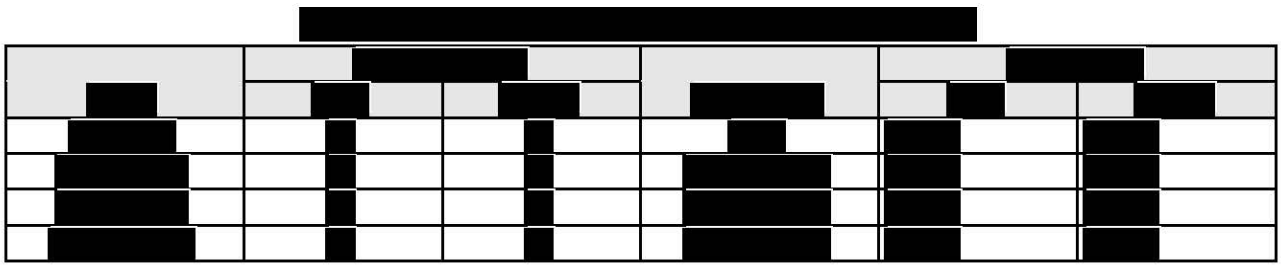
Evaluation by Competent Authorities
Evaluation by Rapporteur Member State
Comments from ...



[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]								
[redacted]								
[redacted]								
[redacted]								

[redacted]

[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								

6.8 Reproductive toxicity

6.8.1 Teratogenicity study in rats

Section A6.8.1/01 Teratogenicity study in rats

Annex Point IIA6.8.1

		Official use only
	1 REFERENCE	
1.1 Reference	[redacted]	
1.2 Data protection	Yes	
1.2.1 Data owner	Sumitomo Chemical Co., Ltd.	
1.2.2 Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s for the purpose of entry into Annex I	
	2 GUIDELINES AND QUALITY ASSURANCE	
2.1 Guideline study	Yes Guidelines of toxicity studies of drugs on Reproduction, Notification No.118 of the Pharmaceutical Affaires Bureau, Ministry of Health and Welfare, Japan (MHW), February 15, 1984 equivalent to OECD 414, US EPA FIFRA § 83-3, Directive 88/302/EEC, Part B, Teratogenicity study - rodent and non-rodent, OJ No L133 of 30 May 1988 (corrigendum OJ No L136 of 2 June 1988)	
2.2 GLP	[redacted]	
2.3 Deviations	[redacted]	
	3 MATERIALS AND METHODS	
3.1 Test material	[redacted]	
3.1.1 Lot/Batch number	[redacted]	
3.1.2 Specification	[redacted]	
3.1.2.1 Description	[redacted]	
3.1.2.2 Purity	[redacted]	

3.1.2.3 Stability	[redacted]
3.2 Test Animals	
3.2.1 Species	Rat
3.2.2Strain	[redacted]
3.2.3 Source	[redacted]
3.2.4 Sex	Male and female
3.2.5 Age/weight at study initiation	[redacted]
3.2.6 Number of animals per group	[redacted]
3.2.7 Control animals	Yes
3.2.8 Mating period	[redacted]
3.3 Administration/ Exposure	Oral
3.3.1 Duration of exposure	Day 7-17 of gestation
3.3.2 Post exposure period	[redacted]
3.3.3 Type	Gavage
3.3.4 Concentration	0, 100, 300 and 1000 mg/kg bw/day
3.3.5 Vehicle	[redacted]
3.3.6 Concentration in vehicle	[redacted]
3.3.7 Total volume applied	[redacted]
3.3.8 Controls	Vehicle
3.4 Examinations	**Animals terminated at day 21 of gestation**
3.4.1 Body weight	[redacted]
3.4.2 Food and water consumption	[redacted]
3.4.3 Clinical signs	[redacted]

3.4.4 Examination of uterine content

3.4.5 Examination of foetuses

3.4.5.1General

3.4.5.2 Skeletal

3.4.5.3 Soft tissue

3.5 Further remarks

Dams

3.5.1 Bodyweight

3.5.2 Food and water consumption

3.5.3 Clinical signs

3.5.4 Examination of uterine content

3.5.6 Other

Offspring

3.5.6 Bodyweight

3.5.7 Clinical signs

3.5.8 Examinations

3.5.9 Behavioural tests

3.5.10 Reproduction test

[redacted]

4 RESULTS AND DISCUSSION

4.1 Maternal toxic effects

[redacted]

4.2 Teratogenic / embryo-toxic effects

4.2.1 P1 Generation

[redacted]

4.2.2 F1 Generation

[redacted]

[redacted]

4.3 Other effects None

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods [redacted]

5.2 Results and discussion

[redacted]

5.3 Conclusion

Maternal NOEL/NOAEL: 100 mg/kg bw/day - based on decreased body weight gain and food consumption and increased water consumption at 300 mg/kg bw/day

Developmental NOEL/NOAEL: 100 mg/kg bw/day - based on skeletal variation at 300 mg/kg bw/day

The NOAEL for teratogenic effects was >1000 mg/kg bw/day, the highest dose tested

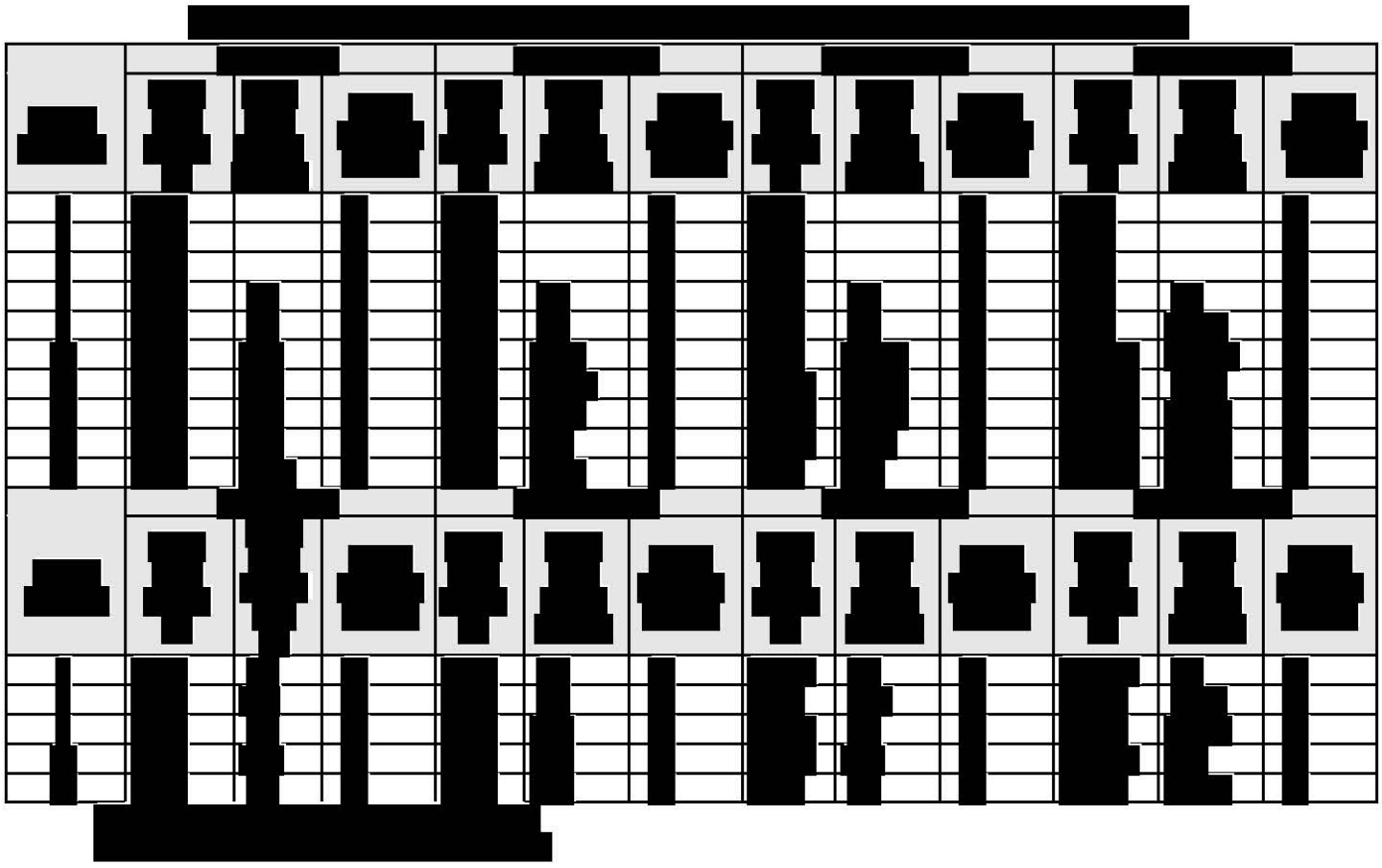
5.3.1 LO(A)EL maternal toxic effects	300 mg/kg bw/day
5.3.2 NO(A)EL maternal toxic effects	100 mg/kg bw/day
5.3.3 LO(A)EL embryotoxic / teratogenic effects	300 mg/kg bw/day
5.3.4 NO(A)EL embryotoxic / teratogenic effects	100 mg/kg bw/day
5.3.5 Reliability	[redacted]
5.3.6 Deficiencies	[redacted]

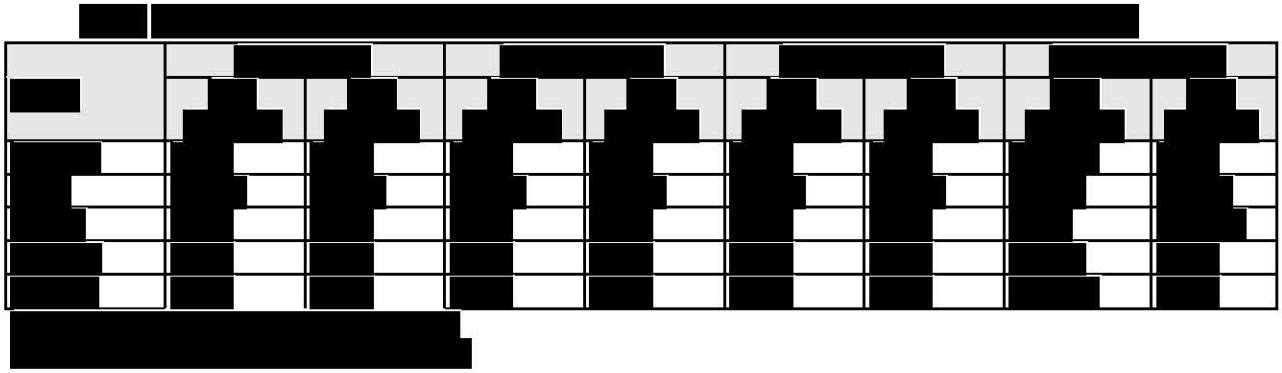
Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
Evaluation by Rapporteur Member State	
[redacted]	[redacted]

[redacted]

Comments from ...

[redacted]





[redacted]

[redacted]

[redacted]

[redacted]

[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Section A6.8.1/02 Teratogenicity study in rabbits

Annex Point IIA6.8.

Official use only

1 REFERENCE

1.1 Reference [redacted]

1.2 Data protection Yes

1.2.1 Data owner Sumitomo Chemical Co., Ltd.

1.2.2 Criteria for data protection Data submitted to the MS after 13 May 2000 on existing a.s for the purpose of entry into Annex I

2 GUIDELINES AND QUALITY ASSURANCE

2.1 Guideline study Yes

Guidelines of toxicity studies of drugs on Reproduction - Notification No.118 of the Pharmaceutical Affaires Bureau (Ministry of Health and Welfare, Japan (MHW), February 15, 1984 equivalent to OECD 414, US EPA FIFRA § 83-3, Directive 88/302/EEC, Part B, Teratogenicity study - rodent and non-rodent, OJ No L133 of 30 May 1988 (corrigendum OJ No L136 of 2 June 1988)

2.2 GLP [redacted]

2.3 Deviations [redacted]

3 MATERIALS AND METHODS

3.1 Test material [redacted]

3.1.1 Lot/Batch number [redacted]

3.1.2 Specification [redacted]

3.1.2.1 Description [redacted]

3.1.2.2 Purity [redacted]

3.1.2.3 Stability	[redacted]
3.2 Test Animals	
3.2.1 Species	Rabbit
3.2.2Strain	[redacted]
3.2.3 Source	[redacted]
3.2.4 Sex	Female
3.2.5 Age/weight at study initiation	[redacted]
3.2.6 Number of animals per group	[redacted]
3.2.7 Control animals	Yes
3.2.8 Mating period	[redacted]
3.3 Administration/ Exposure	Oral
3.3.1 Duration of exposure	Days 6 – 18 of gestation
3.3.2 Post exposure period	10 days (animals were delivered by caesarean section on day 28 of gestation)
3.3.3 Type	Gavage
3.3.4 Concentration	0, 100, 300 and 1000 mg/kg bw
3.3.5 Vehicle	[redacted]
3.3.6 Concentration in vehicle	[redacted]
3.3.7 Total volume applied	[redacted]
3.3.8 Controls	Distilled water
3.4 Examinations	
3.4.1 Body weight	[redacted]
3.4.2 Food consumption	[redacted]
3.4.3 Clinical signs	[redacted]
3.4.4 Examination of uterine content	
	[redacted]
	[redacted]

3.4.5 Examination of foetuses

3.4.5.1General

3.4.5.2 Skeletal

3.4.5.3 Soft tissue

3.5 Further remarks

4 RESULTS AND DISCUSSION

4.1 Maternal toxic effects

4.2 Teratogenic / embryo-toxic effects

[redacted]

4.3 Other effects None

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods [redacted]

5.2 Results and discussion [redacted]

5.3 Conclusion	Maternal NOEL/NOAEL: 100 mg/kg bw/day - based on abortion and premature delivery at 300 mg/kg bw/day due to continuously decreased body weight gain and food consumption. 1000 mg/kg bw/day was the lethal dose for dams Developmental NOEL/NOAEL: 300 mg/kg bw/day - highest non-lethal dose level for dams. Even at the lethal dose level for dams (1000 mg/kg bw/day), no fetal anomalies were treatment-related
5.3.1 LO(A)EL maternal toxic effects	300 mg/kg bw/day based on abortion and premature delivery
5.3.2 NO(A)EL maternal toxic effects	100 mg/kg bw/day
5.3.3 LO(A)EL embryotoxic / teratogenic effects	>1000 mg/kg bw/day, the highest dose tested
5.3.4 NO(A)EL embryotoxic / teratogenic effects	300 mg/kg bw/day, the highest non lethal dose tested
5.3.5 Reliability	[redacted]
5.3.6 Deficiencies	[redacted]

Evaluation by Competent Authorities	
Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
Evaluation by Rapporteur Member State	
[redacted]	[redacted]

Comments from ...

[redacted]

[redacted]

[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

Section A6.8.2/01 **Two generation reproduction study**

Annex Point IIA6.8.2

Official use only

1 REFERENCE

1.1 Reference [redacted]

1.2 Data protection Yes

1.2.1 Data owner Sumitomo Chemical Co., Ltd.

1.2.2 Criteria for data protection Data submitted to the MS after 13 May 2000 on existing a.s for the purpose of entry into Annex I

2 GUIDELINES AND QUALITY ASSURANCE

2.1 Guideline study Yes

US EPA FIFRA § 83-4 equivalent to OECD 416, Directive 88/302/EEC, Part B, Two-generation reproduction toxicity test, OJ No L133 of 30 May 1988 (corrigendum OJ No L136 of 2 June 1988)

2.2 GLP [redacted]

2.3 Deviations [redacted]

3 MATERIALS AND METHODS

3.1Test material [redacted]

3.1.1 Lot/Batch number [redacted]

3.1.2 Specification [redacted]

3.1.2.1 Description [redacted]

3.1.2.2 Purity [redacted]

3.1.2.3 Stability [redacted]

3.2 Test Animals

3.2.1 Species Rat

3.2.2 Strain [redacted]

3.2.3 Source [redacted]

3.2.4 Sex	Male and female
3.2.5 Age/weight at study initiation	[redacted]
3.2.6 Number of animals per group	[redacted]
3.2.7 Mating	[redacted]
3.2.8 Duration of mating	[redacted]
3.2.9 Deviations from standard protocol	[redacted]
3.2.10 Control animals	Yes
3.3 Administration/ Exposure	Oral
3.3.1 Animal assignment to dosage groups	[redacted]
3.3.2 Duration of exposure before mating	70 days for the first generation and 77-90 days after weaning for the second generation
3.3.3 Duration of exposure in general P, F1, F2 males, females	P0 generation: For 70 days pre-mating, up to a 21 day mating period and for a 21 day gestation period. The males were then killed and the females were treated for a further 21-23 days F1 generation: For 21 days during weaning followed by 77-90 days after weaning and up to 21 day gestation period. The males were then killed and females were treated for a further 21-23 days F2 generation: For 21-23 days
3.3.4 Type	In food
3.3.5 Concentration	0, 200, 1000 and 5000 ppm, achieved doses in mg/kg bw/day are shown in Tables below Food consumption was ad libitum
3.3.6 Vehicle	[redacted]
3.3.7 Concentration in vehicle	[redacted]
3.3.8 Total volume applied	[redacted]
3.3.9 Controls	Plain diet
3.4 Examinations	
3.4.1 Clinical signs	[redacted]

3.4.2 Body weight

3.4.3 Food/water consumption

3.4.4 Oestrus cycle

3.4.5 Sperm parameters

3.4.6 Offspring

3.4.7 Organ weights P and F1

3.4.8 Histopathology P and F1

3.4.9 Histopathology F1 not selected for mating, F2

3.5 Further remarks None

4 RESULTS AND DISCUSSION

4.1 Effects

4.1.1 Parent males (F0)

4.1.2 Parent females (F0)

[redacted]

4.1.3 F1 males

[redacted]

4.1.4 F1 females

4.1.5 F2 males

4.1.6 F2 females

[redacted]

4.2 Other None

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

[redacted]

5.2 Results and discussion

[redacted]

5.3 Conclusion

The No-observed-adverse-effect-levels were

Maternal: 1000 ppm (76.4 mg/kg bw/day)

Reproductive: 5000 ppm (386 mg/kg bw/day)

Developmental: 1000 ppm (76.4mg/kg bw/day)

5.3.1 LO(A)EL

5.3.1.1 Parent males	5000 ppm based on reduced body weight and food consumption and absolute/relative liver and kidney weight changes
5.3.1.2 Parent females	5000 ppm based on reduced body weight and food consumption and absolute/relative liver and kidney weight changes
5.3.1.3 F1 males	5000 ppm based on reduced body weight gain during late lactation
5.3.1.4 F1 females	5000 ppm based on reduced body weight gain during late lactation
5.3.1.5 F2 males	5000 ppm based on reduced body weight gain during late lactation
5.3.1.6 F2 females	5000 ppm based on reduced body weight gain during late lactation

5.3.2 NO(A)EL

5.3.2.1 Parent males	1000 ppm
5.3.2.2 Parent females	1000 ppm

5.3.2.3 F1 males	1000 ppm
5.3.2.4 F1 females	1000 ppm
5.3.2.5 F2 males	1000 ppm
5.3.2.6 F2 females	1000 ppm
5.3.3 Reliability	[redacted]
5.3.4 Deficiencies	[redacted]

Evaluation by Competent Authorities
Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
Evaluation by Rapporteur Member State
[redacted]
Comments from ...
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.9 Neurotoxicity study

(An additional data requirement. See Chapter 3, part A)

Pyriproxyfen is not of similar or related structure to those capable of inducing delayed neurotoxicity such as organophosphates. No delayed neurotoxicity can be expected, therefore it was not considered necessary to perform delayed neurotoxicity studies with pyriproxyfen

No neurotoxicity or neuro pathology was observed in mice, rats, dogs, rabbits and no developmental neurobehavioral toxicity in reproductive and developmental studies in rats; therefore there is no concern for neurotoxicity

Evaluation by Competent Authorities
Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
Evaluation by Rapporteur Member State
Comments From

6.10 Mechanistic study – any studies necessary to clarify effects reported in toxicity studies

(An additional data requirement. See Chapter 3, part A)

A study is not considered necessary as none of the effects require clarification.

Evaluation by Competent Authorities
Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
Evaluation by Rapporteur Member State
Comments From

6.11 Studies on other routes of administration (parenteral routes)

(An additional data requirement. See Chapter 3, part A)

No studies available.

Evaluation by Competent Authorities
Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
Evaluation by Rapporteur Member State
Comments From

6.12 Medical data in anonymous form

6.12.1 Medical surveillance data on manufacturing plant personnel

Section A6.12.1/01 **Medical surveillance data on manufacturing plant personnel**

Annex Point IIA6.12

		Official use only
	1 REFERENCE	
1.1 Reference	[redacted]	
1.2 Data protection	Yes	
1.2.1 Data owner	Sumitomo Chemical Co., Ltd.	
1.2.3 Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s for the purpose of entry into Annex I	
	2. GUIDELINES AND QUALITY ASSURANCE	
2.1 Guideline study	No, no guidelines exist for this type of study	
2.2 GLP	[redacted]	
2.3 Deviations	[redacted]	
	3 MATERIALS AND METHODS	
3.1 Test material	Pyriproxyfen	
3.1.1 Lot/Batch number	[redacted]	
3.1.2 Specification	[redacted]	
3.1.2.1 Description	[redacted]	
3.1.2.2 Purity	[redacted]	
3.1.2.3 Stability	[redacted]	
3.2 Type of study	Employee study	
3.3 Method of data collection	Record review	
3.4 Test Persons / Study Population		
3.4.1 Selection criteria	[redacted]	

3.4.2 Number of test persons per group/cohort size	[redacted]
3.4.3 Sex	Males
3.4.4 Age	[redacted]
3.4.5 Diseases	[redacted]
3.4.6 Smoking status	[redacted]
3.5 Controls	[redacted]
3.5.1 Type of control	[redacted]
3.5.2 Number of test persons per group/cohort size	[redacted]
3.5.3 Sex	[redacted]
3.5.4 Age	[redacted]
3.5.5 Diseases	[redacted]
3.5.6 Smoking status	[redacted]
3.6 Administration/ Exposure	
3.6.1 Exposure Route	Combined
3.6.2 Exposure Situation	Workplace [redacted]
3.6.3 Exposure concentration(s)	Information not available
3.6.4 Method(s) to determine exposure	[redacted]
3.6.5 Post exposure period	[redacted]
3.7 Examinations	
3.7.1 Type of disease	[redacted]
3.7.2 Parameters	[redacted]
3.8 Further remarks	[redacted]

4 RESULTS AND DISCUSSION

4.1 Average daily work time	[redacted]
4.2 no of days working with pyriproxyfen/year	[redacted]
4.3 Medical findings	[redacted]

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods	[redacted]
5.2 Results and discussion	No abnormal symptoms or observations were detected
5.3 Conclusion	No occupation-related problems were observed and there were no findings attributable to the exposure to pyriproxyfen technical
5.3.1 Reliability	[redacted]
5.3.2 Validity	[redacted]
5.3.3 Deficiencies	[redacted]
5.4 Other	None

Evaluation by Competent Authorities	
Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
Evaluation by Rapporteur Member State	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]
[redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted]	**Comments from ...**

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]					
			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.12.2 Direct observation, e.g. clinical cases, poisoning incidents if available

There are no documented cases of human intoxication with pyriproxyfen. As there are no other active substances with similar or related structures, extrapolation from cases with other compounds is not possible

Evaluation by Competent Authorities
Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
Evaluation by Rapporteur Member State
Comments From

6.12.3 Health records, both from industry and any other available sources

The only data available are summarised in Section 6.12.1.

Evaluation by Competent Authorities
Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
Evaluation by Rapporteur Member State
[redacted]
Comments From
[redacted]

6.12.4 Epidemiological studies on the general population, if available

There is no information on the exposure of the general population to pyriproxyfen. As pyriproxyfen is also used as an agricultural insecticide exposure may occur through residues in crops and during application of the product. This has not been associated with any known incidence of adverse effects

Evaluation by Competent Authorities
Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
Evaluation by Rapporteur Member State
[redacted]
Comments From
[redacted]

6.12.5 Diagnosis of poisoning including specific signs of poisoning and clinical tests, if available

The poisoning signs after exposure of pyriproxyfen are not known. As there are no other active substances of similar or related structures to pyriproxyfen, extrapolation from the poisoning signs after exposure to other compounds is not possible. Therefore, specific signs of poisoning may not be observed following exposure of pyriproxyfen. Clinical tests useful for diagnostic purpose are not known

Evaluation by Competent Authorities
Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
Evaluation by Rapporteur Member State
[redacted]
Comments From
[redacted]

6.12.6 Sensitisation/allergenicity observations, if available

No information is available to suggest that the use of pyriproxyfen is associated with sensitisation or allergenicity in humans

Evaluation by Competent Authorities
Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
Evaluation by Rapporteur Member State
Comments From

6.12.7 Specific treatment in case of an accident or poisoning: first aid measures, antidotes and medical treatment, if known

An effective antidote for pyriproxyfen is not known. Appropriate symptomatic treatments by a medical doctor are recommended.

Evaluation by Competent Authorities
Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
Evaluation by Rapporteur Member State
Comments From

6.12.8 Prognosis following poisoning

The effects of pyriproxyfen poisoning are not known. Pyriproxyfen was non-irritant to eye and skin, had low acute toxicity and induced no specific signs in animals via oral, dermal and inhalation routes. Therefore, it can be assumed that any exposure to pyriproxyfen will induce nonspecific reactions, including nausea after ingestion, or sore throat and abnormality in respiration after inhalation of large quantities of formulation

Evaluation by Competent Authorities
Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
Evaluation by Rapporteur Member State
[redacted]
Comments From
[redacted]

6.13 Toxic effects on livestock and pets

(An additional data requirement. See Chapter 3, part A.)

Studies are available in lactating goats; this has not been included as it is not considered a key study as there is no significant exposure of livestock based on the use pattern (see below).

The use of pyriproxyfen in biocidal products [redacted] it is evenly spread over the manure and bedding in animal houses and does not directly contaminate feeding troughs or hay/silage containers. Most of the particles will fall into the manure/bedding and not be available for intake by food producing animals.

Hens are considered the most likely of all the livestock species to consume Sumilarv® [redacted] since they consume grit as a normal part of their diet. Intake of Sumilarv® [redacted] by larger species, pigs, cattle and dairy cows is considered negligible and there will be no significant residues in edible tissues or milk from these species.

Particle size analysis shows that < 2.5% of the particles in Sumilarv® [redacted] have a diameter >590 microns and therefore it is very unlikely that the majority of the particles will be consumed by hens. A worst case calculation has been made by assuming that hens will consume 5% of the applied Sumilarv® [redacted] over a 6 week period. A six week period has been selected because it corresponds to the lifetime of a broiler chicken. It is also less than the approximately 8 week period between applications and, therefore, like the assumption of 5% consumption of Sumilarv® [redacted], is also a conservative value. Using figures for housing areas and animal numbers taken from the EU Emissions Scenario document and weights of animals taken from the EU Agchem Livestock Feeding Studies document (DG Health and Consumer Protection, Guidelines for the generation of data concerning residues, Appendix G, Doc. 7031/VI/95/rev.4) the worst case consumption of residues is only 0.009 mg/kg bw/day for free range laying hens.

Using the data from studies of the metabolism of pyriproxyfen in hens the concentration of total residues in liver, kidney, muscle, fat and eggs of hens given this dose was calculated and none of these concentration exceeded 0.011 mg equivs/kg. The metabolism studies in hens were submitted seperatly with this response.

Evaluation by Competent Authorities
Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
Evaluation by Rapporteur Member State
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] can be [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Comments From	
[redacted]	
[redacted]	
[redacted]	
[redacted]	

6.14 Other test(s) related to the exposure of humans

(An additional data requirement. See Chapter 3, part A.)

None

Evaluation by Competent Authorities
Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
Evaluation by Rapporteur Member State
[redacted]
Comments From
[redacted]

6.15 Food and feedingstuffs

Studies are not considered necessary as there is no significant exposure of food or feedingstuffs during the use of pyriproxyfen.

The use of pyriproxyfen in biocidal products [redacted] it is evenly spread over the manure and bedding in animal houses and does not directly contaminate feeding troughs or hay/silage containers. Most of the particles will fall into the manure/bedding and not be available for intake by food producing animals (for further details see 6.13 above).

The following studies on metabolism, distribution and expression of residues in livestock were included in the DAR of pyriproxyfen of November 2005:

In a study with hens [redacted], after eight daily dose administrations of [redacted] at 1.3 mg/day [redacted] of the total administered dose 89% had been recovered in excreta, 6.9% in tissues and 0.18% in eggs. The residue levels were highest in liver (0.75 mg eq/kg), kidney (0.86 mg eq/kg), abdominal fat (0.88 mg eq/kg) and gizzard and GI tract (3.5-3.9 mg eq/kg). Residue levels in other tissues were all within the range 0.033-0.23 mg eq/kg. Residues in egg white and yolk were ≤0.33 mg eq/kg and reached a plateau after approximately 6 days (yolk) and approximately 3 days (white). Pyriproxyfen was detected in egg white and yolk at levels up to 0.13 mg eq/kg and in all analysed tissues (excluding gizzard) at levels within the range 0.014-0.79 mg eq/kg. Pyriproxyfen levels in gizzard and excreta were within the range 15-54% of TRR. [redacted] Excreta contained all metabolites (each >0.05 mg eq/kg) that had also been identified in the tissues. The majority of the radioactivity in the PES was either bound to or incorporated in fatty acids (egg yolk) or associated with the protein fractions (liver and kidney).

In another study with hens [redacted] following eight daily dose administrations of [redacted] at 1.3 mg/day [redacted] of the total administered dose 84% had been recovered in excreta, 3.9% in the tissues and 0.31% in the eggs. The highest residue levels in the tissues were 0.80 mg eq/kg (kidney), 0.69 mg eq/kg (liver), 0.93 mg eq/kg (abdominal fat) and 1.1-1.8 mg eq/kg (gizzard and GI tract). The residue levels in other tissues were all within the range 0.054-0.34 mg eq/kg. Residue levels in eggs were ≤0.43 mg eq/kg. A plateau was reached after approximately 6 days for egg white. For egg yolk the plateau was not reached but until the 8th day, and concentrations might still slightly increase. Pyriproxyfen was detected in egg white and yolk at levels up to 0.17 mg eq/kg and in all analysed tissues (except gizzard) at levels within the range 0.011-0.92 mg eq/kg and in the gizzard and excreta at levels within the range 16-50% of TRR. The major metabolites in eggs and tissues were conjugated 4'-OH-PYR, free 2-OH-PY and PYPAC. DPH-PYR, 4'-OH-PYR, PYPA and free and conjugated 5''-OH-PYR were also detected. Excreta contained all metabolites that had also been identified in the tissues except PYPA and conjugated 4'-OH-PYR. The majority of the radioactivity in the PES was either bound to or incorporated in fatty acids (egg yolk) or associated with the protein fractions (liver and kidney).

In a study with goats [redacted] after five daily dose administrations of [redacted] at 20 mg/day [redacted], of the total administered dose 76% was recovered in excreta, 25% in the tissues and 0.29% in milk. The residue levels in tissues were highest in liver (0.29-0.49 mg eq/kg), kidney (0.16-0.26 mg eq/kg) and GI tract + contents (0.048-8.3 mg eq/kg). The residue levels in other tissues were ≤0.001-0.054 mg eq/kg. Residues in milk were ≤0.096 mg eq/kg and reached a plateau after ~4 days. Pyriproxyfen was detected in milk at levels up to 0.009 mg eq/kg and in all analysed tissues at levels within the range 0.003-0.050 mg eq/kg. Pyriproxyfen levels in urine and faeces were within the range 0.24-0.84% of TRR and 11-13% of TRR, respectively. [redacted] Identified metabolites in urine and faeces all exceeded 10% of TRR and/or 0.05 mg eq/kg [redacted]

In another study with goats [redacted] following five daily dose administrations of [redacted] at 15 mg/day [redacted] of the total administered dose 63-70%

was recovered in excreta, 32% was recovered in the tissues, and 0.44-0.84% in milk. The residue levels in tissues were highest in liver (0.43-0.83 mg eq/kg), kidney (0.23-0.30 mg eq/kg) and GI tract + contents (0.10-20 mg eq/kg). The residue levels in other tissues were 0.012-0.069 mg eq/kg. Residues in milk were ≤0.12 mg eq/kg and reached a plateau within 4 days.

Pyriproxyfen was detected in milk at levels up to 5.6% of TRR (0.004 mg eq/kg) and in all analysed tissues at levels within the range 0.001-0.039 mg eq/kg. Pyriproxyfen levels in urine and faeces were within the range 0.30-0.67% of TRR and 7.0-10% of TRR, respectively. [redacted] Additionally, in liver and kidney four unknown metabolites were detected coded *Unknown 1-4*; they did not exceed 10% of TRR / 0.05 mg eq/kg. *Unknown 1* was also detected in milk (<10% of TRR / <0.05 mg eq/kg). [redacted] In faeces all identified metabolites exceeded 10% of TRR / 0.05 mg eq/kg [redacted]

The notifier was requested to submit study summaries on the hen and goat metabolism studies, in order to complete Document IIIA (6.15) and since they are considered key studies for the evaluation of the secondary exposure of the general population. These study summeries are presented below:

Section 6.15.1/01 **Annex Point IIIA, XI.1.1, 1.3, 1.6**	**Metabolism studies in livestock**	
	1 Reference	**Official use only**
1.1 Reference	[redacted]	
1.2 Data protection	Yes	
1.2.1 Data owner	Sumitomo Chemical Co., Ltd.	
1.2.2 Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of entry into Annex I	
	2 Guidelines and Quality Assurance	
2.1 Guideline study	Yes EPA Guidelines specified in Residue Chemistry, Section 171-4: Nature of the residues, Animals equivalent to Appendix F to Commission Document 1607/VI/97	
2.2 GLP	[redacted]	

2.3 Deviations	[redacted]	
	3 Materials and Methods	
3.1 Test material	[redacted]	
3.1.1 Lot/Batch No	[redacted]	
3.1.2 Specification	[redacted]	
3.1.3 Description	[redacted]	
3.1.4 Purity	[redacted]	
3.1.5 Stability	[redacted]	
3.2 Test animals		
3.2.1 Species	Hen (*Gallus domesticus*)	
3.2.2 Strain	[redacted]	
3.2.3 Source	[redacted]	
3.2.4 Sex	Female	
3.2.5 Age/weight at study initiation	[redacted]	
3.2.6 Number of animals per group	[redacted]	
3.2.7 Control animals	[redacted]	
3.3 Administration/ Exposure		
3.3.1 Administration	Gelatin capsules	
3.3.2 Dose level	The 10 hens in the treatment group received a dose equivalent to 10 ppm pyriproxyfen based on the average daily food consumption in the acclimation period. These doses were given daily for 8 days Control groups received a placebo on the same schedule as the treated animals	

3.4 Examinations		
3.4.1 Observations	[redacted]	
3.4.2 Extraction and analysis	[redacted]	
	4 Results and Discussion	
4.1 Results of test	[redacted]	

	[redacted]	
	5 Applicant's Summary and conclusion	
5.1 Materials and methods	[redacted]	
5.2 Results and discussion	[redacted]	

	[redacted]	
5.3 Conclusion	**The study indicated that ingested pyriproxyfen was extensively degraded in the hens, the primary routes of degradation being hydroxylation and cleavage of ether bonds. Pyriproxyfen and its metabolites were readily eliminated in excreta and residues in eggs and tissues of the animals was very low**	
5.3.1 Reliability	[redacted]	
5.3.2 Deficiencies	[redacted]	

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Section A6.15.1/02 **Annex Point IIIA, XI.1.1, 1.3, 1.6**	**Metabolism studies in livestock**	
	1 Reference	**Official use only**
1.1 Reference	[redacted]	
1.2 Data protection	Yes	
1.2.1 Data owner	Sumitomo Chemical Co., Ltd.	
1.2.2 Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of entry into Annex I	
	2 Guidelines and Quality Assurance	
2.1 Guideline study	Yes EPA Guidelines specified in Residue Chemistry, Section 171-4: Nature of the residues, Animals equivalent to Appendix F to Commission Document 1607/VI/97	
2.2 GLP	[redacted]	
2.3 Deviations	[redacted]	
	3 Materials and Methods	
3.1 Test material	[redacted]	

3.1.1 Lot/Batch No	[redacted]	
3.1.2 Specification	[redacted]	
3.1.3 Description	[redacted]	
3.1.4 Purity	[redacted]	
3.1.5 Stability	[redacted]	
3.3 Test animals		
3.2.1 Species	Hen (*Gallus domesticus*)	
3.2.2 Strain	[redacted]	
3.2.3 Source	[redacted]	
3.2.4 Sex	Female	
3.2.5 Age/weight at study initiation	[redacted]	
3.2.6 Number of animals per group	[redacted]	
3.2.7 Control animals	[redacted]	
3.3 Administration/ Exposure		
3.3.1 Administration	Gelatin capsules	
3.3.2 Dose level	The 10 hens in the treatment group received a dose equivalent to 10 ppm pyriproxyfen based on the average daily food consumption in the acclimation period. These doses were given daily for 8 days Control groups received a placebo on the same schedule as the treated animals	
3.4 Examinations		
3.4.1 Observations	[redacted]	

	[redacted]	
3.4.2 Extraction and analysis	[redacted]	
	4 Results and Discussion	
4.1 Results of test	[redacted]	

	[redacted]	
	5 Applicant's Summary and conclusion	
5.1 Materials and methods	[redacted]	
5.2 Results and discussion	[redacted]	

	[redacted]	
5.3 Conclusion	**Pyriproxyfen was extensively degraded in hens, the primary routes of degradation being hydroxylation and cleavage of ether bonds. Pyriproxyfen and its metabolites were readily eliminated through the excreta and residues in both eggs and tissues of the animals were very low** [redacted]	
5.3.1 Reliability	[redacted]	
5.3.2 Deficiencies	[redacted]	

[redacted]

[redacted]

		0.021

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]