REGISTRATION REPORT
(draft)

Norway

Ranman TwinPack

cyazofamid

June 2007

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PART A – Risk Management

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1 Details of the application

Application for authorisation of Ranman TwinPack was submitted to Norway by IKS Bioscience Europe 5th of August 2004. This product was transferred from BASF to IKS Bioscience Europe in 2003. The application was submitted according to the provisions of Directive 91/414/EEC. Ranman is a new product in Norway but has previously been approved in several of the other Nordic-Baltic countries. The applied use of Ranman is as a fungicide in potatoes.

The active substance (a.s.) in Ranman TwinPack is cyazofamide. France was the rapporteur member state in the EU evaluation process and cyazofamide was included in Annex I 1st of July 2003. Cyazofamide has a minimum purity of 935 g/kg technical product. Due to the fact that it is difficult to remove two of the impurities, which have very similar structure to cyazofamid, this low value is acceptable. The review of cyazofamide in this evaluation is based on the Draft Assesment Report from July 2001, list of endpoints, evaluation tables, reporting tables and addendums from the evaluation process in EU. In general only evaluation of data concerning Ranman was included in this registration report.

Ranman TwinPack is a twinpack product containing a 1 L bottle of cyazofamid 400 SC and a separate bottle containing 0.75 L organo silicone adjuvant. The a.s. can not be used without the adjuvant and the optimum efficiency of the product is obtained at a dilution ratio 4:3 of the a.s. and adjuvant. The bottles are sold in a groupage box (carton) which holds 6 unit boxes of Ranman TwinPack.

In this evaluation the a.s. is defined as IKF-916 (Cas. No: 120116-88-3), the a.s. in the formulation is defined as IKF-916 400 SC and the organo silicone adjuvant is given as the adjuvant. The mix of IKF-916 400 SC and the adjuvant in 4:3-ratio is given as IKF-916 400 SC + adjuvant. The product is given as Ranman TwinPack.

The formulation IKF-916 400 SC [IBE 3878] has been changed. This formulation was examined in most of the experiments evaluated in EU and in this evaluation process. In the new formulation, IKF-916 400 SC [IBE 3919], the concentration of one of the anti-foaming formulation products are increased. Due to the properties of this formulation product, this change does not significantly influence the properties of IKF-916 400 SC and thus new toxicity studies have not been required.

2 Details of the authorisation

2.1 Product identity

Product name:	Ranman TwinPack
Amount of active substance:	400 g/l
Formulation type:	suspension concentrate (SC)
Function:	fungicide

2.2 Classification and labelling

In the EU evaluation process, the product was marked in a kangaroo pack where a bottle of IKF-916 400 SC and a bottle of the adjuvant shared the same bottle neck. In the present application the notifier applies for Ranman TwinPac where the bottles are separated and therefore no longer share the same top.

In the EU evaluation process most of the product studies were preformed with IKF-916 400 SC + adjuvant, which was the most relevant solution to be exposed to when the product was marked in a kangaroo pack. However, the use of Ranman TwinPac causes exposure to IKF-916 400 SC and adjuvant separately at mixing and loading. Hence, The Norwegian Food Safety Authority (NFSA) asked the notifier for toxicity studies for each of these solutions. The notifier confirmed that for IKF-916 400 SC only acute oral and eye irritation studies had been done, while the complete toxicology packet was only done for the mixing solution. For the adjuvant only a safety data sheet was submitted initially. The data on the adjuvant is proprietary of the company Momentive Preformance Materials Benelux BVBA. A data request has been sent to this company and several studies on the adjuvant have been submitted. In the safety data sheet 11.5: “Chronic effects” it was stated that the adjuvant may have effect on fertility, but this kind of studies has not been submitted.

2.2.1 The following is proposed in accordance with Directive 99/45/EC in combination with the latest classification and labelling guidance under Directive 67/548/EEC (i.e. in the 18th ATP published as Directive 93/21/EEC):

Ranman TwinPack - IKF-916 400 SC + adjuvant (based on the evaluation and submitted safety and data sheet)
Hazard symbol
Xi: Irritant
N: Dangerous for the environment

IKF-916 400 SC (based on submitted safety data sheet)
Hazard symbol
N: Dangerous for the environment

Adjuvant (based on submitted safety data sheet)
Hazard symbol
Xn: Harmful
N: Dangerous for the environment

2.2.2 R and S phrases under Directive 2003/82/EC (Annex IV and V)

Risk phrases for the IKF-916 400 SC + adjuvant
R41: Risk of serious damage to eyes
R50/53: Very toxic to the aquatic organisms, may cause lang-term adverse effects in the aquatic environment.

Safety phrases for the IKF-916 400 SC + adjuvant
S(02): Keep out of reach of children
S25: Avoid contact with eyes
S26: In case of contact with eyes, rins immediately with plenty of water and seek medical advice
S35: This material and its container must be disposed of in a safe way
S39: Wear eye/face protection
S (46): (If swallowed, seek medical advice immediately and show this container or label)
S57: Use appropriate containment to avoid environmental contamination

Risk phrases for the IKF-916 400 SC

R50/53: Very toxic to the aquatic organisms, may cause lang-term adverse effects in the aquatic environment.

Safety phrases for the IKF-916 400 SC
S35: This material and its container must be disposed of in a safe way
S57: Use appropriate containment to avoid environmental contamination

Risk phrases for the adjuvant
R20: Harmful by inhalation
R36: Irritating to eyes
R48/20: Harmful: Danger of serious damage to health by prolonged exposure through inhalation
R51/53: Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment

Safety phrases for the adjuvant
S2: Keep out of reach of children
S13: Keep away from food, drink and animal feeding stuffs
S23: Do not breathe vapour
S26: In case of contact with eyes, rins immediately with plenty of water and seek medical advice
S (46): (If swallowed, seek medical advice immediately and show this container or label)
S61: Avoid release to the environment. Refer to special instructions/safety data sheets.

Reasons for classification

Classification on the basis of environmental effects: EC50 = 0.18 mg a.s./Land cyazofamid (IKF-916) is not readily biodegradable.

Classification on the basis of toxicological properties or specific effects on human health:
The classification and labelling in 2.2.1 and 2.2.2 are based on the IKF-916 400 SC + adjuvant solution. The effects of the solution meet the criteria for labelling with R41. However, IKF-916 400 SC alone or IKF-916 alone did not meet the criteria of any labelling according to the evaluation process in EU and submitted safety and data sheet. On the other hand, the adjuvant was according to the submitted safety and data sheet labelled with R20: Harmful by inhalation, R36: Irritating to eyes and R48/20: Harmful: danger of serious damage to health by prolonged exposure through inhalation. In addition, the adjuvant may have effect on fertilisation.

To cover all exposure situations, each of the bottles in the Ranman TwinPack should be labelled based on the respective content, in addition to be labelled for the mix of IKF-916 400 SC + adjuvant.

2.3 Product uses

Ranman TwinPack is a fungicide, and in the Nordic/Baltic countries it is applied for use in potatoes. For GAP see Annex 2.

3 Risk management

3.1 Reasoned statement of the overall conclusions taken in accordance with the Uniform Principles

3.1.1 Physical and chemical properties

For IKF-916 400 SC, small changes are seen in the physical state in the stability tests. The stability of the active ingredient seems acceptable in a new study. The report is, however, not very detailed and we have asked the manufacturer for more data. The SC-formulation has non-Newtonian flow and is surface active.

There are few data on the adjuvant, but the product seems stable. The adjuvant is surface active. The mixture, IKF-916 400 SC + adjuvant, is surface active and shows persistent foaming.

3.1.2 Methods of analysis

The content of IKF-916 is determined by HPLC on a reversed-phase column with UV –detection at 280 nm, using an external standard of IKF-916. The analytical methods are considered acceptable for Annex I inclusion of cyazofamid

3.1.3 Mammalian Toxicology

In the EU evaluation process, Ranman kangaroo pack was evaluated. The product pack has now been changed to two separate bottles, Ranman TwinPack, which causes a risk of exposure to each of the solutions in addition to the mix.

The submitted toxicological data package was mainly on the mix of IKF-916 400 SC + adjuvant. The mix was found to cause harmful irreversible effects to the eyes and the effect required classification with R41: Risk of serious damage to eyes. Only limited studies with IKF-916 400 SC alone were submitted. The safety data sheets on IKF-916 400 SC indicated no labelling. According to the safety and data sheet for the adjuvant, labelling with R20 (Harmful by inhalation), R36 (Irritating to eyes) and R48/20 (Harmful: danger of serious damage to health by prolonged exposure through inhalation) were suggested. On request the manufacturer studies that confirmed the labelling in the safety data sheet. The adjuvant is harmful by inhalation as the LC50 in rats was 1.98 mg/L. The labelling “irritating to eyes” is based on effects on the iris and conjunctiva. The results from a sub acute inhalation study gave reason for the labelling with R48/20. There were deaths in the study at a concentration of 0.25 mg/L. Severe effects were seen on the nasal mucosa and persistent ocular opacities were also seen. The adjuvant may have effect on fertilisation (safety and data sheet 11.5 Chronic effect), but this statement is not supported by any submitted documentation.

Estimate of the operator exposure for the intended use of IKF-916 400 SC showed that glows during mixing/loading and application were necessary to obtain acceptable use. Based on exposure estimate for the workers and bystanders, no unacceptable risk was found.

3.1.4 Residues and consumer exposure

IKF-916 is not considered to be acute toxic to human via dietary exposure. Therefore no acute reference dose has been established and no acute dietary risk assessment has been performed.

The worst case estimate of dietary exposure to IKF-916 from residues in potatoes and tomatoes (authorized use in Southern Europe), using the WHO model or the UK-Consumer model, accounts for less than 0,3% of the ADI. The results of the long-term intake calculations indicate that there is no chronic risk to human health from consumption of crops treated with IKF-916 according to GAP.

EU MRLs for IKF-916 (cyazofamid) is established in Commission Directive 2003/113/EC of 3 December 2003.

3.1.5 Environmental fate and behaviour

Environmental fate and behaviour of IKF-916 has been detailed in the EU process. No additional specific data of Ranman TwinPack has been submitted.

Degradation in soil

IKF-916 degrades fairly rapidly in soil to three main metabolites: CCIM, CCIM-AM and CTCA. CCIM and CCIM-AM degrades quite rapidly, while CTCA degrades slowly in three soils in a laboratory study performed with the metabolite (DT50 267 - 487,5 d). In a study with parental IKF-916 in 3 UK soils and two Japanese soils the degradation of CTCA was faster (DT50 8-73,5 d) Also in field studies from Japan and USA the degradation was less than 90 days. An uncertainty in that kind of studies with the parent is that the amounts of metabolites can be underestimated. The difference was explained with adsorption-desorption processes which more strongly reduce the availability of the metabolites as they are applied directly and thus get longer residence times in soil.

IKF-916 and the two metabolites CCIM and CCIM-AM show no unacceptable persistence and conform to all the triggers of the Uniform Principles. The persistence of the metabolite CTCA is more uncertain. Probably is the degradation in the field more rapidly than in the laboratory study with the application of the metabolite itself.

Mobility in the soil

All studies and modelling of leaching demonstrated that IKF-916 and its metabolites did not leach to the ground water in concentrations exceeding 0.1 μg/L as an annual average. Therefore the triggers in the Uniform Principles are met.

Fate and behaviour in water

IKF-916 was degraded rapidly in the water phase in a water/sediment study. In the sediment significant amounts of the substance was found after 100 days. The primary degradation of the substance in the whole water/sediment system was medium (DT50 11-16.5 d) and the mineralization was negligible.

PEC

Estimation of expected concentrations in soil (PEC_S), surface water (PEC_{Sw}), sediment (PEC_{SED}) and ground water (PEC_{gw}) have been calculated for use in risk assessments, see part B.

The trigger with regard to effects on non target species is considered in the section on ecotoxicology.

Fate and behaviour in air

IKF-916 can not be classified as a volatile substance and atmospheric half-life is calculated to be short.

3.1.6 Ecotoxicology

Birds
The toxicity of IKF-916 and IKF-916 400 SC + adjuvant to birds is considered to be quite low whether it is acute, short term or long term. The risk assessment generally shows that the triggers are complied with in the first worst case calculation. The risks from Ranman TwinPack are considered acceptable under the proposed use and the trigger values of the Uniform Principles are complied with.
Mammals
The situation for mammals close parallels that of birds and consequently the risks from Ranman TwinPack are considered acceptable under the proposed use and the trigger values of the Uniform Principles are complied with.

Aquatic organisms
The toxicity of IKF-916 and IKF-916 400 SC + adjuvant to aquatic organisms is considered moderate to quite high. However, in the toxicity studies with the active ingredient it was difficulties with the limited water solubility of the substance. The toxicity of the metabolites CTCA and CCIM-AM is low and the metabolite CCIM is moderate toxic to fish and toxic to invertebrates and algae.

The risk assessment performed with FOCUS surface water STEP 2 calculator shows TER values greater than the Uniform Principles' trigger values and under Norwegian conditions it is not necessary with buffer zones. However the toxicity leads to a classification of 50/53 of the product.

Based on the log P_{ow} and BCF it can be a risk of IKF-916 to bioaccumulate in fish. The BCF value is above the trigger value of 100 for substances which are not readily biodegradable. However the depuration is rapid and therefore there is small risk for IKF-916 to bioaccumulate in fish.

Bees
The hazard quotients of both IKF-916 and IKF-916 400 SC + adjuvant for bees are clearly below the trigger of 50 in the Uniform Principles. Consequently no unacceptable risk to bees are foreseen and
The product requires no labelling with regard to danger to bees.

Non target arthropods
A number of non target arthropods *(Aphidius rhopalosiphii*, Typhlodromus *pyri, Aleochara bilineata* and *Chrysoperla carnea)* have been tested with IKF-916 and IKF-916 400 SC + adjuvant. No data for LR50 are given and hazard quotients could not be calculated. Hence, the risk assessment is based upon using ESCORT 2 trigger of 50 % for mortality. For IKF-916 400SC + Adjuvant, the laboratory studies show effects but extended laboratory tests show mortality below the Annex VI trigger. This indicates that the effects can be regarded as minor in fields.

Earthworms
The acute toxicity of the active substance and the metabolites to earthworms has been tested in laboratory studies. All tests show a low acute toxicity of IKF-916 and the metabolites CCIM-AM, CTCA and DMSA, with LC50 of more than 1000 mg/kg soil. The metabolite CCIM has a higher acute toxicity, with LC50 of 56 mg/kg soil. One long-term test of the metabolite CTCA shows a NOEC value > 1 mg/kg soil. This was also the highest tested concentration. One additional long-term test of IKF-916 is presented in the addendum of the DAR. Survival, growth and reproduction rates were not significantly reduced in this test. No long-term test is performed on IKF-916 + Adjuvant. Based on these studies from which it is possible to extrapolate it can be

concluded that the product does not give rise to an unacceptable risk to earthworms under the proposed use and thus complies with the triggers of the Uniform Principles.

Non target microorganisms
The effects of IKF-916 and the metabolite CTCA was tested on soil non-target micro-organisms. The results showed no statistically significant effects greater than ±25 % of control values, for both respiration and nitrification.

3.1.7 Efficacy
Ranman TwinPack (cyazofamid + adjuvant) has been tested against potato late blight in Norway for three years (2001-2003) in nine field experiments. The product had very good effect against late blight, and was equal or better than the standard fungicide Shirlan (fluazinam).

3.2 Conclusions

3.2.1 Mammalian toxicology
At the present time the lack of adjuvant data (table 4.5.1) makes it hard to conclude if this product can be allowed on the marked.

3.2.2 Environmental fate/behaviour and ecotoxicology
The documentation of the active substances does not show any unacceptable inherent properties. The ecotoxicological risk of the product is considered low under the proposed conditions of use.

3.3 Further information to permit a decision to be made or to support a review of the conditions and restrictions associated with the authorisation

3.3.1 Mammalian toxicology
Acute data for the IKF-916 400 SC and the adjuvant, and a fertility study with the adjuvant has been requested. At the present time this data has not been submitted.

3.3.2 Environmental fate/behaviour and ecotoxicology
The Norwegian Food Safety Authority requires the two reproduction studies which USEPA already has evaluated in their Pesticide Fact Sheet and requires a new reproduction study of Bobwhite Quail.

PART B

Detailed summary of the risk assessment

Norway

Ranman TwinPack

cyazofamid

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1 Identity of the plant protection product

1.1 Applicant

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1.2 Identity of the active substance

CAS no: 120116-88-3
ISO name: Cyazofamid
Chemical name (IUPAC): 4-chloro-2cyano-N,N-dimethyl-5-P-tolylimidazole-1-sulfonamide

1.3 Identity of the plant protection product

Ranman IKF-916 400 SC: A full specification of the plant protection products IKF-916 400 SC are presented in Part C - Confidential information. However, specification of the adjuvant is still not submitted by the notifier. The formulation of IKF-916 400 SC [IBE 3878] has been replaced by IKF-916 400 SC [IBE 3919]. The previous evaluated formulation was changed by an increase in content of one of the anti-foaming products.

1.4 Function

Preventive contact fungicide.

1.5 Uses applied for

Ranman TwinPack is a foliar fungicide for control of *Phytophtora infestans* (potato late blight). In the Nordic/Baltic countries (Denmark, Sweden, Finland, Norway, Estonia, Latvia and Lithuania) the product is applied for use in potatoes.

The most critical GAP will be 10 x 0,08 kg a.i./ha, PHI 7 days.
For details about GAP in the different countries, see annex 2 (Table of authorised use).

1.6 Background to the application

IKF-916 was listed on annex I of directive 91/414/EEC from 1st July 2003 (see directive 2003/23/EEC), and are registered for use in several of the EU countries.

1.7 Packaging details

1.7.1 Packaging description

Ranman is a twinpack product containing a 1 L bottle of IKF-916 400 SC (containing the a.s.) and a separate bottle containing 0.75 L organo silicone adjuvant. The a.s. can not be used without the adjuvant and the optimum efficiency of the product is obtained at a dilution ratio 4:3 of a.s. and adjuvant. The bottles are sold in a groupage box (carton) which holds 6 unit boxes of Ranman Twinpack.The neck size of both bottles are 50 mm.

2. Physical and chemical properties of the plant protection product

The old and the new SC-formulation seem to have similar physical and chemical properties (Table 2.1). Small changes are seen in the physical state in the stability tests. The stability of the active ingredient seems acceptable in a new study. The report is, however, not very detailed and we have asked the manufacturer for more data. The SC-formulation has non-Newtonian flow and is not surface active.

There are few data on the adjuvant (Table 2.2). The product seems stable. The adjuvant is surface active.

The mixture, IKF-916 400 SC + Adjuvant (Table 2.3), is surface active and shows persistent foaming.

Table 2.1 IKF-916 400 SC (Ranman without adjuvant, IBE 3878, in EU-dossier). New formulation IBE 3919

Study (Annex point)	**Guidelines and GLP**	**Findings**	**Evaluation and conclusion**	**Reference**
2.1 /01 Physical state, colour 2.1/02 Odour	ASTM D1537 97; in-house, GLP	Beige liquid, Monsell designation 5YU9/1 Both formulations Musty paint latex Both formulations	Acceptable Acceptable	Y. Ishihara, 2002 (IBE 3919)
2.2 Explosive and oxidising properties			No oxidizing or explosive properties	
2.3 Flashpoint and flammability	EU Communities L383, method A.9 and A.15. ASTM Method E659-78(94)	No flashpoint observed. Autoflammability at 503 ° C using 100 µL.	No fire hazard	Vargyas, 1999 (IBE 3878)
2.4.1 Acidity/Alkalinity	-	-	Not relevant since the product is neither acidic (pH<4) nor alkaline (pH>10)	-
2.4.2 pH	According to CiPAC MT 75.2. No GLP	pH=7.5 (neat formulation) at 25 ºC, single measurement pH=7.4 (1% aqueous mixture) at 25 ºC. (mean of 3 measurements)	-	Y. Ishihara, 2002 (IBE 3919)
2.5.2 Viscosity	OECD 114 Brookfield viscosity No GLP	mPa·s Rotation 25ºC 45ºC 6rpm 2310 2160 12rpm 1360 1260 30rpm 678 631 60rpm 411 383	The liquid has non-Newtonian flow	T. Shindo, 2002 (IBE 3919)

Study (Annex point)	Guidelines and GLP	Findings			Evaluation and conclusion	Reference
2.5.3 Surface tension	OECD 115 KYOWA CBVP surface tensiometer (model A3)	56.5 mN/m at 20ºC (1 g/L aqueous suspension)			The product is surface active	T. Shindo, 2002 (IBE 3919)
2.6.1 Relative density	CIPAC MT 3.2.2	Density 1,1426 g/cm^3 at 20ºC ± 0,5 ºC			-	B. de Ryckel, 2003 (IBE 3878)
2.6.1 Relative density	CIPAC MT 3.3.2.	Density 1,150 g/cm^3 at 20ºC Density 1,146 g/cm^3 at 30ºC			-	T. Shindo, 2002 (IBE 3919)
2.7.1 Accelerated storage stability	CIPAC 46.3 GLP - Visual observation Observation Visual inspection	<u>Test</u> a.i. content colour odour physical state	<u>Initial</u> Not determined Opaque beige Not specific homogenous liquid	Storage for two <u>weeks at 54ºC</u> Not determined Opaque beige Not specific Liquid with a brown clear liquid at the top, but without sediment at the bottom (no claying). Homogenous after gentle shaking.	Storage in commercial type package. No observable leaking. The physical state of the liquid have changed after two weeks at 54ºC.	B. de Ryckel, 2003 (IBE 3878)
	CIPAC MT 47.2	Persistent foaming - 10 sec. - 1 min. - 3 min. - 12 min.	 10 ml 10 ml 9 ml 8 ml	 21 ml 18 ml 17 ml 17 ml	There are more persistent foaming after two weeks accelerated storage than initially.	
	CIPAC MT 160	Spontaneity of dispersion	95,8 %	97,7 %		

Study (Annex point)	Guidelines and GLP	Findings			Evaluation and conclusion	Reference
2.7.1 Accelerated storage stability	No GLP HPLC/UV detector Munsell system Observation Visual inspection OECD 114, Brookfield viscometer CIPAC MT 161 CIPAC MT 59.3 CIPAC MT 47.2 CIPAC MT 148 CIPAC MT 160 CIPAC MT 75.2	<u>Test</u> a.i. content colour odour physical state viscosity at 25ºC - 6 rpm - 12 rpm - 30 rpm - 60 rpm Suspensibility, - low concentration - high concentration Wet sieving test Persistent foaming - 10 sec. - 1 min. - 3 min. - 12 min. Pourability - residue - rinsed residue Spontaneity of dispersion pH value (1% aqueous solution)	<u>Initial</u> 35,0 % Beige (5Y 9/1) Musty latex paint Viscous liquid 2310 mPa·s 1360 mPa·s 678 mPa·s 411 mPa·s 100,2 % 101,2 % 0,002 % 0 ml 0 ml 0 ml 0 ml 3,36 % 0,25 % 97,2 % 7,4	Storage for two <u>weeks at 54ºC</u> 34,2 % Beige (5Y 9/1) Musty latex paint Viscous liquid 2223 mPa·s 1303 mPa·s 650 mPa·s 395 mPa·s 100,8 % 100,9 % 0 % <1 ml <1 ml 0 ml 0 ml 3,11 % 0,27 % 98,1 % 5,7	Test sample was transferred to a 500 ml polyethylene bottle with screw cap and stored at 54 ºC for two weeks. There were a decreas of pH in a 1 % aqueous solution and a small decrease in a.i. content (2,3 % degradation).	T. Shindo, 2002 (IBE 3919)

Study (Annex point)	Guidelines and GLP	Findings			Evaluation and conclusion	Reference
2.7.2 Low temperature stability	CIPAC MT 39.3 GLP GLP Visual observation Observation Visual inspection CIPAC MT 161 CIPAC MT 59.3	<u>Test</u> a.i. content colour odour physical state Suspencibility, - low concentration - high concentration Wet sieving test	<u>Initial</u> Not determined Opaque beige Not specific Homogenous liquid 100,2 % 100,3 % 0,01 %	Storage for 1 <u>weeks at 0ºC ± 1 ºC</u> Not determined Opaque beige Not specific Homogenous liquid 99,5 % 99,9 % 0,01 %	Storage in glass bottles.	B. de Ryckel, 2003 (IBE 3878)
2.7.2 Low temperature stability	CIPAC MT 39.3	Storing of sample for 7 days at 0ºC±2 ºC. Visual examination showed no separated material. Test for suspensibility at two concentrations at 30 ºC gave 100,9 and 101,1 % for the low and high concentration respectively. The residue retained after wet sieve test (0,75 µm sieve) was 0 %.			The formulation was stable after storage at 0ºC ± 2ºC.	T. Shindo, 2002 (IBE 3919)

Study (Annex point)	Guidelines and GLP	Findings			Evaluation and conclusion	Reference
2.7.3 Shelf life stability	GIFAP Tech. 17 GLP - Visual observation Observation Visual inspection	<u>Test</u> a.i. content colour odour physical state	<u>Initial</u> Not determined opaque beige not specific homogenous liquid	Storage for 2 years <u>at room temperature</u> Not determined opaque beige not specific (faint chemical liquid with a brown clear liquid at the top and at small sediment at the bottom (cake). Homogenous after gentle shaking.	Storage stability in the commercial type package. No major change on commercial type package after 2 years. No observable leaking. A slight weight loss (ranging from -0,7 to -3,1 %).	B. de Ryckel, 2003 (IBE 3878)
	CIPAC MT 148	Pourability - residue - rinsed residue - non-volatile rinced residue	 6,51 % 0,33 % 0,014 %	 6,02 % 0,24 % 0,026 %	There has been a visual change of the test item after two years at room temperature, but very few tests have been conducted.	

Study (Annex point)	Guidelines and GLP	Findings		Evaluation and conclusion	Reference
2.7.3 Shelf life stability and corrosion characteristics	OPPTS 830.6317 and OPPTS 830.6320 GLP	The samples were stored in high-density polyethylene bottles with polypropylene caps. There were no effects on bottle colour, and no flaws, cracking or poor seams. The weight of the container remained constant. The sample remained beige in colour and there was no clumps.	W/W % of IKF-916, CCIM and DMSA found at 0-36 months storage at 25ºC. **Mnth IKF-916 CCIM DMSA** 0 34,8 0,17 0,09 3 35,2 0,22 0,12 6 33,4 0,23 0,14 12 34,4 0,28 0,15 18 34,7 0,31 0,17 24 34,2 0,32 0,18 36 34,5 0,37 0,19	Stored at 25 ºC in the commercial type package. No major change on commercial type package after 2 years. No visually observable corrosion or leaking. The amount of CCIM and DMSA were dobbled in 36 months. The IKF-916 content was stable.	R. C. DeWitt, 2003 (IBE 3878)
2.8.2 Persistent foaming	CIPAC MT 47.2	Volume of foam (cm^3) at Time 0 ml 10 sec 0 ml 1 min 0 ml 3 min 0 ml 12 min		There was no persistent foaming.	Y. Ishihara, 2002 (IBE 3919)
2.8.3 Suspensibility	CIPAC MT 161	Low concentration (0,2 L /700 L water) gave 100,2 % suspensibility at 30 ºC. High concentration 0,2 L/ 150 L water) gave 101,2 % at 30 ºC.		-	T. Shindo, 2002 (IBE 3919)
2.8.3 Spontaneity of dispersion	CIPAC MT 160	97,2 % at 30 ºC.		-	T. Shindo, 2002 (IBE 3919)
2.8.5 Wet sieve test	CIPAC MT 59.3	0,002% retention on a 75 µm sieve.		-	T. Shindo, 2002 (IBE 3919)
2.8.8 Pourability	CIPAC MT 148	Initial residue = 3,36 % Rinsed residue = 0,25 %		-	T. Shindo, 2002 (IBE 3919)

Table 2.2 Adjuvant (Organo silico adjuvant)

Study (Annex point)	**Guidelines and GLP**	**Findings**	**Evaluation and conclusion**	**Reference**
2.1 Physical state Colour Odour	Visual inspection at ambient lab temperature	Clear liquid with a “cloud” on suspension at the bottom, but no sediment. Cloudy after homogenisation. Colour: clear pale yellow liquid with a grey cloud. Grey after homogenisation. Not specific odour.	-	B. de Ryckel, 2003
2.3 Flashpoint and flammability		Flashpoint 116ºC. Auto-ignition point 330ºC	No fire hazard.	Safety data sheet, 09- 01-2004 (BIG)
2.4.1 Acidity/Alkalinity	-	-	Not relevant since the product is neither acidic (pH<4) nor alkaline (pH>10)	-
2.4.2 pH	-	pH=5,3 at 25ºC	-	ISK Bioscience Europe SA, Certificate of analysis, 2001
2.5.2 Viscosity	-	19,4 centistoke	The product does not constitute a hazard to aspiration.	ISK Bioscience Europe SA, Certificate of analysis, 2001
2.5.3 Surface tension	-	20 dyne/cm of 1 % solution at 25ºC	The product is surface active	ISK Bioscience Europe SA, Certificate of analysis, 2001
2.6.1 Relative density	CIPAC MT 3.2.1	1,0108 g/cm^3 at 20ºC ± 0,5ºC	-	B. de Ryckel, 2003

Study (Annex point)	Guidelines and GLP	Findings			Evaluation and conclusion	Reference
2.7.1 Accelerated storage stability	CIPAC 46.3 GLP - Visual observation Observation Visual inspection	<u>Test</u> a.i. content colour odour physical state	<u>Initial</u> Not determined Clear pale yellow liquid with a grey cloud. Grey after homogenisation Not specific Clear liquid with a “cloud” on suspension at the bottom, but no sediment. Cloudy after homogenisation.	Storage for two <u>weeks at 54ºC</u> Not determined Pale yellow. After some days in glass bottle without shaking; formation of a grey cloud in the bottom of the liquid. Grey after homogenisation. Not specific Homogenous liquid without visible matter on suspension or sediment	Storage in commercial type package. Deformation of the bottle (swelling), but no observable leak during turning or shaking. No significant loss of weight.	B. de Ryckel, 2003

Study (Annex point)	Guidelines and GLP	Findings			Evaluation and conclusion	Reference
2.7.2 Low temperature stability	CIPAC 39.3 GLP - Visual observation	<u>Test</u> a.i. content colour	<u>Initial</u> Not determined Clear pale yellow liquid with a grey cloud. Grey after homogenisation	Storage for 1 week <u>at 0ºC ± 1 ºC</u> Not determined grey After some days without shaking(room temp) clear pale yellow liquid with grey clouds at the bottom. Grey after homogenisation.	Storage in glass bottles The product is frozen at 0ºC ± 1 ºC, but appearantly regains its physical state after returning to room temperature.	B. de Ryckel, 2003
	Observation Visual inspection	odour physical state	Not specific Clear liquid with a “cloud” on suspension at the bottom, but no sediment. Cloudy after homogenisation.	Not specific After 7 days, the product is frozen. After returning to room temperature, the liquid became completely cloudy.		

Study (Annex point)	Guidelines and GLP	Findings			Evaluation and conclusion	Reference
2.7.3 Shelf life stability	GIFAP Tech. 17 GLP - Visual observation Observation Visual inspection	<u>Test</u> a.i. content colour odour physical state	<u>Initial</u> Not determined Clear pale yellow liquid with a grey cloud. Grey after homogenisation Not specific Clear liquid with a “cloud” on suspension at the bottom, but no sediment. Cloudy after homogenisation.	Storage for 2 years <u>at room temperature</u> Not determined Grey Not specific Homogenous liquid without visible matter on suspension or sediment	Storage stability in the commercial type package. There is a change in the physical state of the adjuvant after 2 years storage at room temperature. Very few tests have been conducted.	B. de Ryckel, 2003

Table 2.3. IKF-916 400 SC + Adjuvant

Study (Annex point)	**Guidelines and GLP**	**Findings**			**Evaluation and conclusion**	**Reference**
IIIA 2.5.3/02 Surface tension	OECD 115, EEC Method A.5, GLP	20.9 mN/m			The mixture is surface active.	Pelton, 1999 (IBE 3878 + adjuvant)
IIA. 2.5.3 Surface tension	OECD 115 KYOWA CBVP surface tensiometer (model A3)	20.6 mN/m at 20ºC (1 g/L aqueous suspension)			The mixture is surface active.	Shindo, 2002 (IBE 3919 + adjuvant, ratio 4:3 v/v)
2.7.1 Accelerated storage stability	CIPAC MT 46.3 GLP CIPAC MT 161 CIPAC MT 160 CIPAC MT 47.2	<u>Test</u> Suspensibility, - low concentration - high concentration Spontaneity of dispersion Persistent foaming - 10 sec. - 1 min. - 3 min. - 12 min.	<u>Initial</u> 100,0 % 100,1 % 95,4 % 40 ml 39 ml 37 ml 33 ml	Storage for two <u>weeks at 54ºC</u> 100,1 % 100,5 % 96,9 % 38 ml 37 ml 34 ml 30 ml	Storage in commercial type package.	B. de Ryckel, 2003 (IBE 3878 + adjuvant, 4:3)
2.7.2 Low temperature stability	CIPAC MT 39.3 GLP CIPAC MT 161 CIPAC MT 59.3	<u>Test</u> Suspensibility, - low concentration - high concentration Wet sieving test	<u>Initial</u> 100,0 % 100,1 % 0,01 %	Storage for 1 week <u>at 0ºC ± 1 ºC</u> 100,3 % 99,9 % 0,01 %	Storage in glass bottles	B. de Ryckel, 2003(IBE 3878 + adjuvant, 4:3)

Study (Annex point)	Guidelines and GLP	Findings			Evaluation and conclusion	Reference
2.7.3 Shelf life stability	GIFAP Tech 17 GLP CIPAC MT 75.2 CIPAC MT 31.2.3 CIPAC MT 161 CIPAC MT 160 CIPAC MT 59.3 CIPAC MT 47.2	<u>Test</u> pH of a 1 % solution acidity/alkalinity Suspensibility, - low concentration - high concentration Spontaneity of dispersion (at 30ºC) Wet sieving test Persistent foaming - 10 sec. - 1 min. - 3 min. - 12 min.	<u>Initial</u> 6,25 Not determined (pH between 4 and 10) 100,0 % 100,1 % 95,4 % 0,01 % 40 ml 39 ml 37 ml 33 ml	Storage for 2 years <u>at room temperature</u> 5,33 Not determined (pH between 4 and 10) 101,3 % 100,5 % 94,3 % 0,02 % 42 ml 40 ml 38 ml 34 ml	Storage in commercial type package. The pH in a 1 % solution is lower after storage. Persistent foaming present.	B. de Ryckel, 2003 (IBE 3878 + adjuvant, 4:3)
III.A 2.8.2/02 Persistent foaming	CIPAC MT 47.1 GLP	2 cm^3 after 30 min. Volume of foam (cm^3) at Time 13 10 sec 13 1 min 13 3 min 12 12 min			Persistent foaming present	Pelton J.S 1999 (IBE 3878 + adjuvant 4 :3)
	CIPAC MT 47.2	Volume of foam (cm^3) at Time 24,0 10 sec 24,0 1 min 22,5 3 min 21,3 12 min			Persistent foaming present, even more foam than when using the old formulation.	Y. Ishihara, 2002 (IBE 3919 + adjuvant)
Suspensibility	CIPAC MT 161	Low concentration (0,2 L IBE 3919 + 0,15 L adjuvant per 700 L water) gave 100,5 % suspensibility at 30 ºC. High concentration 0,2 IBE 3919 + 0,15 L adjuvant per 150 L water) gave 101,1 % at 30 ºC.			-	T. Shindo, 2002 (IBE 3919 + adjuvant)

3 Methods of analysis

3.1 Analytical methods for analysis of the formulation

3.1.1 Analytical methods of the active substance in the formulation

The formulated product is dispersed in a small volume acetonitrile followed by sonication. After cooling the samples is diluted in acetonitrile and syringe-filtered through 0,5 µm disks. The content of IKF-916 is then determined by HPLC on a reversed-phase column with UV – detection at 280 nm, using an external standard of IKF-916. The method has been fully validated and accepted.

3.1.2 Analytical methods for the relevant impurities, isomers and co-formulants

A validated five-batch-analysis method can detect the impurities CCIM-AM, CCIM, m-916, 2C-916, 3C-916 and 4C-916 by HPLC and DMSA, by ion chromathography. According to the review report (SANCO/10379/2002-final), none of the manufacturing impurities considered in technical cyazofamid are, on the basis of current information, of toxicological or ecotoxicological concern. However, CCIM and CTCA are relevant metabolites in the environment. There are not analytical methods for determining substances in the adjuvant or the co-formulants in IKF-916 400 SC.

3.2 Analytical methods for residue analysis

The simple analytical method for determination of IKF-916 has been validated for all matrixes. As the method is not specific, it has been confirmed (HPLAC/DAD) for all matrixes except air. The same validated method is used for the metabolites CCIM and CTCA.

Matrix	Analyte	Method	LOQ
Potato/tomato	cyazofamid	HPLC/UV	0,01 ppm
Soil	cyazofamid	HPLC/UV	0,01 ppm
Water	cyazofamid	HPLC/UV	0,1 ppb
Air*	cyazofamid	HPLC/UV	0,15 µg/m^3
Animal tissues /fluids	cyazofamid	HPLC/UV	0,01 ppm
Potato/tomato	CCIM	HPLC/UV	0,01 ppm
Soil	CCIM	HPLC/UV	0,01 ppm
Water*	CCIM	HPLC/UV	0,1 ppb
Soil*	CTCA	HPLC/UV	0,01 ppm
Water	CTCA	HPLC/UV	0,1 ppb

* A confirmatory method is required

4 Mammalian toxicology

Summary of Ranman TwinPack

The submitted toxicological data package was on the mix of IKF-916 400 SC + adjuvant. The mix was weakly toxic following acute oral, dermal and inhalation exposure and it did not irritate the skin or trigger sensitisation. However, the mix was found to cause harmful irreversible effects to the eyes. According to Directive 67/548/EEC and 1999/45/EC, the effect requires classification with R41: Risk of serious damage to eyes. Only limited studies with IKF-916 400 SC alone were submitted. The safety data sheets on IKF-916 400 SC indicated no labelling. According to the safety and data sheet for the adjuvant, labelling with R20 (Harmful by inhalation), R36 (Irritating to eyes) and R48/20 (Harmful: danger of serious damage to health by prolonged exposure through inhalation) were suggested. In addition, the adjuvant may have effect on fertilisation (safety and data sheet 11.5 Chronic effect). For more information concerning labelling see 2.2 Classification and labelling in Part A.

Estimate of the operator exposure for the intended use of IKF-916 400 SC showed that glows during mixing/loading and application were necessary to obtain acceptable use. Based on exposure estimate for the workers and bystanders, no unacceptable risk was found.

Summary of cyazofamid – IKF- 916 (from the DAR and addenda)

Absorption of radiolabeled IKF 916 occurred rapidly and accounted for more than70% of administrated dose (AD). Highest levels were found in body tissues with blood, liver and kidney. More than 70% of AD was detected as radiolabeled IKF-916 in the faces. The major urine metabolite in both males and females was CCBA (4-(4-chloro-2-cyanoimidazol-5-yl)benzoic acid) in addition to smaller amounts of CH_3SO –CCIM (4-chloro-5-[α-(methylsulfinyl)-*p*-tolyl]imidazole-2-carbonitrile) and CH_3SO_2 –CCIM (4-chloro-5-[α-(methylsulfonyl)-*p*-tolyl]imidazole-2-carbonitrile). The metabolic pathway of IKF-916 include a rapid hydrolysis of the dimethylsulfonamide group and oxidation of the benzyl methyl group which results in the urinary excretion of CCBA, CH_3SO –CCIM and CH_3SO_2 –CCIM.

IKF-916 was found to have very low toxicity with oral and dermal LD50 for rats above 5000 mg/kg bw and 2000 mg/kg bw respectively. The LC50 in rats was found to be higher than 5.5 mg/L (4-hours, whole-body). In conclusion, IKF-916 was found to have a low order of acute toxicity in both males and females. In addition, IKF-916 did not cause irritation to skin or eyes, nor skin sensitisation in Maximization test.

Four week rat and dog study and a six week mice study were submitted. The only treatment related effects were observed in the kidneys and livers in rats. These included organ weight differences in both tissues, but only the kidney findings were correlated with the microscopic finding of basophilic tubules. The effects were observed at lower doses in males than in females. No observed effect level was applicable. Lowest relevant oral and dermal NOAEL/NOEL was 29.51 and 500 mg/kg bw respectively. For dogs no effect were observed at even 1000 mg/kg bw.

IKF-916 was tested in a battery of five genotoxic tests and the results were negative in all experiments.

The carcinogenic potential of IKF-916 in rats and mice, and chronic toxicity in rats and dogs were studied. IKF-916 showed no carcinogenic potential in any species. The chronic studies with IKF-916 showed kidney and liver effects as the most sensitive indicator of toxicity in rats. In female rats exposed to 20000 ppm, there was evidence of increased kidney and a lower overall body weight. At 5000 ppm, there was increased kidney weight in males and females, and increased liver weights observed in males. Males also exhibited an increase urine volume and chlorine levels at 5000 ppm. In the dog study, no effects were observed at the

highest dose level (1000 mg/kg bw/day) and in mice, no treatment-related effects were observed at 7000 ppm.

A pilot study and subsequent two-generation reproduction study in rats were evaluated. Also, studies to determine the potential for developmental toxicity were conducted in the rats and rabbits. In the reproduction study, there was a treatment-related decrease in high dose F0 and F1 dam body weights during gestation and lactation. For the pups, there was a treatment related decrease in Day 21 pup weights during lactation in both litters of each generation at the highest dose, 20000 ppm. The maternal and neonatal NOEL was set at 2000 ppm. There was no effect on the reproductive parameters. The NOEL for reproductive effects was considered to be 20000 ppm (approximately 1338 mg/kg bwt/day). The teratology studies showed no evidence of maternal or developmental toxicity in either species at the highest dose level (1000 mg/kg bw/day).

Acute oral toxicity studies in rats with the four metabolites of IKF-916, CCIM, CCIM-AM, CTCA and DMSA were evaluated. The acute oral LD50 of each metabolite is summarized in Table 4.1.

Table 4.1. Acute oral LD50 of metabolites of IKF-916

Metabolite	Males (mg/kg bw)	Females (mg/kg bw)
CCIM	324	443
CCIM-AM	>3000	>3000
CTCA	2947	1863
DMSA	3238	2948

The genotoxic potential of the four metabolites was investigated in an in vitro bacterial mutation assay and all results were negative. The metabolites were considered non-mutagenic to bacteria under the conditions of the studies.

In list of endpoints of the 20th of November 2002, following reference values were set:
ADI: 0.17 mg/kg bw/day, based on kidney and liver effects in a two-year rat study and with a safety factor of 100.
AOEL: 0.3 mg/kg bw/day, based on kidney effects observed in a 13 week rat study and with a safety factor of 100.
ARfD: Not required

IKF-916 (cyazofamid) was not classified for health effects.

4.1 Acute toxicity (IIIA 7.1)

The notifier has submitted two oral exposure studies (Table 4.1.1), one with IKF-916 400 SC + adjuvant (4:3, v:v) dispersed in distilled water (study 1), and one study using IKF-916 400 SC alone (study 2). The dose of a.s. in both experiments was 5000 mg/kg bw.

Table 4.1.1. Summary of acute toxicity

Administration route	Species	LD50/LC50 (mg a.s./kg or mg a.s./L)	Risk phrase
**Oral	Rat	> 5000	None
*Oral	Rat	> 5000	None
**Dermal	Rat	> 5000	None
***Inhalation	Rat	> 5	None

***Test material: IKF-916 400 SC dispersed in distilled water*
*****Test material: IKF-916 400 SC + adjuvant (4:3, v:v) dispersed in distilled water*
*******Test material: IKF-916 400 SC + adjuvant + water (4:3:3000, v:v:v), field dilution*

Study 1: After oral administration of a single dose (5000 mg/kg bw) of IKF-916 400 SC + adjuvant (4:3, v:v) dispersed in distilled water, the following most important clinical signs

were observed: Diarrhoea, anogenital staining, staining mouth and mucous faeces among males and females at the day of dosing. At day 4 post treatment, no clinical signs were observed. By necropsy, one of the females had slightly enlarged mesenteric lymph nodes. However, the notifier interprets this finding not to be related to the treatment. In the main study no animals died, while in the dose-range finding study one out of four animals died following administration of 5000 mg/kg bw. The study was conducted and reported in compliance with the OECD guideline 401 (M. Yoshida, November 1999).

Study 2: After oral administration of a single dose (5000 mg/kg bw) of IKF-916 400 SC dispersed in distilled water, no clinical signs were observed. In one male a slight decrease in the size of the left testis was found by necropsy. The notifier considered this finding to be a minor and spontaneous alteration and not related to the treatment. No deaths were recorded in the dose-range finding study or in the main study. The study was conducted and reported in compliance with the OECD guideline 401 (M. Yoshida, December 1999).

The most pronounced clinical observations after dermal exposure to 5000 mg/kg bw of IKF-916 400 SC + adjuvant (4:3, v:v) were discoloration around nose, eyes and anogenital openings. The discoloration was observed one hour after treatment and disappeared by day four post treatment. One male had hair loss on both forelimbs and sores on the right back of the neck starting at day six to eight post treatment and were still present at day 14. The notifier considered this finding to be minor and spontaneous and not related to the treatment. No deaths were recorded in the main study or in the dose-range finding study. The dermal LD50 were higher than 5000 mg/kg bw. (Table 4.1.1). The study was conducted and reported in compliance with the OECD guideline 402 (M. Yoshida, November 1999).

After inhalation exposure exaggerated breathing were observed in the test group during and two hours post treatment. No animals died. Camber concentration was 5.08 mg/l (sd +/- 0,634) of IKF-916 400 SC + adjuvant in distilled water (4:3: 3000 by volume). Mass median aerodynamic diameter (MMAD) of the camber atmosphere was 1.1 µm and approximately 96% of the droplets were less than 7 µm. The inhalation LC50 was higher than 5 mg/L (Table 4.1.1).The study was conducted and reported in compliance with the OECD guideline 403 (D. Coombs, 1999).

Table 4.1.2. Summary of irritation and sensitisation

Study type	Species	Irritation/sensitization	Risk phrase
**Skin irritation	Rabbit	-	None
Eye irritation			
**Study 1	Rabbit	Yes	R41
*Study 2	Rabbit	-	None
***Study 3	Rabbit	-	None
**Skin sensitization	Guinea-pig	-	None

***Test material: IKF-916 400 SC dispersed in distilled water*
***Test material: IKF-916 400 SC + adjuvant (4:3, v:v) dispersed in distilled water*
****Test material: IKF-916 400 SC + adjuvant + water (4:3:3000, v:v:v), field dilution*

Skin irritation: After dermal exposure to IKF-916 400 SC + adjuvant (4:3, v:v), slight erythema (1.4) and edema (0.4) was observed. The product was not classified for skin irritation in accordance to the EU system (4.1.2 and 4.1.3). The study was conducted and reported in compliance with the OECD guideline 404 (M. Yoshida, December 1999).

Table 4.1.3. Observed effects in the skin irritation study

	Erythema/Eschar					
	Observation time Days					
Animal No.	**1**	**2**	**3**	**7**	**10**	
1	0	0	0	0	0	**0**
2	3	3	3	2	0	**3**
3	2	1	1	0	0	**1.3**
4	3	2	1	0	0	**2**
5	2	1	0	0	0	**1**
6	2	1	0	0	0	**1**
						Mean: 1.4
	Edema					
	Observation time Days					
Animal No.	**1**	**2**	**3**	**7**	**10**	
1	0	0	0	0	0	**0**
2	2	2	2	0	0	**2**
3	1	0	0	0	0	**0.3**
4	1	0	0	0	0	**0.3**
5	0	0	0	0	0	**0**
6	0	0	0	0	0	**0**
						Mean: 0.4

The notifier has submitted three eye irritation studies.

Study 1: Exposure to IKF-916 400 SC + adjuvant (4:3, v:v) caused cornea opacity of score 1 or 2 in all animals from 24 to 72 hours post treatment, and the effects became more severe on day seven post treatment. Severe opacity (score 4) was observed in two animals day seven post treatment. Iridial irritation (score 1) was observed in up to six animals from 24 hours to seven days post treatment. Redness (score 1-3), chemosis (score 1-3) and discharge (score 1-3) of the conjunctivae were observed in all animals from one hour to seven days post treatment. By using fluorecein, corneal epithelial damage, greater than 75% of the area, was detected in all rabbits from 24 to 72 hours post treatment (Table 4.1.4). Although the corneal damage had decreased at day seven, some degree of damage was still evident in all rabbits. All the animals showed severe and enduring signs of distress and pain on day seven and were terminated at day eight post treatment.

Table 4.1.4. Results of eye irritation study 1.

Observation	**Average score (24-72h) in the unwashed group**					
	Animal No.					
	1	2	3	4	5	6
Cornea (opacity) Density	1.0	1.0	1.3	1.3	1.3	1.3
Iris	0.3	0.7	**1.0***	**1.0***	0.7	**1.0***
Conjunctivae Redness Chemosis	**2.7*** **2.0***	**2.6*** **2.3***	**2.7*** **2.0***	**2.7*** **2.0***	**2.7*** **2.7***	**2.7*** **2.0***

*Positive ocular effect according to the EU classification system for eye irritation

The irreversible damage of the eyes resulted in classification with R41: Risk of serious damage to eyes, severe and /or irreversible. The study was conducted and reported in compliance with the OECD guideline 405 (M. Yoshida, 1. December 1999).

Study 2: Exposure to IKF-916 400 SC alone caused effect to the conjunctiva, including chemosis (score 1) and /or discharge (score 1) in up to five animals at one hour after administration, but the effects were cleared within 24 hours. According to the EU classification system for eye irritation/corrosion, IKF-916 400 SC was considered as a non-irritant to eyes and was not classified with any risk phase. The study was conducted and reported in compliance with the OECD guideline 405 (M. Yoshida, 7. December 1999).

Study 3: Exposure to IKF-916 400 SC + adjuvant and water (4:3:3000, v:v:v, representing spray concentration), caused no effects to the eyes. The study was conducted and reported in compliance with the OECD guideline 405 (M. Yoshida, 7. December 1999).

Skin sensitization by Magnusson and Klingman method: Based on a range finding study, the concentrations of the test material used at intradermal injection, first topical and second topical application in the main study were 0.2%, 50% and 2.0% respectively. One group was treated with DNCB (dinitrochlorobenzene) and served as a positive control. In this study a mixture of IKF-916 400 SC + adjuvant (4:3, v:v) caused 15% sensitisation (4/20) in the treated group. In the control group 5% (1/20) of the animals showed a positive dermal response. According to the EU classification system the test material was considered to be a non-sensitizer. The study was conducted and reported in compliance with the OECD guideline 406 (M. Yoshida, 1. December 1999).

Conclusion
IKF-916 400 SC + adjuvant solution was weakly toxic following acute oral, dermal and inhalation exposure. It did not irritate the skin or trigger sensitisation. IKF-916 400 SC + adjuvant (4:3, v:v) caused harmful effects to eyes and resulted into classification with R41. However, when the IKF-916 400 SC + adjuvant solution was diluted with water (4:3:3000) into field concentration or IKF-916 400 SC was given alone, no effects on the eyes were observed.

4.2 Dermal absorption (IIIA 7.3)

No study was submitted and EU used a default value of 100%.

4.3 Available toxicological data relating to non-active substances (IIIA 7.4)

Safety data sheets for the co-formulants in IKF-916 400 SC and for the adjuvant have been submitted. Based on the information in the safety data sheet for the adjuvant, we requested more information. The manufacturer submitted several studies on the adjuvant.

Toxicity studies on the organosilicon adjuvant (Silwet L-77)

Acute toxicity studies

The manufacturer has submitted four acute toxicity studies on the adjuvant, one by inhalation, two by dermal application and one by oral administration. There was also submitted an inhalation study of a five percent adjuvant solution (water based). (Table 4.3.1).

Table 4.3.1. Summary of acute toxicity

Administration route	Species	LD50/LC50 (mg/kg or mg/L)	Risk phrase	Reference
Oral	Rat	>2000	None	Driscoll, 1996
Dermal	Rat	>2000	None	Driscoll, 1996
Dermal	Rat	>8000 (4000 b.i.d.*)	None	Naas, 1995
Inhalation	Rat	1.98	R20	Naas, 1995
Inhalation, (5% solution)	Rat	>0.47	None	Hialaski, 2001

* twice a day

Study 1: In this limit-dose study, oral administration of 2000 mg/kg bodyweight undiluted material was given to five male and five female Sprague-Dawley rats. The rats were observed for two weeks before killing and gross pathological examination. There were no deaths in the study. All animals showed clinical symptoms. Hunched posture being the most common symptom followed by ataxia and reduced respiration rate. The symptoms were reversed within four hours to one day in all animals except one male. This male also displayed lethargy, laboured breathing and emaciation. All symptoms were reversed 9 days after administration. This male had reduced body weight gain during the first week of the study, whereas a female had reduced bodyweight gain during the second week of the study. There were no pathological findings. The study was conducted and reported in compliance with the OECD guideline 401 (R. Driscoll, January 1996).

Study 2: In this acute dermal toxicity study, five male and five female Sprague- Dawley rats were given a semi-occluded application of 2000 mg/kg bodyweight to intact skin for a 24-hour period. The animals were observed for two weeks before necropsy. There were no deaths, and no clinical signs or sign of skin irritation during the study. The animals did gain body weight as expected and there were no pathological findings. The study was conducted and reported in compliance with the OECD guideline 402 (R. Driscoll, January 1996).

Study 3: The test material was given to two groups, each comprised of five male and five female Crl:CD®BR rats. The first group was administered a single dose of 2000 mg/kg bodyweight to shaved, intact skin under semi-occlusive dressing for 24 hours. The second group received 4000 mg/kg bodyweight twice a day (b.i.d.), 12 hours apart, resulting in a total dose of 8000 mg/kg bodyweight. There were no deaths in the study. Clinical findings were noted within the first 24 hours after dosing. Hypoactivity (nine rats) and ataxia (five rats) were only observed in the 4000 mg/kg bw b.i.d. group. Red staining around eyes and yellow urogenital staining were observed in both groups, but were more frequent and lasted generally longer in the high dose group. All animals appeared normal day 2. Very slight to slight erythema was seen on seven rats and desquamation was seen on six rats in the 2000 mg/kg bw group. In the 4000 mg/kg bw b.i.d. group, seven rats were observed with very slight erythema, whereas all rats had desquamation. Females were generally more affected than males. Three female rats had a weight loss of 1-3 % during the first week of the study. One male in the 2000 mg/kg bw group had mottles lungs, but that was not considered to be treatment related by the study director. The study was conducted and reported in compliance with the OECD guideline 402 (D. J. Naas, March 1995).

Study 4: In this study three groups, each consisting of five male and five female Crl:CD®BR rats, were exposed to 0.26, 1.1 or 2.0 mg/L aerosol by whole body inhalation exposure for four hours. The MMAD range of the aerosol was 1.71 to 2.83 µm. Two animals in the 1.1 mg/L group and five animals in the 2.0 mg/L died or were euthanized *in extremis* during the study. The LC50 was calculated to be 1.98 mg/L. There were clinical effects in all groups. The most relevant are listed in table 4.3.2.

Table 4.3.2 Clinical observations after exposure to L-77

Group	0.26 mg/L		1.1 mg/L		2.0 mg/L	
Effect	Male	Female	Male	Female	Male	Female
Mortality *	0	0	1	1	2	3
Matting various degrees**	5	5	5	5	5	5
Dried red/yellow material around nose or eyes	3	3	5	5	5	5
Dried/wet	3	2	4	5	5	5

red/yellow material around the mouth						
Corneal opacities***	0	0	1	1	3	4
Rales****	5	5	5	5	5	5

* Animals were found dead/euthanized days 4 and 6 in the 1.1 mg/L group and days 3 to 5 in the 2.0 mg/L group.
** Various degrees of matting (clear, yellow or red, wet or dry). The findings were dose related regarding both frequency and duration. Females were generally more affected than males.
*** All dead /euthanized animals had corneal opacities on both eyes appearing day 1 to day 4. The two other animals in the 2.0 mg/L group had corneal opacity of one eye that appeared day 9 and persisted until the end of the study.
**** The daily occurrences of animals with rales in the observation period were dose dependent. Males in the 1.1 and 2.0 mg/L groups and females in the 2.0 mg/L group had rales until days 11-13. Laboured breathing was seen in the 2.0 mg/L group.

The two highest dose levels gave loss in body weight of all rats from the day of exposure to day 3. All surviving rats regained or surpassed their initial weight by the end of the study.

The animals that were found dead or euthanized *in extremis* had all matting of the external surface (yellow/red and/or clear). There were many pathological findings in the gastrointestinal canal for these rats included darkened intestines, dark red content of the jejunum and stomach, distension of the intestines and stomach, and several dark red irregularly shaped or pinpoint areas in the glandular area of the stomach. Other findings for these animals included bilateral ocular opacity, white irregularly shaped areas in the median lobe of the liver and mottled lungs.

Pathological findings in the rats surviving to the end of the study, was hair loss on various location (one 1.1 mg/L female; one male and two females in the 2.0 mg/L group), ocular opacity (in one male and one female in the 2.0 mg/L group) and one rat with dark red areas in the lungs (1.1 mg/L group).

The study was conducted and reported in compliance with the OECD guideline 403. (D.J. Naas, September 1995)

Study 5: The test article in this study consisted of 5 % active ingredient (organo-silicone) and 95 % water. This corresponds to a total formulation concentration of 11.78 mg/L. One group of five male and five female rats were exposed (nose-only) to an aerosol with a concentration of 0.47 mg/L (gravimetric determination) for four hours. The MMAD range of the aerosol was 1.94 to 2.39 µm. The rats were observed for two weeks before necropsy. There were no mortalities in the study. The administration gave no effect on body weight gain, and gave no test-article related changes of clinical observation, neurobehavioral observation or macroscopically examinations at necropsy. The study was conducted and reported in compliance with the OECD guideline 403. (R. J. Hialaski, October 2001).

Irritation studies

The manufacturer has submitted three irritation studies on the adjuvant; one dermal irritation and two eye irritation studies (Table 4.3.3). Dermal sensitisation was not investigated.

Table 4.3.3. Summary of irritation studies on the organo silicone adjuvant

Study type route	Species	Risk phrase	Reference
Eye irritation	Rabbit	R36	Driscoll 1996
Eye irritation	Rabbit	R36	Fulfs 1994
Dermal irritation	Rabbit	None	Driscoll 1996

Study 1: In this eye irritation study with three New Zealand White rabbits (two males and one female), exposure to the adjuvant caused iridial inflammation of score 1 and cornea opacity of score 1 or 2 in all animals from 24 to 72 hours post treatment. Other ocular effects noted were dulling of the normal lustre of corneal surface and vascularisation of the cornea. Effects on the conjunctivae included redness of score 2 and oedema (chemosis) of score 2 in all animals from 24 to 72 hours post treatment.

Table 4.3.4. Results of eye irritation study 1.

Observation	Average score (24-72h)		
	Animal No.		
	1	2	3
Cornea (opacity) Density	1.0	1.3	1.7
Iris	**1.0***	**1.0***	**1.0***
Conjunctivae			
Redness	2.0	2.0	2.0
Chemosis	**2.0***	**2.0***	**2.0***

*Positive ocular effect according to the EU classification system for eye irritation

All treated eyes appeared normal fourteen days after treatment. The study was conducted and reported in compliance with the OECD guideline 405 (R. Driscoll, January 1996).

Study 2: Three male and three female New Zealand Albino Rabbits were exposed to the adjuvant. There were no effects on the cornea or iris. Effects on the conjunctivae included redness of score 1 to 2, and oedema (chemosis) of score 2 to 2.7 and discharge of score 2 in the animals from 24 to 72 hours post treatment.

Table 4.3.5. Results of eye irritation study 2.

Observation	Average score (24-72h)					
	Animal No.					
	1	2	3	4	5	6
Cornea (opacity) Density	0	0	0	0	0	0
Iris	0	0	0	0	0	0
Conjunctivae						
Redness	1.7	1	1	2	1	1
Chemosis	**2.7***	**2***	**2***	**2.7***	**2***	**2***
Discharge	2	2	2	2	2	2

*Positive ocular effect according to the EU classification system for eye irritation

The study was conducted and reported in compliance with the OECD guideline 405. (J. C. Fulfs, September 1994)

Study 3: In this dermal irritation study, three New Zealand White rabbits were exposed to the adjuvant for four hours. The mean score for skin effects were 0.0 for both erythema and oedema. The study was conducted and reported in compliance with the OECD guideline 404. (R. Driscoll, January 1996).

Subacute

9-days inhalation study in rats

Three groups, each comprised of 10 male and 10 female rats approximately seven weeks of age, (CDF®(F344)/CrlBR), were exposed via whole body inhalation to an aerosol of L-77 for six hours per day for nine consecutive days. The doses were 0.025, 0.08 and 0.25 mg/L. The MMAD for the aerosol was found to be 1.45, 1.49 and 2.01 µm for the 0.025, 0.08 and 0.25 mg/L targets respectively. A concurrent control group received filtered air under similar test

conditions.
One male and one female in the 0.25 mg/L group died. The animals had distension of the caecum and of the intestinal tract or the stomach. Microscopically examination of the nasal cavities showed that both animals had exudate in ventral meatus, mild multifocal erosion and moderate mucosal atrophy. In addition, the male had lymphocytic infiltration and the female had necrosis of squamous epithelium with neutrophilic infiltration.
Clinical signs of test article toxicity included rales and ocular opacities in all test groups, yellow matting of various body surfaces and red staining around nose and mouth in the 0.08 and 0.25 mg/L groups, and clear matting in facial area in the 0.025 mg/L group. Ocular opacities were seen in one animal of the 0.025 and the 0.08 mg/L groups and in 5 rats in the 0.25 mg/L group.
Food consumption was reduced in the 0.08 and 0.25 mg/l group males throughout the study and in 0.25 mg/L females up to day 5. Mean body weight loss or reduced body weight gain were seen in both sexes at the highest dose level up to day 2 and in males in the 0.08 group up to day 2.
Haematological investigations showed an increased mean white blood cell count in the 0.025 mg/L group males and increases in the absolute numbers and percentages of segmented neutrophils in the 0.25 mg/L group males and females. Serum analysis showed significantly reduced albumin levels in the 0.25 mg/L males and females.
Pathological examinations at scheduled necropsy revealed that two females in the 0.25 mg/L group had small thymus glands. The mean absolute and relative thymus weight were also significantly lower than the control group in the 0.25 mg/L group males and females.
The testis and the epididymal semen were investigated in rats at the highest dose level and in the control group. No test compound related effects were found. The stage of oestrus of each female in all groups was determined by vaginal smears. No effects were found. The relevance of the investigations on the reproductive organs can be questioned as seven to eight weeks old rats are not fully mature.
Microscopically examination was done on all nasal cavities (table). The effects were more frequent and severe in the 0.25 mg/l group. The effects on nasal cavities in the 0.08 and 0.25 mg/L groups were considered treatment related.

Table 4.3.X Incidence of microscopic changes in the nasal cavities

Group	**Control**	**0.025 mg/L**	**0.08 mg/L**	**0.25 mg/L**
Exudate, ventral meatus	0	0	2	13
Necrosis, squamous epithelium	0	0	1	3
Necrosis, respiratory epithelium	0	1	1	3
Lymphocytic infiltration	1	3	4	10
Mucosal atrophy	0	0	0	5
Erosion	0	0	0	3
Suppurative inflammation	0	0	0	2
Ulceration	0	0	0	2
Exudate, dorsal meatus	0	0	0	1

For systemic toxicity the NOEC < 0.025 mg/L, based on the occurrence of rales, ocular opacities and matting of body surfaces at all dose levels. (D. J. Naas, 3. October 1995)

There was performed a pathological re-examination of the nasal cavities material in 2001. The pathologist considered the histomorphological changes as less severe compared to the original evaluation. In the high exposure group the attenuation of nasal mucosa seemed to result from atrophy (some with metaplasia) and erosion rather than necrosis. The pathologist assessed that, with the possible exception of the 3 animals with exudate in the 0.08 mg/L group, only the highest dose level gave effects in the nasal cavities that were clearly treatment related.

Table 4.3.Y Incidence of microscopic changes in nasal cavities, re-examination

Group	Control	0.025 mg/L	0.08 mg/L	0.25 mg/L
Inflammatory changes	1	3	7	19
Exudate	0	0	3	16
Lymphocytic infiltration	1	3	4	12
Atrophy	0	0	0	5
Erosion	0	0	0	2
Suppurative ulceration, mild	0	0	0	2

(J. F. Hardisty, 25. October 2001).

Conclusion
The organo-silicone adjuvant had low oral and dermal toxicity, but is harmful by inhalation (Xn;R20). A labelling with R39 might also be appropriate as persistent ocular opacities developed during the observation period in some animals.
There was not seen dermal irritation in the dermal irritation study, but the adjuvant was found irritation to eyes in two studies. The were most severe effects to conjuntiva, but effects to the iris was seen in one study. The adjuvant's sensitization potential was not investigated.
In the 9-days inhalation study, 0.25 mg/L of the organo-silicone adjuvant resulted in treatment related deaths. Thus, the use of the risk phrase R48/20 is appropriate. As the duration of the study was only 9 days, and the most classification should be based on a 90-days study, the adjuvant could be classified as Toxic T;R48/23. On the other hand, rats are obligate nose breathers, whereas man also may have oral respiration. Man thus may be able to avoid extensive passage of a toxic substance through the nose and in that way reduce the toxicity to the nose. But the cause of death is not clearly stated, and may also include other systemic effects.

4.4 Exposure assessments

4.4.1 Operator exposure

The estimation of operator exposure was based on exposure to IKF-916 400 SC and was preformed by using the German model (75th percentile) and the UK POEM model. Body weight of 60 kg and a max GAP for the Nordic countries at 0.08 kg as/ha (Denmark, Estonia, Latvia, Lithuania, Sweden and Norway) was used. Spray volume was set at 150 L/ha and 200 L/ha.

a) Estimation according to the German model (75th percentile) (GM)

Exposure was calculated for applications with tractor-mounted/trailed boom sprayer; hydraulic nozzles field crop sprayers. The maximum dose rate was used as worst case scenario.
Treated area: 20 ha/day
Duration: 6h
Body weight of operator: 60 kg
Max.dose rate: 0.2L product /ha e.i. 0.08 kg a.s./ha

b) Estimation according to the UK-POEM and EUROPOEM I

Exposure was calculated for applications with tractor-mounted/trailed boom sprayer; hydraulic nozzles field crop sprayers. The maximum dose rate and minimum spray volume were used as worst case scenario.
Treated area: 20 ha/day

Duration: 6 h
Body weight of operator: 60 kg
Max.dose rate: 0.2L product /ha e.i. 0.08 kg a.s./ha
Spray volume: 150L/ha and 200 L/ha
Container: 5-litre container size with a 45- or 63-mm closure

Table 4.4.1. Estimated operator exposures for the intended use of IKF-916 400 SC

Estimated systemic exposure to cyazofamid as a proportion of the AOEL:					
Application technique	Crops	Model	PPE	Total systemic exposure (mg/kg bw/day)	% of AOEL (mg/kg bw/day)
Field crop sprayer	Potatoes	German Model	None	**0,497**	**166%**
			PPE 1	0,181	60%
			PPE 2	0,152	51%
		*UK-POEM	None	**0,437**	**146%**
			PPE 1	0,373	124%
			PPE 2	0,125	42%
		**EUROPOEM I	None	**0,595**	**198%**
			PPE 1	0,115	38%
			PPE 2	0,067	22%

* 150L spray volume
** 150L and 200L spray volume (the results were the same)
PPE 1: Gloves during mixing/loading; standard protective garment (plant protection) and sturdy footwear during application
PPE 2: Gloves during mixing/loading and application

Bystander exposure/re-entry
There are no published models available to estimate bystander exposure; therefore, the notifier used the following information to estimate bystander exposure. Data from a spray drift model used by the US EPA has estimated that from a ground application, 1% of what was applied could be expected to drift to adjacent areas. Using that information, it was estimated that the exposure of the bystander to the active ingredient would be 1% of the exposure to the applicator. The exposure to the worker, not using PPE, was estimated to be less than 0.6 mg/kg bw/day (Table 4.4.1). Consequently, bystander exposure would be 0.06 mg/kg bw/day, which is 20% of the AOEL.

Worker exposure
No measurement of worker exposure has been presented, but the notifier has estimated worker exposure for re-entry activities: The application rate is 80g a.s./ha. This would leave a dislodgeable residue of < 8 mg a.s./m^2 of foliage. Assume during the work day, all residues from one square meter are transferred to the skin of a worker. Exposure would be 8 mg a.s./worker or 0.13 mg a.s./kg bw/day for a 60 kg worker. With an AOEL = 0.3 mg/kg bw/day the exposure would account for 43% of systemic AOEL.
Conclusion
Estimate of the operator exposure for the intended use of Ranman shows that glows during mixing/loading and application are necessary to obtain acceptable use. Based on exposure estimates for the workers and bystanders, no unacceptable risk was found.

4.5 Appropriate mammalian toxicology and operator exposure end-points relating to the product and approved uses

In the EU Ranman kangaroo pack was evaluated, while the notifier now applies for a twinpack. This change of package changes the exposure situation drastically. For more details see 2.2: Clasification and labelling in part A and Summary of Ranman TwinPac in 4 Mammalian toxiclogy.

The change in the packing of the product causes the need of an evaluation of the toxicological properties of IKF-916 400 SC and adjuvant alone, as well as in combination, to be able to label the product in a safe way. As shown in Table 4.5.1, the adjuvant alone may cause harmful effects to health. The effects were not covered by the classification of IKF-916 400 SC + adjuvant. As shown in Table 4.5.2 no studies with the adjuvant alone and only a few studies with the IKF-916 400 SC alone have been submitted.

Table 4.5.1 Classification and labelling

Classification and labelling of IKF-916 400 SC + adjuvant (4:3, v:v) based on submitted studies		
Hazard symbol:	Xi	
Indication of danger:	Irritant	
Risk phrases:	R41	Risk of serious damage to eyes
Classification and labelling of IKF-916 400 SC based on submitted safety data sheet and acute oral and eye irritation studies		
Hazard symbol:	None	
Indication of danger:	None	
Risk phrases:	None	
Classification and labelling of the adjuvant based on submitted safety data sheet		
Hazard symbol:	Xn	
Indication of danger:	Harmful	
Risk phrases:	R20	Harmful by inhalation
	R36	Irritating to eyes
	R48/20	Harmful: danger of serious damage to health by prolonged exposure through inhalation
Chronic effects		May have an effect on fertility

Table 4.5.2. Data status for IKF-9160400 SC and the adjuvant

Administration rout	IKF-916 400 SC	Adjuvant
Oral	**submitted**	missing
Dermal	missing	missing
Inhalation	missing	missing
Skin irritation	missing	missing
Eye irritation	**submitted**	missing
Skin sensitisation	missing	missing

Considering the content and properties of the formulation products and the active substance cyazofamid alone, it is not likely that IKF-916 400 SC causes effects that are not covered in the classification of IKF-916 400 SC + adjuvant (4:3, v:v). However, the important issue in this evaluation is the lack of information concerning the adjuvant alone, which seems to have a harmful effect on health.

Estimate of the operator exposure for the intended use of IKF-916 400 SC showed that glows during mixing/loading and application were necessary to obtain acceptable use. Based on exposure estimate for the workers and bystanders, no unacceptable risk was found.

4.6 Any other relevant toxicological data / information

There has not been reported incidence of poisoning episodes with cyazofamid (IKF-916) in humans.

5 Residues

IKF-916 is considered acceptable for Annex I inclusion. In the DAR the use in potatoes and tomatoes was evaluated.

5.1 Metabolism and distribution of residues in plants

The metabolism and distribution of residues in plants were investigated in potatoes, tomatoes and grapes by using radio labelled ^{14}C in the benzene ring ([^{14}C] IKF-916 (Bz)) or in the imidazole ring ([^{14}C] IKF-916 (Im)) of the active substance, added to the 400 SC formulation. The studies demonstrated that the metabolic pathway of cyazofamid was similar in all the investigated plants.

The major radioactive residue found in potato tubers, tomato fruit and grape berries was IKF-916. The parent compound was also the major radioactive residue in foliage from all three crops. With the exception of the incorporation into natural products, CCIM, which never exceeded 10% of TRRs (total radioactive residues), was the major metabolite of IKF-916 in the edible portion of the plants.

5.1.1 Residues in potatoes

Following application of 2000 g a.s./ha (2.5 times the maximum use rate) the total residue levels in potato tubers were ≤ 0.02 mg/kg. The final application was made the week before harvest.
The major contributors to the TRRs were found reincorporated into natural products such as starch, and in soluble natural products like sugars and acids. The amount of the parent compound for all the tuber samples, including the samples exposed to the highest dose, was 2 mg/kg or less. The level of CCIM was at or below 0.3 mg/kg. No other metabolites were detected in tubers. The parent compound remained largely unchanged in the foliage. Even though CCIM accounted for approximately 3% of TRRs, it was the most important single metabolite. All other detectable metabolites could be derived from CCIM.

5.1.2 Residues in tomatoes

Most of the radioactive residues were found on the surface of the tomato fruit. The total residue levels in tomato fruit were ≤ 0.05 mg/kg following application of 400 g a.s./ha. The final application (100 g a.s./ha) was made the day before harvest. Approximately 71 to 87% was found in the pulp and the remainder in the juice. The parent compound accounted for most of the detected radioactive residues (31-68%) from surface of washed fruits. The CCIM (~7%), polar metabolites, primarily natural products, (4-15%), bound residue (6-26%) and CCTS (2-4%) accounted for the majority of the remaining radioactive residues. All other metabolites were present at extremely low to non-detectable levels. The IKF-916 remained largely unchanged in the foliage. The most important single metabolite was CCIM even though it accounted for only 1-5% of TRRs. The majority of the other metabolites could be derived from CCIM.

5.1.3 Residues in grapes

Total residue levels in grapes were 0.4 to 0.5 mg/kg following application of 500 g a.s./ha. The grapes were harvested 44 days after the final application. Approximately 82% of TRRs was in the pulp and 15-16% in the juice. The parent compound accounted for most of the radioactive residues in the fruit (57-58%). Bounded residues (15%), polar metabolites, primarily natural products (10-11%), CCIM (5-7%), 5-CGTC, a glucoside of CCIM (2-3%), and a polar conjugate of CCIM (2-3%) accounted for the majority of the remaining radioactive residues. The most important single metabolite in grapes was CCIM even though it accounted for only 4-6% of TRRs. The majority of other metabolites could be derived from CCIM. All other metabolites were present at <0.01 mg/kg. The TRR in foliage was between 0.4-0.7 mg/kg. Approximately 62-80% of the residues were solvent extractable.

Approximately 34-41% of the TRR in foliage was due to the unchanged IKF-916. TRR levels were 0.2 mg/kg in vin de Goutte and 0.3 mg/kg in vin de Presse. The major metabolite in both wines was CCIM (28-31%). Polar metabolites (14-23%) and 5-CGTC-10 (3-7.5%) were other significant metabolites present at 0.01-0.05 mg/kg level. Approximately 5-11% of TRRs were due to the unchanged parent. The major residue in wine was CCIM.

5.1.4 Residue definition

Based on the chemical composition of identifiable residues in the potato, tomato and grape metabolism studies, the residue in these crops can be defined by quantification of the parent molecule, IKF-916. The major residue found in potato tubers, tomato fruit and grape berries was IKF-916. Parent compound is also the major residue in foliage from all three crops. In wines the CCIM was the major metabolite and exceeded 10% of the TRR and hence, the CCIM should be defined as residue in wines.

5.1.5 Metabolism and distribution of residues in animals

The elimination, distribution and metabolic fate of the synthetic fungicide IKF-916 in laying hens and lactating goats were studied. Hens (10 per group) and goats (2 per group) were orally dosed with 10 ppm [^{14}C] IKF-916 (Bz) or [^{14}C] IKF-916 (Im) relative to food intake for five consecutive days. Low detectable levels of ^{14}C residues were found in milk (<0.05%), while in eggs no residues were detected. Low or not detectable levels of residues were found in breast muscle, thigh muscle, fat, skin and blood following treatment of laying hens and lactating goats. The total tissue residues accounted for less than 0.1% of the administered dose. Only low levels of ^{14}C residues were detected in liver and kidney (goat and hens). The test material was rapidly metabolized and 86% and 59% of the administered dose was excreted by hens and goats, respectively. It is likely that most of the remaining radiolabel compounds were present in the gastrointestinal tract when the animals were terminated. Unmetabolised IKF-916 was the single major component present in excreta from hens. The highest concentration of the unchanged parent compound in goats was found in faeces. Seven and ten metabolites were identified or characterized in the goat study and in the hens study, respectively. The metabolic pathway of IKF-916 in hens and goats were similar to the reported metabolism in rats and plants (potato, tomato and grape).
In the EU list of endpoints, animal residue definition for monitoring and animal residue definition for risk assessment were not proposed because the intake of residues by animals was not significant.

5.2 Summary of residues data and consumer exposure

In the Nordic/Baltic countries Ranman TwinPack is applied for use in potatoes. A maximum application rate at 0,08 kg a.i./ha and a PHI at 7 days is the same for all the countries, while the maximum number of applications vary from 3 to 10 .

The most critical GAP will be 10 x 0,08 kg a.i./ha, PHI 7 days, which correspond to the GAP of IKF-916 (cyazofamid) evaluated for the Annex I inclusion.

Residue trials have been conducted with three different formulations (IBE 3844, IBE 3878 and IBE 3878 + adjuvant). The difference between IBE 3844 and IBE 3878 is that the last one has a smaller particle size of the SC formulation.

A total of 11 residue trials have been conducted in Northern Europe (UK, NL, N-FR and DE) over a 4 year period (1996-1999). All trials were conducted according to critical GAP (0,08 kg a.i./ha, 8-10 applications, PHI 7 days). The results showed no detectable residues above the LOQ (0,01 mg/kg) in the potato tubers at harvest. This also seems logic since the product is a contact fungicide with no systemic activity. Residue decline studies with PHI 0, 1, 3 and 7 days also resulted in no detectable residues at any of the sampling days.

Residue levels with either of the coded products used were very similar, and no significant difference has been observed in residue level between IKF-916 formulation with or without adjuvant.

5.2.1 Short-term intake calculation

IKF-916 is not considered to be acutely toxic to human via dietary exposure. Therefore no acute reference dose has been established and no acute dietary risk assessment has been performed.

5.2.2 Long-term intake calculation

The chronic dietary risk assessment has been based on an ADI value of 0,17 mg/kg/bw/day, and the MRLs for potatoes (0,01 mg/kg) and tomatoes (0,2 mg/kg). (Use in tomatoes applies only Southern Europe). Both the WHO model and the UK-Consumer model have been used. The calculations were based on a 60-kg individual, and assumed that 100% of the crops are treated with IKF-916 and that, when consumed, the residues are at the MRL.

Using the WHO model, dietary exposure to IKF-916 from consumption of potatoes and tomatoes indicate that the TMDI accounts for 0,15% of the ADI. Using the UK-Consumer model, dietary exposure to IKF-916 based on the TMDI, accounts for 0,17% of the ADI for adults, 0,20% of the ADI for children and 0,29% of the ADI for infants.

The worst case estimate of dietary exposure to IKF-916 from residues in tomatoes and potatoes, using the WHO model or the UK-Consumer model, accounts for less than 0,3% of the ADI.

The results indicate that there is neither an acute nor a chronic risk to human health from the consumption of crops treated with IKF-916 according to the GAP.

5.2.3 Residues in succeeding crops

The results of the confined rotational crop study with IKF-916 demonstrated the absence of residues of concern in lettuce, carrot, forage wheat and mature wheat at the 30-day plant-back interval. Total residues at lager time points trended lower and were les than 0,01 ppm for mature lettuce, carrot root and wheat grain for 360-day plant-back samples. Consequently, there should be no need for rotational crop restrictions for these crops at or beyond a 30-day plant-back interval.

5.2.3 Livestock feeding studies

Potatoes are not intended for use as fodder, livestock feeding studies are therefore not conducted.

5.3 Maximum Residue Levels

Maximum Residue Levels (MRLs) for cyazofamid (IKF-916) are established in Commission Directive 2003/113/EC of 3 December 2003. The MRL for potatoes is determined to 0,01 mg/kg.

6 Environmental fate and behaviour

6.1 Fate and behaviour in soil

6.1.1 Route of degradation

Aerobic degradation of IKF-916 in soil occurs via hydrolysis to CCIM (max. 33 % AR after 14 days in a Japanese soil at 25 °C). This compound is further degraded to CCIM-AM (max. 13.7 % AR after 10 days at 20 °C) and then to CTCA (acid-derivative, max. 20.9 % AR after 21 days at 20 °C). The degradation pathway as proposed in the DAR is presented in Fig. 6.1.1. The mineralization of IKF-916 is rather slow with a CO_2 production of 2.3 - 10.8 % AR after 30 days (max. 11.9 and 14.4 % AR after 59 and 45 days) for the two different radioactive labelled moieties (Bz and Im). Bound residues have been shown to reach 33.5 - 45.7 % AR after 30 days and reaching 47.6 - 64 % AR after 45 - 59 days. Maximum amounts of bound residue do not seem to have been reached in these studies.

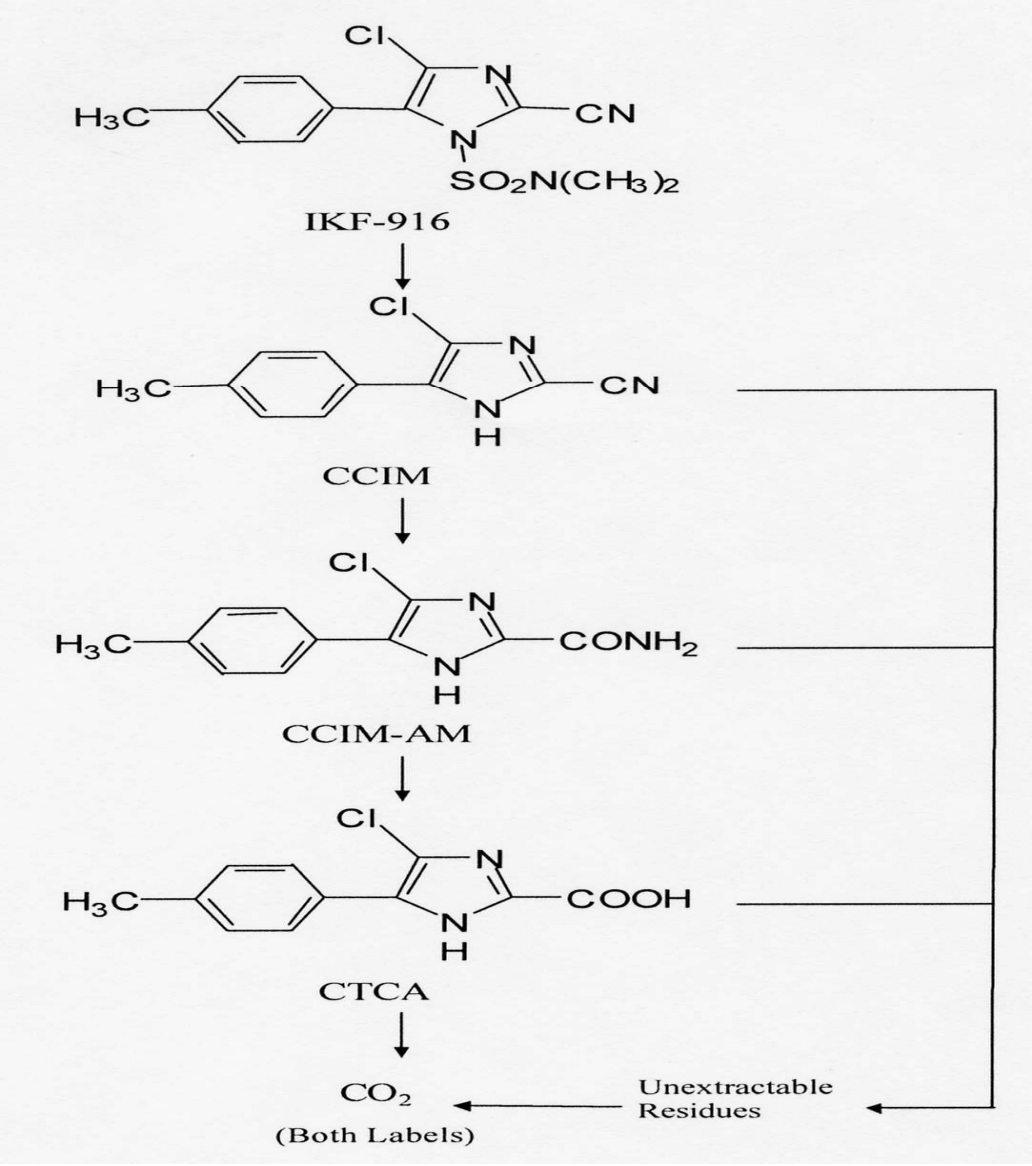

Fig. 6.1.1: Degradation pathway of IKF-916 in soil as proposed in the DAR.

6.2 Rate of degradation

6.2.1 Laboratory studies

Aerobic conditions
Degradation rates of IKF-916 and the metabolites CCIM, CCIM-AM and CTCA are presented in **tables 6.2.2 to 6.2.5.**

Based on data from the degradation studies with IKF-916, recalculations made by RMS and the study of McFadden (1999b) 1. order DT50s are in the range of 3.8 - 15.1 days at 20 °C with a geometric mean of 7.6 days (n = 11). DT50 (1. order) of IKF-916 at 10 °C is in the range of 36.8 days. DT90 (1. order) values are in the range of 21.2 - 50.1 days for IKF-916 at 20 °C and 122.5 days at 10 °C.

Recalculations made by McFadden (1999b) gave geometric mean DT50s (20 °C, 1. order) for the metabolites CCIM, CCIM-AM and CTCA of 9.3, 2.8 and 14.3 days, respectively (**Table 6.2.5**). Amounts of metabolites can be underestimated in studies with the parent and half lives calculated based on these studies can thus be uncertain.

Based on studies with the separate metabolites bi-exponential DT50 of CCIM ranged from 1.2 to 3.4 days with geometric mean of 1.8 days at 20 °C. DT90 values (bi-exponential) were in the range 12-71.2 days (geometric mean 22.2 days) at 20 °C. According to the addendum of the DAR, only bi-exponential kinetics fitted the data to an acceptable extent for this metabolite and no recalculations were made by RMS. RMS proposed that 1. order data from the McFadden study should be used anyway due to their large range of variation (3.8-29.2 days) that also covers the data from the study with only the metabolite.

Based on separate studies performed with only the metabolites, half lives (DT50) were somewhat higher for CCIM-AM than the ones calculated in the McFadden study (1.0 - 11.1 days). For CCIM-AM DT50 values ranged between 7.3 and 14.1days (bi-exponential) at 20 °C in the metabolite study. At 10 °C DT50 values were 8.8 (bi-exponential). For metabolite CCIM-AM DT90 values (bi-exponential) in all soils tested were over 120 days both at 10 and 20 °C (**table 6.2.3**). RMS recalculated the DT50 and DT90 values for metabolite CCIM-AM to 1. order. The recalculated DT50 values are in the range of 37-56.5 days (geometric mean 43 days, r^2 0.71-0.75) and the DT90 values in the range of 123-187 days (geometric mean 143 days) at 20 °C (Addendum to the DAR, September 2002). The recalculated DT50 and DT90 values at 10 °C are 38.5 and 129 respectively (mean values of two moieties, r^2 0.85-0.86). According to RMS first order DT50 values are overestimated with regard to raw data and should be considered as worst case values. RMS concludes however that for a conservative approach, the overall range of first order DT50 values should be 1 - 56.5 days with a geometric mean of 6.9 days, including the results from the McFadden study.

Based on separate studies performed with only the metabolites, half lives were considerably higher (267-487.5 days) for CTCA (Landphair, 1999) than the ones calculated in the McFadden study (8.1-73.5 days). The study duration was to short for CTCA to reach its half life and the conclusion in the study is that DT50 and DT90 > 120 days. Half lives for CTCA were calculated/extrapolated in the study itself and DT50 values ranged from 267 to 488 days (1. order) at 20 °C. At 10 °C DT50 values were 302 days (1. order). RMS recalculated these values, and the results were more or less in the same range as in the study (229-395 days, **table 6.2.4**). These extrapolated values must be regarded as uncertain. RMS used the highest recalculated DT50 value of 395 days in their PEC calculations as an absolute worst case. The applicant argues that the DT50 values generated from the metabolite study is very uncertain and that the highest value from the Japanese study (73.5 days, Tanaka, Kato and Ogyu, 1999) should be used instead.

The reason for the higher degradation rates in some of the metabolite studies is discussed in the DAR and it is suggested that this is due to adsorption-desorption processes which more strongly reduce the availability of the metabolites as they are applied directly and thus get longer residence times in soil. The applicant argues that DT50 values generated from these studies must be regarded as very uncertain due to this. Whether this adsorption is the whole explanation for the great differences in half lives for CTCA is uncertain.

Anaerobic conditions:
Degradation rates of IKF-916 under anaerobic conditions are presented in **table 6.2.2**. Based on bi-exponential kinetics DT50 and DT90 has been calculated to 5.8 and 32.8 days respectively. Under anaerobic conditions mineralization was low with only 1.5-2.9 % CO_2 produced within 120 days and 2.9-3.4 % produced within one year. Bound residues accounted for 68-72 % of applied radioactivity within 120 days and > 80 % within one year.

Photolysis in soil:
A photolysis study (B.8.1.1.3, Shelby 1999) is described in the DAR. This study was conducted according to GLP and SETAC guidelines in a loamy sand soil. In the DAR it is concluded that photolysis has no effect on degradation of IKF-916 in air-dried soil. Under both light and dark conditions IKF-916 is rapidly degraded with a DT_{50} of 8.3 days. The metabolite CCIM accounts for maximum 40 % of AR after 7 days and the metabolite CCBA accounts for maximum 37.6 % of AR after 21 days in light and 53.8 % of Ar after 30 days in the dark. In the DAR it is argued that CCBA is a result of a slow oxidation process not seen in wet soil. In wet soil one can assume that hydrolysis will occur rather than oxidation, and that this metabolite therefore is not observed under “normal” soil moisture conditions. The DAR concludes though that member states must pay attention to the possibility of this metabolite being formed in significant amounts in long dry periods of the year.

Table 6.2.1.: Degradation of IKF-916 in different soils (international soil classification).

Soil	**Sandy loam**	**Ushiku light clay loam (Japan)**	**Nagano clay loam (Japan)**	**US loamy sand (EFS072)**	**UK loamy sand (EFS097)**	**UK sandy loam (EFS099)**	**Germany, sand (EFS100)**	
Aerobic/anaerobic	Anaerobic	Aerobic		Aerobic	Aerobic			
Duration (days)	360	120		59	30	45	45/100	
Sand (%)	62	-	-	77.2	85.3	71.2	94.0	
Silt (%)	20.4	-	-	17.6	5.8	10.5	4.1	
Clay (%)	17.6	38.2	13.0	5.2	8.9	18.3	1.9	
pH	6.6	6.5	6.7	6.5	7.6	6.9	5.9	
Organic C. (%)	2.0	2.6	2.9	1.1	1.2	3.0	0.63	
% of MWHC	-	45-55 (mean 50)	45-55 (mean 50)	75	45	45	45	
Soil WHC (%)	[1]	99.4	59	[2]	37.2	47.5	28.7	
Temperature (°C)	20	25	25	20	20	20	20	10
DT_{50} (days)	**Bi-exp.:** 5.8	4.1 (r^2 > 0.93)	9.4 (r^2 > 0.93)	**1. order:** 8.8 (r^2 >0.95) [3] **1. order:** 15.1[4] (r^2 0.83) **Gustafson-Holden:** 4.5[5]	**Bi-exp.:** 3.5 (r^2 0.99) **1. order:** 6.4 (r^2 >0.94)	**Bi-exp.:** 4.0 (r^2 0.99) **1. order:** 8.4 (r^2 0.92)	**Bi-exp.:** 5.6 (r^2 0.99) **1. order:** 10.0 (r^2 0.92)	**Bi-exp.:** 16.4 (r^2 0.99) **1. order:** 36.8 (r^2 0.88)
DT_{90} (days)	**Bi-exp.:** 32.8	**-**	**-**	**1. order:** 29[3] **1. order:** 50.1[4] **Gustafson-Holden:** 37[5]	**Bi-exp.:** 16.8 **1. order:** 21.2	**Bi-exp.:** 22.4 **1. order:** 27.9	**Bi-exp.:** 21.6 **1. order:** 33	**Bi-exp.:** 200 **1. order:** 122.5
CO_2 (% AR) within 100 days	1.5-2.9 (day 120) 2.9-3.4 (day 360)	-	-	13 (day 59)	5.8 (day 30)	5.7 (day 30)	3.9 (day 45)	4.2 (day 100)
Bound residues (% AR) within 100 days	68.0-71.6 (day 120) 80.1-82.6 (day 360)	-	-	49 (day 59)	44.3 (day 30)	64.0 (day 45)	35.8 (day 45)	38.4 (day 100)
Metabolites > 5 % AR within 100 days (maximum values)	**CCIM:** 27.2 (Bz, day 7) **CCIM-AM:** 14.1 (Bz, day 7) **CTCA:** 21.3 (Bz, day 42)	**CCIM:** 33 (day 14) **CTCA:** 22 (day 14/60)		**CCIM:** 16.3 (Im, day 5) **CCIM-AM:** 13.2 (Im, day 15) **CTCA:** 9.8 (Im, day 44)	**CCIM:** 24.1 (Im, day 7) **CCIM-AM:** 10.7 (Im, day 10) **CTCA:** 20.9 (Im, day 21)	**CCIM:** 18.4 (Im, day 3) **CCIM-AM:** 13.7 (Im, day 7) **CTCA:** 20.9 (Im, day 21)	**CCIM:** 31.3 (Im, day 10) **CCIM-AM:** 10.1 (Im, day 30) **CTCA:** 19.6 (Im, day 21)	**CCIM:** 24.9 (Im, day 10) **CCIM-AM:** 14.4 (Im, day 45) **CTCA:** 16.2 (Bz, day 45)
References	B.8.1.1.2, McCall and Waller, 1998	B.8.1.2.1, Tanaka, Kato and Ogyu, 1999		B.8.1.1.1, Hartman, 1997	B.8.1.1.1, Hartman et al., 1999			

[1] Soil was flooded.
[2] Samples incubated at 75 % of WHC at 0.33 bar. Soil WHC at 33 kPa: 7.73 %.
[3] Based on the 0-26 day period only as described in the study.
[4] Based on data from entire period of 59 days. DT50 values recalculated by RMS in addendum to the DAR (September 2002). Values in the table are mean of the Bz and Im moieties.
[5] Gustafson-Holden (First order multi compartment/FOMC): bi-phasic kinetic model.

Table 6.2.2. Degradation of IKF-916 metabolite CCIM in three soils (international soil classification). 1. order kinetics did not give a good fit to the data so bi-exponential kinetics was used in the study.

Soil	UK Sandy loam (EFS099)	UK Loamy sand (EFS104)	Germany, sand (EFS100)	
Aerobic/anaerobic/sterile	Aerobic			
Duration (days)	112			
Sand (%)	71.2	84.3	94.0	
Silt (%)	10.5	6.0	4.1	
Clay (%)	18.3	9.7	1.9	
pH	6.9	7.6	5.9	
Organic C. (%)	3.0	1.1	0.6	
% of MWHC	45[1]	45[1]	45[1]	
Soil WHC (%)	47.5	30.6	28.7	
Temperature (°C)	20	20	20	10
DT_{50}, days	**Bi-exp.:** 1.5[2]	**Bi-exp.:** 1.2[2]	**Bi-exp.:** 3.4[2]	**Bi-exp.:** 7.0[2]
DT_{90}, days	12.0	12.8	71.2	> 120
CO_2 (% AR) within 100 days	17[2] (day 112)	27.0[2] (day 112)	9.4[2] (day 112)	7.1[2] (day 112)
Bound residues (% AR) within 100 days	23.2[2] (days 21/28)	20.9[2] (day 112)	16.6[2] (day 112)	11.9[2] (days 112/56)
Metabolites > 10 % AR within 100 days (maximum values)	**CCIM-AM:** 32.5 (Im, day 1) **CTCA:** 47.4 (Bz, day 28) **Polar:** 12.1 (Bz, day 4)[3]	**CCIM-AM:** 30.9 (Im, day 1) **CTCA:** 50.2 (Bz, day 14) **Polar:** 11.9 (Im, day 14)[3]	**CCIM-AM:** 20.9 (Bz, day 4) **CTCA:** 36.4 (Im, day 4) **Polar:** 24.8 (Im, day 112)[3]	**CCIM-AM:** 19.8 (Im, day 7) **CTCA:** 34.1 (Im, day 112) **Polar:** 27.7 (Bz, day 112)[3]
References	B.8.1.2.1, Hartman and Korsch, 1999			

[1] Samples incubated at 45 % of WHC. Soil WHC: 47.5, 30.6 and 28.7 for the sandy loam, loamy sand and sand respectively.
[2] Average of Bz and Im moieties.
[3] Significant amounts of polar compounds were derived but no individual compound exceeded 10 % AR. One of these compounds was identified as CCBA-AM.

Table 6.2.3. Degradation of IKF-916 metabolite CCIM-AM in four soils.

Soil	UK Sandy loam (EFS099)	UK Loamy sand (EFS104)	Germany, sand (EFS100)	Loamy sand (EFS104)
Aerobic/anaerobic/sterile	Aerobic			
Duration (days)	112			
Temperature (°C)	20	20	20	10
DT_{50}, days	**Bi-exp.:** 7.3 **1. order:** 37[1]	**Bi-exp.:** 14.1 **1. order:** 38[1]	**Bi-exp.:** 8.0 **1. order:** 56.5[1]	**Bi-exp.:** 8.8 **1. order:** 38.5[1]
DT_{90}, days	**Bi-exp.:** >120 **1. order:** 123[1]	**Bi-exp.:** >120 **1. order:** 127[1]	**Bi-exp.:** >120 **1. order:** 187[1]	**Bi-exp.:** >120 **1. order:** 129[1]
CO_2 (% AR) within 100 days	8.5 (day 112)	14.6 (day 112)	6.8 (day 112)	7.2 (day 112)
Bound residues (% AR) within 100 days[2]	26.4 (day 112)	17.9 (day 112)	11.9 (day 112)	7.2 (day 112)
Metabolites > 10 % AR within 100 days (maximum values)	**CTCA:** 49.5 (Bz, day 84)	**CTCA:** 54.6 (Bz, day 21)	**CTCA:** 57.4 (Bz, day 28)	**CTCA:** 66.6 (Im, day 112)
References	B.8.1.2.1, Lentz and Korsch, 1998			

[1] DT50 and DT90 values were recalculated by RMS in an addendum to the DAR (September 2002) using 1. order kinetics. RMS claims this procedure overestimates the degradation somewhat in this case and that these results must be used as worst case.
[2] Average of Bz and Im moieties.

Table 6.2.4. Degradation of IKF-916 metabolite CTCA in four soils.

Soil	UK Sandy loam (EFS099)	UK Loamy sand (EFS104)	Germany, sand (EFS100)	Loamy sand (EFS104)
Aerobic/anaerobic/sterile	Aerobic			
Duration (days)	120			
Temperature (°C)	20	20	20	10
DT_{50}, days	**1. order:** 267[1] **1. order:** 236[2]	**1. order:** 359.5[1] **1. order:** 395[2]	**1. order:** 487.5[1] **1. order:** 380[2]	**1. order:** 302[1] **1. order:** 229[2]
CO_2 (% AR) within 100 days	6.4 (day 120)[3]	11.1 (day 120)[3]	3.4 (day 120)[3]	11.0 (day 120)[3]
Bound residues (% AR) within 100 days	24.7 (day 120)[3]	16.7 (day 120)[3]	12.1 (day 120)[3]	15.6 (day 120)[3]
Metabolites > 10 % AR within 100 days (maximum values)	None			
References	B.8.1.2.1, Landphair, 1999			

[1] Estimated in the original study.
[2] Recalculated by RMS in an addendum to the DAR (September 2002).
[3] Average of Bz and Im moieties.

Table 6.2.5. Average 1. order degradation rates of IKF-916 and major metabolites calculated using ModelMaker v3.0 (McFadden, 1999b). Calculations in this study were based on data from the route of degradation studies on IKF-916 in section B.8.1.1.1 in the DAR.

Soil	Temp. (°C)	Half life (days)				r^2
		IKF-916	CCIM	CCIM-AM	CTCA	
UK Sandy loam (EFS099)	20	5.3	3.8	4.1	8.1	0.96-0.97
Germany, sand (EFS100)	20	5.9	7.2	2.8	9.1	0.97-0.98
UK loamy sand (EFS097)	20	3.8	4.3	2.4	8.1	0.98
US loamy sand (EFS072)	20	6.9	7.9	11.1	10.9	0.93-0.96
Ushiku light clay loam (Japan)	25/20	5.2/7.7	19.7/29.2	1.0/1.5	49.5/73.5	0.95
Nagano clay loam (Japan)	25/20	7.4/11	16.5/24.5	0.7/1.0	12.2/18.1	0.95
Geometric mean (20 °C):		**6.4**	**9.3**	**2.8**	**14.3**	

Field dissipation studies:

Three field dissipation studies have been conducted, two in USA (Crawford 2001 and Jablonski 2001) and one in Japan (Tanaka et al. 1999). The American studies are described in detail in an addendum to the DAR (September 2002) and the Japanese study is described in detail in the DAR itself. The Japanese study should be regarded as indicative only due to the lack of weather data and analysis of the top 10 cm of the soil only. The two American studies are of higher quality, but they are not performed under climate conditions that can be regarded as representative for northern parts of Europe or Scandinavia. The different studies are described briefly in the text below and in **table 6.2.6**.

In the Japanese study low concentrations of parent and metabolites suggest rapid degradation at the Nagano site. At the Ushiku site concentrations are higher, something that suggests slower degradation at this site. Even though concentrations where somewhat higher, there are no indications of persistence of parent, CCIM or CCIM-AM as there were no significant residues left after 60 days. CTCA is the only substance still present after 60 days (0.21 mg/kg) and this may suggest higher degree of persistence for this metabolite. This is in agreement with lab. data. The study gives no indications though, that accumulation of this metabolite will be a problem under these climate conditions, even after repeated applications (4 x 200 g/ha, 7 days interval).

In the Crawford study no compound was detected below 15 cm with two exceptions only. Fairly low concentrations of IKF-916, CCIM and CCIM-AM indicate rapid

degradation. CTCA was first detected after the 6th application and found to peak at day 14 after last application with a concentration of 0.025 mg/kg. This metabolite was also the only one detected after this time point and was detected in the soil up to one year after last application (< 0,010 mg/kg at day 363). There are no indications in this study that CTCA will accumulate in soil under these climate conditions, even after repeated applications (8x100 g/ha, 7 days interval, June-July).

In the Jablonski study, experimental conditions were the same as in the Crawford study. With a few exceptions compounds were not detected below 15 cm. IKF-916 rapidly disappeared after each treatment. CCIM and CCIM-AM were detected after each application but did not persist beyond 14-28 days after last application. This indicates a rapid degradation of both compounds. CTCA was also found after each application and peaked 90 days after last application with a concentration of 0.023 mg/l. CTCA was not detected after 120 days and there are no indications that accumulation of this metabolite will be a problem under these climate conditions. In this study the metabolite CCBA was detected at very low concentrations (< 0.013 mg/kg) after the last application. This metabolite has been detected in a photodegradation study under dry conditions.

In a position paper (September 2002) referred to in an addendum to the DAR (September 2002) the notifier/applicant tries to explain the discrepancy between DT50 lab and DT50 field for CTCA. As mentioned before one explanation could be that differences in availability are involved. When the metabolite is directly applied to soil, it stays longer in contact with the soil and could therefore be more adsorbed and become more persistent. RMS is of the opinion that differences in microbiological activity also may pay a significant role. It is further stated that differences in persistence between lab and field data is often observed but not fully understood.

Table 6.2.6. Characteristics of study sites and for the field dissipation studies with IKF-916. For comparison annual rainfall and temperatures for south-east Norway are 785 mm and 5.3 °C.

Location	Soil type	% OC	pH	Annual rainfall (mm)	Annual Irrigation (mm)	Annual air temperature (°C)	Half life IKF-916 (days)	Maximum concentrations (mg/kg) of parent and metabolites in the 0-15 cm top soil layer after last application
Japan	Ushiku light clay loam	2.6	6.5	-	-	-	5.6	**IKF-916:** 0.76 (0 DALA*) **CCIM:** 0.18 (3 DALA) **CCIM-AM:** 0.12 (14 DALA) **CTCA:** 0.24 (14 DALA)
Japan	Nagano clay loam	2.9	6.7	-	-	-	3.6	**IKF-916:** 0.16 (0 DALA) **CCIM:** 0.04 (7 DALA) **CCIM-AM:** 0.02 (7 DALA) **CTCA:** 0,03 (60 DALA)
USA, Washington	Loamy sand	0.4	6.5	175	1420	10.5	-	**IKF-916:** 0.051 (0 DALA) **CCIM:** < 0.014 (1 DALA) **CCIM-AM:** < 0.011 (2 DALA) **CTCA:** 0.025 (14 DALA)
USA, New York	Sandy loam	1.9	6.1	673.1	114	7.5	-	**IKF-916:** 0.043 (0 DALA) **CCIM:** 0.017 (2 DALA) **CCIM-AM:** 0.033 (1 DALA) **CTCA:** 0.023 (90 DALA)

***** DALA **-** Days After Last Application.

Overall summary of degradation half lives and kinetics in soil

Table 6.2.7. Summary of all aerobic soil half lives and degradation kinetics of IKF-916 and metabolites derived from the different studies.

Compound	Kinetic model	R^2	Temperature (°C)	DT50 (days)	DT90 (days)	Reference
IKF-916	?	> 0.93	20	6.1	-	Tanaka, Kato and Ogyu, 1999
				14	-	
	Bi-exponential	0.99	20	3.5	16.8	Hartman et al., 1999
				4.0	22.4	
				5.6	21.6	
			10	16.4	200	
	Gustafson-Holden (FOMC)	?	20	4.5	37	Hartman, 1997
	1. order	> 0.95	20	8.8	29	Hartman, 1997. Calculation based on 26 first days of dataset
		0.83	20	15.1	50.1	DAR. Recalculation based on whole dataset from Hartmann, 1997
		> 0.94	20	6.4	21.2	Hartman et al., 1999
		0.92		8.4	27.9	
		0.92		10	33	
		0.88	10	36.8	122.5	
		0.93-0.98	20	5.3	-	McFadden, 1999b, based on data from Hartman, 1997, Hartman et al., 1999 and Tanaka, Kato and Ogyu, 1999
				5.9	-	
				3.8	-	
				6.9	-	
				7.7	-	
				11	-	
CCIM	Bi-exponential	-	20	1.5	12	Hartman and Korsch, 1999
		-		1.2	12.8	
		-		3.4	71.2	
		-	10	7.0	>120	
	1. order	0.93-0.98	20	3.8	-	McFadden, 1999b, based on data from Hartman, 1997, Hartman et al., 1999 and Tanaka, Kato and Ogyu, 1999
				7.2	-	
				4.3	-	
				7.9	-	
				29.2	-	
				24.5	-	
CCIM-AM	Bi-exponential	-	20	7.3	>120	Lentz and Korsch, 1998
		-		14.1		
		-		8		
		-	10	8.8		
	1 .order	0.75	20	37	123	DAR. Recalculation made by RMS based on raw data from study.
		0.73		38	127	
		0.75		56.5	187	
		0.86	10	38.5	129	
		0.93-0.98	20	4.1	-	McFadden, 1999b, based on data from Hartman, 1997, Hartman et al., 1999 and Tanaka, Kato and Ogyu, 1999
				2.8	-	
				2.4	-	
				11.1	-	
				1.5	-	
				1.0	-	
CTCA	1. order	-	20	267	-	Landphair, 1999
		-		360	-	
		-		488	-	
		-	10	302	-	
		0.33 / 0.77*	20	236*	-	DAR. Recalculation made by RMS, based on raw data from the study.
		0.65 / 0.90*		395*	-	
		-/ 0.72*		380*	-	
		0.23 / 0.96*	10	229*	-	
		0.93 -0.98	20	8.1	-	McFadden, 1999b, based on data from Hartman, 1997, Hartman et al., 1999 and Tanaka, Kato and Ogyu, 1999
				9.1	-	
				8.1	-	
				10.9	-	
				73.5	-	
				18.1	-	

* Data on the Bz / Im moieties respectively. DT50 is mean of the two moieties.

6.3 Predicted Environmental Concentrations in soil (PECsoil)

A PEC calculator based on Timme and Frehse (1986) was used to calculate PECsoil for IKF-916 and metabolites. For all compounds a worst case transformation factor and half life was assumed. A worst case $DT50_{1.\ order}$ of 15.1 days, 6 and 10 applications of 80 g IKF-916/ha (7 days interval) and 50 % interception were assumed.

PECsoil was also calculated for the metabolites CCIM (max 33 %, $DT50_{1.\ order}$: 29.2 days, molar ratio: 217/324, dose: 17.7 g/ha), CCIM-AM (max 13.7 %, $DT50_{1.\ order}$: 56.5 days, molar ratio: 235/324, dose: 7.9 g/ha) and CTCA (max 20.9 %, $DT50_{1.\ order}$: 487.5 days, molar ratio: 236/324, dose: 12.2 g/ha).

For CTCA a first order half life of 487.5 days was calculated in the original study. This value was considered worst case but valid and used in the PECsoil calculations. The results of the PECsoil calculations are summarised in **tables 6.3.1** and **6.3.2**. PEC values in bold are used in the risk assessments.

Table 6.3.1. PECsoil values and Time Weighted Average (TWA) for IKF-916 and metabolites at different time points after last application and with 50 % crop interception. 6 applications of 80 g IKF-916/ha (7 days interval) were assumed.

Days after last application	IKF-916		CCIM		CCIM-AM		CTCA	
	PECsoil (mg/kg)	TWA (mg/kg)	PECsoil (mg/kg)	TWA (mg/kg)	PECsoil (mg/kg)	TWA (mg/kg)	PECsoil (mg/kg)	TWA (mg/kg)
0	**0.17**	0.17	**0.05**	0.05	**0.03**	0.03	**0.05**	0.05
1	0.16	0.16	0.05	0.05	0.03	0.03	0.05	0.05
2	0.15	0.16	0.05	0.05	0.03	0.03	0.05	0.05
4	0.14	0.15	0.04	0.05	0.02	0.03	0.05	0.05
7	0.12	0.14	0.04	0.04	0.02	0.02	0.05	0.05
28	0.05	**0.09**	0.03	0.04	0.02	0.02	0.05	**0.05**
50	0.02	0.06	0.01	0.03	0.01	0.02	0.04	0.05
100	0.002	0.04	0.005	0.02	0.008	0.01	0.04	0.04

Table 6.3.2. PECsoil values and Time Weighted Average (TWA) for IKF-916 and metabolites at different time points after the last of 10 applications of 80 g a.s./ha (7 d. interval) and assuming 50 % crop interception.

Days after last application	IKF-916		CCIM		CCIM-AM		CTCA	
	PECsoil (mg/kg)	TWA (mg/kg)	PECsoil (mg/kg)	TWA (mg/kg)	PECsoil (mg/kg)	TWA (mg/kg)	PECsoil (mg/kg)	TWA (mg/kg)
0	**0.19**	0.19	0.06	0.06	0.04	0.04	**0.08**	0.08
1	0.18	0.18	0.06	0.06	0.04	0.04	0.08	0.08
2	0.17	0.18	0.06	0.06	0.04	0.04	0.08	0.08
4	0.16	0.17	0.06	0.06	0.04	0.04	0.08	0.08
7	0.14	0.16	0.05	0.06	0.03	0.04	0.08	0.08
28	0.05	**0.10**	0.03	0.05	0.03	0.03	0.07	**0.08**
50	0.02	0.07	0.02	0.04	0.02	0.03	0.07	0.08
100	0.002	0.04	0.006	0.02	0.01	0.02	0.07	0.07

6.4 Mobility in soil

6.4.1. Adsorption/desorption

Results from the adsorption/desorption studies for IKF-916 and its metabolites have been compiled from the DAR. The results from these studies can be viewed in **Tables 6.4.1. to 6.4.3** in this document. The Kf values indicates a medium to high degree of adsorption for the parent compound (Kf : 4.6-65, Koc: 736-2172, mean 1338, 1/n: 0,97) and the metabolites CCIM (Kf : 3.25-13.9, Koc: 475-1158, mean 753) and CTCA (Kf : 3.94-9.64, Koc: 572-1357, mean 836). Kf values indicate a high to a very high degree of adsorption for metabolite CCIM-AM (Kf: 12.4-45.4, Koc: 1941-3398, mean 2397). The rather low content of org. C in the US loamy sand and the German sand makes the Koc values from these soils a bit unreliable though. There seems to be a correlation between the adsorption of IKF-916 and the content of clay and organic carbon in soil (R = 0.96 and 0.99 respectively, p = 0.05) with increasing adsorption as the content of organic carbon and clay increases. This correlation is also seen for metabolite CCIM-AM (R = 0.99 and 0.97 respectively, p = 0.05). There is also a very week correlation between the adsorption of CTCA and the organic carbon content (R = 0.71, p = 0.05), but for CCIM there was no correlation between adsorption and properties of the soil. When it comes to desorption data indicates that the binding of at least some of the metabolites in some circumstances can be regarded as irreversible. This is clearer for CTCA than for the other compounds.

Table 6.4.1. Adsorption and desorption coefficients for IKF-916 in five soils.

	US loamy sand (EFS072)	UK loamy sand (EFS097)	UK Sandy loam (EFS099)	Germany, sand (EFS100)
pH	6.5	7.6	6.9	5.9
Org. C.	0.66	1.2	3.0	0.63
Kf (ads)	8.5	13.8	65	4.6
Koc (ads)	1293	1150	2172	736
1/n (ads)	0.96	1.00	1.07	0.83
Kf (des)	23.4	20.2	58.4	96.8
Koc (des)	3575	1684	1948	3842
1/n (des)	1.02	0.99	0.96	0.95
Reference	B.8.2.1, Landphair 1998			

Table 6.4.2. Adsorption and desorption coefficients for IKF-916 metabolite CCIM in five soils.

	US loamy sand (EFS072)	UK loamy sand (EFS097)	UK Sandy loam (EFS099)	Germany, sand (EFS100)
pH	6.5	7.6	6.9	5.9
Org. C.	0.66	1.2	3.0	0.63
Kf (ads)	3.25	4.00	13.9	10.4
Koc (ads)	592	475	786	1158
1/n (ads)	0.96	0.93	0.89	1.08
Kf (des)	5.64	5.23	25.5	6.09
Koc (des)	2740	1454	2271	3153
1/n (des)	0.82	0.81	0.84	0.81
Reference	B.8.2.1, Murray 1999			

Table 6.4.3. Adsorption and desorption coefficients for IKF-916 metabolite CCIM-AM in five soils.

	US loamy sand (EFS072)	UK loamy sand (EFS097)	UK Sandy loam (EFS099)	Germany, sand (EFS100)
pH	6.5	7.6	6.9	5.9
Org. C.	0.66	1.2	3.0	0.63
Kf (ads)	14.1	24.1	45.4	12.4
Koc (ads)	3398	1941	2082	2165
1/n (ads)	0.92	1.00	0.94	0.98
Kf (des)	22.4	16.4	105	11.1
Koc (des)	7514	3414	7771	5183
1/n (des)	0.88	0.86	0.88	0.83
Reference	B.8.2.1, Murray 1999			

Table 6.4.4. Adsorption and desorption coefficients for IKF-916 metabolite CTCA in five soils.

	US loamy sand (EFS072)	UK loamy sand (EFS097)	UK Sandy loam (EFS099)	Germany, sand (EFS100)
pH	6.5	7.6	6.9	5.9
Org. C.	0.66	1.2	3.0	0.63
Kf (ads)	3.94	6.05	9.64	7.17
Koc (ads)	1357	816	572	599
1/n (ads)	0.84	0.91	0.88	1.15
Kf (des)	14.0	19.4	51.1	39.1
Koc (des)	5577	2536	4738	8604
1/n (des)	0.86	0.93	0.85	0.96
Reference	B.8.2.1, Murray 1999			

6.4.2. Soil column leaching

An column leaching study (B.8.2.2, Shelby 1998) was conducted according to BBA guidelines and GLP. This study is well described in the DAR and only a short description of the study and its results is presented here. Several sandy soils was treated with a dose equivalent to a field application rate of 100 g a.s./ha. Soil properties are summarised in **table 6.4.5**. No column leachates contained more than 0.4 % radioactivity and total recoveries were in the range of 84.7-95.0 %. This indicates a low potential of mobility. For all soils radioactivity was mainly recovered from the upper soil layer (81.9 - 93.5 %). Most of the radioactivity in the soils was extractable mainly as IKF-916 (46-72 %) and CCIM (11-41 %).

Table 6.4.5. Soil column leaching and soil characteristics.

Soil characteristics	Sand, EFS072, USA	Loamy sand, EFS101, Germany 2.3	Loamy sand, EFS101, Germany 2.2	Sand, EFS101, Germany 2.1
Sand (%)	88.6	79.8	85.1	95.7
Silt (%)	6.1	10.9	8.1	4.3
Leire (%)	5.3	9.3	6.8	0
pH	7.2	6.8	5.9	6.0
Org C. (%)	0.54	1.26	3.22	0.54
WHC	25.2	39.9	55.6	26.5
CEC (meq/100 g)	3.78	10	12	8

An aged column leaching study has also been performed (B.8.2.3, Shelby 1999) and this is well described in the DAR. This study was conducted according to SETAC guidelines and GLP and will just briefly be described here. IKF-916 was applied to a loamy sand soil (1.2 % org. C) with a dose of 100 g a.s./ha. Soil was incubated at 20 °C for 90 hours before placed onto the column. Radioactivity was mainly recovered in the upper soil layer (> 86.6 %). Most of the radioactivity in the soil was extractable mainly as IKF-916 (33.8-38.3 %), CCIM (18.9-25.2 %) and CCIM-AM (ca 10 %). Only 0.8 % of applied radioactivity was recovered in the leachate and half of this was

recovered as CCIM. This indicates a moderate degree of mobility.

6.4.3. Lysimeter studies

No data provided.

6.5. Predicted Environmental concentrations in groundwater (PECgw*)*

Two groundwater simulations have been performed and none of these indicate that groundwater exposure will be a problem. New simulations have not been regarded as necessary by the Norwegian Food Safety Authority.

a) The leaching behaviour of IKF-916 and the metabolites CCIM, CCIM-AM and CTCA to groundwater has been investigated in a study reported in the DAR (B.8.6.1, McFadden 1999a, b) using the models PELMO 2.01 and PELMO 3.0. The use of IKF-916 in potatoes was assessed using the German scenario (Borstel soil. Weather data from Hamburg 1961 wet). Ten applications (7 d. interval) of IKF-916 at 80 g/ha to potatoes were assumed. An average of 55.4 % of IKF-916 was assumed to be turned into CCIM, CCIM-AM and CTCA. For all compounds, PECgw was estimated to be < 0.001 µg/l. For more detailed descriptions of input data results etc, see DAR.

b) A ground water simulation with MACRO v3.3.1 was made by KEMI in Sweden in an assessment of Ranman in 2003/2004. The scenario Önnestad (Loamy sand over sand, 1.87 % org. C, 25 % clay, 42 % silt, 33 % sand) was chosen. The following input data were used: DT50: 6.1 days (20 °C), Koc = 1338, vapour pressure = $1x10^{-5}$ Pa (20 °C). Five applications of 80 g a.s./ha and 25 and 50 % interception was assumed. IKF-916 was applied at day 111 (25 % interception) and 174 (50 % interception). The resulting 80^{th} percentile of 0.000 µg/l clearly indicates that IKF-916 under the simulated conditions is not likely to reach groundwater.

6.6 Fate and behaviour in water

6.6.1. Hydrolysis

A hydrolysis study (Hendrix and Neal, 1997) conducted according to EPA guidelines is reported in the DAR (B.8.4.1.). At 25 °C IKF-916 is hydrolysed to CCIM (max 74-83 % after 30 days) in buffers at pH 4, 5, 7 and 9. CCIM is further degraded to CCIM-AM (max 10 % after 30 days). Half lives of IKF-916 at different pH is summarised in table 6.2.1 (DT50 = 24-27 days). There is no indication of any pH dependence.

Table 6.6.1. Hydrolytically degradation of IKF-916 at different pH values

pH	Temp. (°C)	DT50 (days)
4	20	24.6
5	20	27.2
7	20	24.8
9	20	24.8

In another study (Repko, 1999) reported in the DAR less than 10 % degradation of the metabolites CCIM, CCIM-AM and CTCA was seen after 5 days at 50 °C, indicating a half life of greater than one year at 25 °C. The conclusion in this study is that the three metabolites are hydrolytically stable at 25 °C and pH 4, 7 and 9.

6.6.2. Photolysis

The aqueous photolysis of IKF-916 was investigated in a study (Hendrix, 1999) reported in the DAR (B.8.4.2). The study was performed according to EPA guidelines and GLP. IKF-916 in acetonitrile was dissolved in buffer at pH 5. The solutions were

kept in darkness or exposed to xenon arc lamp (> 290 nm, 12 hour photoperiod) at 25 °C for 30 days. The conclusion from this study was that IKF-916 is rapidly photodegraded in water at pH 25 °C with half lives calculated to be between 28 and 34 minutes using first order kinetics. The major degradation products was CCIM (max 39.6 % after 3-6 hours), CCTS (max 37.9 % after 3-6 hours), HTID (max 18.5 % after 21 days) and p-toluamide derived from the Bz moiety (Max 12.1 % after 36 days). CDTS was a minor metabolite. Recoveries were in the range 88-108 % for the Bz moiety but decreased to 70 % for the Im moiety. This is thought to be a result of a high CO_2 (> 30 %) production from the imidazole ring.

6.6.3. Biodegradability

No data provided. IKF-916 is regarded as not easily biodegradable.

6.6.4. Water/sediment

An aerobic water/sediment study (Hartman et al., 1999) indicated that the degradation of IKF-916 in the whole system was medium with bi-exponential half lives of 10.8 and 16.5 days in two systems (mean 13.7 days). IKF-916 is hydrolysed to CCIM and further degraded to CCIM-AM and to CTCA. Mineralisation is negligible. Due to adsorption significant amounts of IKF-916 was found in the sediment (max. 20.5-35 % after 3-7 days). IKF-916 is rapidly degraded in the water phase with mean bi-exponential and 1. order half lives of 6.2 and 9.3 days, respectively. The study is summarised in **table 6.6.2** and discussed in more detail in the DAR.

Table 6.6.2. Study details, degradation rates and concentrations of IKF-916 and metabolites in two aerobic water/sediment systems.

	EFS092, sandy loam sediment, Ohio	**EFS103, sandy loam sediment, Ohio**
Aerobic/ anaerobic/ sterile	Aerobic	
Temperature (°C)	20	
Duration	100 days	
DT_{50} (water) (days)	7.4 (bi-exp) 9.9 (1. order)	4.9 (bi-exp) 8.7 (1. order)
DT_{90} (water) (days)	36.4 (bi-exp) 32.9 (1. order)	23.8 (bi-exp) 28.7 (1. order)
DT_{50} (sediment) (days)	-	-
DT_{90} (sediment) (days)	-	-
DT_{50} (whole system) (days)	16.5 (bi-exp)	10.8 (bi-exp)
DT_{90} (whole system) (days)	58.3 (bi-exp)	38.4 (bi-exp)
CO_2 (%) within 100 days	2.6	0.6
Bound residues (%) within 100 days	44.8	46.1
Metabolites > 5 % AR, max % within 100 days	**Water:** CCIM: 29, CCIM-Am: < 10, CTCA: < 10 **Sediment:** CCIM: 19.5, CCIM-AM: < 10, CTCA: 24.6	

6.7. Predicted environmental concentrations in surface water (PECsw)

6.7.1. Surface water

NFSA has simulated exposure of surface water using the FOCUS surface water STEPS 1 and 2 calculator. NFSA has used the worst case application scheme from the Swedish GAP with 10 applications and 7 days intervals between the applications.

Table 6.7.1. IKF-916 input data for FOCUS surface water scenarios.

	DT_{50} days (20°C)				Koc	Water solubility (mg/l)	Aplication rate (g/ha)	Number of applic/application intervall
	Soil	Water/sediment	Surface water	Sediment				
IKF-916	6.40	13,7	6,20	16,50*	1338,00	0.12	80	10/7

*No data available. NFSA have used the DT50 value from the water/sediment study "Ohio-sandy loam sediment" (whole system) (see table 6.6.2).

Table 6.7.2 The maximum PECsw and PECsed values obtained by STEP1-2 for IKF-916.

	PECsw (µg/l)			
	Initial	Day 21 (twa)	Day 28 (twa)	PECsed (µg/kg dw)
STEP 1	103,1428	60.7	52.7	810 (21 d)
STEP 2	1,4904	0.74	0.62	10.6 (21 d)

STEP 1: The application rate is assumed to be the maximum season's usage applied as a single dose, unless the DT50 in water is less than the third of the interval between treatments. For IKF-916 the DT50 is higher than this limit. The run-off are further included as a single fixed loading of 15 % of the application rate which occurs on the day of application. This is therefore really "worst case".

STEP 2: A number of refinements are included compared to STEP 1 to make the scenario more reasonable. Applications are assumed to be made sequentially at the rates and interval specified. Degradation and partitioning then occurs between applications. Spray drift is considered separately for each treatment date, but the percentile for individual drift inputs is adjusted so that the overall probability of drift represents the 90th percentile loading. At Step 2, interception of the soil deposit is also included, and NFSA has assumed it to be 50 percent for potatoes. Four days after the last treatment, a percentage of the residue remaining on the treated field (determined using the soil degradation rate) is then added to the ditch as a run-off/erosion or drainage input and is added directly to the sediment layer of the ditch. The magnitude of this loss is dependent on season (autumn, spring or summer) and region. STEP 2 still represents very much a worst-case scenario. NFSA has used the PECsw values from the STEP 2 calculations for the TER calculations.

6.7.2. Spray drift

Spray drift is estimated in order to determine buffer zones in Norway. Spray drift is in this case calculated according to Rautmann et al. (2001).

Table 6.7.3. Calculation of PECsw and buffer zones in Norway.

Buffer zones, metre	PEC, µg/l Potatoes (H<50 cm)
1	0.74
5	0.15
10	0.08
20	0.04
30	0.03

6.8 Fate and behaviour in air

6.8.1 Photochemical oxidative degradation in air

The theoretical calculation of the potential for photooxidation of IKF-916 has been carried out using the methods of Atkinson (1988). The half life in the upper atmosphere in the presence of hydroxyl radicals was calculated to be 0.26 days. For

details, see physiochemical section of the DAR.

6.8.2 Volatilisation from soil surface

No data provided. IKF-916 has low vapour pressure (< 1.33 x 10^{-5} Pa) and medium high Henry law's constant (< 4.03x10^{-2} pa m^3 $mol^{-1)}$ which indicates a medium risk of volatilisation.

6.9 Appropriate fate and behaviour end-points relating to the product and approved uses

Not relevant.

6.10 Any other relevant data / information

No other information.

7 Ecotoxicology

7.1 Effects on birds

Six laboratory tests are performed on birds, using bobwhite quail and mallard ducks as test organisms. Five of these tests describe effects of the active substance, and one show the effect of the preparation. The toxicity of IKF-916 and IKF-916 400SC + Adjuvant to birds is summarized in table 7.1.1 (from the DAR).

Table 7.1.1. Toxicity of IKF-916 and IKF-916 400SC + Adjuvant to birds.

Test Substance	Time-scale	Species	LD/LC50 [1]	NOEL/NOEC [1]
IKF-916	Acute (oral)	*C. virginianus*	>2000 mg/kg bw	2000 mg/kg bw
IKF-916	Acute (oral)	*A. platyrhynchos*	>2000 mg/kg bw	-
IKF-916	Short term (5 d; dietary)	*A. platyrhynchos*	>2000 mg/kg diet[2] (>700 mg/kg bw/d)	2000 mg/kg diet
IKF-916	Short term (5 d; dietary)	*C. virginianus*	>5000 mg/kg diet[2] (>1750 mg/kg bw/d)	5000 mg/kg diet
IKF-916	Long term / Reproduction (20½ wk; dietary)	*C. coturnix japonica*	-	1000 mg/kg diet[2] (350 mg/kg bw/d)
IKF-916 400SC + Adjuvant	Acute (oral)	*C. virginianus*	>2000 mg/kg bw	128 mg/kg bw

[1] mg as or preparation
[2] Default values of 0.35 for dietary studies have been used to convert mg/kg diet (ppm) to mg/kg bw/day. These values have been proposed by the PPR panel in opinion of azinphos-methyl (EFSA Q 2003-007).

Acute and short-term toxicity of IKF-916 to birds is low, with LC50 values of 2000 mg/kg bw and 700 mg as/kg bw/d, respectively. The long-term toxicity is low, with NOEC of 350 mg as/kg bw/day.

The test of the preparation (IKF-916 400SC + Adjuvant) showed a NOEL of 128 mg/kg bw. This is a considerably lower value than the active substance, but still the toxicity is low. The reason for the NOEC result was observations of behaviour among the birds. Observed effects were hunched posture in nearly all birds at the dose of 350 mg/kg bw and above, and lethargy in about half of the birds on the day of the dosing.

NFSA have information from a US EPA “Pesticide Fact Sheet” of Cyazofamid about some evidence of reproductive effects for Bobwhite quail and Japanese quail. USEPA writes: “neither quail study elicited a definitive NOAEC nor a normal dose response. To address these issues the agency is requiring a new Bobwhite Quail study. The Agency will reevaluate the uses when that study is received and reviewed”. We have tried to contact EPA for more information and references of the two studies of reproduction which we have not received, but we have not succeeded.

The tier 1 risk assessment is based on birds in leafy crops (potato), for Norwegian standard species. 6 or 10 applications per year, with minimum 7 days intervals, are representative for the Nordic/Baltic countries, and calculations are based on this. TER values are presented in table 7.1.2, and they are all above the Annex VI trigger.

Table 7.1.2. Risk assessment for birds in potato.

Type of bird	Time-scale	Fir/bw	RUD	Application rate (kg as/ha)	MAF*	ETE	TER	Annex VI value
6 applications								
Herbivorous, Skylark	Acute	0.76	87	0.08	1.9	10.1	199	10
	Short-term	0.76	40	0.08	2.5	6.1	115	10
Insectivorous, Skylark, Yellowhammer	Acute	1.04	52	0.08	1.9	8.2	243	10
	Short-term	1.04	29	0.08	2.5	6.0	116	10
	Long-term	1.04	29	0.08	2.5	6.0	21	5
10 applications								
Herbivorous, Skylark	Acute	0.76	87	0.08	2.58	13.7	147	10
	Short-term	0.76	40	0.08	2.58	6.3	111	10
Insectivorous, Skylark, Yellowhammer	Acute	1.04	52	0.08	2.58	11.1	179	10
	Short-term	1.04	29	0.08	2.58	6.2	112	10
	Long-term	1.04	29	0.08	2.58	6.2	20	5

* MAF after 10 applications is calculated in the DAR.

Conclusion

According to the results in the tables above, there is no reason for concern regarding acute or long-term effects on birds, and it is not necessary to perform tier 2 risk assessments. The assessment is based on the highest intended doses in the Nordic/Baltic countries.

7.2 Effects on aquatic organisms

The effects of IKF-916, IKF-916 400SC + Adjuvant and the metabolites CCIM, CCIM-AM, CTCA, DMSA, CCBA and CCTS to aquatic organisms have been studied with three trophic levels: fish, algae and invertebrates. Two studies with the sediment-dwelling larvae of the midge *Chironomus riparius* is also reported. The results from acute and chronic toxicity studies in the DAR have been compiled in table 7.2.1. The studies with the active ingredient indicate no effects in the area of the water solubility of the substance. However there is smaller problems with the water solubility in the studies with the preparation IKF-916 400SC + Adjuvant and the studies give us a better picture of the toxicity of the substance. For the risk assessment of IKF-916 the values of the most sensitive organisms is in bold. The acute toxicity of IKF-916 to fish, invertebrates and algae is quite high, with LC50 values of 0.56, 0.18 and 0.059 mg as/l respectively. The toxicity to sediment dwelling midge is moderate with NOEC = 0.1 mg as/l. The metabolites DMSA and CTCA has low toxicity to the tested aquatic organisms, the metabolite CCIM-AM is not toxic in concentrations below the water solubility and the metabolite CCIM is moderate toxic to fish and toxic to invertebrates and algae.

Table 7.2.1 Summary of acute and chronic aquatic toxicity data.

Time-scale	Test Substance	Test Species	End point /toxicity	Reference
Fish – acute toxicity				
96 h, flow-through	IKF-916	*Oncorhynchus mykiss*	LC_{50} > 0.14 mg as/l (limit of the water solubility of the as).	Bogers, M., 1999 a, 8.2.1/01
96 h, flow-through	IKF-916	*Oncorhynchus mykiss*	**LC_{50} > 0.10 mg as/l** and **NOEC = 0.052 (measured conc.).**	Latham, M and Morris, D.S., 1998, 8.2.1/07
96 h, flow-through	IKF-916	*Lepomis macrochirus*	LC_{50} > 0.14 mg as/l (limit of the water solubility of the as).	Bogers, M., 1999 b, 8.2.1/02.
96 h, flow-through	IKF-916	*Cyprinius carpio*	LC_{50} > 0,14 mg as/l (limit of the water solubility of the as).	Bogers, M., 1999 c, 8.2.1/03.
96 h, static	CCIM	*Oncorhynchus mykiss*	LC_{50} = 3,8 mg CCIM/l.	Bogers, M., 1999 d, 8.2.1/04.
96 h, static	CCIM-AM	*Oncorhynchus mykiss*	LC_{50} > 100 mg CCIM-AM/l (nominal conc.). LC_{50} > 7,88 mg CCIM-AM/l (measured conc.).	Bogers, M., 1999 e, 8.2.1/05.
96 h, static	CTCA	*Oncorhynchus mykiss*	LC_{50} > 100 mg CTCA/l (nominal conc.). LC_{50} > 92,2 mg CTCA/l (measured conc.).	Bogers, M., 1999 f, 8.2.1/06.
96 h, static	DMSA	*Oncorhynchus mykiss*	LC_{50} > 100 mg DMSA/l (nominal conc.).	Seyfried, B., 1999 a, 8.2.1/08.
96 h, flow-through	IKF-916 400SC + Adjuvant	*Oncorhynchus mykiss*	LC_{50} =0.56 mg as/l (equivalent to 2.8 mg IKF-916 400SC + Adjuvant/l). NOEC = 0.26 mg as/l (equivalent to 1.28 mg IKF-916 400SC + Adjuvant/l) (measured conc.).	Bogers, M., 1999 l, 10.2.1/01.
Fish – chronic toxicity				
28 d, flow-through	IKF-916	*Oncorhynchus mykiss*	**NOEC = 0.13** mg as/l/l (growth rate) (measured conc.).	Peither, A., 1999 a, 8.2.2.1
28 d, flow-through	IKF-916 400SC + Adjuvant	*Oncorhynchus mykiss*	NOEC = 0.21 mg as/l l (equivalent to 1.02 mg IKF-916 400SC +	Peither, A., 1999 d, 10.2.4

Time-scale	Test Substance	Test Species	End point /toxicity	Reference
			adjuvant/l).	
Aquatic invertebrates				
48 h, flow-through	IKF-916	*Daphnia magna*	**EC_{50} >0.14 mg as/l** (limit of the water solubility of the as).	Bogers, M., 1999 g, 8.2.4/01.
48 h, static	CCIM	*Daphnia magna*	EC_{50} =0.42 mg CCIM/l (0% immobility at 0.32 mg/l and 100% immobility at 0,56 mg/l).	Migchielsen, M.H.J., 1999a, 8.2.4/02.
48 h, static	CCIM-AM	*Daphnia magna*	EC_{50} >0.4 mg CCIM-AM/l (limit of the water solubility).	Migchielsen, M.H.J., 1999b, 8.2.4/03.
48 h, static	CTCA	*Daphnia magna*	EC_{50} >100 mg CTCA/l (nominal concentration).	Migchielsen, M.H.J., 1999c, 8.2.4/04.
48 h, static	DMSA	*Daphnia magna*	EC_{50} >100 mg DMSA/l, (nominal concentration).	Seyfried, B., 1999 b, 8.2.4/05.
48 h, static	IKF-916 400SC + Adjuvant	*Daphnia magna*	**EC_{50} =0.18 mg as/l**, (equivalent to 0.79 mg IKF-916 400SC + Adjuvant/l).	Migchielsen, M.H.J., 1999d, 10.2.1/02.
21 d, semi-static	IKF-916	*Daphnia magna*	**NOEC=0.11 mg as/l** (no toxic effects on survival and reproduction up to its water solubility limit).	Peither, A., 1999 b, 8.2.5
Sediment dwelling organisms				
23 d, static	IKF-916	*Chironomus riparius*	**NOEC=0.1 mg as/l** (highest dose tested, no signs of intoxication were observed).	Memmert, U., 1999a, 8.2.7/01
48 h, static	CTCA	*Chironomus riparius*	LC_{50} > 100 mg/l.	Memmert, U., 1999b, 8.2.7/02
Algae				
96 h, static	IKF-916	*Selenastrum capricornutum*	E_rC_{50} > 0.1 mg as/l. **E_bC_{50} = 0.025 mg as/l.** NOE_rC = 0.01 mg as/l. (nominal conc.).	Bogers, M., 1999 h, 8.2.6/01.
72 h, static	IKF-916	*Selenastrum capricornutum*	E_rC_{50} = 60.9 mg as/l. E_bC_{50} = 0.858 mg as/l mg as/l. NOE_bC = 0.22 mg CCIM/l.	Tadayoshi, T., 1997, 8.2.6/02

Time-scale	Test Substance	Test Species	End point /toxicity	Reference
			NOE_bC = 0.0257 mg as/l. (nominal conc.).	
72 h, static	CCIM	*Selenastrum capricornutum*	E_rC_{50} = 1.34 mg CCIM/l. NOE_rC = 0.22 mg CCIM/l. E_bC_{50} = 0.68 mg CCIM/l. NOE_bC = 0.22 mg CCIM/l. (nominal conc.).	Bogers, M., 1999 i, 8.2.6/03.
72 h, static	CCIM-AM	*Selenastrum capricornutum*	E_rC_{50} >0.4 mg CCIM-AM/l. E_bC_{50} >0.4 mg CCIM-AM/l (measured conc.).	Bogers, M., 1999 j, 8.2.6/04.
72 h, static	CTCA	*Selenastrum capricornutum*	E_rC_{50} >100 mg CTCA/l E_bC_{50} >100 mg CTCA/l NOEC = 50 mg CTCA/l. (nominal conc.)	Bogers, M., 1999 k, 8.2.6/05.
72 h, static	DMSA	*Scenedesmus subspicatus*	E_rC_{50} >100 mg CTCA/l E_bC_{50} >100 mg CTCA/l NOEC = 100 mg CTCA/l. (nominal conc.)	Seyfried, B, 1999 c, 8.2.6/06.
72 h, static	IKF-916 400SC + Adjuvant	*Selenastrum capricornutum*	E_rC_{50} > 0.85 mg as/l. (equivalent with 4.15 mg IKF-916 400SC + Adjuvant/l). E_bC_{50} = 0.059 mg as/l (equivalent with 0.29 mg IKF-916 400SC + Adjuvant/l) (measured conc.).	Bogers, M., 1999 m, 10.2.1/03.
Aquatic plants				
No data				

7.2.1. Risk assessment

PEC values in surface water has been calculated in chapter 6.2 using the FOCUS surface water steps 1 and 2 calculator.

STEP 1

The maximum number of application in the Nordic/Baltic countries is 10 applications of 80 g as/ha in potatoes. The results for acute and chronic risk assessments based on values obtained by STEP 1 calculation are presented in table 7.2.2. Lowest end point value obtained with different species group has been used as a worst case. The TER values in bold are below the Annex VI trigger.

Table 7.2.2. Acute and chronic TER values for aquatic organisms based on STEP1 PECsw.

Species	Study duration	L(E)C50/NOEC (µg/L)	PEC (µg/L)	TER	Annex VI Trigger
Fish	96 h	100	103.1	**0.97**	100
Fish	28 d	130	52.7	**2.5**	10
Daphnia	48 h	140	103.1	**1.4**	100
Daphnia	21 d	110	60.7	**1.8**	10
Algae	72 h	25	103.1	**0.24**	10

STEP 2

All TER values in the calculations of STEP 1 are below the trigger of Annex VI. Therefore new TER values were calculated based on STEP 2 values (table 7.2.3). We assume that it is more realistic to use LC50 values from the studies with IKF 916 + Adjuvant, since the acute toxicity values from the studies with IKF 916 are uncertain because of problems with the water solubility of the substance (all the values are stated as >, the substance is not acute toxic in the water solubility area and the acute and chronic toxicity values are nearly the same) Therefore calculations of TER from the studies with IKF 916 + Adjuvant is also presented in table 7.2.3.

Table 7.2.3. Acute and chronic TER values for aquatic organisms based on STEP2 PECsw.

Species	**Study duration**	**L(E)C50/NOEC (µg/L)**	**PEC (µg/L)**	**TER**	**Annex VI Trigger**
Fish*	96 h	560	1.5	373	100
Fish	96 h	100	1.5	**67**	100
Fish	28 d	130	0.62	210	10
Daphnia* magna	48 h	180	1.5	120	100
Daphnia magna	48 h	140	1.5	**93**	100
Daphnia magna	21 d	110	0.74	149	10
Algae	72 h	25	1.5	17	10

*Values from studies with IKF 916 + Adjuvant.

Conclusions

The STEP 2 calculations of TER for fish and *Daphnia magna* show acceptable risk if the acute toxicity values from studies with IKF 916 + Adjuvant are used. If using the values from the studies with IKF 916, TER is slightly below the Annex VI Trigger, but the real value is uncertain, and the studies with IKF 916 show that the substance is not acute toxic in the water solubility area (0.12 mg/l) for daphnia and fish. For algae TER calculation indicate acceptable risk. STEP 3 calculations for a better refinement of PEC is therefore not considered as necessary, since STEP 2 is a worst-case scenario.

7.2.2. Buffer zones

According to Norwegian legislation, buffer zones to water bodies have to be determined to protect aquatic organisms from spray drift. TER values for different buffer zones are therefore calculated for the most sensitive aquatic species, the algae (*Selenastrum capricornutum*). The calculations are based on E_bC_{50} = 0.025 mg as/l and PEC values according to Rautmann et al, 2001.

Table 7.2.4. TER values for different buffer zones for the most sensitive aquatic species (Selenastrum capricornutum).

Buffer zones, metres	TER, acute toxicity for Potato
1	34
5	165
10	323
20	625
30	938

According to these calculations it is not necessary with buffer zones when using Ranman in Norway.

7.2. 3. Bioconcentration

IKF-916 (log Pow = 3.2) is likely to bioaccumulate in fish with a maximum BCF of 286 (whole body). This is above the trigger value of 100 for substances which are not readily biodegradable. However depuration is rapid and therefore there is no risk for IKF-916 to bioaccumulate in fish.

7.3. Effects on terrestrial vertebrates other than birds

Acute toxicity to rat is low, with a LD50 of more than 5000 mg/kg bw for both IKF-916, IKF-916 400SC and the representative preparation IKF-916 400SC + Adjuvant. The toxicity is summarized in table 7.3.1, as presented in the DAR.

Table 7.3.1. Toxicity of IKF-916, IKF-916 400SC and IKF-916 400SC + Adjuvant to rat.

Test Substance	Time-scale	LD50	NOEC
IKF-916	acute	> 5000 mg/kg bw*	-
IKF-916 400 SC	acute	> 5000 mg/kg bw	-
IKF-916 400SC + ADJUVANT®	acute	> 5000 mg/kg bw	-
IKF-916	chronic- 13 weeks	-	500 ppm* (175 mg/kg bw/d)
IKF-916	Chronic/oncogenicity	-	500 ppm* (175 mg/kg bw/d)
IKF-916	Chronic/teratogenicity	-	1000 mg/kg bw/day

***** Default values of 0.35 for dietary studies have been used to convert mg/kg diet to mg/kg bw/day. These values have been proposed by the PPR panel in opinion of azinphos-methyl (EFSA Q 2003-007)

The tier 1 risk assessment is based on medium sized herbivorous mammals, Norwegian standard species, and 6 applications with minimum 7 days interval. TER values are all well above the Annex VI trigger.

Table 7.3.2. Risk assessment for mammals in leafy crops (potato).

Time-scale	Fir/bw	RUD	Application rate (kg as/ha)	MAF*	ftwa	Toxicity (mg/kg bw/day)	ETE	TER	Trigger value
6 applications									
Acute	0.28	87	0.08	1.9	1	5000	3.7	1350	10
Long-term	0.28	40	0.08	2.5	0.53	1000	1.2	147	5
10 applications									
Acute	0.28	87	0.08	2.58	1	5000	5.0	995	10
Long-term	0.28	40	0.08	2.58	0.53	1000	1.2	142	5

* MAF after 10 applications is calculated in the DAR.

Conclusion

The results in the table above raise no concern for acute or long-term effects on medium sized herbivorous mammals, and there is no need to perform tier 2 risk assessments. The assessment is based on the highest intended doses.

7.4. Effects on bees

The toxicity of IKF-916 and IKF-916 400SC + Adjuvant to bees is low on mortality, with LD50 of more than 100 µg/bie in the four completed tests. When it comes to observations, the contact test with IKF-916 400SC + Adjuvant showed apathetic and discoordinated movements among the bees in a dose related matter from 12.5 to 100 µg IKF-916 400SC/bee. The toxicity of IKF-916 and IKF-916 400SC + Adjuvant to bees is summarized in table 7.4.1.

Table 7.4.1. Toxicity of IKF-916 and IKF-916 400SC + Adjuvant to honey bees, *Apis mellifera*.

Test Substance	Time-scale	LD50
IKF-916	96 h (oral)	> 151.7 µg as/bee
IKF-916	96 h (contact)	> 100 µg as/bee
IKF-916 400SC + Adjuvant	48 h (oral)	> 115,7 µg IKF-916 400 SC/bee
IKF-916 400SC + Adjuvant	48 h (contact)	> 100 µg IKF-916 400SC/bee

The acute and contact LD50 values have been used to calculate hazard quotients for leafy crops scenarios, and the lowest LD50 values have been used in the risk assessment.

Table 7.4.2. Hazard quotients for honey bees (*Apis mellifera*), with an application rate of 80 g as/ha.

Test Substance	Route	Hazard Quotient (HQ)
IKF-916	Oral	0.5
	Contact	0.8
IKF-916 400SC + Adjuvant	Oral	0.7
	Contact	0.8

Conclusion: The estimated hazard quotient values are below the relevant Annex VI trigger of 50. Hence, there are no concerns related to effects on bees.

7.5 Effects on other arthropod species

Acute toxicity of IKF-916 is low on both mortality and parasitic effect, to all test organisms. Table 7.5.1 summarizes the toxicity of IKF-916.

Table 7.5.1. Toxicity of IKF-916 to parasitic wasps (*Aphidius rhopalosiphi),* predatory mites (*Typhlodromus pyri*), ground dwelling predators (*Aleochara bilineata*) and foliage dwelling predators (*Chrysoperla carnea*), as presented in the DAR.

Species	Stage	Dose (g as/ha)	Corrected mortality, %	Reduction of parasitation / reproduction, %
A. rhopalosiphi	adults	209.4	2.5	- 0.68
T. pyri	protonymph	209.4	- 2.5	10
A. blineata	adults	210.6	-	11
C. carnea	larvae	209.4	6.7	- 19.3

Acute toxicity of IKF-916 400SC + Adjuvant is quite high on both mortality and parasitic effect in the laboratory studies, while it is low in the extended laboratory study, Table 7.5.2 summarizes the toxicity of IKF-916 400SC + Adjuvant.

Table 7.5.2. Toxicity of IKF-916 400SC + Adjuvant to parasitic wasps (*Aphidius rhopalosiphi),* predatory mites (*Typhlodromus pyri*), ground dwelling predators (*Aleochara bilineata*) and foliage dwelling predators (*Chrysoperla carnea*), as presented in the DAR.

Species	Stage	Dose (g IKF-916 400SC/ha + Adjuvant)*	Corrected mortality,%	Reduction of parasitation / reproduction, %
Laboratory tests				
Tier 1 (glass plate)				
A. rhopalosiphi	adults	446 + 300 (160 g as/ha)	0	34.8
T. pyri	protonymphs	223 +150 (80 g as/ha)	79.55	-3
	protonymphs	446 +300 (160 g as/ha)	70.45	11
A. bilineata	adults	224 + 150 (80 g as/ha)	-	3.4
	adults	444 + 300 (160 g as/ha)	-	-1.2
	adults	1116 + 750 (400 g as/ha)	-	5.6
C. carnea	larvae	222 + 150 (80 g as/ha)	3.5	31.1
	larvae	444 +300 (160 g as/ha)	14.3	31.7
Extended laboratory tests (natural substrate)				
A. rhopalosiphi	48-h adults	80 x 10 times	1.7	2.6
T. pyri	1-2 d protonymphs	80 x 10 times	5.5	10.3
C. carnea	larvae	80 x 10 times	11.8	6.1

No data for LR50 are given, and hazard quotients could not be calculated. Hence, the risk assessment is based upon using ESCORT 2 trigger of 50 % for mortality. According to the table 7.5.2, two tier 1 laboratory tests show mortality above the limit, but one additional, extended laboratory test shows mortality below the trigger value.

Conclusion: For the preparation (IKF-916 400SC + Adjuvant), the laboratory studies show effects but extended laboratory tests show mortality below the Annex VI trigger. This indicates that the effects can be regarded as minor in fields.

7.6. Effects on earthworms

All tests show a low acute toxicity of IKF-916 and the metabolites CCIM-AM, CTCA and DMSA, with LC50 of more than 1000 mg/kg soil. The metabolite CCIM has a higher acute toxicity, with LC50 of 56 mg/kg soil.

Degradation of the metabolite CTCA in soil can be slow in laboratory studies (max. DT50 value 488 d). One long-term test of the metabolite shows a quite low NOEC value. NOEC was above 1 mg/kg soil which was also the highest tested concentration. One additional long-term test of IKF-916 is presented in the addendum of the DAR. Survival, growth and reproduction rates were not significantly reduced in this test. No long-term test is performed on IKF-916 + Adjuvant.

Table 7.6.1. Effects of IKF-916 and its metabolites on earthworms (*Eisenia foetida*).

Test Substance	Time-scale	LC50 (mg/kg soil)[1]	NOEC (mg/kg soil)	PEC / TWA[3]	TER	Annex VI Trigger
6 applications						
IKF-916	Acute	>1000	>1000	0.17	5882	10
IKF-916	Long-term	-	4	0.09	44	5
CCIM	Acute	56	6.3	0.05	1120	10
CCIM-AM	Acute	>1000	1000	0,05	33333	10
CTCA	Acute	>1000	1000	0.05	20000	10
CTCA	Long-term	-	1	0.05	20	5
DMSA	Acute	>1000	1000	-	-	
CCBA	Acute	>500	500	-	-	
10 applications[2]						
IKF-916	Acute	>1000	>1000	0.19	5263	10
IKF-916	Long-term	-	4	0.10	40	5
CTCA	Acute	>1000	1000	0.08	12500	10
CTCA	Long-term	-	1	0.08	13	5

[1] Mg as or metabolite/kg soil
[2] Calculations of TER after 10 applications are made only for the substances with PEC different from the PEC after 6 treatments.
[3] Time Weighted average, 28 d, is used in the calculations of TER (long term)

The tier 1 risk assessment is based on application to soil 50 % with plant cover. PEC is calculated after 6 and 10 treatments (maximum per year). According to table 7.6.1 TER (acute) is well above the trigger value for both the parent compound and the metabolites. TER (long term) is considerably lower, but still above the trigger.

No data are given on degradation time for the metabolite DMSA and CCBA, and therefore no PECs are estimated.

Conclusion
The estimated TER values are above the relevant Annex VI trigger values. Hence, there are no concerns related to effects on earthworms.

7.7 Effects on micro-organisms

7.7.1. Respiration and nitrogen conversion

The effects of IKF-916 and the metabolite CTCA was tested on soil non-target micro-organisms. The results showed no statistically significant effects greater than ±25 % of control values, for both respiration and nitrification.

Table 7.7.1. Effects of IKF-916 and the metabolite CTCA on soil non-target micro-organisms. The duration of both tests was 28 d.

	Respiration and Nitrogen conversion
IKF-916[1]	
Dose (mg/kg dry soil)	0.27
Effect	< 25 %
IKF-916 400SC+Adjuvant[2]	
Dose (mg/kg dry soil)	1.07
Effect	< 15 %
CTCA[1]	
Dose (mg/kg dry soil)	0.133
Effect	< 25 %

[1] From the DAR
[2] From the Addendum of the DAR

The metabolites CCIM, CCIM-AM and CTCA are considered as potentially relevant in soil, but toxicity tests on soil microflora respiration and nitrogen turnover has only been performed with CTCA. According to the notifier it is likely that soil micro-

organisms were exposed to these metabolites during the test conducted with IKF-916, and further testing can be considered redundant.

Conclusion:The effect of IKF-916, IKF-916 400SC + Adjutant and CTCA is below the Annex VI trigger of 25 %, and intended uses raise no concern.

7.7.2. Activated sludge respiration

Effects of IKF-916 and the metabolite CTCA was tested on inhibition of activated sludge respiration. The toxicity was low, and the results are summarized in table 7.7.2.

Table. 7.7.2. Effects of IKF-916 400SC + Adjuvant and the metabolite CTCA on inhibition of activated sludge respiration.

Test Substance	Time-scale	EC50 (mg/l)*	NOEC (mg/l)*
IKF-916 400SC+Adjuvant	3 h	446	160
DMSA	3 h	>1000	1000

* mg IKF-916 400SC or active substance / l nominal concentration

Conclusion: The risk of effects on activated sludge respiration is low, and intended uses raise no concern.

7.6 Appropriate ecotoxicological end-points relating to the product and approved uses

No information.

7.7 Any other relevant data / information

No information.

8 Efficacy

Considered acceptable for Annex I inclusion of the <active>, see DAR', or:

8.1 Efficacy evaluation

The active ingredient is a fungicide with activity against fungus from the class of Oomycetes, especially against *Phytophtora infestans*. IKF-916 inhibits respiration specifically at cytochrome bc1 complex in the mitochondria of O*omycetes* fungi. It acts on the Qi site of the complex. IKF-916 inhibits all stages in the life cycle of *P. infestans* including germination and formatin of zoosporangia, germination of cystospores, zoospore motility and mycelial growth. IKF-916 is a cyanoimidazole (new chemical class) compound. It works protective and needs to be applied before the disease attack. Depending on the disease pressure, a good protection against the disease can be expected over a period of 7 to 10 days.

In Norway Ranman TwinPack has been tested against potato late blight in 9 field experiments at 4 locations during 2001-2004. Two of these locations (Ås and Rygge) are in the south eastern part of Norway, one location (Jæren) is in the south western part of the country and the fourth location (Stjørdal) is in central Norway. Different potato cultivars were used with medium late blight resistance. In the first year 200 ml/ha of Ranman TwinPack was tested. In 2002 and 2003 also the dosage 150 ml/ha was included. The spray interval varied from 8- 21 days depending of the disease pressure. The experiments were randomized complete block design with four replicates. All experiments, except one were infected with natural inoculum. The remaining experiment was infected from spreader rows. Spray volume in all trials was 400 l/ha, nozzle XR TeeJet 11002 at 5 bar. Leaf blight was assessed at different dates after the onset of the epidemic. Tuber blight was assessed after incubation at approx 15 ˚C for at least three weeks after harvest.

Ranman TwinPack had very good effect against late blight on the foliage and was at least as effective as the standard product Shirlan (fluazinam). This was also the case at the reduced dose rate of Ranman TwinPack. The incidence of tuber blight tended to be lower than by use of Shirlan.

8.2 Phytotoxicity

There have not been any specific tests for this in Norway, but no phytotoxic effects have been observed during the efficacy evaluation.

8.3 Resistance

According to the DAR the risk of resistance appearance is very low considering the fact that IKF-916 has a different mode of action from other fungicides and because it is a contact fungicide *P. infestans* will only be exposed to high concentrations thus precluding exposure to low concentrations which could lead to resistance.

There have not been any specific tests for resistance in Norway, but no resistance problems have been observed during the efficacy evaluation. However since cyazofamid has strobilurine-like effect resistance problems might occur in the future if no anti resistance strategies are used.

Remark: In the DAR 10 applications were defended, but ISK Biosciences Europe now prefers to reduce the application of IKF-916 to 6 maximum, in order to optimize the resistance management. The companies proposed Anti Resistance Strategy is to

use Ranman TwinPack in single or block applications in alternation with fungicides from different cross-resistance group.

8.5 Any other relevant data / information

REGISTRATION REPORT

Annex 1

List of data submitted in support of the evaluation

Annex point	Author	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or Unpublished	Data protection claimed Y/N	Owner

- **Annex 2 – Table of authorised uses**

Active substance: cyazofamid Date:

Crop and/ or situation	Member State or Country	Product name	F G or I	Pests or Group of pests controlled	Formulation		Application				Application rate per treatment			PHI (days)	Remarks:
					Type	Conc. of as	method kind	growth stage & season	number min max	interval between applications (min)	kg as/hL min max	water L/ha min max	kg as/ha min max		
(a)			(b)	(c)	(d-f)	(i)	(f-h)	(j)	(k)					(l)	(m)
Potato	Denmark	Ranman TwinPack	F	Late blight *(Phytophtora infestans)*	EC (?)	40%	Convention all sprayer		6		0,02-0,04	200-400	0,08	7	
Potato	Estonia	Ranman TwinPack	F	Late blight *(Phytophtora infestans)*	SC	40%	Overall spray	Before infection	3			200-400	0,08	7	
Potato	Finland	Ranman TwinPack	F	Late blight *(Phytophtora infestans)*	SC	40%	Field boom sprayer with hydraulic boom and nozzles	First application when warning systems forecast indicates significant disease attack. Last treatment BBCH 95-97	1 - 6	5 to 10 day intervals depending on the disease pressure	0,02-0,04	200-400	max. 0,08	7	

Potato	Latvia	Ranman TwinPack	F	Late blight *(Phytophtora infestans)*	SC	40%	Overall spray	BBCH 35-79	1-6		0,02-0,04	200-400	0,08	7	
Potato	Lithuania	Ranman TwinPack	F	Late blight *(Phytophtora infestans)*	SC	40%	Spraying	On infection	5	7 - 10		200-400	0,06 – 0,08	7	
Potato	Norway	Ranman TwinPack	F	Late blight *(Phytophtora infestans)*	SC	40%	Overall spray	Before infection	6			200-400	0,06-0,08	7	
Potato	Sweden	Ranman TwinPack	F	Late blight *(Phytophtora infestans)*	SC	40%	Overall spray	BBCH 95-97	8-10		0,016-0,053	150-500	0,08	7	

(a) For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (*e.g.* fumigation of a structure)
(b) Outdoor or field use (F), glasshouse application (G) or indoor application (I)
(c) *e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds
(d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
(e) GCPF Codes - GIFAP Technical Monograph No 2, 1989
(f) All abbreviations used must be explained
(g) Method, *e.g.* high volume spraying, low volume spraying, spreading, dusting, drench

(h) Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plant - type of equipment used must be indicated
(i) g/kg or g/l
(j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
(k) Indicate the minimum and maximum number of application possible under practical conditions of use
(l) PHI - minimum pre-harvest interval
(m) Remarks may include: Extent of use/economic importance/restrictions

g. wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
ISBN 3-8263-3152-4), including where relevant, information on season at time of application
(e) GCPF Codes - GIFAP Technical Monograph No 2, 1989
(k) Indicate the minimum and maximum number of application possible under practical conditions of use
(f) All abbreviations used must be explained
(l) PHI - minimum pre-harvest interval
(g) Method, *e.g.* high volume spraying, low volume spraying, spreading, dusting, drench
(m) Remarks may include: Extent of use/economic importance/restrictions