UNITED NATIONS

UNEP

SC

UNEP/POPS/POPRC.8/INF/13

Distr.: General
24 August 2012

English only

Stockholm Convention on Persistent Organic Pollutants

Persistent Organic Pollutants Review Committee
Eighth meeting
Geneva, 15–19 October 2012
Item 5 (e) and (f) of the provisional agenda*

Technical work: assessment of alternatives to endosulfan; assessment of alternatives to DDT

Fact sheets on chemical alternatives to endosulfan and DDT

Note by the Secretariat

As referred to in documents UNEP/POPS/POPRC.8/8 and UNEP/POPS/POPRC.8/9, fact sheets on chemical alternatives to endosulfan and DDT are set out in the annex to the present note. They have not been formally edited.

* UNEP/POPS/POPRC.8/1.

K1282363 280912

Annex

Fact sheets on chemical alternatives to endosulfan and DDT

Content

*Chemicals with asterisk are alternatives to both endosulfan and DDT. Chemicals without asterisk are alternatives to endosulfan.

Assessment of POP criteria and other hazard indicators

1. Alpha-cypermethrin[1]

CONCLUSIONS

Assessment of POP properties – comparison with the criteria of Annex D and other hazard indicators

1.1 Persistence

1. Alpha-cypermethrin is stable to hydrolysis at acidic conditions. DT50 values at pH 7 and 9 are 101 days and 7 days, respectivly. Aqueous photolysis contributes to the degradation of alpha-cypermethrin in water. For the aquatic environment a DT50 whole system from water/sediment study indicate no accumulation in water or sediment (DT50 6 to 35 days at pH values of 7.1 to 8.2). Reported DT50 values for soil range from 25 days to 100 days (lab studies) and from 14 to 112 days in field. The modelled P-score is 0.824 indicating high persistency. However this estimate is based on ultimate mineralization. Alpha-cypermethrin does not fulfil the persistence criteria according to Annex D 1 (b) (i).

1.2 Bioaccumulation

2. Alpha-cypermethrin has a log Kow of 5.5. The experimentally derived BCF in fish considered in the EU risk assessment on biocidal product was 910 L/kg. The modelled B-score for alpha-cypermethrin is 0.581, suggesting bioaccumulation. Based on the empirical evidence (BCF in fish) alpha-cypermethrin does not fulfil the bio-accumulation criteria according to Annex D 1 (c) (i)..

1.3 Long-range transport (LRT)

3. Alpha-cypermethrin has a calculated half-life in air of 3.5 hours (< 2 days). Therefore it has alow LRT potential and it is unlikely that the compound fulfils the Annex D 1 (d) (iii) criteria.

1.4 Ecotoxicity (including pollinator toxicity)

4. Alpha-cypermethrin is highly toxic to aquatic species and is classified according to EU-GHS as aquatic acute and chronic category 1, e.g. very toxic to aquatic life with acute and long lasting effects. It reveals high toxicity toward honey bees and other pollinators. Alpha-cypermethrin therefore fulfils in addition to the reported toxicity to human health (see below) Annex D 1 (e) (ii).

1.5 Toxicity to human health (including mutagenicity, carcinogenicity and adverse effects on the reproductive, endocrine, immune or nervous systems)

5. Alpha-cypermethrin is the name given to the compound consisting of two of the four cis-isomers of Cypermethrin. The acute oral and inhalation toxicity of Alpha-cypermethrin is approximately 2–4 times greater than that of Cypermethrin. However other than this there is no indication that it would have different toxicological effects. Thus, read-across to Alpha-cypermethrin from studies performed with Cypermethrin is not considered acceptable.

6. Alpha cypermethrin is classified by EU-GHS for oral acute toxicity category 3. In addition it may according to the latest EU evaluation qualify also for respiratory acute toxicity category 4. However orally with polar solvents no signs of toxicity were observed up to the limit dose level. The substance is not classified for skin or eye irritation, though according to the latest EU evaluation classification for skin irritation may be possible. No skin sensitization potential was observed with the Magnusson and Kligman test.

7. Alpha-cypermethrin is not classified for carcinogenicity, mutagenicity or reproductive toxicity according to the GHS system in the EU and comprehensive data and evaluations available support this conclusion.

8. Alpha-cypermethrin is not listed in the EU endocrine disrupter database but cypermethrin is listed in the EU endocrine disrupter database within category 2. This means that it is persistent or a HPVC chemical with at least some in vitro evidence of biological activity related to endocrine disruption.

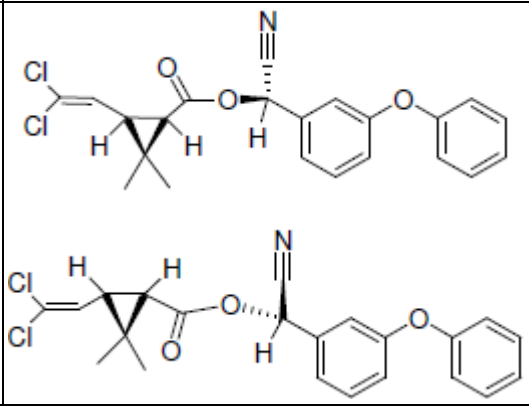
[1] Alpha-cypermetrin is an alternative to both endosulfan and DDT.

9. The substance did not induce delayed neurotoxicity. Repeated dose toxicity studies showed that the main target organ of Alpha-cypermethrin is the nervous system (CNS and peripheral motor nerves). The critical effect used for limit value derivation was observed in a 1 year dog study were local effects (skin reddening and hair loss) considered as a consequence of systemic toxicity. In the latest evaluation available this lead to an lowest external limit dose (ADI) proposal of 0.015 mg/kg bw day and an internal limit dose (AEL) of 0.01 mg/kg bw day.

1.6 Identity of the substance and physical and chemical properties

a) Name and other identifiers of the substance

Table 1: Substance identity

Common name:	ALPHA-CYPERMETHRIN
IUPAC name:	Racemate comprising (S)-á- cyano-3 phenoxybenzyl-(1R)-cis-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylate and (R)-á- cyano-3 phenoxybenzyl-(1S)-cis-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylate (= cis-2 isomer pair of cypermethrin)
CAS number:	67375-30-8
Molecular weight:	416.3
Chemical structure:	

b) Chemical group

Pyrethroid

c) Physico-chemical properties

Table 2: Overview of selected physico-chemical properties

Property	Value	Remarks and Reference
Vapour pressure	5.6 x 10^{-7} Pa (25°C)	EU biocides CAR 2011
Water solubility	4.6 µg/L (pH 7)	EU biocides CAR 2011
Partition coefficient n-octanol/water (log value)	5.5	PPDB 2012
Partition coefficient air/water (log value)	-4.765	EPI Suite 4.0 (KAOWINv1.10)[2]
Partition coefficient air/octanol (log value)	10.27	EPI Suite 4.0 (KAOWINv1.10)
Henry´s Law Constant	0.069 Pa m^3 mol-1	EU biocides CAR 2011

[2] http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm

1.7 Classification and labelling

d) Harmonised Classification according to GHS

Regulation (EC) No 1272/2008 – 1nd amendment 2009: for alpha-cypermethrin

Category	Hazard-Phrase
Acute Tox. 3	H301 Toxic if swallowed
STOT SE 3	H335 May cause respiratory irritation
STOT RE 2	H373 May cause damage to organs through prolonged or repeated exposure
Aquatic Acute 1	H400 Very toxic to aquatic life
Aquatic Chronic 1	H410 Very toxic to aquatic life with long lasting effects

e) Proposed reclassification according to GHS

EU biocides CAR 2011: for alpha cypermethrin

Category	Hazard-Phrase
Acute Tox. 3	H301 Toxic if swallowed
Acute tox 4	H332 Harmful if inhaled
Skin irrit. 2	H315 Causes skin irritation
STOT SE 3	H335 May cause respiratory irritation
STOT RE 2	H373 May cause damage to organs through prolonged or repeated exposure
Aquatic Acute 1	H400 Very toxic to aquatic life
Aquatic Chronic 1	H410 Very toxic to aquatic life with long lasting effects

1.8 Environmental fate Properties

f) Abiotic Degradation

g) Hydrolysis

EU biocides CAR 2011: Hydrolysis of alpha-cypermethrin takes place at alkaline buffer solutions forming 3-phenoxybenzaldehyde (CAS-no. 39515-51-0) as the only major metabolite. Reported values are in line with EFSA review report 2004.

EFSA review report 2004:

I. at pH 4, 50 °C : hydrolytical stability (no degradation after 10 days)
II. at pH 7, 20 °C : DT50 = 101 days
III. at pH 9, 20 °C : DT50 = 7.3 days

1.9 Phototransformation/photolysis

10. EU biocides CAR 2011: Aqueous photolysis contributes to degradation of alpha-cypermethrin in water. Three resulting metabolites were formed: 3-phenoxybenzaldehyde, 3-phenoxybenzoic acid and cis + trans-2,2-dimethyl-3-(2',2'-dichlorovinyl)cyclopropane carboxylic acid isomers, which are also sensitive to photodegradation. Increasing amounts of carbon dioxide suggesting that alpha-cypermethrin and its photolytic transformation products are rapidly degraded.

1.10 Biodegradation

11. Retrieved DT_{50} values for soil (lab and field) and water sediment are summarized in Table 3.

Table 3: Half-lives in soil (lab and field), water and sediment

Degradation 50%	days	Reference	Comments
DT_{50} soil lab (days):	25 – 125 (20°C)	EFSA review report 2004	-
DT_{50} water (days):	0.4-2.1 (a.s.) 2.1-3 d (3 phenoxybenzoic acid) 13.9-36.8 d (dimethylcyclopropane carboxylic acid)		-
DT_{50} water sediment/whole system (days):	6.4-35.4		EFSA conclusion: up to 62-55% of applied moved into sediment at day 2; no accumulation in water or sediment; pH values of sediment and water range from 7.1 to 8.2
DT_{50}soil field (days):	14-112 3 year study UK		
DT_{50} soil lab (days):	100	PPDB 2012	persistent
DT_{50} water (days):	1.3	PPDB 2012	moderately fast
DT_{50} water sediment/whole system (days):	21	PPDB 2012	fast
DT_{50}soil field (days):	35	PPDB 2012	moderately persistent

C

AR 2011 state that based on the vapour pressure (3.4×10^{-7} Pa at 25 °C) and the Henry`s Law Constant (0.069 Pa × m³/mol at 25 °C), volatilisation of alpha-cypermethrin is negligible. Calculations of the chemical lifetime in the troposphere resulted in a half-life of 3.47 hours (QSAR estimates). According to this result (t1/2 <2 days), Alpha-cypermethrin is rapidly degraded by photochemical processes and no accumulation of alpha-cypermethrin in the air is to be expected. Therefore it can be concluded that the compound has a low LRT potential.

1.12 Bioaccumulation

13. EU biocides CAR 2011: According to the experimentally derived BCF in fish, alpha-cypermethrin is not considered to be a bioaccumulable substance with a BCF value of 910 L/kg.

14. WHO 2012: A BCF of 1204 was calculated based on an experiment in rainbow trout with cypermethrin. The same value is listed in PPDB 2012.

PB-score[3]

15. Alpha-Cypermethrin has a P-score of 0.824 and a B-score of 0.289 resulting in an overall B-score of 1.11.

1.13 Human health hazard assessment

16. EU biocides CAR 2011: Alpha-cypermethrin is related to Cypermethrin in the following way: Cypermethrin has three chiral centres, one at cyclopropyl C1, a second at cyclopropyl C3, and a third at the benzylic alpha-carbon atom. This pyrethroid therefore consists of a mixture of eight isomers (four diastereoisomeric pairs). The active components of Cypermethrin are 1R cis alpha-S and 1R trans alpha-S. Alpha-cypermethrin is the name given to the compound consisting of two of the four cis-isomers of Cypermethrin: 1R cis alpha-S and 1S cis alpha-R, present each at 12.5 % in Cypermethrin. Consequently, the acute oral and inhalation toxicity of alpha-cypermethrin is approximately 2–4 times greater than that of cypermethrin.

[3] http://www.rivm.nl/bibliotheek/rapporten/601356001.html.

17. Overall, since alpha-cypermethrin is a component of cypermethrin, there is no indication that it would have different toxicological effects. Thus, read-across to alpha-cypermethrin from studies performed with Cypermethrin is not considered acceptable.

i) Acute toxicity

18. EU biocides CAR 2011 for alpha-cypermethrin: The data presented coincide with the EU-GHS classification, i.e. acute toxicity category 3 and 4 for the oral route and respiratory route, respectively. Bioavailablity seems to strongly depend on solvents, with polar solvents no signs of toxicity were observed up to the limit dose level. Alpha-cypermethrin causes skin irritation and may cause respiratory irritation but it does not show skin sensitizing properties in a Magnusson and Kligman test. In humans paresthesia and peripheral sensory phenomena and irritation of respiratory tract was reported.

19. EFSA review report 2004: The acute toxicity data reported are in agreement with the actual EU-GHS classification but not with the EU biocides CAR 2011 proposal for skin irritation and respiratory category 4 classification.

i) Mutagenicity and Carcinogenicity

20. EU biocides CAR 2011 for alpha-cypermethrin: All three in vitro genotoxicity assays were negative and also the in vivo micronucleus, mammalian chromosome aberration and UDS tests were unequivocally negative. In consequence, it is concluded that Alpha-cypermethrin has no genotoxic potential. Tumours or other signs of carcinogenicity were not observed upon chronic oral administration of Alpha-cypermethrin to rats and mice.

21. EFSA review report 2004: The report is in agreement with the conclusions presented in the EU biocides CAR 2011.

22. US EPA RED 2006: Cypermethrin is classified in category C as possible human carcinogen. No quantification is required.

j) Toxicity for reproduction

23. EU biocides CAR 2011 for alpha-cypermethrin: No teratogenic or embryotoxic effects were observed in rats or rabbits. Within a 3-generation study with cypermethrin no adverse effects on reproductive performance or fertility was observed. The data can be read across to alpha-cypermethrin.

24. EFSA review report 2004: The report is in agreement with the conclusions presented in the EU biocides CAR 2011.

k) Neurotoxicity

25. EU biocides CAR 2011 for alpha-cypermethrin: Repeated dose toxicity studies showed that the main target organ of Alpha-cypermethrin is the nervous system (CNS and peripheral motor nerves). After acute and repeated dose studies clinical neurological signs were observed. A 4-week neurotoxicity study aiming at the identification of the toxic mechanism showed that the effects of Alpha-cypermethrin are rather due to a pharmacological effect than the consequence of structural damage, despite sporadic incidences of slight degeneration of the sciatic nerve. Neurobehavioral changes are reversible within 3 days following single dose. In humans paresthesia and peripheral sensory phenomena and irritation of respiratory tract was reported.

26. EFSA review report 2004: The report is in agreement with the conclusions presented in the EU biocides CAR 2011.

27. WHO 2012: A study is cited indicating no delayed neurotoxicity potential in chicken.

l) Immunotoxicity

-

m) Endocrine disruption

28. Alpha-cypermethrin is not listed in the European database for endocrine disrupters. However cypermethrin is listed within category 2, which means that it is persistent or an HPVC with at least some in vitro evidence of biological activity related to endocrine disruption.

n) Mode of action

29. Representing a type II pyrethroid the mode of action is sodium channel blocking resulting in respective neurotoxicity (CS syndrome).

o) Acceptable Exposure Levels

30. EU biocides CAR 2011 for alpha-cypermethrin: The most sensitive species in chronic toxicity tests was the dog, with a 1-year oral NOAEL of 2.0 mg/kg bw day. The critical effects were local effects (skin reddening and hair loss) considered as a consequence of systemic toxicity. Taking into account the oral absorption factor of 0.45 and an assessment factor of 100 this results in a systemic long term limit value (internal AEL) of 0.009 mg/kg bw day.

31. EFSA review report 2004: Though derived from the 90 day dog study the same systemic long term limit value using the same assessment factor (100) and correction for oral absorption (0.45) is presented (AOEL systemic = 0.01 mg/kg bw day). An external limit value (ADI) is presented on the basis of the 1 year dog study and an assessment factor of 100: 0.015 mg/kg bw day.

1.14 Environmental hazard assessment

p) Aquatic compartment (including sediment)

32. EFSA review report 2004 and WHO 2012 reported the toxicity reference values for aquatic organisms listed in Table 4 for risk assessment. The table presents a selection of listed values. Please refer to the original documents for more information.

Table 4: Toxicity reference values for the aquatic compartment

Exposure scenario/ Study type	Organism /Species	Endpoint	Toxicity value	Reference
Acute 96 hour	Fish	LC_{50}	2.8 µg/l	EFSA, WHO
Chronic, 21 days	Fish	NOEC	< 0.032 µg/l	EFSA, WHO
Acute 48 hour	Aquatic invertebrates	EC_{50}	0.3 µg/l	EFSA,WHO
Chronic, 21 days	Aquatic invertebrates	NOEC	0.03 µg/l	EFSA,WHO
Acute 96 hour	Sediment dwellers	LC_{50}	0.0024 µg/l	EFSA, WHO
Acute 72 hour	Algae	EC50	> 100 µg/l	EFSA, WHO
Mesocosm 126 days	Aquatic community	NOEAEC	0.015 µg/l	EFSA, WHO
Acute 96 hour	Fish	LC_{50}	8.4 µg/l	WHO
Early life stage tox.	Fish	NOEC	0.03 µg/l	WHO
Acute 24 hour	Aquatic invertebrates	EC_{50}	0.14 µg/l	WHO

q) Terrestrial compartment

33. EFSA review report 2004 and WHO 2012 used the toxicity reference values for terrestrial organisms listed in Table 10 for risk assessment. The table presents a selection of listed values. Please refer to the original documents for more information.

Table 5: Toxicity reference values for the terrestrial compartment

Exposure / Study type	Organism /Species	Endpoint	Toxicity value	Reference
Acute, oral	Rat	LD_{50}	57 mg/kg	EFSA
Long term 2-generations	Rat	NOAEL	5 mg/kg	EFSA
Acute	Birds	LD_{50}	> 2025 mg/kg	EFSA

Exposure / Study type	Organism /Species	Endpoint	Toxicity value	Reference
Reproduction 20 weeks	Birds	NOEC	130 mg/kg food	EFSA
Acute	Earthworms	LC_{50}	> 100 mg/kg soil	EFSA
reproduction	Earthworms	NOEC	100 g/kg soil	EFSA
Acute	Earthworms	LC_{50}	57,4 (39.2-84) mg/kg soil	WHO
Dietary Toxicity	Birds	LC_{50}	>5000 mg/kg diet	WHO
Chronic Reproduction	Birds	NOEC	150 mg/kg diet	WHO

r) Toxicity to pollinators

34. EFSA review report 2004 indicate high toxicity to bees and other pollinators. The acute oral toxicity is 0.059 µg/bee and the acute contact toxicity is 0.033 µg/bee.

1.15 Other information

35. No further critical toxicological information is provided in the WHO 2012 report.

36. Toxicological information presented in the PAN –pesticides database and in the footprint database is largely consistent with the toxicological information summarized above, but they seem to lack the data on mutagenicity and carcinogencity and reproduction toxicity presented above.

1.16 References

EFSA review report 2004: Alpha-Cypermethrin,SANCO/4335/2000 final; 13 February 2004 http://ec.europa.eu/food/plant/protection/evaluation/existactive/list_alpha_cypermethrin.pdf

WHO (2012) WHO specifications and evaluations for public health pesticides- Alpha-Cypermethrin, January 2012.

EU biocides CAR (2011) Evaluation Report Alpha-Cypermethrin, Product-type 18. 2011. available at http://ec.europa.eu/environment/biocides/annexi_and_ia.htm, 2012-03-26

EU Endocrine Disruption Database (2012) http://ec.europa.eu/environment/endocrine/strategy/short_en.htm, 2012-04-16

PPDB (2012) Pesticide Properties Database: Cypermethrin http://sitem.herts.ac.uk/aeru/footprint/en/index.htm

2. Bendiocarb[4]

CONCLUSIONS

Assessment of POP properties – comparison with the criteria of Annex D and other hazard indicators

2.1 Persistence

37. Bendiocarb hydrolytically degraded depending on the pH with DT50 values of <1 day to maximum 47 days (at acidic pH). Photolysis was shown to be only a minor route of removal of bendiocarb, however on soil surfaces photolytic degradation was fast. DT50 values in laboratory soil studies range from a few days to weeks. Bendiocarb did degrade reasonably rapidly in the aquatic environment with a DT50 value of 9 days under aerobic conditions in a sediment/water system. Based on the experimental evidence it is concluded that bendiocarb does not meet the persistency criteria of Annex D 1 (b) (i).

2.2 Bioaccumulation

38. Bendiocarb has a log Kow of 1.7 and an experimental derived BCF in fish of 6. Therefore, the bioaccumulation criterion according to Annex D 1 (c) (i) is not fulfilled.

2.3 Long-range environmental transport (LRT)

39. The fate of bendiocarb in air was investigated using the quantitative structure activity relationship estimation method which considers the reaction with the daily air concentrations of hydroxyl (OH) radicals. A maximum estimated half-life of 13.2 h was predicted, however the active substance is not considered volatile. Based on a calculated DT50 value <2 days it can be expected that bendiocarb does not meet the Annex D 1 (d) (iii) criterion.

2.4 Ecotoxicity (including pollinator toxicity)

40. Beendiocarb is highly toxic to aquatic organisms and is classified according to EU-GHS as aquatic acute and chronic category 1. According to the available data, the most sensitive chronic endpoint for bendiocarb is that derived for a 21 day Daphnia study (NOEC of 0.88 µg /l). The compound is also (highly) toxic to terrestrial organism like birds, bees and earthworms. Based on its high ecotoxicity and toxicity to human health (see below) Annex D 1 (e) (ii) is considered to be fulfilled.

2.5 Toxicity to human health (including mutagenicity, carcinogenicity and adverse effects on the reproductive, endocrine, immune or nervous systems)

41. Bendiocarb is of acute systemic toxicity qualifying for GHS category 3. Available data indicate no skin sensitizing potential.

42. Bendiocarb is not classified for carcinogenicity or mutagenicity by EU-GHS and also the latest US EPA and WHO evaluations support this conclusion. Sufficient data are available.

43. Bendiocarb is also not classified for reproductive toxicity and the latest EU biocides assessment report (AR) supports this conclusion.

44. No immunotoxicity is reported. Bendiocarb is not listed in the EU endocrine disrupter database. No delayed neurotoxicity was observed in a respective study.

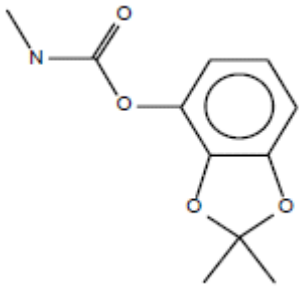
45. Belonging to the group of carbamates the critical effects appear to be cholinesterase inhibition and related neurotoxic effects. The latest proposed long term limit values is 0.0065 mg/kg bw day (EU Biocides AR) which is in a similar magnitude with the WHO proposal.

[4] Bendiocarb is an alternative to both endosulfan and DDT.

2.6 Identity of the substance and physical and chemical properties

a) Name and other identifiers of the substance

Table 2: Substance identity

Common name:	Bendiocarb
IUPAC name:	2,2-dimethyl-1,3-benzodioxol-4-yl methylcarbamate
CAS number:	22781-23-3
Molecular weight:	223.23
Chemical structure:	

b) Chemical group

Carbamate

c) Physico-chemical properties

Table 2: Overview of selected physico-chemical properties

Property	Value	Remarks and Reference
Vapour pressure	1.9 10^{-3} Pa at 20°C	EU biocides AR 2011
Water solubility	0.3 g/l	EU biocides AR 2011
Partition coefficient n-octanol/water (log value)	1.7	EU biocides AR 2011
Partition coefficient air/water (log value)	-5.797	EPI Suite v 4.1 (KOAWIN v. 1.10)[5]
Partition coefficient air/octanol (log value)	7.5	EPI Suite v 4.1 (KOAWIN v. 1.10)
Henry´s Law Constant	1.54 x 10^{-3} Pa m^3 mol^{-1}	EU biocides AR 2011

2.7 Classification and labelling

d) Harmonised Classification according to GHS

Regulation (EC) No 1272/2008:

Category	H-phrase	
Acute Tox. 3	H331	Toxic if inhaled.
Acute Tox. 3	H301	Toxic if swallowed.
Acute Tox. 4	H312	Harmful in contact with skin.
Aquatic Acute 1	H100	Very toxic to aquatic life
Aquatic Chronic 1 (M=100)	H410	Very toxic to aquatic life with long lasting effects.

[5] http://www.epa.gov/oppt/exposure/pubs/episuite.htm

2.8 Environmental fate properties

e) Abiotic degradation

f) Hydrolysis

46. EU biocides AR 2011: Bendiocarb has been shown to hydrolyse with a DT50 of 2 d (at 25°C and pH 7). At pH 7, a major hydrolysis product, NC 7312 (2,2-dimethyl-1,3-benzodioxol-4-ol) was identified, which was recorded to reach 88 % of the applied parent compound under the conditions tested. At pH 5 and pH 9 DT50 values were 1116 hours and 0.7 hours, respectively.

g) Phototransformation/photolysis

47. EU biocides AR 2011: Photolysis was shown to be only a minor route of removal of bendiocarb with a DT50 of 187 days predicted from the available data after adjustment for natural sunlight. HSDB 2012 reported a photolysis half-life in water of 37 days and in soil of <1 day at 25°C.

h) Biodegradation

48. EU biocides AR 2011: Biodegradation of bendiocarb was investigated under aerobic conditions in 3 soils, a sandy loam, a silty clay loam and sand and shown to be reasonably rapid with DT50 values between 2 and 10 days (when adjusted to 12°C). PPDB 2012 reports varying literature values for half-lives in soil from a few days to a few weeks depending on soil type but states a DT50 (typical) of 3.5 days.

49. In water/sediment systems EU biocides AR 2011 identified a DT50 value of 9 days (whole system) and the metabolite NC 7312, which further degraded to CO_2 in aerobic sediment/water systems with DT50 values between 22.6 d (sediment-water system) to 132.8 d (filtered water) calculated for 12°C. Degradation of bendiocarb under anaerobic conditions was shown to follow the same route as under aerobic conditions but at a slightly higher rate (DT50 5 day).

2.9 Potential for long range transport

50. EU biocides AR 2011: The fate of bendiocarb in air was investigated using the quantitative structure activity relationship estimation method which considers the reaction with the daily air concentrations of hydroxyl (OH) radicals (AOPWIN, EPI SUITE[6]). A maximum estimated half-life of 13.2 hours was predicted, however the active substance is not considered volatile, as shown by the reported vapour pressure of 1.9 mPa (at 20°C). Due to the lack of persistence no multimedia fate modelling with the OECD tool was performed.

2.10 Bioaccumulation

51. EU biocides AR 2011 states that bendiocarb has a low potential to bioconcentrate and hence bioaccumulate in fish with a bioconcentration factor (BCF) of 6.0 found for the whole body of the fish. These findings are further supported by the results from calculating a BCF using a QSAR from the 'Technical Guidance Document on Risk Assessment in support of Commission Directive 93/67/EEC (new notified substances), Commission Regulation (EC) No 1499/94 (existing substances) and Directive 98/8/EC (biocidal products)' (EC, 2003). This returned a value of 5.6, which agrees very closely with the study results.

i) PB-score

-

2.11 Human health hazard assessment

j) Acute toxicity

52. EU biocides AR 2011: The data presented coincide with the EU-GHS classification, i.e. acute toxicity category 3 for the respiratory and oral route and category 4 for the dermal route. It does not show skin sensitizing properties in a Buehler test.

53. US EPA factsheet 1999: For oral exposure, bendiocarb is in Acute Toxicity Category I, the highest of four categories for this effect. In addition, bendiocarb is in Acute Toxicity Category II for dermal and inhalation routes of exposure, Acute

[6] http://www.epa.gov/oppt/exposure/pubs/episuite.htm

Toxicity Category III for primary dermal irritation and Acute Toxicity Category IV for primary eye irritation.

k) Mutagenicity and Carcinogenicity

54. EU biocides AR 2011: Bendiocarb gave a positive result in an in vitro cytogenicity assay on human lymphocytes with metabolic activation. However, it was negative in several other in vitro (bacterial reverse mutation assays and unscheduled DNA synthesis assay) tests and in three in vivo assays (clastogenicity, chromosome aberrations in bone marrow and dominant lethal mutations in germ cells). Consequently the available data do not support GHS classification for mutagenicity. No treatment-related tumours were identified in lifetime studies in rats or mice exposed to bendiocarb in the diet.

55. US EPA factsheet 1999: There was no evidence of mutagenicity following in vivo or in vitro exposure to bendiocarb. It is classified as a "Group E" chemical, showing no evidence of carcinogenicity in laboratory animals or in humans.

l) Toxicity for reproduction

56. EU biocides AR 2011: A fertility study did not indicate treatment-related effects on fertility and post-implantation losses occurred only in the presence of maternal toxicity in rats and rabbits. A slight delay in ossification in rabbit foetuses, secondary to maternal toxicity, was attributed to bendiocarb but was not sufficient to classify for developmental toxicity. Consequently the available data do not support GHS classification for reproductive toxicity.

57. US EPA factsheet 1999: Developmental and reproductive toxicity studies did not show evidence of increased susceptibility of rat or rabbit fetuses following in utero exposure or in offspring following pre- and/or post-natal exposure.

m) Neurotoxicity

58. EU biocides AR 2011: No signs of delayed neurotoxicity were reported in hens following a single oral gavage dose of bendiocarb that resulted in mortalities. However Inhibition of erythrocyte and brain cholinesterase activity is directly attributable to its insecticidal mode of action and considered to be the most sensitive marker of toxicity in rats and dogs. This effect was critical for the derivation of the long term and medium term limit values (AEL).

59. US EPA factsheet 1999: The existing studies with acute and subacute administration of bendiocarb indicate a rapid onset of cholinesterase inhibition and accompanying symptoms.

n) Immunotoxicity

-

o) Endocrine disruption

60. Bendiocarb is not listed in the EU endocrine disrupter database 2012.

p) Mode of action

61. EU biocides AR 2011: Inhibition of erythrocyte and brain cholinesterase activity is directly attributable to its insecticidal mode of action and considered to be the most sensitive marker of toxicity in rats and dogs.

q) Acceptable Exposure Levels

62. EU biocides AR 2011: A long term limit value of 0.0065 mg/kg bw day was proposed on the basis of a 2 year dog study and application of an assessment factor of 100. Inhibition of cholinesterase activity was considered as the respective critical effect.

63. WHO 2009: An ADI of 0.004 mg/kg bw is reported from an evaluation from 1984.

64. US-EPA factsheet 1999: The chronic population adjusted dose (cPAD) is 0.0004 mg/kg/day. A total assessment factor of 300 was applied, where the additional to standard factor of 3 was used because of data gaps for acute and subchronic neurotoxicity studies in rats.

65. Preference is given to the later proposals of WHO and EU, which are in a similar magnitude.

2.12 Environmental hazard assessment

r) Aquatic compartment (including sediment)

Bendiocarb is highly toxic to aquatic organism (cf. Table 3)

Table 3: Toxicity reference values (most sensitive species of each group) Source: EU biocides AR 2011

Test compound/Species	Time-scale	Endpoint	Toxicity
Fish			
Bendiocarb/*Cyprinodon variegatus*	96 h	LC_{50}	0.86 mg l^{-1}
Bendiocarb/*Salmo gairdneri*	78 d	$NOEC_{larval\ growth}$	0.07 mg l^{-1}
NC 7312/*Salmo gairdneri*	96 h	LC_{50}	10 mg l^{-1}
Invertebrates			
Bendiocarb/*Daphnia magna*	48 h	EC_{50}	0.038 mg l^{-1}
Bendiocarb/*Daphnia magna*	21 d	$NOEC_{reproduction}$	0.00088 mg l^{-1}
NC 7312/*Daphnia magna Straus*	48 h	EC_{50}	25.4 mg l^{-1}
Algae			
Bendiocarb/ *Pseudokirchneriella subcapitata*	72 h	E_rC_{50} NOE_rC*	0.408 mg l^{-1} 0.087 mg l^{-1}
NC 7312/*Desmodesmus subspicatus*	72 h	E_rC_{50} NOE_rC	88.3 mg l^{-1} 0.95 mg l^{-1}

s) Terrestrial compartment

66. EU biocides AR (2011) reported an acute toxicity (LC50) to earthworms of 188 mg/kg soil. US-EPA factsheet 1999 identified a high acute risk to birds after application of a product on turf. Bendiocarb is highly toxic to bees (US-EPA 2009). PPDB 2012 states an oral LD50 for honeybees of 0.1 µg/bee. According to PAN-UK 2012 bendiocarb is thus toxic to some beneficial organisms such as honeybees, but also to earthworms and predators of plant pest. There had been a number of bendiocarb related deaths reported to the Wildlife Incident Investigation Scheme, run by the UK government's Department for the Environment Food and Rural Affairs. Although reporting to this scheme is low. It has been confirmed that from 1999 to 2003, the use of bendiocarb has caused the death of 53 (bee) colonies in the UK. For earthworms bendiocarb is extremely toxic, in one study a standard rate was applied and it reduced the population by 90%.

2.13 Other information

67. WHO 2009: does not contain further critical toxicological information.

68. Toxicological information presented in the PAN –pesticides database and in the footprint database is largely consistent with the toxicological information summarized above, but they point to the fact that some data are available indicating that there may be a concern for reproductive toxicity hazard.

2.14 References

EU Endocrine Disruption Database (2012)
http://ec.europa.eu/environment/endocrine/strategy/short_en.htm, 2012-04-16
EU Biocides AR (2011) Assessment Report Bendiocarb PT18, September 2011, available at
http://ec.europa.eu/environment/biocides/annexi_and_ia.htm
HSDB 2012 Hazardous Substance Database, TOXNET, http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB
PAN-UK (2012) Bendiocarb factsheet http://www.pan-uk.org/pestnews/Actives/Bendiocarb.htm, 2012-04-07
PPDB (2012) Pesticide Properties DataBase, University of Hertfordshire,
http://sitem.herts.ac.uk/aeru/footprint/en/ 2012-04-18
US-EPA factsheet (1999) R.E.D. facts Bendiocarb, September 1999
http://www.epa.gov/oppsrrd1/REDs/factsheets/0409fact.pdf
WHO (2009) WHO specifications and evaluations for public health pesticides-Bendiocarb, January 2009, http://www.who.int/whopes/quality/Bendiocarb_eval_WHO_jan_2009.pdf, 2012-04-06

3. Bifenthrin[7]

CONCLUSIONS

Assessment of POP properties – comparison with the criteria of Annex D and other hazard indicators

69. Bifenthrin has been considered by the EU ad hoc working group on PBT[8]. 0Bifenthrin has been discussed in November 2007 at a meeting of the TC NES subgroup on identification of PBT and vPvB substances. The group concluded that bifenthrin fulfils the P, vP (very persistent) and T criteria. Concerning bioaccumulation there was no unanimity, a majority of the Working group described bifenthrin as a borderline case for the B criterion (trigger: BCF exceeds a value of 2 000 L/kg). It was concluded that bifenthrin is not considered as fulfilling the B criterion (EU biocides AR 2010)

3.1 Persistence

70. The TC NES subgroup based their conclusion vP on DT50 values (12°C) in water/sediment studies that range from 176 to 524 days (for the whole system) and DT50 values (12°C) in soil degradation studies that range from 252 to 695 days (laboratory and field studies). Also without temperature adjustment to 12°C the DT50 values exceed 180 days in soil and water/sediment systems. Therefore it can be concluded that available experimental data show that bifenthrin is persistent and meets the Annex D 1 (b) (i) criterion.

3.2 Bioaccumulation

71. To evaluate the B criteria, 3 tests on fish bioaccumulation were made available to the TC NES subgroup group. In addition, the applicant provided information on the sediment-bound characteristics of bifenthrin and a new study of fish fed with spiked sediment. In the BCF key study done with *Lepomis macrochirus* according to OECD 305 guideline, the steady-state BCF for uptake of bifenthrin estimated in whole fish was 1,414 L/kg. The Working group took notice of this new information but questioned the usefulness of these additional sediment data. While there was no unanimity, a majority of the Working group described bifenthrin as a borderline case for the B criterion and considered bifenthrin as not fulfilling the B criterion (BCF >2000) according to the EU biocides AR 2010.

72. Bifenthrin has a log Kow of 6.6. Experimental BCF values are reported that exceed 5,000 (i.e. BCF of 6090 in bluegill sunfish). However the modelled B-score of 0.38 suggest a lower bioaccumulation potential. Biomagnification through the aquatic food chain and a high risk from bioaccumulation through the terrestrial food chain could not be excluded based on the available information.

73. It can be concluded that available evidence is equivocal to conclude on the bioaccumulation of bifenthrin according to Annex D 1 (c) (i).

3.3 Long-range environmental transport (LRT)

74. The EU biocides AR 2010 on bifenthrin reported no indication of long-range transport. Bifenthrin has a calculated DT50 in air of 13 hours that is below the threshold of 2 days. Therefore it is no likely that bifenthrin meets the Annex D 1 (d) (iii) criterion.

[7] Bifenthrin is an alternative to both endosulfan and DDT.

[8] http://esis.jrc.ec.europa.eu/index.php?PGM=pbt

3.4 Ecotoxicity (including pollinator toxicity)

75. The TC NES subgroup based their conclusion that bifenthrin fulfills the T-criteria on ecotoxicity data on *Daphnia magna*, NOEC (21 days, reproduction) = 9.5 x 10^{-4} µg/L (flow through). This is in line with the proposed EU-GHS classification as aquatic acute and chronic category 1 indicating high toxicity to aquatic organisms.Bifenthrin is highly toxic to bees, but slightly toxic on an acute basis to birds, terrestrial phase amphibians and reptiles. Bifenthrin showed no adverse effects to reproduction at the highest concentration tested for birds.

76. Based on the high aquatic toxicity and toxicity to human health of bifenthrin (see below) Annex D 1 (e) (ii) is fulfilled.

3.5 Toxicity to human health (including mutagenicity, carcinogenicity and adverse effects on the reproductive, endocrine, immune or nervous systems)

77. No EU-GHS harmonised classification is actually available for bifenthrin.

78. However according to the actual EU biocides final AR from 2010 bifenthrin is acutely toxic qualifying for acute oral and respiratory GHS class 3. It is also a skin sensitizer when tested with the Magnusson and Kligmann test; it is negative in the Buehler test that applies a less stringent exposure regime.

79. Some positive or equivocal in vitro genotoxicity results were observed, but the in vivo genotoxicity results are negative which suggests the conclusion that there is no relevant mutagenic potential. Bifenthrin did not induce tumours in the rat, but in mice equivocal tumour findings were reported which might be considered as limited evidence of carcinogenicity qualifying for GHS category 2. On the same data basis US EPA characterised bifenthrin as “possible human carcinogen”. In contrast WHO/JMPR concluded in their latest evaluation from 2012 that bifenthrin is unlikely to pose a carcinogenic hazard to humans.

80. Within reproductive toxicity studies reported in the most actual reviews from EU and US EPA or WHO no specific adverse fertility or developmental effects were observed.

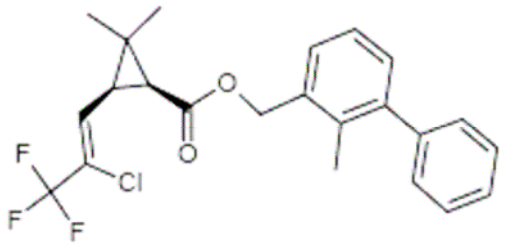
81. Bifenthrin is listed in the EU endocrine disrupter database within category 1 which means it is persistent in the environment or produced at high volumes and shows evidence of endocrine disruption activity in at least one species using intact animals.

82. Bifenthrin did not induce delayed neurotoxicity. Within a developmental neurotoxicity study no specific sensitivity of developing or young rats was observed. The critical effect used for limit value derivation is the clinical neurotoxicity sign tremor. The long term external oral limit values (ADI) in the latest evaluations available are consistently about 0.015 mg/kg bw day. An internal limit value corrected for oral absorption of 0.0075 mg/kg bw day is proposed by the latest European evaluations. In line with the neurotoxic findings at low doses within the EU biocides AR specific target organ toxicity category 1 for the nervous system is proposed.

3.6 Identity of the substance and physical and chemical properties

a) Name and other identifiers of the substance

Table 1: Substance identity

Common name:	Bifenthrin
IUPAC name:	2-methyl-3-phenylbenzyl (1RS)-cis-3-(2-chloro-3,3,3-trifluroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate
CAS number:	82657-04-3
Molecular weight:	422.88
Chemical structure:	

b) Chemical group

83. Pyrethroid

c) Physico-chemical properties

Table 2: Overview of selected physico-chemical properties

Property	Value	Remarks and Reference
Vapour pressure	2.4x 10^{-5} at 25°C (Pa) 1.8x10^{-7} mm Hg	EU biocides AR 2010 US EPA, 2010
Water solubility	<1 µg/L at 20°C, pH 4.05	EU biocides AR 2010
Partition coefficient n-octanol/water (log value)	6.6	EU biocides AR 2010
Partition coefficient air/water (log value)	-4.39	EPI Suite v 4.1 (KOAWIN v. 1.10)[9]
Partition coefficient air/octanol (log value)	10.99	EPI Suite v 4.1 (KOAWIN v. 1.10)
Henry´s Law Constant	101 Pa m³/mol	EU biocides AR 2010

3.7 Classification and labelling

d) Harmonised Classification according to GHS

84. Not available

e) Proposal for harmonised classification according to EU-GHS (Regulation (EC) No 1272/2008

85. Proposal from EU Biocides AR 2010:

Category	H-Phrase	
Carc.2	H351	Suspected of causing cancer
Acute Tox. 3	H331	Toxic if inhaled
Acute Tox. 3	H301	Toxic if swallowed
Skin Sens. 1	H317	May cause an allergic skin reaction
STOT Rep. 1	H372 (nervous system)	Causes damage to central nervous system through prolonged or repeated exposure by oral route
Aquatic. Acute 1	H400	Very toxic to aquatic life
Aquatic. Chronic 1	H410	Very toxic to aquatic life with long lasting effects

DAR 2010: The proposal is identical to the one presented above from the EU biocides review, with the exception that no STOT RE 1 is proposed.

3.8 Environmental fate properties

f) Abiotic degradation

g) Hydrolysis

86. EU biocides AR 2010: Bifenthrin showed hydrolytic stability.

h) Phototransformation/photolysis

87. EU biocides AR 2010 states no UV/VIS absorption above 290 nm. However photolytic and photo-oxidative degradation of bifenthrin under artificial light yielded a DT50 of 10 days. Estimated half life under natural sunlight conditions was DT50 = 24.4 days (40°N, Madrid conditions) and DT50 = 209 – 300 days (late summer 41°N).

i) Biodegradation

88. EU biocides AR 2010 reported DT50 values in water/sediment systems of 93 to 276 days at 20°C. For the same endpoint EFSA 2011 cited DT50 whole system values of 85 to 324 days (n=4, geometric mean 161 days). In soil laboratory

[9] http://www.epa.gov/oppt/exposure/pubs/episuite.htm

degradation studies the DT50 (geometric mean, n=4, 20°C, degradation kinetics according to best fit) was 192 days. Field DT50 values with a geometric mean of 85 days range from 47 to 267 days. PPDB 2012 and EFSA 2011 reported for lab studies a DT50 range of 54 to 174 days. According to US EPA 2010 bifenthrin is very persistent in both laboratory and filed studies. Half-life in soil ranged from 97 to 250 days. Under anaerobic conditions bifentrhin is considered to be stable (US EPA 2010b) Also EFSA 2011 reported high persistence in field studies. The range of the actual DT50 values from the reliable field dissipation studies were between 15 to 199 days, while the DT90 values were between 221 to 965 days.

3.9 Potential for long range transport

89. EU biocides AR 2010 reported a calculated overall OH rate constant of 29.6 x 10^{-12} cm^3 mol^{-1} sec^{-1}. Assuming a 24-h day and an OH concentration of 5.0 x 10^5 cm^{-1} this gives a half-life of 0.54 days or 13 hours. Bifenthrin has a low volatility. It has a moderate volatility from water because its estimated Henry's law constant is 101 Pa m^3 mol^{-1}which is equivalent with an air-water partition coefficient of 0.04 L/L. However, emission from surface water to atmosphere is not expected because of the strong adsorption of bifenthrin to sediment.

3.10 Bioaccumulation

90. US EPA 2010 indicates that bifenthrin is very lipophilic and bioaccumulative. US EPA 2010b states a BCF of 6090, whole body - bluegill sunfish.

91. DAR 2006: Bioaccumulation was studied in rat for 70 days (15 days depuration phase). Maximum concentrations of radioactivity were detected in fat and skin. Estimated half-lives were around 50 days for fat and skin.

92. Laboratory studies in fish indicate a bioaccumulation potential with BCF ranging from 1,030 (*Cyprinus carpio*, 70 days accumulation phase, plateau reached) to 30,000 (*P. promelas*, 357 days, plateau not reached). Bioconcentration is a function of species, the life stage and the exposure level. All values were defined based on a ratio between fish or tissue and water concentrations; except for *L. macrochirus* for which the k1/k2 expressed BCF was 6,090 for the whole body. However, all available BCF represent the overall radioactivity measured including all bifenthrin and its metabolites. Thus no BCF specifically for bifenthrin is defined from the available data. Metabolism studies in *L. macrochirus* indicated that 67 to 87% of AR (applied radioactivity) corresponds to bifenthrin. Bioaccumulation in the presence of sediment seems to be lower (BCF in *P.promelas* if 45-63), however based on the opinion of the evaluating authority data are insufficient to ensure that the risk of bio-accumulation is low for aquatic species.

93. EU biocides AR 2010: In standard bioaccumulation assays, the bioaccumulation factor (BCF) for fish varies from 666 to 6,090. The higher value corresponds to an old study with the bluegill sunfish *Lepomis macrochirus*, which was redone by the applicant in order to met current standard. A BCF of 1,414 with *Lepomis macrochirus* was obtained. The maximum BCF measurement in carp was BCF = 1,082.

94. In a Full Life Cycle assay, fish exposed continuously during their complete life to bifenthrin exhibits a high BCF, reaching 28,000 after 254 days.

95. Conversely, a higher tier study shows that, in natural environment, the strong adsorption of bifenthrin to sediment can significantly lower the bioaccumulation of the substance in organisms.

96. In November 2007, the Technical Committee for PBT assessment evaluated the bioaccumulation status of this substance and concluded that bifenthrin does not fulfil the B criterion (BCF <2,000).

97. DAR 2010: In the reassessment of bioconcentration in 2010 a BCF of 1,709 was chosen for risk assessment with a clearance time (CT50) of 22 to 28 days in fish. This value is also recommended by EFSA 2011.

98. DAR 2010: A food web bioaccumulation model that has been evaluated against field data for fish measured in agricultural settings after extensive bifenthrin applications was applied using evaluative bioaccumulation and exposure assumptions. Time-dependent bioaccumulation and exposure calculations were determined by linking the output from a five-year FOCUS model scenario as input for the food web predictions. Bifenthrin is found in each level of the food chain but no biomagnification has been observed. There was no biomagnification into the highest trophic level (omnivorous fish) indicating that bifenthrin does not biomagnifiy over 5 years of simulated exposure. However EFSA 2011 identified a data gap concerning biomagnification in the aquatic food chain and a high risk from bioaccumulation through the food chain for aquatic organisms could not be excluded on the basis of the available data.

99. EFSA 2011 stated that a high risk from bioaccumulation through the terrestrial food chain was not excluded and a data gap for further assessment was identified for outdoor uses

100. PB-score
101. Bifenthrin has a P-score of 0.9 and a B-score of 0.38 resulting in an overall B-score of 1,28.

3.11 Human health hazard assessment

h) Acute toxicity

102. EU biocides AR 2010: The acute toxicity data presented are in agreement with GHS the classification proposal listed above: Acute toxicity category 3 for the oral and the inhalation route and skin sensitizing when tested with the Magnusson and Kligman test.
103. The DAR 2010 is in agreement with the information summarized in the EU biocides AR 2010. In addition a negative Buehler test for skin sensitization is listed.
104. US EPA 2010: Bifenthrin has a moderate order of acute toxicity via the oral route (category II) and a low order of acute toxicity via the dermal route (category III) of exposure. There are no acute inhalation studies on bifenthrin technical; however, acceptable studies on the end-use products are available. Bifenthrin has a lower vapour pressure. Bifenthrin is neither an eye nor skin irritant, nor is it a dermal sensitizer.

i) Mutagenicity and Carcinogenicity

105. EU biocides AR 2010: Assays employed to evaluate the genotoxicity of bifenthrin technical were conducted in vitro using bacterial and mammalian cell lines and in vivo using rats and mice. The studies all yielded negative results, except for one mouse lymphoma assay and one unscheduled DNA synthesis (UDS) test. Equivocal results were obtained in another gene mutation assay on CHO cells (non-key study). Three in-vivo genotoxicity tests have been performed, a cytogenetic assay in rats, a micronucleus assay in mice, and an unscheduled DNA synthesis assay in rats. Based on these in-vivo studies, there is no convincing evidence that bifenthrin possesses mutagenic/clastogenic potential. In rats no treatment related tumors were observed but in mice equivocal response in the urinary bladder of the male mice (increased incidence of pericytoma, initially classified as leiomyosarcoma), which might be considered as limited evidence of carcinogenicity effects (GHS category 2).
106. The DAR 2010 is in agreement with the information summarized in the EU biocides AR 2010.
107. US EPA 2010: There was no conclusive evidence of carcinogenic potential of bifenthrin in the rat. A mouse oncogenicity study provided some evidence of carcinogenic potential in this species; therefore, the Agency has characterised bifenthrin as a “possible human carcinogen” and used the reference dose (RfD) approach for risk assessment purposes.
108. WHO 2012: Bifenthrin has been evaluated by the WHO IPCS [2000-2002, Report No.WHO/PCS/01.5] and by the FAO/WHO JMPR in 1992 and 2009. The JMPR concluded that the results of the long-term studies in rats and mice and a series of studies designed to evaluate genotoxicity indicated that bifenthrin is unlikely to pose a carcinogenic hazard to humans.

j) Toxicity for reproduction

109. EU biocides AR 2010: No specific developmental effects were observed in rabbits and rats when administered by the oral route. No effect on reproductive performance or fertility was observed in a two generation study at doses which produced maternal toxicity.
110. The DAR 2010 is in agreement with the information summarized in the EU biocides AR 2010.

k) Neurotoxicity

111. EU biocides AR 2010: Bifenthrin was tested in an acute oral delayed neurotoxicity study and was not considered to be a delayed neurotoxicant when administered to adult hens up to doses of 5000 mg/kg bw. Within a developmental neurotoxicity study no specific sensitivity of developing or young rats was observed. Within repeated dose studies as well as carcinogenicity and reproductive toxicity studies the critical effect was tremor.

112. The DAR 2010 is in agreement with the information summarized in the EU biocides AR 2010.

113. US EPA 2010: The Agency received an acceptable developmental neurotoxicity test (DNT) for bifenthrin in 2006. The study does not show any evidence of increased susceptibility of offspring following exposure to bifenthrin. However, based on the Agency´s review of existing pyrethroid data, EPA has come to the conclusion that the DNT is not a particular sensitive study for comparing the sensitivity of young and adult animals to pyrethroids. The Agency is investigating the need for additional experimentation, specific to the mode of action and pharmacokinetic characteristics of pyrethroids, to evaluate the potential for increased susceptibility of young organisms.

l) Immunotoxicity

-

m) Endocrine disruption

114. EU Endocrine Disruption Database 2012: Listed as category 1 suspected endocrine disrupter, which means that it is persistent in the environment or produced at high volumes with evidence of endocrine disruption activity in at least one species using intact animals.
115. US EPA 2010: Bifenthrin is among the group of 58 pesticide active ingredients receiving endocrine disrupter screening program test orders.

n) Mode of action

116. US EPA 2010: Bifenthrin is a Type I pyrethroid (i.e., it lacks a cyano group at the alpha carbon position of the alcohol moiety) neurotoxic pesticide. All pyrethroids act as axonic poisons, affecting both the peripheral and central nervous systems and share similar modes of action. Pyrethroids, including bifenthrin, stimulate repetitive action ain the nervous system by binding to voltage-gated sodium channels, prolonging the sodium ion permeability during the excitatory phase of the action potential.

o) Acceptable Exposure Levels

117. EU biocides AR 2010: The lowest NOAEL from all repeated dose studies including the 2 year mouse and rat studies stemmed from the 52 week dog study. The critical effects were clinical signs of neurotoxicity. On this basis a long term systemic limit value of 0.0075 mg/kg bw day was proposed considering oral absorption rate of 50% and an assessment factor of 100.
118. DAR 2010: The same study and value has been used as for biocides. In addition to the systemic limit value an external oral limit value (ADI) was derived on the same basis but not accounting for the reduced oral absorption rate, i.e. 2 times the internal value: 0.015 mg/kg bw day.
119. WHO 2012: An ADI was allocated on the basis of the NOAEL of 0 to 0.01 mg/kg/bw/day using a 100-fold safety factor. This result was supported by the same NOEL in the rat teratology study, although in the latter study gavage, rather than dietary administration, was used.

3.12 Environmental hazard assessment

p) Aquatic compartment (including sediment)

120. Bifenthrin is highly toxic to aquatic organisms (cf. Table 3). This finding is in line with US EPA 2010 suggesting high toxicity on an acute and chronic basis to freshwater fish and invertebrates. High toxicity to estuarine/marine fish and invertebrates on an acute basis is also reported.
121. The table presents a selection of listed values. Please refer to the original documents for more information.

Table 3. Toxicity reference values (data from EU biocides AR 2010)

Exposure scenario/Study type	Organism/Species	Endpoint	Toxicity value
Acute, 96 hours (h)	fish	Rainbow trout	LC50	0.1 µg/L
Chronic, 76 days (d) ELS, flow-through	Mammals	Rainbow trout	NOEC	0.012 µg/L
Chronic, 120d, flow	Birds	Fathead minnow	NOEC	0.040 µg/L

Exposure scenario/Study type		Organism/Species	Endpoint	Toxicity value
through				
Chronic, 21d, flow through	Invertebrates	*Daphnia magna*	NOEC	0.00095 µg/L
Chronic, 28d, flow through	Invertebrates	*Mysidopsis bahia*	NOEC	0.0012 µg/L
Acute 10d, spiked sediment	Sediment dwellers	*Chironimus riparius*	LC50 EC50 (growth)	<544 µg/Kg ww 170 µg/kg ww
Chronic, 28d, spiked water	Sediment dwellers	*Chironimus riparius*	NOEC	1647 µg/kg ww

q) Terrestrial compartment

122. US EPA 2010 classifies bifenthrin slightly toxic on an acute basis to birds, terrestrial phase amphibians and reptiles. Bifenthrin showed no adverse effects to reproduction at the highest concentration tested for birds (cf. Table 4).

Table 4: Toxicity reference values (source: EU biocides AR 2010)

Exposure scenario/Study type		Organism/Species	Endpoint	Toxicity value
Acute, 32-day dietary	Mammals	Rat	LD50	390 mg/kg
Chronic, teratology study	Mammals	Rabbit	NOAEL	25 mg a.s./kg bw/day
Acute toxicity	Birds	Bobwhite quail	LD50	1800 mg a.s./kg bw
Dietary toxicity	Birds	Bobwhite quail	LD50	4450 mg/kg diet
Dietary toxicity	Birds	Mallard duck	LD50	1280 mg/kg diet
Reproductive toxicity	Birds	Bobwhite quail	NOEC	>75 mg/kg diet
Chronic toxicity	Earthworms	*Eisenia sp.*	NOEC	2.13 mg/kg dw

r) Toxicity to pollinators

123. US EPA 2010 concludes that bifenthrin is highly toxic to terrestrial invertebrates, including beneficial insects such as honeybees (cf. Table 5).

Table 5: Toxicity values

Study type	Organism	Toxicity value	Reference
Acute oral toxicity	Bees	0.12 – 0.13 µg a.s./bee	EU biocides AR 2010
Acute contact toxicity	Bees	0.044-0.11 µg a.s. /bee	EU biocides AR 2010

3.13 Other information

124. The summary provided above is in agreement with the toxicological information provided in the footprint database and in the PAN pesticides database with the exception that both of these databases indicate that reproductive toxicity results are unclear or positive, respectively.

3.14 References

DAR (2006) Draft Assessment Report Bifenthrin, June 2006, available at http://dar.efsa.europa.eu/dar-web/provision
DAR (2010) BIFENTHRIN, Additional Report to the DAR, October 2010, available at http://dar.efsa.europa.eu/dar-web/provision
EFSA (2011) Conclusion on the peer review of the pesticide risk assessment of the active substance bifenthrin, EFSA Journal 9(5):2159 http://www.efsa.europa.eu/en/efsajournal/doc/2159.pdf
EU biocides AR (2010) Assessment Report Bifenthrin, Product-type 18, September 2010, available at http://ec.europa.eu/environment/biocides/annexi_and_ia.htm
EU Endocrine Disruption Database (2012) http://ec.europa.eu/environment/endocrine/strategy/short_en.htm, 2012-04-16
PPDB (2012) Pesticide Properties DataBase, University of Hertfordshire, http://sitem.herts.ac.uk/aeru/footprint/en/, 2012-04-18
US EPA (2010) Bifenthrin summary document, Registration Review: initial docket, June 2010. http://www.epa.gov/oppsrrd1/registration_review/bifenthrin/index.html
US EPA (2010b) Revised EFED Registration Review Problem Formulation for Bifenthrin December 22, available at: http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2010-0384-0033
Wegmann F. Cavin L, MacLeod M, Scheringer M, Hungerbühler K. (2009) Environmental Modeling & Software 24, 228-237
WHO (2012) WHO specifications and evaluations for public health pesticides- Bifenthrin, January http://www.who.int/whopes/quality/Bifenthrin_WHO_specs_eval_Jan_2012.pdf

4. Chlorpyriphos

CONCLUSIONS

Assessment of POP properties – comparison with the criteria of Annex D and other hazard indicators

4.1 Persistence

125. Chlorpyriphos degrades hydrolytically with DT50 values of maximum 63-73 days at pH 5 to 23 days at pH 8, all 25°C. Photolysis can contribute to the removal of the compound in water. The vapour pressure of 1.43 mPa (25°C) and the Henry law constant of $2.8x10^{-04}$ indicate that the substance is volatile, so volatilization might play a role in the overall dissipation process, but to which quantities remains unknown. Based on DT50 soil field values (14 days and 21 days, dissipation) and the DT50 water-sediment/whole system data (22 to 51 days) indicate that the persistence cut-off criteria according to Annex D 1 (b) (i) half-life: 6 months in soil or sediment, 2 months in water are not fulfilled. However, DT50 values in soil of 2 weeks to over 1 year were reported, depending on the soil type, climate, and other conditions. In addition the degradate TCP appears to be more persistent than chlorpyriphos in soil. Therefore the database is equivocal to conlude on the persistence criterion.

4.2 Bioaccumulation

126. It is concluded, that the B-criterion according to Annex D 1 (c) (i) for chlorpyriphos based on the BCF in fish is not fulfilled (experimental BCF value is 1,374). None of the estimated and experimental BCF values of chlorpyriphos and its metabolites is higher than 5,000; the estimated log Kow values of the metabolites are <5, the parent compound, chlorpyriphos gives an experimental log Kow value of 5 indicating a bioaccumulation potential. Also modelled data (B-score of 0.61) suggest high bioaccumulation. Bioaccumulation of this chemical may occur along the food chain supported by monitoring data that may indicate bioaccumulation. Therefore more information is needed to conlude on the B criterion of chlorpyriphos.

4.3 Long-range transport (LRT)

127. Monitoring data indicate the long-range transport of chlorpyriphos. The LRT screening criteria are fulfilled according to Annex D 1 (d) (i). Chlorpyriphos does not fulfill the Annex D 1 (d) (iii) criterion of half life in air >2 day.

4.4 Ecotoxicity (including pollinator toxicity)

128. Chlorpyriphos and its metabolite are moderately to very highly toxic to both fish and aquatic invertebrates. In addition chlorpyriphos is highly acutely toxic to honey bees. Therefore and in addition to the reported toxicity in laboratory animals (cf. section below) Annex D 1 (e) (ii) is fulfilled

4.5 Toxicity to human health (including mutagenicity, carcinogenicity and adverse effects on the reproductive, endocrine, immune or nervous systems)

129. Chlorpyriphos is classified by EU-GHS as acutely toxic category 3 with the oral route. The data identified in the evaluations are in agreement with this classification and also support that it is not skin or eye irritating or skin sensitizing when tested with the M&K and Buehler test.

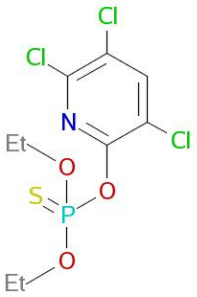
130. The available data do indicate no genotoxic or carcinogenic or reproductive toxicity potential. The substance is listed in the EU endocrine disrupter database within category 3a which means that there are data but no evidence of endocrine disruption.

131. Representing an organophosphate the critical effect is acetyl cholinesterase inhibition. Whereas EFSA and WHO propose external long term limit dose value of 0.01 mg/kg bw day engaging an assessment factor of 100 US EPA proposed a value of 0.0003 mg/kg bw day engaging an assessment factor of 1000.

4.6 Identity of the substance and physical and chemical properties

a) Name and other identifiers of the substance

Table 1: Substance identity

Common name:	Chlorpyriphos
IUPAC name:	O,O-diethyl-O-3,5,6-trichloro-2-pyridyl phosphorothioate
CAS number:	2921-88-2
Molecular weight:	350.6 [1]
Chemical structure:	

[1] EFSA review report 2005

b) Chemical group

132. Organophosphate

c) Physico-chemical properties

Table 2: Overview of selected physico-chemical properties

Property	Value	Remarks and Reference
Vapour pressure	$3.35 \cdot 10^{-3}$ Pa at 25° C (99.8 %) $1.43\ 10^{-3}$ Pa at 20ºC (99.8%)	EFAS review report 2005
Water solubility	1.05 mg/l at 20°	EFSA review report 2005
Partition coefficient n-octanol/water (log value)	4.7 (20°C, neutral pH) 5.0	EFSA review report 2005 PPDB 2012
Partition coefficient air/water (log value)	-3.9	Epi-Suite
Partition coefficient air/octanol (log value)	8.92	Epi-Suite (using log Kow 5)
Henry´s Law Constant	0.478 Pa x m^3 x mol^{-1}	EFAS review report 2005

4.7 Classification and labelling

d) Harmonised Classification according to CLP Regulation (EC) No 1272/2008 Annex VI

Category	Hazard-Phrase
Acute Tox. 3	H301 – Toxic if swallowed
Aquatic Acute 1	H400 - Very toxic to aquatic life.
Aquatic Chronic 1	H410 - Very toxic to aquatic life with long lasting effects
M = 10 000	

4.8 Environmental fate properties

e) Abiotic degradation

f) Hydrolysis

133. EFSA review report 2005: Hydrolytic degradation, half-lives:
134. pH 4.7-5, 25°C: 63-73 days
135. pH 6.9-7, 25°C: 16-35 days
136. pH 8.1, 25°C: 23 days
137. Major metabolites: TCP (3,5,6-trichloropyridinol) and O-ethyl-O-(3,5,6-trichloro-2-pyridoyl) phophorothioc acid ("phosphorothioate") both > 10% AR.

g) Phototransformation/photolysis

138. EFSA review report 2005: Photolysis half-life values as a function of latitude and season were determined: DT50: 15 days (mid-summer 20°N), 30 days (mid-summer 40°N) or 29200 days (mid-winter 60°N). Photostability in water (DT50) of 39.9 days were reported for natural river water under natural sunlight and 29.6 days (pH 7, natural sunlight).

h) Biodegradation

139. Experimental data have been reviewed and summarized previously by numerous international organizations like the EFSA, US-EPA.
140. Retrieved DT50 values for soil (lab and field) and water sediment are summarized in Table 3.

Table 3: Degradation data from EFSA review report 2005 and PPDB 2012

CAS No.	Chlorpyriphos 2921-88-2	TCP 6515-38-4	Chlorpyriphos oxon 5598-15-2	Reference
DT_{50} soil lab (days):	74	10-67	Not available	EFSA 2005
DT_{50} water sediment/whole system (days):	22-51	No data	Not available	EFSA 2005
DT_{50}soil field (days):	North America: 1-77 In literature: 1.3 – 120 Proposed value by the Rapporteur: **14**	France: 8 Spain: 96	Not available	EFSA 2005
DT_{50} soil lab (days):	76	38.5	Not available	PPDB 2012
DT_{50} water sediment/whole system (days):	36.5	19.6	Not available	PPDB 2012
DT_{50}soil field (days):	21.0	52	Not available	PPDB 2012

141. According to US EPA, 2006, the major route of dissipation of chlorpyriphos appears to be aerobic and anaerobic metabolism. Based on data, chlorpyriphos appears to degrade slowly in soil under both aerobic and anaerobic conditions. The vapour pressure of 1.43 mPa (25°C) and the Henry law constant of $2.8x10^{-04}$ indicate that the substance is volatile (ref. PPDB 2012), so volatilization might play

a role in the overall dissipation process in the field, but to which quantities remains unknown.

142. EXTOXNET (2012) states that the half-life of chlorpyrifos in soil is usually between 60 and 120 days, but can range from 2 weeks to over 1 year, depending on the soil type, climate, and other conditions.

i) Major metabolite: TCP

143. The environmental fate of the major chlorpyriphos metabolite, TCP, indicates that it is mobile in soils and persistent in soils when not exposed to light (US EPA 2006). The water solubility of TCP (80.9 mg/L, PPDB) is higher than the parent compound (1.05 mg/L, US EPA 2006). According to the PPDB database, field DT50 values of TCP (52 days) are higher than for the parent compound (21 days). This is in line with the conclusion of the US EPA (2006), which stated that "the degradate TCP appears to be more persistent than chlorpyriphos". Substantial amounts of TCP remained 365 days after application and it exhibits much lower soil/water partitioning than chlorpyriphos.

144. Due to the lower Koc values and the higher water solubility of the metabolite compared to the parent compound, the role of volatilization in the overall dissipation process might be higher than for chlorpyriphos. The Henry law constant of $3.5x10^{-04}$ indicates that the metabolite is volatile (PPBD). Therefore the uncertainty to estimate the persistency for TCP is higher than for the parent compound.

145. For TCP no P-scores are available. The DT50 soil field values [8 and 96 days (ref. to EFSA (2005)) and 52 days (ref. to PPDB)] are higher for the metabolite than for the parent compound. In contrast the DT50 water-sediment/whole system data [19.6 days (ref. to PBBD] indicate a lower DT50 value for the metabolite than for the parent.

j) Metabolite: Chloropyrifos oxon

146. The database for the metabolite chloropyrifos oxon is small according to US EPA RED 2009. No information on photodegradation for the metabolites of chlorpyriphos was available (US EPA (2006, 2009), HSBD, EFSA (2005).

4.9 Potential for long range transport

147. Information on photodegradation for chlorpyriphos in air is missing (ref. US EPA (2009)). Also no information on photodegradation for the metabolites of chlorpyriphos was available (US EPA (2006, 2009), HSBD, EFSA (2005).

148. Results of the phototransformation in air according to EPI Suite TM v4.0 (AOPWIN v 1.92) are based on a 12h day are summarised in Table 4.

Table 4: Phototransformation in air

Guideline / Test method	Molecule / radical	Rate constant for reaction with OH-radicals (k_{OH}) [cm^3 $molecule^{-1}$ sec^{-1}]	Half-life ($t_{1/2}$) [d]	OH-radical concentration (OH-radicals/cm^3)
AOPWIN	OH	91.6678 E-12	0.117	1.5×10^6

149. The OECD "Pov and LRTP Screening Tool"[10] has been developed with the aim of using multimedia models for estimating overall persistence (Pov) and long-range transport potential (LRTP) of organic chemicals at a screening level in the context of PBTs/POPs assessments. The input parameters for Kow, Kaw and half-life in air were taken from Tables 1 and 4, half-lives for water (from PBT profiler[11]: 4320 hours) and soil (499 hours according to PPDB 2012) were assumed.

150. The calculated CTD (characteristic travel distance) for chlorpyriphos is 369 km and is below the reference chemicals α-HCH, c-octaBDE and PeBD. The calculated TE value is below 0.001%. While according to the model chlorpyriphos can be assessed as a chemical with low potential for LRT, monitoring data (ref. to AMAP 2009, Hageman et. al 2006, Hermanson et al. 2005) from remote regions are present which indicate the LRT of chlorpyriphos. Several scientific studies have identified the presence of chlorpyrifos in Arctic seawater, snow, ice cores, estuarine sediments, marine fog, air,

[10] http://www.oecd.org/LongAbstract/0,3425,en_2649_34379_40718985_119669_1_1_1,00.html

[11] http://www.pbtprofiler.net/

and biota. Additionally, the Arctic Monitoring and Assessment Programme, implemented as part of the AEPS, reported that chlorpyrifos has also been identified in Alaska fish, surface water, ice and fog from the Bering and Chukchi Seas, air in the eastern Canadian archipelago, and subarctic and arctic lakes in Canada (AMAP 2009).

4.10 Bioaccumulation

151. No experimental bioconcentration data are available for the metabolites TCP; so Epi-Suite[12] was used to quickly estimate the bioaccumulation potential Results are presented in Table 5. For comparison also the parent compound chlorpyriphos has been included.

Table 5: Estimated log Kow and BCF values of chlorpyriphos, TCP and chlorpyriphos-oxon using Epi-Suite; Abbreviations: exp experimental values, est estimated values

	Chlorpyriphos	**TCP**	**Chloropyrifos-oxon**
CAS No.	2921-88-2	6515-38-4	5598-15-2
Log Kow	4.96 (exp)	3.01 (est), 3.21 (exp)	2.89 (est)
BCF	870.2 (est, log Kow 4.96)	60.95	5.6

152. EFSA review report 2005 supported a BCF value of 1,374 and a clearance time of 2-3 days. EFSA review report 2005 indicated in the section adsorption, distribution and metabolism in mammals, that the there is a low potential for accumulation. Chlorpyriphos was nearly completely exctreted within 48 hours, mainly via urine (approx. 80%).

153. According to US EPA RED 2006 chlorpyriphos has been detected in fish tissues. Chlorpyriphos residues in aquatic species may result in dietary exposure for aquatic birds and mammals feeding on aquatic organisms. Chlorpyriphos rapidly depurates from fish when aquatic chlorpyriphos exposures cease.

154. Inchem 2005 concluded that bioaccumulation of this chemical may occur along the food chain, for example in fish and algae.

155. Monitoring data may indicate bioaccumulation: A 2008 study showed levels of chlorpyrifos in fish (turbot, lake trout, and whitefish) of freshwater lakes in Denali, Gates of the Arctic, Noatak national parks in Alaska ranging from 0.041-0.1 ng/g wet weight (ww) (Ackermann 2008).

156. For TCP no experimental data were found in the indicated data sources. The low soil/water partitioning of TCP suggests that the bioaccumulation potential of TCP is probably low (US EPA RED 2006).

157. **PB-score**

158. Chlorpyriphos: P-score: 0.819, B-score: 0.609, PB-score: 1.428

4.11 Human health hazard assessment

k) Acute toxicity

159. EFSA review report 2005: The data presented coincide with the actual EU-GHS classification for acute oral toxicity category 3, no skin or eye irritation and no skin sensitization with the M&K as well as Buehler tests. However the data presented may allow in addition also acute dermal toxicity category 4 classification.

160. US EPA RED 2006: The data presented are in agreement with the EFSA review 2006.

l) Mutagenicity and Carcinogenicity

161. EFSA review report 2005: The available data do not indicate genotoxic or carcinogenic potential.

162. WHO 2009: The 1999 JMPR concluded that chlorpyriphos is unlikely to pose a carcinogenic risk to humans. Also a list of negative genotoxicity studies is presented.

m) Toxicity for reproduction

163. EFSA review report 2005: Decreased body weight and survival of pups as well as increased embryofoetotoxicity was reported in reproduction and developmental studies only at parental toxic dose levels.

n) Neurotoxicity

164. EFSA review report 2005: There is no evidence of delayed neurotoxicity in 13 weeks study in hens. The critical effect in the short term and long term studies was on the nervous system, in specific acetyl cholinesterase inhibition.

165. US EPA RED 2006: Plasma and red blood cell cholinesterase inhibition appears as the critical effect in repeated dose studies in rats and dogs and rat DNT study.

[12] http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm

o) Immunotoxicity

166. -

p) Endocrine disruption

167. Chlorpyriphos is listed in the EU endocrine disrupter database 2012within category 3a, which means that there are data but no evidence of endocrine effects from the database.

q) Mode of action

168. Representing an organophosphate the mode of action is acetyl cholinesterase inhibition.

169. US EPA RED 2006: Chlorpyriphos can cause cholinesterase inhibition in humans; that is, it can overstimulate the nervous system causing nausea, dizziness, confusion, and at very high exposures (e.g., accidents or major spills), respiratory paralysis and death.

r) Acceptable Exposure Levels

170. EFSA review report 2005: The critical effect in the short term and long term studies was on the nervous system, in specific acetyl cholinesterase inhibition. An external limit dose value (ADI) of 0.01 mg/kg bw day was derived from 2 year studies in rats, mice and dogs with the application of an assessment factor of 100. A systemic limit dose value (AOEL) of 0.01 mg/kg bw day was derived from the 90 day studies in rats, mice and dogs with the application of an assessment factor of 100.

171. US EPA RED 2006: A chronic external limit dose (Chronic RfD) of 0.0003 mg/kg bw day is proposed based on significant plasma and RBC cholinesterase inhibition at the LOAEL of 0.022 to 0.3 mg/kg bw day in long term dog and rat studies as well a DNT study. An assessment factor of 1000 has been applied due to increased susceptibility and sensitivity to chlorpyriphos among neonates when compared with adults, and for the qualitative increased susceptibility occurring at the high dose in the developmental neurotoxicity (DNT) study (cholinesterase inhibition in dams versus structural effects on developing brain of the offspring). In addition, recent data in the literature suggest that the inhibition of cholinesterase may not be essential for adverse effects on brain development. Further uncertainty arises from the lack of an offspring No Observed Adverse Effect Level (NOAEL) in the DNT. In that study, structural alterations in brain development were the toxicity endpoint of concern and were seen at the lowest dose tested. The registrant has submitted a rebuttal to the EPA review of the DNT study. This rebuttal is under review.

172. WHO 2009: The 1999 JMPR reaffirmed an ADI of 0-0.01 mg/kg bw. This was on the basis of a NOAEL of 1 mg/kg bw per day for inhibition of brain acetylcholinesterase activity in studies in rats, mice and dogs, using a 100-fold safety factor, and on a NOAEL of 0.1 mg/kg bw per day for inhibition of erythrocyte acetylcholinesterase activity in the study of human subjects exposed for nine days, using a 10-fold safety factor.

173. International limit values for worker protection (GESTIS-Database): For 14 countries limit values for eight hours between 0.1 and 0.2 mg/m^3 inhalable aerosol and for 5 countries short term limit values between 0.4 and 0.6 mg/m^3.

4.12 Environmental hazard assessment

s) Aquatic compartment (including sediment)

174. Aquatic toxicity studies indicate that chlorpyriphos is moderately to very highly toxic to both fish and aquatic invertebrates (ref. to US EPA RED 2006). In only one study, TCP was found to be much less toxic for invertebrates than chlorpyriphos. (ref. to Table 6).

Table 6: Aquatic toxicity data for chlorpyriphos and TCP

Substance	Habitate	Organism	Time Scale Endpoint	Toxicity value	Reference
Chlorpyriphos	Fish freshwater	Bluegill Sunfish	Acute LC50	1.8 ppb	US EPA RED 2006
Chlorpyriphos	Fish freshwater	mosquitofish	Acute LC50	595 ppb	US EPA RED 2006
Chlorpyriphos	Estuarine fish	-	Acute LC50	0.96 ppb	US EPA RED 2006
Chlorpyriphos	Estuarine fish	Atlantic silverside	NOAEC repr	0.28 ppb	US EPA RED 2006
Chlorpyriphos	Fish freshwater	Fathead minnow	NOAEC repr	0.57 ppb	US EPA RED 2006
Chlorpyriphos	Fish freshwater	-	NOEC 35 days ELS	0.00014 mg/L	EFSA 2005
TCP	Fish freshwater	-	NOEC 31 days	0.0808	EFSA 2005
Chlorpyriphos	Fresh water Invertebrate	*Daphnia magna*	Acute LC50	0.1 ppb	US EPA RED 2006
Chlorpyriphos	Estuarine water Invertebrate	Oyster embryo larvae	Acute LC50	2000 ppb	US EPA RED 2006
Chlorpyriphos	Estuarine water Invertebrate	Mysid shrimp	Acute LC50	**0.035 ppb**	US EPA RED 2006
Chlorpyriphos (technical)	Invertebrates		48h EC50	**0.0001 mg/L**	EFSA 2005
Chlorpyriphos	Fresh water Invertebrate	*Daphnia magna*	NOAEC repr	**0.04 ppb**	US EPA RED 2006
Chlorpyriphos	Fresh water Invertebrate	Stonefly *P. californica*	NOAEC repr	50 ppb	US EPA RED 2006
Chlorpyriphos	Estuarine water Invertebrate	Stonefly *P. californica*	NOAEC repr	50 ppb	US EPA RED 2006
Chlorpyriphos	Estuarine water Invertebrate	Mysid shrimp	NOAEC repr	**<0.0046 ppb**	US EPA RED 2006
Chlorpyriphos (technical)	Invertebrate	*M. bahia*	NOEC 35 days	**0.0046 mg/L**	EFSA 2005
Chlorpyriphos (technical)	Algae	-	72 h EC50	1.2 mg/L	EFSA 2005
Chlorpyriphos (technical)	Algae	-	NOECacute	0.1- 0.001 mg/L	EFSA 2005
Chlorpyriphos	Estuarine algae	*S. costatum*	Acute LC50	140-300 ppb	US EPA RED 2006

t) Terrestrial compartment

175. Lower toxicity values have been reported within the EFSA review report 2005. Terrestrial toxicity values used in the risk assessment are summarized in Table 7.

Table 7: Terrestrial toxicity values

Substance		Organism	Time Scale Endpoint	Toxicity value	Reference
Chlorpyriphos	Mammals	Mouse (female)	Acute LCD50	64 mg/kg bw	EFSA 2005
Chlorpyriphos	Mammals	Rat	NOAEL (2 generation study)	1 mg/kg bw/day	EFSA 2005
Chlorpyriphos	Birds	*Passer domesticus*	acute	122 mg as/kg	EFSA 2005
Chlorpyriphos	Birds	*Cotumix coturnix*	Acute LD50	13.3 mg/kg bw	EFSA 2005
Chlorpyriphos	Birds	SSD 95th percentile	Acute	6.9 mg/kg bw	EFSA 2005
Chlorpyriphos (formulated)	Birds	*Phasianus colchicus*	Acute LD50	8.41 mg/kg bw	EFSA 2005
Chlorpyriphos	Birds (dietary study)	Mallard duck	LC50	203 ppm	EFSA 2005
Chlorpyriphos	Birds	Mallard duck	NOEC repr.	25 ppm	EFSA 2005
Chlorpyriphos	Earthworms	-	14 day LC50	129 mg/kg	EFSA 2005
TCP	Earthworms	-	14 day LC50	9.8 mg/kg	EFSA 2005
Chlorpyriphos	Earthworms	-	55 day NOEC repr.	9.5 kg as/ha (12.7 mg as/kg)	EFSA 2005
TCP	Earthworms	-	55 day NOEC	4.6 mg/kg dry soil	EFSA 2005

u) Toxicity to pollinators

176. Chlorpyriphos is highly toxic to bees. The acute oral and contact LC 50 is according to EFSA review report 2005 0.25 µg/bee and 0.059 µg/bee, respectivley.

4.13 References

AMAP (2009) Arctic Monitoring and Assessment Programme Report (AMAP)—Arctic Pollution. 2009. Persistent Organic Pollutants p 25. available at: http://www.amap.no/

Ackerman (2008) Atmospherically deposited PBDEs, pesticides, PCBs, and PAHs in western U.S. national park fish: concentrations and consumption guidelines. Environ. Sci. Technol. 42(7):2334-41

CLP Regulation (2008) CLP Regulation (EC) No 1272/2008 Annex VI Table http://ec.europa.eu/enterprise/sectors/chemicals/documents/classification/

EFSA review report (2005) Review report for the active substance chlorpyriphos. SANCO/3059/99 - rev. 1.5, 3 June 2005, available at http://ec.europa.eu/sanco_pesticides/public/index.cfm?event=activesubstance.selection

Hageman, et al. 2006. Atmospheric Deposition of Current-Use and Historic-Use Pesticides in Snow at National Parks in the Western United States. Environ. Sci. Technol., 2006, 40 (10), pp 3174–3180. http://pubs.acs.org/doi/abs/10.1021/es060157c

HSDB (2012) http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB

Hermanson M. H., Isaksson E., Teixeira C., Muir D. C. G., Compher K. M., Li Y. F., Igarashi M., Kamiyama K., (2005) Environ. Sci. Technol. 39, 8163.

INCHEM (2005) http://www.inchem.org/documents/icsc/icsc/eics0851.htm

PPDB (2012) Pesticide Properties DataBase, University of Hertfordshire, http://sitem.herts.ac.uk/aeru/footprint/en/ 2012-04-18

US EPA RED (2006) Reregistration Eligibility Decision for Chlorpyrifos, available at http://www.epa.gov/oppsrrd1/REDs/factsheets/chlorpyrifos_fs.htm

US EPA (2009) Chlorpyrifos Final Work Plan, Registration Review September 2009, available at http://www.epa.gov/oppsrrd1/registration_review/chlorpyrifos/

WHO (2009) WHO specifications and evaluations for public health pesticides- chlorpyrifos, March 2009, available at http://www.who.int/whopes/quality/newspecif/en/

5. Cyfluthrin[13]

CONCLUSIONS

Assessment of POP properties – comparison with the criteria of Annex D and other hazard indicators

5.1 Persistence

177. Cyfluthrin is susceptible to photolytic degradation in aqueous media and soil. Results from biodegradation studies indicates moderate persistence ($DT50_{field}$ are in the range from 26 to 40 days). If metabolites are included a $DT50_{field}$ based on total residues of 26 to 116 days could be observed. In water/sediment systems cyfluthrin showed rapid degradation. The modelled P-score is 0.92 indicating high persistency. The modelled result of 259 days for Pov (overall persistency independent from environmental media) from the OECD tool indicates this as well. However the P-score and Pov are related to ultimate mineralization and not to a DT50 value. Therefore it can be concluded that based on the presented experimental information cyfluthrin does not meet the persistency criterion of Annex D 1 (b) (i).

5.2 Bioaccumulation

178. The log Kow of 6 indicate a potential of bioaccumulation, however the experimental derived BCF value in fish is 506 (with delayed elimination). The modelled B-score for cyfluthrin is 0.01 suggesting low bioaccumulation. Therefore cyfluthrin does not meet the bioaccumulation criterion of Annex D 1 (c) (i).

5.3 Long-range environmental transport (LRT)

179. Cyfluthrin has a calculated DT50 in air of 10 to 26 hours. Depending on the input parameters the results of the OECD multimedia fate model suggest a LRT potential below the reference POPs. But for target-oriented LRTP indicator (TE) the model limits for higher concern are exceeded. However the input value DT50 water is not derived from experimental findings and represents most likely an overestimation. The calculated DT50 in air is <2 days. Therefore it can be concluded that more information for cyfluthrin is needed to conclude on the Annex D 1 (d) criterion.

5.4 Ecotoxicity

180. Cyfluthrin is highly toxic to aquatic species and is classified according to EU-GHS as aquatic acute and chronic category 1. For terrestrial vertebrates cyfluthrin is highly to moderately toxic to mammals. No toxic effects to birds after acute exposure, but higher toxicity for reproductive effects were observed. Cyfluthrin is considered as non-toxic to earthworms. Based on the high ecotoxicity and toxicity to human health (see below) it is concluded that cyfluthrin meets Annex D 1 (e) (ii).

5.5 Toxicity to human health (including mutagenicity, carcinogenicity and adverse effects on the reproductive, endocrine, immune or nervous systems)

181. Cyfluthrin is classified by EU-GHS for acute toxicity category 2 for oral and 3 for respiratory exposure. The substances are within the EU-GHS system not irritant on skin or eye and are not skin sensitizing when tested with the Magnusson and Kligman method.

182. Sufficient studies are available to estimate the genotoxic, carcinogenic and reproductive toxicity potential. It was concluded that Cyfluthrin is neither genotoxic nor carcinogenic nor a reproductive toxin. It is not listed in the EU endocrine disrupter database.

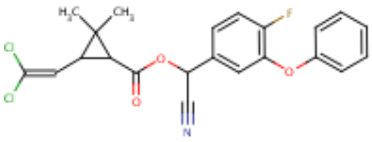
183. Cyfluthrin did not induce delayed neurotoxicity. It was concluded that for pyrethroids no adverse results are to be expected from developmental neurotoxicity studies. For risk assessment the critical effects are general behavioural disturbances and axonal degeneration in the CNS. The long term external oral limit values (ADI) in the latest evaluations available are in the range of 0.003 mg/kg bw day (EFSA) and 0.02 mg/kg bw day (WHO). Internal limit values of 0.002 mg/kg bw day and 0.000243 mg/kg bw day were proposed by EFSA for the oral and respiratory route, respectively.

[13] Cyfluthrin is an alternative to both endosulfan and DDT.

5.6 Identity of the substance and physical and chemical properties

a) Name and other identifiers of the substance

Table 1: Substance identity

Common name:	Cyfluthrin
IUPAC name:	(RS),-α-cyano-4-fluoro-3-phenoxybenzyl-(1RS, 3RS; 1RS, 3SR) -3-(2,2-dichlorovinyl)-2,2-dimethycyclopropanecarboxylate
CAS number:	68359-37-5 (unstated stereochemistry)
Molecular weight:	434.3
Chemical structure:	

EFSA final review report 2002: Cyfluthrin is a mixture of four diastereoisomers and the ratio of each of the diastereoisomers to their sum shall be:

Diastereoisomer I (1*R*,3*R*,I*R* + 1*S*,3*S*,I*S* = 1:1; cis): 23-27%
Diastereoisomer II (1*R*,3*R*,I*S* + 1*S*,3*S*,I*R* = 1:1; cis): 17-21%
Diastereoisomer III (1*R*,3*S*,I*R* + 1*S*,3*R*,I*S* = 1:1; trans): 32-36%
Diastereoisomer IV (1*R*,3*S*,I*S* + 1*R*,3*S*,I*R* = 1:1; trans): 21-25%

b) Chemical group

184. Pyrethroid

c) Physico-chemical properties

Table 2: Overview of selected physico-chemical properties

Property	Value			Remarks and Reference
Vapour pressure	Isomer I: $9.6 \cdot 10^{-7}$ Pa at 20 °C II: $1.4 \cdot 10^{-8}$ Pa at 20 °C III: $2.1 \cdot 10^{-8}$ Pa at 20 °C IV: $8.5 \cdot 10^{-8}$ Pa at 20 °C			EFSA review report 2002
Water solubility	Isomers I: II: III: IV:	pH 3, 20 °C 2.5 µg/l 2.1 µg/l 3.2 µg/l 4.3 µg/l	pH 7, 20 °C 2.2 µg/l 1.9 µg/l 2.2 µg/l 2.9 µg/l	EFSA review report 2002
Partition coefficient n-octanol/water (log value)	Isomers I and III: 6.0 at 22 oC Isomers II and IV: 5.9 at 22 oC			EFSA review report 2002
Partition coefficient air/water (log value)	-5.96			EPI Suite v 4.1 (KOAWIN v. 1.10)[14]
Partition coefficient air/octanol (log value)	-			-
Henry´s Law Constant	Isomers I: $1.9 \cdot 10^{-1}$ Pa·m³·mol^{-1} II: $3.2 \cdot 10^{-3}$ Pa·m³·mol^{-1} III: $4.2 \cdot 10^{-3}$ Pa·m³·mol^{-1} IV: $1.3 \cdot 10^{-2}$ Pa·m³·mol^{-1}			EFSA review report 2002

5.6 Classification and labelling

d) Harmonised Classification according to GHS

Regulation (EC) No 1272/2008 – 1nd amendment 2009: for cyfluthrin

Category	H-Phrase	
Acute Tox. 2	H300	Fatal if swallowed
Acute Tox. 3	H331	Toxic if inhaled
Aquatic Acute 1	H400	Very toxic to aquatic life
Aquatic Chronic 1	H410 (M= 1000)	Very toxic to aquatic life with long lasting effects

5.7 Environmental fate properties

e) Abiotic degradation

f) Hydrolysis

185. EFSA review report 2002 states fast degradation at 20°C and pH 9 with a DT50 value of <2 days. At all other pH values no or very slow degradation occurs.

186. US EPA RED 2010 reports that the primary routes of dissipation are aqueous and soil photolysis (cf. section below) and hydrolysis in alkaline media.

g) Phototransformation/photolysis

187. EFSA review report 2002 states that cyfluthrin photolytically degrades with a DT50 of 12 days (light source: medium-pressure mercury lamp). Under natural sunlight (August/September, Kansas, 38°49' North) the DT50 is <1 day. Main metabolites were FPBacid (4-fluoro-3-phenoxybenzoic acid), FPBald (3-phenoxy-4-fluoro-benzylaldehyde) and DCVA (3-(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropanecarboxylic acid (permethric acid)).

h) Biodegradation

188. According to US EPA RED 2010 the terrestrial field dissipation data confirm the pattern observed in the laboratory studies indicating that the chemical follows mixed routes of dissipation in the field. Laboratory studies showed that cyfluthrin is moderately persistent. These finding is in line with recorded DT50 values for cyfluthrin in Table 3.

[14] http://www.epa.gov/oppt/exposure/pubs/episuite.htm

Table 3: Biotic degradation of cyfluthrin and major metabolites

Study type	Results	Reference	Remarks
DT_{50} soil lab (days):	Cyfluthrin: 4-54 d (n=9, depending on soil type, moisture content and temperature, mean=51 d) (20°C) DCVA: 12-62 d DT50 FPBacid <DCVA	EFSA review report 2002	-
DT_{50} soil $_{field}$ (days):	Cyfluthrin: 26 – 40 (Germany, n=2) Total residues DT50: 26-116 d (USA, n=3)		-
DT_{50} water sediment/water (days):	Cyfluthrin: <1 d FPBacid: app. 10 d		Residues in sediment reached a maximum of 68% of applied after 6 hours, pH sediment 4.5/5 and 6.9/7, pH water 7.6 and 8.2
DT_{50} water sediment/whole system(days):	Cyfluthrin: <1 – 4 d		Apparently rapid degradation of cyfluthrin in sediment - more rapid than other pyrethroids.

5.8 Potential for long range transport

189. According to the EFSA review report 2002 the chemical lifetime in troposphere for cyfluthrin is 25.7 h (according to Atkinson, reaction with OH radicals, concentration: $5x10^5$ OH/cm^3)

190. Results of the Phototransformation in air according to EPI Suite TM v4.0 (AOPWIN v 1.92) are based on a 12h day are summarised in Table 4.

Table 4: Phototransformation in air

Guideline / Test method	Molecule / radical	Rate constant for reaction with OH-radicals (k_{OH}) [cm^3 $molecule^{-1}$ sec^{-1}]	Half-life ($t_{1/2}$) [h]	OH-radical concentration (OH-radicals/cm^3)
AOPWIN	OH	12.5011 E-12	10.3	1.5×10^6

191. The OECD "Pov and LRTP Screening Tool"[15] has been developed with the aim of using multimedia models for estimating overall persistence (Pov) and long-range transport potential (LRTP) of organic chemicals at a screening level in the context of PBTs/POPs assessments. The result for cyfluthrin is plotted against the reference chemicals α-HCH, c-octaBDE and PeBD. The criteria lines were not modified and take as proposed in the tool (Pov limit: 195 days, CTD limit: 5096 km, TE limit: 2.25%).

192. The input parameters for Kow and Kaw were taken from Table 2, half-lives for water and soil are listed in Table 5.

193. Table 5: Half-lives for air, water and soil (input parameters for the OECD Tool)

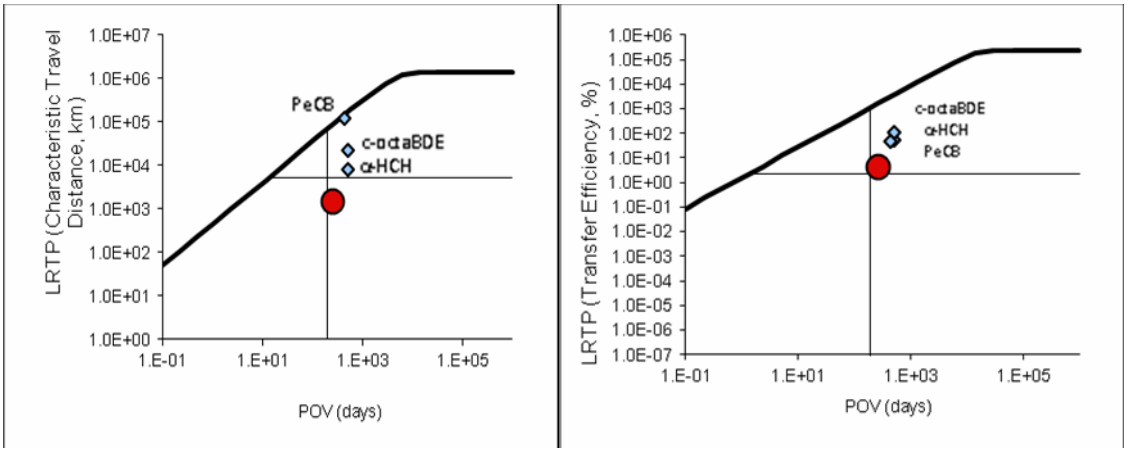
Half-Lives	Value (h)	Source
Water	4320	PBT profiler[16]
Soil (DT50 lab)	1224	Table 3

194. Input parameter of a DT50 air of 25.7 hours resulted in a calculated CTD (characteristic travel distance) for cyfluthrin of 1438 km and lies below the proposed limits for CTD and the results of α-HCH, c-octaBDE and PeBD. The calculated TE value is 4.1 %. Pov is 259 days. Therefore cyfluthrin can be assessed as a chemical with a potential for LRT lower than the reference POPs (see Figure 1).

[15] http://www.oecd.org/document/24/0,3343,en_2649_34379_45373336_1_1_1_1,00.html

[16] http://www.pbtprofiler.net/

Figure 1: Results from the OECD Tool (CTD and TE) for cyfluthrin (red point) and selected reference compounds (α-HCH, c-octaBDE, PeBD).



195. According to Wegmann et al. 2009 compounds that are less problematic from an environmental exposure point of view are in the bottom-left corner (low Pov, low LRT), while substances of environmental concern are found in the upper right region (high Pov, high LRT). In the TE plot cyfluthrin is in the upper right quadrant (though on the boundaries) indicating POP-like persistence and LRT potential.

5.9 Bioaccumulation

196. EFSA review report 2002 states a BCF in fish of 506 with a depuration half-life (CT50) of 9 days. HSDB 2012 lists an estimated BCF of 170 in aquatic organisms.

i) PB-score

197. Cyfluthrin has a P-score of 0.92 and a B-score of 0.01 resulting in an overall PB-score of 0.93.

5.10 Human health hazard assessment

j) Acute toxicity

198. EFSA review report 2002: The acute systemic LD50 estimates are in the range of GHS class 2 or 3. The substance is non irritant on skin and eye and is not sensitizing when tested with the Magnusson and Kligman method.

199. US EPA RED 2010: The acute oral toxicity of cyfluthrin ranges from Toxicity Category I to III, depending on the administration vehicle. Inhalation toxicity categories also varied by vehicle from Category II to III. Toxicity was low (Category IV) via the dermal route. Cyfluthrin is a slight eye (Category III) and dermal (Category IV) irritant, but neither is a dermal sensitizer.

200. WHO 2004: The hazards associated with cyfluthrin have been well characterized. The acute oral LD50 for rats varied from 16 to 1189 mg/kg body weight, depending on the vehicle used, showing that the formulating agent has a strong influence on the acute oral toxicity. Cyfluthrin is toxic by inhalation but acute toxicity by the dermal route is low. Cyfluthrin did not induce skin irritation in rabbits but case reports in humans have shown that local skin irritation can arise from exposure to cyfluthrin formulations. Cyfluthrin caused eye irritation in rabbits. It did not induce dermal sensitization in guinea pigs.

k) Mutagenicity and Carcinogenicty

201. EFSA review report 2002: There is no evidence for genotoxic or carcinogenic potential.

202. US EPA RED 2010: The toxicity profile was sufficient for characterization of potential carcinogenic, mutagenic, developmental, and reproductive effects in the most recent risk assessments. Cyfluthrin is classified as “not likely to be carcinogenic to humans.”

203. WHO 2004: Studies on mutagenicity in microbes, with or without metabolic activation, were consistently negative. Cyfluthrin did not induce micronuclei or dominant lethal mutations in mice. Cyfluthrin showed no potential for carcinogenicity.

l) Toxicity for reproduction

204. EFSA review report 2002: Reduced viability index and growth retardation of offspring, coarse tremors of pups during lactation as well as miscarriage and post-

implantation resorptions (rabbit), delayed ossification and decreased foetal weights (rat) were observed only at parental toxic doses.

205. US EPA RED 2010: The toxicity profile was sufficient for characterization of potential developmental and reproductive effects in the most recent risk assessments.

206. WHO 2004: In a 3-generation study and in two developmental toxicity studies in rats, no effects on reproductive functions were observed and cyfluthrin showed no evidence of teratogenicity or embryotoxicity.

m) Neurotoxicity

207. EFSA review report 2002: No evidence of delayed neurotoxicity in hens. For risk assessment the critical effects are general behavioural disturbances and axonal degeneration in the CNS.

208. US EPA registration review 2011: Based on the Agency's review of existing pyrethroid data, EPA has come to the conclusion that the development neurotoxicity study (DNT) is not a particularly sensitive study for comparing the sensitivity of young and adult animals to pyrethroids. EPA has recently determined that, as an alternative to the generation and submission of a new DNT study, pyrethroid registrants may instead choose to cite the six previously submitted DNT studies for pyrethroid pesticides. The Agency is also investigating the need for additional experimentation, specific to the mode of action and pharmacokinetic characteristics of pyrethroids, to evaluate the potential for increased susceptibility of young organisms.

n) Immunotoxicity

209. US EPA registration review 2011: The Agency anticipates requiring an immunotoxicity study.

o) Endocrine disruption

210. Cyfluthrin is not listed in the EU endocrine disrupter database.

p) Mode of action

211. US EPA RED 2010: Cyfluthrin is a Type II pyrethroid insecticide.

q) Acceptable Exposure Levels

212. EFSA review report 2002: A long term ADI of 0.003 mg/kg bw day is reported that was derived from a mouse study and application of an assessment factor of 100. A systemic inhalation AOEL of 0.000243 is reported that was derived from a 13 week inhalation study in rat and application of an assessment factor of 100. This is much lower compared to the systemic AOEL of 0.002 mg/kg bw day also using an assessment factor of 100.

213. US EPA RED 2010: In the most recent risk assessment, neurotoxic endpoints were chosen for all exposure scenarios, with the exception of the inhalation exposure which route-specific studies were used. The point of departure (POD) for the short-term inhalation exposure was chosen from the 28-day rat inhalation study and is based on decreased body weight. The POD for intermediate- and long-term inhalation exposure is based on decreased body weight and body weight gain observed in the 90-day inhalation study in rats. A dermal study is available, but was not used for endpoint selection because developmental effects were not evaluated in that study.

214. WHO 2004: Toxicological evaluations by the FAO/WHO JMPR and the FAO/WHO JECFA established an ADI for cyfluthrin of 0-0.02 mg/kg body weight, based on the depression of body weight gain in a long-term feeding study on rats.

215. International limit values for worker protection (GESTIS-Database): 8 hours and short term limit values between 0.01 to 0.1 mg/m^3 for Germany and Switzerland

5.11 Environmental hazard assessment

r) Aquatic compartment (including sediment)

216. US EPA RED 2010: For aquatic species, numerous aquatic studies have been submitted to the Agency. Cyfluthrin is classified as very highly toxic to aquatic organisms based on data for aquatic vertebrates and invertebrates. An acceptable toxicity study with green algae suggests that cyfluthrin has low toxicity to nonvascular aquatic plants. No vascular aquatic plant data has been submitted to the Agency. Toxicity reference values for aquatic species are listed in Table 5 (source: EFSA review report 2002).

Table 5: Toxicity reference values

Exposure scenario/Study type	Organism/Species		Time Scale Endpoint	Toxicity value	Reference
Acute, 96 hours (h)	Fish	Rainbow trout	LC50	0.00047 mg/L	EFSA review report 2002
Acute, 48 h	Fish	Rainbow trout	LC50	**0.00068 mg/L**	
Chronic, 307 days (d)	Fish	Fathead minnow	NOEC	0.040 µg/L	
Chronic, 58 d	Fish	Rainbow trout	NOEC	0.00014 mg/L	
Chronic, 21 d	Invertebrates	*Daphnia magna*	NOEC	0.00002 mg/L	
Acute 96 h	Algae	*Scenedesmus subspicatus*	EC50	>10 mg/L	
Chronic, 28 d	Sediment dwellers	*Chironimus riparius*	EC5	0.00011 mg/L	

s) Terrestrial compartment

217. US EPA RED 2010: For terrestrial species, cyfluthrin is practically nontoxic to birds, moderately toxic to mammals, and highly toxic to terrestrial invertebrates on an acute basis. Chronic effects were seen in rats at levels as low as 150 ppm (cf. Table 6 lists also toxicity for acute time scale for mammals) and at 250 ppm for birds. No terrestrial plant data have been submitted to the Agency. Table 6 presents a selection of listed values from EFSA review report 2002. Please refer to the original documents for more information. EFSA review report 2002 indicates high acute toxicity to mammals.

Table 6: Toxicity reference values (a.s….active substance, bw ….body weight)

Exposure scenario	Organism/Species		Time Scale Endpoint	Toxicity value	Reference
Acute	Mammals	Rat	LD50	16-155 mg/kg bw (depending on vehicle)	EFSA review report 2002
Acute toxicity	Birds	Bobwhite quail	LD50	>2000 mg/kg bw	
Acute toxicity	Birds	Canary	LD50	~ 100 mg/kg bw	
Dietary toxicity	Birds	Bobwhite quail	LD50	554 mg/kg bw/day	
Reproductive toxicity	Birds	Mallard duck	NOEL	250 ppm	
Acute toxicity	Earthworms	*Eisenia foetida*	LC50	>1000 mg/kg	
Chronic toxicity	Earthworms	*Eisenia foetida*	NOEC	>100 g a.s./ha	

5.12 Other Information

218. Toxicological information presented in the PAN –pesticides database and in the PPDB footprint database is largely consistent with the toxicological information summarized above.

5.13 References

EFSA review report (2002) Cyfluthrin, 6843/VI/97-final; 2 Dec. 2002, http://ec.europa.eu/food/plant/protection/evaluation/existactive/list1-29_en.pdf 2012-04-04

EU Endocrine Disruption Database (2012) http://ec.europa.eu/environment/endocrine/strategy/short_en.htm, 2012-04-16

HSDB (2012) Hazardous Substances Data Bank http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB 2012-04-16

US EPA RED (2010) Summary document registration review; EPA-HQ-OPP-2010-0684, available at http://www.epa.gov/pesticides/chemicalsearch 2012-04-04

US EPA registration review (2011): Cyfluthrin final work plan registration review, EPA-HQ-OPP-2010-0684 available at http://www.epa.gov/pesticides/chemicalsearch 2012-04-04

Wegmann F. Cavin L, MacLeod M, Scheringer M, Hungerbühler K. (2009) Environmental Modeling & Software 24, 228-237

WHO (2004) Specifications and evaluations for public health pesticides- **Cyfluthrin**, November 2004 http://www.who.int/whopes/quality/en/Cyfluthrin_spec_eval_WHO_Nov_2004.pdf 201204-016

6. Cypermethrin

CONCLUSIONS

Assessment of POP properties – comparison with the criteria of Annex D and other hazard indicators

6.1 Persistence

219. Cypermethrin is stable to hydrolysis at pH values below 7. Cypermehtrin degrades moderately fast in water/sediment systems indicating no persistency in the aquatic environment (also at pH values below 7). Field studies conducted on rice (with zeta-cypermethrin) show high persistence in aquatic sediments. Half-lives of cypermethrin in soil laboratory studies reach from 31 to 107 days, assuming persistency; field data from different locations show maximum half lives of 199 days (range <14 to 199, median 16 days). There are also findings that cypermethrin did not appear to persist in soil under field conditions. The modelled P-score for cypermethrin is 0.824, indicating persistency. Taking the higher measured half-lives in European soils as well as evidence from modelled information, it might be reasonable to conclude that cypermethrin meet the persistence criterion of Annex D 1 (b) (i).

6.2 Bioaccumulation

220. The log Kow of 5.3-5.6 and the experimental derived maximum BCF value of 1204 indicate a potential of bioaccumulation. The modelled B-score for cypermethrin is 0.28 suggesting moderate bioaccumulation. Based on the experimental and modelled evidence cypermethrin does not meet the bioaccumulation criterion of Annex D 1 (c) (i).

6.3 Long-range environmental transport (LRT)

221. Cypermethrin has a calculated half-life in air of 3.5 to 6 hours (< 2 days). Therefore it is unlikely that cypermethrin fulfils the Annex D 1 (d) (iii) criterion.

6.4 Ecotoxicity (including pollinator toxicity)

222. Cypermethrin is highly toxic to fish, algae and aquatic invertebrates; it is classified according to EU-GHS as toxic for aquatic life with acute and long lasting effects. In addition cypermethrin is highly acutely toxic to honey bees and other pollinators. It therefore fulfils in addition to the reported toxicity to human health (see below) Annex D 1 (e) (ii).

6.5 Toxicity to human health (including mutagenicity, carcinogenicity and adverse effects on the reproductive, endocrine, immune or nervous systems)

223. Cypermethrin possesses three chiral carbon atoms and is therefore a racemic mixture of 8 isomers (four cis and four trans-isomers).

224. The acute toxicity seems to depend on the racemic mixture, with cis:trans/40:60 being least toxic (rat LD50 = 1732 mg/kg bw in arachis oil). Actual EU-GHS classification is available for the 40:60 mixture as acute category 4 for the oral and respiratory route, but the LD50 for dermal exposure is above 2000 mg/kg bw. The 40:60 mixture is also classified for respiratory irritation (STOT SE3). No classification is required for skin or eye irritation or dermal sensitization (negative LLNA).

225. Cypermethrin is not classified for carcinogenicity, mutagenicity or reproductive toxicity according to the GHS system in the EU and comprehensive data and evaluations available support this conclusion. However according to US EPA it is classified as category C, possible human carcinogen.

226. Cypermethrin is listed in the EU endocrine disrupter database within category 2. This means that it is persistent or a HPVC chemical with at least some in vitro evidence of biological activity related to endocrine disruption. Specific data are available indicating that cypermethrin causes immunosuppression.

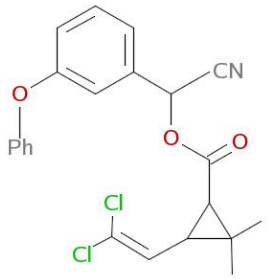
227. The substance did not induce delayed neurotoxicity. In rats the acute clinical signs typical for type II pyrethroids were observed (CS syndrome). In humans paresthesia and peripheral sensory phenomena and irritation of respiratory tract were observed. The developmental neurotoxicity study was considered acceptable and without indication of specific effects. Besides liver toxicity in terms of increased liver weight and inhibition of liver ATPase activity and induction of microsomal enzyme activities and some kidney effects the nervous system was the target organ critical for limit dose derivation. The latest internal long term limit dose (AEL) was proposed on the basis of the 2 year rat

study, application of a safety factor of 100 and consideration of 50% oral absorption rate = 0.025 mg/kg bw day.

6.6 Identity of the substance and physical and chemical properties

a) Name and other identifiers of the substance

Table 1: Substance identity

Common name:	CYPERMETHRIN
IUPAC name:	(RS)-α-cyano-3 phenoxybenzyl-(1RS)-cis, trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylate (4 isomer pairs : cis-1, cis-2, trans-3, trans-4)
CAS number:	52315-07-8
Molecular weight:	416.3
Chemical structure:	

b) Chemical group

228. Pyrethroid

c) Physico-chemical properties

Table 2: Overview of selected physico-chemical properties

Property	Value	Remarks and Reference
Vapour pressure	2.3 x 10^{-7} Pa at 20 °C	EFSA review report 2005
Water solubility	<9 µg/L at 20°C	EFSA review report 2005
Partition coefficient n-octanol/water (log value)	range of discrete isomer pairs : 5.3 to 5.6 at 25°C	EFSA review report 2005
Partition coefficient n-air/water (log value)	-4.765	EPI Suite v 4.1 (KOAWIN v. 1.10)[17]
Partition coefficient n-air/octanol (log value)	10.07	EPI Suite v 4.1 (KOAWIN v. 1.10)
Henry´s Law Constant	0.024 $Pa.m^3.mol^{-1}$ (20°C)	EFSA review report 2005

6.7 Classification and labelling

d) Harmonised Classification according to GHS

Regulation (EC) No 1272/2008: cypermethrin cis:trans/40:60 mixture:

Category	**Hazard-Phrase**
Acute Tox. 4	H302 Harmfull if swallowed
Acute Tox. 4	H332 Harmfull if inhaled
STOT SE 3	H335 May cause respiratory irritation
Aquatic Acute 1	H400 Very toxic to aquatic life
Aquatic Chronic 1	H410 Very toxic to aquatic life with long lasting effects

[17] http://www.epa.gov/oppt/exposure/pubs/episuite.htm

6.8 Environmental fate properties

e) Abiotic Degradation

f) Hydrolysis

229. EU biocides CAR 2010: Cypermethrin cis:trans/40:60 is degraded under alkaline condition. For pH under 7 and in acidic condition, cypermethrin cis:trans/40:60 is stable. The increase in temperature increase the degradation rate of cypermethrin cis:trans/40:60 at 12°C and pH 9, cypermethrine has a derived DT_{50} of 1.65 day.

230. PPDB 2012: Aqueous hydrolysis DT_{50} at 20°C and pH 7: 179 days: persistent

g) Phototransformation/photolysis

231. EU biocides CAR 2010: Light accelerates the degradation of cypermethrin cis:trans/40:60 on soil surface and in water. However data on distribution of radioactivity and DT50 for cis- and trans-isomers indicate that soil photolysis is a minor route of degradation of the active substance. Cypermethrin cis:trans/40:60 is degraded by photolysis in water. When irradiated the reported DT50 values are between 7 and 9 days.

h) Biodegradation

232. US EPA RED 2006: Cypermethrin is moderately persistent in the environment and degrades through a combination of biotic and abiotic mechanisms. In soil, under both aerobic and anaerobic conditions, cypermethrin biodegrades relatively slowly, with half-lives on the order of about 2 months (cf. Table 3 for additional DT50 values). In contrast, degradation is enhanced in water, with aerobic and anaerobic metabolism half-lives of 9 to 17 days. If released to surface water, cypermethrin partitions to sediment, where it may degrade more slowly.

233. In terrestrial field dissipation studies, cypermethrin did not appear to persist in soil, where the major routes of degradation are photolysis and aerobic biodegradation. Field studies conducted on rice (with zeta-cypermethrin) show high persistence in aquatic sediments. If cypermethrin is applied repeatedly, it is possible that the chemical can accumulate in the sediment in ever larger amounts, with slow biodegradation.

234. Retrieved DT_{50} values for soil (lab and field) and water sediment are summarized in Table 3. EU biocides CAR 2010 concluded that cypermethrin cis:trans/40:60 is biodegradable in a water/sediment compartment (as demonstrated also at lower pH values of 5.8 (water) and 6.1 (sediment)).

Table 3: Half-lives of cypermethrin in soil, water and sediment

Study type	Results	Reference	Comment
DT_{50} soil lab (days):	cis-isomers (3 soils) = 31-107, median = 88 trans-isomers (3 soils) = 13-58, median = 48	EFSA review report 2005	-
DT_{50} water (days):	3		-
DT_{50} water sediment/whole system (days):	17		-
DT_{50}soil field (days):	<14-199, median = 16, 19 measurements, France, Spain (2-year studies in 2 locations) , UK (3-year studies in 2 locations), Germany		-
DT_{50} soil lab (days):	60	PPDB 2012	Moderately persistent
DT_{50} water (days):	3	PPDB 2012	Fast
DT_{50} water sediment/whole system (days):	17	PPDB 2012	Moderately fast
DT_{50}soil field (days):	69	PPDB 2012	Moderately persistent

6.9 Potential for long range transport

235. EU biocides CAR 2010 states that photolysis in air was investigated by the mean of the EPIWIN AOP model. EPIWIN AOP v1.91 gives an indirect photolysis rate constant of 21.4274 x 10^{-12} cm^3/$molecule^{-sec}$; half-life = 0.499 days (12-hr day ; 1.5 x 10^6 OH/cm^3) or 5.9 hours. The EFSA review report 2005 lists an estimated DT50 of 3.47 hours for photooxidation of cypermethrin in air.

236. As the active substance has a short half life in air, it can be expected that the potential for LRT is low.

6.10 Bioaccumulation

EU biocides CAR 2010: Cypermethrin cis:trans/40:60 tends to bioaccumulate in water organism with a typical bioaccumulation factor (fish) of 374.4 (±45.35) and a depuration rate of 0.00158 l/h. The value of the BCF compared to the relatively low depuration rate could offer an explanation for the high toxicity of cypermethrin cis:trans/40:60 in aquatic organisms. EFSA REVIEW REPORT 2005: Bioaccumulation fish: *Salmo gairdneri* BCF: 1204

i) PB-score

237. Cypermethrin has a P-score of 0.82 and a B-score of 0.28 resulting in an overall B-score of 1.11.

6.11 Human health hazard assessment

238. EU biocides CAR 2010: Cypermethrin possesses three chiral carbon atoms and is therefore a racemic mixture of 8 isomers (four cis and 4 trans-isomers). The technical products commonly available contain more than 92% cypermethrin and the ratio cis- to trans-isomers varies from 48/52 to 40/60. A R configuration at the cyclopropane C-1 position is essential for neurotoxicity; the corresponding 1-S enantiomer is non-toxic. The configuration of the alpha-cyano group also influences toxicity: alpha S configuration of the alpha-cyano carbon is a potent mammalian toxicant, whereas the alpha-R enantiomers are essentially non-toxic. Thus, the active components of cypermethrin are 1R-cis-alpha-S and 1R-trans-alpha-S, e.g. approximately 25% of the mixture.

j) Acute toxicity

239. EU biocides CAR 2010: The acute toxicity seems to depend on the racemic mixture, with cis:trans/37:63 beeing most toxic by the oral route (rat LD 50 =250 mg/kg bw in corn oil) and cis:trans/40:60 being least toxic (rat LD50 = 1732 mg/kg bw in arachis oil). Comparable acute toxicity was observed by the respiratory route but the dermal LD was above 2000 mg/kg bw. Actual EU-GHS classification is available for the 40:60 mixture as acute category 4 for the oral and respiratory route. In addition EU-GHS classification is harmonised for specific target organ toxicity single exposure, category 3 – may cause respiratory irritation. In humans paresthesia and peripheral sensory phenomena and irritation of respiratory tract were observed. It was slightly irritating to rabbit skin and eye but does not require classification. The 40:60 mixture was not dermally sensitizing in the local lymph node assay in mice.

240. EFSA review report 2005: The data provided are consistent with those presented in the EU biocides CAR 2010.

241. US EPA RED 2006: Technical grade cypermethrin has moderate acute toxicity via the dermal and inhalation routes (Category III & IV), and is not a skin sensitizer. It is more toxic via the oral route (Category II).

k) Mutagenicity and Carcinogenicity

242. EU biocides CAR 2010: Standard genotoxicity assays with the 40:60 mixture were negative in in vitro bacterial and mammalian cell systems and also in vivo with the micronucleus test. Open literature provides some inconsistent evidence of genotoxicity in vitro as well as in vivo. However the global weight of evidence suggests that cypermethrin 40:60 should not be considered as gentoxic and no classification is proposed. Cypermethrin 40:60 was also tested in a combined chronic /carcinogenicity study in the rat and overall results were negative.

243. EFSA review report 2005: The data provided are consistent with those presented in the EU biocides CAR 2010.

244. US EPA RED 2006: Cypermethrin is classified in category C as possible human carcinogen. No quantification is required.

l) Toxicity for reproduction

245. EU biocides CAR 2010: Cypermethrin 40:60 tested within teratogenicity studies with rats and rabbits did not show adverse effects upon the progress and outcome of pregnancy. Also a three generation study with the 40:60 mixture did not negatively affect the reproduction parameters or survival of the offspring. Also taking into consideration the available open literature it was concluded that there is no evidence giving rise to concern for an additional risk for the newborn or young humans that should trigger further investigations.
246. EFSA review report 2005: The data provided are consistent with those presented in the EU biocides CAR 2010.
247. US EPA RED 2006: The toxicology database for cypermethrin is complete and there are no data gaps. The scientific quality is relatively high and the toxicity profile of cypermethrin can be characterized for all effects, including potential developmental, reproductive and neurotoxic effects. The data provided no indication of increased susceptibility of rats or rabbits to in utero and/or postnatal exposure.

m) Neurotoxicity

248. EU biocides CAR 2010: In adult laying hens the 40:60 mixture did not produce immediate or delayed signs of poisoning, nor any histopathological lesions in the nervous system. However in rats the acute clinical signs typical for type II pyrethroids were observed (CS syndrome). Besides liver toxicity in terms of increased liver weight and inhibition of liver ATPas activity and induction fo microsomal enzyme activities and some kidney effects the nervous system was the target organ critical for limit dose derivation. In humans paresthesia and peripheral sensory phenomena and irritation of respiratory tract were observed.
249. EFSA review report 2005: The data provided are consistent with those presented in the EU biocides CAR 2010.
250. US EPA RED 2006: Cypermethrin is a known neurotoxicant. It is a member of the pyrethroid class of insecticides, which are known to induce clinical signs of neurotoxicity in mammals, but do not generally induce neuropathologic lesions. For cypermethrin, neuromuscular effects (i.e. gait abnormalities, tremors, reduced motor activity, changes in FOB parameters and convulsions) occurred across species, sexes and routes of administration. These clinical signs occurred following an acute exposure and appeared to be transient in nature. Effects occurred mainly in oral studies in the dog and the rat, but similar signs were also observed in an inhalation study. Effects were not observed in dermal studies in either rats (zeta-cypermethrin) or rabbits (cypermethrin: nonabraded animals; abraded animals did exhibit decreases in activity). The DNT study has now been submitted, reviewed, and found to be acceptable. The Agency has determined that the FQPA safety factor should be reduced to 1X, since there are no residual uncertainties for pre- and/or post-natal toxicity. In addition, EPA has concluded that there is no need to change any previously-selected endpoints based on the submitted DNT, and that and the dietary (food and drinking water) and non-dietary exposure assessments are protective of potential exposures to infants and children.

n) Immunotoxicity

251. EU biocides CAR 2010: Cypermethrin cis:trans/40:60 causes immunosuppression: both the humoral and cell-mediated immune response are impaired by cypermethrin.

o) Endocrine disruption

252. EU biocides CAR 2010: The estrogenic potential of cypermethrin cis:trans/40:60 based on ER-mediated mechanisms remains equivocal. Contradictory results were revealed in different studies. In summary, the estrogenic and antiandrogenic effect of cypermethrin cis:trans/40:60 (and pyrethroids in general) depend on the assays or cells used. Results indicate that data obtained with high concentrations (> 10 ìM) should be interpreted carefully (solubility of test chemical, cell toxicity). Possibly, cypermethrin cis:trans/40:60 is an estrogen-like chemical that might act through signalling pathways other than direct ER binding, and as such, might function as an endocrine modulator. However, at present no definite conclusions can be drawn.
253. Cypermethrin is listed within category 2 of the EU endocrine disrupter database

2012, which means that it is persistent or an HPVC with at least some in vitro evidence of biological activity related to endocrine disruption.

254. US EPA RED 2006: The available database provides no evidence that cypermethrin induces endocrine disruption.

p) Mode of action

255. EU biocides CAR 2010: The clinical signs observed are characteristic for the acute poisoning with a type II pyrethroid: choreoathetosis accompanied by salivation (CS syndrome). In the rat, cypermethrin cis:trans/40:60 also produces epileptic activity during repeated administration. The neurotoxic effect of cypermethrin cis:trans/40:60on peripheral nerves (axons, endoneurium) was highly correlated with exposure time. Cypermethrin cis:trans/40:60 exerts its toxicity by opening the voltage-gated sodium channel slowly for extended times, leading to a prolonged sodium current in the target neurons. Furthermore, the decrease in the Na+, K+-ATPase pump activity is involved in the paroxysmal epileptic activity induced by cypermethrin cis:trans/40:60. Cypermethrin cis:trans/40:60 also inhibits GABAA receptors.

256. US EPA RED 2006: It is likely that the toxic action of pyrethroids is primarily due to their blocking action on some aspect of the synaptic function of the nerve axon.

q) Acceptable Exposure Levels

257. EU biocides CAR 2010: The relevant critical endpoints of cypermethrin cis:trans/40:60 in the toxicological studies are identified as the effect on the central nervous system, characterised by clinical signs (CS syndrome) and peripheral nerve damage; a decrease in delayed type hypersensitivity; and the effect on the liver, characterised by increase in organ weight associated with increased microsomal enzyme activity. The internal long term limit dose value (AEL) was derived from the 2 year rat study by application of a safety factor of 100 and consideration of 50% oral absorption rate = 0.025 mg/kg bw day.

258. EFSA review report 2005: An external long term limit value is provided (ADI) derived from the same 2 year rat study and the application of an assessment factor of 100 (but no correction for oral absorption) as 0.05 mg/kg bw day. An internal medium term limit dose value of 0.06 mg/kg bw day is provided on the basis of the 90 day study, an assessment factor of 100 and correction for oral absorption by 50%.

6.12 Environmental hazard assessment

r) Aquatic compartment (including sediment)

259. A compilation of results from aquatic toxicity tests is displayed in Table 4.

Table 4: Toxicity reference values for the aquatic compartment

Exposure scenario/Study type	Organism	TimeScale Endpoint	Toxicity value	Reference
Acute (96 hours (h))	Fish	LC50	2,8 µg/L	EFSA review report 2005
Chronic (34 days (d))	Fish	NOEC	0.03 µg/L	
Acute (48h)	Invertebrates	EC50	0.3 µg/L	
Chronic (21d)	Invertebrates	NOEC	0.04 µg/L	
Acute	Algae	EC50	>100 µg/L	
Mesocosm (102d)	Aquatic invertebrates and algae	EAC (ecologically acceptable concentration)	0.05 µg/L	
Acute (10d)	Benthic amphipod	LC50	3.6 µg /kg sediment	US EPA RED 2006
Acute (10d)	benthic amphipod	LC50	0.00257 µg/L pore water	
Acute(96h)	Estuarine/ Marine Invertebrates	LC50	0.00475 µg/L	
Chronic (28d)	Estuarine/ Marine Invertebrates	NOAEC	0.000781 µg/L	

s) Terrestrial compartment

260. A compilation of results from terrestrial toxicity tests is displayed in Table 5.

Table 5: Toxicity reference values for the terrestrial compartment (source: EFSA review report 2005)

Exposure scenario/Study type	Organism	Time Scale Endpoint	Toxicity value
Acute oral	Rat	Acute LD50	287mg/kg
Chronic dietary	Rat	LD50 (long term) (2-gen.)	100 mg/kg food
Acute oral	Bird: *Anas platyrhynchos*	Acute LD50	>1000 mg/kg
Acute dietary	Bird: *Colinus virginianus*	Dietary LD50	>1376 mg/kg bw/d
Chronic dietary (Reproduction)	Bird: *Colinus virginianus*	NOEC	92 mg/kg bw/d
Acute	Earthworms	LC50	>100 mg/kg
Chronic	Earthworms	NOEC	> 100 g/ha

261. US EPA RED 2006 states that chronic, dietary-based risk quotients (RQs) for birds are all below the Level of concern (LOC) for chronic risk (LOC 1). It was not possible to calculate a chronic dose-based RQ for birds because there were no acceptable dose-based toxicity values for birds available. For mammals, chronic, dose-based RQs range from <0.1 to 9.3 (15 g mammals feeding on short grass in cotton), exceeding the chronic LOC (1) for most scenarios. The chronic dietary-based RQ (1.1) exceeded the chronic LOC (1) for mammals feeding on short grass in cotton. Cypermethrin exposure can present acute toxic risk to earthworms

t) Toxicity to pollinators

262. EFSA review report 2005: Acute oral toxicity: 0.035 µg/bee; Acute contact toxicity: 0.020 µg/bee

263. US EPA RED 2006: Cypermethrin exposure can present acute toxicity to beneficial non-target insects, such as honey bees.

6.13 Other information

264. No further critical toxicological information is provided in the WHO 2012 report.

265. Toxicological information presented in the PAN –pesticides database and in the footprint database is largely consistent with the toxicological information summarized above.

266. EFSA concludes that member states must pay particular attention to the protection of aquatic organisms, bees and non-target arthropods. Conditions of authorisation should include risk mitigation measures, where appropriate.

6.14 References

EFSA review report (2005) Cypermethrin SANCO/4333/2000 final; 15 February 2005. http://ec.europa.eu/food/plant/protection/evaluation/existactive/list_cypermethrin.pdf

EU biocides CAR (2010) Competent Authority Report Cypermethrin, Product-type 8 (Wood preservative), March 2010, available at http://ec.europa.eu/environment/biocides/annexi_and_ia.htm, 2012-03-26

EU Endocrine Disruption Database (2012) http://ec.europa.eu/environment/endocrine/strategy/short_en.htm, 2012-04-16

PPDB (2012) Pesticide Properties Database: Cypermethrin http://sitem.herts.ac.uk/aeru/footprint/en/index.htm

US EPA RED (2006) Cypermethrin, EPA OPP-2005-0293, June 14, 2006. Cypermethrin, EPA OPP-2005-0293

7. Deltamethrin[18]

CONCLUSIONS

Assessment of POP properties – comparison with the criteria of Annex D and other hazard indicators

7.1 Persistence

267. Deltamethrin is stable to hydrolysis at pH 5 to 7. It is degraded fast at pH 9 (2.5 days) and pH 8 (DT50: 31 days) Photolysis is not considered an important removal process. In soil deltamethrin is degraded at a relatively fast to moderate rate and the substance is not expected to accumulate in soil. In water sediment studies, deltamethrin will rapidly partition to the sediment, to suspended organic matter and to biota. In water/sediment systems, the degradation DT50 was estimated to 45 and 141 days in two different systems at 20°C (whole system) and the dissipation DT50 in sediment to 55 and 133 days at 20°C. However the pH in the aqueous phase was high enough for hydrolysis. The modelled P-score for deltamethrin is 0.745, indicating persistency. Also findings suggesting high persistency of deltamethrin were reported: Deltamethrin has the potential to persist in aquatic environments, where it may partition to sediment (DT50 26-120 days in aerobic aquatic metabolism study, DT50 32-36 days in anaerobic soil metabolism). Deltamethrin appears to be moderately to highly persistent in terrestrial environments (terrestrial field dissipation 14 to 231 days). Therefore it can be concluded that experimental degradation data in soil may exceed the threshold of 180 days as specified in Annex D 1 (b) (i). Experimental data on persistence in water at pH≤7 were not assessed. Also modelled information suggests high persistency.

7.2 Bioaccumulation

268. Concerning the log Kow values of 4.6 and 6.2 are reported that indicate a potential of bioaccumulation. The experimental derived BCF value in fish is 1400. Bioaccumulation of deltamethrin in sediment dwellers was also observed (BAF of up to 305).The modelled B-score for deltamethrin is 0.129 not indicating a high bioaccumulation potential. Therefore it is likely that deltamethrin does not meet the bioaccumulation criterion of Annex D 1 (c) (i).

7.3 Long-range transport (LRT)

269. Deltamethrin has a calculated half-life in air of 16 hours (<2 days) indicating moderately fast degradation in air. Therefore it is unlikely that deltamethrin fulfils the Annex D 1 (d) (iii) criterion.

7.4 Ecotoxicity (including pollinator toxicity)

270. Deltamethrin is highly toxic to fish and arthropods (including daphnids and chironomids, bees and other terrestrial insects). It is classified according to EU-GHS as very toxic to aquatic life with acute and long lasting effects. Based on its high aquatic toxicity and toxicity to humans Annex D 1 (e) (ii) is fulfilled.

7.5 Toxicity to human health (including mutagenicity, carcinogenicity and adverse effects on the reproductive, endocrine, immune or nervous systems)

271. Deltamethrin was classified within the EU GHS system for acute toxicity category 3 for the oral and respiratory route. It was not irritating and not sensitizing when tested with the M&K and Buehler method.

272. Deltamethrin was not genotoxic within the standard in vitro test battery and the rat and mouse studies did not indicate evidence for carcinogenicity according to the European evaluations. IARC concluded that deltamethrin is not classifiable as to its carcinogenicity to humans (group 3). The available data indicated that developmental or reproductive effects were only observed at parentally toxic doses and no respective classification is proposed.

273. Deltamethrin is listed within category 1, which means that it is persistent in the environment or produced at high volumes with evidence of endocrine disruption activity in at least one species using intact animals. US EPA indicated that a new immunotoxicity study is required.

274. Representing a type II pyrethroid the critical effect is neurotoxicity. No delayed neurotoxicity study was required. Within acute and subchronic neurotoxicity studies clinical signs of neurotoxicity

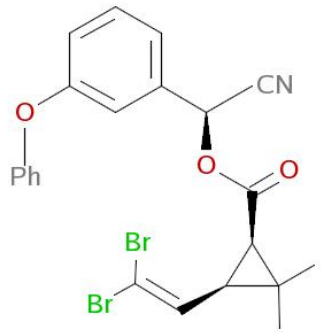
[18] Deltamethrin is an alternative to both endosulfan and DDT.

were observed, with the subchronic studies also in terms of alternations in the FOB. In higher doses also mortalities and reduced body weight gain were observed. Within a developmental neurotoxicity study adverse effects were only observed at parentally toxic doses. The clinical neurotoxicity effects in the 90 day and the 1-year dog studies were the basis for the derivation of a systemic long term limit value of 0.0075 mg/kg BW day. An assessment factor of 100 and an oral absorption rate of 75% was taken into consideration.

7.6 Identity of the substance and physical and chemical properties

a) Name and other identifiers of the substance

Table 1: Substance identity

Common name:	Deltamethirn
IUPAC name:	(S)-α-cyano-3-phenoxybenzyl (1R,3R)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate
CAS number:	52918-63-5
Molecular weight:	505.2
Chemical structure:	

b) Chemical group

275. Pyrethroid

c) Physico-chemical properties

Table 2: Overview of selected physico-chemical properties

Property	Value	Remarks and Reference
Vapour pressure at 25°C (mPa)	0.0000124	PPDB 2012
Water solubility at 20°C (mg/l)	0.0002	PPDB 2012
Partition coefficient n-octanol/water (log value, pH 7, 20°C)	4.6	PPDB 2012
Partition coefficient n-octanol/water (log value)	6.2	HSDB 2012
Partition coefficient air/water (log value)	-3,69	EPI Suite v 4.0[19]
Partition coefficient air/octanol (log value)	8.2	EPI Suite v 4.0
Henry´s Law Constant at 25°C ($Pa.m^3.mol^{-1}$)	3.10×10^{-02}	PPDB 2012

7.7 Classification and labelling

d) Harmonised Classification according to GHS

Regulation (EC) No 1272/2008 – 1nd amendment 2009

[19] http://www.epa.gov/oppt/exposure/pubs/episuite.htm

Category	Hazard-Phrase
Acute Tox. 3 *	H331 Toxic if inhaled.
Acute Tox. 3 *	H301 Toxic if swallowed.
Aquatic Acute 1	H400 Very toxic to aquatic life.
Aquatic Chronic 1	H410 Very toxic to aquatic life with long lasting effects.

7.8 Environmental fate properties

e) Abiotic degradation

f) Hydrolysis

276. EU biocides AR 2011: The hydrolysis of deltamethrin was shown to be insignificant at pH 5 and 7. At pH 9, however, hydrolysis was significant with a half-life of 2.5 days (25°C). At pH 8, the DT50 was 31 days (23°C).
277. PPDB 2012: Aqueous hydrolysis DT50 (days) at 20°C and pH 7: stable (pH sensitive: Stable pH 5 to pH 7, DT50 31 days at pH 8, 2.5 days at pH 9, 25°C)

g) Phototransformation/photolysis

278. EU biocides AR 2011: Direct photochemical reactions do not occur at a rate that makes this a significant route of degradation of deltamethrin under natural conditions in water. In soil, direct and indirect photochemical reactions may contribute to the degradation of deltamethrin, but other routes of transformation account for the major loss of parent compound.
279. PPDB 2012: Aqueous photolysis DT50 (days) at pH 7: 48 days: stable

h) Biodegradation

280. EU biocides AR 2011: Deltamethrin was not readily biodegradable in laboratory tests. In aquatic environments, deltamethrin will very rapidly partition to the sediment, to suspended organic matter and to biota. In water/sediment systems, the degradation DT50 was estimated to 45 and 141 days in two different systems at 20°C and the dissipation DT50 in sediment to 55 and 133 days at 20°C. The pH values of the aqueous phase of these systems were 8.0 to 9.1 and hydrolysis may have contributed to the degradation observed. So it cannot be excluded that the rate of degradation would be slower in more acidic/neutral systems. PH of the sediments was lower (7.1/7.5). The difference in degradation rate between the two systems probably reflects difference in amount of fine-textured material and amount of organic matter. $DT50_{soil}$ from DAR 2002 are displayed in Table 3. EU biocides AR 2011 concluded that hydrolysis was probably an insignificant route of degradation in the soils. The DT50 values of the major metabolite of deltamethrin, Br2CA (decamethrinic acid), has been calculated to 0.7-11.6 days in three soils with a geometric mean of 2.0 days (normalised to 25°C and field capacity).
281. US EPA summary 2010: Deltamethrin has the potential to persist in aquatic environments, where it may partition to sediment (DT50 26-120 days in aerobic aquatic metabolism study, anaerobic soil metabolism 32-36 days). Deltamethrin appears to be moderately to highly persistent in terrestrial environments (terrestrial field dissipation 14 to 231 days). The metabolite Br2CA (observed in multiple studies) appears to persist much more than former compounds. It was observed in laboratory studies and in the field.

Table 3: DT50 values of deltamethrin in soil, water and sediment

Degradation 50%	days	Reference	Comment
DT_{50} soil lab	20-35 (3 studies, median 28), all 25°C	DAR 2002	main metabolite soil Br2CA (2,2-dimethylcyclopropanecarboxylic acid)
DT_{50}soil field	21	PPDB 2012	Non Persistent
DT_{50} water sediment/water	17	PPDB 2012	Slow
DT_{50} water sediment/whole system	65	PPDB 2012	Moderately fast
DT_{50}soil field	2-3 weeks US (Minnesota), both cropped and bare soil 1-4 weeks, 4 bare soils in Germany	DAR 2002	-

DT_{50} sediment	55 and 133 (20°C)	EU biocides AR 2011	2 experimental systems with different carbon content
DT_{50} water sediment/whole system	45 and 141 (20°C)	EU biocides AR 2011	60% of the applied radioactivity was found in the sediments immediately after application

282. EU biocides AR 2011: Due to its low vapour pressure, deltamethrin is not expected to volatilise to air from plants and soil at significant levels, which was confirmed in a wind tunnel study. However, the calculated Henry's law constant is 1.252×10^{-3} $Pa.m^3.mol^{-1}$, indicating that deltamethrin has a tendency to volatilise from water. If present in air, the data on indirect photooxidation indicate degradation when reacting with hydroxyl radicals with a DT50 of 16 hours (reference to Atkinson, AOPWIN-model). Based on the moderate degradation rate in air no multimedia fate modelling was performed.

7.10 Bioaccumulation

283. DAR, 2002: Deltamethrin showed a high potential for bioaccumulation with a laboratory BCF (*Lepomis macrochirus*) of 1400 (whole fish). Bioconcentration in fish at this level was confirmed in a microcosm study. Bioconcentration (of total ^{14}C) in chironomids from spiked sediments has also been shown. Micro/mesocosm studies also showed a significant and rapid uptake in plants. Thus, at continuous or repeated exposure to deltamethrin, there is a clear risk for bioaccumulation in biota. BCF/BAF values are 1400 (fish) as total ^{14}C. Major part of ^{14}C consisted of deltamethrin; 213-305 (chironomidae, sediment-exposed, 24 h value, based on total ^{14}C), 145-303 (chironomidae, overlaying water, 24 hour value, based on total ^{14}C)

i) PB-score

284. Deltamethrin has a P-score of 0.745 and a B-score of 0.129 resulting in an overall B-score of 0.875.

7.11 Human health hazard assessment

j) Acute toxicity

285. EU biocides AR 2011: The data presented are in agreement with the actual EU GHS classification: category 3 for oral and respiratory exposure, no skin or eye irritation, not sensitizing when tested with the M&K method and the Buehler method.

286. EFSA review report 2002: The conclusions presented are in agreement with the EU biocides final CAR 2011.

287. WHO 2012: Deltamethrin is not a skin/eye irritant, nor a skin sensitizer.

k) Mutagenicity and Carcinogenicity

288. EU biocides CAR 2011: Within the available in vitro test battery deltamethrin was not genotoxic. The available rat and mice carcinogenicity studies did not indicate evidence for carcinogenicity.

289. EFSA review report 2002: The conclusions presented are in agreement with the EU biocides final CAR 2011.

290. IARC 1999: Deltamethrin induced micronuclei and chromosomal aberrations in bone marrow and abnormal sperm morphology in mice treated in vivo. The only other indication of genotoxic potential was induction of chromosomal aberrations in plants. Deltamethrin was tested for carcinogenicity in one experiment in mice and in one experiment in rats by oral administration. In mice, no increase in tumour incidence was seen. In rats, a statistically significant increase in the incidence of unspecified thyroid adenomas was observed in low-dose males and high-dose females. Conclusively there was inadequate evidence for the carcinogenicity of deltamethrin in experimental animals. No data were available from studies in humans. Therefore Deltamethrin was considered as not classifiable as to its carcinogenicity to humans (Group 3).

291. WHO 2012: There is no evidence of genotoxic, carcinogenic or mutagenic effects.

l) Toxicity for reproduction

292. EU biocides CAR 2011: No developmental toxicity was observed at maternal toxic doses in rats and rabbits. In mice an increased incidence of supernumerary ribs at maternal toxic doses was observed. Within a reproductive toxicity study in rat increased pup mortality, reduced lactation index and reduced pup weight were only observed at parental toxic dose levels.

293. EFSA review report 2002: The conclusions presented are in agreement with the EU biocides final CAR 2011.

294. WHO 2012: There is no evidence of teratogenic or reproductive toxicity effects.

m) Neurotoxicity

295. EU biocides CAR 2011: No delayed neurotoxicity study or data were required or available. Within an acute and subchronic neurotoxicity study in rats neurotoxic effects in terms of clinical signs and functional alternations in functional observation batteries were observed that were in higher doses accompanied with mortalities and reduced body weight gain. Within a developmental neurotoxicity study in rats vocalizations in male pups and delayed onset of balanopreputial separation at maternal toxic dose were observed. Medical data from manufacturing, formulating and packaging plants indicate that transitory skin sensations were the most prevalent finding (paraesthesia, transient local burning, tingling, pickling sensations, itching, numbness of the facial skin – erythema in some cases). Cases of intoxications (mostly occupational due to inappropriate handling of products) have been reported. Two cases of occupational acute deltamethrin poisoning died of convulsions and another died of pulmonary oedema. No late sequeala of pyrethroid poisoning have been described in the scientific literature.

296. EFSA review report 2002: The conclusions presented are in agreement with the EU biocides final CAR 2011.

n) Immunotoxicity

297. US EPA summary 2010: the toxicology database for deltamethrin is essentially complete, with the exception of the immunotoxicity data. The Agency expects to require an immunotoxicity study (Guideline # 870.7800).

o) Endocrine disruption

298. EU Endocrine Disruption Database 2012: Listed within category 1, which means that it is persistent in the environment or produced at high volumes with evidence of endocrine disruption activity in at least one species using intact animals.

299. EU biocides CAR 2011: As part of the evaluation of the application for the inclusion of Deltamethrin in Annex I of the Biocidal Products Directive (98/8/EC) toxicology and ecotoxicology data have been assessed. It is concluded that there was no evidence of endocrine disruption effects from these studies. However, it should be noted that due to limitations in the test guidelines available at the time, the potential for endocrine effects may not have been fully investigated.

p) Mode of action

300. ATSDR 2003: The primary site of action for pyrethrins and pyrethroids is the sodium channel of nerve cells, Type II pyrethroids include a cyano group; their effects in rodents are usually characterized by pawing and burrowing behavior, followed by profuse salivation, increased startle response, abnormal hindlimb movements, and coarse whole body tremor that progresses to sinuous writhing (choreoathetosis). Clonic seizures may be observed prior to death. Body temperature is not increased, but may decrease. The term CS-syndrome (from choreoathetosis and salivation) has been applied to Type II responses.

q) Acceptable Exposure Levels

301. EU biocides CAR 2011: A systemic long term internal limit dose value (AEL) of 0.0075 mg/kg bw day was derived from the clinical neurotoxicity effects in the 1-year dog study, considering an oral absorption rate of 75% and a standard assessment factor of 100.

302. EFSA review report 2002: The same systemic long term limit dose value (AOEL systemic) of 0.075 mg/kg bw day was developed on the basis of the neurotoxic effects in the 1 year dog study and the 90 day dog study and the standard assessment factor of 100. An external long term limit dose value (ADI) of 0.01 mg/kg bw day was developed on the basis of the same studies and assessment factor.

303. WHO 2010: the FAO/WHO JMPR has allocated an ADI of 0.01 mg/kg bw.

7.12 Environmental hazard assessment

r) Aquatic compartment (including sediment)

304. Toxicity data for aquatic species are for example available from EFSA review report 2002 and EU biocides CAR 2011 and PPBD 2012. The compound is classified as very highly toxic to aquatic organisms based on data for aquatic vertebrates and invertebrates. Toxicity reference values for aquatic species are listed in Table 4.

Table 4: Toxicity reference values for the aquatic compartment

Exposure scenario/ Study type	Organism /Species	Endpoint	Toxicity value	Reference
Acute 96 hour	Fish	LC_{50}	0.00026 mg/l (0.26 µg/l)	PPBD
Chronic, 21 days	Fish	NOEC	< 0.032 mg/l (32 µg/l)	PPBD
Acute 48 hour	Aquatic invertebrates	EC_{50}	0.00056 mg/l (0.56 µg/l)	PPBD
Chronic, 21 days	Aquatic invertebrates	NOEC	0.0041 mg/l (4.1 µg/l)	PPBD
Acute 96 hour	Aquatic crustaceans	LC_{50}	0.0000017 mg/l (0.0017 µg/l)	PPBD
Acute 96 hour	Sediment dwellers	LC_{50}	0.01 mg/l (10 µg/l)	PPBD
Acute 72 hour	Algae	EC50	9.1 mg/l (9100 µg/l)	PPBD
Mesocosm	Aquatic community	NOEAEC	0.0032 mg/l 3.2 µg/l	PPBD
Chronic 28 day	Sediment dwelling organisms	NOEC	0.0000035 mg/l 0.0035 µg/l based	EU CAR
Chronic 28 day	Sediment dwelling organisms	NOEC	31 µg/kg ww sediment	EU CAR
Chronic Chronic	Mesocosm Mesocosm	NOEC $NOEC_{mortality}$	0.0048 µg/l 0.009 µg/l	EU CAR EU CAR

s) Terrestrial compartment

305. Toxicity reference values for the terrestrial compartment derived from PPDB 2012 and the EU biocides CAR 2011 are summarized in Table 5. Deltamethrin shows low toxicity to birds at short as well as long-term exposure.

Table 5: Toxicity reference values for the terrestrial compartment

Exposure scenario/ Study type	Organism /Species	Endpoint	Toxicity value	Reference
Acute, oral	Rat	LD_{50}	87 mg/kg	PPBD
Acute, dietary	Rat		2.5 mg/kg	PPBD
Acute	Birds	LD_{50}	> 2250 mg/kg	PPBD
Acute, dietary	Birds	LD_{50}	> 5620 ppm mg/kg	PPBD
Acute/14 day	Earthworms	LC_{50}	> 1290 mg/kg	EU-CAR
Chronic Reproduction	Birds	NOEL	55-70 mg/kg	EU-CAR
Chronic/28 days	Soil dwellers (spring tails)	NOEC	0.78 mg/kg	EU-CAR
Chronic/28 days	microorganisms	NOEC	> 0.5 mg/kg soil	EU-CAR

t) Toxicity to pollinators

306. DAR 2002: Deltamethrin showed very high contact and oral toxicity to honey bee, *Apis mellifera*, in laboratory studies. Acute oral toxicity: LD50 79 ng/bee; LD50 (48 h): 280 ng /bee; Acute contact toxicity: LD50 (48 h) 1.5 ng/bee: LD50 (48 h) 10 ng/bee

307. Deltamethrin showed very high contact toxicity (almost 100% mortality at an application rate of 13.5 g/ha) to some terrestrial arthropods (*Coccinella septempunctata, Chrysoperla carnea* and *Trichogramma cacoeciae*) in laboratory studies. According to both EPPO and Annex VI to Directive 91/414/EEC there is a high predicted risk if more than 30% of the individuals are affected. Also in the field studies there were effects observed, although those results were somewhat difficult to quantify due to different practical circumstances.

7.13 Other information

308. Toxicological information presented in the PAN –pesticides database and in the footprint database is largely consistent with the toxicological information summarized above with the exception that the reproductive toxicity and developmental study results summarized from EFSA above seem not respected or insufficient for a conclusion in these two databases.

7.14 References

ATSDR (2003) TOXICOLOGICAL PROFILE FOR PYRETHRINS AND PYRETHROIDS, September 2003, http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=787&tid=153

DAR (2002) Draft Assessment Report. Deltamethrin. 2002, http://dar.efsa.europa.eu/dar-web/provision, 2012-03-26

EU biocides CAR (2011) Competent Authority Report, Deltamethrin. Product-type 18 (Insecticides), 2011.

EU Endocrine Disruption Database (2012) http://ec.europa.eu/environment/endocrine/strategy/short_en.htm, 2012-04-16

EFSA review report (2002) Deltamethrin 6504/VI/99-final October 2002, available at http://ec.europa.eu/sanco_pesticides/public/index.cfm?event=activesubstance.selection

PPDB (2012) Pesticide Properties DataBase, University of Hertfordshire, http://sitem.herts.ac.uk/aeru/footprint/en/ 2012-04-18

IARC (1999) IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 53, Occupational Exposures in Insecticide Application, and Some Pesticides , available at http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php

US EPA summary (2010) Deltamethrin Summary Document, Registration Review; Initial Docket March 2010, EPA-HQ-OPP2009-0637-0002, available at http://www.epa.gov/pesticides/chemicalsearch

WHO Report (2010) available at http://www.who.int/whopes/quality/newspecif/en/

8. Dicofol

CONCLUSIONS

Assessment of POP properties – comparison with the criteria of Annex D and other hazard indicators

8.1 Persistence

309. Dicofol is susceptible to pH dependant hydrolyses at neutral and alkaline pH values. Photogedradation is not considered to be a major dissipation route in the environment. No data for water/sediment systems at pH<7 were reported. DT50 values from soil laboratory tests span a wide range from 9 to 468 days. The rate of degradation was fastest in soils with higher pH. O,p'-dicofol degraded faster than p,p'-dicofol. Though it can be assumed that under environmental conditions DT50 values for dicofol are less than 90 days, studies submitted on the fate of dicofol do not provide sufficient information to estimate persistence of dicofol degradates in the environment. As a result, conservative estimates for persistence of dicofol (considering the parent and major degradates) are as high as 313 days (half-life). UN ECE concluded that dicofol is persistent in acid water and meets the persistence indicative numerical value of EB decision 1998/2[20].

310. Therefore it might be reasonable to conclude that dicofol and its residues meet the persistence criterion of Annex D 1 (b) (i).

8.2 Bioaccumulation

311. Dicofol has a log Kow of 4.3 that is below the trigger of 5. However, dicofol meets the Annex D 1 (c) (i) criterion based on BCF values in fish >5,000. The modelled B-score is also very high. This conclusion is in line with the UN ECE result on dicofol.

8.3 Long-range environmental transport (LRT)

312. Dicofol has a calculated half-life in air > 2 days. The model result (multimedia fate) demonstrates that dicofol has overall persistency (Pov) and LRT properties similar to those of several known POPs. UN ECE concluded that dicofol had the potential for LRT based on vapour pressure, atmospheric half-life and qualitative information of its presence in Arctic air.

313. Dicofol fulfils the Annex D 1 (d) (ii) and (iii) criteria.

8.4 Ecotoxicity (including pollinator toxicity)

314. Dicofol is highly toxic to aquatic organsisms and classified according to EU-GHS as aquatic acute and chronic category 1. Dicofol has shown reproductive effects on birds. UN ECE 2009 concluded that dicofol had the potential to adversely affect human health and/or the environment based on toxicity to mammals and aquatic animals. Based on its high aquatic toxicity and toxicity to human health (see below) Annex D 1 (e) (ii) is fulfilled.

8.5 Toxicity to human health (including mutagenicity, carcinogenicity and adverse effects on the reproductive, endocrine, immune or nervous systems)

315. Dicofol was classified in the EU-GHS system for acute toxicity category 4 for oral and dermal route, though for the latter the reported data are inconsistent. The substance was classified in the EU-GHS system for skin irritation and also skin sensitization. The reported data are in agreement with this, skin sensitization is supported by a positive modified Buehler test.

316. The European, US and IARC reports are in agreement that the substance did not show genotoxic properties within a series of in vitro and in vivo tests and that the carcinogenicity studies are negative in rats but positive in male mice and the latter study was considered as not adequate. This resulted so far in no EU GHS classification, an US group C, possible human carcinogen classification and an IARC conclusion that the available data are insufficient to evaluate the carcinogenicity of dicofol to humans.

317. Dicofol was consistently reported as non developmental toxic and as showing adverse effects on reproduction only at parentally toxic doses. However US EPA required a reevaluation of the reproductive toxicity studies with regard to ovarian histology and estrous cyclicity.

[20] http://www.unece.org/fileadmin/DAM/env/documents/2000/ece/eb/ece%20eb%20air.60.e.pdf

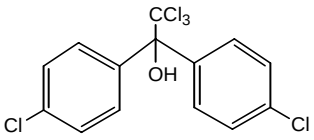
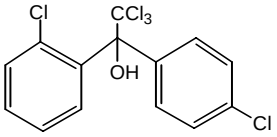
318. The substance is listed within category 2, which means that it is persistent or an HPVC with at least some in vitro evidence of biological activity related to endocrine disruption.

319. Representing an organochlorine neurotoxic effects are expected. However no neurohistopathological changes were observed. For shorter exposures functional neurological effects as well as body weight reduction and feed consumption were critical effects. For chronic exposures DAR 2006 considered liver and adrenal gland effects in a chronic rat study as critical, applied the standard assessment factor of 100 and derived a long term limit dose value (ADI) of 0.0022 mg/kg bw day. US EPA 1998 considered hormonal toxicity in a chronic dog study as critical, applied an assessment factor of 300 due to uncertainties in the respective databases and derived a chronic reference dose of 0.0004 mg/kg bw day.

8.6 Identity of the substance and physical and chemical properties

a) Name and other identifiers of the substance

Table1: Substance identity

Common name:	Dicofol
IUPAC name:	2,2,2-trichloro-1,1-bis(4-chlorophenyl)ethanol
CAS number:	115-32-2
Molecular weight:	370.49
Chemical structure/isomeric forms:	 p,p'-dicofol CAS No. 115-32-2  o,p-'dicofol CAS No. 10606-46-9

b) Chemical group

320. Organochlorine

c) Physico-chemical properties

Table 2: Overview of selected physico-chemical properties

Property	Value	Remarks and Reference
Vapour pressure at 25°C (mPa)	0.25	PPDB 2012
Water solubility at 20°C (mg/l)	0.8	PPDB 2012
Partition coefficient n-octanol/water (log value, pH 7, 20°C)	4.3	PPDB 2012
Partition coefficient air/water (log value)	-5.01	EPI Suite v 4.0[21]
Partition coefficient air/octanol (log value)	9.3	EPI Suite v 4.0
Henry´s Law Constant at 25°C ($Pa.m^3.mol^{-1}$)	2.45×10^{-02}	PPDB 2012

8.7 Classification and labelling

d) Harmonised Classification according to GHS

Regulation (EC) No 1272/2008

Category	Hazard-Phrase
Acute Tox. 4	H312 Harmful in contact with skin.
Acute Tox. 4	H302 Harmful if swallowed.
Skin Irrit. 2	H315 Causes skin irritation.
Skin Sens. 1	H317 May cause an allergic skin reaction.
Aquatic Acute 1	H400 Very toxic to aquatic life.
Aquatic Chronic 1	H410 Very toxic to aquatic life with long lasting effects.

[21] http://www.epa.gov/oppt/exposure/pubs/episuite.htm

8.9 Environmental fate properties

321. US EPA 2009 and DAR 2006: Dicofol occurs in formulated end-use products as two isomers, o,p'-dicofol and p,p'-dicofol, at a ratio of 1:4.5. Major degradates of dicofol include the o,p'- and p,p'-isomers of DCBP (dichlorobenzophenone), FW-152 (2,2-dichloro-1,1-bis(4-chlorophenyl)ethanol), DCBH (dichlorobenzhydrol), OH-DCBP (3-hydroxy-dichlorobenzophenone) and CBA (chlorobenzoic acid) and DCBA (dichlorobenzilic acid).
322. US EPA RED 1998 compared dicofol to DDT stating that dicofol has an environmentally significant water solubility providing dicofol with a pathway for degradation; DDT does not. Dicofol has an environmental half-life of weeks compared to years for DDT. While dicofol has some ability to accumulate, DDT has a much greater ability to do so. Most importantly, dicofol does not degrade to DDE, but to degradates less toxic than dicofol, whereas DDT degrades to DDE which has been identified as the toxic moiety.

e) Abiotic degradation

f) Hydrolysis

323. According to Rasenberg 2003 the stability of dicofol in water is pH-dependent. The p'p-isomer hydrolyses with a half-life of 85, 4 and 0.02 days at pH 5, 7 and 9, respectively. The half-life for the o,p'-isomer is 47, 0.3 and 0.006 days at pH 5, 7 and 9, respectively. The main hydrolysis products are the corresponding dichlorobenzophenons (DCBP). These appeared to resist further degradation. The reported half-lives are in line with the values given in DAR 2006.
324. UN ECE 2009 states that the Task Force concluded dicofol was persistent based on a half-life in water at pH 5 or below.

g) Phototransformation/photolysis

325. DAR 2006: The aqueous photolysis half-lives for p,p'-dicofol and o,p'-dicofol are 243 days and 28 days, respectively (after correcting for hydrolysis in pH 5 buffer). In photosensitized samples the degradation of both isomers of dicofol was quicker. Lower half-life values were reported in Rasenberg 2003.
326. US EPA 2009: Photodegradation is not expected to be significant route of dissipation of dicofol in the environment.

h) Biodegradation

327. DAR 2006 lists a water/sediment test in two systems with a pH >7.0. Under these conditions, both isomers of dicofol are rapidly degraded with first-order DT50 values in the water phase of 6 to 9 hours for p,p'-dicofol and approximately one hour for o,p'-dicofol. DT50 values in the whole sediment/water system are between 7 and 13 hours for p,p'-dicofol and less than 2 hours for o,p'-dicofol. Isomer specific accumulation of DCBP, DCBH, FW-152 and DCBA was observed in sediments. The evaluating EU member state considered a new study with water/sediment systems at pH <7 essential for the assessment of the fate of dicofol in the aquatic environment.
328. US EPA 2009 states that anaerobic soil metabolism studies indicate that dicofol will degrade relatively rapidly in sediment with a half-life less than 30 days.
329. DAR 2006: In aerobic soil under laboratory conditions (20-25°C), o,p' dicofol is degraded more rapidly than p,p' dicofol The data showed that the rate of degradation was fastest in soils with higher pH and that o,p'-dicofol degraded faster than p,p'-dicofol. Reported DT50 values span a wide range from 9 to 468 days (n=4).
330. According to DAR 2006 soil dissipation at five different sites was reported in the dossier, four in the USA and one in Europe (Switzerland). The study located in Switzerland and two sites from California were not considered valid because of the analysis method and poor recoveries. For the remaining sites with a pH <6 dissipation of p,p'-dicofol and o,p'-dicofol was observed throughout the study, however it was not possible to calculate accurate dissipation parameters.
331. US EPA RED 1998: Laboratory and field studies show that dicofol isomers have a short to intermediate half-life (days to months) and are moderately persistent in the environment as a result of normal label uses. In ecological monitoring studies conducted in New York, Florida, and California, dicofol dissipated from the soil surface with a half-life ranging from two to four months.
332. US EPA 2009: Based on the available environmental fate data for dicofol, this

chemical is not expected to persist in the environment, with half-lives less than 90 days, depending upon the specific environmental conditions. However, studies submitted on the fate of dicofol do not provide sufficient information to estimate persistence of dicofol degradates in the environment. As a result, conservative estimates for persistence of dicofol (considering the parent and major degradates) are as high as 313 days. The primary route of dissipation is soil metabolism.

333. Also UNECE 2009 indicated that the persistency of dicofol would be longer if its transformation products were included in the determination of half-life in soil, sediment and water.

334. PPDB 2012 lists a DT50 typical of 80 days and a DT50 lab (20°C) of 45 days.

8.10 Potential for long range transport

335. Results of the phototransformation in air according to EPI Suite TM v4.0 (AOPWIN v 1.92) are based on a 12 hour day are summarised in Table 3. This result is also given in DAR 2006.

Table 3: Phototransformation in air

Guideline / Test method	Molecule / radical	Rate constant for reaction with OH-radicals (k_{OH}) [cm^3 $molecule^{-1}$ sec^{-1}]	Half-life ($t_{1/2}$) [h]	OH-radical concentration (OH-radicals/cm^3)
AOPWIN	OH	3.4310 E^{-12}	37.41	1.5 x 10^6

336. The OECD "Pov and LRTP Screening Tool"[22] has been developed with the aim of using multimedia models for estimating overall persistence (Pov) and long-range transport potential (LRTP) of organic chemicals at a screening level in the context of PBTs/POPs assessments. The input parameters for Kow and Kaw were taken from Tables 2, half-lives for air, water and soil are listed in Table 4.

337. With a calculated CTD (characteristic travel distance) of 2142/1467 km *o,p´*- and *p,p´*-dicofol and its degradates have Pov and LRT properties similar to those of several known POPs. The calculated TE (transfer efficiency) and Pov values are 9.5/3.4% and 37/138 days for *o,p´*- and *p,p´*-dicofol (US EPA, 2009).

Table 4: Half-lives for air, water and soil (input parameters for the OECD Tool).

Half-Lives	Value (h) *o,p´*-dicofol / *p,p´*-dicofol	Reference
Water	408/1536	US EPA 2009
Soil	612/2304*	
Air	74.4	

* DAR 2006 used for PEC calculation in soil DT50: o,p'-dicofol: 18.1 day; p,p'-dicofol: 204 day

338. UN ECE 2009 concluded that dicofol had the potential for LRT by satisfying the guidance and the indicative numerical values of EP 1998/2 based on vapour pressure and atmospheric half-life and qualitative information on presence in Arctic air.

8.11 Bioaccumulation

339. DAR 2006: Bioaccumulation of p,p'-dicofol in fish is demonstrated since BCF is 25,000 and a slow clearance was estimated, the depuration rate (CT90) is 110 days.

340. US EPA RED 1998: p,p'-dicofol residues accumulated in bluegill sunfish with bioconcentration factors of 6,600. 17,000, and 10,000X in fillet, viscera, and whole fish, respectively, during 28 days of exposure. The estimated elimination half-life was 33 days. No information is available on the bioaccumulation in fish for o,p'-dicofol.

341. UN ECE concluded on the high bioaccumulation potential of dicofol based on log Kow and BCF.

i) PB-score

342. Dicofol has a high PB score of 1.89 (P-score 0.95 and B-score 0.94)

[22] http://www.oecd.org/document/24/0,3343,en_2649_34379_45373336_1_1_1_1,00.html

8.12 Human health hazard assessment

j) Acute toxicity

343. DAR 2006: The acute toxicity data presented were in agreement with the actual EU GHS classification for oral acute toxicity category 4. In contrast the dermal acute toxicity category 4 was not supported since a dermal LD50 > 5000 mg/kg bw was presented. There is no classification for the respiratory route and consistently an LC50 rat > 5 mg/L was presented. The substance is irritant to the skin, but no to the eye and it is sensitizing when tested with the modified Buehler test.

344. US EPA RED 1998: The data summarized are largely in agreement with data presented in the EFSA DAR 2006 with the exception that Docofol was not sensitizing in guinea pigs: Based on a LD50 value of 587 mg/kg in CRCD rats, dicofol was placed in Toxicity Category III for acute oral toxicity. An acute dermal toxicity test with CRCD rats reported the dermal LD50 to be greater than 5.0 g/kg, placing dicofol in Toxicity Category IV for dermal toxicity. When tested in New Zealand white rabbits for dermal toxicity, the LD50 was between 2 and 5 g/kg, placing dicofol in Toxicity Category III. The acute inhalation LC50 was greater than 4.2 mg/L in one study and greater than 5 mg/L in another study. Based on these results in rats, dicofol was placed in Toxicity Category IV. A primary eye irritation study with rabbits indicated dicofol to be a moderate eye irritant, placing it in Toxicity Category III. A primary dermal irritation study in rabbits showed dicofol to be a moderate irritant, placing it in Toxicity Category III. Dicofol was shown to be a non-sensitizer in guinea pigs.

k) Mutagenicity and Carcinogenicity

345. DAR 2006: On the basis of several gene mutation tests in vitro, chromosome aberration in vitro and in vivo and DNA damage tests in vitro it was concluded that there is no genotoxic potential. Negative rat carcinogenicity tests were reported. However in a not adequate study in male mice an increase of hepatocellular adenomas and combined adenomas/carcinomas in was observed and further data were required for mice.

346. US EPA RED 1998: On the basis of in vitro mutagenicity tests in bacteria and mammalian cells as well as in vitro chromosomal aberration tests and in vivo chromosomal aberration test in rat bone marrow it was concluded that Dicofol did not demonstrate mutagenic activity and no additional tests were required. Also the negative carcinogenicity studies in rats and the carcinogenicity study with positive findings in male mice livers were reported. The Agency (HED Carcinogenicity Peer Review Committee (CPRC)) has classified dicofol as a nonquantifiable "Group C," possible human carcinogen.

347. IARC 1998: Dicofol was negative in bacterial tests for mutagenicity and for DNA damage, with or without exogenous metabolic activation. The experimental protocols and results of studies with eukaryotes were not presented in adequate detail for an evaluation to be made. No overall evaluation of the mutagenicity of dicofol could be made. Dicofol (technical-grade) was tested for carcinogenicity in mice and rats by administration in the diet. It induced hepatocellular carcinomas in male mice. The study in rats was considered to be inadequate for evaluation. Results of the experiment in mice provide *limited evidence* that dicofol is carcinogenic to experimental animals. No data on humans were available. The available data are insufficient to evaluate the carcinogenicity of dicofol to humans.

l) Toxicity for reproduction

348. DAR 2006: No teratogenic effects were observed in rats and rabbits. Effects adverse to reproduction (histology in ovary, adrenal gland, mating index, pup viability index and lactation index) were observed only above parentally toxic doses.

349. US EPA RED 1998: A teratogenicity study in rats was reported without findings for developmental toxicity. In rabbits an increased incidence of abortions occurred only at the maternal LOAEL. A two generation study was reported with adverse effects on reproduction only at parentally toxic doses. For the one generation study a reevaluation of estrous cyclicity was requested. In addition ovarian histopathology samples should be re-examined to attempt to resolve the inconsistencies in the study results.

350. IARC 1998: Dicofol (technical-grade), even when given at high doses, had no

effect on reproduction or foetal development in mice; however, high doses in rats appeared to have an adverse effect on preimplantation stages of embryonal development.

m) Neurotoxicity

351. DAR 2006: Dicofol produced neurotoxic effects in adult rats in neurotoxicity tests without neurohistopathological changes: In the acute study a decrease in body weight and feed consumption and urine- or fecal- stained fur was observed, whereas in the subchronic study decrease in body weight and feed consumption as well as alterations in a functional observation battery and decreased motor activity were observed.
352. US EPA RED 1998: Results from an acute and a subchronic neurotoxicity study were reported. In the acute study at higher doses increased incidence of ataxia and of uncoordinated landing and also signs of being asleep were observed. At the LOAEL decreased body weights and reduced food consumption were observed. In the subchronic study decreased motor activity and increased liver weight were observed. In none of the studies histological changes in the central or peripheral nervous system were observed.

n) Immunotoxicity

353. -

o) Endocrine disruption

354. EU Endocrine Disruption Database 2012: The substance is listed within category 2, which means that it is persistent or an HPVC with at least some in vitro evidence of biological activity related to endocrine disruption.
355. US EPA RED 1998: A study of the adverse effects of organochlorine contamination on alligators in Lake Apopka, Florida, was summarized. Uncertainty was reported with regard to other potential sources for the reproductive effects in alligators.

p) Mode of action

356. -

q) Acceptable Exposure Levels

357. DAR 2006: An external long term limit dose value (ADI) of 0.0022 mg/kg bw day was provided on the basis of liver and adrenal gland effects in the 2 year rat study and a standard assessment factor of 100. The value was considered as provisional since a new mouse study was required. For shorter term limit dose values (e.g AOEL) the neurotoxicity appeared critical.
358. US EPA RED 1998: To estimate chronic dietary risk, the endpoint chosen was hormonal toxicity observed in a chronic toxicity study in dogs. The NOAEL was 0.12 mg/kg/day and the LOAEL was 0.82 mg/kg/day, based on inhibition of adrenal cortical trophic hormone (ACTH) stimulated release of cortisol in both sexes of dogs. The NOAEL is divided by an Uncertainty Factor of 300 (10X for inter-species variation, 10X for intra-species extrapolation, and 3X for additional uncertainty), resulting in the chronic RfD of 0.0004 mg/kg/day. The additional safety factor of 3X is applied to the chronic dietary risk assessment for all population subgroups since the dose and endpoint for this risk assessment is based on inhibition of adrenal cortical trophic hormone (ACTH) stimulated release of cortisol in male and female of dogs and there is a data gap for the developmental neurotoxicity study.

8.12 Environmental hazard assessment

r) Aquatic compartment (including sediment)

359. US EPA 1998: Results of the acute toxicity studies indicate that dicofol is highly toxic to freshwater fish, invertebrates and estuarine/marine organisms. Table 5 lists the ecotoxicity data on vertebrates according to DAR 2006.

Table 5: Toxicity reference values

Exposure scenario/Study type	Organism/Species		Time Scale Endpoint	Toxicity value	Remark
Acute, 96 hours (h)	Fish	Rainbow trout	LC50	0.11 mg/L	-
Chronic, 99 days (d)	Fish	Rainbow trout	NOEC	0.009 mg/L	-
Chronic, 209 d (static)	Fish	Fathead minnow	NOEC	0.0045 mg/L	-
Acute, 96 h	Fish	Rainbow trout	LC50	2.29 mg/L	Test substance: p,p´-DCBP
Acute, 96 h	Fish	Rainbow trout	LC50	0.24 mg/L	Test substance: p,p´-DFW-152

s) Terrestrial compartment

360. US EPA RED 1998 indicate moderately toxicity to avian species on an acute oral basis and slight toxicity on a subacute dietary basis. DAR 2006 reported higher toxicity to birds in a long term study (cf. Table 6). US EPA evaluated several chronic studies as well as reproductive effects. Avian reproductive studies indicate that dicofol, at least for certain species, can affect avian reproductive parameters such as shell strength, shell thickness, and egg production. In field studies however a cause-effect relationships between unsuccessful nesting related to eggshell thing and dicofol residues cannot be determined from the studies.

361. Belfroid et al. 2005 concluded that new information in the UN ECE dossier confirmed that dicofol caused eggshell thinning.

Table 6: Toxicity reference values (bw ….body weight)

Exposure scenario	Organism/Species		Time Scale Endpoint	Toxicity value	Reference
Acute	Mammals	Rat	LD50	578 mg/kg bw/d	DAR 2006
Long-term	Mammals	Rat	NOEL	1.7 mg/kg bw/d	
Long-term	Birds	Mallard duck	NOEC	2.5 mg/kg feed or 0.3 mg/kg bw/d	
Acute toxicity	Earthworms	*Eisenia foetida*	NOEC	>354 mg/kg	

t) Toxicity to pollinators

362. US EPA RED 1998 indicated slight toxicity to bees (cf. toxicity reference values in Table 7).

Table 7: Toxicity reference values

Study type	Organism	Time Scale Endpoint	Toxicity value LC50	Reference
Acute oral toxicity	Bees	Acute oral	57.1 µg a.s./bee (formulation tested)	DAR 2006
Acute contact toxicity	Bees	Acute contact	36.3 µg a.s. /bee (formulation tested)	DAR 2006

8.13 Other information

363. Toxicological information presented in the PAN –pesticides database and in the footprint database is largely consistent with the toxicological information summarized above

8.14 References

Belfroid, H. Blok and F. Balk (2005) Addendum to the risk profile of Dicofol, 2 December 2005, Final Report 9R5744.01.
http://www.unece.org/fileadmin/DAM/env/lrtap/TaskForce/popsxg/2008/Dicofol_Addendum%20to%20RA%20dossier_proposal%20for%20submission%20to%20UNECE%20POP%20protocol.pdf, 2010-04-16
DAR (2006) Dicofol Draft Assessment Report, July 2006.
EU Endocrine Disruption Database (2012)
http://ec.europa.eu/environment/endocrine/strategy/short_en.htm, 2012-04-16
IARC (1998) Dicofol, Monograph VOL.: 30, Sup 7 1987
http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php, 2012-04-16
PPDB (2012) Pesticide Properties DataBase, University of Hertfordshire, http://sitem.herts.ac.uk/aeru/footprint/en/ 2012-04-18
Rasenberg MHC (2003) Risk Profile and Summary Report for Dicofol, Dossier prepared for the UNECE Convention on Long-range Transboundary Air Pollution's Expert Group on POPs, Ministry of VROM/DGM,
http://www.unece.org/fileadmin/DAM/env/lrtap/TaskForce/popsxg/2008/Dicofol_RA%20dossier_proposal%20for%20submission%20to%20UNECE%20POP%20protocol.pdf, 2012-04-16.
UN ECE (2009) Report by the Co-chairs of the Task Force on Persistent Organic Pollutants,ECE/EB.AIR/WG.5/2009/7,
http://www.unece.org/fileadmin/DAM/env/documents/2009/EB/wg5/wgsr45/ece.eb.air.wg.5.2009.7.e.pdf 2012-04-16.
US EPA RED (1998) Reregistration Eligibility Decision Dicofol
http://www.epa.gov/pesticides/reregistration/REDs/0021red.pdf, 2012-04-16
US EPA (2009) Risks of Dicofol Use to Federally Threatened California Red-legged Frog (*Rana aurora draytonii*), Pesticide Effects Determination Environmental Fate and Effects Division Office of Pesticide Programs Washington, D.C. 20460, June 15, 2009
http://www.epa.gov/espp/litstatus/effects/redleg-frog/dicofol/analysis.pdf, 2012-04-16

9. Etofenprox[23]

CONCLUSIONS

Assessment of POP properties – comparison with the criteria of Annex D and other hazard indicators

9.1 Persistence

364. Etofenprox is hydrolytically stable but degrades according to the results from aquous and soil photolysis studies. An evaluated comprehensive dataset demonstrates that etofenprox is rapidly and completely degraded in soil without giving rise to significant or persistent degradation products. DT50 values in water-sediment systems of etofenprox and its metabolite are in the same range than results from soil studies for water and whole system. DT50 in sediment is longer with a maximum of 56 days (for the metabolite). Though etofenprox has a P-score of 0.7 (based on mineralization) it can be concluded that etofenprox does not meet the Annex D criterion 1 (b) (i).

9.2 Bioaccumulation

365. Etofenprox has a log Kow >5 indication a potential for bioaccumulation. The BCF in fish is 3,921. However this value is based on a single study. The modelled B-score of 0.5 is in agreement with the experimental high BCF value. Based on the (limited) available data it can be concluded that etofenprox does not meet the criterion 1 (c) (ii) of Annex D.

9.3 Long-range environmental transport

366. Etofenprox has a calculated half-life in air of 2 hours (<2 days). Therefore it is unlikely that etofenprox fulfils the Annex D 1 (d) (iii) criterion.

9.4 Ecotoxicity (including pollinator toxicity)

367. Etofenprox shows high toxicity to aquatic organisms that qualify for EU-GHS classification acute and chronic category 1. Etofenprox is of low toxicity to birds. Etofenprox shows no effects on earthworms up to 47 mg/kg dry artificial soil. Etofenprox is toxic to bees. Based on its high aquatic toxicity Annex D 1 (e) (ii) is fulfilled.

9.5 Toxicity to human health (including mutagenicity, carcinogenicity and adverse effects on the reproductive, endocrine, immune or nervous systems)

368. Etofenprox was of low acute toxicity, did not induce skin or eye irritation or skin sensitization with the M&K test. No GHS classification is necessary for acute toxicity. It did not show genotoxic potential within a series of in vitro and in vivo tests. In a rat 2 year study thyroid tumors were observed but the available mode of action data support the assumption o f a threshold and low relevance form humans. By weight of evidence the renal tumors in the mouse were not considered significant and overall the European evaluations conclude that there is no concern for carcinogenicity. US EPA concludes that etofenprox is not likely to be carcinogenic to humans at doses that do not alter thyroid homeostasis. Based on a weight of evidence analysis etofenprox is not considered a specific reproductive toxicant however haemorrhage effects observed in weanlings and kinetic data supporting high milk excretion rates might indicate a hazard for breast fed children and a respective need for GHS labelling. Though representing structurally a pyrethroid-like pesticide etofenprox did not appear neurotoxic, neither in acute nor repeated dose studies. Within the developmental neurotoxicity study some minor functional neurological effects appeared at dose levels causing also adverse parental effects. Etofenprox is listed in the EU database for endocrine disrupters within category 3b, which means that insufficient data are available for an evaluation of respective effects.

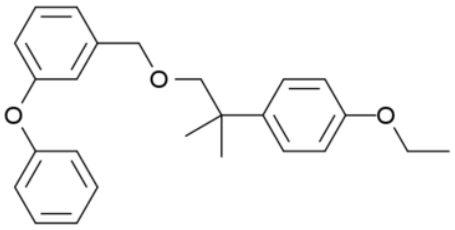
369. A systemic and external long term limit value of 0.03 mg/kg bw day was proposed consistently throughout several evaluations based on either the long term rat or the mouse study and assessment factor of 100. The critical target organs were liver, kidney and thyroid.

[23] Etofenprox is an alternative to both endosulfan and DDT.

9.6 Identity of the substance and physical and chemical properties

a) Name and other identifiers of the substance

Table 1: Substance identity

Common name:	Etofenprox
IUPAC name:	2-(4-ethoxyphenyl)-2-methylpropyl 3-phenoxybenzyl ether
CAS number:	80844-07-1
Molecular weight:	376.49
Chemical structure:	

b) Chemical group

370. Pyrethroid-ether

c) Physico-chemical properties

Table 2: Overview of selected physico-chemical properties

Property	Value	Reference
Vapour pressure at 25°C (mPa)	$8.13x10^{-04}$	PPDB 2012
Water solubility at 20°C (mg/l)	0.0225	PPDB 2012
Partition coefficient n-octanol/water (log value, pH 7, 20°C)	6.9	PPDB 2012
Partition coefficient air/water (log value)	-6.03	EPI Suite v 4.1 (KOAWIN v. 1.10)[24]
Partition coefficient air/octanol (log value)	12.93	EPI Suite v 4.1 (KOAWIN v. 1.10)
Henry´s Law Constant at 25°C ($Pa.m^3.mol^{-1}$)	0.0136	PPDB 2012

9.7 Classification and labelling

d) Harmonised Classification according to GHS

371. Not available

e) Proposed classification

372. EU biocides CAR 2011 (according to Regulation (EC) No 1272/200):

Category	**Hazard-Phrase**
STOT RE2	H373 – May cause damage to organs (liver, kidney) H362 –May cause harm to breast fed children
Aquatic acute 1 (M=100)	H400 - Very toxic to aquatic life
Aquatic chronic 1 (M=1000)	H410 – Very toxic to a aquatic life with long lasting effects

[24] http://www.epa.gov/oppt/exposure/pubs/episuite.htm

373. This classification proposal is actually in discussion within the ECHA/RAC process and especially the human toxicology classification proposals are challenged.

f) Self classification

374. ECHA CLP inventory

Category	Hazard-Phrase
Aquatic acute 1	H400 - Very toxic to aquatic life
Aquatic chronic 1 or 2	H410 – Very toxic to a aquatic life with long lasting effects or H411

9.8 Environmental fate properties

g) Abiotic degradation

h) Hydrolysis

375. AR 2007 states that etofenprox is hydrolytically stable under relevant environmental conditions.

i) Phototransformation/photolysis

376. AR 2007 reported for photo-chemically degradation a DT50 of 4.7 days for buffer solution and 7.8 days for pond water. Etofenprox degrades in aqueous solution predominantly to α-CO (2-(4-ethoxyphenyl)-2-methylpropyl 3-phenoxybenzoate). This finding is in line with DAR 2005. Etofenprox also degrades in a soil photolysis study.

j) Biodegradation

377. DAR 2005: The comprehensive database demonstrates that etofenprox is rapidly and completely degraded in soil without giving rise to significant or persistent degradation products. AR 2007 confirms that etofenprox is of short persistence in the environment (cf. Table 3) and potential effects of exposure of fish and aquatic invertebrates are the main areas of concern.

Table 3: Biotic degradation of etofenprox and major metabolite

Study type	Results	Reference	Remarks
DT_{50} soil lab (days):	7-25 (20°C, aerobic): geometric mean: 12 (n=4)	AR 2007	-
DT_{50} water (days) from water/sediment study:	Etofenprox: 2.1-10.5 (n=2)		Etofenprox partitioned fast into the sediment (after 0d 63-70%)
DT_{50} sediment (days) from water/sediment study:	Etofenprox: 18-32 4´-OH: 26-56 (n=2)		4´-OH: 2-(4-ethoxyphenyl)-2-methylpropyl 3-(4-hydroxy) phenoxybenzyl ether
DT_{50} water sediment/whole system (days):	Etofenprox: 6.5-20 (n=2) 4´-OH: 22-30		-

9.9 Potential for long range transport

378. AR 2007: The photo-chemical degradation of etofenprox in air has been estimated to be very fast. The calculated DT50 is 2.07 hours. In addition etofenprox has a moderate persistence in the environment; therefore no multimedia fate modelling was performed.

k) Bioaccumulation

379. Etofenprox has a log Kow of 6.9 indicating a bioaccumulation potential. The experimental derived BCF is 3,951 in whole fish according to AR 2007. In edibles a value of 1,554 and in non-edibles a BCF of 7,213 was recorded. Also DAR 2005 indicates that etofenprox has a potential for bioaccumulation according to the

results of the same bluegill sunfish study, but states reversible accumulation with depuration factors of 9 to16 days.

380. No other studies and/or information on terrestrial bioaccumulation are available.

l) PB-score

381. Etofenprox has a P-score of 0.7 and a B-score of 0.5 resulting in an overall B-score of 1.5.

9.10 Human health hazard assessment

m) Acute toxicity

382. EU biocides CAR 2011: The LD50 values for all routes are above the limits requiring classification, the substance is not irritant and not skin sensitising with the M&K test.

n) Mutagenicity and Carcinogenicity

383. EU biocides CAR 2011: The substance did not show genotoxic potential in any *in vitro* and *in vivo* assays employed (Ames-Test, in vitro cytogenicity test with human lymphocytes, in vitro gene mutation test V79 cells, in vitro UDS, in vivo micronucleus test). In the 2 year rat study thyroid follicular cell adenoma were observed but the available MOA data support the assumption of a threshold and low relevance for humans. Some renal tumor findings appeared in the carcinogenic mouse study but the weight of evidence analysis including statistical considerations it was concluded that there was no evidence for carcinogenic potential in the mouse.

384. US EPA summary document 2007: The Committee classified etofenprox as "Not likely to be carcinogenic to humans at doses that do not alter thyroid homeostasis."

o) Toxicity for reproduction

385. EU biocides CAR 2011: Several developmental and reproductive toxicity studies were summarized. Adverse effects on the offspring in the absence of parental toxicity were observed but on the basis of a total weight of evidence analysis it was concluded that there is no concern for specific reproductive toxicity requiring classification. However since haemorrhage effects were observed in weanlings and the kinetic data support high milk excretion rates a label for H362 – may cause harm to breast fed babies is proposed. The C&L proposal is actually challenged in the ECHA / RAC process.

p) Neurotoxicity

386. EU biocides CAR 2011: No data are available for delayed neurotoxicity since the substance has no structural similarities known or implicated in producing this type of effect. No neurotoxic effects were observed in the rat studies for acute neurotoxicity or in the 13-week neurotoxicity rat study at the highest doses tested, that were 2000 and 604 mg/kg bw, respectively. Within the developmental neurotoxicity study some minor functional neurological effects appeared in the developing rat with NOAELs that were the same as the overall parental NOAELs which indicated that the developing animal was not more susceptible that the parental animals.

387. Etofenprox is structurally a pyrethroid-like substance but the typical neurotoxic type I (C syndrome) or II (CS syndrome) effects were not observed.

q) Immunotoxicity

388. -

r) Endocrine disruption

389. Etofenprox is listed in the EU database for endocrine disrupters 2012 within category 3b, which means that insufficient data are available for an evaluation of respective effects.

s) Mode of action

390. US EPA summary document 2007: Etofenprox is a synthetic pyrethroid-like substance. It differs in structure from pyrethroids in that it lacks a carbonyl group. Etofenprox contains an ether moiety whereas pyrethroids contain ester moieties. Its

mode of action against insects is very similar to that of pyrethroids, and its main action site is the neuronal axon; however, its toxicity in test animals is different from that of a pyrethroid.

t) Acceptable Exposure Levels

391. EU biocides CAR 2011: The systemic long term limit dose (AEL) of 0.037 mg/kg bw day was proposed on the basis of a 2 year rat feeding study and application of an assessment factor of 100 to the NOAEL. The liver was the respective critical target organ.
392. EFSA review report 2009: An external long term limit dose (ADI) of 0.03 mg/kg bw day is proposed.
393. US EPA summary document 2007: An external long term limit dose (RfD) of 0.037 is proposed on the basis of the same study as the EU biocides draft CAR 2011 and the application of an assessment factor of 100. The LOAEL of this critical study is at 25.5 mg/kg/day and is based on increased thyroid weights. Related to increased liver weights and histopathological changes in liver and thyroid that occurred at the higher dose.
394. WHO 2007: An external long term limit dose (ADI) of 0-0.03 mg/kg bw/day was allocated by the JMPR, based on a long term study in mice and a 100 fold safety factor.

9.11 Environmental hazard assessment

u) Aquatic compartment (including sediment)

395. AR 2007: Etofenprox is highly toxic to fish, daphnids and chironomids in standard laboratory aquatic tests and less toxic to algae. The metabolite α-CO is less acutely toxic to fish, daphnids or algae than the active ingredient itself (cf. Table 4). The metabolite α-CO is less acutely toxic to fish, daphnids or algae than the active ingredient itself. The metabolite 4'-OH shows lower toxicity to chironomids than etofenprox. DAR 2005 and US EPA summary document 2007 confirm high toxicity to aquatic organisms.

Table 4: Toxicity reference values for aquatic species (most sensitive species of each group)

Species	Time-scale	Endpoint	Toxicity (mg/l)
Fish – Test substance: etofenprox			
Oncorhynchus mykiss	96 h, flow-through	Mortality, LC_{50}	0.0027
Brachydanio rerio	40 d, flow-through	Mortality and development, NOEC	0.025
Fish – Test substance: metabolite α-CO			
Oncorhynchus mykiss	96 h, flow-through	Mortality, LC_{50}	> 0.048
Invertebrates – Test substance: etofenprox			
Daphnia magna	48 h, static renewal	Mortality, EC_{50}	0.0012
Daphnia magna	21 d, semi-static	Reproduction, NOEC	0.000054
Invertebrates – Test substance: metabolite α-CO			
Daphnia magna	48 h, static	Mortality, EC_{50}	> 0.044
Algae – Test substance: etofenprox			
Pseudokirchneriella subcapitata	72 h, static	Biomass, E_bC_{50}	>0.05625
Pseudokirchneriella subcapitata	72 h, static	Biomass, NOEC	0.05625
Algae – Test substance: metabolite α-CO			
Pseudokirchneriella subcapitata	96 h, static	Biomass, E_bC_{50}	>0.053
Sediment dwelling organisms – Test substance: etofenprox			
Chironomus riparius	10 d, static water-sediment system	Mortality, EC_{50}	>0.0209

Chironomus riparius	25 d, static water-sediment system	Emergence, Development , NOEC	0.0038
Sediment dwelling organisms – Test substance: metabolite 4'-OH			
Chironomus riparius	48 h, static	Mortality, LC_{50}	0.0502
Microorganisms – Test substance: etofenprox			
Activated sludge	3 h, static	Respiration rate, NOEC	≥100 mg/l or ≥water solubility

v) Terrestrial compartment

396. US EPA summary document 2007: Etofenprox is practically acute non-toxic to mallard ducks. Two avian subacute dietary toxicity tests also show that etofenprox is practically non-toxic to avian test species (cf. toxicity reference values in Table 5).

Table 5: Toxicity reference values (bw....body weight)

Exposure scenario	Organism/Species		Time Scale Endpoint	Toxicity value	Reference
Acute toxicity	birds	mallard duck	LD_{50}	> 2000 mg/kg bw	AR 2007
Dietary toxicity	birds	mallard duck, bobwhite quail	LC_{50}	LC_{50} > 5000 mg as/kg diet	
Reproductive toxicity	birds	bobwhite quail	NOEL	1000 mg/kg diet	
Acute toxicity	earth-worms	*Eisenia foetida*	LC_{50}	>47.2 mg/kg dry soil (measured)	

w) Toxicity to pollinators

397. DAR 2005 states that the 24-hour acute oral and contact LD_{50}values of etofenprox technical were 0.27 and 0.13 µg a.i./bee, respectively.

9.12 Other information

398. The toxicological information provided in the DAR 2005 is in agreement with the EU biocides CAR 2011. However no classification proposal is presented.

399. The toxicological information provided in the US EPA summary document 2007 is in agreement with the EU biocides draft CAR 2011. However no classification proposal is presented with regard to STOT RE or risk for breast fed babies.

400. The summary provided above is in agreement with the toxicological information provided in the PPDB database and in the PAN pesticides database with the exception that both of these databases indicate that reproductive toxicity results are unclear or positive, respectively and the latter database presents the US EPA conclusion that at high doses etofenprox is likely to be carcinogenic.

9.13 References

AR (2007) Assessment Report, Etofenprox, Product-type 8 (Wood preservatives), September 2007, available at http://ec.europa.eu/environment/biocides/annexi_and_ia.htm, 2012-03-26

DAR (2005) Draft Assessment Report Etofenprox, June 2005 http://dar.efsa.europa.eu/dar-web/provision, 2012-03-26

EFSA review report 2009, Review report for the active substance etofenprox, 22 October 2009 http://ec.europa.eu/sanco_pesticides/public/index.cfm?event=activesubstance.selection, 2012-03-26

EU Endocrine Disruption Database (2012) http://ec.europa.eu/environment/endocrine/strategy/short_en.htm, 2012-04-16

EU biocides draft CAR 2011 Etofenprox Product-type PT 18 (Insecticide), http://ec.europa.eu/environment/biocides/evaluation_reports.htm, 2012-04-16

PPDB (2012) Pesticide Properties DataBase, University of Hertfordshire, http://sitem.herts.ac.uk/aeru/footprint/en/ 2012-04-18

US EPA summary report (2007) Summary Document Registration Review: Initial Docket, Case

Number 7407, EPA-HQ-OPP-2007-0804, August 2007
http://www.epa.gov/pesticides/chemicalsearch
WHO (2007) WHO SPECIFICATIONS AND EVALUATIONS FOR PUBLIC HEALTH PESTICIDES ETOFENPROX,
http://www.who.int/whopes/quality/en/Etofenprox_eval_WHO_july_2007.pdf, 2012-04-16

10. Esfenvalerate

CONCLUSIONS

Assessment of POP properties – comparison with the criteria of Annex D and other hazard indicators

10.1 Persistence

401. The reported DT_{50} soil field values [62 to 123 days], DT_{50} water-sediment/whole system data [54 to 80 days], DT_{50} water [30 days] and a high Koc value in combination with low water solubility, might indicate that the persistence cut-off criterion according to Annex D 1 (b) (i) is not fulfilled. However there are also reported findings that esfenvalerate will persist in some environments, especially soils and sediments. Degradation values in soil under aerobic and anaerobic conditions from open literature (quoted in a governmental report) exceeds >180 days. The modelled P-score of 0.72 indicates also high persistence. Therefore persistence in soil cannot be excluded and Annex D 1 (b) (i) is met.

10.2 Bioaccumulation

402. The log K_{ow} of esfenvalerate is 6.24 and the experimentally retrieved BCF values (2,850 – 3,650) are <5,000. The B-score of 0.001 for esfenvalerate is lower than the cut-off value of 0.5.
403. Based on experimentally derived BCF values esfenvalerate does not meet the criterion on bioaccumulation according to Annex D 1 (c) (i).

10.3 Long-range transport (LRT)

404. Esfenvalerate is not persistent in the atmosphere (calculated DT50 values of 6 and 29 hours) and is not expected to migrate through LRT. However results from the OECD multimedia fate model indicate a high CTD and TE. The half-life in air is <2 days. However more information would facilitate a conclusion on the Annex D 1 (d) criterion.

10.4 Ecotoxicity (including pollinator toxicity)

405. Esfenvalerate is very highly toxic to fish, algae and aquatic invertebrates; in addition esfenvalerate is highly acutely toxic to honey bees. According to the EU-GHS is classified as aquatic acute and chronic category 1.
406. Based on its high aquatic toxicity and toxicity to human health (see section below) esfenvalerate meets the Annex D 1. (e) (ii) criterion.

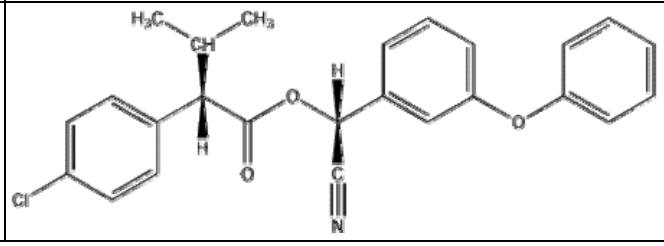
10.5 Toxicity to human health (including mutagenicity, carcinogenicity and adverse effects on the reproductive, endocrine, immune or nervous systems)

407. Esfenvalerate was classified for EU-GHS category 3 with the oral and respiratory route. It was also classified for skin sensitization with positive M&K test data. The substance was no skin or eye irritant
408. The substance was not classified for carcinogenicity or mutagenicity within the EU-GHS system. Also US EPA and IARC evaluations were in agreement with this conclusion. The available data did not indicate concern for developmental or reproductive toxicity. Esfenvalerate is listed in the EU database for endocrine disrupters within category 3b, which means that insufficient data are available for an evaluation of respective effects.
409. Representing a type II pyrethroid the primary toxicological effect is neurotoxicity, though no irreversible effects were observed. For long term limit value derivation body weight gain reduction was the critical systemic effect. With the application of a standard assessment factor of 100 an ADI of 0.02 mg/kg bw day was proposed.

10.6 Identity of the substance and physical and chemical properties

a) Name and other identifiers of the substance

Table 1: Substance identity

Common name:	Esfenvalerate
IUPAC name:	(S)-α-cyano-3-phenoxybenzyl (S)-2-(4-chlorophenyl)-3-methylbutyrate
CAS number:	66230-04-4
Molecular weight:	419.90
Chemical structure:	

b) Chemical group

410. Pyrethroid

c) Physico-chemical properties

Table 2: Overview of selected physico-chemical properties

Property	Value	Remarks and Reference
Vapour pressure at 25°C (mPa)	0.0000012	PPDB 2012
Water solubility at 20°C (mg/l)	0.001	PPDB 2012
Partition coefficient n-octanol/water (log value, pH 7, 20°C)	6.24	PPDB 2012
Partition coefficient air/water (log value)	-5.85	EPI Suite 4.0 (KOAWIN v 1.10)[25]
Partition coefficient air/octanol (log value)	12.09	EPI Suite 4.0 (KOAWIN v 1.10)
Henry´s Law Constant at 25°C ($Pa.m^3.mol^{-1}$)	4.90×10^{-04}	PPDB 2012

10.7 Classification and labelling

d) Harmonised Classification according to GHS

411. Regulation (EC) No 1272/2008 – 1nd amendment 2009

Category	Hazard-Phrase
Acute Tox. 3	H331 Toxic if inhaled.
Acute Tox. 3	H301 Toxic if swallowed.
Skin Sens. 1	H317 May cause an allergic skin reaction.
Aquatic Acute 1	H400 Very toxic to aquatic life.
Aquatic Chronic 1	H410 Very toxic to aquatic life with long lasting effects.

10.8 Environmental fate properties

e) Abiotic degradation

f) Hydrolysis

412. EFSA review report 2005: Reported a DT_{50} value at pH 4 to 5 of 192 days at 25°C; at pH 7: value was not calculated due to variability of results; and at pH 9 the reported DT_{50} value is 65 days at 25°C. Due to the cleavage of the ester bond CPIA (p-chlorophenylisovaleric acid) is generated.

[25] http://www.epa.gov/oppt/exposure/pubs/episuite.htm

g) Phototransformation/photolysis

413. EFSA review report 2005: Natural sunlight at 25°C in distilled water: DT_{50} 10 days: Artificial sunlight, sterilised water: DT_{50}: 6 days; Relevant metabolite: 27% CPIA by day 7

414. PPBD 2012: The photolysis of esfenvalerate is moderately fast.

h) Biodegradation

415. Experimental data have been reviewed and summarized previously by numerous international organizations like EFSA (cf. Table 4.) and US-EPA. US EPA summary 2009 intended to require additional data on aerobic aquatic metabolism, and on anaerobic aquatic metabolism to conduct a complete risk assessment (ref. to US EPA 2009).

416. US EPA 2008 state that esfenvalerate will persist in some environments, especially soils and sediments. Samsoe-Petersen et al. 2001 reviewed by US EPA 2008 measured degradation rates of [chlorophenyl-^{14}C]esfenvalerate and [phenoxyphenyl-^{14}C]esfenvalerate in pond sediment and 50 percent mineralization occurred between 73 and 350 days based on $^{14}CO_2$ evolution. This indicates that esfenvalerate sorbed onto sediment is likely to persist. However, the half-lives were based on measured $^{14}Co_2$ and it can be assumed that conversion of the SS-isomer to other isomers was not considered.

417. Overall data indicate that esfenvalerate is likely to bind to organic matter in soils and will degrade in the order of months to years via microbial degradation. The open literature also reported data on aerobic and anaerobic metabolism. Laskowski 2002 referenced in US EPA 2008 reported that aerobic soil half-lives ranged from 15 to 546 days with an average of 107 days. Kelley 2007 referenced in US EPA 2008 reported anaerobic soil half-lives ranged from 104 to 203 days with an average of 154 days.

Table 4. Biotic degradation of esfenvalterate

Study type.	Results	Reference	Remark
DT_{50} soil lab (days):	28 – 50 (20°C) 26.0 – 74 (25°C)	EFSA review report 2005	-
DT_{50} water (days):	Esfenvalerate 30.3% at time 0; Esfenvalerate 2.7 – 3.4% at 100 days	EFSA review report 2005	Water/sediment study on Japanese pond and river sediment at 25 °C and UK natural aquatic systems at 10 °C-
DT_{50} water sediment/whole system (days):	54 – 80 days	EFSA review report 2005	EFSA conclusion: Esvenvalerate is not persistent in aquatic systems
DT_{50}soil field (days):	62 – 123 d, after summer application; 68 – 87 days, after autumn application	EFSA review report 2005	$CONH_2$ Esf. > 0.01 mg/kg in all field dissipation studies

10.8 Potential for long range transport

418. The vapor pressure of 0.0000012 mPa (25°C) and the Henry law constant of $4.9x10^{-04}$ indicate that the substance is non-volatile (ref. PPDB 2012). HSDB 2012 reported according to a model of gas/particle partitioning of semivolatile organic compounds in the atmosphere, esfenvalerate is expected to exist solely in the particulate phase in the ambient atmosphere.

419. EFSA review report 2005 indicated a DT50 in air of 1.2 days according to the Atkinson method. US EPA 2008 referenced Comb 2002, MRID 467253-04 estimated a half-life of 5.8 hours using the Simplified Molecular Input Line Entry System (SMILES), indicating that esfenvalerate is not persistent in air. However these estimates might be prolonged due to the presence of the compound in primarily in the gas-phase.

420. The OECD "Pov and LRTP Screening Tool"[26] has been developed with the aim of using multimedia models for estimating overall persistence (Pov) and long-range transport potential (LRTP)

[26] http://www.oecd.org/document/24/0,3343,en_2649_34379_45373336_1_1_1_1,00.html

of organic chemicals at a screening level in the context of PBTs/POPs assessments. The input parameters for Kow and Kaw were taken from Tables 2, half-lives for air, water and soil are listed in Table 5.

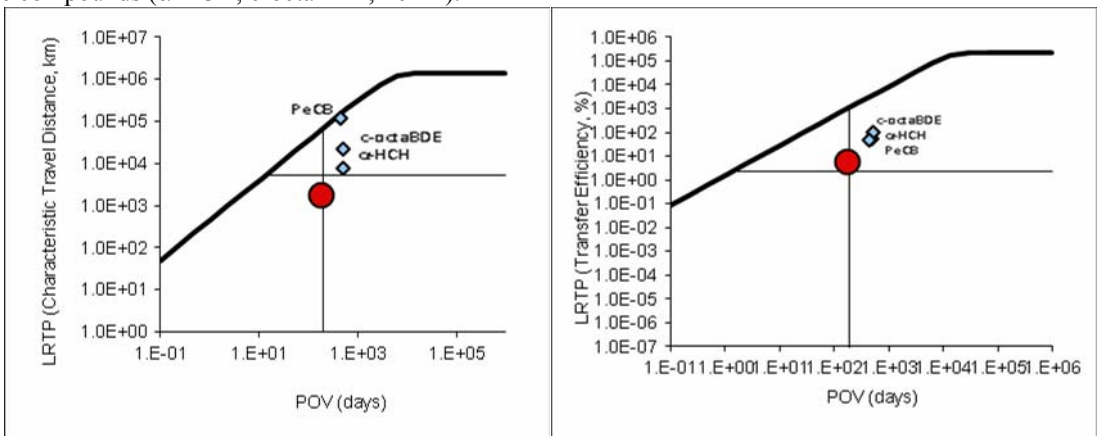
Table 5: Half-lives for air, water and soil (input parameters for the OECD Tool).

Compartment	Value (h)	Reference
Water (from water/sediment study)	195 (80 days)	See section above
Soil (DT50 $_{field}$)	2952 (123 days)	
Air	28.8	

421. ccording to Wegmann et al. 2009 compounds that are less problematic from an environmental exposure point of view are in the bottom-left corner (low Pov, low LRT), while substances of environmental concern are found in the upper right region (high Pov, high LRT).

422. With a calculated CTD (characteristic travel distance) of 1791 km esfenvalerate has LRT properties lower than alpha-HCH, PeCB and octaBDE (cf. Figure 1). However esfenvalerate is between the bottom right and left quadrant for CTD. For TE the model indicates intermediate concern. The calculated TE (transfer efficiency) and Pov values are 6% and 177 days. In the TE plot esfenvalaerate is on the boundaries of the upper left and right quadrant indicating to some extent POP-like persistence and LRT potential.

Figure 1: Results from the OECD Tool (CTD and TE) for esfenvalerate (red point) and s elected reference compounds (α-HCH, c-octaBDE, PeBD).



10.9 Bioaccumulation

423. EFSA review report 2005: The logK_{OW} is 6.24 and the experimentally retrieved BCF values are in the range of 2,850 – 3,650. US EPA 2008 reported a range of 340 to 3650 for total isomer residues in carp.

i) PB-score

424. Esfenvalerate has a PB-score of 0.719 (P-score 0.718 and B-score 0.001).

10.10 Human health hazard assessment

j) Acute toxicity

425. EFSA review report 2005: The data presented are in agreement with the actual EU GHS classification for acute toxicity class 3 for the oral and respiratory route and skin sensitization tested with the M&K method. The substance is not irritant.

426. US EPA summary 2009: Esfenvalerate is considered moderately acutely toxic via the oral route (category II), but is less toxic by the dermal route (Category III). Esfenvalerate is a mild skin irritant but is not a skin sensitizer.

k) Mutagenicity and Carcinogenicity

427. EFSA review report 2005: The substance was negative within in vitro and in vivo studies for genotoxicity and it was not carcinogenic in studies with mice and rats.

428. US EPA summary 2009: Esfenvalerate is classified as a group “E” carcinogen (no evidence of carcinogenicity).

429. IARC 1999: Fenvalerate was tested for carcinogenicity in two experiments in mice and in two experiments in rats by oral administration. There was no increase in the incidence of tumours in mice. In rats, there was an increased incidence of

benign mammary tumours in females in one study. In another study at a higher dose, no increase in tumour incidence was seen in animals of either sex. Administration of fenvalerate to mice in vivo induced chromosomal aberrations and micronucleus in bone marrow and morphological abnormalities in sperm. Induction of chromosomal aberrations and sister-chromatid exchange was observed in cultured human cells, and aneuploidy was seen in insects. fenvalerate inhibited gap-junctional intercellular communication in cultured mammalian cells. It did not induce mutation in insects or bacteria. It was concluded that there is inadequate evidence for the carcinogenicity of fenvalerate in experimental animals and no data were available form studies in humans. Consequently fenvalerate was not classifiable as to its carcinogenicity to humans (Group 3).

l) Toxicity for reproduction

430. EFSA review report 2005: No specific adverse effects to reproduction or development were reported, but parental toxicity in terms of body weight reduction or reduced body weight gain, food consumption and neurotoxicity.

m) Neurotoxicity

431. EFSA review report 2005: Within acute toxicity studies at lethal doses some neurotoxic effects were observed in rats. Within a 3 months neurotoxicity study no irreversible neurotoxic effects were observed.

432. US EPA summary 2009: The primary effects seen in subchronic and chronic studies are signs of neurotoxicity (e.g. decreased motor activity and hindlimb grip strength) and decrease in body weight.

433. US EPA summary 2009: US EPA registration review 2011: Based on the Agency's review of existing pyrethroid data, EPA has come to the conclusion that the DNT is not a particularly sensitive study for comparing the sensitivity of young and adult animals to pyrethroids. EPA has recently determined that, as an alternative to the generation and submission of a new DNT study, pyrethroid registrants may instead choose to cite the six previously submitted DNT studies for pyrethroid pesticides. The Agency is also investigating the need for additional experimentation, specific to the mode of action and pharmacokinetic characteristics of pyrethroids, to evaluate the potential for increased susceptibility of young organisms.

n) Immunotoxicity

434. -

o) Endocrine disruption

435. Esfenvalerate is listed in the EU database for endocrine disrupters (2012) within category 3b, which means that insufficient data are available for an evaluation of respective effects.

p) Mode of action

436. ATSDR 2003: The primary site of action for pyrethrins and pyrethroids is the sodium channel of nerve cells, Type II pyrethroids include a cyano group; their effects in rodents are usually characterized by pawing and burrowing behavior, followed by profuse salivation, increased startle response, abnormal hindlimb movements, and coarse whole body tremor that progresses to sinuous writhing (choreoathetosis). Clonic seizures may be observed prior to death. Body temperature is not increased, but may decrease. The term CS-syndrome (from choreoathetosis and salivation) has been applied to Type II responses.

q) Acceptable Exposure Levels

437. EFSA review report 2005: With short term studies clinical neurotoxic symptoms were critical. However for the derivation of the long term limit dose value (ADI) of 0.02 mg/kg bw day the adverse effects in the reproduction study and the long term studies (body weight gain reduction) were considered as critical. A standard assessment factor of 100 was engaged.

10.11 Environmental hazard assessment

r) Aquatic compartment (including sediment)

438. The substance has been notified and classified and labelled according to EU-GHS as acute and chronic aquatic category 1 with H400 and H410. These classification and labeling is in agreement with the data found in the PPDB 2012 and within the EFSA review report 2005. Herein, esfenvalerate is quoted as very highly toxic to fish, algae and aquatic invertebrates. The expected toxicity of metabolites of esfenvalerate does not exceed the parent toxicity. Table 6 lists the toxicity data according to the EFSA review report 2005.

Table 6: Toxicity reference values

Exposure scenario/Study type	Organism/Species	Time Scale Endpoint	Toxicity value	Remark
Acute	Fish	Acute LC_{50}	0.1 µg/L	-
	Fish (mesocosm)	NOEC	0.25 µg/L	-
Acute	Invertebrates	Acute EC_{50}	0.052 µg/L	-
	Invertebrates (mesocosm)	EAC	0.08 µ/L	-
		NOEC	0.01 µg/L	
	Algae	EbC_{50}	6.5 µg/L	-
		ErC_{50}	10 µg/L	

s) Terrestrial compartment

439. Terrestrial toxicity data were evaluated from EFSA review report 2005. These data have been summarized in Table 7. To conduct a complete risk assessment US EPA identified data gaps within the terrestrial toxicity data base, following studies are required to complete the data set: Avian acute oral for a passerine species, avian reproduction for an upland game bird and waterfowl, terrestrial plants seedling emergence, vegetative vigor tests.

Table 7. Toxicity reference value (source: EFSA review report 2005)

Exposure scenario/Study type	**Organism**	**Species**	**Time Scale Endpoint**	**Toxicity value**
Acute	Mammals	Rat	Acute LD_{50}	7.9 mg a.s/kg bw/day
Acute	Mammals	Rat	LD_{50}	88.5 mg/kg bw
Acute	Birds	Bobwhite quail	Acute LD_{50}	1,312 mg as/kg
Acute	Birds	Bobwhite quail/Mallard duck	Dietary LD_{50}	>5,000 mg/kg bw
Chronic	Birds	Bobwhite quail/Mallard duck	NOEC repr.	125 ppm
Acute	Earthworms	*Eisenia sp.*	Acute LC_{50}	212.5 mg/kg

t) Toxicity to pollinators

440. Esfenvalerate is highly acutely toxic to bees (ref. to Table 8).

Table 8: Toxicity reference values

Study type	**Organisms**	**Toxicity value LC_{50}**	**Reference**
Acute oral toxicity	Bees	0.21 µg/bee	EFSA review report 2005
Acute contact toxicity	Bees	0.06 a.s. µg/bee	EFSA review report 2005

10.12 Other information

441. Toxicological information presented in the PAN –pesticides database and in the footprint database is largely consistent with the toxicological information summarized above with the exception that the reproductive toxicity and developmental study results summarized from EFSA above seem not respected or insufficient for a conclusion in these two databases.

10.13 Reference

ATSDR (2003) TOXICOLOGICAL PROFILE FOR PYRETHRINS AND PYRETHROIDS, September 2003, http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=787&tid=153
EFSA review report (2005): Review report for the active substance esfenvalerate
EU Endocrine Disruption Database (2012) http://ec.europa.eu/environment/endocrine/strategy/short_en.htm, 2012-04-16
HSDB (2012) Hazardous Substance Database: Esfenvalerate, http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB, 2012-04-1
IARC (1999) Occupational Exposures in Insecticide Application, and Some Pesticides, Summary of Data Reported and Evaluation, 53, April 1999, available at http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php
PPDB (2012) Pesticide Properties DataBase, University of Hertfordshire, http://sitem.herts.ac.uk/aeru/footprint/en/ 2012-04-18
US EPA summary (2009) Esfernvalerate Summary Document Registration Review: Initial Docket December 2009, Docket Number: EPA-HQ-OPP-2009-0301, available at http://www.epa.gov/pesticides/chemicalsearch
US EPA (2008) Risks of Esfenvalerate Use to Federally Threatened California Red-Legged Frog (*Rana aurora draytonii*), February 2008, http://www.epa.gov/espp/litstatus/effects/redleg-frog/esfenvalerate/analysis.pdf
Wegmann F. Cavin L, MacLeod M, Scheringer M, Hungerbühler K. (2009) Environmental Modeling & Software 24, 228-237

11. Fenitrothion[27]

CONCLUSIONS

Assessment of POP properties – comparison with the criteria of Annex D and other hazard indicators

11.1 Persistence

442. Hydrolysis is of minor importance for fenitrothion elimination in the environment (pH dependant DT50 values of 100-200 days). Photochemical half-lives in water of 3 to 4 days indicate there may be some potential for photolysis to contribute towards degradation of free fenitrothion in the aquatic environment. In soil the active substance is rapid degraded with DT50 values of 2 days. However also longer DT50 values (up to 48 days) are reported. In water/sediment systems fenitrothion and its residues are expected to degrade with short DT values of <10 days. Therefore it can be concluded that fenitrothion does not meet Annex D criterion 1 (b) (i).

11.2 Bioaccumulation

443. Fenitrothion has a log Kow value <5. Experimental BCFs in the range of 20 to 450 for a number of different aquatic species were reported. Depuration in fish is considered to be fast. Based on these findings fenitrothion does not meet the criterion 1 (c) (ii) of Annex D.

11.3 Long-range transport

444. The half-life in air was calculated as <6 hours indicating that fenitrothion is not expected to persist in air or pose a risk of long-range transport in air. Therefore it is unlikely that fenitrothion fulfils the Annex D 1 (d) (iii) criterion.

11.4 Ecotoxicity (including pollinator toxicity)

445. Fenitrothion shows high toxicity to aquatic organisms that qualify for EU-GHS classification acute and chronic category 1 suggesting long lasting very toxic effects to aquatic life. Fenitrothion is considered highly toxic to honeybees and earthworms. Fenitrothion is very toxic to birds. Chronic effects in avian reproductive testing were observed. Based on its high aquatic toxicity and toxicity to terrestrial species (e.g. birds) as well as toxicity to human health (see below) Annex D 1 (e) (ii) is fulfilled.

11.5 Toxicity to human health (including mutagenicity, carcinogenicity and adverse effects on the reproductive, endocrine, immune or nervous systems)

446. Fenitrothion is of low acute systemic toxicity qualifying for GHS category 4. In the EU GHS system it is actually not classified for skin sensitization though data are available that support respective classification.

447. Fenitrothion is not classified for carcinogenicity or mutagenicity by EU-GHS and also the latest US EPA and IPCS evaluation support this conclusion. Sufficient data are available.

448. Fenitrothion is also not classified for reproductive toxicity. No immunotoxicity is reported.

449. However Fenitrothion is listed in the EU endocrine disrupter database within category 1 which means it shows evidence of endocrine disruption activity in at least one species using intact animals.

450. No delayed neurotoxicity was observed in a respective study. However representing an organophosphorous compound the critical effect is cholinesterase inhibition. Proposed long term limit values range between 0.0013 mg/kg bw day (US EPA) and 0.005 mg/kg bw day (DAR).

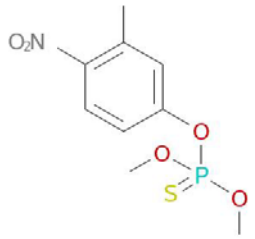
11.6 Identity of the substance and physical and chemical properties

a) Name and other identifiers of the substance

Table 1: Substance identity

Common name:	Fenitrothion
IUPAC name:	O,O-dimethyl O-4-nitro-m-tolyl phosphorothioate
CAS number:	122-14-5

[27] Fenitrothion is an alternative to both endosulfan and DDT.

Molecular weight:	277.24
Chemical structure:	

b) Chemical group

451. Organophosphate

c) Physico-chemical properties

Table 2: Overview of selected physico-chemical properties

Property	Value	Remarks and Reference
Vapour pressure	5.40E^{-05} mmHg	20°C, EXP
Water solubility	14 mg/L at 30°C	US EPA 2009
Partition coefficient n-octanol/water (log value)	2.69 3.43	US EPA 2009
Partition coefficient air/water (log value)	-4.42	EPI Suite v 4.1 (KOAWIN v. 1.10)
Partition coefficient air/octanol (log value)	7.72	EPI Suite v 4.1 (KOAWIN v. 1.10)
Henry´s Law Constant	9.30E^{-07} atm-m^3/mole	25°C, EST

11.7 Classification and labelling

d) Harmonised Classification according to GHS

Regulation (EC) No 1272/2008:

Category	**Hazard-Phrase**
Acute Tox. 4	H302- Harmful if swallowed
Aquatic Acute 1	H400- Very toxic to aquatic life
Aquatic Chronic 1	H410- Very toxic to aquatic life with long lasting effects

11.8 Environmental fate properties

452. According to DAR 2005 the following major metabolites (>10% of applied) were identified:

453. In soil: NMC (3-methyl-4-nitrophenol, in surface water: A-NMC (*O*-acetyl-3-methyl-4-nitrophenol), AM-FNT (*O*-(4-amino-3-methylphenyl) *O*,*O*-dimethyl phosphorothioate) and DM-AM-FNT (*O*-(4-amino-3-methylphenyl) *O*-hydrogen *O*-methyl phosphorothioate) and in sediment: NMC.

454. US EPA 2009: Fenitrothion has the potential for formation of the toxic degradation products through an oxidative desulfonation reaction. Two oxon degradation products were identified in several of the environmental fate studies, fenitrooxon and desmethyl fenitrooxon. Based upon applied radioactivity the two oxons - fenitrooxon (<4.3% applied) and desmethyl fenitrooxon (<4.3% applied) are minor degradation products.

e) Abiotic degradation

f) Hydrolysis

455. DAR 2005: Fenitrothion was only slowly hydrolysed in buffer solutions at pH 5, 7 and 9 at 25°C. Mean DT50 values were extrapolated well beyond the end of the study as 195.5, 183 and 100.5 days, respectively. Therefore, at environmentally relevant pH and temperature, it is unlikely that hydrolysis will contribute significantly to the degradation of fenitrothion in water.

g) Phototransformation/photolysis

456. DAR 2005 states a half-life in water of 3.3-3.6 days for photolysis. The one major degradate CA-FNT, which was not found in the dark control, declined to not detectable levels by the study end. These results indicate there may be some potential for photolysis to contribute towards degradation of free fenitrothion in the aquatic environment, perhaps more in Southern than Northern Europe.

h) Biodegradation

457. DAR 2005: Aerobic degradation of fenitrothion in soil under laboratory conditions is considered to be rapid, with DT50 values of around 2 days in 5 soils at 20-25°C. Only one major soil metabolite was formed under these conditions, NMC, which also degraded rapidly with DT50 values of up to 3.3 days. Under anaerobic laboratory conditions, fenitrothion also degraded rapidly, with a first order DT50 of 0.8 days at 25°C (in sandy loam).

458. US EPA 2009 reported <1% (of applied) fenitrooxon and desmethyl fenitrooxon in the soil metabolism study. However somewhat longer aerobic metabolism half-lives from other reports are cited (DT50 24 to 48 days from three or more studies).

459. In water/sediment systems DAR 2005 states that fenitrothion declined rapidly in the total system and in both the water and sediment phases with first order DT50 values of <2 days. In the water phase and total system, single phase and 2-phase exponential models respectively, were used with an accumulation phase, to estimate degradation rates for the major metabolites. The resulting DT50 values were <10 days.

11.9 Potential for long range transport

460. DAR 2005: The half-life in air was calculated as <6 hours indicating that fenitrothion is not expected to persist in air or pose a risk of long range transport in air. Based on this finding no multimedia fate modeling was performed.

11.10 Bioaccumulation

461. US EPA 2009 reports log Kow values of 2.69 and 3.43 indicating a low potential for bioaccumulation. DAR 2005: The BCF was 30 at 0.05 mg/L in a fish bioconcentration study. The depuration of fenitrothion was rapid (90% elimination in whole fish in less than 7 days). IPCS 1992 states BCFs for fenitrothion with continuing exposure to range from 20 to 450 for a number of different aquatic species.

i) PB-score

462. -

11.11 Human health hazard assessment

j) Acute toxicity

463. DAR 2005: Acute systemic toxicity and skin/eye irritation results are in agreement with the actual EU-CLP entry with the exception that the dermal LD50 would qualify the substance in addition for acute dermal category 4 (H312) and the results from the Magnusson and Kligman maximisation test for skin sensitization may be considered sufficient for respective classification.

464. US EPA Registration review 2009: Fenitrothion is acutely toxic (Toxicity Category II) via the oral, dermal, and inhalation routes of exposure, causes minor eye and dermal irritation, and is not a dermal sensitizer.

465. IPCS 1992: Fenitrothion is an insecticide of moderate toxicity with oral LD50 values in rats and mice ranging from 330 to 1416 mg/kg body weight. Acute dermal toxicity in rodents ranged from 890 mg/kg body weight to more than 2500 mg/kg body weight. Fenitrothion is only minimally irritating to the eyes and is nonirritating to the skin. The chemical showed dermal sensitizing potential in one of two studies on guinea-pigs.

k) Mutagenicity and Carcinogenicity

466. DAR 2005: On the basis of bacterial and mammalian in vitro tests and in vivo and somatic germ cells fenitrothion is not considered as genotoxic. On the basis of studies in rats and mice it is also not considered as carcinogenic.

467. US EPA Registration review 2009: Fenitrothion is not classified as a carcinogen.

No evidence of carcinogenicity was seen in the mouse and rat carcinogenicity studies. There is no concern for mutagenicity.

468. IPCS 1992: No carcinogenic effects were found in any of the long-term studies reported. Fenitrothion was not mutagenic in *in vitro* and *in vivo* studies.

l) Toxicity for reproduction

469. DAR 2005: Effects on pup body weight, viability and lactation in rats and incidence of abortions was observed only at maternally toxic doses and not considered as specific effect.

470. IPCS 1992: Fenitrothion has not been found to be teratogenic at doses of up to 30 mg/kg body weight in rabbits and up to 25 mg/kg body weight in rats. Dose levels exceeding 8 mg/kg body weight were maternally toxic.

471. Developing young rats exhibited behavioral deficits post-natally following *in utero* exposure. A NOEL for this effect was established at 5 mg/kg body weight per day.

472. Multigeneration reproduction studies on rats did not indicate any morphological effects. A NOAEL of 120 mg/kg diet, based on reproductive parameters, was demonstrated in these studies.

m) Neurotoxicity

473. DAR 2005: There was no evidence of delayed neurotoxicity in hens after acute or subacute exposure. In acute neurotoxicity study in rats tremors, reduced body temperature and motor activity were observed at ≥ 50 mg/kg bw in both sexes but there were no findings in males at 12.5 mg/kg bw and no neuropathological changes in both sexes. In a sub-chronic neurotoxicity study in rats with neuropathological assessments a NOAEL of 20 ppm (1.32 mg/kg bw/day)was identified based on impaired body weight gain and reduction in erythrocyte and brain cholinesterase at 60 ppm (3.99 mg/kg bw/day). Inhibition of cholinesterase activity was the critical effect for long and medium term limit dose derivation.

474. IPCS 1992: Delayed neurotoxicity has not been reported as a result of exposure to fenitrothion. Fenitrothion has been tested in short-term studies on rats, dogs, guinea-pigs, and rabbits and in long-term carcinogenicity studies on rats and mice. In short-term studies on rats and dogs ,the no-observed-adverse-effect levels (NOAELs), based on brain-ChE activity, were, respectively, 10 mg/kg diet and 50 mg/kg diet.

475. Long-term studies on rats and mice indicated a NOAEL (based on brain ChE activity) of 10 mg/kg diet.

n) Immunotoxicity

476. -

o) Endocrine disruption

477. EU Endocrine Disruption Database (2012): Fenitrothion was listed as category 1 suspected endocrine disrupter, i.e. produced at high volumes with evidence of endocrine disruption activity in at least one species using intact animals.

p) Mode of action

478. US EPA Registration review 2009: As with other OPs, the principal toxic effects induced by fenitrothion are related to its cholinesterase-inhibiting activity.

479. IPCS 1992: Fenitrothion is an organophosphate and causes cholinesterase activity depression in plasma, red blood cells, and brain and liver tissues. It is metabolized to fenitrooxon, which is more acutely toxic. Its toxicity may be potentiated by some other organophosphate compounds.

q) Acceptable Exposure Levels

480. DAR 2005: The following long and medium term limit dose values were derived on the basis of acetyl cholinesterase inhibition as critical effect and application of an assessment factor of 100: ADI = 0.005 mg/kg bw day; ARfD = 0.013 mg/kg bw day

481. US EPA Reregistration Review 2009: Population adjusted dose (PAD) acute, dietary = 0.13 mg/kg bw day; PAD chronic, dietary = 0.0013 mg/kg bw day. For both PADs an assessment factor of 100 was used. The critical effects were tremors

and impaired motor coordination for the acute exposure value and Plasma ChE inhibition and histophathology changes of the lymph nodes for the chronic exposure value.

482. International limit values for worker protection (GESTIS-Database, 2012): The limit values for 8 hours are 1 mg/m3 in Austria and 0.02 mg/m3 in Poland, a short term limit value of 0.1 mg/m3 is reported for Poland.

11.12 Environmental hazard assessment

r) Aquatic compartment (including sediment)

483. IPCS 1992: Fenitrothion is highly toxic for aquatic invertebrates in both freshwater (cf. Table 3) and seawater with LC50 values of a few µg/litre for most species tested. Field observations and studies on experimental ponds have shown effects on populations of invertebrates. However, most of the changes observed were temporary, even at concentrations considerably higher than those likely to occur after recommended usage. Fish are less sensitive to fenitrothion than invertebrates. The most sensitive life stage is the early larva. Field studies after application of fenitrothion to forests showed no effects on wild populations of fish or on the survival of caged test fish with measured water concentrations of fenitrothion of up to 0.019 mg/litre. Repeated application of fenitrothion to forests had no effect on fish populations.

484. US EPA 2009 identified the most conservative toxicological endpoint for aquatic species is 1.5 ppb from an acute toxicity study with brown shrimp, a marine/estuarine species.

485. Concerning toxicity of identified metabolites (cf. Table 3) DAR 2005 reports a 48 h EC50 for fenitrothion of 8.6 µg a.s./l and the 48 h EC50 for AM-FNT (the precursor to DM-AM-FNT) was 5.88 mg/l. AM-FNT was therefore three orders of magnitude less toxic than fenitrothion.

Table 3: Toxicity reference values for aquatic species, most sensitive species of each group (Table from DAR 2005) (a.s....active substance)

Group	Test substance	Time-scale	Endpoint	Toxicity (mg/l)
Laboratory tests				
Oncorhynchus mykiss	Technical fenitrothion	Acute	LC50 (96h)	1.3 mg a.s./L
Daphnia magna	Technical fenitrothion	Acute	EC50 (48h)	0.0086 mg a.s./L
Selenastrum capricornutum	Technical fenitrothion	Acute	EbC50 (72h)	1.3 mg a.s./L
Oncorhyncus mykiss	Technical fenitrothion	Chronic	NOEC (96 days)	0.088 mg a.s./L
Daphnia magna	Technical fenitrothion	Chronic	NOEC (21 days)	0.087 µg a.s./L
Daphnia magna	AM-FNT	Acute	EC50 (48h)	5.8 mg metabolite/l
Daphnia magna	NMC	Acute	EC50 (48h)	18 mg metabolite/L
Microcosm or mesocosm tests				
Microcosm study conducted with Daphnia magna – NOEC = 0.17 µg a.s./l.				

11.13 Terrestrial compartment

486. NRA (1999): Reports from acute, dietary and reproductive testing in quail and mallards are available. Laboratory and field information for a large number of species has been obtained from the scientific literature. Fenitrothion is slightly to very highly toxic to birds by acute oral and dietary routes. Chronic effects in avian reproductive testing were observed. Available field data from Scotland, Canada and Senegal indicate that a proportion of the bird population will receive a significant exposure to fenitrothion in sprayed areas, and that some birds will die and others suffer sub-lethal effects. US EPA 2009 indicated in bobwhite quail an acute oral LD50 of 23 mg/kg bw, for

subactue dietary an LC50 of 157 ppm and a chronic NOAEC/LOAEC of 13/17 ppm based on reduced egg production (most sensitive species).

487. Fenitrothion is considered highly toxic to honeybees and earthworms.

s) Toxicity to pollinators

488. DAR 2005 states that the acute oral and contact LD50 values of fenitrothion were 0.20 and 0.16 µg a.i./bee, respectively.

11.14 Other Information

489. Toxicological information present in the PAN –pesticides database and in the footprint database are consistent with the CMR, endocrine and neurotoxicity information summarized above.

11.15 References

DAR (2005) Draft Assessment Report Fenithrothion, January 2005 http://dar.efsa.europa.eu/dar-web/provision, 2012-03-26

EU Endocrine Disruption Database (2012) http://ec.europa.eu/environment/endocrine/strategy/short_en.htm, 2012-04-16

GESTIS-Database (2012) http://gestis-en.itrust.de/nxt/gateway.dll/gestis_en/000000.xml?f=templates$fn=default.htm$3.0, 2012-04-16

NRA (1999) The NRA review of fenitrothion, Interim Report, June 1999, http://www.apvma.gov.au/products/review/docs/fenitrothion_summary.pdf, 2012-04-16

IPCS (1992) INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY, ENVIRONMENTAL HEALTH RITERIA 133, FENITROTHION, WHO Geneva, 1992 http://www.inchem.org/documents/ehc/ehc/ehc133.htm 2012-04-20

US EPA (2009) Registration Review – Problem formulation for the Ecological Risk Assessment of Fenitrothion February 2009 http://www.epa.gov/pesticides/chemicalsearch 2012-04-16

US EPA Reregistration Review (2009) US EPA Fenitrothion Summary Registration review: initial docket March 2009, Docket Number: EPA-HQ-OPP-2009-0172 http://www.epa.gov/pesticides/chemicalsearch, 2012-04-16

12. Fenvalerate

CONCLUSIONS

Assessment of POP properties – comparison with the criteria of Annex D and other hazard indicators

12.1 Persistence

490. Fenvelerate is stable to hydrolysis at pH values below 7, it is also stable to photodegradation. Half lives of fenvalerate in soil are in the range of 30 to 80 days, assuming moderate persistency; the modelled P-score for fenvalerate is 0.718, indicating persistency. In field studies half-lives of up to 287 days were reported. Considering the experimental evidence of a reported (dissipation) half-live in soil of 287 days as well as modelled information that indicate high persistence, the P criterion according to Annex D 1 (b) (i) is fulfilled.

12.2 Bioaccumulation

491. Log Kow values in the range of 4.6 to 6.2 and BCF values in various aquatic species of 120 to 4700 show (high) potential of bioaccumulation. The modelled B-score for fenvalerate is low (0.001) suggesting low bioaccumulation potential. Monitoring data show increasing amounts of fenvelarate with trophic level. Therefore fenvalerate does not meet the bioaccumulation criterion of Annex D 1 (c) (i) though reported BCF values are close to 5000. More information may facilitate a conlcuison on the bioaccumulation potential of fenvalerate.

12.2 Long-range environmental transport (LRT)

492. Fenvalerate has a calculated half-life in air of 6 hours (<2 days) indicating fast degradation in air. Therefore it is unlikely that fenvalerate fulfils the Annex D 1 (d) (iii) criterion.

12.3 Ecotoxicity (including pollinator toxicity)

493. Fenvalerate is highly toxic to fish and arthropods (including daphnids and chironomids, bees and other terrestrial insects) as well as to amphibians. It can be concluded that fenvalerate fulfils the criteria according to Annex D 1 (e) (ii) based on its high reported ecotoxicity and toxicity to human health (see below).

12.4 Toxicity to human health (including mutagenicity, carcinogenicity and adverse effects on the reproductive, endocrine, immune or nervous systems)

494. No EU-GHS classification is available for fenvalerate. However according to the data presented by WHO it may qualify for GHS category 4 for oral and dermal route. When administered to rabbits dermally for 24 hours dermal irritation persistent for 7 days was observed. With rabbit eye exposure also severe eye effects were observed. The substance was not skin sensitizing.

495. IARC considered fenvalerate as not classifiable as to its carcinogenicity to humans (group 3). This is in agreement with WHO conclusion that summarizes also that no mutagenicity was observed in a series of in vitro and in vivo tests. Also no reproductive toxicity was observed in a three generation rat study and in mouse and rabbit teratogenicity studies.

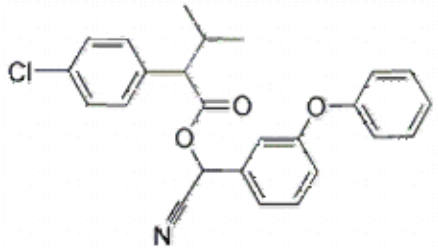
496. The substance is listed within category 2, which means that it is persistent or an HPVC with at least some in vitro evidence of biological activity related to endocrine disruption.

497. Neurological dysfunction is the most sensitive indicator of fenvalerate toxicity in rats, and is apparent in the early phase of repeated-dose studies. These appeared reversible including the observed adverse histopathological findings. A long term external limit dose value (RfD, ADI) of about 0.02 mg/kg bw day was consistently reported by US EPA and WHO/IPCS.

12.5 Identity of the substance and physical and chemical properties

a) Name and other identifiers of the substance

Table 1: Substance identity

Common name:	Fenvalerate
IUPAC name:	(RS)-α-cyano-3-phenoxybenzyl (RS)-2-(4-chlorophenyl)-3-methylbutyrate
CAS number:	51630-58-1
Molecular weight:	419.90
Chemical structure:	

b) Chemical group

498. Pyrethroid

c) Physico-chemical properties

Table 2: Overview of selected physico-chemical properties

Property	Value	Remarks and Reference
Vapour pressure at 25°C (mPa)	0.0192	PPDB 2012
Water solubility at 20°C (mg/l)	0.001	PPDB2012
Partition coefficient n-octanol/water (log value, pH 7, 20°C)	5.01	PPDB2012
Partition coefficient air/water (log value)	-5.85	Epi Suite 4.1(KOAWIn v1.10)[28]
Partition coefficient air/octanol (log value)	10.86	Epi Suite 4.1(KOAWIn v1.10)
Henry´s Law Constant at 25°C ($Pa.m^3.mol^{-1}$)	4.20×10^{-02}	PPDB 2012

12.6 Classification and labelling

d) Harmonised Classification according to GHS

499. Not available

e) Self classification

500. Notified CLP classification and labelling according to CLP-inventory [29]

Category	Hazard-Phrase
Acute tox 3 or 4 or no (oral)	H301 or H302 or no
Acute tox 4 or no (respiratory)	H332 or no
Skin irrit. 2 or no	H315 or no
Eye irrit. 2 or no	H319 or no
Skin sens. 1 or no	H317 or no
STOT SE 1 or 3 or no	H370 or H335 or no
STOT RE 1 or no	H372 or no
Aquatic acute 1 or no	H400 or no
Aquatic chronic 1 or no	H410 or no

[28] http://www.epa.gov/oppt/exposure/pubs/episuite.htm

[29] http://clp-inventory.echa.europa.eu/

12.7 Environmental fate properties

f) Abiotic Degradation

g) Hydrolysis

501. IPCS 1990: Fenvelarate was stable at pH 5.0 and 7.0 (half-lives of 130-220 days), while at pH 9.0 it underwent hydrolysis (half-lives of 64.6-67.2 days) mainly via ester bond cleavage. The main product was 2-(4-chlorophenyl)-3-methylbutyric acid, which amounted to 14.9% of the applied ^{14}C after 28 days.

h) Phototransformation/photolysis

502. ATSDR 2003 reported DT50 values of 8 to 100 days
503. IPCS 1990: In water and on soil surfaces, fenvalerate is photo-degraded by sunlight. Ester cleavage, hydrolysis of the cyano group, decarboxylation to yield 2-(3-phenoxyphenyl)- 3-(4-chlorophenyl)-4-methylpentane-nitrile (decarboxy-fenvalerate) and other radical-initiated reactions have been shown to occur.

i) Biodegradation

504. IPCS 1990: The persistence of fenvalerate has been evaluated in water and sediment. Insecticide emulsion was sprayed on the surface of the water at the normal rate and at twice the recommended dosage. The dissipation of the insecticide from water was rapid. About 74-80% of the pesticide was lost within 24 hours at both application rates. However, residues were found to be adsorbed onto sediment, and these persisted beyond 30 days. In soil, persistence was moderate, lasting around 30 days. According to ATSDR 2003 fenvalerate and deltamethrin appear to be the most persistent compounds in commercial use, especially in soils containing a high clay content or a large percentage of organic matter (cf. Table 3).

Table 3: DT50 values of fenvalerate in soil, water and sediment

Degradation 50%	days	Reference	Comment
DT_{50} soil lab	40	PPDB 2012	Moderately persistent
	77 (20°C)	PPDB 2012	
DT_{50}soil field	35	PPDB 2012	-
DT_{50} soil lab	75-80	ATSDR 2003	In sandy loam and silty clay loam soils
DT_{50}soil field	~ 60	ATSDR 2003	Ref. to Lee 1985
DT_{50}soil field	88 -287	ATSDR 2003	Ref. to USDA Pesticide Database
DT_{50} sediment/ seawater system	12	ATSDR 2003	pH 7.3 to 7.7

12.8 Potential for long range transport

505. Results of the Phototransformation in air according to EPI Suite TM v4.0 (AOPWIN v 1.92) are based on a 12h day are summarised in table 4.

Table 4 Phototransformation in air

Guideline / Test method	Molecule / radical	Rate constant for reaction with OH-radicals (k_{OH}) [cm^3 $molecule^{-1}$ sec^{-1}]	Half-life ($t_{1/2}$) [h]	OH-radical concentration (OH-radicals/cm^3)
AOPWIN	OH	22.2947 E-12	5.757	1.5×10^6

506. Based on the fast degradation rate in air no multimedia fate modelling was performed.

j) Bioaccumulation

507. PPBD 2012: BCF: 1664: high bioaccumulation potential

508. IPCS 1990: Fenvalerate is readily taken up by aquatic organisms. Bioconcentration factors ranged from 120 to 4700 for various organisms (algae, snail, *Daphnia* and fish) in model ecosystem studies. The fenvalerate taken up by aquatic organisms is rapidly lost on transfer to clean water. The compound can, therefore, be regarded as having no tendency to bioaccumulate in practice.

k) PB-score

509. Fenvalerate has a P-score of 0.718 and a B-score of 0.001 resulting in an overall B-score of 0.719.

12.9 Human health hazard assessment

510. US EPA IRIS 2003: Pydrin (=Fenvalerate), was composed of 4 stereoisomers: A-alpha, B-alpha, A-beta and B-beta in equal proportions. However, only the A-alpha isomer possessed significant insecticidal activity. The highly purified A-alpha isomer was found to be 5 times more toxic using neurological dysfunction as an endpoint.

l) Acute toxicity

511. WHO data sheet on pesticides 1996: Acute oral LD50 values between 80 and 450 mg/kg bw are reported when applied in DMSO and > 3200 mg/kg bw when applied in aqueous suspension. Acute dermal LD50 were between 1000 mg/kg bw and higher than 5000 mg/kg bw and acute respiratory LD50 values were higher than 100 mg/m3. These values indicate that the substance may qualify for GHS category 4 for oral and dermal route. Immediate clinical signs of neurotoxicity were observed. 24 hours dermal exposure of rabbits induced dermal irritation that persisted for 7 days. Severe conjunctivitis, corneal opacity and iritis occurred 30 minutes after instillation of 0.2 ml of the test formulation to rabbit eyes. No skin sensitization was detected in a guinea pig test.

m) Mutagenicity and Carcinogenicity

512. IARC 1991: No human data are available. There is inadequate evidence for the carcinogenicity of fenvalerate in experimental animals. Fenvalerate is not classifiable as to its carcinogenicity to humans (Group 3).

513. US EPA IRIS 2003: The NOAELs of several chronic / carcinogenicity studies with mice and rats are above the NOAEL of the 13 week rat study that is based on a LOAEL with clinical neurological signs. However it is explained that this substance has not undergone a complete evaluation and determination under US EPA's IRIS program for evidence of human carcinogenic potential.

514. WHO data sheet on pesticides 1996: No mutagenicity was observed within several bacterial strains and V79 Chinese hamster cells. Also no mutagenicity was observed in host-mediated assays with bacteria and yeast in mice. No chromosomal damage was observed in hamster bone marrow and there is equivocal evidence for a negative result from a dominant lethal mutation test in mice. No evidence of carcinogenicity was observed in ddY and B6C3F1 mice fed on a diet containing up to 3000 mg/kg/diet and 1250 mg/kg/diet, respectively. An equivocal increase in spindle-cell sarcoma of the dermis and subcutis was observed in Sprague Dawley rats receiving 1000 mg/kg diet, but when reviewed and re-classified according to the cell-type involved the incidence was not significant.

n) Toxicity for reproduction

515. US EPA IRIS 2003: The NOAELs of one three generation reproduction study in the rat and two teratology studies in mouse and rabbit are above the NOAEL of the

13 week rat study that is based on a LOAEL with clinical neurological signs. No explicit conclusion is presented with regard to classification.

516. WHO data sheet on pesticides 1996: No teratogenic effect was observed in mice and rabbits following oral administration of 50 mg/kg b.w./day on gestation days 6-15 and 6-18, respectively. In a standard three-generation reproduction study in rats, a reduced body weight in the F2b generation at 250 mg/kg diet was the only adverse effect observed. The weight loss was not supported by histopathological findings.

o) Neurotoxicity

517. US EPA IRIS 2003: Neurological dysfunction is the most sensitive indicator of pydrin (=Fenvalerate) toxicity in rats, and is apparent in the early phase of repeated-dose studies. Therefore, the NOEL observed in the 13-week study could adequately reflect the NOEL that would be expected if a chronic study had been run based on the most sensitive parameter (neurological dysfunction). Therefore, it was decided to use a l00-fold uncertainty factor with the NOEL observed in the 13-week study in order to determine the RfD.

518. WHO data sheet on pesticides 1996: Transient hypersensitivity, behavioural changes, hind limb ataxia and deficits in motor performance have been observed in rats, mice and hamsters following acute or chronic exposure to fenvalerate. Dose dependant histopathological changes include axonal breaks, swelling and degeneration of the myelin and increases in lysosomal enzyme activity in the posterior fibular and sciatic nerves. No adverse clinical or histopathological findings were observed following a single oral administration of 200 mg/kg b.w. to rats. Lesions of the sciatic nerve were observed in rats following 10 days administration of 3000 mg/kg diet and were still apparent three weeks after cessation of exposure, but not after a six week recovery period. No adverse histopathological effects have been reported in the sciatic nerves of animals following chronic and subchronic exposure, confirming the recovery from the transient episodes of ataxia displayed during early stages of these studies.

p) Immunotoxicity

519. -

q) Endocrine disruption

520. EU Endocrine Disruption Database 2012: The substance is listed within category 2, which means that it is persistent or an HPVC with at least some in vitro evidence of biological activity related to endocrine disruption.

r) Mode of action

521. WHO data sheet on pesticides 1996: Based on fenvalerate similarities with deltamethrin, toxicity is probably due to effects on both peripheral and central nervous system caused by interference with sodium ion permeability in stimulated nerve membranes. The toxic signs in laboratory animals include restlessness, tremors, piloerection, choreo-athetosis and salivation (CS-syndrome). Fenvalerate is classified as type II pyrethroid.

s) Acceptable Exposure Levels

522. US EPA IRIS 2003: A long term external limit dose value (RfD) of 0.025 mg/kg bw day was developed on the basis of a subchronic oral study and clinical neurological effects at the LOAEL with additional signs of toxicity at higher doses (reduction of body weight and food consumption, adverse effects on pituitary gland and salivary glands). The standard assessment factor of 100 was applied since neurological dysfunction is the most sensitive indicator of pydrin (=fenvalerate) toxicity in rats, and is apparent in the early phase of repeated-dose studies.

523. IPCS 1990: Since 1986, an acceptable daily intake (ADI) of 0-0.02 mg/kg body weight has been established.

12.10 Environmental hazard assessment

t) Aquatic compartment (including sediment)

524. IPCS 1990: In laboratory tests, fenvalerate is highly toxic for aquatic organisms (cf. Table 5). In field tests under aquatic conditions the compound strongly absorbs to sediments.

525. HSDB 2012: Amphibians are likely to be sensitive to low-level contamination events of fenvelerate. Tadpole growth was delayed following exposure to fenvalerate and tadpoles and salamander larvae responded to prodding not by darting away but by twisting abnormally. Both effects may result in greater vulnerability to predation.

Table 5: Toxicity reference values for the aquatic compartment

Exposure scenario/ Study type	Organism /Species	Endpoint	Toxicity value	Reference
Acute 96 hour (h)	Fish	LC_{50}	0.0036 mg/l (3.6 µg/l)	PPBD
Acute 48 h	Aquatic invertebrates	EC_{50}	0.00003 mg/l (0.03 µg/l)	PPBD
Chronic, 21 days (d)	Aquatic invertebrates	NOEC	0.00008 mg/l (0.08 µg/l)	PPBD
Acute 96 h	Aquatic crustaceans	LC_{50}	0.000005 mg/l (0.005 µg/l)	PPBD
Acute 72 h	Algae	EC50	50 mg/l	PPBD
Chronic 96 h	Algae	NOEC	10 mg/l	PPBP
Acute 96 h	Fish	LC_{50}	0.3 µg/l	IPCS
Chronic 28 d	Fish	LC_{50}	0.56 µg/l	IPCS
Acute	Aquatic invertebrates	LC_{50}	0.008 µg/l	IPCS
Chronic, 21 d	Aquatic invertebrates	NOEC	<0.005 µg/l	IPCS
Chronic 96 h	Algae	NOEC	>1000 µg/l	IPCS

u) Terrestrial compartment

526. IPCS 1990: Fenvalerate has moderate to low acute oral toxicity to mammals. However, LD50 values differ considerably (82 to > 3200 mg/kg) according to animal species and vehicle of adminis-

527. tration. Fenvalerate has very low toxicity to birds when given orally or applied to the diet. Table 6 summarized toxicity values from PPDB 20121

Table 6: Toxicity reference values for the terrestrial compartment

Exposure scenario/ Study type	Organism /Species	Endpoint	Toxicity value	Reference
Acute, oral	Rat	LD_{50}	451 mg/kg	PPBD
Dietary, 2-years	Rat	NOEL	250 ppm diet	PPBD
Acute	Bird	LD_{50}	9932 mg/kg	PPBD
Acute 14 day	Earthworms	LC_{50}	40 mg/kg	PPBD

Acute, oral	Rat	LD_{50}	82-3200 mg/kg	IPCS
Acute, oral	Bird	LD_{50}	>1500 mg/kg	IPCS
Acute, dietary	Bird	LD_{50}	>15000 mg/kg	IPCS

v) Toxicity to pollinators

528. PPBD 2012: Honeybees - Acute 48 hour LD50: 0.23 µg/ bee: High toxicity (contact); Harmful: Also to other arthropods

529. IPCS 1990: Fenvalerate is highly toxic to honey bees. The topical LD50 is 0.41 µg/bee, but there is a strong repellent effect of fenvalerate to bees, which reduces the effect in practice. There is no evidence of significant kills of honey bees under normal use. Fenvalerate is more toxic to predator mites than to the target pest species.

12.11 Other information

530. Toxicological information presented in the in the footprint database and in the PAN –pesticides database is largely consistent with the toxicological information summarized above, with the exception that the latter indicates suspicion for endocrine disruption.

531. ATSDR 2003: The enhanced insecticidal activity of esfenvalerate over fenvalerate is responsible that esfenvalerate has become the preferred compound in the United States because it requires lower application rates than fenvalerate and is thus a more powerful insecticide. Esfenvalerate contains a much higher percentage of the alpha-S-cyano phenoxybenzyl alcohol isomer than fenvalerate.

12.11 References

ATSDR (2003) Toxicological profile for pyrethrins and pyrethroids. http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=787&tid=153, 2012-04-16

EU Endocrine Disruption Database (2012) http://ec.europa.eu/environment/endocrine/strategy/short_en.htm, 2012-04-16

HSDB (2012) Hazardous Substance Database: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB, 2012-04-14

IPCS (1990) International Programme on Chemical Safety. Environmental Health Criteria 95. Fenvalerate. World Health Organization, Geneva, 1990.

IARC (1991) IARC Monograph VOL.: 53 available at http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php, 2012-04-23

PPDB (2012) Pesticide Properties Database: Fenvalerate http://sitem.herts.ac.uk/aeru/footprint/en/index.htm, 2012-04-24

US EPA IRIS (2003) US EPA IRIS Pydrin October 28, 2003, available at ttp://www.epa.gov/pesticides/chemicalsearch, 2012-04-23

WHO data sheet on pesticides (1996) WHO/FAO sheets on pesticides No 90, Fenvalerate. July 1996 (WHO/PCS/DS/96.90),available http://www.who.int/ipcs/publications/ehc/en/index.html, 2012-04-23

13. Flucythrinate

CONCLUSIONS

Assessment of POP properties – comparison with the criteria of Annex D and other hazard indicators

13.1 Persistence

532. Flucythrinate showed pH dependant hydrolytic degradation rates with DT50 from 40 days to 9 days (pH 3 to 9). Flucythrinate is of low to moderate persistence with reported DT50 soil lab values of 21 to 60 days. Dissipation half-lives of flucythrinate in agricultural soil range from 9.4–11.9 days. No DT50 water sediment/whole system and DT50 values in water were available in the screened data sources. The modelled P-score is 0.616, which is higher than the trigger of 0.5. However this modelled values is related to mineralization. Based on the available empirical evidence (DT50 <2 months from hydrolysis study, DT50 soil ≤2 months) it is likely that flucythrinate does not meet the persistence criterion of Annex D 1 (b) (i).

13.2 Bioaccumulation

533. Flucythrinate does fulfil the Annex D 1 (c) (i) criterion based on the on a log K_{OW} of 6.2. However also a value of 4.7 is reported. The experimentally derived BCF value of 2,300 in oysters indicated that the trigger value of 5,000 is not fulfilled. OSPAR indicated a BCF value of 5,000 and an estimated a BCF of 11,749. The modelled B-score is 0.545 is slightly higher than the trigger of 0.5.
534. Due the equivocal database, no final conclusion on bioaccumulation criterion according to Annex D 1 (c) (i) can be drawn.

13.3 Long-range transport (LRT)

535. Flucythrinate has a calculated half-life in air of 3 hours (<2 days) indicating fast degradation in air. Therefore it is unlikely that flucythrinate fulfils the Annex D 1 (d) (iii) criterion.

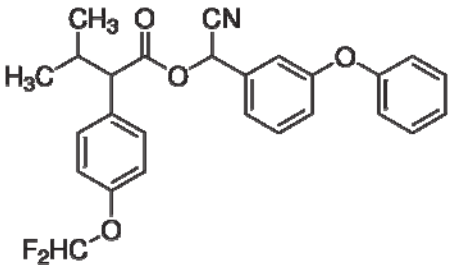
13.4 Ecotoxicity (including pollinator toxicity)

536. Flucythrinate is self-classified by different notifiers according to CLP regulation as acute aquatic 1 and chronic aquatic 1. Pyrethroids including flucythrinate are practically non-toxic to bird species, but are highly toxic to fish, aquatic invertebrates and crustaceans. In addition, flucythrinate is highly toxic to bees with a reported topical application (contact) LD50 of 0.078 µg per bee.
537. Based on its high aquatic toxicity and toxicity to humans Annex D 1 (e) (ii) is fulfilled.
538. 13.5 Toxicity to human health (including mutagenicity, carcinogenicity and adverse effects on the reproductive, endocrine, immune or nervous systems)
539. There is no EU GHS harmonised classification available for Flucythrinate. However within the self classifications provided in the CLP inventory acute systemic toxicity categories were presented up to category 1 for respiratory route and category 3 for the oral route and category 4 for the dermal route. There is also one self classification for skin and eye irritation. The data summarized below are in agreement with this. The toxicological profile of flucythrinate was similar to that of related pyrethroids, although the acute oral toxicity was relatively high.
540. The in vitro genotoxicity tests and a rat dominant lethal test are negative. The carcinogenicity test results in rats and mice were considered as negative. Also the rat and rabbit developmental toxicity tests and the three generation rat study did not indicate specific concern for reproductive toxicity. The substance is not listed in the EU endocrine disrupter database.
541. Representing a pyrethroid of type II the critical toxicological effects are of neurotoxic nature. Short and long term mouse, rat and dog studies support that the toxicological profile of flucythrinate is similar to that of related pyrethroids. Applying a standard assessment factor of 100 to the NOAELs of these studies a long term limit value of 0.02 mg/kg bw day was proposed.

13.5 Identity of the substance and physical and chemical properties

a) Name and other identifiers of the substance

Table 1: Substance identity

Common name:	Flucythrinate
IUPAC name:	(*RS*)-α-cyano-3-phenoxybenzyl (*S*)-2-(4-difluoromethoxyphenyl)-3-methylbutyrate
CAS number:	70124-77-5
Molecular weight:	451.46
Chemical structure:	

b) Chemical group

542. Pyrethroid

c) Physico-chemical properties

Table 2: Overview of selected physico-chemical properties

Property	Value	Remarks and Reference
Vapour pressure at 25°C (mPa)	0.0012	PPDB 2012
Water solubility at 20°C (mg/l)	0.5	PPDB 2012
Partition coefficient n-octanol/water (log value, pH 7, 20°C)	4.7	PPDB 2012
Partition coefficient air/water (log value)	-5.45	EPI Suite v 4.1 (KOAWIN v. 1.10)
Partition coefficient air/octanol (log value)	10.15	EPI Suite v 4.1 (KOAWIN v. 1.10)
Henry´s Law Constant at 25°C ($Pa.m^3.mol^{-1}$)	1.08×10^{-03}	PPDB 2012

13.6 Classification and labelling

d) Harmonised Classification according to GHS

543. Not available

e) Self classification

544. Various entries in CLP Inventory (http://echa.europa.eu/web/guest/information-on-chemicals/cl-inventory-database) therefore we provide the range of entries here:

Category	Hazard-Phrase
Flam.Liq.3 to no classification	H226
Acute Tox 3.(oral)	H301
Acute Tox 4. to no classification (dermal)	H312
Acute tox 1. to 3 (respiratory)	H330, H331
Skin irrit. 2 to no classification	H315
Eye irrit. 2 to no classification	H319
STOT RE 2 to no classification	H373
Aquatic acute 1	H400
Aquatic chronic 1 to no classification	H410

13.7 Environmental fate properties

f) Abiotic degradation

g) Hydrolysis

545. PPDB 2012: The degradation is pH sensitive and the DT_{50} ranges from 40 days at pH3, 6.3 days at pH 9, all at 27°C.

h) Phototransformation/photolysis

546. PPDB 2012: Aquatic photolysis DT_{50} at pH 7 is 4 days, which is moderately fast.

i) Biodegradation

547. ATSDR 2003: The half-life flucythrinate in agricultural soil was 9.4–11.9 days, respectively, depending upon the application rate.

548. PPDB 2012: Flucythrinate is of low to moderate persistence with reported field half-lives of 21 to 60 days. Observed persistence will vary according to soil type and other variables. It is nearly insoluble in water and has a very strong tendency to bind to soil particles.

549. Ectoxnet 2012: Breakdown in water: In pond waters and in laboratory degradation studies, pyrethroid concentrations decrease rapidly due to sorption to sediment, suspended particles, and plants.

Table 3: Biotic degradation of flucythrinate

Study type	Results	Reference	Remarks
DT_{50} soil lab (days):	60 (typical) 21	PPDB 2012 PPDB 2012	Moderately persistent Non persistent
DT_{50} water (days) from water/sediment study:	No information	PPDB 2012	-
DT_{50} water sediment/whole system (days):	No information	PPDB 2012	-

13.8 Potential for long range transport

550. According to AOPWIN v1.92[30] the photo-chemical degradation of flucthrinate in air has been estimated to be fast. The calculated DT50 is 2.75 hours (assuming a 12 hours day and a OH concentration of 1.5 x 10^6 OH/cm^3). The OH Rate Constant is 46.6260 x10^{-12} cm^3/$molecule^{-sec}$.

13.9 Bioaccumulation

551. According to the PPDB 2012 a BCF of 11,749 was estimated, which indicates a high potential for bioaccumulation. The experimentally derived log Kow is 6.2 (Hansch et al; 1995). Flucythrinate is rapidly metabolised in mammals and eliminated via urine and feces (unaltered parent) during the first 24 hours without adsorbing into the bloodstream (ref. to Extoxnet 2012). Fish half-lives for elimination of several pyrethroids by trouts are longer than for mammals (>48 hours). Flucythrinate accumulated in the edible tissues of bluegill sunfish to 487 times the concentration in the surrounding water (ref. to Extoxnet). In a 28-day laboratory study, a steady-state BCF of 2300 was measured in eastern oysters (*Crassostrea virginica*) (ref. to Schimmel et al., 1983). The available information on bioconcentration and bioaccumulation of flucythrinate was summarized by OSPAR 2002 (ref. to Table 4).

[30] http://www.epa.gov/oppt/exposure/pubs/episuite.htm

Table 4: Bioaccumulation/Bioconcentration of flucythrinate (source: OSPAR 2002)

4	**BIOACCUMULATION/BIOCONCENTRATION**			
4.1	Log Kow	7	QSAR-DK: EPIWIN 3.02	high potential for bioaccumulation
4.1	Log Kow	2	KemI Report 9/88. Solna, Sweden, Nationals Chemicals Inspectorate, 1988 (In Swedish)	low potenial for bioaccumulation
4.2	BCF	11749	QSAR-DK: EPIWIN 3.02	very high bioconcentration factor
4.2	BCF	5000	Spehar et al. 1983	Very high bioconcentration factor

j) PB-score

552. Flucythrinate has a P-score of 0.616 and a B-score of 0.545 resulting in an overall B-score of 1.161.

13.10 Human health hazard assessment

k) Acute toxicity

553. Extoxnet 2012: The data summarized are roughly in line with the actual classification proposals: Flucythrinate was highly toxic via the oral route. The oral LD50 for technical flucythrinate was between 67 and 81 mg/kg in rats and mice. Flucythrinate was moderately toxic via the dermal route with a reported dermal LD50 in rabbits of greater than 1000 mg/kg and in guinea pigs of greater than 2000 mg/kg. Flucythrinate is moderately toxic via the inhalation route. The 4-hour inhalation LC50 for technical flucythrinate in rats is 4.85 mg/L. Flucythrinate can cause mild to severe skin irritation. Flucythrinate may also cause extreme eye irritation. It failed to produce allergic reactions in guinea pigs. Skin application on human volunteers caused more severe paresthesia (i.e., abnormal sensations such as burning or tingling) on the earlobes than on the forearms. This condition lasted for approximately 24 hours after application on earlobes and 4 to 5 hours on forearms. When 13.8 mg/cm2 was applied to the forearms of volunteers, paresthesia appeared 4 to 5 hours later and lasted for 3 days.

554. IPCS 1985: The data presented are in agreement with those presented in Extoxnet. The toxicological profile of flucythrinate is similar to that of related pyrethroids, although the acute oral toxicity is relatively high.Signs of flucythrinate toxicity included decreased activity, salivation and tremors. Death usually occurred within two days and recovery among survivors was generally complete by six days.

l) Mutagenicity and Carcinogenicity

555. Extoxnet 2012: Ames tests using several strains of bacteria exposed to concentrations as high as 1000 ug/plate and a rat dominant-lethal test at up to 10.0 mg/kg showed no evidence that flucythrinate causes mutations. No tumor formation was observed in mice or rats fed doses of up to 6 mg/kg for 24 months.

556. IPCS 1985: Flucythrinate was without mutagenic activity in a number of ssays with microorganisms and mammalian cells (AMES, UDS with primary rat-hepatocytes, CHO/HGPRT mutation test). Flucythrinate has no dominant lethal effect in rats. The toxicological profile of flucythrinate is similar to that of related pyrethroids, although the acute oral toxicity is relatively high. The production of hepatocellular tumours in the mouse is not considered to be of biological significance, considering the known susceptibility of the mouse to this effect.

m) Toxicity for reproduction

557. Extoxnet 201 : In a three-generation reproductive study, rats given 1.5, 3 or 6 mg/kg/day showed reduced parental and pup weights, and decreased pup survival. Reduced litter size occurred at 3 and 6 mg/kg/day. It is unlikely that reproductive effects due to flucythrinate will be seen under normal circumstances in humans. Flucythrinate did not cause birth defects. No teratological effects were observed in studies with rats or rabbits. The highest dose tested was 8.0 mg/kg/day for rats and 60 mg/kg/day for rabbits.

558. IPCS 1985: The results from the three generation study are summarized like in Extoxnet but in addition skin irritation observed as hair loss, scabbing and open lesions were reported and a NOAEL of 30 ppm (1.5 mg/kg bw day) was proposed. The results of a rat teratogenicity study indicated that daily treatment up to 4 mg/kg was without effect, while daily treatment up to 8 mg/kg, which produced severe maternal toxicity in the rat, produced no teratogenic effect. The results of a rabbit teratogenicity study indicated a no-effect level at 30 mg/kg based on implantation rates and minor variations and no teratogenic effects at 60 mg/kg, although treatment at this level caused maternal toxicity. In summary Flucythrinate is not teratogenic in the rat or rabbit. The compound was observed to cause mild maternal weight reduction in a reproduction study, but not at levels causing concern.

n) Neurotoxicity

559. Extoxnet 2012: Rats fed 15 mg/kg/day for 28 days showed severe motor symptoms (involuntary muscular movement), and rats fed 7.5 mg/kg/day showed moderate motor symptoms. In both cases, symptoms disappeared within 48 hours after resumption of a normal diet. Symptoms exhibited by animals in other short-term feeding studies include vomiting, diarrhea, incoordination, excessive salivation and urination, and hypersensitivity. No adverse effects were observed when rats and dogs were fed flucythrinate for 90 days at doses of up to 3 mg/kg/day for rats and 3.75 mg/kg/day for dogs. Dogs fed 7.5 mg/kg/day for 2 years exhibited vomiting and decreased body weight gain. Rats fed 6 mg/kg/day for 2 years also exhibited decreased body weight gain. Pyrethroids primarily affect the central nervous system. Long-term, high-dose feeding studies have shown liver and kidney effects.

560. IPCS 1985: Short and long term mouse, rat and dog studies are summarized. The toxicological profile of flucythrinate is similar to that of related pyrethroids, although the acute oral toxicity is relatively high.

o) Immunotoxicity

561. -

p) Endocrine disruption

562. -

q) Mode of action

563. ATSDR 2003: The primary site of action for pyrethrins and pyrethroids is the sodium channel of nerve cells, Type II pyrethroids include a cyano group; their effects in rodents are usually characterized by pawing and burrowing behavior, followed by profuse salivation, increased startle response, abnormal hindlimb movements, and coarse whole body tremor that progresses to sinuous writhing (choreoathetosis). Clonic seizures may be observed prior to death. Body temperature is not increased, but may decrease. The term CS-syndrome (from choreoathetosis and salivation) has been applied to Type II responses.

r) Acceptable Exposure Levels

564. Extoxnet 2012 : An external limit value (ADI) of 0.02 mg/kg bw day is referenced.

565. IPCS 1985: An estimate for an external limit value (ADI) is provided as 0 - 0.02 mg/kg b.w. This is based on studies in mouse, rat and dog with NOAELs of 4.0, 1.6 and 2.5 mg/kg bw day, respectively.

13.11 Environmental hazard assessment

s) Aquatic compartment (including sediment)

566. Flucythrinate is very highly toxic to fish, aquatic crustacean, and aquatic invertebrates (cf. Table 6). The 96-hours LC_{50} values for fish are generally below 0.001 mg/L (PPDB, ECETOC, EXTOXNET).

Table 6. Toxicity reference values

Exposure scenario/Study type	Organism/Species		Time Scale Endpoint	Toxicity value	Reference
Acute, 96 hours	Fish	*O. mykiss*	LC_{50}	0.32 mg/L	PPDB 2012
Acute, 48 hours	Aquatic Invertebrates	*Daphnia magna*	EC_{50}	0.0083 mg/L	PPDB 2012
Acute, 96 hours	Aquatic crustaceans	*Americamysis bahia*	LC_{50}	0.000006 mg/L	PPDB 2012
Acute, 96 hours	Fish	*P. promelas*	LC_{50}	0.00019 mg/L	EnviChem 2012

t) Terrestrial compartment

567. Pyrethroids including flucythrinate are practically non-toxic to bird species (cf. Table 7).

Table 7. Toxicity reference values

Exposure scenario/Study type	Organism/Species		Time Scale Endpoint	Toxicity value	Reference
Acute	Bird	*Anas platyrhynchoss*	LD_{50}	2510 mg/kg	PPDB 2012
Acute, oral	Mammals	*Rat*	Oral LD_{50}	67 mg/kg	PPDB 2012
Short-term, dietary	Mammals	*Americamysis bahia*	NOEL	60 ppm diet	PPDB 2012

u) Toxicity to pollinators

568. PPDB 2012: Flucythrinate is highly toxic to bees with a reported topical application (contact) LD_{50} of 0.078 µg per bee.

13.12 Other information

569. No additional critical information on the toxicology is available in the HSDB entry as screened on April 13, 2012.

570. Toxicological information presented in the PAN –pesticides database and in the PPDB database is largely consistent with the toxicological information summarized above with the exception that the data availability seems comparatively less complete.

13.13 References

Agnihotri NP, Jain HK.(1987) Persistence of flucythrinate and fluvalinate in soil, water and sediment. Pesticides 21(6):36-38.

ATSDR (2003) Toxicological profile for pyrethrins and pyrethroids; US Department of Health and Human Services, Public Health Service,. Agency for Toxic Substancees and Disease Registry, September 2003 www.atsdr.cdc.gov/toxprofiles/tp155.pdf, 2012-04-16

ECHA Classification &Labelling inventory (2012)
http://echa.europa.eu/web/guest/regulations/clp/cl-inventory, 2012-04-16

Ecotox Database, US EPA (2012)
http://cfpub.epa.gov/ecotox/, 2012-04-16

Extoxnet (2012):
http://extoxnet.orst.edu/pips/flucythr.htm, 2012-04-16

EnviChem (2012)
http://www.ymparisto.fi/default.asp?contentid=373872&lan=EN , 2012-04-16

Hansch et al. (1995) Exploring QSAR. Hydrophobic, Electronic, and Steric Constants. ACS Prof Ref Book. Heller SR, consult. ed., Washington, DC: Amer Chem Soc p.185 (1995)

IPCS (1985) Pesticide Residues in Food , Part II Toxicology, Flucythrinate, WHO, 1985,
http://www.inchem.org/pages/jmpr.html

OSPAR (2002)
http://www.ospar.org/v_substances/get_page.asp?v0=70124775.xls, 2012-04-16

PPDB (2012) Pesticide Properties DataBase, University of Hertfordshire,
http://sitem.herts.ac.uk/aeru/footprint/en/, 2012-04-18

Schimmel SC. (1983). J Agric Food Chem 31: 104-13.

Spehar,R.L., D.K.Tanner, and B.R.Nordling(1983) Toxicity of the Synthetic Pyrethroids, Permethrin and AC 222, 705 and Their Accumulation in Early Life Stages of Fathead Minnows and Snails Aquat. Toxicol. 3(2):171-182

14. Flufenoxuron

CONCLUSIONS

Assessment of POP properties – comparison with the criteria of Annex D and other hazard indicators

571. Flufenoxuron has been considered by the EU ad hoc working group on PBT[31]. Flufenoxuron has been discussed at the 10th and 11th meeting of the TC NES subgroup on identification of PBT and vPvB substances. At the 11th meeting, the group concluded that flufenoxuron fulfils the P, vP (very persistent), B, vB (very bioaccumulative) and T criteria: Flufenoxuron is a PBT/vPvB substance (EU Draft final CAR 2010)

14.1 Persistence

572. TC NES subgroup based their conclusion vP on DT50s (extrapolated to 12°C) in soil degradation studies from 68 to 235 days (5 soils, 2 labels). However without the temperature adjustment no reported DT50 value exceed the threshold of 180 days. The later holds true for sediment DT50 values as well. DT50 (dissipation) in water from water/sediment systems are <1 days; hydrolysis is very slow (DT50 up to 94 days). The calculated P-score of 0.99 (related to mineralization) and the modelled overall persistence (Pov) of 179 days (below the trigger of 195 days) suggested high persistence. Therefore it can be concluded that available information is equivocal to conclude on the persistence of flufenoxuron according to Annex D 1 (b) (i).

14.2 Bioaccumulation

573. TC NES subgroup based their conclusion vB on the BCF key study done with *Oncorhynchus mykiss* according to OECD 305 guideline, the BCF value for uptake of flufenoxuron in fish from clean water based on the fitted steady state concentration at the exposure level of 40 ng/L is 25,000 L/kg. Also the experimental log Kow value is >5. Based on evaluated data flufenoxuron meets the Annex D 1 (c) (i) criterion based on a BCF >5,000 in fish.

14.3 Long-range environmental transport (LRT)

574. Flufenoxuron has a calculated half-life in air of 27 hours. However the calculated DT50 value might be an underestimation based on modelled information indicating that flufenoxuron is expected to exist solely in the particulate phase. Results from the OECD multimedia fate model indicate no exceedance of model limits (upper right quadrant) but transfer efficiency is borderline. Compared to other reference POPs (alpha-HCH, PeCB, octaBDE) the active substance has a lower potential for LRT. The half-life in air is <2 days. However more information would facilitate a conclusion on the Annex D 1 (d) criterion.

14.4 Ecotoxicity (including pollinator toxicity)

575. TC NES subgroup based their conclusion on ecotoxicity data on *Daphnia magna*, NOEC (21 d, reproduction) = 0.0065 µg/L (semi-static, measured concentrations). Flufenoxuron is proposed to be classified according to EU-GHS as aquatic acute and chronic category 1 indicating high toxicity to aquatic organisms. Based on its high aquatic toxicity and toxicity to human health (see below) Annex D 1 (e) (ii) is fulfilled.

14.5 Toxicity to human health (including mutagenicity, carcinogenicity and adverse effects on the reproductive, endocrine, immune or nervous systems)

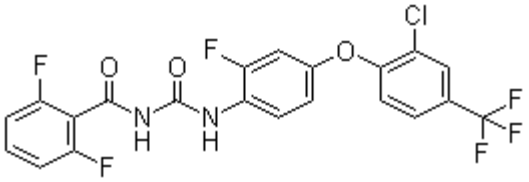
576. Flufenoxuron has a low acute oral, dermal or inhalation toxicity. It is not a skin or eye irritant. Flufenoxuron is not a skin sensitizer. There is no evidence for mutagenicity and carcinogenicity. However in multigeneration studies an increasing number of litter losses (associated with changes in litter size and cumulative pup losses) and difficulties for newborn to gain weight were observed. Based on the presence of flufenoxuron in milk produced by the treated dams and effects on pup survival and their development during lactation, a classification Lact. (May cause harm to breast-fed children) is proposed. The long-term acceptable exposure level and the chronic reference dose were set to 0.0175 mg/kg bw/day and 0.0375 mg/kg/day, respectively.

[31] http://esis.jrc.ec.europa.eu/index.php?PGM=pbt

14.6 Identity of the substance and physical and chemical properties

a) Name and other identifiers of the substance

Table 1: Substance identity

Common name:	Flufenoxuron
IUPAC name:	1-[4-(2-chloro-α,α,α-trifluoro-p-tolyloxy)-2-fluorophenyl]-3-(2,6-difluorobenzoyl)urea
CAS number:	101463-69-8
Molecular weight:	488.7 $g.mol^{-1}$
Chemical structure:	

b) Chemical group

577. Benzoylurea

c) Physico-chemical properties

Table 2: Overview of selected physico-chemical properties

Property	Value	Remarks and Reference
Vapour pressure at 25°C (mPa)	6.52×10^{-09}	PPDB (2012)
Water solubility at 20°C (mg/l)	0.0043	PPDB (2012)
Partition coefficient n-octanol/water (log value, pH 7, 20°C)	5.11	PPDB (2012)
Partition coefficient air/water (log value)	-9.97	EPI Suite v 4.0[32]
Partition coefficient air/octanol (log value)	15.08	EPI Suite v 4.0
Henry´s Law Constant at 25°C ($Pa.m^3.mol^{-1}$)	2.64×10^{-06}	PPDB (2012)

14.7 Classification and labelling

d) Harmonised Classification according to GHS

578. Proposal by EU Draft final CAR 2010:

Category	Hazard-Phrase
STOT RE 2	May cause haemolytic anemia through prolonged or repeated exposure by oral route
Lact.	May cause harm to breast-fed children
Aquatic acute category 1	Very toxic to aquatic life
Aquatic chronic category 1	Very toxic to aquatic life with long lasting effect

14.8 Environmental fate properties

e) Abiotic degradation

f) Hydrolysis

579. EU biocides CAR 2009: Flufenoxuron is stable to hydrolysis in buffer solutions at pH 5 and 7 at 25 °C, while hydrolysis takes place to a certain but very low extent (DT_{50} = 88-94 days, studies conducted with two different labels) in buffered solution at pH 9, forming one major metabolite.

g) Phototransformation/photolysis

580. EU biocides CAR 2009: Photolysis contributes to degradation of the active substance in water and several studies confirm its UV-instability. One major metabolite (Reg.No. 102719; 2,6-difluorobenzamide, log Kow 0.86) was identified. The calculated half-life of flufenoxuron for the top layer of aqueous systems in spring and summer varied from 39.2 days in April to 21.7 days in June.

h) Biodegradation

581. EU biocides CAR 2009: In a water/sediment simulation test flufenoxuron moved rapidly from water into sediment with a DT50 in the water of 0.3 to 0.4 days and

[32] http://www.epa.gov/oppt/exposure/pubs/episuite.htm

was degraded with a DT50 in the whole system of 45 to 61 days at 20°C (85 to 116 days at a reference temperature of 12°C). The DT50 for the molecule in the sediment was 46 to 65 days at 20°C (87 to 123 days at a reference temperature of 12°C) According to the evaluating EU member state there is a risk of persistence and accumulation of the molecule in the sediment compartment. One major metabolite (Reg.No. 4064702) was detected in water (up to 9.3%) and in sediment (up to 19%). However the risk assessment concluded that flufenoxuron is the only relevant residue. Under anaerobic conditions no degradation was detected. Flufenoxuron was aerobically degraded in soils with half-lives of 36 to 124 days (at 20°C) with Reg. No.4064702 as the only significant metabolite, accounting for 8% of applied. Reg.No. 4064702 itself was degraded with a half-life of 47 to 59 days. These values were recalculated to a reference temperature of 12°C. The DT50 for Flufenoxuron were 68 and 235 days at 12°C (with a geometric mean value of 175 (158) days used for risk assessment). The DT50 for Reg.No. 4064702 ranged from 89 to 112 days at 12°C. However the risk assessment concluded that flufenoxuron is the only relevant residue in all compartments.

582. Field studies conducted in South regions only revealed a moderate to fast dissipation of flufenoxuron in soils; the $DT50_f$ values varied between 6 and 67 days (n = 4).

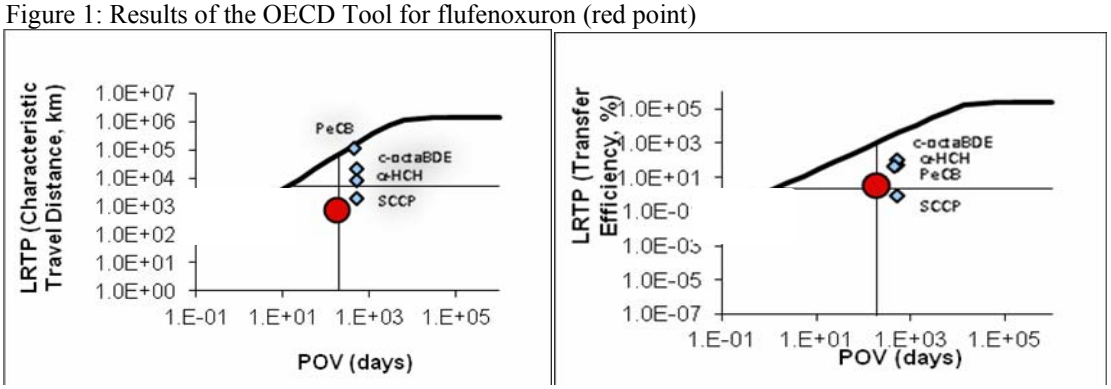
583. PPDB 2012 states a DT 50 lab 20°C of 73 days. According to HSDB 2012 flufenoxuron was applied at a nominal concentration of 97.5 g active ingredient/ha annually for three years via tractor-driven mist blower to experimental apple orchards in Sittingbourne, Kent U.K. Monitoring over a three-year period indicated that flufenoxuron does remain in the soil at low residue concentrations.

14.9 Potential for long range transport

584. EU biocides CAR 2009 concluded that based on the vapour pressure (6.52×10^{-12} Pa at 20 °C) and the Henry's constant (7.46×10^{-6} Pa × m^3/mol at 25°C), volatilization of flufenoxuron is negligible. Calculations of the chemical lifetime in the troposphere resulted in a half life of <1.12 days or 27 hours (QSAR estimates). According to these results ($t_{1/2}$ <2 days), flufenoxuron is degraded by photochemical processes and no accumulation of flufenoxuron in the air is to be expected. However HSDB 2012 reported that according to a model of gas/particle partitioning of semivolatile organic compounds in the atmosphere, flufenoxuron is expected to exist solely in the particulate phase. Thus the calculated DT50 value might be an underestimation.

585. Result from OECD "Pov and LRTP Screening Tool"[33] indicate a Pov (overall persistence) of 178 days, a CTD (characteristic travel distance) of 721 km and a TE (transfer efficiency) of 3% based on half-life inputs of DT50 air: 27 hours, DT50 water 24 hours and DT50 soil 2976 hours (124 days, cf. section 4.2). The result for flufenoxuron is plotted against the reference chemicals α-HCH, c-octaBDE and PeBD. The criteria lines were not modified and take as proposed in the tool (Pov limit: 195 days, CTD limit: 5096 km, TE limit: 2.25%). As shown by Figure 1 the results suggest a LRT potential that is below the values for the reference chemicals (except TE). According to Wegmann 2009 compounds that are less problematic from an environmental exposure point of view are in the bottom-left corner (low Pov, low LRT), while substances of environmental concern are found in the upper right region (high Pov, high LRT). However fluvenoxuron is between the bottom right and left quadrant for CTD. For TE the model indicates intermediate concern. In the TE plot fluvenosuron is on the boundaries of the upper left and right quadrant indicating to some extent POP-like persistence and LRT potential.

Figure 1: Results of the OECD Tool for flufenoxuron (red point)



[33] http://www.oecd.org/document/24/0,3343,en_2649_34379_45373336_1_1_1_1,00.html

14.10 Bioaccumulation

586. EU biocides CAR 2009: Different studies have been carried out in order to assess the bioaccumulation process of flufenoxuron in organisms. The highest bioconcentration factor in whole fish was 25,000. Flufenoxuron is considered to be a very bioaccumulative substance with a BCF >5,000. An earthworm bioaccumulation study revealed a $BCF_{earthworms}$ relative to the concentration of ^{14}C-flufenoxuron in dry weight soil of 4. These results are in contrast to the low modelled B-score of 0.11..

587. PPDB 2012 lists a BCF value of 70,500 and a depuration (CT50) of 21 days.

i) PB-score

588. Flufenoxuron has a PB score of 1.11 (P-score 0.99 and B-score 0.11)

14.11 Human health hazard assessment

j) Acute toxicity

589. US EPA 2006 categorized flufenoxuron in toxicity category IV based on an acute oral LD50 of >5000 mg/kg. No data on other acute toxicity routes, irritation and dermal sensitization were given.

590. EU biocides CAR 2009 states that Flufenoxuron has a low acute oral, dermal or inhalation toxicity. It is not a skin or eye irritant. Flufenoxuron is not a skin sensitizer.

591. HSDB 2012 described clinical symptoms such as the oxidization of iron in the haemoglobin ring to the ferric form leads to the inability of haemoglobin to bind or transport oxygen.

k) Mutagenicity and Carcinogenicity

592. US EPA 2006 concluded that flufenoxuron is not likely to be carcinogenic to humans. PAN 2012 does not flag flufenoxuron for carcinogenicity. According to HSDB 2012 flufenoxuron is not listed in IARC carcinogenicity ratings. These findings are in line with EU biocides CAR 2009.

l) Toxicity for reproduction

593. EU Draft final CAR 2010: No teratogenic effect was observed in rats and rabbits. No effect on fertility was observed in male or female rats. However, in a multigeneration study, an increasing number of litter losses (associated with changes in litter size and cumulative pup losses) and difficulties for newborn to gain weight were observed. Based on the presence of flufenoxuron in the milk produced by the treated dams and effects on pup survival and their development during lactation, a classification has been proposed.

594. US EPA 2006 defined a LOAEL of 14/16 mg/kg/day for male/female based on decreased body weights during lactation.

595. PAN 2012 does not list flufenoxuron for reproductive and developmental toxicity.

m) Neurotoxicity

596. EU biocides CAR 2009 states that flufenoxuron is not neurotoxic.

n) Immunotoxicity

597. -

o) Endocrine disruption

598. Flufenoxuron is not listed as an endocrine disrupter according to PAN 2012. Flufenoxuron is not listed in the EU database for endocrine disrupters 2012.

p) Mode of action

599. PPDB 2012 states that flufenoxuron is a growth regulator with contact and stomach action and is an inhibitor of chitin biosynthesis

q) Acceptable Exposure Levels

600. EU biocides CAR 2009 reports that a NOAEL of the one-year dog study (NOAEL = 3.5 mg/kg bw/d) is used for the derivation of a medium to long-term AEL, resulting in a long-term AEL of 0.0175 mg/kg bw/d (safety factor: 200).

601. US EPA Chronic RfD = 0.0375 mg/kg/day based on a NOAEL= 3.75 mg/kg/day (safety factor 100).

14.12 Environmental hazard assessment

r) Aquatic compartment (including sediment)

602. EU biocides CAR 2009: Long-term NOEC values are available for all three trophic levels in the aquatic compartment (fish, *Daphnia* and algae). Among the laboratory derived data, the result obtained in a chronic laboratory toxicity study with *Daphnia magna* was by far the lowest (21 d-NOEC = 0.00449 µg a.s./L).

603. The study considered relevant for the risk assessment in CAR 2009 has been conducted with *Chironomus riparius* exposed to flufenoxuron spiked sediment and provides a NOEC of 80 µg a.s./$kg_{dry\ sediment.}$

s) Terrestrial compartment

604. For the terrestrial compartment, NOEC values from long-term toxicity tests (earthworms, plants, microorganisms and soil dwelling arthropods) are available. The lowest NOEC, which was the result of chronic laboratory study on *Folsomia candida* (28-d) was 0.117 mg/kg dry soil.

605. PPDB 2012 lists an acute LC50 of >2000 mg/kg for birds. Also the dietary LD50 >1243 mg kg bw-1 d-1 indicates low toxicity to birds.

t) Toxicity to pollinators

606. PPDB 2012 reports an acute 48 hours LD50 contact of >100 µg/bee suggesting moderate to low toxicity to bees. However due to the mode of action toxicity to immature stages might be considerable higher.

14.13 References

EU biocides CAR (2009) Document I Overall Summary and Assessment Flufenoxuron, Product-type 8, April 2009, http://circa.europa.eu/Public/irc/env/bio_reports/library?l=/review_programme/ca_reports/wood_preservatives/docipdf/_EN_1.0_&a=d

EU Draft final CAR (2010) Flufenoxuron Product-type PT 18 (Insecticide), November 2010 http://ec.europa.eu/environment/biocides/evaluation_reports.htm, 2012-04-16

EU Endocrine Disruption Database (2012) http://ec.europa.eu/environment/endocrine/strategy/short_en.htm, 2012-04-16

HSDB (2012) Hazardous Substances Data Bank http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB 2012-04-16

PPDB (2012) Pesticide Properties DataBase, University of Hertfordshire, http://sitem.herts.ac.uk/aeru/footprint/en/, 2012-04-18

PAN 2012 Pesticide Database, http://www.pesticideinfo.org/, 2012-04-18

US EPA (2006) Pesticide factsheet Flufenoxuron, September 2006 http://www.epa.gov/opprd001/factsheets/flufenoxuron.pdf, 2012-04-16

Wegmann F. Cavin L, MacLeod M, Scheringer M, Hungerbühler K. (2009) Environmental Modeling & Software 24, 228-237

15. Hexaflumuron

CONCLUSIONS

Assessment of POP properties – comparison with the criteria of Annex D and other hazard indicators

15.1 Persistence

607. Hexaflumuron is stable to hydrolysis at neutral to acidic pH values. No DT_{50} data are available for the water-sediment system. The DT_{50} soil lab is 57 days, however a value of 190 days at 10°C is also reported. The DT_{50} soil field is 170 days, respectively. The modelled P-score is 0.973 and higher than the trigger of 0.5. The DT_{50} soil field values are higher than the DT_{50} soil lab values.
608. Therefore it might be reasonable to conclude that hexaflumuron meets the persistence criterion of Annex D 1 (b) (i) due to its stability in water at pH<7, a DT_{50} value in soil >180 days and modelled information suggesting high persistence. However, the available database is quite limited.

15.2 Bioaccumulation

609. The log Kow of hexaflumuron is 5.68, which is higher than the trigger value of 5. The BCF value was estimated with 4,700. The modelled B-score is 0.869, which is also higher than the trigger value. In summary it is concluded that the B criterion is fulfilled.
610. Hexaflumuron does fulfil the Annex D 1 (c) (i) criteria based on a log K_{OW} of 5.68.

15.3 Long-range environmental transport (LRT)

611. Hexaflumuron has a calculated half-life in air of 6 hours (<2 days) indicating moderately fast degradation in air. Based on half-life in air <2 days hexaflumuron does not fulfil the Annex D 1 (d) (iii) criterion.

15.4 Ecotoxicity (including pollinator toxicity)

612. No harmonised classification for hexaflumuron according to EU-GHS is available. Hexaflumuron is self-classified according to the EU CLP inventory as acute aquatic 1 and chronic aquatic 1. US EPA classified hexaflumuron as highly toxic to freshwater fish and freshwater invertebrates on acute exposure basis. Based on its high aquatic toxicity Annex D 1 (e) (ii) is fulfilled.

15.5 Toxicity to human health (including mutagenicity, carcinogenicity and adverse effects on the reproductive, endocrine, immune or nervous systems)

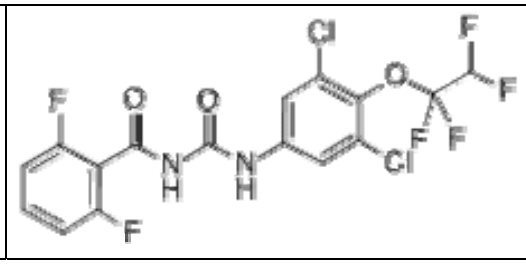
613. There is no EU GHS harmonised classification for hexaflumuron, but a self classification according to the EU CLP inventory for acute respiratory toxicity category 4. US EPA reported an acute toxicity study package which indicates no need for classification for acute systemic toxicity, skin or eye irritation or skin sensitization. Comprehensive in vitro and in vivo data for genotoxicity were reported as negative and a 2 year rat study and a 80 weeks mouse study did not indicate carcinogenicity. Also the developmental rat and rabbit studies as well as the fertility study did not indicate specific concern for these endpoints. The lowest NOAEL of 0.5 mg/kg bw day was reported from a 1 year dog study on the basis of adverse effects on the peripheral blood cells. This could be translated to a limit value of 0.005 mg/kg bw day (factsheet authors comment), but the only explicit ADI proposal identified in the databases was 0.02 mg/kg bw day.

15.6 Identity of the substance and physical and chemical properties

a) Name and other identifiers of the substance

Table 1: Substance identity

Common name:	Hexaflumuron
IUPAC name:	1-[3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)phenyl]-3-(2,6-difluorobenzoyl)urea
CAS number:	86479-06-3
Molecular weight:	461.14

Chemical structure:	

b) Chemical group

614. Benzoylurea

c) Physico-chemical properties

Table 2: Overview of selected physico-chemical properties

Property	Value	Remarks and Reference
Vapour pressure at 25°C (mPa)	0.059	PPDB 2012
Water solubility at 20°C (mg/l)	0.027	PPDB 2012
Partition coefficient n-octanol/water (log value, pH 7, 20°C)	5.68	PPDB 2012
Partition coefficient air/water (log value)	-3.39	EPI Suite v 4.0[34]
Partition coefficient air/octanol (log value)	9.07	EPI Suite v 4.0
Henry´s Law Constant at 25°C ($Pa.m^3.mol^{-1}$)	1.01	PPDB 2012

15.7 Classification and labelling

d) Harmonised Classification according to GHS

615. Not available

e) Self classification

616. Notified CLP classification and labelling according to CLP-inventory[35]

Category	Hazard-Phrase
Acute tox. 4	H332 Harmful if inhaled
Aquatic acute 1	H400 Very toxic to aquatic life
Aquatic chronic 1	H410 Very toxic to aquatic life with long lasting effects

15.8 Environmental fate properties

f) Abiotic degradation

g) Hydrolysis

617. PPDB 2012: No data available. US EPA 1993: Hexaflumuron was stable in sterile aqueous pH 5 buffer solution and relatively stable in pH 7 buffer solution.

h) Phototransformation/photolysis

618. PPDB 2012: Aquatic photolysis half-life is 6.3 days, moderately fast.

i) Biodegradation

619. Only for soil biodegradation (dissipation) estimates are available (cf. Table 3)

Table 3: Biotic degradation of hexaflumuron

Study type	Results	Reference	Remarks
DT_{50} soil lab (days):	Hexaflumuron: 57 d (aerobic)	PPDB	Moderately persistent
DT_{50} soil field (days):	Hexaflumuron: 170 d	PPDB	persistent
DT_{50} water (days) from water/sediment study:	-	-	No data in PPDB
DT_{50} water sediment/whole system (days):	-	-	No data in PPDB

[34] http://www.epa.gov/oppt/exposure/pubs/episuite.htm

[35] http://clp-inventory.echa.europa.eu/

620. HSDB 2012 reported 3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)phenyl urea and 3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)phenyl amine as soil metabolites. Levels of both metabolites generally increased with incubation time, and the greatest levels were observed at the higher temperatures and moisture contents in an aerobic soil degradation experiment. The half-life of (^{14}C-aniline) hexaflumuron in soil under different temperature and moisture regimes were as follows: 159 days (moisture, 50% of 0.33 bar; 25 deg C); 90 days (moisture, 75% of 0.33 bar; 25 deg C); 64 days (moisture, 100% of 0.33 bar; 25 deg C); 190 days (moisture, 75% of 0.33 bar; 10 deg C); 90 days (moisture, 75% of 0.33 bar; 25 deg C); 56 days (moisture, 75% of 0.33 bar; 35 deg C).

15.9 Potential for long range transport

621. According to AOPWIN v1.92[36] the photo-chemical degradation of hexaflumuron in air has been estimated to be moderately fast. The calculated DT50 is 6.1 hours (assuming a 12 hours day and a OH concentration of 1.5 x 10^6 OH/cm^3). The OH Rate Constant 21.0492 x10^{-12} cm^3/molecule^{-sec}.

15.10 Bioaccumulation

622. PPDB 2012: The log Kow is 5.68 and the estimated BCF is 4,700.

623. UE EPA 2010: Hexaflumuron has the potential to bioaccumulate in food webs. IPCS INCHEM 1995 concluded that bioaccumulation takes place, especially in fish.

j) PB-score

624. Hexaflumuron has a P-score of 0.97 and a B-score of 0. 87 resulting in an overall PB-score of 1.84.

15.11 Human health hazard assessment

k) Acute toxicity

625. PPDB 2012: The substance is irritant to skin, eyes and respiratory tract.

626. US EPA summary 2009: Submitted acute toxicity studies indicate hexaflumuron is of low acute toxicity

627. US EPA 1993: Data are presented indicating acute oral and dermal LD50 values above 5000 and 2000 mg/kg bw day, respectively and an acute respiratory LC50 above 7 mg/L. Eye and skin irritation study results in rabbits were reported with slight eye irritation that resolved within 24 hours and slight skin irritation at 72 hours that resolved in 7 days. Within guinea pigs sensitization test it was not sensitizing.

628. HSDB 2012: The oral and the dermal rat LD50s are higher than 5000 mg/kg bw day.

l) Mutagenicity and Carcinogenicity

629. US EPA summary 2009: Mutagenicity studies did not show hexaflumuron to be a mutagen. Chronic toxicity/carcinogenicity study in rats noted microscopic changes in the liver and there was no increase in tumors. A cancer classification for hexaflumuron has not been made.

630. US EPA 1993: Negative results of an AMES test, an in vitro mammalian gene mutation test, an in vitro chromosomal aberration test in rat lymphcytes and an in vivo mouse micronucleus test were reported. The substance was not oncogenic in rats at dietary dose levels up to 500 mg/kg bw day for 104 weeks. It was not oncogenic in mice during 80 weeks of treatment at dietary levels up to 25 mg/kg bw day.

m) Toxicity for reproduction

631. US EPA summary 2009: No developmental or maternal toxicity occurred at the limit dose in developmental studies in rats and rabbits. In the reproduction study, anemia occurred in adults and decreased pup weights and increased pup mortality occurred.

632. US EPA 1993: It was not developmentally toxic in rats or rabbits at oral dose levels up to 1000 mg/kg bw day. Furthermore it was reported to have no effects on fertility, reproductive performance or fetal development at 125 mg/kg bw day, the highest level tested in a two-generation study.

[36] http://www.epa.gov/oppt/exposure/pubs/episuite.htm

n) Neurotoxicity

633. PAN pesticides database 2012: The substance is not an acetyl cholinesterase inhibitor.

o) Immunotoxicity

634. -

p) Endocrine disruption

635. -

q) Mode of action

636. US EPA 1993: Hexaflumuron is a benzoyyl phenylurea, a chitin-synthetase inhibiting insecticide. It disrupts the molting process in insects which results in death at immature stages.

r) Acceptable Exposure Levels

637. Pesticides Properties Database April 2012: ADI = 0.02 mg/kg bw day

638. US EPA 1993: The substance was not oncogenic in rats at dietary dose levels up to 500 mg/kg bw day for 104 weeks. While no gross clinical signs were noted, an increased incidence and severity of liver pale cell foci were observed at 500 mg/kg day the NOEL was 75 mg/kg bw day It was not oncogenic in mice during 80 weeks of treatment at dietary levels up to 25 mg/kg bw day.. No other toxic effects were noted. In beagle dogs the target organ was peripheral blood cells. The NOEL for the one year feeding study was 0.5 mg/kg bw day, with Heinz body formation and reversible increases in methemoglobin observed at 5 and 25 mg/kg bw day (comment factsheet author: with the application of a standard assessment factor of 100 this may translate to a limit value of 0.005 mg/kg bw day)

15.12 Environmental hazard assessment

s) Aquatic compartment (including sediment)

639. US EPA summary 2009: Based on available data, hexaflumuron is classified as highly toxic to freshwater fish and freshwater invertebrates (cf. Table 4) on acute exposure basis. No data are available that describe the chronic toxicity of hexaflumuron to fresh water aquatic organisms or its toxicity to marine/estuarine animals or aquatic plants.

Table 4. Toxicity reference values

Exposure scenario/Study type	Organism/Species		Time Scale Endpoint	Toxicity value	Reference
Acute	Fish	*Lepomis macrochirus*	LC_{50}	100 mg/kg	PPDB 2012
Acute, EC50	Invertebrates	*Daphnia magna*	EC_{50}	0.0001 mg/kg	PPDB 2012

t) Terrestrial compartment

640. US EPA summary 2009: Based on available data hexaflumuron is classified as practically non-toxic to mammals and birds on an acute oral basis (cf. Table 5). On a subacute dietary basis, hexaflumuron is classified as slightly toxic to birds. No data are available to describe the toxicity of hexaflumuron to terrestrial plants.

Table 5. Toxicity reference values (source: PPDB 2012)

Exposure scenario/Study type	Organism/Species		Time Scale Endpoint	Toxicity value
Acute, oral	Mammals	Rat	LD50	>5000 mg/kg
Short term, dietary	Mammals	Rat	NOEL	75 mg/kg
Acute toxicity	Birds	*Colinus virginianus*	LD50	2000 mg/kg

u) Toxicity to pollinators

641. US EPA summary 2009: No data are available to describe the toxicity of hexaflumuron to honey bees. US EPA 2010: requested a study investigating the acute toxicity to honey bees and a field test for pollinators. The LD_{50} bee oral & contact was indicated with >0.1 mg/bee (ref. to Tomlin, C.D.S. (ed.)). However due to the mode of action toxicity to immature stages might be considerable higher.

15.13 References

IPCS INCHEM (2005) International Chemical Safety Card Hexaflumuron, ICSC: 1266 http://www.inchem.org/documents/icsc/icsc/eics1266.htm
HSDB (2012) Hazardous Substance Database, http://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+7049, 2012-04-16
PAN pesticide database (2012) http://www.pesticideinfo.org/, 2012-04-16
PPDB (2012) Pesticide Properties DataBase, University of Hertfordshire, http://sitem.herts.ac.uk/aeru/footprint/en/ 2012-04-18
Tomlin, C.D.S. (ed.). 1994. The Pesticide Manual - World Compendium. 10th ed. Surrey, UK: The British Crop Protection Council
US EPA 1993: Hexaflumuron Registration File 062719-EU-EL; 062719-EU; 062719-EUG
US EPA summary 2009: Hexaflumuron Summary Document Registration Review: Initial Docket, September 2009, Docket Number: EPA-HQ-OPP-2009-0568
US EPA 2010: Hexaflumuron Final Work Plan Registration Review Case # 7413, March 2010, Docket Number: EPA-HQ-OPP-2009-0568
http://www.pesticideinfo.org/

16. Cyhalothrin, Lambda-cyhalothrin[37] and Gamma-cyhalothrin

CONCLUSIONS

Assessment of POP properties – comparison with the criteria of Annex D and other hazard indicators

16.1 Persistence

642. Based on a combination of data for cyhalothrin, lambda-cyhalothrin and gamma-cyhalothrin these active substances are moderately persistent in the environment and degrade slowly through a combination of biotic and abiotic mechanisms. (Reported findings for cyhalothrin suggest no photolysis). Lambda-cyhalothrin is stable to aqueous hydrolysis below pH 7; however also fast hydrolytic degradation at low pH values was reported. Photolysis may contribute to the removal of lambda-cyhalothrin in water. Under both aerobic and anaerobic soil metabolism conditions, cyhalothrin, lambda-cyhalothrin and gamma-cyhalothrin biodegrade at moderate rates, with comparable half-lives of several weeks. In aquatic metabolism conditions, lambda-cyhalothrin and gamma-cyhalothrin may biodegrade at moderate rates under aerobic condition, with half-lives in the order of about 21-53 days (aerobic, both chemicals), but more slowly under anaerobic condition, with a half-life of 142 days (lambda-cyhalothrin only). The modelled P-score is 0.92 indicating high persistency. However the P-score is related to ultimate mineralization and not to a DT50 value. Therefore it can be concluded that based on the presented experimental information cyhalothrin, lambda- cyhalothrin and gamma-cyhalothrin do not meet the persistence criterion of Annex D 1 (b) (i). However there are indications that under anaerobic conditions in aquatic environment half-lives are prolonged and persistency under low temperatures cannot be excluded.

16.2 Bioaccumulation

643. The log Kow of >5 and the experimental derived BCF values of 1660 -2240 indicate high potential of bioaccumulation. Also higher reported values for cyhalothrin, bioaccumulation ~4600x, based on a study performed in fish are available. The modelled B-scores are 0.581 suggesting bioaccumulation potential as well. Based on the reported BCF values in fish cyhalothrin, lambda-cyhalothrin and gamma-cyhalothrin do not meet the Annex D 1 (c) (i) criterion. However log Kow>5 for all three compounds are reported and the highest BCF of 4600 is close to the Annex D threshold of 5000.

16.3 Long-range transport

644. The estimated reported DT50 values in air for lamda cyhalothrin are 4 and 12 hours. These values can be considered for screening for cyhalothrin and gamma cyhalothrin as well. Therefore it is unlikely that these active substances will meet the Annex 1 (c) (iii) criterion.

16.4 Ecotoxicity (including pollinator toxicity)

645. Lambda-cyhalothrin and gamma-cyhalothrin are highly toxic to aquatic species and lambda-cyhalothrin is classified according to EU-GHS as aquatic acute and chronic category 1. For terrestrial vertebrates lambda-cyhalothrin is highly toxic to mammals. No toxic effects to birds after acute exposure, but higher toxicity for reproductive effects were observed. Lambda-cyhalothrin is considered as non-toxic to earthworms. Based on the high toxicity to aquatic organisms and toxicity to human health (see below) it is concluded that lambda-cyhalothrin, cyhalothrin and gamma-cyhalothrin meet the Annex D criterion 1 (e) (ii).

16.5 Toxicity to human health (including mutagenicity, carcinogenicity and adverse effects on the reproductive, endocrine, immune or nervous systems)

646. Read across between cyhalothrin and lambda-cyhalothrin is considered justified based on the similarity of effects observed in subchronic lambda-cyhalothrin and cyhalothrin studies as well as comparative toxicokinetic and metabolism studies. In terms of acute oral toxicity gamma-cyhalothrin is estimated as 2 times more toxic compared to lambda cyhalothrin and the latter 3 times more toxic compared to cyhalothrin. However long term limit values were derived from lambda-cyhalothrin so that there is no critical impact on risk assessment for long term exposure and for short term exposure the point of departure for gamma-cyhalothrin should be reduced by a factor of 2. Based on the US

[37] Lamba-cyhalthrin is an alternative to both endosulfan and DDT.

EPA summary the other available data support that toxicities of lambda-cyhalothrin and gamma-cyhalothrin are comparable which allows combining the respective databases.

647. Lambda-cyhalothrin is classified for acute toxicity category 4 for the dermal route, category 3 for the oral route and category 2 for the respiratory route. It is not irritating and not sensitizing within a guinea pig maximisation test (M&K method). For cyhalothrin and gamma-cyhalothrin no harmonised EU GHS classification is available.

648. Cyhalothrin did not induce genotoxic effects in vitro or in vivo and there was no evidence of carcinogenicity in rats. Some equivocal carcinogenic effects were observed in a mouse study. However the European evaluations did not consider these sufficient for classification. US EPA concluded from the studies with cyhalothrin that cyhalothrin, lambda-cyhalothrin and gamma-cyhalothrin as "not likely to be carcinogenic to humans"

649. With cyhalothrin no teratogenic or reproductive toxicity effects were observed within developmental rat and rabbit studies or a 3 generation rat study. Nevertheless lambda-cyhalothrin is listed within the EU endocrine disrupter database within category 1, which means that it is persistent in the environment or produced at high volumes with evidence of endocrine disruption activity in at least one species using intact animals.

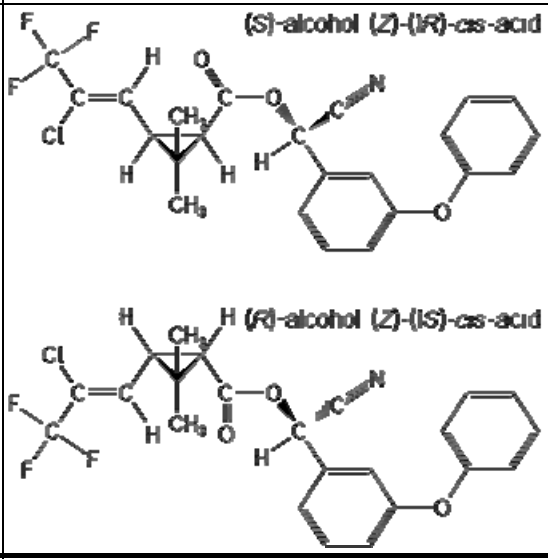
650. Representing a type II pyrethroid the critical effect is neurotoxicity. No delayed neurotoxicity study was required. Within a developmental neurotoxicity study with lambda-cyhalothrin adverse effects were only observed at parentally toxic doses. The clinical neurotoxicity effects accompanied with gastrointestinal effects and reduced food intake in the 90 day and the 1-year dog studies with lambda-cyhalothrin were the basis for the derivation of a systemic long term limit value of 0.0025 mg/kg bw day. An assessment factor of 100 and an oral absorption rate of 50% was taken into consideration. The value was considered reliable also for cyhalothrin and gamma-cyhalothrin.

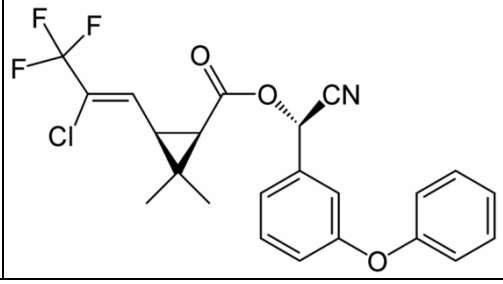
16.6 Identity of the substance and physical and chemical properties

a) Name and other identifiers of the substance

651. Lambda-cyhalothrin is the pure cis 1R-alphaS and cis 1S-alphaR enantiomeric pair whereas cyhalothrin is a 50/50 mixture of lambda-cyhalothrin and the cis 1R-alphaR and cis 1S-alphaS enantiomeric pair.

Table 1: Substance identity

Common name:	Cyhalothrin
IUPAC name:	(RS)-α-cyano-3-phenoxybenzyl (1RS,3RS)-3-[(Z)-2-chloro-3,3,3-trifluoropropenyl]-2,2-dimethylcyclopropanecarboxylate
CAS number:	68085-85-8
Molecular weight:	449.85
Chemical structure:	
Common name:	Lambda-cyhalothrin
IUPAC name:	(*R*)-a-cyano-3-phenoxybenzyl (1*S*)-cis-3-[(*Z*)-2-chloro-3,3,3-trifluoropropenyl]-2,2-dimethylcyclopropanecarboxylate and (*S*)-a-cyano-3-phenoxybenzyl (1*R*)-cis-3-[(*Z*)-2-chloro-3,3,3-trifluoropropenyl]-2,2-dimethylcyclopropanecarboxylate
CAS number:	91465-08-6
Molecular weight and	See above

chemical structure:	
Common name:	Gamma-cyhalothrin
IUPAC name:	(*S*)-α-cyano-3-phenoxybenzyl (1*R*,3*R*)-3-[(*Z*)-2-chloro-3,3,3-trifluoropropenyl]-2,2-dimethylcyclopropanecarboxylate
CAS number:	76703-62-3
Molecular weight:	449.85 g.mol^{-1}
Chemical structure:	

b) Chemical group

-

c) Physico-chemical properties

Table 3: Overview of selected physico-chemical properties

Property	Cyhalothrin	Lamda-cyhalothrin	Gamma-cyhalothrin	Reference
Vapour pressure at 25°C (mPa)	1.00 x 10^{-09}	0.0002	3.45 x 10^{-04}	PPDB 2012
Water solubility at 20°C (mg/l)	0.004	0.005	0.000002	PPDB 2012
Partition coefficient n-octanol/water (log value, pH 7, 20°C)	6.8	6.9	4.96 (range 4.96-5.65)	PPDB 2012
Partition coefficient air/water (log value)	-4.22	-4.22	-4.21	EPI Suite v 4.0[38]
Partition coefficient air/octanol (log value)	11.02	11.12	9.97	EPI Suite v 4.0
Henry´s Law Constant at 25°C (Pa.m³.mol^{-1})	1.80 x 10^{-02}	2.00 x 10^{-02}	3.19 x 10^{-02} (Dimensionless)	PPDB 2012

16.7 Classification and labelling

d) Harmonised Classification according to GHS

652. No harmonised classification according to EU-GHS for cyhalothrin and gamma-cyhalothrin available.

653. Regulation (EC) No 1272/2008 – 1nd amendment 2009: Lambda cyhalothrin:

Category	Hazard-Phrase
Acute Tox. 2	H330 Fatal if inhaled.
Acute Tox. 3	H301 Toxic if swallowed.
Acute Tox. 4	H312 Harmful in contact with skin.
Aquatic Acute 1	H400 Very toxic to aquatic life.
Aquatic Chronic 1	H410 Very toxic to aquatic life with long lasting effects.

16.8 Environmental fate properties

e) Abiotic Degradation

f) Hydrolysis

654. Cyhalothrin: PPDB 2012: Hydrolysed slowly at pH 7 to pH 9, faster at pH 9

655. Lamda-cyhalothrin: PPDB 2012: Very Persistent: pH 5.2 and pH 6.9, DT_{50} ~7 days at pH 9. These findings are in line with the EFSA review report 2001. However WHO, 2006 reported half-live values according to the OECD 111 test method for lambda-cyhalothrin: pH4: 4.27 days at 20°C, pH 7: 5.03 days at 20°C, and pH 9: 3.36 days at 20°C suggesting fast hydrolytic degradation.

[38] http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm

656. Gamma-cyhalothrin: PPDB 2012: Aqueous hydrolysis DT_{50}: 136 days at 20°C and pH 7 (persistent), stable at pH 5, 1.1 days at pH 9

g) Phototransformation/photolysis

657. Cyhalothrin: PPDB 2012: stable to phototransformation/photolysis

658. Lamda-cyhalothrin: EFSA review report 2001: Indicated DT_{50} in water 13 days (latitudes 40 and 50°N). Average quantum yield at 270-290 nm 0.092. Calculated DT_{50} values in European waters range from 5 days (summer) to 75 days (winter). However photolysis is considered to be negligible under field conditions.

h) Biodegradation

659. US EPA 2010 concluded that based on a combination of data for lambda-cyhalothrin and gamma-cyhalothrin, they are moderately persistent in the environment and degrade slowly through a combination of biotic and abiotic mechanisms. On soil, lambda-cyhalothrin is fairly stable (with very little degradation on the order of only ~13% in 35 days). Under both aerobic and anaerobic soil metabolism conditions, cyhalothrin, lambda-cyhalothrin and gamma-cyhalothrin biodegrade at moderate rates, with comparable half-lives of several weeks. Various aerobic soil studies are available with all three test substances. Lambda-cyhalothrin and gamma-cyhalothrin may biodegrade more slowly under anaerobic conditions with a half-life of 142 days (lambda-cyhalothrin only).

660. PPDB (2012) states that for cyhalothrin lab soil studies indicate a DT50 range of 32 to 82 days (geometric mean: 57 days, 20°C).

661. Degradation values for lambda-cyhalothrin are displayed in Table 3.

Table 3: Degradation estimates of lambda-cyhalothrin in soil, water and sediment

Degradation 50%	days	Reference	Comment
DT_{50} soil lab (20°)	56 (29 -100)	EFSA review report 2001	
DT_{50}soil field	23 (6-40)		Soils from Germany and US (n=10)
DT_{50} water sediment/water	< 1		Rapid dissipation from water: after 1 day 10-13% of applied was present the water phase pH dependent
DT_{50} water sediment/whole system	7- 15 days		

662. Degradation values for gamma-cyhalothrin are similar to lambda-cyhalothrin and range according to PPDB (2012) from a DT50 lab (20°C) of 42 days (geometric mean) to a DT50 typical of 50 days. The DT50 from the water phase only is given with 15 days, however no pH values is stated in PPDB (2012).

16.9 Potential for long range transport

663. According to EU biocides AR 2011 the estimated T1/2 in air of lambda-cyhalothrin is 0.51 days (12.2 hours) based on rate constant for gas-phase reaction with hydroxyl radicals 31.46 cm^3/molecule x sec and assuming a global (day and night) annual average OH-radical concentration of 0.5 x 10^6 molecules/cm^3. EFSA review report 2001 lists a DT50 value for photo-oxidative degradation of 4.1 hours.

664. This value can be considered for screening for cyhalothrin and gamma-cyhalothrin as well. The estimation program AOPWIN[39] do not considered specific isomeric forms.

16.10 Bioaccumulation

665. Cyhalothrin: PPDB 2012: BCF: 1950 in whole fish assuming high bioaccumulation potential (this value is also recorded for the other two compounds). However a higher value was identified by US EPA 2010.

666. Lambda-cyhalothrin: EFSA review report 2001 BCF: 1660-2240 (whole fish). US EPA 2010 also lists BCF values from open literature in *Chironomus riparius* that range from 1300 to 3400.

667. US EPA 2010: Lambda-cyhalothrin and gamma-cyhalothrin are highly bioaccumulative (~4600x), based on a study performed with cyhalothrin in fish, and they depurate at moderately slow rates (~9 days). There is the potential for bioaccumulation and biomagnification.

i) PB-score

668. Lambda-cyhalothrin has a P-score of 0.919 and a B-score of 0.581 resulting in an overall B-score of 1.500. The same values were reported for cyhalothrin.

[39] http://www.epa.gov/oppt/exposure/pubs/episuite.htm

16.11 Human health hazard assessment

669. EU biocides CAR 2011: The human health effect assessment of lambda-cyhalothrin is based on data obtained for lambda-cyhalothrin or cyhalothrin. Lambda-cyhalothrin is the pure cis 1R-alphaS and cis 1S-alphaR enantiomeric pair whereas cyhalothrin is a 50/50 mixture of lambda-cyhalothrin and the R157836 (the cis 1R-alphaR and cis 1S-alphaS) enantiomeric pair. Read across between the two substances is considered justified based on the similarity between effects observed in the two 90 day studies performed in rats with identical dose levels of either lambda-cyhalothrin or cyhalothrin. Read across is further supported by a bridging study demonstrating that the absorption, tissue distribution, metabolism and excretion of lambda-cyhalothrin and cyhalothrin is quantitatively and qualitatively similar in rat. However lambda-cyhalothrin appears to be approximately three times more potent than cyhalothrin in both rats and mice when comparing the acute oral toxicity of lambda-cyhalothrin reported in this dossier to the acute oral toxicity of cyhalothrin reported in literature. Since all reference values used were derived from NOAELs obtained in studies performed with lambda-cyhalothrin, the difference in potency has no impact on the risk assessment of the representative formulations containing lambda-cyhalothrin.

670. US EPA summary document 2010: The relative toxicities of lambda-cyhalothrin and gamma-cyhalothrin are comparable, making **it possible for the** Agency to combine the toxicity databases for purpose of risk assessment. The database for gamma-cyhalothrin was supplemented by available data for lambda-cyhalothrin and vice versa because the toxicity profiles of lambda-cyhalothrin and gamma-cyhalothrin are expected to be similar to each other.

j) Acute toxicity

671. EU biocides CAR 2011: The acute toxicity data are in agreement with the actual EU GHS classification: category 4 for the dermal route, category 3 for the oral route and category 2 for the respiratory route. The substance was not sufficiently irritant to skin or eye to require respective classification. The substance was not sensitizing within a guinea pig maximisation test (M&K method).

672. EFSA review report 2001: The conclusions presented were in agreement with EU biocides CAR 2011.

673. US EPA summary document 2010: The acute toxicity profiles for the cyhalothrins were similar. Oral, dermal and inhalation routes of exposure resulted in toxicity category II. Only gamma-cyhalothrin was slightly more toxic (category I) for inhalation. Cyhalothrin and lambda-cyhalothrin were moderately irritating to the eye (category III). They were mildly irritating to the skin (category IV). Gamma-cyhalothrin appeared to be more irritating (category I and II, for eye and skin irritation, respectively). None of the cyhalthrins were dermal sensitizers.

674. WHO 2011: WHO/IPCS has evaluated lambda-cyhalothrin and classified it as 'Moderately Hazardous' (Class II), on the basis of acute oral toxicity data. The hazards and risks were summarised as follows: Harmful, irritating to eyes, skin and upper respiratory system.

k) Mutagenicity and Carcinogenicity

675. EU biocides CAR 2011: Genotoxicity and carcinogenicity studies and were carried out with cyhalothrin. No genotoxic effects were observed in the standard in vitro test package, reinforced with an additional UDS test and in vivo mouse micronucleus test. There is also no evidence of carcinogenicity in rats. An increased incidence of mammary adenocarcinomas was observed in female mice (above incidence in concurrent and historical controls). However the results of the studies performed do not give sufficient evidence for classification of lambda cyhalothrin as a carcinogenic substance.

676. EFSA review report lambda-cyhalothrin 2001: The conclusions presented were in agreement with EU biocides CAR 2011.

677. US EPA summary document 2010: The agency classified cyhalothrin, lambda-cyhalothrin and gamma-cyhalothrin as "not likely to be carcinogenic to humans" based on the lack of evidence of carcinogenicity in mice and rats. Carcinogenicity studies are not available for lambda- or gamma-cyhalothrin. However the general cyhalothrin carcinogenicity studies in rats and mice were considered to be sufficient for classification as "not likely to be carcinogenic to humans". There is no evidence of mutagenicity for cyhalothrin, lambda-cyhalothrin or gamma-cyhalothrin.

l) Toxicity for reproduction

678. EU biocides CAR 2011: Reduced bodyweights with associated effects on mean litter weight were observed in a three generation rat study with cyhalothrin. It was

concluded that there were no adverse effects on adult fertility or reproduction. The teratogenicity studies performed with cyhalothrin on rats and rabbits did not reveal any foetal effects.

679. EFSA review report 2001: The conclusions presented were in agreement with EU biocides CAR 2011.

m) Neurotoxicity

680. EU biocides CAR 2011: Clinical signs of neurotoxicity from lambda-cyhalothrin were reported in dogs and rats. Within the developmental neurotoxicity study no respective specific effects were observed with lambda-cyhalothrin. Cases of subjective facial sensation (also known as 'SFS' or paraesthesia) were reported to have occurred at all stages of *lambda*-cyhalothrin handling, from small-scale laboratory work to commercial synthesis and formulation operations. Subjective facial sensation is a collection of skin-associated symptoms, including itching, tingling, burning, cold or numbness due to skin contact with *lambda*-cyhalothrin. The face was most commonly affected. These symptoms can cause discomfort and may in some individuals last for up to 24 hours after exposure. Recovery was apparently complete and there was no evidence of lasting damage.

681. EFSA review report 2001: The conclusions presented were in agreement with EU biocides CAR 2011.

682. US EPA summary document 2010: The number of reported incidents involving lambda-cyhalothrin is relatively large. The majority of health effects involved dermal, neurological, gastrointestinal and respiratory symptoms. These symptoms were of low to moderate severity, however, two of the incidents resulted in death. Most of the cases occurred at home in a residual setting, although there were cases that occurred in occupational settings as well. This exposure occurred while the patients were applying or using the product either indoors or outdoors. Many incidents appeared to occur because the product was used improperly. A moderate number of low severity incidents involving gamma-cyhalothrin have been reported. In addition, the number of high severity incidents is low. Most of the cases occurred at home in a residential setting. Patients reported inhaling the product, or accidentally getting the product on their faces, hands, arms and/or legs. These exposures occurred while the patients were applying or using the products either indoors or outdoors.

683. WHO 2011: Ingestion could lead to neurological symptoms such as tremors and convulsions.

n) Immunotoxicity

684. US EPA summary document 2010: The agency anticipates requiring an immunotoxicity study (GLN 870.7800) in order to conduct a complete human health risk assessment for lambda-cyhalothrin and gamma-cyhalothrin.

o) Endocrine disruption

685. EU Endocrine Disruption Database (2012): Listed within category 1, which means that it is persistent in the environment or produced at high volumes with evidence of endocrine disruption activity in at least one species using intact animals.

686. EU biocides CAR 2011: As part of the evaluation of the application for the inclusion of lambda-cyhalothrin in Annex I of the Biocidal Products Directive (98/8/EC) toxicology and ecotoxicology data are assessed. It is concluded that there was no clear evidence of endocrine disruption effects from these studies. However, it should be noted that due to limitations in the test guidelines available at the time, the potential for endocrine effects may not have been fully investigated.

p) Mode of action

687. ATSDR 2003: The primary site of action for pyrethrins and pyrethroids is the sodium channel of nerve cells, Type II pyrethroids include a cyano group; their effects in rodents are usually characterized by pawing and burrowing behaviour, followed by profuse salivation, increased startle response, abnormal hindlimb movements, and coarse whole body tremor that progresses to sinuous writhing (choreoathetosis). Clonic seizures may be observed prior to death. Body temperature is not increased, but may decrease. The term CS-syndrome (from choreoathetosis and salivation) has been applied to Type II responses.

688. US EPA summary document 2010: As with the other pyrethroids, lambda- and gamma-cyhalothrin cause neurotoxicity in insects and mammals by the modulation of nerve axon sodium channels. Pyrethroids interfere with the ability of the nervous system to relay nerve transmissions, potentially resulting in tremors, conclusions,

salivation and other clinical effects. Based on similar mammalian toxicity profiles for cyhalothrin technical, lambda-cyhalothrin and gamma-cyhalothrin, the toxicity databases were combined for purposes of risk assessment. Endpoints for risk assessment were based on neurological effects observed in lambda-cyhalothrin studies. However, the points of departure were reduced by a factor of 2 for acute dietary, dermal and inhalation scenarios because of the increased toxicity observed and/or presumed in rat gamma-cyhalothrin studies. There was no evidence of increased quantitative and qualitative susceptibility in rats or rabbits. The endpoints chosen for risk assessment were considered protective, and the degree of concern and residual uncertainties were low.

q) Acceptable Exposure Levels

689. EU biocides CAR 2011: A systemic long term limit value (AEL) of 0.0025 mg/kg bw/day was derived based on the NOAEL obtained in the one-year dog study, an oral absorption of 50% and an assessment factor of 100. The respective critical effects were neurological effects (unsteadiness, lack of muscular co-ordination), gastro-intestinal effects and reduced food intake. In the long term rat studies also neurological effects were observed as critical, but they were accompanied with hepatic changes including increased liver weight and reduced body weight.

690. EFSA review report 2001: The same systemic long term limit value (AOEL systemic) was derived on the same data and assessment factors. In addition an external long term limit value (ADI) of 0.05 mg/kg bw day was derived on the same data without consideration of the oral absorption rate

691. WHO 2011: The JMPR allocated an ADI of 0-0.02 mg/kg bodyweight for cyhalothrin, based on short term and chronic testing on rats, mice, rabbits, guinea pigs and dogs. The data were considered by the JMPR and WHO to be applicable to lambda-cyhalothrin.

16.12 Environmental hazard assessment

692. According to US EPA (2010) *lambda*-cyhalothrin and *gamma*-cyhalothrin has the following

693. Environmental Hazards statement: This pesticide is extremely toxic to fish and aquatic organisms and toxic to wildlife

r) Aquatic compartment (including sediment)

694. Toxicity data for aquatic species are for example available from EFSA review report 2001 and EU biocides AR 2011. Lambda-cyhalothrin is classified as very highly toxic to aquatic organisms based on data for aquatic vertebrates and invertebrates as well as for sediment dwelling organisms. Toxicity reference values for aquatic species are listed in Table 4. Toxicity values reported for cyhalothrin and gamma-cyhalothrin are within the same range (deviation factor max. of 10) suggesting high toxicity in chronic exposure conditions to invertebrates.

695. US EPA summary document 2010: Gamma-cyhalothrin is very highly toxic to fish and aquatic invertebrates. Chronic toxicity data for sensitive freshwater fish species as well as invertebrates are lacking, also no data on aquatic plants are available. There are concerns of increased toxic effects of gamma- and lambda-cyhalothrin together with piperonyl butoxide on nontarget species.

Table 4: Toxicity reference values for the aquatic compartment

Exposure scenario/ Study type	Organism /Species	Endpoint	Toxicity value	Reference
Acute 96 hour	Fish	LC_{50}	0.21 µg/l	EFSA review report 2001
Chronic, 21 days	Fish	NOEC	0.25 µg/l	
Acute 48 hour	Aquatic invertebrates	EC_{50}	0.36 µg/l	
Acute 96 hour	Neonate aquatic invertebrates	EC_{50}	0.016 µg/l	
Acute 96 hour	Neonate aquatic invertebrates	NOEC	0.006 µg/l	
Chronic, 21 days	Sediment dwelling	NOEC	0.16µg/l	

Exposure scenario/ Study type	Organism /Species	Endpoint	Toxicity value	Reference
	organisms			
Acute 96 hour	Algae	EC50	>0.3 mg/l	
Acute 96 hour	Aquatic crustaceae	LC_{50}	0. 00 3µg/l	PPDB 2012
Chronic, 21 days	Aquatic invertebrates	NOEC reproduction	0.00198 µg/l	EU biocides AR 2011
Chronic, 21 days	Sediment dwelling organisms	NOEC	0.0175µg/l	
Field study, 14 days	Various species	NOAEC	0.0175	

s) Terrestrial compartment

696. EFSA review report 2001 and EU biocides AR 2011: Lambda-cyhalothrin is toxic to vertebrates and highly toxic to bees and other arthropods. Chronic toxicity field studies with earthworms revealed a low NOEC of 29 µg/kg soil (ww). The chronic dietary intake NOEC for birds in a reproduction study was estimated to be 3 mg/kg bw/day. Acute LD50 for cyhalothrin and gamma cyhalothrin suggested no acute toxicity to birds (PPDB 2012). The low chronic NOEC for earthworms of gamma-cyhalothrin is in line with the finding in Table 5 for lambda-cyhalothrin.

Table 5: Toxicity reference values for the terrestrial compartment for lambda-cyhalothrin

Exposure scenario/ Study type	Organism /Species	Endpoint	Toxicity value	Reference
Acute, oral	Mice	LD_{50}	20 mg/kg	EFSA review report 2001
Short term dietary	Rat	NOEL	0.7 mg/kg/d	
Acute	Birds	LD_{50}	>3950 mg/kg	
Dietary	Birds	LC_{50}	>5300 mg/kg	
Reproduction	Birds	NOEC	>30mg/kg /food	
Acute 14 day	Earthworms	LC_{50}	>1000 mg/kg	
Short term Dietary	Birds	LC_{50}	> 3978 mg/kg	EU biocides AR 2011
Reproduction	Birds	NOEC	> 30mg/kg /food =3mg/kg/bw/d	
Acute 14 day	Earthworms	LC_{50}	>247mg/kg	
Chronic 3 years	Earthworms, field study	NOEC	0.029 mg/kg /ww soil	
28 days reproduction	Soil dwelling arthropod	NOEC	1.29 mg/kg /ww soil	
28 days	Plants	EC_{50}	0.11mg/kg ww soil	
28 days	Microorganisms	EC_{50}	1.1 mg/kg ww soil	

t) Toxicity to pollinators

697. Cyhalothrin and gamma-cyhalothrin: PPDB 2012: Acute 48 hour LD50 contact = 0.005 µg/bee

698. Lambda-cyhalothrin: EFSA review report 2001: Acute oral toxicity: LD50 (48 h) = 0.91 µg/bee

699. Acute contact toxicity: LD50 (48 h) = 0.038 µg/bee

700. EU biocides AR 2011: The most sensitive of the other tested arthropod species was the predatory mite *T. pyri*, with a 48 hour LR50 = 0.0037 g a.s./ha in a study with direct exposure of dried residues on glass plates.

16.13 Other Information

701. Toxicological information presented in the PAN –pesticides database and in the footprint database is largely consistent with the toxicological information summarized above with the exception that the reproductive toxicity and developmental study results summarized above seem not respected or insufficient for a conclusion in the PAN database and the negative conclusion on carcinogenicity and the EU endocrine disruption database listing was not acknowledged in the footprint database. It seems that read across between the cyhalothrin and the lambda- and gamma- enantiomers was not similarly taken into consideration for these databases.

702. In the review report of the EC work programme for review of existing active substances provided for the placing of plant protection products on the market, it is mentioned that for the protection of aquatic organisms, risk mitigation measures should be applied. For the protection of bees Member States should prescribe appropriate risk mitigation measures (e.g. buffer zones) if products containing lambda-cyhalothrin are applied at high doses. Depending on crop and application rate, Member States should prescribe appropriate risk mitigation measures to avoid unacceptable effects on non-target arthropods when authorisations are granted for plant protection products containing this active substance.

16.14 References

EU biocides AR (2011) Assessment Report for lambda-cyhalothrin. Product-type 18. (Insecticide) May 2011, available at http://ec.europa.eu/environment/biocides/annexi_and_ia.htm

EU biocides CAR (2011) Competent Authority Report lambda-cyhalothrin, Product-type 18, May 2011.

EU Endocrine Disruption Database (2012) http://ec.europa.eu/environment/endocrine/strategy/short_en.htm, 2012-04-16

EFSA review report (2001) Review report for the active substance lambda-cyhalothri,. 7572/VI/97-final January 2001, available at http://ec.europa.eu/sanco_pesticides/public/index.cfm?event=activesubstance.selection

US EPA summary document (2010) Lambda-Cyhalothrin Summary Document Registration Review: Initial Docket December 2010. http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2010-0480

US EPA (2010) EFED Registration Review Problem formulation for Lambda-Cyhalotrin and Gamma-Cyhalothrin November 2010. http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2010-0480-0005

WHO (2011) Specifications and evaluations for public health pesticides. Lambda- Cyhalothrin. available at http://www.who.int/whopes/quality/newspecif/en/

PPDB (2012) Pesticide Properties Database, http://sitem.herts.ac.uk/aeru/footprint/en/index.htm, 2012-04-18

17. Lufenuron

CONCLUSIONS

Assessment of POP properties – comparison with the criteria of Annex D and other hazard indicators

17.1 Long-rang environmental transport

703. Lufenuron has a calculated DT50 in air <2 days. The multimedia OECD model results indicate a high Pov, but a low LRT potential compared with reference POPs like alpha-HCH, PeCB and octa-BDE. Therefore it is unlikely that lufenuron fulfils the Annex D 1 (d) (iii) criterion. But for target-oriented LRTP indicator (TE) the model limits for higher concern are slightly exceeded. Therefore it can be concluded that more information for lufenuron is needed to conclude on the Annex D 1 (d) criterion.

17.2 Ecotoxicity (pollinator toxicity)

704. Acute oral and contact toxicity to bee is low; however detrimental effects in a bee brood test were identified at the lowest tested dose.

705. Based on its high aquatic toxicity and toxicity to human health (see section below) lufenuron meets Annex D 1 (e) (ii) criterion.

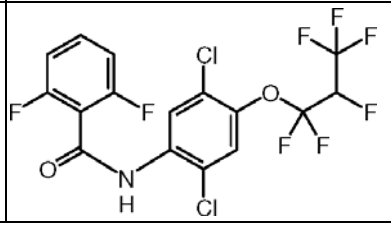
17.3 Toxicity to human health (including mutagenicity, carcinogenicity and adverse effects on the reproductive, endocrine, immune or nervous systems)

706. Lufenuron is classified according to the EU GHS system for skin sensitization. The reported data indicated no need for EU GHS classification for acute systemic effects, skin or eye irritation. The comprehensive data for in vitro and vivo genotoxicity as well as mouse and rat carcinogenicity did not indicate concern for respective hazards. Also the two generation study and the rabbit and rat developmental studies did not indicate specific concern for reproductive toxicity hazard. Lufenuron is not in the EU endocrine disrupter database and a specific investigation for pituitary, adrenal and genital organs effects suggested there is no respective concern. The critical effect within short and long term studies appeared to be clinical signs of neurotoxicity. However the histology of the peripheral and central nervous system was not affected. A respective EU GHS STOT RE classification might be required. A systemic long term limit value of 0.015 mg/kg bw day was derived from the NOAEL of the 1-year dog study and an assessment factor of 100.

17.4 Identity of the substance and physical and chemical properties

a) Name and other identifiers of the substance

Table 1: Substance identity

Common name:	Lufenuron
IUPAC name:	(RS)-1-[2,5-dichloro-4-(1,1,2,3,3,3-hexafluoropropoxy)phenyl]-3-(2,6-difluorobenzoyl)urea
CAS number:	103055-07-8
Molecular weight:	511.16
Chemical structure:	

b) Chemical group

707. Benzoylurea

c) Physico-chemical properties

Table 2: Overview of selected physico-chemical properties

Property	Value	Remarks and Reference
Vapour pressure at 25°C (mPa)	4.00 x 10^{-03}	PPDB (2012)
Water solubility at 20°C (mg/l)	0.046	PPDB (2012)
Partition coefficient n-octanol/water (log value, pH 7, 20°C)	5.12	PPDB (2012)
Partition coefficient air/water (log value)	-8.633	EPI Suite v 4.1 (KOAWIN v. 1.10)[40]
Partition coefficient air/octanol (log value)	13.753	EPI Suite v 4.1 (KOAWIN v. 1.10)
Henry´s Law Constant at 25°C ($Pa.m^3.mol^{-1}$)	3.14 x 10^{-02}	PPDB (2012)

17.4 Classification and labelling

d) Harmonised Classification according to EU-GHS

Regulation (EC) No 1272/2008:

Category	Hazard-Phrase
Skin Sens. 1	H317 May cause an allergic skin reaction.
Aquatic Acute 1	H400 Very toxic to aquatic life.
Aquatic Chronic 1	H410 Very toxic to aquatic life with long lasting effects.

17.5 Potential for long range transport

708. Results of the **Phototransformation** in air according to EPI Suite TM v4.0 (AOPWIN v 1.92) are based on a 12h day are summarised in Table 3.

Table 3 Phototransformation in air

Guideline / Test method	Molecule / radical	Rate constant for reaction with OH-radicals (k_{OH}) [cm^3 $molecule^{-1}$ sec^{-1}]	Half-life ($t_{1/2}$) [d]	OH-radical concentration
AOPWIN	OH	10.3680 E-12	1.03 (12.83 hours)	1.5 x 10^6 OH-radicals/cm^3

709. The OECD "Pov and LRTP Screening Tool" (OECD 2006) has been developed with the aim of using multimedia models for estimating overall persistence (Pov) and long-range transport potential (LRTP) of organic chemicals at a screening level in the context of PBTs/POPs assessments. The Tool calculates metrics of (overall persistency) Pov and LRTP from a multimedia chemical fate model, and provides a graphical presentation of the results. The result for Lufenuron is plotted against the reference chemicals α-HCH, c-octaBDE, PeBD, and SCCP. The criteria lines were not modified and take as proposed in the tool (Pov limit: 195 days, CTD limit: 5096 km, TE limit: 2.25%; Klasmeier et al., 2006). According to Wegmann 2009 compounds that are less problematic from an environmental exposure point of view are in the bottom-left corner (low Pov, low LRT), while substances of environmental concern are found in the upper right region (high Pov, high LRT).

710. The input parameters for Kow, Kaw and half-life in air were taken from tables 2 and 3, half-lives for water and soil are listed in table 4.

Table 4: Half-lives for water and soil

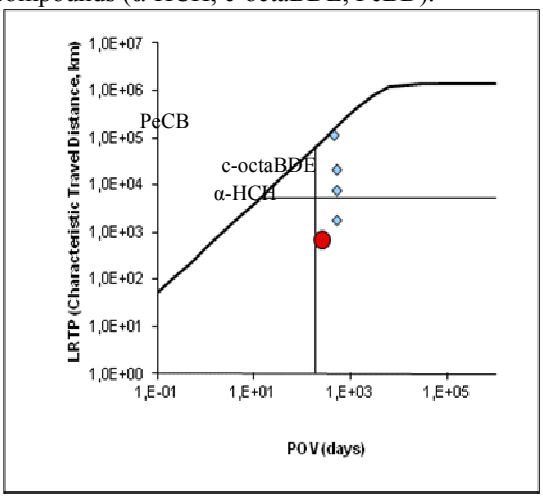
Half-Lives (h)	Value	Source
Water	4320	PBT profiler[41]
Soil ($DT50_{field}$)	6144	PPBD 2012

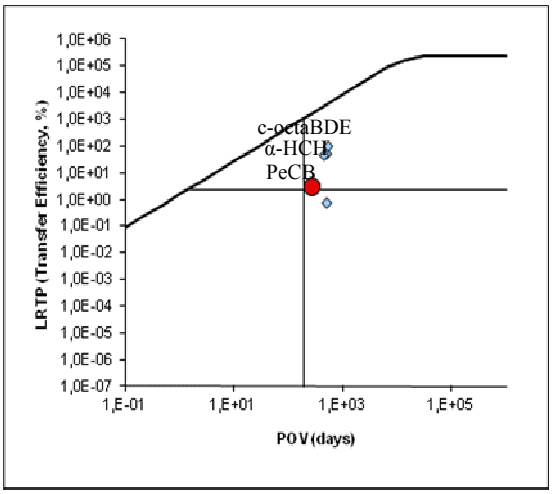
711. With a calculated CTD (characteristic travel distance) of 730 km lufenuron lies below the reference chemicals. The calculated TE (transfer efficiency) value is 3.2% which indicates a higher TE although below the reference chemicals α-HCH, c-octaBDE, PeBD (see Figure 1). In the TE plot lufenuron is on the boundaries indicating the possibility of POP-like persistence and LRT potential.Pov is considered to be 369 days therefore lufenuron is in the bottom right quadrant.

[40] http://www.epa.gov/oppt/exposure/pubs/episuite.htm

[41] http://www.pbtprofiler.net/

Figure 1: Results from the OECD Tool (CTD and TE) for lufenuron (red point) and selected reference compounds (α-HCH, c-octaBDE, PeBD).





17.6 Human health hazard assessment

e) Acute toxicity

712. DAR 2007: The data presented are in agreement with the actual EU GHS classification, that is no classification for acute systemic toxicity, non irritant, but sensitizing with the M&K method.

f) Mutagenicity and Carcinogenicity

713. DAR 2007: Lufenuron showed negative results in bacterial mutation tests, an in vitro mammalian gene mutation test, an in vitro chromosomal aberration test, in vitro UDS tests as well as in an in vivo mouse micronucleus test and UDS test with mammalian liver cells. The substance did also not sow carcinogenic potential within mouse and rat carcinogenicity studies.

g) Toxicity for reproduction

714. DAR 2007: Within a two generation study no effects on the reproductive parameters were observed, in the offspring a minimal delay in the emergence of the righting reflex was observed and increased body weights were observed in parental animals. The parental, reproductive and offspring NOAELs were considered as identical. Within the rabbit and the rat developmental studies no teratogenic effects were observed up to limit doses that induced slight but significant reductions in body weight gain and food consumption in the rat. Consequently no classification is proposed.

h) Neurotoxicity

715. DAR 2007: The critical effect within short term and long term studies in rat, mice and dog studies were clinical signs of neurotoxicity as tonic-clonic convulsions and death. In a subchronic neurotoxicity study in the rat lufenuron induced single episodes of spontaneous clonic-tonic convulsion or fasciculations and facilitated pentylenetetrazol-induced generalised convulsions. Neurological parameters, motor activity, startle response and startle habituation, complex spatial learning, as well as histology of the peripheral and central nervous system were not affected by treatment. A respective classification for EU GHS STOT RE might be required.

i) Immunotoxicity

716. -

j) Endocrine disruption

717. DAR 2007: An investigation into the effects of lufenuron on the rat endocrine system, focused on the pituitary, adrenal and genital organs, suggested that there is no effect on the endocrine system in either sex.

k) Mode of action

718. -

l) Acceptable Exposure Levels

719. DAR 2007: The clinical signs of neurotoxicity appeared to be the critical effects in the short and long term studies. The lowest NOAEL was observed in the 1- year dog study, application of an assessment factor of 100 resulted in an external and a systemic long term limit value of 0.015 mg/kg bw day.

17.7 Environmental hazard assessment

m) Toxicity to pollinators

720. DAR 2007 states that the 24-hour acute oral and contact LD_{50}values of lufenuron were >200 and >197 µg/bee, respectively. A 21 d bee brood test caused detrimental effects to bee brood of the lowest tested dose of 0.33 g a.s/L (formulation tested).

17.8 Other information

721. Compared to the information summarized above the toxicological information presented in the PAN –pesticides database seems incomplete with regard to acute toxicity, carcinogenicity and reproductive toxicity and endocrine disruption. The toxicological information in the footprint database is largely consistent with the toxicological information summarized above with the exception that the reproductive toxicity and developmental study result were not considered or considered as insufficient for a clear conclusion.

17.9 References

DAR (2007) Draft Assessment Report Lufenuron, July 2007 http://dar.efsa.europa.eu/dar-web/provision, 2012-03-26

PPDB (2012) Pesticide Properties DataBase, University of Hertfordshire, http://sitem.herts.ac.uk/aeru/footprint/en/ 2012-04-18

Klasmeier, J., Matthies, M., Macleod, M., Fenner,K., Scheringer,M., Stroebe, M., Le Gall, A.C.,, McKone,T., van de Meent, D., Wania, F. (2006): Application of multimedia models for screening assessment of long-range transport potential among and overall persistence. Environmental Science and Technology 40, 53-60.

OECD (2006): The OECD Pov and LRTP Screening Tool 2.0. Software and Manual, OECD, Paris, www.oecd.org/env/riskassessment.

Wegmann F. Cavin L, MacLeod M, Scheringer M, Hungerbühler K. (2009) Environmental Modeling & Software 24, 228-237

18. Malathion[42]

CONCLUSIONS

Assessment of POP properties – comparison with the criteria of Annex D and other hazard indicators

18.1 Persistence

722. Malathion is susceptible to pH dependant hydrolytic degradation (DT50 values range from 107 days at pH 5 to 0.49 days at pH 9). The parent compound and its metabolites are degraded in laboratory soil test with DT50 values form <1 day to 11 days. Also results from water/sediment studies suggest rapid break-down for malathion (DT50 <1 day). The modelled P-score of malathion is also low. Based on the presented information it can be concluded that malathion does not meet the persistence criterion of Annex D 1 (b) (i).

18.2 Bioaccumulation

723. Malathion does not fulfil the Annex D 1 (c) (i) criterion on bioaccumulation based on a log Kow of 2.75 and an experimentally derived BCF of 103. In addition the modelled B-score is 0.00.

18.3 Long Range Transport

724. Malathion has a calculated a half-life in air of 0.8 hours. According to the rapid degradation of malathion in air (<2 days) and a lack of experimental evidence of persistency the LRT potential of malathion is considered to be low. Therefore it can be concluded that malathion does not fulfill the Annex D 1 (d) (iii) criterion.

18.4 Ecotoxicity (including pollinator toxicity)

725. Malathion is highly toxic to aquatic organisms and is classified according to GHS as aquatic acute and chronic category 1. For terrestrial vertebrates on a chronic basis, malathion is moderately toxic to avian species and less toxic to mammals. However DAR- 2009 considers a reproduction NOEC of 13.5 mg a.s./kg bw/day for Bobwhite quail relevant for risk assessment that is below the dietary value of 2400 ppm from the dietary study used by US-EPA Red 2009.Malathion is acutely slightly toxic to earthworms, but its toxicity to bees is high.

726. Based on its high ecotoxicity and toxicity to human health (see below) Annex D 1 (e) (ii) is fulfilled

18.5 Toxicity to human health (including mutagenicity, carcinogenicity and adverse effects on the reproductive, endocrine, immune or nervous systems)

727. Malathion is of low acute systemic toxicity qualifying for acute oral GHS class 4.

728. Malathion is not classified for carcinogenicity, mutagenicity or reproductive toxicity according to the GHS system in the EU.

729. The in vitro genotoxicity results are inconclusive, but the in vivo genotoxicity results are negative which suggests the conclusion that there is no relevant mutagenic potential. Some carcinogenicity findings lead to IARC class 3 (evidence inadequate in humans and inadequate or limited in animals) and US-EPA conclusion for “suggestive evidence for carcinogenicity”. Genotoxicity of the impurity Isomalathion cannot be excluded.

730. Within reproductive toxicity studies decreased pup weights in rats and increased resorptions in the rabbit were reported but the results were considered not sufficient for a classification proposal.

731. Malathion is listed in the EU endocrine disrupter database within category 2. This means that it is persistent or a HPVC chemical with at least some in vitro evidence of biological activity related to endocrine disruption.

732. Some literature studies are indicated that show that malathion can affect immune function, but this was not considered as important for risk quantification by US EPA.

733. Malathion is classified for skin sensitization.

734. The substance did not induce delayed neurotoxicity. The critical effect used for limit value derivation is cholinesterase inhibition. In the latest evaluation available this lead to an lowest ADI proposal of 0.03 mg/kg bw day.

[42] Malathion is an alternative to both endosulfan and DDT.

18.6 Identity of the substance and physical and chemical properties

a) Name and other identifiers of the substance

Table 1: Substance identity

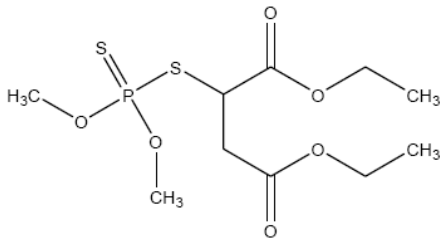
Common name:	malathion (ISO)
IUPAC name:	1,2-bis(ethoxycarbonyl)ethyl O,O-dimethyl phosphorodithioate
CAS number:	121-75-5
Molecular weight:	330.6
Chemical structure	

Table 2: Toxicological relevant impurities

Impurities	Typical concentration	Remarks
Isomalathion	must not exceed 2 g/kg (EFSA review report 2010-01-22) ≤ 0.03 % isomalathion (Annex VI to EU CLP regulation)	DAR2009: acetyl cholinesterase inhibitor which enhances the toxicity of malathion. Positive results in genotoxicity studies may be due to isomalathion, this has been reported also in literature.
malaoxon	must not exceed 1 g/kg (EFSA review report 2010-01-22)	DAR 2009: acetyl cholinesterase inhibitor which enhances the toxicity of malathion.

b) Chemical group

735. Organophosphate

c) Physico-chemical properties

Table 3: Overview of selected physico-chemical properties

Property	Value	Remarks and Reference
Vapour pressure	4.5 x10^{-4} Pa	PPDB 2012
Water solubility	148 mg/L (25°C)	DAR 2009
Partition coefficient n-octanol/water (log value)	2.75	PPDB 2012
Partition coefficient n-air/water (log value)	-6.7	EPI SUITE[43]
Partition coefficient n-octanol/air (log value)	9.45	EPI SUITE
Henry´s Law Constant at 25°C	1.00 X 10^{-03} Pa m^3 mol^{-1}	PPDB 2012

18.7 Classification and labelling

d) Harmonised Classification according to GHS

Regulation (EC) No 1272/2008 – 1nd amendment 2009

Category	Hazard-Phrase
Acute Tox. 4	H302
Skin Sens. 1	H317
Aquatic Acute 1	H400
Aquatic Chronic 1	H410, M=1000

18.8 Environmental fate properties

e) Abiotic degradation

f) Hydrolysis

736. PPDB 2012: Aqueous hydrolysis DT50 at 20°C and pH 7 is 6.2 days. The degradation is pH sensitive and the DT50s range from 107 days at pH 5 to 0.49 days at pH 9, all at 25°C.

[43] http://www.epa.gov/oppt/exposure/pubs/episuite.htm

g) Phototransformation/photolysis

737. EnviChem 2012: Aquatic photolysis half-lives from 833 days to 41.3 days at pH 6 for summer sunlight 30 °N (source: Howard 1991). PPDB 2012 lists a DT50 value of 98 days at pH7.

h) Biodegradation

738. EFSA 2006: The available data demonstrate that in soil malathion degrades to the major (>10% applied radioactivity (AR)) metabolites malathion monocarboxylic acid (MMCA) malathion dicarboxylic acid (MDCA). In soil malathion and MMCA exhibited very low persistence and MDCA exhibited low persistence. (cf. Table 4) In sediment water systems malathion exhibited very low persistence breaking down to the major metabolites MMCA (which exhibited low persistence) and MDCA (which exhibited medium persistence). All the compounds remained primarily in the water phase of the test sediment water system. US EPA 2006 state that Malathion is generally nonpersistent; but open literature studies suggest that its persistence is longer on soil that is of dry, sandy, low nitrogen, low carbon, and acidic quality.

Table 4: Biotic degradation of malathion and major metabolites

Study type	Results	Reference	Remarks
DT_{50} soil lab (days):	Malathion: <1 d (20°C) MMCA: <1 d MDCA: 3 d (geometric mean, n=4)	EFSA DAR-LOEP 2009	-
DT_{50} soil lab (days):	Malathion: <1 to ~11d	US-EPA RED 2009	-
DT_{50} water (days) from water/sediment study:	Malathion: <1 d MMCA: 3-4d MDCA:15-17d	EFSA DAR-LOEP 2009	Malathion remained in the water phase
DT_{50} water sediment/whole system (days):	Malathion: <1 d MMCA: 3-4d MDCA:13-21d	EFSA DAR-LOEP 2009	-

18.9 Potential for long range transport

739. Results of the Phototransformation in air according to EPI Suite TM v4.0 (AOPWIN v 1.92) are based on a 12h day are summarised in table 5.

Table 5 Phototransformation in air

Guideline / Test method	Molecule / radical	Rate constant for reaction with OH-radicals (k_{OH}) [cm^3 $molecule^{-1}$ sec^{-1}]	Half-life ($t_{1/2}$) [d]	OH-radical concentration
AOPWIN	OH	77.4198 E-12	0.14	1.5 x 10^6 OH-radicals/cm^3

740. According to these results malathion is rapidly degraded by photochemical processes. Du to the lack of persistency no multimedia fate modelling with the OECD tool was performed.

18.10 Bioaccumulation

741. According to PPDB 2012 a BCF of 103 was estimated. EnviChem 2012 listed a range for BCF of 1.3 - 21.0 in *Cyprinus carpio* (source: AQUIRE 1994)

i) PB-score

742. Malathion has a P-score of 0.11 and a B-score of 0.00 resulting in an overall B-score of 0.11.

18.11 Human health hazard assessment

j) Acute toxicity

743. DAR 2009: Acute systemic toxicity and skin/eye irritation results are in agreement with the actual EU-CLP entry. In the Magnusson and Kligman test for skin sensitization a response was observed that was considered sufficient for classification.

744. US EPA RED 2009: Malathion exhibits low acute toxicity via the oral, dermal, and inhalation routes (Toxicity Category III or IV, LD50 oral > 5000 mg/kg bw, LD50 dermal > 2000mg/kg bw, LC50 respiratory > 5.2 mg/L). It exhibits only slight eye and dermal irritation and is not a dermal sensitizer.

k) Mutagenicity and Carcinogenicity

745. DAR 2009: In vitro results appear inconclusive with negative AMES and UDS tests but a positive mouse lymphoma gene mutation test and a positive in vitro chromosome aberration tests. However an in vivo chromosome aberration study in rat bone marrow and an in vivo UDS test were negative which suggests that there is no genotoxic potential and no classification is proposed.

746. Increased nasal tumors were observed in the rat as well as liver tumors at high dose levels. The nasal tumors were probably secondary to a local irritation. The content of the impurity isomalathion is considered to be critical also with regard to genotoxicity of the compound. The results were not considered sufficient for a classification proposal.

747. US EPA RED 2009: Malathion has been classified as having "suggestive evidence of carcinogenicity" in accordance with the EPA Proposed Guidelines for Carcinogen Risk Assessment (July 1999; i.e. less than likely to be carcinogenic or carcinogenic to humans). The classification is based on the following evidence: 1) the occurrence of liver tumors in mice and rats only at excessive doses; 2) the presence of a few rare tumors in rats, which cannot be distinguished as either treatment related or due to random occurrence; 3) the evidence for mutagenicity is not supportive of a mutagenic concern in carcinogenicity; and 4) malaoxon, a structurally related chemical, is not carcinogenic in rats. The chronic dietary risk assessment is considered protective of any potential carcinogenic effects.

748. IARC Monograph 1987: The substance is listed as group 3 carcinogen, which means not classifiable as to its carcinogenicity to humans. All substances not qualifying for group 4 (non-carcinogen) or groups 1 and 2 (at least possibly carcinogenic to humans) are listed in this group 3.

l) Toxicity for reproduction

749. DAR 2009: Malathion induced a decrease in rat pup weights at non maternally toxic dose levels and increased incidence of resorptions in the rabbit that were considered not related to maternal toxic effects. However the results appeared not sufficient for a classification proposal.

m) Neurotoxicity

750. DAR 2009: No indications of delayed neurotoxicity were observed. Brain acetyl cholinesterase inhibition was observed as well as clinical signs and results in behavioral assessment in a rat developmental study. Though accompanied with kidney and liver effects the acetyl cholinesterase inhibition was observed as the most dominant effect and consequently the basis for limit dose derivation (ADI, AOEL).

751. US EPA RED 2009: ChE inhibition provides the critical effect for determining the point of departure for the oral, dermal and inhalation (aggregate only) routes of exposure. The comparative ChE in the young demonstrate that juvenile animals are more sensitive than adults.

n) Immunotoxicity

752. US EPA RED 2009: "Published literature studies have shown that malathion can affect immune function, depending on route, magnitude, and frequency of administration. … Although the immunotoxicity study is identified as a data gap, it is not considered important to the quantification of risk from malathion. Rather it will be used to further characterize the hazard from malathion in terms of its effects on the immune system, and it is not expected to have an effect on the hazard values used in the risk assessment. Therefore, no additional safety factor is necessary to account for the lack of a guideline immunotoxicity study."

o) Endocrine disruption

753. EU Endocrine Disruption Database 2012: The substance is listed within category 2, which means that it is persistent or an HPVC with at least some in vitro evidence of biological activity related to endocrine disruption.

754. US EPA RED 2009: In the available toxicity studies on malathion, there was no estrogen or androgen mediated toxicity. Thyroid effects were observed in the combined chronic/carcinogenicity study in rats, which included an increase in parathyroid hyperplasia in male and female rats, and a significant trend in thyroid follicular cell adenomas and/or carcinomas and thyroid c-cell carcinomas (all in males). However, the FIFRA SAP did not consider the thyroid effects of concern or necessarily related to malathion exposure.

p) Mode of action

755. DAR 2009, US EPA RED 2009: Malathion belongs to a group of pesticides called organophosphates (OPs), which share a common mechanism of toxicity by affecting the nervous system via cholinesterase inhibition.

q) Acceptable Exposure Levels

756. DAR 2009: A long term limit value (ADI) and a medium term limit value (AOEL) of 0.03 mg/kg bw of were proposed on the basis of a rat 2year study and a rat 90 day study, respectively. An assessment factor of 1000 was used for both values due to the uncertainties for the toxicological impact of the impurity isomalathion in the relevant studies. The acetyl cholinesterase inhibition was considered as the critical effect.

757. US EPA RED 2009: Lowest AEL: incidental oral children: 0.07 mg/kg bw day, several other AELs available for adults, and dermal and respiratory exposure. The acetyl cholinesterase inhibition was considered as the critical effect.

758. International limit values for worker protection (GESTIS-Database): 1-15 mg/m^3 for 8 hours

18.12 Environmental hazard assessment

r) Aquatic compartment (including sediment)

759. US EPA RED 2009 used the toxicity reference values for aquatic organisms listed in Table 6 for risk assessment. The findings by US EPA are in line with DAR 2009 indicating that malathion is extremely toxic to fish (lowest LC50 0.022 µg/l) and daphnia (EC50 0.72 µg/l) in the laboratory (21 studies for aquatic toxicity were submitted). The NOEC of the mesocom study was 5.0 µg a.s./l and the EAC (Ecologically Acceptable Concentration) was set as 30 µg a.s./l (long term effects were not observed).

Table 6: Toxicity reference values (source: USEPA RED 2009)

Exposure Scenario	Species	Exposure Duration	Toxicity Reference Value	Toxicity Category/Effect
Freshwater Fish				
Acute	Bluegill sunfish	69 hr	LC_{50} = 30 ppb	Very highly toxic
Chronic	Rainbow trout	97 day	NOEC 21 ppb	LOEC = 44 ppb
Freshwater Invertebrates				
Acute	Water flea, *Daphnia magna*	48 hr	EC_{50} = 1.0 ppb	Highly toxic
Chronic	Water flea, *Daphnia magna*	21 day	NOEC = 0.06 ppb	LOEC = 0.01 ppb

s) Terrestrial compartment

760. US-EPA RED 2009 and DAR 2009 used the toxicity reference values for terrestrial organisms listed in Table 7 for risk assessment. The table presents a selection of listed values. Please refer to the original documents for more information.

Table 7. Toxicity reference values

Exposure scenario/Study type	Organism/Species		Time Scale Endpoint	Toxicity value	Reference
Acute, 32-day dietary	Mammals	Rat	LD50	390 mg/kg	US EPA RED 2009
Chronic, teratology study	Mammals	Rabbit	NOAEL	25 mg a.s/kg bw/day	DAR 2009
Acute toxicity	Birds	Bobwhite quail	LD50	359 mg as/kg	DAR 2009
Dietary toxicity	Birds	Bobwhite quail	LD50	554 mg/kg bw/day	DAR 2009
Reproductive toxicity	Birds	Bobwhite quail	NOEC	13.5 mg/kg bw/day	DAR 2009
Acute, 8-day dietary	Birds	Ring-necked pheasant	LC50.	2369 ppm	US-EPA RED 2009
Chronic, 21-week dietary	Birds	Bobwhite quail	LOEL	2400 ppm	US EPA RED 2006

Exposure scenario/Study type	Organism/Species	Time Scale Endpoint	Toxicity value	Reference
Acute toxicity	Earthworms	LC50	116 mg/kg	DAR 2009

t) Toxicity to pollinators

761. EFSA 2006 states that the toxicity to bees is high and risk mitigations measures are also needed to protect other non-target arthropods off field. Table 8 displays toxicity values.

Table 8: Toxicity values

Study type	Organism	Time Scale Endpoint	Toxicity value	Reference
Acute oral toxicity	Bees	Acute oral	0.40 µg a.s./bee (formulation tested)	DAR 2009
Acute contact toxicity	Bees	Acute contact	0.16 µg a.s. /bee (formulation tested)	DAR 2009

18.13 Other information

762. US-EPA RED 2009: Human RA for outdoor Mosquito control measures available, acceptable risks indicated.

763. The toxicological summary provided above is in agreement with the toxicological information provided in the footprint database and in the PAN pesticides database.

764. WHO specifications and evaluations for public health pesticides- Malathion 2003: does not contain further critical toxicological information

18.14 References

DAR (2009) Additional Report to the DAR Malathion. February 2009 http://dar.efsa.europa.eu/dar-web/provision

EnviCHem (2012) Data bank of Environmental Properties of Chemicals – EnviChem http://www.ymparisto.fi/default.asp?contentid=141944&lan=en 2012-04-06.

EFSA (2006) Scientific Report, Conclusion on the peer review of malathion, Efsajournal, 63, 1-86, January 2006 http://www.efsa.europa.eu/de/efsajournal/pub/63r.htm

EU Endocrine Disruption Database (2012) http://ec.europa.eu/environment/endocrine/strategy/short_en.htm, 2012-04-16

IARC Monograph (1987) Monograph 30, Sup 7 http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php

PPDB (2012) Pesticide Properties DataBase, University of Hertfordshire, http://sitem.herts.ac.uk/aeru/footprint/en/ 2012-04-18

US EPA RED (2009): Reregistration Eligibility Decision for Malathion, Case No. 0248. http://www.epa.gov/oppsrrd1/REDs/malathion_red.pdf

19. Novaluron

CONCLUSIONS

Assessment of POP properties – comparison with the criteria of Annex D and other hazard indicators

19.1 Persistence

765. The reported half-life (in soil: 7-14 days, in aquatic environments. 9.7 -19.7 days) and the DT_{50} values (field, soil: 96.5 days, water sediment: 17.5 days, water only from water sediment studies: 0.95 days) indicate that the persistence criterion according to Annex D 1. (b) (i) is not fulfilled.

766. Novaluron does not meet the persistence criterion according to Annex D 1. (b) (i).

19.2 Bioaccumulation

767. Novaluron does meet the Annex D 1. (c) (i) criterion based on the experimentally obtained BCF value of 14,431 in fish.

19.3 Long-range environmental transport (LRT)

768. Novaluron has a calculated half-life in air of 4.5 hours (<2 days) indicating fast degradation in air. Therefore it is unlikely that novaluron fulfils the Annex D 1 (d) (iii) criterion.

19.4 Ecotoxicity (including pollinator toxicity)

769. Novaluron is highly toxic to aquatic invertebrates and sediment swelling organism. It is moderate toxic to bees (oral 48 hr LD_{50} >100 µg/bee); due to mode of action immature bees might be highly sensitive. Novaluron is self-classified according to EU-GHS as acute and chronic aquatic toxic category 1. Therefor novaluron fulfils the Annex D 1 (e) (ii) criterion.

19.5 Toxicity to human health (including mutagenicity, carcinogenicity and adverse effects on the reproductive, endocrine, immune or nervous systems)

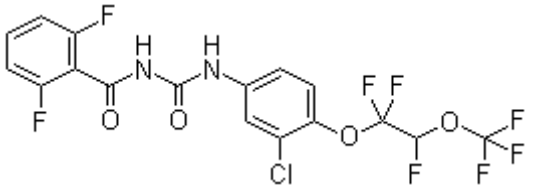
770. Novaluron is not classified for acute systemic toxicity, skin or eye irritation or skin sensitization and the comprehensive data available do not indicate a respective need. Novaluron was not genotoxic within a comprehensive in vitro and in vivo study package and it was not carcinogenic in respective mouse and rat studies. Also the multigeneration study in rats and the developmental toxicity studies in rats and rabbits did not indicate specific adverse effects. There was no evidence for neurotoxicity in standard studies and in an acute neurotoxicity study in the rat.

771. The erythrocyte has been identified as the primary target of novaluron toxicity with secondary effects apparent in the spleen and at high doses in the liver. A systemic long term limit value of 0.002 mg/kg bw day is proposed by the author of this POP factsheet.

19.6 Identity of the substance and physical and chemical properties

a) Name and other identifiers of the substance

Table 1: Substance identity

Common name:	Novaluron
IUPAC name:	(*RS*)-1-[3-chloro-4-(1,1,2-trifluoro-2-trifluoromethoxyethoxy)phenyl]-3-(2,6-difluorobenzoyl)urea
CAS number:	116714-46-6
Molecular weight:	492.70
Chemical structure:	

772. The manufacturing process indicates that no toxicologically significant impurities, such as chlorinated dioxins, nitrosamines and hexachlorobenzenes are formed (ref. to US EPA fact sheet (2001)).

b) Chemical group

773. Benzoylurea

c) Physico-chemical properties

Table 2: Overview of selected physico-chemical properties

Property	Value	Remarks and Reference
Vapour pressure	1.60 X 10^{-02} mPa	PPDB 2012
Water solubility	0.003 mg/L (20°C)	PPDB 2012
Partition coefficient n-octanol/water (log value)	4.3	PPDB 2012
Partition coefficient air/water (log value)	-10.55	Epi Suite(KOA win v1.10 estimate)[44]
Partition coefficient air/octanol (log value)	14.85	Epi Suite
Henry´s Law Constant	2.00 Pa m^3 mol^{-1} (25°C)	Volatile, PPDB 2012

19.7 Classification and labelling

d) Harmonised Classification according to CLP

774. Not available

e) Self classification

775. Notified CLP classification and labelling (2 notification) according to CLP-Inventory[45]

Category	Hazard-Phrase
Aquatic acute 1	H400
Aquatic chronic 1	H410

19.8 Environmental fate properties

f) Abiotic degradation

776. US EPA 2012: In general, Novaluron is stable to abiotic processes.

g) Hydrolysis

777. US EPA 2012: Novaluron was stable at 25°C to hydrolysis at pH 5, 7 and 9.

h) Phototransformation/photolysis

778. US EPA 2012: Novaluron was stable to soil photodegradation and aqueous photolysis.

i) Biodegradation

779. Novaluron is an enantiomer (R,S) and is degraded in soil and water via microbial-mediated processes. The parent compound degraded to chlorophenyl urea and 2,6-difluorobenzoic acid (max. PPDB 2012). Hydrolysis of the degradation products leads to the formation of chloroanelin from chlorophenyl urea and 2,6 difluorobenamide from 2,6-difluorobenzoic acid. Novaluron is not persistent; however, it appears to be more persistent under actual use conditions and under low temperature (ref. to US EPA 2012)).

780. Novaluron is not regarded as persistent according to the screening criteria of Annnex D (cf. Table 3). Metabolites of Novaluron have not been assessed.

Table 3: Biotic degradation of novaluron

Study type	Results	Reference	Remarks
DT_{50} soil lab (days):	Novaluron: 72 d (typical)	PPDB 2012	Moderately persistent
Hal-lives: Soil: 20°C	7-14 d	US-EPA 2012	-
Aquatic environments	9.7 – 19.7 d (total system)	US-EPA 2012	-
DT_{50} field (days):	Novaluron: 96.5 d	PPDB 2012	Moderatly persistent
DT_{50} water (days) from water/sediment study:	Novaluron: 0.95 d	PPDB 2012	Fast
DT_{50} water/sediment :	Novaluron: 17.5 d	PPDB 2012	Fast

19.9 Potential for long range transport

781. Results of the Phototransformation in air according to EPI Suite TM v4.0 (AOPWIN v 1.92) are based on a 12 hour day are summarised in Table 4.

[44] http://www.epa.gov/oppt/exposure/pubs/episuite.htm

[45] http://clp-inventory.echa.europa.eu/

Table 4 Phototransformation in air

Guideline / Test method	Molecule / radical	Rate constant for reaction with OH-radicals (k_{OH}) [cm^3 $molecule^{-1}$ sec^{-1}]	Half-life ($t_{1/2}$) [d]	Half-life ($t_{1/2}$) [h]	OH-radical concentration
AOPWIN	OH	28.7469 E-12	0.37	4.46	1.5×10^6 OH-radicals/ cm^3

782. Based on the fast degradation rate in air no multimedia fate modelling was performed.

19.9 Bioaccumulation

783. Health Canada 2006: A log Kow of 4.3 indicates the potential for bioaccumulation, which is supported by two bioconcentration studies. In these studies, novaluron was readily accumulated by fish during exposure. Novaluron steady state concentrations were attained within 21-35 days, with bioconcentration factors of 14,220-14,645 x for the whole body. The clearance pattern from the whole body was first-order with half-lives of 11-14 days. Approximately 40 days were required for 95% novaluron depuration from the whole body.

784. US EPA 2012: The relatively high level of novaluron bioconcentration by fish, its resistance to significant transformation and its slow rate of loss during depuration suggest that it may have some potential for persistence in the aquatic food chain, particularly when frequent applications are made. The highest mean BCF in whole fish was 14,431.

785. Both references indicate a high bioaccumulation potential.

j) PB-score

786. Novaluron has a PB-score of 1.239 (P-score 0.989 and B-score 0.250).

19.10 Human health hazard assessment

k) Acute toxicity

787. DAR 2008: Within the EU GHS system novaluron is not classified for acute toxicity and the summarized data did not indicate a need for classification for acute systemic toxicity or skin or eye irritation or skin sensitization when tested with the M&K and Buehler test.

788. US EPA factsheet 2001: Novaluron has low to moderate acute toxicity (Toxicity Category IV for oral and inhalation and III for dermal route). It is not an eye and dermal irritant and is not a skin sensitizer.

789. WHO 2004: The results presented are in agreement with the EU and US reports summarized above.

l) Mutagenicity and Carcinogenicity

790. DAR 2008: Novaluron was found not to be genotoxic in *in vitro* and *in vivo* tests which included specific gene mutation assays in bacteria and mouse lymphoma cells, chromosome aberration assays in cultured human lymphocytes and a mouse micronucleus test, a DNA repair assay in bacterial cells and an unscheduled DNA synthesis assay in cultured human epithelioid cells. There was no evidence of oncogenic potential in the rat or mouse.

791. US EPA factsheet 2001: Mutagenecity of novaluron was tested for gene mutation, chromosomal aberration and DNA damage by *in vitro* assays. Novaluron was not cytotoxic with or without S9 activation in *Salmonella typhimurium* and did not induce a genotoxic response in any strain. In a mammalian cell chromosome aberration assay, novaluron produced no evidence of clastogenic activity in the lymphocytes, in the presence or absence of S9 activation. In an unscheduled DNA synthesis (UDS) assay, novaluron produced sporadic increase in gross and net nuclear grain counts; but, was considered non-mutagenic as the sporadic increases in grain counts were not reproducible. In a differential killing assay using *Bacillus subtilis* strains M45 and H17, novaluron was equivocal for bacterial DNA damage in the absence of S9 activation; but, was negative in the presence of S9 activation. Based on the available studies, there is no concern for mutagenicity. Two additional studies are needed to confirm the negative findings observed in the five mutagenicity studies already evaluated by the Agency.

792. WHO 2004: There was no evidence of mutagenic or oncogenic potential in the rat or mouse.

m) Toxicity for reproduction

793. DAR 2008: There was no evidence of reproductive effects in rats treated with novaluron at the highest test dose of about 1000 mg/kg bw day in the

multigeneration study. The observed effects were consistent with the findings in other short-term and long-term toxicity studies in rats. No developmental effects were observed in rats and rabbits and in the rabbit study the maternal NOAEL was below the developmental NOAEL.

n) Neurotoxicity

794. DAR 2008: There was no evidence for neurotoxicity in standard studies and in an acute neurotoxicity study in the rat.

o) Immunotoxicity

795. -

p) Endocrine disruption

796. -

q) Mode of action

797. DAR 2008: The mechanism of the effect on erythrocytes was not investigated by specific testing but the applicant submitted plausible postulation of the nature of events leading to the spectrum of effects observed. It is considered that novaluron causes oxidative damage to the mature erythrocyte. However there was no evidence of damage to the production of red blood cells. Haematopoesis is noted to be increased in both normal sites (sternum, femur) and in functional reserve sites (spleen, liver). The de novo produced cells remained normal but there was evidence of the presence of greater than usual immature cells in the circulation.

798. US EPA factsheet 2001: Novaluron belong to a new class of pesticide chemicals called benzoylphenyl ureas. Some compounds of this group are broad spectrum insecticides with insect hormonal mimicking mode of action. These IGRs affect chitin synthesis of immature insects disrupting their normal growth and development.

799. WHO 2004: The information provided is consistent with the EU evaluation indicated above.

r) Acceptable Exposure Levels

800. DAR 2008: The erythrocyte has been identified as the primary target of novaluron toxicity with secondary effects apparent in the spleen and at high doses in the liver. The spectrum of effect is essentially similar in rats, mice and dogs and the underlying mechanism considered to be the same. An external long term limit value (ADI) of 0.01 mg/kg bw day was proposed on the basis of the 2 year dietary rat study and an assessment factor of 100. The critical effects were haematological effects, organ weight changes in the spleen, haemosiderosis of spleen and cortical tubular pigment in kidneys. For the derivation of a systemic (short term) AOEL of 0.009 mg/kg bw day 21% oral absorption was considered, an assessment factor of 100 and the NOAEL of the 90 day oral mice and rats studies. Therefore the author of this POP factsheet considered it appropriate to present a systemic long term limit value of 0.002 mg/kg bw day for this comparative evaluation.

19.11 Environmental hazard assessment

s) Aquatic compartment (including sediment)

801. The substance has been notified according to EU-GHS and self-classified as aqautic acute and chronic toxic category 1. The toxicity values are listes in Table 6.

Table 6: Toxicity reference values

Exposure scenario/Study	Organism/Species		Time Scale Endpoint	Toxicity value	Reference
Acute 96 hour	Fish	*Oncorhynchus mykiss*	LC_{50}	> 1.0 mg/L	PPDB 2012
Chronic 21 day	Fish	*Oncorhynchus mykiss*	NOEC	0.00616 mg/L	PPDB 2012
Acute 48 hour	Aquatic	*Daphnia magna*	EC50	0.058 mg/L	PPDB 2012
Chronic 21 day	invertebrates	*Daphnia magna*	NOEC	0.00003 mg/L	PPDB 2012
Chronic 28 day	Sediment dwellers	*Chironomus riparius*	NOEC	0.00004 mg/L	PPDB 2012
Acute, 7day	Aquatic plants	*L. gibba*	EC_b50	0.075 mg/L	PPDB 2012
Acute, 72 hour	Algae	*P. subcapitata*	EC50	9.68 mg/L	PPDB 2012

t) Terrestrial compartment

802. Toxicity values for earthworms are displayed in Table 7. DAR 2008 reported low acute toxicity to birds (LD50 >2000 mg/kg bw) and a long term NOEL of 1.4 mg/kg bw/days from a duck reproductive toxicity study (based on numbers of eggs laid).

Table 7: Toxicity reference values

Exposure scenario/Study type	Organism/Species	Time Scale Endpoint	Toxicity value	Reference
Acute 14 day	*Eisenia foetida*	LC_{50}	> 1000 mg/kg	PPDB 2012
Chronic 14 day	*Eisenia foetida*	NOEC, reproduction	3.0 mg/kg	PPDB 2012

u) Toxicity to pollinators

803. Toxicity data on adult honey bees indicated the potential risk of novaluron to adult pollinators is low and other beneficial insects. Novaluron interferes with the molting phase of invertebrate development, which means that immature insects are affected. Within the PPDB 2012 the acute oral LD_{50} was indicated to be higher than 100 µg/bee.

19.12 Other information

804. Toxicological information presented in the PAN –pesticides database is largely consistent with the toxicological information summarized above with the exception that it seems that the negative reproductive/developmental toxicity study results were not taken into consideration or considered insufficient for a conclusion. The toxicological information presented in the PPDB is largely consistent with the toxicological information summarized above with the exception that the negative mutagenicity data were not taken into consideration.

19.13 REFERENCES

DAR (2008) Draft Assessment Report Novaluron. January 2008, available at http://dar.efsa.europa.eu/dar-web/provision
Epi Suite US EPA (2012) http://www.epa.gov/oppt/exposure/pubs/episuite.htm, 2012-04-16
EU Endocrine Disruption Database (2012) http://ec.europa.eu/environment/endocrine/strategy/short_en.htm, 2012-04-16
Health Canada´s Pest Management Regulatory Agency Health Canada (2006) Proposed Registration decision novaluron, http://publications.gc.ca/collections/Collection/H113-9-2006-5E.pdf
PPDB (2012) Pesticide Properties DataBase, University of Hertfordshire, http://sitem.herts.ac.uk/aeru/footprint/en/, 2012-04-18
US EPA (2012) Registration of Novaluron for Indoor and Outdoor Use on Residential Sites, http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2010-0466-0011
US EPA factsheet (2001) Pesticide factsheet Novaluron, September, 2001, http://www.epa.gov/opprd001/factsheets/novaluron.pdf
WHO Report (2004) WHO SPECIFICATIONS AND EVALUATIONS FOR PUBLIC HEALTH PESTICIDES http://www.who.int/whopes/quality/en/Novaluron_evaluation_Dec_2004.pdf

20. Pirimiphos-methyl[46]

CONCLUSIONS

Assessment of POP properties – comparison with the criteria of Annex D and other hazard indicators

20.1 Persistence

805. Pirimiphos-methyl is susceptible to photolysis and pH-dependant hydrolytic degradation (DT50 from 7 to 79 days). The parent compound is degraded in laboratory soil tests with DT50 values of 3 to 21 days. Dissipation half-lives in field studies range from 18 to 67 days. Pirimiphos-methyl is suspected to volatilize from soil surfaces. No experimental DT50 values for water were available, however adsorption and volatilization will contribute in addition to hydrolyses to removal from the water phase. The modelled P-score of 0.52 is slightly above the trigger of 0.5, however based on the overall evidence it is concluded that pirimiphos-methyl does not meet the persistence criterion of Annex D 1 (b) (i).

20.2 Bioaccumulation

806. Pirimiphos-methyl has a log Kow in the range of 3.9-4.2. Its estimated BCFs are below 1000. The modelled B-score is 0.17. Thus the parent compound does not fulfill the Annex D 1 (c) (i) criterion on bioaccumulation.

20.3 Long-range transport

807. The calculated a half-life in air was 0.8 hours. According to the rapid break-down of pirimiphos-methyl in air (<2 days) the potential for LRT is considered to be low. Therefore pirimiphos-methyl does not meet the Annex D 1 (d) (iii).

20.4 Ecotoxicity

808. Pirimiphos-methyl is highly toxic to birds, aquatic species and invertebrates. It is classified according to EU-GHS as aquatic acute and chronic category 1. Based on its high ecotoxicity and toxicity to human health (see below) Annex D 1 (e) (ii) is fulfilled.

20.5 Toxicity to human health (including mutagenicity, carcinogenicity and adverse effects on the reproductive, endocrine, immune or nervous systems)

809. Pirimiphos-methyl is of low acute systemic toxicity that qualifies for GHS category 4. It is not sensitizer and is not classified for carcinogenicity, mutagenicity or reproductive toxicity or specific target organ toxicity according to the GHS system in the EU.
810. The data reported indicate no concern for mutagenicity and no or equivocal carcinogenicity findings in animals. Similarly the data reported do not indicate specific reproductive or developmental toxicity.
811. The standard repeated dose studies did not indicate specific immunotoxicity and the substance is not listed in the EU endocrine disrupter database
812. The substance did not induce delayed neurotoxicity. The critical effect used for limit value derivation is cholinesterase inhibition in brain and erythrocytes. In the latest evaluation available this lead to an ADI proposal of 0.004 mg/kg bw day.

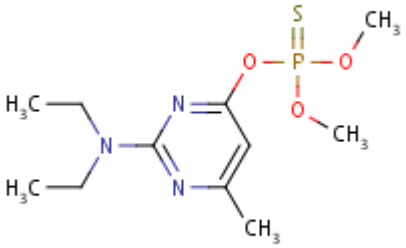
20.6 Identity of the substance and physical and chemical properties

a) Name and other identifiers of the substance

Table 1: Substance identity

Common name:	Pirimiphos-methyl
IUPAC name:	O-(2-diethylamino-6-methylpyrimidin-4-yl) O,O-dimethyl phosphorothioate
CAS number:	29232-93-7
Molecular weight:	305.34

[46] Pirimiphos-methyl is an alternative to both endosulfan and DDT.

Chemical structure:	

b) Chemical group

813. Organophosphate

c) Physico-chemical properties

Table 2: Overview of selected physico-chemical properties

Property	Value	Remarks and Reference
Vapour pressure	0.002 Pa	with 20°C, EXP
Water solubility	8.6 mg/L	with 20°C, EXP
Partition coefficient n-octanol/water (log value)	3.9 4.2	PPDB, 2012 EPISUITE, EXP
Partition coefficient air/water (log value)	-4.54	EPI Suite v 4.0
Partition coefficient air/octanol (log value)	8.44	EPI Suite v 4.0
Henry´s Law Constant	7.01 x 10^{-7} atm-m^3/mole	with 25°C, EST

20.7 Classification and labelling

d) Harmonised Classification in Annex VI of the CLP

Regulation (EC) No 1272/2008:

Category	Hazard-Phrase	
Acute Tox. 4	H302	Harmful if swallowed
Aquatic Acute 1	H400	Very toxic to aquatic life
Aquatic Chronic 1	H410	Very toxic to aquatic life with long lasting effects

20.8 Environmental fate properties

e) Abiotic degradation

f) Hydrolysis

814. US EPA RED 2006: Pirimiphos-methyl hydrolyzes rapidly at acidic pHs and is relatively stable at neutral and alkaline pH; calculated half-lives are 7.3 days at pH 5, 79.0 days at pH 7, and 54-62 days in pH 9. A degradate, O-2-diethylamino-6-methylpyrimidin-4-yl o-methyl-phosphorothioate, was recovered at significant amounts in the pH 7 and pH 9 solutions that did still contain the organophosphate moiety and therefore, may still have significant toxicological activity.

g) Phototransformation/photolysis

815. DAR 2005: The active substance is photolabile with a DT50 <30 minutes at pH 5 and 7 in a photolysis study.

h) Biodegradation

816. PPDB 2012 states a DT50 (geometric mean) of 12 day (range 3-21 days) for laboratory degradation studies at 20°C and a DT50 field of 39 days (range 18-67 days). HSDB 2012 reported a dissipation half-life of pirimiphos-methyl of 5.2-5.9 days on soil, but more that 40% of the loss of pirimiphos-methyl within 24-hrs may be attributed to volatilization coupled with photodegradation from the surface soil. This finding is in agreement with DAR 2005 where pirimiphos-methyl was

significantly volatilised from soil and leaf surfaces in a laboratory study.

817. No DT50 for water was identified, however based on its physico-chemical properties and observed hydrolyzes it is not expected that the parent compound will persist in aquatic environments. According to DAR 2005 no water/sediment study was submitted. If released into water, pirimiphos-methyl is expected according to HSDB 2012 to adsorb to suspended solids and sediment based upon the estimated Koc. 89.2% of pirimiphos-methyl was lost in a water/sediment mixture in 1 day; however, the primary loss mechanisms were by adsorption and volatilization rather than biodegradation (HSDB, 2012).

20.8 Potential for long range transport

818. DAR 2005: Calculations of the chemical lifetime in the troposphere with hydroxyl radicals (AOPWIN Program version 1.8) resulting in a half life of <0.067 days using a 12 hour day (1.5×10^6 HO/cm^3) or 0.8 hours. According to these results pirimiphos-methyl is rapidly degraded by photochemical processes. Du to the lack of persistency no multimedia fate modelling with the OECD tool was performed.

20.9 Bioaccumulation

819. PPDB 2012 estimates the BCF of 741 L/kg ww, the BCF modelled with EPISUITE (based on a log Kow of 4.2) yields a value of 274 L/kg ww. No experimental derived value was available in the indicated information sources.

i) PB-score

820. Pirimiphos-methyl has a P-score of 0.52 and a B-score of 0.17 resulting in an overall B-score of 0.67.

20.10 Human health hazard assessment relevant for the PBT assessment

j) Acute toxicity

821. DAR 2005: Acute systemic toxicity and skin/eye irritation results are in agreement with the actual EU-CLP entry. In the Magnusson and Kligman test for skin sensitization a weak response was observed that was not considered sufficient for a classification proposal.

822. US EPA RED 2006: Acute systemic toxicity results are not in agreement with the actual EU-CLP entry. However there is agreement that the substance is not a dermal sensitizer.

	EPA Toxicity category	Results
Acute dermal	III	LD50 ≥3.5 g/Kg for females and between 2.2-3.5 g/kg for males
Acute oral	III	LD50 2.4 g/kg
Acute inhalation	IV	LC50 ≥4.7mg/L
Eye irritation	II	Irritant
Dermal irritation	III	Moderate irritant
Dermal sensitizer	N/A	Non-sensitizer

k) Mutagenicity and Carcinogenicity

823. DAR 2005: Positive bacterial mutation results in the literature were not reproduced in a well performed unpublished study. Equivocal increases in SCE (sister chromatide exchange, questionable biological significance) were observed but the weight of in vitro evidence is negative. Also the in vivo genotoxicity is negative. Carcinogenicity studies were negative in mice and in rat an equivocal brain and pancreas tumour incidence was observed in a poorly reported rat study. The latter could qualify the substance for GHS class 2 classifications, however a respective evaluation and decision is still pending.

824. No IARC monograph is available.

l) Toxicity for reproduction

825. DAR 2005: The substance was not toxic to reproduction and not teratogenic. Shifted pelvic position was observed at a maternally toxic dosage (cholinesterase inhibition) in rabbits (borderline effect, considered to be a variation rather than a malformation).

m) Neurotoxicity

826. DAR 2005: The substance did not induce delayed neurotoxicity. Brain and erythrocyte cholinesterase inhibition was observed in animals and in humans. It represents the critical effect leading to the proposals for the ADI of 0.004 mg/kg bw day (AF = 100), for the AOEL of 0.02 mg/kg bw day and for the ARfD of 0.15 mg/kg bw day.
827. US EPA RED 2006: Marked plasma, RBC and brain cholinesterase inhibition was observed at the lowest dose levels in the short term dermal and inhalation studies (15 mg/kg bw day) and in the intermediate dermal and inhalation studies (0.2 mg/kg bw day).

n) Immunotoxicity

828. DAR 2005: Toxicological findings from repeated dose studies on lymphocyte and leukocyte counts were isolated, inconsistent and seen in the presence of other toxicity. Therefore these findings were not considered indicative of specific immunotoxicity.

o) Endocrine disruption

829. The substance is not listed in the EU Endocrine Disrupter Database 2012.

p) Mode of action

830. US EPA RED 2006: The substance is an organophosphate insecticide which causes cholinesterase inhibition by all routes of exposure.

q) Acceptable exposure levels

831. EFSA review report 2011: ADI 0.004 mg/kg bw; ARfD 0.15 mg/kg bw; AOEL 0.02 mg/kg bw
832. Assessment factors of 100 were used accounting for the standard uncertainties. The critical effect was the acetyl cholinesterase inhibition.
833. US EPA RED 2006: Population adjusted dose (PAD) acute, dietary = 0.005 mg/kg bw day; PAD chronic, dietary = 0.000067 mg/kg bw day. For both PADs an assessment factor of 3000 was used, accounting in addition to the standard uncertainties also for LOAEL-NOAEL extrapolation and the lack of complete toxicity database. The critical effect was the acetyl cholinesterase inhibition.
834. International limit values (GESTIS): No international limit value listed in GESTIS

20.11 Environmental hazard assessment

r) Aquatic compartment (including sediment)

835. According to US EPA RED 2006 pirimiphos-methyl is highly toxic to aquatic species and invertebrates. Table 3 lists toxicity reference values according to DAR 2005 and PPDB 2012..

Table 3: Toxicity reference values

Group	Time-scale	Endpoint	Toxicity (mg/l)	Reference
Oncorhynchus mykiss	96 hours	LC50	0.404 mg a.s./L	DAR 2005
Oncorhynchus mykiss	96 hours	LC50	0.20 mg a.s./L	
Cyprinus carpio	96 hours	LC50	1.4 mg a.s./L	
Daphnia magna	48 hours	EC50	0.00021 mg a.s./L	
Selenastrum capricornutum	96 hours	EC_b50	1.0 mg a.s./L	
Oncorhynchus mykiss	21 days	NOEC	0.023 mg a.s/L	PPDB 2012
Daphnia magna	21 days	NOEC	0.08 µg s.s/L	PPDB 2012
Chironimus riparius	96 hours	LC50	0.039 mg a.s/L	PPDB 2012

s) Terrestrial compartment

836. US EPA RED 2006 Pirimiphos-methyl is highly toxic to birds. A LC50 in Bowhite quail of 207 ppm was reported (CCID, 2012). Pirimiphos-methyl is much less acutely toxic to mammals than it is to birds. The LD50 value for mammals is 2,400 mg/kg.

20.12 Other Information

837. WHO specifications and evaluations for public health pesticides-Pirimiphos-methyl 2004: does not contain further critical toxicological information
838. Toxicological information present in the PAN –pesticides database and in the PPDB database are largely consistent with the toxicological information summarized above.
839. There are no significant agricultural approved outdoor uses in the US and European Union.

20.13 References

CCID (2012) New Zealand EPA HSNO Chemical Classification and Information Database, April 2012. http://www.epa.govt.nz/search-databases/Pages/HSNO-CCID.aspx, 2012-04-16
DAR (2005) Pirimiphos-methyl Draft Assessment Report, February 2005. http://dar.efsa.europa.eu/dar-web/provision
EFSA review report (2011) Review report for the active substance pirimiphos-methyl, January 2011, http://ec.europa.eu/food/plant/protection/evaluation/existactive/list1_pirimiphos-methyl_en.pdf
EU Endocrine Disruption Database (2012) http://ec.europa.eu/environment/endocrine/strategy/short_en.htm, 2012-04-16
Gestis (2012) Gestis-databse on hazardous substances, http://ww.dguv.de/ifa/en/gestis/stoffdb/index.jsp, 2012-04-16
HSDB (2012) Hazardous Substances Data Bank,Toxnet, http://toxnet.nlm.nih.gov/cgi-bin/sis/search 2012-04-02
PPDB (2012) Pesticide Properties DataBase, University of Hertfordshire, http://sitem.herts.ac.uk/aeru/footprint/en/ 2012-04-18
US EPA RED (2006) Reregistration Eligibility Decision for Pirimiphos-methyl, http://www.epa.gov/oppsrrd1/REDs/pirimiphos_methyl_red.pdf
WHO (1983) DATA SHEETS ON PESTICIDES No. 49, PIRIMIPHOS-METHYL, IPCS Inchem, http://www.inchem.org/documents/pds/pds/pest49_e.htm 2012-04-02

21. Propargite

CONCLUSIONS

Assessment of POP properties – comparison with the criteria of Annex D and other hazard indicators

21.1 Persistence

840. Propargite degrades rapidly under alkaline hydrolytic conditions and is moderately persistent to persistent under neutral and acidic pH values. Propargite is degraded in laboratory soil tests with DT_{50} values from 46.6 – 121.3 days (geometric mean: 59 days). The DT_{50} field values ranged from 10.2 to 24.2 days (n=4, 4 EU fields). Water-sediment studies indicate for the whole system, as well as for the water phase only, a fast or moderately fast dissipation (DT50 whole system 20 days). US EPA concluded that propargite is moderately persistent (metabolism half-lives 38-168 days) for soil and aquatic photolysis and aerobic/anaerobic metabolism. Degradates are propargite glycol ether and p-tertiary butylphenoxy cyclohexanol. EFSA indicated that propargite glycol ether is not persistent. Propargite has a P-score of 0.6, which is higher than the trigger value of 0.5.

841. Though metabolism half-lives are quite high no reported experimental value exceed the thresholds defined in Annex D. Based on the presented information it can be concluded that propargite does not meet the persistence criterion of Annex D 1 (b) (i).

21.2 Bioaccumulation

842. The log Kow for propargite is 5.7 and the estimated log Kow for the metabolite propargite glycol ether is 4.71. DAR 2007 considered the measured BCF_{fish} values (775) as not appropriate, and used a calculated BCF_{fish} of 13,964 for the risk assessment. US EPA used the same bioconcentration study (BCF 775) and concluded that the bioaccumulation potential of propargite is low. Propargite has a modelled B-score of 0.7, which is higher than the trigger value. Therefore only estimated values were used to assess the bioacummulation potential.

843. Propargite preliminary fulfils the Annex D 1 (c) (i) criterion based on log Kow >5 and on modelled BCF data. The interpretation of the database (BCF study) is equivocal.

21.3 Long-range environmental transport (LRT)

844. The vapour pressure of $<4.04 \times 10^{-5}$ Pa at 20°C and Henry's constant of 6.4×10^{-7} atm m^3/mol indicate that propargite will not partition into air to a significant extent. A calculated half-life of 2.2 hours in air (assuming a 12 hour day) has been proposed. According to the rapid degradation of propargite in air (<2 days) it can be concluded that it is unlikely that this compound does meet the Annex D 1 (d) (iii) criterion.

21.4 Ecotoxicity (including pollinator toxicity)

845. Toxicity values indicate that propargite is highly toxic to fish and invertebrates. US EPA 2009 concluded that propargite poses a potential for adverse effects on reproduction in birds and mammals. It is also expected to be highly toxic to amphibians. Propargite is highly toxic to aquatic organisms and is classified according to EU-GHS as aquatic acute and chronic 1.

846. Based on its high aquatic toxicity and toxicity to human health (see below) Annex D 1 (e) (ii) is fulfilled.

21.5 Toxicity to human health (including mutagenicity, carcinogenicity and adverse effects on the reproductive, endocrine, immune or nervous systems)

847. Propargite is classified by the EU GHS system for acute respiratory category 3, eye damage category 1 and skin irritation category 2. Data presented by US EPA and EFSA would support also GHS classification for skin sensitization (modified Buehler test and modified M&K test) and eventually skin corrosion.

848. The in vitro and in vivo genotoxicity data are negative but might not be considered as fully conclusive due to test guideline deviations. However the carcinogenicity data and conclusions are consistent with the actual EU GHS classification for carcinogenicity category 2.

849. The toxicity database includes an acceptable two-generation reproduction study in rats and acceptable prenatal developmental toxicity studies in rats and rabbits. These studies did not show an increased sensitivity for reproductive, offspring of developmental effects. However some

malformations observed in the rabbit might support classification for developmental toxicity GHS category 2.

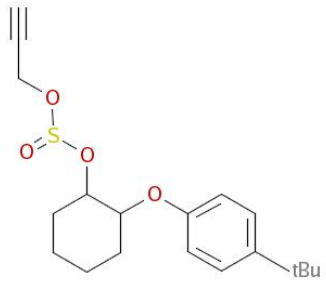
850. No specific neurotoxicity studies were required for this substance.

851. A provisional long term limit value (ADI) of 0.007 mg/kg bw day was proposed on the basis of the 2 years rat study and an assessment factor of 500, that should also account for the unexplained tumors in this study. The other critical effects were anemia in rats and dogs and higher late incidence of testicular degeneration in rats. The substance might also qualify for GHS classification for STOT RE 2.

21.6 Identity of the substance and physical and chemical properties

a) Name and other identifiers of the substance

Table 1: Substance identity

Common name:	Propargite
IUPAC name:	2-(4-tert-butylphenoxy)cyclohexyl prop-2-ynyl sulphite
CAS number:	2312-35-8
Molecular weight:	350.47
Chemical structure:	

b) Chemical group

852. Sulfite ester

c) Physico-chemical properties

Table 2: Overview of selected physico-chemical properties

Property	Value	Remarks and Reference
Vapour pressure at 25°C (mPa)	0.00404	PPDB 2012
Water solubility at 20°C (mg/l)	0.215	PPDB 2012
Partition coefficient n-octanol/water (log value, pH 7, 20°C)	5.7	PPDB 2012
Partition coefficient air/water (log value)	-4.58	EPI Suite v 4.0[47]
Partition coefficient air/octanol (log value)	10.28	EPI Suite v 4.0
Henry´s Law Constant at 25°C ($Pa.m^3.mol^{-1}$)	6.5×10^{-02}	PPDB 2012

21.7 Classification and labelling

d) Harmonised Classification according to GHS

Regulation (EC) No 1272/2008:

Category	Hazard-Phrase
Carc. 2	H351 Suspected of causing cancer.
Acute Tox. 3	H331 Toxic if inhaled.
Skin Irrit. 2	H315 Causes skin irritation.
Eye Dam. 1	H318 Causes serious eye damage.
Aquatic Acute 1	H400 Very toxic to aquatic life.
Aquatic Chronic 1	H410 Very toxic to aquatic life with long lasting effects.

[47] http://www.epa.gov/oppt/exposure/pubs/episuite.htm

21.8 Environmental fate properties

e) Abiotic degradation

f) Hydrolysis

853. DAR 2007: At normal pH/temperatures, the rate of hydrolysis is moderate (66.3 days at 25°C, pH = 7), with rate rapidly increasing with increasing pH and temperature (0.2 days at 40°C, pH = 9).

854. US EPA RED 2008: Propargite degrades rapidly under alkaline hydrolytic conditions (half-life = 2.2 days) and is moderately persistent to persistent under neutral (half-lives = 75 days) and acid (pH 5 half-life = 120 days) hydrolytic conditions.

g) Phototransformation/photolysis

855. DAR 2007: Rate of photolysis is rapid (DT50 = 15.4 days).

h) Biodegradation

856. US EPA RED 2008: Propargite is moderately persistent (metabolism half-lives = 38-168 days) and immobile. Degradates are carbon dioxide, propargite glycol ether (TBPC, 2-[4-(1,1-dimethylethyl) phenoxy] cyclohexane-1-ol, also identified as 2-(p-tertiarybutyl) phenoxycyclohexanol) and PTBP (p-tertiary butylphenoxy cyclohexanol).

857. DAR 2007: The available data demonstrate that in soil the major route of degradation was total mineralisation to CO_2 and incorporation into bound residues (max. 37.6% at 120 DAT). Propargite was metabolised to form TBPC. Also TBPC-sulphate and TBPC acid were found. Under anaerobic and soil photolytic conditions TBPC was a major metabolite (max. 23.7%). No EU-soil field study exists for TBPC. In one US-study TBPC was detected in concentrations of 12.1% after a second application, it reached 13.5% after 10 days and declined to 7.2% 1 year later. No DT_{50} values are available for TBPC. For TBPC sulfate and an unknown metabolite a DT_{50} of 9.7d (silty clay loam soil, Spain) and a DT_{50} of 267 days was calculated for US sandy loam soil (n=5). It is important to note, that metabolites with a cyclohexyl ring might be form as well, and as a consequence the degradation route with ^{14}C-cyclohexyl-propargite is required.

Table 4: Biotic degradation of propargite and major metabolites

Study type	Results	Reference	Remarks
DT_{50} soil lab (days) (20°C):	Propargite: 46.6 – 121.3 d Propargite: 59 d (geometric mean, n=5,)	DAR 2007	-
DT_{50} soil field (days):	Propargite: 10.2 – 24.2 d, n=4 Propargite: 67 – 99 d, n=2 (mean 81.9d)	DAR 2007	EU-field studies US-field studies
DT_{50} water (days) from water/ sediment study:	Propargite: 3.7 – 5.1 d TBPC: 12-17 d	DAR 2007	
DT_{50} sediment (days) from water/sediment study:	Propargite: 29.6 and 22 d (n=2)	DAR 2007	^{14}C-phenylpropargite partitioned into sediment
DT_{50} water sediment/whole system (days):	Propargite: 19.7 – 17.7 d, (n=2) TBPC: 12 – 25 d	DAR 2007	TBPC was found as a major metabolite

2 1 9 potential for long range transport

858. DAR 2007 states that the vapour pressure of 4.04 x 10^{-5} Pa at 20°C and Henry's constant of 6.4 x 10^{-7} atm m^3/mol indicate that the compound will not partition into air to a significant extent. A theoretical half-life of 2.155 hr (based on a 12 hr day) has been calculated for propargite (Atkinson calculation), indicating that any compound reaching the air would be rapidly degraded. The LRT potential of propargite is considered to be low.

21.10 Bioaccumulation

859. DAR 2007: The log K_{OW} for propargite is 5.7 and the estimated log K_{OW} for TBCP is 4.71. The measured BCF values (775) were not considered appropriate, thus the test concentrations were too near at the LC_{50}. So, the calculated BCF_{fish} of 13,964 was used for the risk of bioconcentration and secondary poisoning. To refine the risk assessment EFSA DAR 2007 concluded that for propargite a long term risk for birds for fish eating and earthworm eating birds is necessary. A TBPC risk assessment related to bird consumption of accumulating earthworms and fish.

860. US EPA RED 2008: In a study conducted with bluegill sunfish (*Lepomis macrochirus*) at a

concentration of 3.1 ug/L propargite for 35 days, bioconcentration factors were 260x for fillet, 1550x for viscera, and 775x for whole fish tissues. A steady state of bioaccumulation was reached after approximately 10 days of exposure. Depuration was relatively rapid, with 82% of the accumulated radioactive residues eliminated after 14 days in non-treated water. Based on these data, propargite does not appear to bioaccumulate significantly in fish.

i) PB-score

861. Propargite has a P-score of 0.6 and a B-score of 0.7 resulting in an overall PB-score of 1.4.

21.11 Human health hazard assessment

j) Acute toxicity

862. EFSA review report 2011: The data presented are in agreement with the actual EU-GHS classification for acute respiratory toxicity category 3, skin irritation category 2, eye damage category 1. However data are presented indicating also skin sensitization when tested with a modified Buehler method and modified M&K method.

863. US EPA RED 2008: The data presented are in agreement with those in the EFSA DAR. With regard to US EPA categories they correspond to category III. In contrast to the EFSA DAR US EPA considers the substance corrosive on rabbit skin and eye.

k) Mutagenicity and Carcinogenicity

864. EFSA review report 2011: The acceptable genotoxicity tests were negative (mammalian in vitro gene mutation tests, in vitro UDS with rat hepatocytes, in vivo mouse micronucleus tests) but the bacterial mutation tests and the in vitro chromosomal aberration test were not acceptable due to significant deviations and considered as not conclusive. Results from rat and mice carcinogenicity studies were evaluated and the rat tumors might be considered sufficient for carcinogenicity classification, GHS category 2.

865. US EPA factsheet 2010: Propargite is classified as a probable human carcinogen based on the appearance of intestinal tumors in test animals. The cancer concern was based on a 2-year cancer bioassay conducted on Sprague Dawley rats. In that study, propargite caused fatal tumors of the intestine in both male and female rats.

l) Toxicity for reproduction

866. EFSA review report 2011: Within the rat 2 generation study the parental NOAEL was based on lower body weight, lower body weight gain and lower food consumption and it was slightly below the reproductive NOAEL (minimal shortening of the gestation) and the offspring NOAEL (lower pup weight from birth until weaning). Within the rat and rabbit developmental studies the maternal NOAELs (lower body weight gain, ano-genital and body surface staining, decreased defacation) were also slightly below the developmental NOAELs. However in the rabbit a higher frequency of fused vertebrae and skull bones was observed that might support classification for developmental toxicity GHS category 2.

867. US EPA RED 2008: The toxicity database includes an acceptable two-generation reproduction study in rats and acceptable prenatal developmental toxicity studies in rats and rabbits. These studies show no increased sensitivity to fetuses as compared to maternal animals following acute in utero exposure in the developmental rat and rabbit studies and no increased sensitivity to pups as compared to adults in a multi-generation reproduction study in rats. Although propargite produced developmental effects in the rabbit, these effects were observed at the maternally toxic dose.

m) Neurotoxicity

868. EFSA review report 2011: No specific neurotoxicity studies were required for this substance.

869. US EPA RED 2008: The Agency determined that a developmental neurotoxicity study is not required.

n) Immunotoxicity

870. –

o) Endocrine disruption

871. -

p) Mode of action

872. -

q) Acceptable Exposure Levels

873. EFSA review report 2011: Propargite causes anemia in rats and dogs and higher late incidence of testicular degeneration in rats. It causes also intestinal tumours (most often jejunum) in 2 strains of rats not fully explained by cell proliferation at doses higher than 15 mg/kg/j. Clear no effect levels for this tumour were established in male rats CD/SD at 3.46 and 3.73 mg/kg/j and 24.2 and 25.2 mg/kg/j in females. No tumours were observed in mice studies. Propargite induced abortions and fused bones (sternebrae and skulls) at maternal toxic levels in rabbits. A provisional long term limit value (ADI) of 0.007 mg/kg bw day was proposed on the basis of the 2 years rat study and an assessment factor of 500. The additional to standard factor of 5 was included since the carcinogenic properties in two rat strains remained unexplained. The substance might also qualify for GHS classification for STOT RE 2.

21.12 Environmental hazard assessment

r) Aquatic compartment (including sediment)

874. According to the toxicity values presented below (cf. Table 5), propargite is highly toxic to fish and invertebrates (DAR 2007).

Table 5. Toxicity reference values

Exposure scenario/Study type	Organism/Species		Time Scale Endpoint	Toxicity value	Reference
Propargite					
Acute	Fish	*O.mykiss*	LC_{50}	43 µg/L	DAR 2007
Acute	Invetebrates	*D.magna*	EC/LC_{50}	14 µg/L	DAR 2007
Acute	Algae	*S. capricornutum*	EC/LC_{50}	>1080 µg/L	DAR 2007
Chronic	Fish	*P. promelas*	NOEC	5.7 µg/L	DAR 2007
Chronic	Invertebrates	*D. magna*	NOEC	9 µg/L	DAR 2007
Chronic	Sediment dwellers	*C. riparius*	NOEC	320 µg/L	DAR 2007
TBCP					
Acute	Fish	*O. mykiss*	EC/LC_{50}	1490	DAR 2007
Acute	Invertebrates	*D. magna*	EC/LC_{50}	3350	DAR 2007

s) Terrestrial compartment

875. US EPA RED 2008: Propargite poses a potential for adverse effects on reproduction in birds and mammals. It is also expected to be highly toxic to amphibians. Toxicity vales from DAR 2007 are summarized below in Table 6, which indicate low toxicity towards earthworms.

Table 6. Toxicity reference values (b.w. .... body weight)

Exposure scenario/Study type	Organism/Species		Time Scale Endpoint	Toxicity value	Reference
14-day toxicity test	Earth - worm	*E. fetida*	LC_{50} NOEC	189 mg a.s./kg soil dw 180 mg a.s./kg soil dw	DAR 2007
Reproduction	Birds	Mallard duck	NOEC	100 mg/kg diet (13.5 mg/kg/d)	DAR 2007
Reproduction	Birds	Bobwhite quail	NOEC	300 mg/kg diet (142 mg/kg/d)	DAR 2007
Acute oral	Rat		LD50	2639 mg/kg	DAR 2007
Reproduction	Rat		NOEL	67 mg/kg b.w./d	DAR 2007

t) Toxicity to pollinators

876. DAR 2007 Contact and oral toxicity LC50 values are 47.92 and > 100 µg a.s./bee.

21.13 Other information

877. Toxicological information presented in the PAN –pesticides database and in the PPDB database is largely consistent with the toxicological information summarized above with the exception that the reproductive toxicity and developmental study results seem to be interpreted as supportive of a respective classification.

21.14 REFERENCES

DAR (2007). Propargite Draft Assessment Report, May 2007, available at http://dar.efsa.europa.eu/dar-web/provision

PPDB (2012) Pesticide Properties DataBase, University of Hertfordshire, http://sitem.herts.ac.uk/aeru/footprint/en/ 2012-04-18

EFSA review report (2011) Review report for the active substance propargite; Document SANCO/11598/2011 rev1, available at http://ec.europa.eu/sanco_pesticides/public/index.cfm?event=activesubstance.selection

US EPA RED (2008) Reregistration Eligibility Decision (RED) for Propargite http://www.epa.gov/oppsrrd1/REDs/propargite_red.pdf, 2012-04-16

US EPA factsheet (2010) Propargite RED Facts, EPA 738-F-01-012, http://www.epa.gov/oppsrrd1/REDs/factsheets/propargite_fs.htm

22. Propoxur[48]

CONCLUSIONS

Assessment of POP properties – comparison with the criteria of Annex D and other hazard indicators

22.1 Persistence

878. Propoxur is persistent to hydrolysis at acid and neutral pH values. The compound is degraded under laboratory soil test conditions with DT50 values of 30-79 days, assuming moderate persistence. Concerning the degradation of propoxur in water or sediment a DT50 value of 2 days (for whole system in a water/sediment study) has been reported (but no information on pH available to proof biodegradation below pH <7). Based on the presented information it can be concluded that propoxur does not meet the persistence criterion of Annex D 1 (b) (i), however there exists no proof of biodegradation in aquatic environments below a pH value of 7.

22.2 Bioaccumulation

879. Propoxur does not fulfil the Annex D 1 (c) (i) criteria on bioaccumulation based on an estimated BCF of 75 and a log Kow of 0.14.

22.3 Longe-range transport

880. Propoxur has a calculated half-life in air of 4 hours (<2 days). Therefore it is unlikely that propoxur fulfils the Annex D 1 (d) (iii) criteria.

22.4 Ecotoxicity (including pollinator toxicity)

881. Propoxur is highly toxic to aquatic organisms and is classified according to GHS as aquatic acute and chronic category 1. Also the acute toxicity of propoxur for birds and mammals is high. It reveals moderate toxicity to honey bees and is assumed to be harmful for other arthropods. Based on its high ecotoxicity and toxicity to human health (see below) Annex D 1 (e) (ii) is fulfilled.

22.5 Toxicity to human health (including mutagenicity, carcinogenicity and adverse effects on the reproductive, endocrine, immune or nervous systems)

882. Propoxure is classified within the EU GHS system for acute oral toxicity category 3 and this is supported by the available data. It is not irritating and not skin sensitizing, but it might qualify also for acute respiratory category 4.

883. Propoxure showed little if any genotoxic activity within in vitro and in vivo tests. However it was classified by US EPA as group B, probable human carcinogen. No concern for reproductive toxicity was reported on the basis of developmental rat and rabbit studies as well as two generation rat studies.

884. Representing a carbamate dominant neurotoxic effects were observed in the acute and repeated dose studies. No histological effects on the nervous tissue were reported but the critical effect for limit dose derivation is acetyl cholinesterase inhibition. US EPA derived a long term limit value (RfD) of 0.005 mg/kg bw day on the basis of a human LOAEL for red blood cell cholinesterase inhibition and an assessment factor of 10 for intraspecies variability and 3 for LOAEL to NOAEL extrapolation. WHO proposed a long term limit value (ADI) of 0.02 mg/kg bw day on the basis of the same study but without the additional factor of 3 since the lowest dose was considered as a NOAEL since depression of erythrocyte cholinesterase did not exceed 20% and the recovery was very rapid.

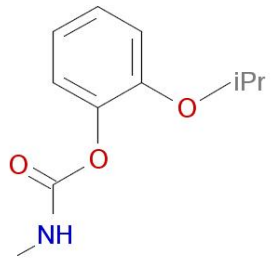
22.6 Identity of the substance and physical and chemical properties

a) Name and other identifiers of the substance

Table 1: Substance identity

Common name:	Propoxur
IUPAC name:	2-isopropoxyphenyl methylcarbamate
CAS number:	114-26-1
Molecular weight:	209.24

[48] Propoxur is an alternative to both endosulfan and DDT.

Chemical structure:	

b) Chemical group

885. Carbamate

c) Physico-chemical properties

Table 2: Overview of selected physico-chemical properties

Property	Value	Remarks and Reference
Vapour pressure at 25°C (mPa)	1.3	PPDB 2012
Water solubility at 20°C (mg/l)	1800	PPDB 2012
Partition coefficient n-octanol/water (log value, pH 7, 20°C)	0.14	PPDB 2012
Partition coefficient air/water (log value)	-7.23	EPI Suite v 4.0[49]
Partition coefficient air/octanol (log value)	8.75	EPI Suite v 4.0
Henry´s Law Constant at 25°C ($Pa.m^3.mol^{-1}$)	1.50×10^{-04}	PPDB 2012

22.7 Classification and labelling

d) Harmonised Classification according to GHS

Regulation (EC) No 1272/2008:

Category	Hazard-Phrase
Acute Tox. 3	H301 Toxic if swallowed
Aquatic Acute 1	H400 Very toxic to aquatic life.
Aquatic Chronic 1	H410 Very toxic to aquatic life with long lasting effects.

22.8 Environmental fate properties

e) Abiotic Degradation

f) Hydrolysis

886. PPBD 2012: Persistent: Aqueous hydrolysis DT50 (days) at 20°C and pH 7: 180

887. WHO 2005: Half-life at 22ºC >1 year at pH 4, 93.2 days at pH 7, 30.1 hours at pH 9

888. US EPA RED 1997: Propoxur is apparently hydrolytically stable at acid to neutral pHs (3 to 7) but degrades rapidly at alkaline pH values.

g) Phototransformation/photolysis

889. PPDB 2012: Fast: Aqueous photolysis DT50 (days) at pH 7: 0.01 day

h) Biodegradation

890. PPBD 2012 lists the degradation estimates according to Table 3. The metabolite 2-(1-methylethoxy)phenol in soil was identified.

891. US EPA RED 1997: Based on supplemental data, propoxur is likely to be moderately persistent (the metabolic half-life is on the order of several months). mobile, and may potentially leach to groundwater.

Table 3: Half-lives of propoxur in soil, water and sediment

Degradation 50%	days	Reference	Comment
DT_{50} soil lab:	79	PPDB	Moderately persistent
	30 (20°C)	PPDB	Moderately persistent
DT_{50}soil field:	28	PPDB	Non Persistent
DT_{50} water sediment/whole system:	2	PPDB	Fast

[49] http://www.epa.gov/oppt/exposure/pubs/episuite.htm

22.9 Potential for long range transport

892. According to AOPWIN v1.92 the photo-chemical degradation of propoxur in air has been estimated to be fast. The calculated DT50 is 4.05 hours (assuming a 12 hours day and a OH concentration of 1.5 x 10^6 OH/cm^3).

22.10 Bioaccumulation

893. PPBD 2012: The calculated bioconcentration factor of 75 is considered to be low.

i) PB-score

894. Not available.

22.11 Human health hazard assessment

j) Acute toxicity

895. US EPA factsheet 1997: In studies using laboratory animals, propoxur generally has been shown to be of moderate acute toxicity. It has been placed in Toxicity Category II (the second highest of four categories) for effects via the oral route of exposure, and Toxicity Category III for the dermal and inhalation routes. The data presented support EU GHS classification for oral category 3 only and no skin irritation was well as not skin sensitization.

896. WHO 2005: The data presented support the actual classification with the exception of a respiratory LC50 of 0.65 mg/L that may support an additional GHS classification in respiratory category 4.

k) Mutagenicity and Carcinogenicity

897. US EPA factsheet 1997: Propoxur showed little if any genotoxic activity when tested with bacterial mutation tests and in vitro mammalian mutation and chromosomal aberration tests as well as in vivo hamster bone marrow chromosomal aberration tests and in mouse micronucleus test. However on the basis of dietary carcinogenicity studies in mouse and rat it has been classified as a Group B_2 probable human carcinogen. The agency has calculated a unit risk, Q_1* of 3.7 x 10^{-3} based on male rat bladder tumors. Also the results were reported from a chronic inhalation study in rats and a chronic feeding study in dogs.

l) Toxicity for reproduction

898. US EPA RED 1997: The available developmental rat and rabbit studies and the two rat reproductive toxicity studies (2-generations) do not suggest any increased sensitivity of infants and children to propoxur from pre- and post-natal exposures.

m) Neurotoxicity

899. US EPA summary 2009: Propoxur inhibits acetylcholinesterase (AChE). Toxicological characteristics of propoxur involve maximal ChE inhibition (typically within 15 minutes to an hour) followed by rapid reactivation of the enzyme and then recovery (minutes to hours). As such, the critical duration of exposure for propoxur is acute ChE inhibition of brain and red blood cell AChE measured at the peak time of effect. At the time of the 1996 risk assessment, the Agency did not have a comparative cholinesterase assay that evaluated the sensitivity of young animals compared to adult animals to address the FQPA factor in risk assessment. Therefore, the Agency retained a 10X FQPA factor for propoxur. The neurotoxic effects were critical for the limit value derivation.

900. At least in the low and medium dose ranges no adverse histological effects were identified in the acute and repeated dose studies that included neurotoxicity studies with FOBs.

n) Immunotoxicity

901. US EPA summary 2009: The toxicity database for propoxur is nearly complete. However, EPA plans to require an immunotoxicity study (870.7800) and a comparative cholinesterase assay.

o) Endocrine disruption

902. -

p) Mode of action

903. Representing a carbamate the critical effect of propoxur is acetyl cholinesterase inhibition.

q) Acceptable Exposure Levels

904. US EPA factsheet 1997: The Agency has calculated a reference dose (RfD), the amount of pesticide believed not to cause adverse effects if consumed daily over a 70- year lifetime, of 0.005 mg/kg/day, based on a human study with a LOEL of 0.15 mg/kg, the lowest dose tested. This dose was associated with transient red blood cell cholinesterase inhibition. An uncertainty factor of 10 was applied to account for intra-species variability and an additional factor of 3 was applied to compensate for the lack of a NOEL. The FAO/WHO joint committee on pesticide residue (JMPR) in 1989 proposed an acceptable daily intake (ADI) of 0.02 mg/kg/day on the basis of an acute no-effect level in humans. In the JMPR evaluation of the human study, the NOEL was considered to be 0.2 mg/kg/day since the depression of erythrocyte cholinesterase did not exceed 20% and the recovery was very rapid.

905. International limit values for worker protection (GESTIS-Database): Long-term limit values between 0.5 and 2 mg/m^3 inhalable aerosol are presented by a total of 16 institutions and countries.

22.12 Environmental hazard assessment

r) Aquatic compartment (including sediment)

906. Toxicity data for the aquatic compartment are summarized in Table 4. According to US EPA RED 1997 propoxur is moderately toxic to freshwater fish (some LC s are in the range of >1-10 ppm); 50 and very highly toxic to freshwater invertebrates (daphnid EC is <1 ppm).

Table 4: Toxicity reference values for the aquatic compartment (source PPDB 2012)

Exposure scenario/ Study type	Organism /Species	Endpoint	Toxicity value
Acute 96 hour	Fish	LC_{50}	6.2 mg/l
Acute 48 hour	Aquatic invertebrates	EC_{50}	0.15 mg/l
Acute 96 hour	Sediment dwelling organisms	LC_{50}	38.1mg/l

s) Terrestrial compartment

907. Toxicity data for the terrestrial compartment are summarized in Table 5.

908. US EPA RED 1997: Based on the results of studies propoxur is categorized as very highly toxic to birds on an acute basis (some LD s are <10 mg/kg); highly toxic to birds on a subacute dietary basis (an LC is in the range of 51-500 ppm).

Table 5: Toxicity reference values for the terrestrial compartment

Exposure scenario/Study type	Organism /Species	Endpoint	Toxicity value	Reference
Acute	Rat	LD_{50}	~50 mg/kg	PPBD
Short-term, dietary	Rat	NOEL	200 ppm diet	PPBD
Acute	Birds	LD_{50}	25.9 mg/kg	PPBD
Acute	Birds	LD_{50}	3.55 -60.4 mg/kg	US EPA RED

t) Toxicity to pollinators

909. PPBD 2012: Honeybees: Acute 48 hour LD50: 1.35 µg/bee: Moderate

22.13 Other information

910. The data and information presented in WHO 2005 is largely in agreement with the data and information provided above.

911. Propoxur has been excluded from Annex 1 (EC Directive 1107/2009 (repealing 91/414) and is not included in Annex I of the Biocidal Products Directive 98/8/EC (Commission Decision **of April 14th 2009 concerning the** non-inclusion of certain substances in Annex I, IA or IB to Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market with regard to product type 18).

22.14 References

PPDB (2012) Pesticide Properties Database: Propoxur
http://sitem.herts.ac.uk/aeru/footprint/en/index.htm
GESTIS (2012) Database on hazardous substances,
http://www.dguv.de/ifa/en/gestis/stoffdb/index.jsp, 2012-04-18
US EPA summary (2009) US EPA Propoxur Summary Document for Registration Review Document ID: EPA-HQ-OPP-2009-0806-0002, available at
http://www.epa.gov/oppsrrd1/registration_review/propoxur/index.html
US EPA factsheet (1997) Factsheet Propoxure RED. EPA738-R-97-009. available at
http://www.epa.gov/oppsrrd1/registration_review/propoxur/index.html
US EPA Red (1997) Reregistration Eligibility Decision (RED) PROPOXUR, August 2007, available at http://www.epa.gov/oppsrrd1/registration_review/propoxur/index.html
WHO (2005) WHO Specifications and evaluations for public health pesticides, Propoxur. 2-isopropoxyphenyl methylcarbamate.

23. Pyridalyl

CONCLUSIONS

Assessment of POP properties – comparison with the criteria of Annex D and other hazard indicators

23.1 Long-range environmental transport (LRT)

912. Pyridalyl has a calculated DT50 in air <2 days (3.6 hours). The multimedia OECD model results indicate a high Pov and transfer efficiency. Also the characteristic travel distance is around 3000 km. Results do not exceed values calculated for alpha-HCH, PeCB, and octa-BDE (reference POPs). In the TE plot pyridalyl is in the upper right quadrant indicating POP-like persistence and LRT potential. Therefore more information is needed to conclude on the LRT of pyridalyl with respect to the Annex D 1 (d) criterion.

23.2 Ecotoxicity (including pollinator toxicity)

913. Pyridalyl is practically non-toxic to honeybees. Although this suggests low potential for risk to honeybees, some risk to non-target insects would presumably be possible because pyridalyl is an insecticide and its specificity has not been comprehensively evaluated. Greatest risk would presumably be to lepidopteran species. Pyridalyl is classified according to EU-GHS as aquatic acute and chronic category 1 indicating high toxicity to aquatic life with long lasting effects. Based on its high aquatic toxicity Annex D 1 (e) (ii) can be considered as fulfilled.

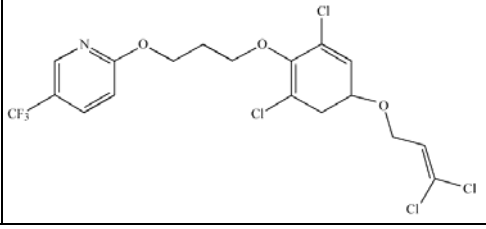
23.3 Toxicity to human health (including mutagenicity, carcinogenicity and adverse effects on the reproductive, endocrine, immune or nervous systems)

914. No EU GHS harmonised classification is available for pyridalyl. However self classification for skin sensitisation is available that is supported by the data referenced below. Available data support that no EU GHS classification is required for acute systemic toxicity and not for eye irritation.
915. Negative results were reported with in vitro and in vivo mutagenicity assays as well as with mice and rat carcinogenicity studies. US EPA classified the substance as “not likely to be carcinogenic to humans”.
916. Acceptable developmental toxicity studies in rats and rabbits as well as a two generation study in rats did not indicate concern for reproductive toxicity. On the basis of a weight of evidence evaluation it was concluded that pyridalyl does not directly target the immune system and no specific immunotoxicity studies were required. Similarly the standard studies did not indicate any specific concern for neurotoxicity and no specific studies were required. Within a non guideline subacute steroid hormone study in rats no treatment-related effects were found.
917. An external long term limit value (RfD) of 0.034 mg/kg bw day was proposed on the basis of decreased body weights, weight gain and food efficiency in the 2 year rat study and application of an assessment factor of 100. Also an oral NOAEL of 2.8 mg/kg bw day with an occupational target MOE of 100 was proposed.

23.4 Identity of the substance and physical and chemical properties

a) Name and other identifiers of the substance

Table 1: Substance identity

Common name:	Pyridalyl
IUPAC name:	2,6-dichloro-4-(3,3-dichloroallyloxy)phenyl 3-[5-(trifluoromethyl)-2-pyridyloxy]propyl ether
CAS number:	179101-81-6
Molecular weight:	491.12
Chemical structure:	

b) Chemical group

918. Unclassified

c) Physico-chemical properties

Table 2: Overview of selected physico-chemical properties

Property	Value	Remarks and Reference
Vapour pressure at 20°C (mPa)	6.2×10^{-8}	US EPA 2008
Water solubility at 20°C (mg/l)	0.00015	US EPA 2008
Partition coefficient n-octanol/water (log value, pH 7, 20°C)	8.1	PPDB 2012
Partition coefficient air/water (log value)	-6.643	EPI Suite v 4.1 (KOAWIN v. 1.10)[50]
Partition coefficient air/octanol (log value)	14.74	EPI Suite v 4.1 (KOAWIN v. 1.10)

[50] http://www.epa.gov/oppt/exposure/pubs/episuite.htm

23.5 Classification and labelling

d) Harmonised Classification according to GHS

919. No EU GHS harmonised classification available

e) Self classification

EU-CLP inventory[51]

Category	Hazard-Phrase
Skin sens. 1	H317 May cause an allergic skin reaction.
STOT RE 2 (liver)	H373 May cause damage to organs through prolonged or repeated exposure
Aquatic Acute 1	H 400
Aquatic Chronic 1	H410 Very toxic to aquatic life with long lasting effects.

23.6 Potential for long range transport

920. Results of the phototransformation in air according to EPI Suite TM v4.0 (AOPWIN v 1.92) are based on a 12h day are summarised in table 3.

Table 3: Phototransformation in air

Guideline / Test method	Molecule / radical	Rate constant for reaction with OH-radicals (k_{OH}) [cm^3 $molecule^{-1}$ sec^{-1}]	Half-life ($t_{1/2}$) [h]	OH-radical concentration [OH-radicals/cm^3]
AOPWIN	OH	35.3291 E-12	3.633	1.5×10^6

921. The OECD "Pov and LRTP Screening Tool" (OECD 2006) has been developed with the aim of using multimedia models for estimating overall persistence (Pov) and long-range transport potential (LRTP) of organic chemicals at a screening level in the context of PBTs/POPs assessments. The Tool calculates metrics of Pov and LRTP from a multimedia chemical fate model, and provides a graphical presentation of the results. According to Wegmann et al. 2009 compounds that are less problematic from an environmental exposure point of view are in the bottom-left corner (low Pov, low LRT), while substances of environmental concern are found in the upper right region (high Pov, high LRT). The result for pyridalyl is plotted against the reference chemicals α-HCH, c-octaBDEand PeBD. The criteria lines were not modified and take as proposed in the tool (Pov limit: 195 days, CTD limit: 5096 km, TE limit: 2.25%; Klasmeier et al., 2006).

922. The input parameters for Kow, Kaw and half-life in air were taken from Tables 2 and 3, half-lives for water and soil are listed in table 4.

Table 4: Half-lives for air, water and soil

Half-Lives (h)	Value	Source
Water	4320	PBT profiler[52]
Soil ($DT50_{field}$)	3751	PPBD 2012

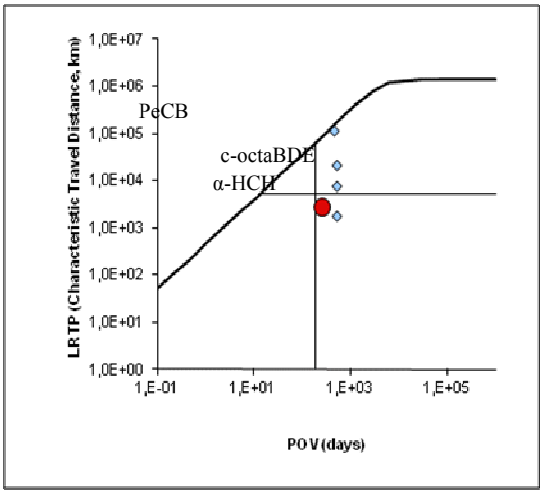
923. With a calculated CTD (characteristic travel distance) of 2,829 km pyridalyl lies below the other reference values and the limit value of the model. The calculated TE (transfer efficiency) value is 12.4% which indicates a TE above the limit value but below the reference chemicals α-HCH, c-octaBDE, PeBD (see figure 1). In the TE plot pyridalyl is in the upper right quadrant indicating POP-like persistence and LRT potential. Pov is calculated to be 260 days.

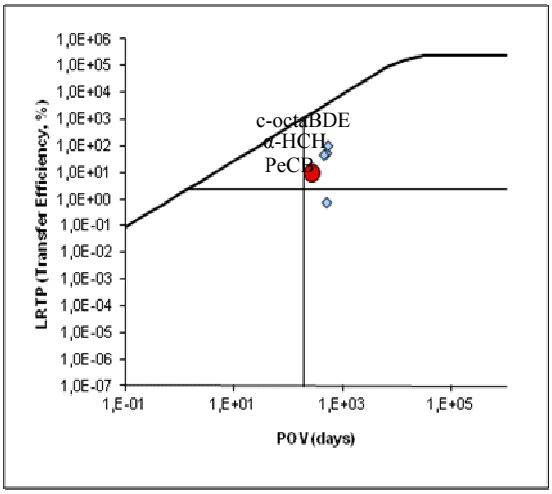
924. US EPA 2009 calculated CTD and TE for aldrin that has also a short half-life in air. Results for pyridalyl exceed the LRT estimates for aldrin and endrin.

Figure 1: Results from the OECD Tool (CTD and TE) for pyridalyl (red point) and selected reference compounds (α-HCH, c-octaBDE, PeBD).

[51] http://echa.europa.eu/web/guest/regulations/clp/cl-inventory

[52] http://www.pbtprofiler.net/





23.7 Human health hazard assessment

f) Acute toxicity

925. US EPA 2008: Technical pyridalyl has low acute toxicity (Toxicity Category IV) via the oral, dermal and inhalation routes of exposure. Pyridalyl is not an eye or dermal irritant, but showed sensitization in both the Buehler and Maximization assays.

g) Mutagenicity and Carcinogenicity

926. US EPA 2008: There is no concern for mutagenicity resulting from exposure to pyridalyl based on negative results from various in vivo and in vitro mutagenicity assays. Pyridalyl is classified as “Not Likely to be Carcinogenic to Humans” based on lack of carcinogenicity in mice and rats and overall negative findings in various mutagenicity assays.

h) Toxicity for reproduction

927. US EPA 2008: Acceptable developmental toxicity studies in the rat and rabbit, as well as a two-generation reproductive toxicity study in the rat, were available. A potential concern for effects of pyridalyl exposure on the developing immune system was raised due to findings suggestive of delayed thymus development. These concerns were mitigated by the overall weight of the evidence, which suggests that pyridalyl does not directly target the immune system. Consequently the HED HIARC determined that a developmental immunotoxicity study was not required.

i) Neurotoxicity

928. US EPA 2008: There was no concern for neurotoxicity resulting from exposure to pyridalyl. No neurotoxicity studies were submitted; however no evidence of neurotoxicity was seen in either the subchronic and chronic toxicity studies or the developmental and reproductive toxicity studies.

j) Immunotoxicity

929. US EPA 2008: It was concluded that pyridalyl does not directly target the immune system.

k) Endocrine disruption

930. US EPA 2008: Within a non guideline subacute steroid hormone study in rats no treatment-related effects were found on testosterone, estradiol or progesterone concentrations, uterine weight, or the estrus cycle. No histopathological effects were found in the adrenal gland and no effects on serum corticosterone concentration were found.

l) Mode of action

931. -

m) Acceptable Exposure Levels

932. US EPA 2008: Pyridalyl has been tested in chronic studies with dogs, rats and mice. Observations in the combined chronic toxicity/oncogenicity study in rats included decreased body weight gain, hematological alterations and histopathological alterations of the spleen. In the 78week feeding study in mice decreased body weight gain and food consumption/efficiency, and increased liver and kidney weights were observed. In a 12month oral study with dogs, pyridalyl produced alterations in blood biochemistry and increased liver weights. An external long term limit value (RfD) of 0.034 mg/kg bw day was proposed. For derivation an assessment factor 100 was engaged, the critical effects were decreased body weights, weight gain and food efficiency in the 2 year rat study. Also an oral NOAEL of 2.8 mg/kg bw day with an occupational target MOE of 100 was proposed.

23.8 Environmental hazard assessment

n) Toxicity to pollinators

933. US EPA 2008: Pyridalyl is practically non-toxic to honeybees. Although this suggests low potential for risk to honeybees, some risk to non-target insects would presumably be possible because pyridalyl is an insecticide and its specificity has not been comprehensively evaluated. Greatest risk would presumably be to lepidopteran species.

934. PPDB 2012 reports a NOEL of >100 µ/bee concerning acute toxicity.

23.9 Other information

935. Toxicological information presented in the PAN –pesticides database and in the PPDB database is largely consistent with the toxicological information summarized above with the exception that the reproductive toxicity and developmental study results summarized above seem not respected or insufficient for a conclusion in these databases.

23.10 References

OECD (2006): The OECD Pov and LRTP Screening Tool 2.0. Software and Manual, OECD, Paris, www.oecd.org/env/riskassessment.

PPDB (2012) Pesticide Properties DataBase, University of Hertfordshire, http://sitem.herts.ac.uk/aeru/footprint/en/ 2012-04-18

Klasmeier, J., Matthies, M., Macleod, M., Fenner,K., Scheringer,M., Stroebe, M., Le Gall, A.C., McKone,T., van de Meent, D., Wania, F. (2006): Application of multimedia models for screening assessment of long-range transport potential among and overall persistence. Environmental Science and Technology 40, 53-60.

US EPA (2008) Summary Document Registration Review: Initial Docket, Case Number 7407, EPA-HQ-OPP-2007-0804, August 2007 http://www.epa.gov/pesticides/chemicalsearch

US EPA (2009) Risks of Dicofol Use to Federally Threatened California Red-legged Frog (*Rana aurora draytonii*), Pesticide Effects Determination Environmental Fate and Effects Division Office of Pesticide Programs Washington, D.C. 20460, June 15, 2009 http://www.epa.gov/espp/litstatus/effects/redleg-frog/dicofol/analysis.pdf, 2012-04-16

Wegmann F. Cavin L, MacLeod M, Scheringer M, Hungerbühler K. (2009) Environmental Modeling & Software 24, 228-237

24. Tralomethrin

CONCLUSIONS

Assessment of POP properties – comparison with the criteria of Annex D and other hazard indicators

24.1 Persistence

936. Degradation estimations of aqueous hydrolysis indicate persistence in water (DT_{50} at 20°C, pH 7). There is no aerobic aquatic metabolism study for the parent, tralomethrin available. The persistence of tralomethrin in soil (half-live 64-84 days) is expected to be moderate. Tralomethrin is degraded to deltamethrin in soil and in (aquous) photolysis. In general, it appears that the rate of transformation of tralomethrin to deltamethrin is in the range of days to possible several days proven by several degradation studies on tralomethrin in soil. Deltamehtrin displays higher persistence than the parent compound. Therefore conclusions on deltamethrin are relevant as well. Based on the available experimental information tralomethrin does not fulfil the persistence criterion of Annex D. For deltamethrin it can be concluded that experimental degradation data in soil can exceed the thresholds of Annex D 1 (b) (i) criterion. Persistency/degradation in water at pH≤7 was not assessed. Also modelled information suggests degradation values exceeding the Annex D thresholds. Therefore Annex D 1 (b) (i) criterion for tralomethrin and its residues is met.

24.2 Bioaccumulation

937. It is concluded, that the bioaccumulation criterion according to Annex D 1 (c) (i) for tralomethrin based on estimated and experimental obtained BCF values in fish from 490 to 1200 is not fulfilled.

24.3 Long-range transport

938. Tralomethrin has a calculated half-life in air of 7 hours (<2 days) indicating fast degradation in air. Therefore it is unlikely that tralomethrin fulfils the Annex D 1 (d) (iii) criterion.

24.4 Ecotoxicity (including pollinator toxicity)

939. Tralomethrin and the main metabolite deltamethrin are very highly toxic on an acute basis to estuarine/marine and freshwater fish, aquatic-phase amphibians, and aquatic invertebrates. Tralomethrin and deltamethrin are also toxic on a chronic basis to freshwater fish and freshwater invertebrates. Tralomethrin is highly toxic to estuarine/marine invertebrates on a chronic basis. Tralomethrin and deltamethrin are both highly toxic to terrestrial invertebrates, including beneficial insects such as honeybees. It can be concluded that tralomethrin fulfils the criterion of Annex D 1. (e) (ii) based on high ecotoxicity and toxicity to human health (see below) of the parent compound and its metabolite deltamethrin.

24.5 Toxicity to human health (including mutagenicity, carcinogenicity and adverse effects on the reproductive, endocrine, immune or nervous systems)

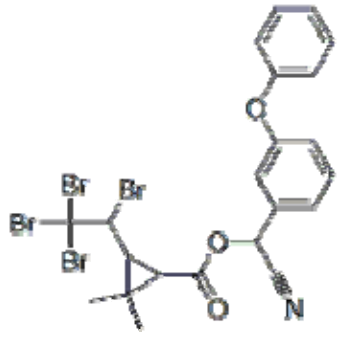
940. In humans, tralomethrin is metabolized completely and immediately into deltamethrin. As a result, EPA assumes that tralomethrin and deltamethrin have equivalent toxicity for human health risk assessment purposes. Thus, for further information please see POP factsheet for deltamethrin.

24.6 Identity of the substance and physical and chemical properties

a) Name and other identifiers of the substance

Table 1: Substance identity

Common name:	Tralomethrin
IUPAC name:	(S)-α-cyano-3-phenoxybenzyl (1R,3S)-2,2-dimethyl-3-[(RS)-1,2,2,2-tetrabromoethyl]cyclopropanecarboxylate
CAS number:	66841-25-6
Molecular weight:	665.0

Chemical structure:	

b) Chemical group

941. Pyrethroid

c) Physico-chemical properties

Table 2: Overview of selected physico-chemical properties

Property	Value	Remarks and Reference
Vapour pressure at 25°C (mPa)	4.80×10^{-06}	PPDB 2012
Water solubility at 20°C (mg/l)	0.08	PPDB 2012
Partition coefficient n-octanol/water (log value, pH 7, 20°C)	5	PPDB 2012
Partition coefficient air/water (log value)	-7.79	EPI Suite v 4.0
Partition coefficient air/octanol (log value)	12.79	EPI Suite v 4.0
Henry´s Law Constant at 25°C ($Pa.m^3.mol^{-1}$)	1.60×10^{-10}	PPDB 2012

24.7 Classification and labelling

d) Harmonised Classification according to GHS

942. No EU GHS Harmonised Classification

e) Self classification

Notified CLP classification and labelling (2 notification) according to CLP-Inventory[53]

Category	Hazard-Phrase
Acute Tox. 4	H 302 Harmful if swallowed.
Skin Irrit. 2	H315 Causes skin irritation.
Eye Irrit. 2	H319 Causes serious eye irritation.
Aquatic Acute 1	H400 Very toxic to aquatic life.
Aquatic Chronic 1	H410 Very toxic to aquatic life with long lasting effects.

24.8 Environmental fate properties

f) Abiotic Degradation

g) Hydrolysis

943. PPDB 2012: Aqueous hydrolysis DT_{50} (days) at 20°C and pH 7: stable: very persistent. HSDB 2012 reported base-catalyzed second-order hydrolysis half-lives of 36 and 4 years were estimated for pH values of 7 and 8, respectively.

h) Phototransformation/photolysis

944. PPDB 2012: Aqueous photolysis DT_{50} (days) at pH 7: 0.05, fast. US EPA 2010 indicated that tralomethrin may undergo epimerization and subsequent transformation to deltamethrin-iso and formation of BR2CA (3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylic acid).

i) Biodegradation

945. PPDB 2012: Aerobic: DT_{50} soil: 3 days; 27 days (lab, 20°C); Main metabolite in soil: deltamethrin

946. US EPA 2010: There are many uncertainties related to the rate and extent at which tralomethrin undergoes transformation to deltamethrin (e.g. methods could

[53] http://clp-inventory.echa.europa.eu/

not distinguish between these compounds). In general, it appears that the rate of transformation of tralomethrin to deltamethrin is in the range of days to possible several days proven by several degradation studies on tralomethrin in soil.

947. HSDB 2012: Tralomethrin's half-life in soil has been reported to have a range of 64-84 days. If released into water, tralomethrin is expected to adsorb to suspended solids and sediment based upon its Koc.

948. US EPA 2010: There is no aerobic aquatic metabolism study for the parent, tralomethrin availalbe. Therefore findings on deltamethrin were used (cf. factsheet on deltamethrin). US EPA states that deltamethrin has the potential to persist in aquatic environments, where it may partition to sediment (DT50 26-120 days in aerobic aquatic metabolism study, anaerobic soil metabolism 32-36 days). Deltamethrin appears to be moderately to highly persistent in terrestrial environments (terrestrial field dissipation 14 to 231 days). The metabolite Br2CA (observed in multiple studies) appears to persist much more than former compounds. It was observed in laboratory studies and in the field.

24.9 Potential for long range transport

949. Results of the Phototransformation in air according to EPI Suite TM v4.0 (AOPWIN v 1.92) are based on a 12h day are summarised in Table 3.

Table3 Phototransformation in air

Guideline / Test method	Molecule / radical	Rate constant for reaction with OH-radicals (k_{OH}) [cm^3 $molecule^{-1}$ sec^{-1}]	Half-life ($t_{1/2}$) [d]	Half-life ($t_{1/2}$) [h]	OH-radical concentration
AOPWIN	OH	17.6102 E-12	0.61	7.3	1.5 x 10^6 OH-radicals/cm^3

Based on the fast degradation rate in air no multimedia fate modelling was performed.

24.10 Bioaccumulation

950. PPDB 2012: Bioaccumulation Potential: high: BCF: 1200 calculated

951. HSDB 2012: According to a classification scheme, an estimated BCF of 250 from an estimated log K_{OW} of 7.56 and a regression-derived equation suggests the potential for bioconcentration in aquatic organisms is high.

952. US EPA 2010 reported maximum BCFs of 490x, 68x, 920x for whole fish, edible and non-edible tissues, respectively. Residues were equal amounts of tralomethrin another pyrethroide-like metabolite.

953. US EPA summary 2010: Terrestrial bioaccumulation is suggested to be low due to rapid elimination of the body in animal experiments.

j) PB-score

954. Tralomethrin has a P-score of 0.899 and a B-score of 0.00 resulting in an overall B-score of 0.899.

24.11 Human health hazard assessment

955. US EPA summary 2010: In humans, tralomethrin is metabolized completely and immediately into deltamethrin. As a result, EPA assumes that tralomethrin and deltamethrin have equivalent toxicity for human health risk assessment purposes.

956. US EPA summary 2010: Tralomethrin has moderate acute toxicity through the oral and inhalation routes of exposure and low or mild acute toxicity through the dermal route of exposure. Tralomethrin is moderately irritating to the eye, non-irritating to the skin and is not a skin sensitizer.

957. For further information please see POP factsheet for deltamethrin.

24.12 Environmental hazard assessment

k) Aquatic compartment (including sediment)

958. US EPA summary 2010: Tralomethrin and deltamethrin are classified as very highly toxic on an acute basis to estuarine/marine and freshwater fish (see also Table 4), aquatic-phase amphibians, and aquatic invertebrates. Tralomethrin and deltamethrin are also toxic on a chronic basis to freshwater fish and freshwater invertebrates. Tralomethrin is highly toxic to estuarine/marine invertebrates on a chronic basis. No data are available to evaluate toxicity of tralomethrin and deltamethrin to aquatic plants.

Table 4: Toxicity data for the aquatic compartment

Exposure scenario/ Study type	Organism /Species	Endpoint	Toxicity value	Reference
Acute 96 hour	Fish	LC50	0.0016 mg/l	PPBD 2012
Acute 48 hour	Aquatic invertebrates	EC_{50}	0.000038 mg/l	

l) Terrestrial compartment

959. US EPA summary 2010: Tralomethrin and deltamethrin are practically nontoxic on an acute basis to birds, terrestrial phase amphibians and reptiles. Chronic tralomethrin exposure to birds can result in reproductive effects (reduced eggshell thickness and reduction of live three-week embryos). Similar reproductive effects from deltamethrin exposure have not been observed.

Table 6: Toxicity data for the terrestrial compartment

Exposure scenario/ Study type	Organism /Species	Endpoint	Toxicity value	Reference
Acute	Rat	LD50	99 mg/kg	PPBD 2012
Chronic,dietary	Rat	NOEL	0.75mg/kg	PPBD 2012
Acute	Birds	LD50	2510 mg/kg	PPBD 2012

m) Toxicity to pollinators

960. US EPA summary 2010: Tralomethrin and deltamethrin are both highly toxic to terrestrial invertebrates, including beneficial insects such as honeybees.

961. PPDB 2012: Honeybees - Acute 48 hour LD_{50}: 0.13 µg/bee^{-1} Contact: High Toxicity

24.13 Other information

962. WHO 2004: According to WHO tralomethrin has been classified as pesticide of category II: moderately hazardous.

963. EC Directive 1107/2009 (repealing 91/414): Status: Excluded from Annex 1 (PPDB 2012)

24.14 References

Epi Suite US EPA (2012) http://www.epa.gov/oppt/exposure/pubs/episuite.htm, 2012-04-16

PPDB (2012) Pesticide Properties DataBase, University of Hertfordshire, http://sitem.herts.ac.uk/aeru/footprint/en/, 2012-04-18

HSDB (2012) Hazardous Substance Database, http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB, 2012-04-14

US EPA summary (2010) Tralomethrin Summary Document. Registration Review: Initial Docket March 2010. Docket Number EPA-HQ-OPP-2010-0116. http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2010-0116

US EPA (2010) EFED Revised Registration Review Problem Formulation for Tralomethrin, March 2010. http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2010-0116

Assessment of CATEGORY 3 substances (chemical alternatives to endosulfan)

25. Beta-cypermethrin: Bioaccumulation

25.1 Identity of the substance and physical and chemical properties

964. ATSDR (2003) reported that cypermethrin is formulated as four different insecticides (alpha-, beta-, theta- and zeta-cypermethrin) depending upon the ratio of the different isomers; and each of these products has different toxicological properties.

a) Name and other identifiers of the substance

Table 1: Substance identity

Common name:	Beta-cypermethrin
IUPAC name:	(*R*)-α-cyano-3-phenoxybenzyl (1*S*,3*S*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate and (*S*)-α-cyano-3-phenoxybenzyl (1*R*,3*R*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate
CAS number:	65731-84-2
Molecular weight:	416.3 g.mol-1

b) Physico-chemical properties

Table 2: Overview of selected physico-chemical properties

Property	Value	Reference
Vapour pressure at 25°C (mPa)	1.80 X 10^{-04}	PPDB 2012
Water solubility at 20°C (mg/l)	0.051	PPDB 2012
Partition coefficient n-octanol/water (log value, pH 7, 20°C)	4.7	PPDB 2012
Henry´s Law Constant at 20°C (dimensionless)	6.03 X 10^{-07}	PPDB 2012

25.2 Bioaccumulation

965. No BCF was available for beta-cypermethrin; therefore it was selected as category 3 substance. Beta-cypermethrin has a log Kow of 4.7, which is below the Annex D threshold for bioaccumulation of 5. In addition due to its chemical relation to cypermethrin and alpha-cypermethrin (both of them have a log Kow >5) it can be expected that the BCF will not exceed the values obtained for the both chemicals (cf. factsheet on cypermethrin and alpha-cypermethrin). Both chemicals do not meet the Annex D criteria 1 (c) (i).

25.3 Conclusion

966. Beta-cypermethrin has a log Kow of 4. 7 that is below the Annex D threshold of 5. Due to its chemical similarity to alpha-cypermethrin and cypermethrin (experimental derived BCF values <5000) it can be concluded that the bioaccumulation criterion Annex D 1 c (i) is not met.

25.4 Reference

PPDB (2012) Pesticide Properties DataBase, http://sitem.herts.ac.uk/aeru/footprint/en/, 2012-04-26

ATSDR (2003) U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service Agency for Toxic Substances and Disease Registry, Toxicological Profile for pyrethrins and pyrethroids, Sept. 2003 http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=787&tid=153

26. Chlorfluazuron: Persistence and Bioaccumulation

967. Information on chlorfluazuron was very limited. PPDB 2012 reported registered use in Australia, but not in US or Europe.

26.1 Identity of the substance and physical and chemical properties

a) Name and other identifiers of the substance

Table 1: Substance identity

Common name:	Chlorfluazuron
IUPAC name:	1-[3,5-dichloro-4-(3-chloro-5-trifluoromethyl-2-pyridyloxy)phenyl]-3-(2,6-difluorobenzoyl)urea
CAS number:	71422-67-8
Molecular weight:	540.6

b) Physico-chemical properties

Table 2: Overview of selected physico-chemical properties

Property	Value	Reference
Vapour pressure at 25°C (mPa)	1×10^{-5}	PPDB 2012
Water solubility at 20°C (mg/l)	6.4	PPDB 2012
Partition coefficient n-octanol/water (log value, pH 7, 20°C)	5.8	PPDB 2012
Henry´s Law Constant at 25°C ($Pa.m^3.mol^{-1}$)	4.4×10^{-4}	PPDB 2012 (non volatile)

c) Persistence

968. PPDB 2012 reported a DT50 soil (aerobic) of 90 days according to best avialalbe data. Concerning hydrolysis (at all pH values) and photolysis the compound can be considered as stable.

26.2 Bioaccumulation

969. No further information on bioaccumulation was identified. Therefore conclusions are based on log Kow.

26.3 Conclusion

970. Concerning degradation the data set is very limited. In soil DT50 values suggest slow degradation, however in water based on the hydrolytic stability at all pH values persistence cannot be excluded. Persistence in aquatic environments was not fully evaluated due to data gaps. No final conclusion can be made on Annex D criterion 1 (b) (i).

971. Chlorfluazuron has a log Kow of 5.8 indicating a potential for bioaccumulation. However no other information concerning bioaccumulation was available in the consulted data sources. Based on the log Kow >5 the bioaccumulation criterion of Annex D 1 c (i) is met.

972. However due to the limited data set more information is needed to strengthen the assessment and conclusion on prothiofos.

26.4 Reference

PPDB (2012) Pesticide Properties DataBase, http://sitem.herts.ac.uk/aeru/footprint/en/, 2012-04-26

27. Prothiofos: Persistence and Bioaccumulation

973. Information on prothiofos was very limited. PPDB 2012 reported registered use in Australia, but not in US or Europe.

27.1 Identity of the substance and physical and chemical properties

a) Name and other identifiers of the substance

Table 1: Substance identity

Common name:	Prothiofos
IUPAC name:	(RS)-(O-2,4-dichlorophenyl O-ethyl S-propyl phosphorodithioate)
CAS number:	34643-46-4 3
Molecular weight:	345.29

b) Physico-chemical properties

Table 2: Overview of selected physico-chemical properties

Property	Value	Reference
Vapour pressure at 25°C (mPa)	0.3	PPDB 2012
Water solubility at 20°C (mg/l)	0.07	PPDB 2012
Partition coefficient n-octanol/water (log value, pH 7, 20°C)	5.67	PPDB 2012
Henry´s Law Constant at 25°C ($Pa.m^3.mol^{-1}$)	3.05	PPDB 2012 (moderate volatile)

c) Classification (NITE database, 2006) for the Environment

974. Date Classified: Dec. 18, 2006 (Environmental Hazards: Mar. 31, 2006)

975. Reference Manual: GHS Classification Manual (Feb. 10, 2006)

Hazard class	Classification	Rational for the classification
Hazardous to the aquatic environment (acute)	Category 1	It was classified into Category 1 from 48 hours EC50=0.002mg/L of the crustacea (Daphnia magna) (Agricultural Chemical Registration Data, 2004).
Hazardous to the aquatic environment (chronic)	Category 1	Since acute toxicity was Category 1 and there was no rapidly degrading (BIOWIN), and since there wasbio-accumulation (log Kow=5.67 (PHYSPROP Database, 2005)), it was classified into Category 1.

27.2 Persistence

976. PPDB 2012 reported a DT50 field of 45 days. Concerning hydrolysis the compound can be considered as stable at pH ≤7 (DT50 120 days at pH 4, 280 days at pH 7, 12 days at pH 9, all at 22°C).

27.3 Bioaccumulation

977. No further information on bioaccumulation was identified. Therefore conclusions are based on log Kow.

27.4 Conclusion

978. Concerning the P-criterion the data set is very limited. In soil DT50 values suggest moderate degradation, however in water based on the hydrolytic stability at pH ≤7 persistence cannot be excluded. Persistence in aquatic environments was not fully evaluated due to data gaps. No final conclusion can be made on Annex D criterion 1 (b) (i).

979. Prothiofos has a log Kow of 6.67 indicating a potential for bioaccumulation. However no other information concerning bioaccumulation was available in the consulted data sources. Based on the log Kow >5 the bioaccumulation criterion of Annex D c (i) is met.

980. However due to the limited data set more information is needed to strengthen the assessment and conclusion on prothiofos.

27.5 Reference

PPDB (2012) Pesticide Properties DataBase, http://sitem.herts.ac.uk/aeru/footprint/en/, 2012-04-26

NITE database (2006), Classification Prothiofos available at echemPortal, http://www.echemportal.org/echemportal/index?pageID=0&request_locale=en, 2012-04-26

28. Pyridaben: Bioaccumulation

28.1 Identity of the substance and physical and chemical properties

a) Name and other identifiers of the substance

Table 1: Substance identity

Common name:	PYRIDABEN
IUPAC name:	2-tert-butyl-5-(4-tert-butylbenzylthio)-4-chloropyridazin-3(2*H*)-one
CAS number:	96489-71-3
Molecular weight:	364.9

b) Physico-chemical properties

Table 2: Overview of selected physico-chemical properties

Property	Value	Reference
Vapour pressure at 25°C (mPa)	0.001	PPDB 2012
Water solubility at 20°C (mg/l)	0.022	PPDB 2012
Partition coefficient n-octanol/water (log value, pH 7, 20°C)	6.37	PPDB 2012
Henry´s Law Constant at 25°C ($Pa.m^3.mol^{-1}$)	0.3	PPDB 2012

28.2 Bioaccumulation

981. PPDB 2012 reported a BCF value of 48. However Ding et al. 2004 reported a BCF at 0.1 µg/L and 1 µg/L exposure of 5,600 and 4,920 in *Brachio rerio* after 14 days. Unfortunately this article is in Chinese language, so no detailed evaluation explaining these high values could be done.

982. According to RIVM 2008 and DAR 2007 BCF values <500 are reported. Three studies in DAR 2007 in carp or rainbow trout suggested BCF values of <25, 309-401 and 293-398 (summarized in RIVM, 2008. RIVM 2008 concluded that pyridaben has a BCF <100 L/kg thus an assessment of secondary poisoning is not triggered. However US EPA 2010 identified bioconcentration of pyridaben in the food chain as a potential source. US EPA 2011 listed a BCF from full life cycle test data indicating an accumulation of pyridaben in fathead minnow of 3780 x, BCF in rainbow trout are one order of magnitude lower (and in line with the reported values in DAR 2007). Metabolism by fish decreases the bioaccumulation potential of pyridaben from the estimates based on log Kow alone. However US EPA 2011 demands a BCF data for oysters to provide information on bioaccumulation in aquatic invertebrates. The modelled B-score is 0.91 suggesting high bioaccumulation.

28.2 Conclusion

983. Pyridaben has a log Kow of 6.37 indicating a potential for bioaccumulation. Several experimental studies are available that metabolism in fish may reduce the bioaccumulation potential of pyridaben in fish as demonstrated by low evaluated BCF values according to standard test protocols. However, also very high BCF values were reported. BCF values in aquatic invertebrates are not available to date. Due to the equivocal data base no final decision regarding the fulfilment of the bioaccumulation criterion Annex D 1 (c) (i) can be drawn.

28.3 Reference

DAR (2007) Draft Assessment Report Pyridaben, August 2007, http://dar.efsa.europa.eu/dar-web/provision

RIVM (2008) Environmental risk limits for pyridaben, RIVM Letter report 601716021/2008, http://www.rivm.nl/bibliotheek/rapporten/601716021.pdf

Ding Z, Yang Y, Jin H, Shan Z, Yu H, Feng J, Zhang X, Zhou J. (2004) [Acute toxicity and bio-concentration factor of three pesticides on Brachydanio rerio] Ying Yong Sheng Tai Xue Bao. May;15(5):888-90. [Article in Chinese]

US EPA (2010) Pyridaben Summary Document Registration Review: Initial Docket, September, 2011. http://www.epa.gov/oppsrrd1/registration_review/pyridaben/ index.html

US EAP(2011) EFED Response to Comments on the Preliminary Problem Formulation for Pyridaben in Support of the Registration Reivew, February, 2011, available at http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2010-0214

29. Spinetoram: Bioaccumulation

984. US EPA 2009: For the hazard characterisation for human health that spinosd and spinetoram should be considered identical.

29.1 Identity of the substance and physical and chemical properties

985. US EPA 2009: Spinetoram consists of two components in an approximate ratio of 3 to 1, XDE-175-J and XDE-175-L, respectively. These two components are not isomers. The only difference between XDE-175-J and XDE-175-L is that XDE-175-L contains an extra methyl group at carbon 4 on the central ring. Since these two components have very similar physical and chemical as well as fate properties, XDE-175-J was selected to represent the spinetoram mixture in the ecological risk assessment.

a) Name and other identifiers of the substance

Table 1: Substance identity

Common name:	Spinetoram
IUPAC name:	mix of 50–90% (2*R*,3a*R*,5a*R*,5b*S*,9*S*,13*S*,14*R*,16a*S*,16b*R*)-2-(6-deoxy-3-*O*-ethyl-2,4-di-*O*-methyl-a-*L*-mannopyranosyloxy)-13-[(2*R*,5*S*,6*R*)-5-(dimethylamino)tetrahydro-6-methylpyran-2-yloxy]-9-ethyl-2,3,3a,4,5,5a,5b,6,9,10,11,12,13,14,16a,16b-hexadecahydro-14-methyl-1*H*-as-indaceno[3,2-d]oxacyclododecine-7,15-dione
CAS number:	187166-40-1 / 187166-15-0
Molecular weight:	748.01 / 760.03

b) Physico-chemical properties

Table 2: Overview of selected physico-chemical properties

Property	**Value**	**Reference**
Vapour pressure at 25°C (mPa)	5.3 X 10^{-02}	PPDB 2012
Water solubility at 20°C (mg/l)	20.0	PPDB 2012
Partition coefficient n-octanol/water (log value, pH 7, 20°C)	4.2	PPDB 2012
Henry´s Law Constant at 20°C (dimensionless)	8.14 X 10^{-07}	PPDB 2012

29.2 Bioaccumulation

986. US EPA (2009) state that since the octanol/water partitioning coefficients for XDE-175-J and XDE-175-L are high (log Kow 4.09 and 4.4, respectively); these two components are expected to bioconcentrate in fish. In rainbow trout exposed to XDE-175-J at 17.3 ng/mL, BCFs for edible tissue, nonedible tissue, and whole fish were 11, 53, and 46 mL/g, respectively. In rainbow trout exposed to XDE-175-L at 22.3 ng/mL, the BCFs for edible tissue, nonedible tissue, and whole fish were 104, 330, and 344 mL/g, respectively. XDE-175-J and XDE-175-L rapidly metabolized, yielding 2-4 more polar metabolites; correspondingly, N-dimethyl-XDE-175-J and N-dimethyl-XDE-175-L were positively identified, along with 3'-O-deethyl-XDE-175-L.

29.3 Conclusion

987. Spinetoram has log Kow values of 4.1 and 4.4 that are below the Annex D threshold of 5. Experimental retrieved BCF values based on whole fish are 46 and 344 for the two compounds. Therefore it can be concluded that the bioaccumulation criteria of Annex D c (i) is not met.

29.4 Reference

PPDB (2012) Pesticide Properties DataBase, http://sitem.herts.ac.uk/aeru/footprint/en/, 2012-04-26
US EPA (2009) Pesticide facht sheet Spinetoram, October 2009, http://www.epa.gov/opprd001/factsheets/spinetoram.pdf

30. Tolfenpyrad: Persistence and Bioaccumulation

30.1 Identity of the substance and physical and chemical properties

a) Name and other identifiers of the substance

Table 3: Substance identity

Common name:	Tolfenpyrad
IUPAC name:	4-chloro-3-ethyl-1-methyl-*N*-[4-(p-tolyloxy)benzyl]pyrazole-5-carboxamide
CAS number:	129558-76-5
Molecular weight:	383.9

b) Physico-chemical properties

Table 2: Overview of selected physico-chemical properties

Property	**Value**	**Remarks, Reference**
Vapour pressure at 25°C (mPa)	5×10^{-04}	Volatile, PPDB 2012
Water solubility at 20°C (mg/l)	0.09	PPDB 2012
Partition coefficient n-octanol/water (log value, pH 7, 25°C)	5.6	PPDB 2012
Henry´s Law Constant at 20°C (dimensionless)	9.06×10^{-07}	PPDB 2012

30.2 Persistence

988. US EPA 2009: Tolfenpyrad is expected to be somewhat persistent in the environment. Laboratory photolysis studies yield a DT50 of 24 days; the DT50 in aerobic soil degradation studies was 15 days. PPDB 2012 reports a DT50 value soil value of 4 days. Tolfenpyrad is hydrolytically stable.

989. Tolfenpyrad is essentially stable to hydrolysis at all tested pH values. No field studies or water/sediment studies are available.

30.3 Bioaccumulation

990. No further information on bioaccumulation was identified. Therefore conclusions are based on log Kow.

30.4 Conclusion

991. In soil DT50 values suggest fast degradation of tolfenpyrad with DT50 values of 4 to 15 days, however in water based on the hydrolytic stability at all pH values persistence cannot be excluded. No field data or water/sediment studies were available. Persistence in aquatic environments was not fully evaluated due to data gaps. No final conclusion can be made on Annex D criterion 1 (b) (i), though rapid degradation in soil is reported.

992. Tolfenpyrad has a log Kow of 5.6 indicating a potential for bioaccumulation. However no other information concerning bioaccumulation was available in the data sources as specified in section IV 2a) of the core report. Based on the log Kow >5 the bioaccumulation criterion of Annex D 1 c (i) is met.

993. However due to the limited data set more information is needed to strengthen the assessment and conclusion on tolfenpyrad.

30.5 Reference

PPDB (2012) Pesticide Properties DataBase, http://sitem.herts.ac.uk/aeru/footprint/en/, 2012-04-26

US EPA (2009) Environmental fate and effects review for the new chemical registration for tolfenpyrad, September 2009 http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0743-0004