active dose, the potential to induce tumours is negligible. Therefore, but because of the tumour effect, an irreversible second end-point, an uncertainty factor of 250 is proposed for extrapolation to man.

This gives *:* *AELongt-term= 0.07 mg/kg bw/day.*

Acceptable Operator Exposure long-term (AOELlong-term)

The AOEL, being the sum total of the doses absorbed via different routes, equals the AEL long-term:

AOEL = 0.07 mg/kg bw/day

The AOEL is 1200 lower than the LOAEL producing liver tumours in the rat, which seems sufficient for a non genotoxic carcinogenic substance (1000 being a minimum).

2.4.4 Establishment of the (theoretical) drinking water limit.

Assuming that exposure through drinking water should not account for more than 10 % of the ADI (P), assuming an average consumption of 2 l of water per person per day (C) and an average body weight of 60 kg a limit of 0.45 mg/l is proposed.

$$MAC = \frac{ADI \times bw \times P}{C} = \frac{0.15 \times 60 \times 0.1}{2} = 0.45 \text{ mg/l}$$

MAC = maximum allowable concentration

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

Health risks for humans :
Based on the acute toxicity studies in animals, the acute hazard of the test substance is very low. It should not be classified for acute toxicity. After oral administration of kresoxim-methyl, there was a rapid but saturable and low absorption from the GI tract. Kresoxim-methyl was rapidly and completely metabolized. The compound does not accumulate in the body.
The risk for humans that genotoxicity, reproductive or developmental toxicity, long term oral toxicity will develop from the repetitive, adequate use of kresoxim-methyl, or that the substance will accumulate in the body is negligible. The carcinogenic effect noted in the long term rat studies was the result of tumour promoting properties of kresoxim-methyl, i.e.,the metabolic stress on hepatocytes, for which a threshold could be defined.
Because of a low vapour pressure, less than 10^{-6} Pa, and the rapid clearance of the substance from the air, Kresoxim-methyl will not reach consumers via the air.

Health risk for animals:
The acute hazard of the test substance is very low. After subchronic dermal exposure of rats, no systemic toxic effects were reported. Short-term toxicity studies showed a low toxicity of the active substance . The target organ is the liver. The results of chronic toxicity studies demonstrated that this compound has a low toxicity potential. Kresoxim-methyl caused the development of malignant liver tumours in rats at high dose levels.

Exposure resulting from the application of formulations containing kresoxim-methyl :

Risk for the operator :
MENTOR (BAS 492 01F) is a SE containing 150 g/l kresoxim-methyl and 300g/l fenpropimorph to be used in cereals.
For the intended use and type of application (spraying), the relevant way of exposure will be skin and inhalation. The estimated operator exposure was calculated on the basis of the German model.

* For kresoxim-methyl, the estimated exposure, without protective equipment, is 9.32 mg/person by dermal route and 0.0034 mg/person by inhalation route. The degree of exposure (E = 0.185) is <1.

* For fenpropimorph, the estimated exposure, without protective equipment, is 18.39 mg/person by dermal route, and 0.0067mg/person by inhalation which gives a E = 7.03
When protective equipment is used, as recommended by good agricultural practices (GAP), and as indicated on the labelling (gloves during mixing and protective garment with boots during application), the estimated dermal exposure to fenpropimorph will be reduced to 2.284 mg/person, giving a E= 0.884.
Fenpropimorph is a cholinesterase inhibitor and might theoretically, in toxic doses interfere with the metabolism of kresoxim-methyl. This will, however, not have any practical consequences: 1) fenpropimorph is a very weak cholinesterase inhibitor ; 2) when working according to GAP, exposure will be very low ; 3) the animal experiment showed that, even with severe cholinesterase inhibition, the toxicity of kresoxim-methyl was not exacerbated.
Application of MENTOR in the field, using protective equipment as indicated by GAP, is deemed to be without risk for the operator.

CANDIT (BAS 490 02 F) is a WG containing 50% kresoxim-methyl, to be used in orchards. For the intended use and type of application (spraying), the relevant way of exposure will be skin and inhalation. The estimated operator exposure was calculated on the basis of the German model. In the absence of any protective equipment, the estimated operator exposure is 10.80 mg/person by dermal route and 0.0208 mg/person by inhalation route, which gives a E=0.218.
Application of CANDIT in the field, is deemed to be without risk for the operator.

ALLEGRO (BAS 494 02 F) is a SE containing 125 g/l kresoxim-methyl and 125 g/l epoxiconazol to be used in cereals. For the intended use and type of application (spraying), the relevant way of exposure will be skin and inhalation.
The estimated operator exposure was calculated on the basis of the German model.
* In the absence of any protective equipment, the estimated operator exposure to kresoxim-methyl is 11.1 mg/person by dermal exposure and 0.004 mg/person for inhalation , which gives a E= 0.221.
* For epoxiconazol, the estimated operator exposure is 11.10 mg/person by dermal route and 0.004 mg/kg by inhalation route corresponding to a E = 1.964
When protective equipment is used, as recommended by good agricultural practices (GAP),and as indicated on the labelling (gloves during mixing and protective garment with boots during application), the estimated exposure to kresoxim methyl and epoxiconazole will be reduced to 1.36 mg/person by dermal exposure which gives an E= 0.0277 for kresoxim methyl and E= 0.244 for epoxiconazole.
Application of ALLEGRO in the field, using protective equipment as indicated by GAP, is deemed to be without risk for the operator.

Risk for the bystander:
The usual form of application of MENTOR, CANDIT and ALLEGRO are by tractor-mounted boom sprayers , without bystanders. Bystander exposure has, therefore, not to be calculated.
Due to the low vapour pressure of kresoxim-methyl, problems for bystanders as a result of inhalation are not anticipated.

Risk for the worker :
Worker exposure is also assumed to be far below the AOEL, even more than for the operator.
In cereal crops, re-entry of workers after application is not requested. Furthermore, the proposed pre-harvest interval of 35 days for MENTOR as well as for CANDIT and ALLEGRO is indicating a comfortable margin of safety for harvesters.
The use of plant protection products MENTOR, CANDIT or ALLEGRO should not involve any significant risk for workers carrying out normal operations in treated crops or in handling harvested products.

Human exposure resulting from ingestion of residues :

The calculation orf the TMDI according to the WHO guidelines resulted in an intake of residues representing about 1% of the ADI for a mean consumer.
Kresoxim-methyl should therefore not pose any risk to the consumer.

2.5 Methods of analysis

Validated methods were presented by the applicant to quantify the active substance and its impurities in the technical substance as manufactured , in the formulations and to determine the residues of the active substance and metabolites in food and feed, soil, water, air and in the biological fluids.

A.s. technical and formulations :
The methods submitted allow to determine the purity and the impurities of the technical a.s. as well as the a.s. content of the formulations .

Feed and food of plant origin :
The methods provided allow to determine kresoxim-methyl and its metabolites BF 490-2, BF 490-3 and BF 490-9 which were chosen as relevant residue relevant to be monitored for enforcement of MRLs in products of plant origin (wheat, apple, tomato, red pepper, melon, cucumber, onion, grapes and process fractions, apple and process fractions)
The applicability of a multi-residue method was tested.

Feed and food of animal origin :
The methods provided allow to determine kresoxim-methyl and its metabolites BF 490-1, BF 490-2 and BF 490-9 in conformity with the residue definition proposed for enforcement of MRLs for products of animal origin (milk, liver, kidney, skeletal muscle, fat and eggs).

Soil, water, air :
The methods provided allow to determine kresoxim-methyl and its main metabolite BF 490-1which were chosen as relevant substances in the definition of the residue relevant to environment.

2.6 Definition of the residues

2.6.1 Definition of the residues relevant to MRLs

Plant products :
Parent compound is the major component of the total residues in three metabolism studies on plants.
There is no metabolite of particular toxicological concern formed in plants.
Methods of analysis are available for the parent compound in plant products.

The residue definition for monitoring is proposed as parent compound only.

Conversion factors for assessment of consumer safety (calculation based on the ratio extractable residues/residue to be monitored):
- apple : 1
- grape : 2
- wheat : 3

Animal products :
The metabolism studies in goat and hens indicate an extensive degradation of kresoxim-methyl. The major component of the total residue differs from tissue to tissue.
In the feeding study with cows, the metabolite 490M1 appeared to be the major residue for liver, kidney and fat.

With the exception of 2 metabolites observed in laying hens (490M59 and 490M58), there is no metabolite of particular toxicological concern formed in livestock. However, as the potential intake of kresoxim-methyl by laying

hens is negligible, these hereabove mentioned metabolites are not currently relevant for assessment of the security of consumers.

Methods of analysis are available for residues of metabolites 490M2 and 490M9 in milk and for residues of metabolites 490M1, 490M2 and 490M9 in liver, kidney, muscle and fat of beef. A method of analysis for the determination of kresoxim-methyl and the metabolite 490M48 in eggs is also available.
With the exception of eggs, there is no analytical method for determination of parent compound in animal products.

The residue definition is proposed as:
- 490M9 (2-[2-(4-hydroxy-2-methylphenoxymethyl)phenyl]-2-methoxyiminoacetic acid) for milk, expressed as kresoxim-methyl;
- 490M1 (2-methoxyimino-2-[2-(o-tolyloxymethyl)phenyl]acetic acid) for liver, kidney, muscle and fat, expressed as kresoxim-methyl;
- kresoxim-methyl for eggs.

These metabolites can be considered as good indicator of the residue level in the respective tissues, and inclusion of other metabolites in the residue definition of animal products would increase the work of laboratories.
They can be considered as non fat soluble.

Conversion factors for assessment of consumer safety (calculation based on the ratio extractable residues/residue to be monitored):
- milk : 2
- muscle and fat : 3
- liver and kidney : 4
- eggs : 10

2.6.2 Definition of the residues relevant to the environment

The active substance is rapidly degraded to a free acid metabolite (BF 490-1) which is more persistent than the parent compound. Therefore both compounds have to be taken into account in the definition of the residue :

- Kresoxim-methyl
- BF 490-1 : (E)-2-[2-(2-methylphenoxy)-methyl]-phenyl-2-(methoxyimido) acetic acid

2.7 Residues

2.7.1 Residues relevant to consumer safety

The intended uses provided by the notifier are summarized in annex B, section B.6.4.
Main uses concern pome fruits, grapes and cereals. The intake of residues resulting from these agricultural practices by the consumer represents about 1% of the ADI for a mean consumer.
Intended uses on other crops are currently under development. For these crops, the assessment of the security of the consumer is not yet possible.

2.7.2 Residues relevant to worker safety

See point 2.4.5

2.7.3 Compliance with existing MRLs and/or proposed MRLs

There are currently no existing EC MRLs.

Based on the available residue data and feeding studies with dairy cows, the following MRLs can be proposed:

Expression of the residue	Products	MRL (mg/kg)
Kresoxim-methyl	Pome fruits	0.05 or 0.1
Kresoxim-methyl	grapes	0.5
Kresoxim-methyl	Other commodities of plant origin	0.05*
490M9 : (2-[2-(4-hydroxy-2-methylphenoxymethyl)phenyl]-2-methoxy-iminoacetic acid), expressed as kresoxim-methyl	milk	0.002*
490M1 (2-methoxyimino-2-[2-(o-tolyloxymethyl)phenyl]acetic acid), expressed as kresoxim-methyl	meat, liver, fat	0.01*
490M1 (2-methoxyimino-2-[2-(o-tolyloxymethyl)phenyl]acetic acid), expressed as kresoxim-methyl	kidney	0.05
kresoxim-methyl	eggs	0.01*

2.8 Fate and behaviour in the environment

2.8.1 Fate and behaviour in soil

Route of degradation :
The active substance is very rapidly degraded by the action of micro-organisms in aerobic conditions to free acid metabolite (BF 490-1). This metabolite is further degraded via the diacid metabolite 490 M4 to CO_2 and bound residues

The photolysis degradation seems to be slight (DT_{50} = 35 days). After 15 days 64.9% of the radioactivity is recovered as unchanged a.s., 2.4% as metabolite BF 490-1 and 22% as the sum of 11 unknown compounds.

The transformation of the a.s. to free acid metabolite (BF 490-1) was not affected by anaerobic conditions in comparison with aerobic conditions (DT_{50} < 1 day). Nevertheless the further metabolization of the free acid metabolite to CO_2 and bound residue was drastically reduced.

The degradation is drastically reduced in sterile conditions demonstrating the importance of biotic action in the degradation of the a.s.

Rate of degradation in the lab :
Kresoxim-methyl is rapidly degraded under aerobic conditions (DT_{50} <2 to 4.7 days DT_{90} < 1 to 5.2 days)
The degradation of the sum of a.s. and free acid metabolite BF 490-1 is slower (DT_{50} = 22 to 44(511) days under favorable conditions of moisture and temperature; DT_{50} = 129 to 294 days in less favorable conditions; DT_{90} 73-4599 days)

In all the lab tests performed, bound residues were under the threshold value of 70% after 100 days. The mineralization rate was > 5% after 100 days.

Field dissipation rate :
Dissipation of kresoxim-methyl was studied under various field conditions (temperature, types of soil).
The a.s. dissipated rapidly in the field (DT_{50} <1 to 3.8 days; DT_{90}= <1 to 18.4 days)
Metabolite BF 490-1 dissipated less rapidly (DT_{50} = 8 to 35 days ; DT_{90}= 18-117 days)

Adsorption :
Kresoxim-methyl is slightly adsorbed on soil (Koc = 219 to 372).
The adsorption of the free acid metabolite BF 490-1 is low (Koc = (<17) -17 to 24)

Mobility :
The leaching of the a.s. and free acid metabolite on soil column is very important : in lab leaching tests with soils poor in organic material (0.6 to 1.3 %) 33.2 to 76.9 % of applied residues are found in leachate.
On the other hand, in soils containing more organic material (2.1 to 2.6 %) leaching is reduced : 0.2 to 2.6 % (24.3 %) of applied residues are detected in leachate. Similar results are obtained in the aged residue test.

During the two-year lysimeter study, 0.66% to 0.88 % of the applied radioactivity was detected in the leachate.
The concentrations of kresoxim-methyl recorded in the leachate were <0.01 µg/l.
The concentrations of metabolite BF 490-1 recorded in the leachate were in the ranges 0.003-0.006 µg/l (leaching during the second year after the application of the a.s.) and 0.013 -0.038 µg/l (leaching during the year where the applications of a.s. were made)

PEC soil :
The following assumptions were made to estimate the PEC soil of kresoxim-methyl :
- DT_{50} = 3.8 days ; this value is taken as 'worst case' DT_{50} of the field dissipation data; generally the transformation

of the a.s to the BF 490-1 metabolite is in the range of less than one day to a few days (lab and field studies)
- 50 % interception of the a.s. by the crop
- soil layer of 5 cm and soil density of 1.5 g/cm^3
- the degradation rate was calculated according to first order kinetics.
- Due to the quick transformation of the a.s on the soil after multiple applications (max of 2 applications in cereals, 8 applications in orchard) the risk of acumulation is negligible.

- scenario in cereals : the highest application rate of 150 g a.s./ha (application of 1.2 l/ha ALLEGRO in Belgium) leads to an initial PEC of 0.100 mg a.s./kg soil. The risk assessment to soil organisms is based on this figure.
- scenario in apples and pears : the highest application rate of 100 g a.s./ha (application of 200 g/ha CANDIT) leads to an initial PEC of 0.067 mg a.s./kg soil

The same assumptions were made to estimate the PEC soil of metabolite BF 490-1(except DT_{50} = 35 days in the field)
- scenario in cereals : the highest application rate of 150 g a.s./ha (application of 1.2 l/ha ALLEGRO in Belgium) leads to an initial PEC of 0.100 mg metabolite/kg soil. The risk assessment to soil organisms is based on this figure.
- scenario in apples and pears : the highest application rate of 100 g a.s./ha (application of 200 g/ha CANDIT) leads to an initial PEC of 0.067 mg metabolite /kg soil

PEC groundwater :
It is sensible to turn one's attention to metabolite BF 490-1 when assessing the risk of the active substance to ground water. Indeed :
- Kresoxim-methyl is very rapidly transformed to the metabolite BF 490-1 (DT_{90} of <1-5 days)
- Kresoxim-methyl is potentially less mobile than the acid metabolite (Koc = 219-338)
- The physico-chemical properties of the metabolite BF 490-1 show that this substance is more persistent than the parent compound (DT_{50} field = 8-35 days; DT_{50} lab = 22-44(511) under favorable temperature and moisture conditions, DT_{50} = 129-294 days in less favorable conditions; stable under anaerobic conditions)
- The physico-chemical properties of the metabolite BF 490-1 show that this substance is more mobile than the parent compound (Koc = (<17) 17-24; important leaching in soils with less than 2% OC; concentrations up to 0.38 µg/l in the lysimeter study)

PECgw were calculated for the main metabolite of kresoxim-methyl (BF 490-1) with the simulation model PESTLA 2.3 for 5 scenarios taking into account different soil (brown mediterranean, grey-brown podzolic and podzolized soils), weather (North Western Europe, Western part of Central Europe, Southern Europe) and crop (2 X 150 g a.s./ha in cereals; 8 X 100 g a.s./ha in orchard) conditions in Europe.

A step-by-step procedure was used to calculate the PEC for different scenarios with different sets of physico-chemicals parameters with increasing level of being close to reality :
- PECgw of BF 490-1 based on parameters derived from the lab studies (best case : DT_{50} = 22 days, Kom = 13.9 dm^3/kg 1/n= 0.91) (average case : DT_{50} = 37.33 days, Kom = 5.95 dm^3/kg 1/n= 0.90) (worst case : DT_{50} = 59 days, Kom = 0.1 dm^3/kg 1/n= 0.94) are all above 0.1 µg/l.

- The maximum and annual mean "realistic PECgw", calculated using an efficient parameter combination (DT_{50} = 14.2 days, Kom = 22 dm^3/kg 1/n= 0.90) and realistic soil scenarios, are all below 0.1 µg/l BF 490-1. This last assessment can be accepted since it is based on realistic field lysimeter data performed in conditions enhancing leaching (sandy soil with low organic material and additional irrigation).

2.8.2 Fate and behaviour in water

Pathways of degradation :
Kresoxim-methyl is rapidly hydrolyzed under alcaline conditions (DT_{50} = 7 hours at pH 9, DT_{50} = 34 days at pH 7, stable at pH 5) and has a low solubility (2 mg/l). It is non volatile.

In a water/sediment system the a.s. is rapidly transformed to free acid metabolite BF 490-1.
- Both DT_{50} in sediment and water are less than 2 days.
- After 7 days, kresoxim-methyl accounts for 2.7% to 3.5 % of the radioactivity respectively in water and sediment. Free acid metabolite accounts at this time for 17.4-12.9 % in sediment, 62.3-68.3 % in water.
- After 100 days, 59.1-63.5 % radioactivity is in water, 34.2-24.8 % is in sediment. The free acid form is dominant; 7-12% of radioactivity is found as bound residue in the sediment. The mineralization is slow : after 100 days incubation 8-10% radioactivity is recovered as CO_2

The photolysis is a minor degradation pathway.

PEC surface water :
In the worst case situation (1 application of CANDIT in orchard, 100g a.s./ha, 30 cm water depth, 4% drift with 20 m buffer zone, 20% drift with 5 m buffer zone) the PECs are respectively 0.007 mg a.s./l and 0.001 mg a.s./l

In the worst case situation for cereal crops (1 application of ALLEGRO, 150 g a.s./ha, 30 cm water depth, 5 % drift with 1m buffer zone) the initial PEC is 0.003 mg a.s./l

2.8.3 Fate and behaviour in air

The maximum half-life of the a.s. is 11.1 hours.

2.9 Effects on non-target species

2.9.1 Effects on terrestrial vertebrates

Toxicity to birds :
The studies show that the a.s. has no inacceptable effects to birds (LD_{50} > 2510 mg/kg, LC_{50} > 5000 mg/kg feed, NOEC (reproduction) = 500 mg/kg feed)

TER birds :
The risk assessment to birds was performed for two worst case scenarios : cereals and apples

1 - Cereals
Risk assessment to birds exposed to kresoxim-methyl sprayed in cereals crop. The notifier based its assessment on measured concentration of the a.s. on the leaves. Just after the application of 105 g a.s/ha (0.7 l MENTOR/ha) the residue found on the leaves is equivalent to 5 mg a.s. /kg leaves. It is assumed that the birds food consumption is 30% bw.

Risk assessment to birds exposed to kresoxim-methyl sprayed in cereals crop made by the rapporteur (150 g a.s. corresponding to the worst case situation : application of ALLEGRO in wheat in Belgium). The initial concentration of a.s. in potential feed (4.65 mg a.s./kg leaves) was estimated according to Hoerger and Kenaga (1972). It is assumed that the birds food consumption is 30% bw.

We can conclude that the TER estimated via the Hoerger and Kenaga model are in accordance with the TER estimated via residue measurement of the cereals crop. It was shown that the risk to leaf-eating and insectivorous birds resulting from the exposure to the a.s. in cereals crop is negligible : TER acute = 1473; TER short term = 1000, TER long term = 100

2 - Apples
Risk assessment to birds exposed to kresoxim-methyl sprayed in orchard (100 g a.s. corresponding to the worst case situation : application of CANDIT in apples). The initial concentration of a.s. in potential feed is estimated according to Hoerger and Kenaga (1972). It is assumed that the birds food consumption is 30% bw.

We take into account for the evaluation of the risk to birds the estimated concentrations on the leaves. These concentrations are also equivalent to the estimated concentrations of a.s. on small insects. We conclude that the risk to leaf-eating and insectivorous birds resulting from the exposure to the a.s. in apple crop is negligible : TER acute = 2312; TER short term = 1613, TER long term = 161

TER small mammals :
The following toxicological endpoints were chosen to realize the risk assessment to small mammals
LD_{50} acute oral rat = 5000 mg/kg bw
NOAEL 28 days oral rat = 365 mg/kg food

Two scenarios were taken into account :

1 - Cereals
The risk assessment to mammals exposed to kresoxim-methyl sprayed in cereals crop was made taking into account the same assumptions as chosen in the risk to birds evaluation (150 g a.s. corresponding to the worst case situation : application of ALLEGRO in wheat in Belgium). It is assumed that the mammals food consumption is 30% bw.
The initial concentration of a.s. in potential feed (4.65 mg a.s./kg leaves and leafy crops - 16.8 mg a.s./kg on grass) was estimated according to Hoerger and Kenaga (1972).

The TER acute and short term (22-3584) are all above the threshold value of 10 indicating a low risk to small mammals (insect or leaf eating, grass eating mammals). Long term TER were not calculated since the exposure of the small mammals is not continuous (maximum of 2 applications/year)

2 - Apples
The risk assessment to mammals exposed to kresoxim-methyl sprayed in apples was made taking into account the same assumptions as chosen in the risk to birds evaluation (100 g a.s./ha application of CANDIT). It is assumed that the mammals food consumption is 30% bw.
The initial concentration of a.s. in potential feed (3.1 mg a.s./kg leaves and leafy crops - 11.2 mg a.s./kg on grass) was estimated according to Hoerger and Kenaga (1972)

The TER acute and short term (33-5376) are all above the threshold value of 10 indicating a low risk to small mammals (insect or leaf eating, grass eating mammals).
Long term TER were not calculated. It seemed more sensible to evaluate directly the long term and reproduction data than to perform calculations of long term TER based on unverified assumptions.

2.9.2 Effects on aquatic species

Toxicity in laboratory :
- The lab studies (acute and short-term) demonstrate that kresoxim-methyl is very toxic to fish, daphnia and algae :
LC_{50} (96 h, fish) = 0.15 to 0.62 mg/l,
LC_{50} (24-48h, daphnia) = 0.186 to 1.51 mg/l
EC_{50} (72 h, algae) = 0.063 mg/l

- Similar effects were observed with the formulations MENTOR, CANDIT, ALLEGRO

- The main metabolite BF 490-1 (acid form resulting from the hydrolysis) has a low toxicity :
LC_{50} (trout) >100 mg/l
EC_{50} (daphnia) >100 mg/l
EC_{50} (algae) > 500 mg/l

Effects in microcosm :
- In order to investigate the toxicity of kresoxim-methyl in conditions closer to agricultural practice, a microcosm study was performed mimicking the 'worst case' drift situation (100 g a.s./ha in orchard, drift 4, 20 and 100%, 6 applications).
This study shows that the effects of the a.s. in a microcosm are less important than in laboratory studies with single test species.
- Nevertheless effects on some zooplankton species were observed at the highest dose (unrealistic situation of overspray)
- Kresoxim-methyl degraded rapidly between the applications; there was never accumulation of the a.s. in water
The degradation of metabolite BF 490-1 is less rapid and there was a steady increase of this substance in water up to the last application. The degradation was rapid during mid-summer but slowed down during autumn and winter
- There was no accumulation of a.s and its free acid metabolite in the sediment.

Bioaccumulation behaviour :
- The water/octanol partition coefficient = 2500 indicates a high potential of bioaccumulation of the active substance. This is confirmed by the BioConcentration Factors determined experimentally (whole fish : 220; viscera : 430; fillets : 52). The depuration is rapid. The major compound in the organism is Kresoxim-methyl, the secondary compound BF 490-4 reaching up to 21.7 % in the viscera. Due to its low stability in water environment, Kresoxim-methyl does not risk to be concentrated in aquatic organisms.
- A theorical concentration in fish of 1.47 mg a.s./kg can be expected in the worst case situation (PEC = 0.0067 mg/l , apples, application of 100 g a.s/ha, spray drift = 20 % at 5m; BCF = 220). This concentration is transient due to very rapid depuration (DT_{50} = 0.37day).
The comparison of this figure (1.47 mg a.s./kg fish) with the relevant toxicological endpoints (NOAEL rats 90 d = 500 mg/kg food, NOEC mallard duck and quail = 5000 mg/kg food) showed that the risk of secondary poisoning is low.

Acute risk assessment for kresoxim-methyl :

The risk assessment to aquatic organisms was performed for two worst case scenarios : cereals and apples

1 - Cereals
Risk assessment for aquatic organisms exposed to kresoxim-methyl sprayed in cereals crop made by the rapporteur (150 g a.s. corresponding to the worst case situation : application of ALLEGRO in wheat in Belgium). The initial concentration of a.s. in water is estimated according to the BBA drift pattern (Ganzelmeier, 1995) taking into account a water depth of 30 cm.
The TERacute for the 1 m spray drift situation are below the threshold value of 100 (60-74 for fish and daphnia) showing a potential risk to aquatic organisms. Nevertheless this potential risk was addressed by the notifier (submission of a microcosm experiment mimicking the worst case situation in orchard)

2 - Apples
Risk assessment to aquatic organisms exposed to kresoxim-methyl sprayed in orchard (100 g a.s. corresponding to the worst case situation : application of CANDIT in apples). The initial concentration of a.s. is estimated according to the BBA drift pattern (Ganzelmeier, 1995) taking into account a water depth of 30 cm.
The calculation of the TER acute (below 100) showed that a potential risk to aquatic organisms was existing.
Therefore higher tiered experiment was submitted (microcosm) to evaluate the risk in situations closer to actual practice. In the microcosm experiment mimicking the drift situation in apple orchard (worst case situation) , minute effects were observed in the unrealistic overspray situation. No effect was observed in the drift situations treatments.

Acute risk assessment for metabolite BF 490-1 :
The risk was determined in the worst case situation of spray drift during application in orchard. We take the figure of 19.1 µg/l which is the maximum concentration measured in the microcosm study (concentration of metabolite just after the last application of 100 g a.s./ha) as worst case situation.
TER of 5236-26178 were calculated for fish, aquatic invertebrate and algae indicating a negligible risk.

Long term risk assessment for kresoxim-methyl and metabolite BF 490-1 :
The results of the microcosm study revealed that this risk is low : effects were observed only in the unrealistic overspray situation. No effect was observed in the drift situations treatments.

2.9.3 Effects on bees and other arthropods

Bees :
The calculation of Q_{HC} and Q_{HO} (<< 50) shows that the bees are not at risk due to the application of kresoxim-methyl and the formulations MENTOR (0.7 l product/ha cereals) and CANDIT (200 g product/ha apples). No further testing of the effects of kresoxim-methyl to bees is required.

Beneficial arthropods :
The effects of kresoxim-methyl were studied by means of the formulation CANDIT.
The formulation CANDIT (WG containing 500 g/kg kresoxim-methyl) is harmless to *Typhlodromus pyri* (predatory mites), *Trichogramma cacoeciae* (parasitic Hymenoptera) and *Poecilus cupreus* (soil dwelling predators).
The formulation is slightly harmful with important reduction of the adults fertility to *Coccinella septempunctata* (plant dwelling predators) in laboratory. This formulation is harmless to *Coccinella septempunctata* in semi-field test.
Several field trials were performed to evaluate the effects of the formulation on *Typhlodromus pyri* in apples (4 to 12 applications/ year; 0.1 to 0.2 kg a.s./ha) and vines (8 applications/year; 0.15 kg a.s./ha). The trials showed that the formulation is harmless to *Typhlodromus pyri* (In some cases slightly harmful : after a high number of applications not reflecting the actual use)
One trial was performed in pears to evaluate the effects of the formulation on *Anthocoris* species (pear sucker predator). The trial showed that the formulation is slightly harmlful to *Anthocoris* species.

The formulation MENTOR (SE containing 150 g/kg kresoxim-methyl and 300 g/kg fenpropimorph) is harmless to *Typhlodromus pyri* (predatory mites), *Aleochara bilineata* (soil dwelling predators) in laboratory. The formulation is slightly harmful with important reduction of adults fertility to *Chrysopa carnea* (plant dwelling predators) in laboratory.
The formulation is harmful to harmless to *Aphidius* species (parasitic Hymenoptera) depending upon the type of test (*A. matricariae* - 100 % mortality in lab test; *A. matricariae* - 37 % reduction parasitic rate in semi-field test; *A. rhopalosiphi* - 0% mortality in extended lab test). Fenpropimorph would be the co-formulant toxic to arthropods.

2.9.4 Effects on earthworms and other soil macro-organisms

Two artificial soil studies were performed showing that kresoxim-methyl (NOEC = 937 mg a.s./kg soil) and the free acid metabolite (NOEC = 1000 mg a.s./kg soil) are not toxic to earthworms.

The calculation of TER shows that the effects on the earthworms are nihil (application of ALLEGRO in cereals, 150 g a.s. or metabolite/ha, 50% interception, 5 cm soil layer, 1.5 kg/dm3, è TER = 9370)

2.9.5 Effects on soil micro-organisms

Four laboratory studies were performed to investigate the effects of the a.s. and the free acid metabolite respectiviely on the soil respiration and the nitrogen turnover. Even at the ten-fold dose (corresponding to 1.5 kg a.s./ha), only negligible effects were observed (less than 15 % reduction of both processes).

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

No specific studies were provided by the notifier.

2.9.7 Effects on biological methods of sewage treatment

Effects of the a.s. and the free acid metabolite to *Pseudomonas putida* were investigated. Even at the concentration of 1000 mg a.s./l no effects on oxygen consumption and bacterial growth were observed.

2.10 Classification and labelling

Proposals for the classification and labelling of the kresoxim-methyl :

Classification:	carcinogenicity; cat.3, Xn, R40, N, R50/53	
Labelling:		
Hazard symbol	Xn, N	
Indication of danger:	harmful, dangerous for the environment	
Risk phrases:	R40	possible risks of irreversible effects
	R50/53	very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
Safety phrases:	S2	keep out of reach of the children
	S 60	This material and its container must be disposed of as hazardous waste.
	S61	Avoid release to the environment. Refer to special instructions/ safety data sheets

Table 2.10-1 : Justification of the proposals for the classification and labelling of kresoxim-methyl

Proposals	Justification
Carcinogenicity cat.3 Xn, R40	Study 2 year, rat, oral : hepatocellular carcinoma and non genotoxic mechanism
N, R50/53	EC_{50} (*Ankistrodesmus bibraianus* -72 h) = 0.063 mg/l poorly biodegradable : < 20 % BOD of COD after 28 days

Proposals for the classification and labelling of formulation MENTOR :

According to the Dir. 78/631/EEC, on basis of physico-chemistry and acute toxicity tests performed on the formulation, Mentor need not to be classified.

However, some member states apply dir.88/379/EEC . Therefore, Mentor should be classified on basis of the carcinogenic properties of Kresoxim-methyl and labelled as follows

Classification:	carcinogenicity; cat.3, Xn, R40, N, R50/53	
Labelling:		
Hazard symbol	Xn, N	
Indication of danger:	harmful, dangerous for the environment	
Risk phrases:	R40	possible risks of irreversible effects
	R50/53	very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
Safety phrases:	S2	keep out of reach of the children
	S13	keep away from food, drink and animal feeding stuffs
	S20/21	when using, do not eat, drink or smoke
	S36/37	wear suitable protective clothing and gloves
	S 60	This material and its container must be disposed of as hazardous waste.
	S61	Avoid release to the environment. Refer to special instructions/ safety data sheets

Proposals for the classification and labelling of formulation ALLEGRO :

According to the Dir. 78/631/EEC, on basis of physico-chemistry and acute toxicity tests performed on the formulation, Allegro need not to be classified.

However, some member states apply dir. 88/379/EEC. Therefore, Allegro should be classified on basis of the carcinogenic properties of Kresoxim-methyl and labelled as follows

Classification:	carcinogenicity; cat.3, Xn, R40, N, R50/53	
Labelling:		
Hazard symbol	Xn, N	
Indication of danger:	harmful, dangerous for the environment	
Risk phrases:	R40	possible risks of irreversible effects
	R50/53	very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
Safety phrases:	S2	keep out of reach of the children
	S13	keep away from food, drink and animal feeding stuffs
	S20/21	when using, do not eat, drink or smoke
	S36/37	wear suitable protective clothing and gloves
	S 60	This material and its container must be disposed of as hazardous waste.
	S61	Avoid release to the environment. Refer to special instructions/ safety data sheets

Proposals for the classification and labelling of formulation CANDIT :

According to the Dir. 78/631/EEC, on basis of physico-chemistry and acute toxicity tests performed on the formulation, Candit need not to be classified.

However, some member states apply dir. 88/379/EEC. Therefore, Candit should be classified on basis of the carcinogenic properties of Kresoxim-methyl and labelled as follows:

Classification:	carcinogenicity; cat.3, Xn, R40, N, R50/53	
Labelling:		
Hazard symbol	Xn, N	
Indication of danger:	harmful, dangerous for the environment	
Risk phrases:	R40	possible risks of irreversible effects
	R50/53	very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
Safety phrases:	S2	keep out of reach of the children
	S13	keep away from food, drink and animal feeding stuffs
	S20/21	when using, do not eat, drink or smoke
	S36/37	wear suitable protective clothing and gloves
	S 60	This material and its container must be disposed of as hazardous waste.
	S61	Avoid release to the environment. Refer to special instructions/ safety data sheets

LEVEL 3

Kresoxim-methyl

Proposed decision with respect to the application for inclusion

of the active substance in Annex I

3.1 Background to the proposed decision

The information provided by the notifier was sufficient to evaluate the a.s. according Directive 91/414/CEE. The evaluation of the data and the risk assessment performed showed that the use of the a.s. according to GAP do not cause unacceptable risk to human beings and to the environment. It is therefore proposed to include kresoxim-methyl in Annex I of the Directive 91/414/EEC.

3.2 Proposed decision concerning inclusion in Annex I

The active substance 'Kresoxim-methyl' is included in Annex I as follows :

Kresoxim-methyl

(1) Identity (IUPAC)

methyl (E)-2-methoxyimino-2-[2-(o-tolyloxymethyl)phenyl]acetate

(2) Purity requirements

- pure active substance : min 910 g/kg ; typical 950 g/kg

(3) General restrictions to be taken into account in the authorizations

-

(4) Deadline of the inclusion

3.3 Rationale 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

-

LEVEL 4

Kresoxim-methyl

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

Supplementary information concerning the active substance

Point addressed : 5.8.2 Supplementary studies (toxicology)
Information or study required : Study evaluating the impact of cholinesterase inhibition on the toxicity of Kresoxim-methyl (28 days study on rats) (study ongoing)
Deadline : -

Point addressed: 5.8 Further toxicological studies (toxicology)
Information or study required : Evaluation of the toxicological significance of metabolites 490M58 and 490M59 formed in hens, in case of a use extension leading to residues in the feedingstuffs of poultry.
Deadline : -

Point addressed : 5.9.1Report on medical surveillance on manufacturing plant
Information or study required : medical data concerning workers in manufacturing plants
Deadline : -