SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

Propargite

EC No 219-006-1

CAS No 2312-35-8

Evaluating Member State(s): The Netherlands

Dated: 8 October 2020

Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2019

Member State concluded the evaluation without any further need to ask more information from the registrants under Article 46(1) decision.

Further information on registered substances here:
http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

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Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

Propargite was originally selected for substance evaluation in order to clarify concerns about:

- Suspected PBT/vPvB
- Potential endocrine disruptor.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

In Europe it is prohibited to place propargite on the market or use plant protection products containing propargite. Propargite is not included in the list of approved active substances under Regulation (EC) No 1107/2009, which replaces Directive 91/414/EEC. As a consequence, propargite is not approved for placing on the market pursuant to Regulation (EC) No 1107/2009 concerning the placing of plant protection products on the market. Disposal, storage, placing on the market and use of existing stocks of plant protection products containing propargite was prohibited as of 31 December 2012.

Propargite is added to Part 1 and 2 of Annex I of the EU PIC Regulation. Chemicals listed in Part 1 of Annex I are subject to the export notification procedure; chemicals listed in Part 2 of Annex I, in addition to being subject to export notification procedure, qualify also for the PIC notification procedure. Exports of such chemicals are subject to the explicit consent of the importing country according to Article 14 (6) of the PIC Regulation.

In 2015, a Compliance Check (CCH) was performed and a draft decision was sent to the Registrant. In the draft decision the Registrant was requested to submit an extended one-generation reproductive toxicity study. As a result, the Registrant provided comments and updated the registration dossier. Based on the update, it was concluded that the information in the dossier currently addresses the concerns raised by ECHA in the CCH draft decision. The CCH procedure was terminated.

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State to the following conclusions, as summarised in the table below.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION Conclusions	Tick box
Need for follow-up regulatory action at EU level	
Harmonised Classification and Labelling	
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	
No need for regulatory follow-up action at EU level	X

4. FOLLOW-UP AT EU LEVEL

4.1. Need for follow-up regulatory action at EU level

4.1.1. Harmonised Classification and Labelling

According to the harmonised classification and labelling (CLP) approved by the European Union, this substance is toxic if inhaled, is very toxic to aquatic life, is very toxic to aquatic life with long lasting effects, causes serious eye damage, is suspected of causing cancer and causes skin irritation (see section 7.6.1)

4.1.2. Identification as a substance of very high concern, SVHC (first step towards authorisation)

Not applicable (see section 5.1 for further information).

4.1.3. Restriction

Not applicable

4.1.4. Other EU-wide regulatory risk management measures

Not applicable

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

5.1. No need for regulatory follow-up at EU level

The evaluation of the available information on the substance has led the evaluating Member State to the following conclusions in relation to the concerns investigated.

PBT

Propargite meets the T and vP criteria. For bioccumulation, no conclusions can be drawn in absence of reliable data. The eMSCA therefore considers that a new bioaccumulation study according to OECD guideline 305 would be needed to draw a definitive conclusion on the bioaccumulation potential of propargite.

ED

Environment

Two pubertal assays showed that propargite disrupted the EAS pathways. However, these assays do not provide population relevant information. Therefore, the available evidence in mammals is not enough for the identification of endocrine disruptor for the environment. Propargite was positive for anti-androgenicity in the Hershberger assay. However, there are no observations in fish indicating anti-androgenicity and disruption of the HPG axis, although the fish test may have limitation in detecting anti-androgenicity. Propargite induced population relevant effects on survival and growth in fish and birds as well as reproduction effects in birds. These endpoints are considered as "sensitive to, but not diagnostic of, EATS".

Thyroid-related effects were observed in the absence of systematic toxicity in the amphibian metamorphosis assay (AMA). However, the population relevant adverse effects on growth have been only observed at day 7, but not at day 21 in this study. Overall, it is concluded that there is a lack of convincing evidence for potential interaction with the EAS pathways for the environment. Though, there is evidence for potential interaction with the thyroid pathways for the environment. The eMSCA considers that a Larval Amphibian Growth and Development Assay (LAGDA) would be needed to draw a definitive conclusion on the potential for ED-mediated adverse population-relevant effects in amphibians.

Human health

Inconsistent EAS activities have been reported in the High-Throughput Screening (HTS) of the EDSP21/ToxCast tests. Test guideline *in vitro* EDSP Tier 1 assays, however, show that propargite is inactive. Two tests, male and female pubertal assays, have studied EATS-mediated endpoints. They showed that propargite induced adverse effects on pubertal development in females (ovary, uterus and vaginal estrus and opening and body weight) and in males (PPS, seminal vesicle plus coagulating gland with and without fluid, ventral prostate, dorso-lateral prostate, and LABC, and testosterone), indicative for an anti-androgen mode of action/disturbance of the HPG axis, as also observed in the Hershberger assay. The two pubertal tests showed also that propargite decreased thyroid gland weight, altered thyroid gland histology and increased T4, even at concentrations at which no overt toxicity was observed. These observations on thyroid related adversity indicate that propargite is a thyroid disrupting chemical for human health and it affects the HPG axis.
No reproductive effects have been observed in the two-generation toxicity test at doses up to 40 mg/kg bw/day. However, in these tests numerous EATS mediated parameters, e.g. thyroid hormones and thyroid histology, have not been examined. Consequently, the potential adversity of the endocrine disrupting mode of actions identified is still not fully investigated, such as developmental neurotoxicity. This information could obtained in performing an OECD TG 426 in which also higher doses can be tested as done in the available two-generation study.

Propargite is only produced and formulated at one facility in Europe. In Europe it is prohibited to place propargite on the market or use plant protection products containing propargite. The total production is exported outside Europe. Consequently, there is no exposure to consumers, but the workers may be exposed. According to the CSR, for the production and formulation several Risk management Measures (RMM)s are in place to minimize the exposure to workers. Considering that the production and formulation is restricted to one site, and the substance cannot be placed on the EU internal market, further testing is not considered proportionate. Nevertheless, the evaluating Member State strongly recommends that the registrant seeks for further reduction of the exposure when feasible and monitors that the instructions for personal protection are followed by the workers, in view of the strong indications for endocrine disruption properties of the substance and the fact that the substance is classified as a carcinogen cat 2. Should there be new registrations or new uses for propargite (change of circumstances) the substance can be put again in the CoRAP to obtain further information on the endocrine disruption potential for the human health.

According to the chemical safety report of the registrant, at the site of the facility risk mitigating measures are in place which are sufficient to avoid emission to water and air. The potential emission to soil is very low. Consequently, under these circumstances no risk can be identified in Europe that would require further testing, as it is not foreseen that a test outcome would lead to additional RMMs in the EU. Should there be new registrations, new uses for propargite (change of circumstances) or should the local inspectors report that the emissions are substantial and contrary to the low environmental exposure reported in the chemical safety report, the substance can be put again in the CoRAP to obtain further information on the potential PBT/vPvB properties and the endocrine disruption potential for the environment.

Table 2

REASON FOR REMOVED CONCERN The concern could be removed because	Tick box
Clarification of hazard properties/exposure Propargite meets the T and vP criteria. However, no conclusions can be drawn for B. There is no convincing evidence for potential interaction with the EAS pathways for human health and the environment. There is, however, evidence for potential interaction with the thyroid pathway for human health and the environment. Propargite is only produced and formulated at one facility in Europe and cannot be placed on the EU internal market. On basis thereof, further testing for both human health and the environment is therefore not considered proportionate. This is further supported by the risk mitigation measures that are in place at the one site for protection of workers and for avoiding emission to water and air and the fact that the substance is classified as a carcinogen cat 2. *Details see text above*	x
Actions by the registrants to ensure safety, as reflected in the registration dossiers (e.g. change in supported uses, applied risk management measures, etc.)	

The registrant is recommended to seek for further reduction of the exposure when feasible and monitors that the instructions for personal protection are followed by the workers, in view of the strong indications for endocrine disruption properties of the substance and the fact that the substance is classified as a carcinogen cat 2.

Should there be new registrations or new uses (change of circumstances) propargite could be put again in the CoRAP to obtain further information on the PBT and endocrine disruption potential for the human health and the environment.

5.2. Other actions

not applicable

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

not applicable, see section 5

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

Propargite was originally selected for substance evaluation in order to clarify concerns about:

-Suspected PBT/vPvB

-Potential endocrine disruptor.

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Endocrine disruption	The available data are indicative that propargite has an anti-androgen mode of action/disturbance of the HPG axis and has thyroid disrupting properties affecting the HPT axis.
Persistency	Propargite is considered very Persistent on the basis of degradation studies in soil.
Bioaccumulation	Propargite is potentially bioaccumulative. Final conclusions cannot be drawn in absence of reliable endpoints that are corrected for growth and normalised to 5% lipid.
Toxicity	Propargite is considered toxic on the basis of aquatic toxicity to fish and crustacean.

7.2. Procedure

Propargite was included in the Community Rolling Action Plan (CoRAP) for substance evaluation in 2016 by the competent authority of the Netherlands. The scope of the evaluation was PBT. In 2019 the CoRAP was updated to include the concern for endocrine disruption as well. Other human health hazard endpoints were only evaluated in relation to the primary concerns and were therefore not fully assessed. The evaluation was based on the updated registration dossier from October 2017.

7.3. Identity of the substance

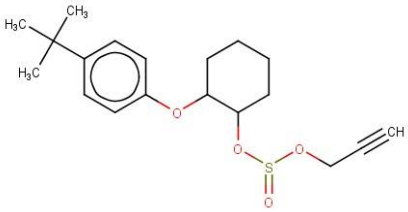
Table 4

SUBSTANCE IDENTITY	
Public name:	Propargite
EC number:	219-006-1
CAS number:	2312-35-8

Index number in Annex VI of the CLP Regulation:	607-151-00-7
Molecular formula:	C19H26O4S
Molecular weight range:	350.47
Synonyms:	IUPAC name: 2-(4-tert-butylphenoxy)cyclohexyl prop-2-yn-1-yl sulfite

Type of substance ☒ Mono-constituent ☐ Multi-constituent ☐ UVCB

Structural formula:



7.4. Physico-chemical properties

Table 5

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	*Oily, viscous liquid with a strong, sweet odour and a brownish yellow colour*
Vapour pressure	*<4.04 x 10^{-5} Pa at 20°C*
Water solubility	*215 µg/L at 20°C and pH 6.5*
Partition coefficient n-octanol/water (Log Kow)	*5.7 (determined with HPLC method)*
Flammability	*Flashpoint: 71.4°C and Auto-ignition at 336°C*
Explosive properties	*non explosive*
Oxidising properties	*no oxidising properties*
Stability in organic solvents and identity of relevant degradation products	*not critical*
Dissociation constant	*>12*

7.5. Manufacture and uses

7.5.1. Quantities

Table 6

AGGREGATED TONNAGE (PER YEAR)				
☐ 1 – 10 t	☐ 10 – 100 t	☐ 100 – 1000 t	☒ 1000- 10,000 t	☐ 10,000-50,000 t
☐ 50,000 – 100,000 t	☐ 100,000 – 500,000 t	☐ 500,000 – 1000,000 t	☐ > 1000,000 t	☐ Confidential

7.5.2. Overview of uses

Propargite is a pestice against mites that was registered as plant protection product in the EU until 2011 and is no longer approved as plant protection product or biocide. Currently, propargite is only used in the EU for formulation of plant protection products for export.

Table 7

USES	Use(s)
Uses as intermediate	-
Formulation	In the EU, propargite is used for the formulation of plant protection products.
Uses at industrial sites	-
Uses by professional workers	-
Consumer Uses	-
Article service life	-

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

Table 8

HARMONISED CLASSIFICATION ACCORDING TO ANNEX VI OF CLP REGULATION (REGULATION (EC) 1272/2008)							
Index No	**International Chemical Identification**	**EC No**	**CAS No**	**Classification**		**Spec. Conc. Limits, M-factors**	**Notes**
				Hazard Class and Category Code(s)	**Hazard statement code(s)**		
607-151-00-7	propargite (ISO) 2-(4-*tert*-	219-006-1	2312-35-8	Skin Irrit. 2 Eye Dam. 1 Acute Tox. 3 *	H315 H318 H331	M=10	

	butylphenoxy) cyclohexyl prop-2-ynyl sulphite			Carc. 2 Aquatic Acute 1 Aquatic Chronic 1	H351 H400 H410		

7.6.2. Self-classification

- In the registration: None. The harmonized classification is followed.
- The following hazard classes are in addition notified among the aggregated self classifications in the C&L Inventory:

  Acute Tox. 4; H302
  Acute Tox. 3; H311
  Acute Tox. 2; H330

7.7. Environmental fate properties

7.7.1. Degradation

QSAR calculations

Calculations performed with the programm EPI Suite - BioWin v4.10[2] show that degradation of propargite would be rather slow. For example, Biowin 2 and 7 estimates that propargite does not biodegrade fast (score: 0.1911 and -0.3157 respectively). Likewise, Biowin 3 and 4 give biodegradation time frames from days to weeks and months. Biowin 5 and 6 indicate the propargite is not readily biodegradable (score 0.1196 and 0.0146). Only the linear model of Biowin 1 indicated that the substance would biodegrade fast (sore 0.5287), but the general conclusion is that propargite is not readily biodegradable.

Abiotic degradation

For abiotic degradation, the REACH dossier contains data on hydrolysis and photodegradation in air, water and soil. The hydrolysis study (Van der Gaauw 2002) reports that propargite is stable in water with a pH 4 and has a half-life of 66.3 days for pH 7, both at 25°C. For phototransformation in air, water, and soil half-lives are reported in the range of 2.2 hours, 3.9 to 15.4 days and 37.5 days for air, water and soil respectively (Concha 2003, McCorquodale and Patterson 2003 Korpalski 1990).

Biotic degradation

Ready biodegradability

The REACH dossier contains one OECD 301B screening study on ready biodegradability of propargite (Coenen, 1989). The study was performed at two concentrations of 10 and 20 mg/L. Over 28 days the observed degradation was not significant with levels of 2% and 5.9% over 28 days.

Sediment

An OECD 308 water-sediment simulation study is available in the REACH dossier (Völkel, 2001) performed with river and pond sediment. The reported half-lives for the whole system are 22.5 and 18.3 days respectively at 20°C (41.8 and 37.6 days recalculated to

[2] US-EPA. 2010. BIOWIN v4.10 (computer program). Washington, USA, US-EPA

12°C). These endpoints are derived with a first order model. $^{14}CO_2$ production was 51.8 and 39.9% of applied radioactivity after 106 days for river and pond respectively. Formation of NER was 29.3 and 28.9% respectively. Composition of the NER is only given as fraction fulvic acid, humic acid and humins. NER was not included as parent in the calculation of the DT50 presented in the DAR. Considering the decay curve of the parent and the concurrent formation curve of the NER showing that NER is not formed with the initial dissipation of the parent, and considering the amount of CO_2 formed (see figure below), it is considered unlikely that the NER will contain a high fraction of the parent if any at all. The half-live calculations based on the analysed propargite only are considered realistic. It is therefore concluded that propargite in this study does not meet the P criteria.

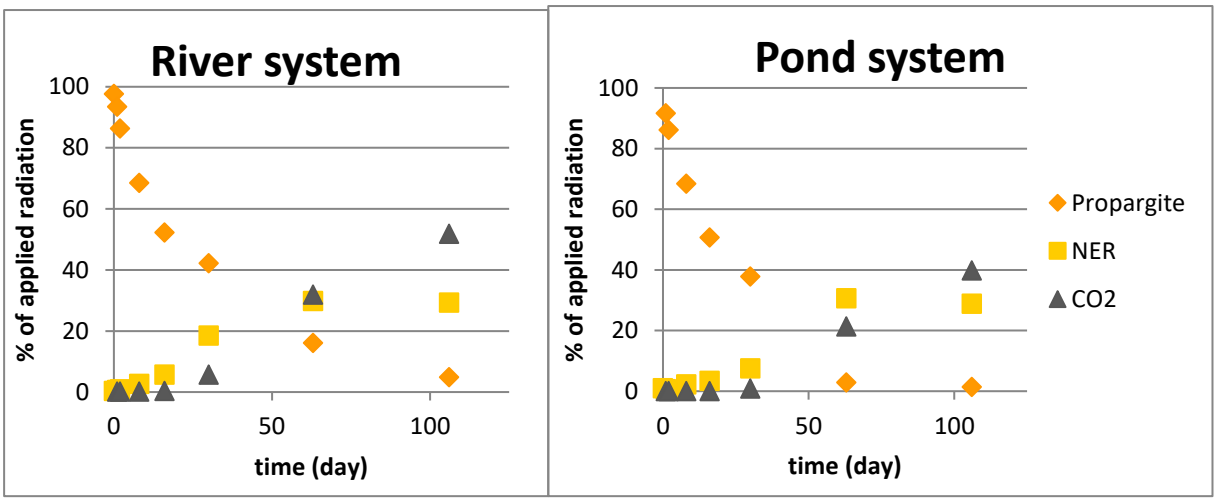


Figure 1. Degradation in river and pond sediment (Völkel 2001).

Also a 30 days degradation experiment in a lake water-sediment system is available (Comezoglu, 1993). Development of volatiles was 0.68% after 30 days and the total concentration of propargite reduced to 60%. One main metabolite (M1, identified as p-tertiobutylphenoxycyclohexan-1-ol (TBPC)) was detected with a maximum concentration of 38.8% after 30 days. From this study a half live of 38.4 days is reported based on first order degradation. This endpoint is considered invalid because of the short duration of the study over which less than 50% degradation occurred.

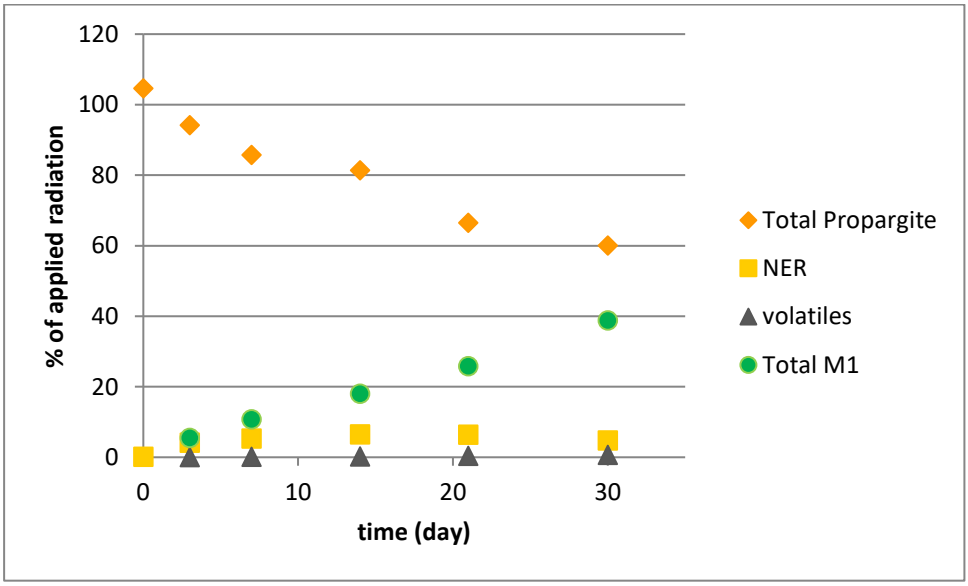


Figure 2. Degradation in a lake water-sediment study (Comezoglu, 1993)

Soil

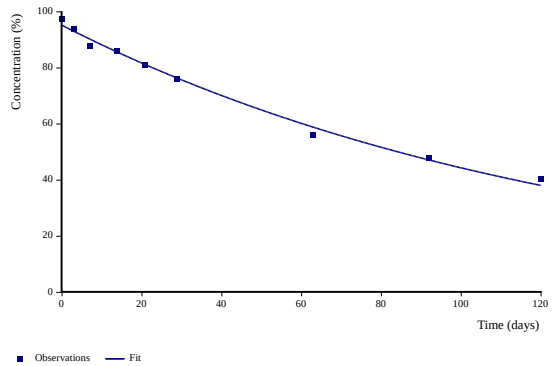
In the REACH dossier, half-lives for five soils are available from four studies on aerobic degradation (Dzialo et al. 2003, Dzialo 1988, Galicia 1990 and Comezoglu and Ly 1995). These studies are performed at 20-25°C. Half-lives are reported ranging from 39.5 (sandy loam) to 168 days (silt clay loam). On the basis of data in the REACH dossier, all half lives are recalculated using Cake 3.3 software[3] and following FOCUS guidance[4] for selection of the most appropriate degradation model. The resulting half-lives are presented in the table below. After correction to 12°C, four of the five endpoints exceed the P criterion of 120 days and two even exceed the vP criterion of 180 days. In the calculations, NER is not included as parent. This is considered appropriate as also concluded above for sediment.

Table 9. Overview of recalculated half-lives in aerobic soil

		DT_{50} recalculated	T exp.	best fit	DT_{50} normalised to 12°C
Dzialo et al. 2003	silt loam	90.6	20	SFO	192
Dzialo et al. 2003	silty clay loam	55.5	20	SFO	118
Dzialo 1988	sandy clay loam	46.6	25	SFO	155
Galicia 1990	loamy sand	50.4	22	SFO	128
Comezoglu and Ly 1995	sandy loam	226	25	DFOP	752

In addition, an anaerobic study in a sandy clay loan soil is available as supporting evidence in the REACH dossier. This study was performed for 60 days and reported a half live of 64 days. Recalculation as performed for the other soil studies results in a half live of 68.5 days on the basis of the single first-order (SFO) model. Normalisation to 12°C gives a half lives of 228 days.

Silt loam



Silty clay loam

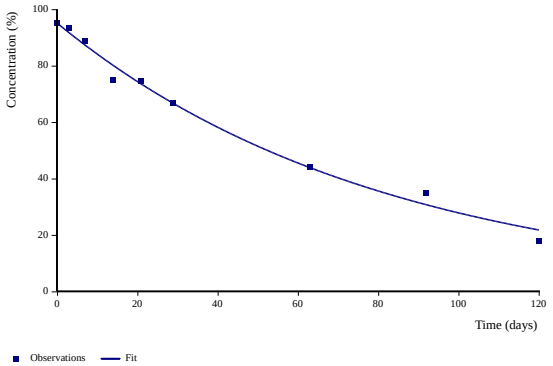


Figure 3. Fitted SFO curves for degradation in silt loam and silty clay loam (Dzialo et al. 2003)

[3] Tessella (2016). CAKE - Computer Assisted Kinetic Evaluation, version 3.3, Tessella.

[4] FOCUS (2006). Guidance Document on Estimating Persistence and Degradation Kinetics from Environmental Fate Studies on Pesticides in EU Registration, version 2.0. Brussels, European Commission.

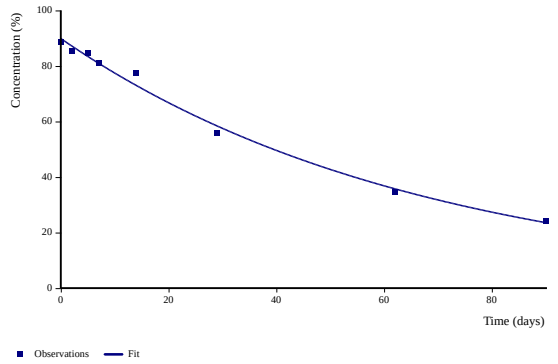


Figure 4 . Fitted SFO curve for degradation in sandy clay loam (Dzialo 1988)

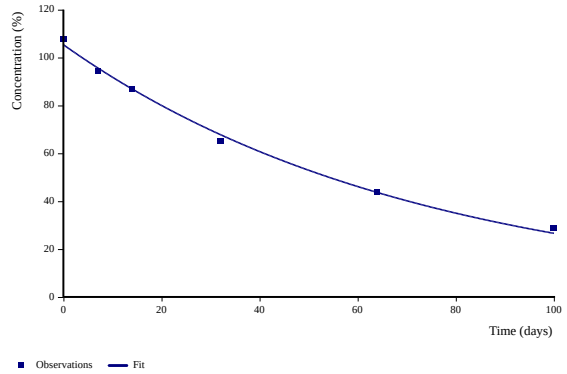


Figure 5. Fitted SFO curve for degradation in loamy sand (Galicia 1990)

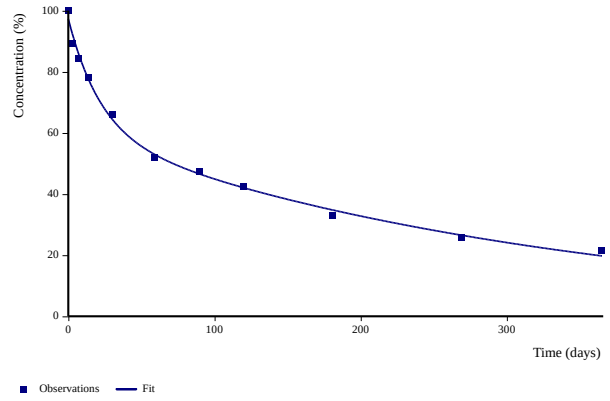


Figure 6. Fitted Double First-Order in Parallel (DFOP) curve for degradation in sandy loam (Comezoglu and Ly 1995)

Conclusion

The available data on persistency in sediment indicate that propargite is not persistent in sediment. The half-lives on aerobic degradation in most soils exceeds the persistency criterion and in some soils the criterion for very Persistent is exceeded. Therefore, propargite should be considered as very Persistent. This is confirmed by the study on hydrolysis and the supporting study on anaerobic degradation in soil.

7.7.2. Environmental distribution

Not relevant for the concerns examined thefore not assessed.

7.7.3. Bioaccumulation

The key study in the REACH dossier for propargite reports a BCF of 1840 L/kg from a study with bluegill sunfish (*Lepomis macrochirus*) (Suprenant, 1988). This endpoint is based on kinetics (k1/k2, 35 days of accumulation and 14 days of depuration) after exposure at flow-through conditions at a nominal concentration of 3.1 µg/L. The kinetic endpoint does however differ much from the steady state BCF (whole body 775 L/kg (260 L/kg in edible tissue and 1550 L/kg in non-edible tissue) and has been recalculated on the basis of the concentrations given in the REACH dossier. The recalculated kinetic BCF for the whole fish is 1140 L/kg. As the lipid content has not been reported, to which extent this BCF would deviate from a value normalised to 5% body fat. Due to a lack of information on the weight of the animals a growth correction is also not possible. By day 14 of the depuration period, 82, 91 and 89 % of the ^{14}C-residues present on the last day of exposure had been eliminated in the edible, non-edible and whole fish tissues, respectively.

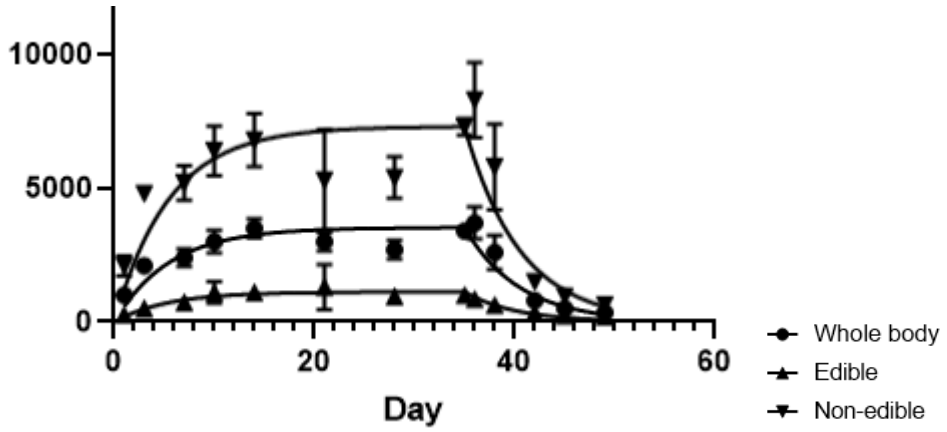


Figure 7. Uptake and depuration in *Lepomis macrochirus* (Suprenant, 1988)

The supporting study (Hasbrouck Sleight III, 1972) in the REACH dossier, also performed with bluegill sunfish, reports BCFs of 170 L/kg and 1591 L/kg (steady state) for edible and non-edible tissues respectively after exposure for 35 days at flow-through conditions to a concentration of 0.025 mg/L. Also in this case it is unclear if the endpoint has been normalised to 5% body fat and if growth correction has been performed. In the DAR both studies have been disregarded and a calculated BCF of 13964 L/kg has been used in the assessment. That calculation is based on a HPLC detemined log K_{ow} value. Both studies are performed with ^{14}C labeled substance.

Conclusion

The availble studies are insufficient to draw conclusion on the bioaccumulative properties of propargite. However, the study from 1988 does not exclude that a lipid and growth corrected BCF exceeds the B criterion of 2000 L/kg.

The eMSCA therefore considers that a new bioaccumulation study according to OECD guideline 305 would provide definitive information to allow conclusions to be drawn about the bioaccumulation potential of propargite. However, propargite is only produced and formulated at one facility in Europe, at which risk mitigating measures are in place that, according to the chemical safety report of the registrant, are sufficient to avoid emission to water and air. The potential emission to soil is very low. In Europe it is prohibited to place propargite on the market or use plant protection products containing propargite. The total production is exported outside Europe. Consequently, under these circumstances no risk can be identified in Europe that would require further testing. Should there be new registrations, new uses for propargite (change of circumstances) or should the local inspectors report that the emissions are substantial and contrary to the

low environmental exposure reported in the chemical safety report, the substance can be put again in the CoRAP to obtain further information on the potential PBT/vPvB properties

7.8. Environmental hazard assessment

7.8.1. Aquatic compartment (including sediment)

In the REACH dossier and DAR endpoints for fish, crustacean and algae are available (presumed to be from the same reports in both dossiers). A NOEC for larval development (length and weigth) of the F1 larvae of 5.7 µg/L for Pimephales promelas is reported (Dionne, 1996). This is a 272 days full life cycle study under flow-through conditions performed according to the EPA OPP 72-5 test guideline. The testwater had a pH of 6.9-7.6, the temperature was 24-26°C,the hardness was 33-35 mg/L $CaCO_3$ and the endpoints are based on mean measured concentrations (1.4, 2.8, 5.7, 11 and 27 µg/L). Mortality was significantly affected at 27 µg/L for F0 (20%), and F1 (100%). Hatching succes of F1 was also significantly affected at 27 µg/L compared to the control. Supporting studies in the REACH dossier are a prolonged fish toxicity test with Oncorhychus mykiss according to OECD TG 204 (Sousa, 1990) and an early life stage (ELS) toxicity study with Pimephales promelas (Forbis & Franklin, 1983) performed according to ASTM guideline 1981 E-47.01. The OECD 204 study was a 21 day flow-through study. The test water had a pH of 7.1-7.1, temperature of 13-14°C and hadness of 30-35 mg/L CaCO3. The mean measured test concentrations were 0, 14, 21, 32, 52 and 100 µg/L. At 14 µg/L, sublethal effects such as partial or complete loss of equilibrium, darkened pigmentation, erratic swimming and lethargy were observed. Therefore the NOEC was concluded as <14 µg/L. The ELS study was performed for 35 days under flow-through conditions. The test water had a pH of 7.8-8.2, temperature of 23-25°C and hardness of 255 mg/L $CaCO_3$. Mean measured test concentrations were: 0, 1.9, 3.2, 7.5, 16 and 28 µg/L. Significant mortality (100%) was observed at 28 µg/L and therefore the NOEC was concluded as 16 µg/L where survival was somewhat reduced (70% ± 12) compared to the control and solvent control (78% ± 6.4 and 80% ± 6.7 respectively) but not significant. Growth parameters (length and weight) were not significantly affected.

For invertebrates, only one study is available in the REACH dossier (Forbis & Franklin, 1984). The reported study is performed according to ASTM 1981 E-47.01 test guideline. *Daphnia magna* was tested for 21 days under flow-through conditions. The test water had a pH of 8.1-8.4, temperature of 20-21°C and alkalinity of 368 ppm. Mean measured exposure concentration were : 0, 2.5, 4.1, 9.0, 14 and 38 µg/L. At 38 µg/L total mortality was observed. Up to 14 µg/L mortality and reproduction were not affected but at this concentration a significant reduction in adult length was observed. Therefore the NOEC was concluded as 9 µg/L.

Algae (*Selenastrum capricornutum*) were not sensitive to propargite at any of the tested concentrations (Giddings, 1990).

The NOECs for the full life cycle study with *P. promelas* and the NOEC for *D. magna* meet the T criterion of <10 µg/L.

Conclusion

Propargite meets the T criterium.

7.8.2. Terrestrial compartment

Not relevant for the concerns examined thefore not assessed.

7.8.3. Microbiological activity in sewage treatment systems

Not relevant for the concerns examined, therefore not assessed.

7.8.4. PNEC derivation and other hazard conclusions

The substance meets the PBT criteria for Toxicity and very Persistent. Meeting the criteria bioaccumulation cannot be excluded. Additional test would be required for a definitive conclusion.

7.8.5. Conclusions for classification and labelling

With lowest NOEC of 5.7 µg/L for *Pimephales promelas* as reported by Dionne (1996), the substance should be classified as Aquatic chronic 1 with an M-factor of 10. This is in line with the current harmonised classification.

7.9. Human Health hazard assessment

Not relevant for the concerns examined therefore not evaluated.

7.10. Assessment of endocrine disrupting (ED) properties

The estrogenic, androgenic, thyroidal and steroidogenic (EATS) modalities are the focus of this document. With respect to species addressed, the focus of this assessment is on vertebrates, for which the current understanding of the EATS modalities and availability of test methods is most advanced. Due to the scarce knowledge on the endocrinology for invertebrates, this assessment does not specifically cover those organisms.

7.10.1. Endocrine disruption – Environment

The following assessment is intended to identify propargite as endocrine disruptor for the Environment. The basis of this assessment is the WHO definition on endocrine disruptor with reference to the ECHA/EFSA guidance on endocrine disruptor for pesticides and biocides. The sources of data are:

1. registration dossier in the ECHA website
2. EFSA evaluation reports
3. US EPA EDSP21 Dashboard and ToxCast database
4. literature search in pubmed

Data used for the following assessment are from the registration dossier, the EDSP21/ToxCast databases and the EFSA reports. An additional literature search was performed in the Pubmed using the keyword "propargite" leading to 90 studies (accessed on 2 September 2019). Except one *in vitro* study on human β-cell and dopamine neuron loss, none of the literature studies deal with endocrine related effects.

EATS Endocrine activity

In vitro EATS assays

Propargite has been tested in the US EPA Endocrine Disruption Screening Program (EDSP) for the 21st Century (EDSP21), the Toxicity Forecaster (ToxCast), and the EDSP Tier 1 screening assays. These *in vitro* assays correspond to the OECD level 2 assays. The main results are briefly summised as follows:

1. EDSP21 results
   1) among 28 assays, positive in 7 ER/Anti-ER assays
   2) among 18 assays, positive in 9 AR/Anti-AR assays
   3) among 11 thyroid related assays, positive in 3 assays
   4) among 3 steroidogenesis assays, positive in 1 assay

2. ToxCast results
   1) among 18 assays for mammalian ERs, 3 assays active for anti-ER activity;
   2) among 11 assays for mammalian ARs, 5 assays showed positive/active for AR binding and anti-AR transcriptional activity;
   3) among 4 mammalian TR assays, one active for anti-TR activity.
   4) aromatase activity, PPARγ antagonist and GR antagonists were showed in the transcriptional assays too.

3. EDSP Tier 1 *in vitro* screening assays
   1) ER Binding Assay, tested at 10^{-11}-10^{-3} M, with a conclusion of not ER-binder.
   2) ERα Transcriptional Activation Assay tested at 10^{-12}-10^{-3} M , with a conclusion of not ER-active
   3) AR Binding Assay, tested at 10^{-11}-10^{-3} M, with conclusion of not AR-binder
   4) Aromatase Assay, tested at 10^{-10}-10^{-3} M, with conclusion of non-inhibitor of aromatase activity
   5) Steroidogenesis Assay, tested at 10^{-10}-10^{-4} M, with results of not active

EDSP21 and ToxCast results are High-Throughput Screening (HTS) results which have not yet been validated. The results are not further summarised here. For this reason, only the 5 EATS *in vitro* tests from EDSP Tier 1 are summurised as follows.

Rat Estrogen Receptor Binding Assay (OECD TG 493, OCSPP 890.1250)

In an estrogen receptor (ER) binding assay, similar to OECD TG493, uterine cytosol from Sprague-Dawley rats was used as the source of ER to conduct binding experiments. A saturation binding experiment was performed to demonstrate that the ER in the rat uterine cytosol was present in reasonable numbers and was functioning with appropriate affinity for the radiolabeled reference estrogen prior to conducting ER competitive binding experiments. A competitive binding experiment was conducted to measure the binding of a single concentration of [^{3}H]-17β-estradiol (1 nM) in the presence of increasing concentrations (10^{-11} to 10^{-3} M) of propargite. DMSO was used as the solvent vehicle at a final concentration of approximately 2%. A total of three competitive binding assay runs were performed, and each run included 19-norethindrone as a weak positive control, octyltriethoxysilane as a negative control, and 17β-estradiol as the natural ligand reference material.

Competitive binding assays were performed using two different cytosol preparations. For Runs 1 and 2, the mean dissociation constant (K_d) for [^{3}H]-17β-estradiol was 0.0.081 ± 0.006 nM and the mean estimated B_{max} was 0.061±0.001 nM (52.70 ± 1.05 fmol/l00 µg of cytosol protein) for the uterine cytosol preparation. For Run 3 the mean K_d for [^{3}H]-17β-estradiol was 0.303 ± 0.090 nM and the mean estimated B_{max} was 0.143 ± 0.003 nM (33.59 ± 0.70 fmol/100 µg of cytosol protein) for the cytosol preparation. The K_d and B_{max} values for both cytosol preparations were within the range recommended in the test guideline.

In the competitive binding experiment, precipitation was observed at 10^{-3} M propargite in the first two runs. Therefore data at this concentration were not evaluated; the highest concentration tested in the third run was 10^{-4} M.. The mean [^{3}H]-17β-estradiol binding in the presence of propargite was >85% at concentrations ≤10^{-4} M in all three runs; therefore, an estimated mean log IC_{50} and relative binding affinity (RBA) were not calculated for propargite.

The estimated mean log IC_{50} was −9.2M for the natural ligand (17β-estradiol) and −5.6 M for the weak positive control (19-norethindrone). Compared to the natural ligand, the mean RBA was 0.022% for 19-norethindrone. All performance criteria were met for 17β-estradiol, 19-norethindrone, and the negative control, octyltriethoxysilane.

Based on the results of the three runs, propargite is classified as Not Interactive in the Estrogen Receptor Binding Assay.

Human Estrogen Receptor Transcriptional Activation (OECD TG 455, OCSPP 890.1300)

In an estrogen receptor transcriptional activation assay, similar to OECD TG455, hERa-HeLa-9903 cells cultured *in vitro* were exposed to propargite at logarithmically increasing concentrations from 10^{-12} to 10^{-5} M in DMSO (0.1 %) for 24 hours. Cells were maintained in Eagles Minimum Essential Medium without phenol red, supplemented with 60 mg/L kanamycin and 10% dextran-coated charcoal-treated fetal bovine serum. Two independent runs were performed, and each run used 96-well plates with each propargite concentration tested in replicates of 6 wells/plate. Cells were exposed to the test agent for 24±2 hours to induce reporter (luciferase) gene products. Luciferase expression in response to activation of the estrogen receptor was measured upon addition of a luciferase substrate and detection with a luminometer with acceptable sensitivity.

Propargite was tested up to and including the limit of cytotoxicity, 10^{-5} M. Acceptance criteria were mostly met for either run of the assay, generally indicating increased sensitivity of the assay. The mean RPC_{Max} for propargite was 3.6% in the first run, and -1.7% in the second run; the associated PC_{Max} was 10^{-8} M in both runs. Because the RPC_{Max} < PC10 in both assay runs, propargite was considered negative for estrogen receptor transcriptional activation in this test system.

Rat Androgen receptor (AR) binding assay (OCSPP 890.1150)

In an androgen receptor (AR) binding assay, ventral prostate cytosol from Sprague Dawley rats was used as the source of AR to conduct a competitive binding experiment. A saturation binding experiment was conducted to demonstrate that the AR in the rat prostate cytosol was present in reasonable numbers and was functioning with appropriate affinity for the radiolabeled reference androgen (R 18 81).

The competitive binding assay was conducted to measure the binding of a single concentration of [^{3}H]-Rl881 (1nM) in the presence of increasing concentrations (10^{-11} to 10^{-3} M) of propargite. Dimethyl sulfoxide (DMSO) was used as a vehicle at a final assay concentration of approximately 3.2%. Three independent runs were conducted on separate days. The assay included dexamethasone as a weak positive control, and R1881 as the ligand reference standard.

The mean dissociation constant (K_d) for [^{3}H]-Rl881 was 1.080±0.690 nM, and the estimated B_{max} was 1.071±0.167 fmol/l 00 µg protein for the single batch of prostate cytosol that was used in the assay. Only one of the three K_d values was within the range reported in the EPA validation program (0.685 to 1.57 nM), and all B_{max} values were below the recommended range (7 to 16 fmol/100 µg protein). In the competitive binding experiment, precipitation of propargite was visually observed at the highest concentration tested (10^{-3} M) in Run 1. Therefore, the highest concentration used for data evaluation was 10^{-4} M. In Runs 2 and 3, propargite was tested at 10^{-11} to 10^{-4} M; however precipitation was observed at 10^{-4} M in Run 2. Therefore, the highest propargite concentrations used for data evaluation in Runs 2 and 3 were 10^{-5} M and 10^{-4} M, respectively. The specific binding in the presence of propargite was 75-78% at 10^{-4} M in Runs 1 and 3, and 89-107% at concentrations ≤10^{-5} M in all three runs. Propargite is classified as a non-binder as specific [^{3}H]-R1881 binding was >75% at all concentrations tested in all three runs. An IC_{50} and relative binding affinity (RBA) could not be calculated for propargite.

The estimated average log IC_{50} was −9.0 M for R1881 and −4.5 M for the dexamethasone. Compared to R1881, the mean RBA for dexamethasone was 0.0032% for the two valid runs (Runs 2 and 3); performance criteria were met for these two runs. Run 1 was considered invalid because the concentrations prepared for R1881 and dexamethasone were lower than expected due to an error in stock preparation. Therefore, the curve for dexamethasone was not fully defined (bottom percent binding was not achieved). However, as the performance was consistent between the other two runs, it is considered unlikely that information from an additional run would change the interpretation of this study. The range of concentrations for R1881 in Run 1 fully defined the curve, but the concentration range was off by more than an order of magnitude.

Based on the results from the three runs, propargite is classified as a Non-Binder in the Androgen Receptor Binding Assay.

Aromatase Assay (OCSPP 890.1200)

In an *in vitro* aromatase (CYP 19) assay, propargite was incubated with human recombinant aromatase and tritiated androstenedione ([Iβ-^{3}H(N)]-androst-4-ene-3, 17-dione; [^{3}H]-ASDN) in dimethyl sulfoxide (DMSO) at concentrations of 10^{-10} M to 10^{-3} M for 15 minutes to assess the potential of propargite to inhibit aromatase activity.

Aromatase activity was determined by measuring the amount of tritiated water produced at the end of a 15-minute incubation period for each concentration of chemical. Tritiated water was quantified using liquid scintillation counting (LSC). Four independent runs of the assay were conducted, and each run included a full activity control, a background activity control, a positive control series (10^{-10} to 10^{-5} M) using a known inhibitor (4-hydroxyandrostenedione; 4-OH ASDN), and the test chemical series (10^{-10} to 10^{-4} M) with three repetitions per concentration.

Aromatase activity in the full activity controls ranged from 0.173-0.293 nmol·mg-protein^{-1} ·min^{-1} for the three successful tests (Runs 2 - 4), with a mean and standard deviation (SD) of 0.224 ± 0.048 nmol· mg-protein^{-1} ·min^{-1}. Activity in the background controls ranged from 0.45% to 0.76% and averaged 0.64% of the full control activity. The response of each full activity control was generally between 90 to 110% of the average full activity. The response of the full activity controls and background controls were acceptable.

For the positive control substance (4-OH ASDN), aromatase activity averaged 0.224 ± 0.042 nmol· mg-protein^{-1} min^{-1} at the lowest tested concentration (10^{-10}M) and 0.002 ± 0.00 nmol· mg-protein^{-1}·min^{-1} at the highest tested concentration (10^{-5} M). These results were generally within the recommended ranges for the top of the curve, bottom curve, Hill Slope, log IC_{50}, and coefficient of variation for replicates of each concentration. For 4-OH ASDN, the estimated mean log IC_{50} was −7.17 M and the Hill slope was −0.94. Confidence in these numbers is high due to the small variation.

The highest concentration of propargite successfully tested was 10^{-4} M, as precipitation was noted at concentrations of ≥$10^{-3.5}$ M. For propargite, aromatase activity averaged 0.216 ± 0.046 nmol· mg-protein^{-1}·min^{-1} at the lowest tested concentration (10^{-10}M) and 0.216 ± 0.041 nmol· mg-protein^{-1}·min^{-1} at the highest successfully tested concentration (10^{-4} M). The lowest portion of the response curve across runs was greater than 75% activity at all soluble concentrations of propargite. As a percent of the full activity control, aromatase activity for propargite was ≥96.5% at all concentrations from 10^{-10} to 10^{-4} M. An IC50 for propargite could not be calculated as inhibition was <5% at ≤10−4 M. Based on the data from the average response curve, propargite is classified as a Non-inhibitor of aromatase activity in this assay.

Steroidogenesis Assay (OECD TG 456, OCSPP 890.1550)

In a steroidogenesis assay, H295R cells cultured *in vitro* in 24-well plates were incubated with propargite at concentrations of 100, 10, 1, 0.1, 0.01, 0.001, and 0.0001 µM for 48 hours in triplicate for four independent experiments. Dimethyl sulfoxide (DMSO) was used as the vehicle, at a final concentration of 0.05%. Because of cytotoxicity greater than 20%, the highest acceptable concentration for analysis was 0.1 µM in Runs 2 and 4 and 1 µM in Run 3. Run 1 was not analyzed because one of the forskolin concentrations on the quality control plate was incorrect (3.33 µM, instead of 1 µM).

Testosterone and estradiol levels were measured using HPLC-MS/MS. A Quality Control (QC) plate was run concurrently with each independent run of a test chemical plate to demonstrate that the assay responded properly to positive control agents at two concentration levels. The positive controls included a known inhibitor (prochloraz) and inducer (forskolin) of estradiol and testosterone production.

Guideline acceptability recommendations and requirements were met, including adequate production of testosterone and estradiol, acceptable reproducibility (low %CV), and appropriate induction and inhibition with positive controls. Precipitation of the test compound was not observed at propargite concentrations up to 100 µM.

No treatment-related effect was observed on testosterone or estradiol levels. A statistically significant reduction in testosterone was observed at the 0.001 µM concentration in Run 4; however, this was not reproducible in the other runs. Based on hormone responses in at least three independent runs, propargite treatment did not result in statistically significant and reproducible alterations in testosterone or estradiol production. Propargite was inactive the steroidogenesis assay.

Summary of in vitro results

Both EDSP21 and ToxCast tests show that propargite is active in EATS assays. However, 5 *in vitro* EDSP Tier 1 tests, which were performed according to the test guidelines, show that propargite is inactive in EAS assays.

In vivo EATS assays

Propargite has been tested in the 6 EDSP Tier 1 *in vivo* screening assays, which corresponds to the OECD level 3/4 assays. The main results in these 6 *in vivo* EATS assays are summarised as follows:

Uterotrophic Assay (OECD TG 440, OCSPP 890.1600, level 3)

In an uterotrophic assay conducted to screen for potential estrogenic activity, propargite in corn oil was administered daily via oral gavage to groups of eight ovariectomized female SpragueDawley rats at dose levels of 0 (vehicle), 125, or 400 mg/kg/day for three consecutive days on post-natal days (PND) 61-63. A positive control group was treated with 17α-ethynyl estradiol (EE) by daily oral gavage at a dose level of 0.1 mg/kg/day. All animals were terminated and necropsied on PND 64 approximately 24 hours after the final dose to determine wet and blotted uterine weights.

All animals survived until scheduled termination. At 400 mg/kg/day, four different rats were observed with greasy rectal area during the study period. No clinical signs of toxicity were observed in the 125 mg/kg/day animals. Body weights in the 125 mg/kg/day group were comparable to the vehicle control group throughout the duration of the assay. Body weights were significantly decreased at 400mg/kg/day (12%, Day 4), and the overall body weight gain was significantly decreased (213%). Uterine weights in the propargite treated groups were comparable to the vehicle controls.

The body weights for the positive control (EE) group were consistent throughout the duration of the assay; overall body weight gain for the EE animals was decreased (198%, not significant) in comparison with the vehicle controls. Absolute wet and blotted uterus weights for the EE group were increased by 164% and 126%, respectively. These increased uterine weights were in the expected range.

The high dose tested in this study (400 mg/kg/day) was adequate based on the observed decreases in body weight and overall body weight gain. No statistically significant changes were seen in uterine weight in this assay. Propargite was negative in the uterotrophic assay.

Hershberger Assay (OECD TG 441, OCSPP 890.1400, level 3)

In a Hershberger assay screening for androgenic activity, propargite in corn oil was administered daily via oral gavage to groups of 56- to 57-day old, castrated male Sprague Dawley rats (8/group) at dose levels of 0 (vehicle), 47, or 150 mg/kg/day. An androgenic positive control group consisting of eight castrated rats exposed to 0.4 mg/kg/day testosterone propionate (TP) by subcutaneous (s.c.) injection was also included as a positive control.

To screen for potential anti-androgenic activity, propargite in corn oil was administered daily via oral gavage to 56- to 57-day old, castrated male Sprague Dawley rats (8/group) at dose levels of 15, 47, or 150 mg/kg/day in conjunction with a daily dose of reference androgen TP at 0.4 mg/kg/day by s.c. injection. The negative control group consisted of eight castrated male rats dosed daily with TP (0.4 mg/kg/day) by s.c. injection in corn oil, and the anti-androgenic positive control group consisted of eight castrated male rats dosed orally with flutamide (FT) in corn oil at 3 mg/kg/day in conjugation with a daily s.c. dose of TP (0.4 mg/kg/day).

For both androgenic and anti-androgenic testing, the animals were dosed for 10 consecutive days and necropsied approximately 24 hours after the final dose administration to determine weights of the five androgen-dependent tissues.

All animals survived until scheduled termination. No clinical signs of toxicity were observed in the 15 or 47 mg/kg/day dose groups of the androgen agonist or antagonist assays. At 150 mg/kg/day, one rat exhibited an un-groomed appearance in the androgen agonist assay. At 150 mg/kg/day (+TP), one rat exhibited an un-groomed appearance and oil fur around the anus, and another rat exhibited an un-groomed appearance in the androgen antagonist assay.

In the androgen agonist assay, body weights and overall body weight gains for the 47 mg/kg/day treatment group were comparable to controls throughout the duration of the assay. At 150 mg/kg/day, body weights were decreased as compared to the controls ($p<0.05$) by 15% on Day 11, and overall (Days 1-11) body weight gains were decreased ($p<0.05$) by 75%. Animals dosed with TP (positive control) had increased ($p<0.05$) overall body weight gains (↑38%) compared to controls.

In the androgen agonist assay, no statistically significant increases were observed in any of the accessory sex organs of propargite-dosed animals. Animals in the TP control group had increases ($p\leq0.05$) in all five accessory sex organ weights. For the vehicle control, the maximum guideline-specified %CV were exceeded for the ventral prostate (48% vs. 45%), Cowper's gland (71% vs. 55%), and glans penis (38% vs. 22%). The maximum guideline-specified %CV was exceeded for the Cowper's gland in the 150 mg/kg/day propargite group (83% vs. 55%). All other %CV values were less than the maximum recommended values.

In the androgen antagonist assay, body weights and overall body weight gains for the 15 mg/kg/day treatment group were comparable to controls throughout the duration of the assay. The overall (Days 1-11) body weight gains were decreased ($p<0.05$) by 26% at 47 mg/kg/day and decreased ($p<0.05$) by 77% at 150 mg/kg/day. Body weight at Day 11 was decreased by 6% in the 47 mg/kg bw/day group and 17% in the 150 mg/kg/day ($p<0.05$) group. Significant ($p<0.05$) accessory Dose-dependent sex organ weight decreases were observed in all propargite-treated groups. At 15 mg/kg/day, the ventral prostate weight was significantly decreased (↓18%) and the levator ani-bulbocavernosus (LABC) weight was significantly decreased (↓16%). At 47 mg/kg/day, the ventral prostate weight was significantly decreased (↓26%) and the LABC weight was significantly decreased (27%). At 150 mg/kg/day, accessory sex organ weight decreases ($p\leq0.05$) were noted as follows: 33% in seminal vesicles; 41% in ventral prostate; and 37% in LABC. Animals dosed with TP + FT (positive control) had decreased ($p\leq0.05$) accessory sex organ weights in all five target tissues as expected. The CVs for all treatment groups were compared to the performance criteria values as stated in the guideline.

In conclusion, propargite was negative for androgenicity in the Hershberger assay as no statistically significant increases were seen in two or more of the five androgen responsive tissue weights in the androgen agonist assay. Propargite was positive for anti-androgenicity in the Hershberger assay, as statistically significant decreases were seen in ventral prostate and LABC weights at the two lower doses in this study in the absence of overt toxicity.

Fish Short-term Reproduction Assay (fish, OECD TG 229, OCSPP 890.1300, level 3)

The 21-day short-term reproduction assay of propargite with fathead minnows (*Pimephales promelas*) was conducted under flow-through conditions. Adult fish (20 spawning groups; 2-3 males and 3-4 females in each group; 6 months old), were exposed to propargite at nominal concentrations of 0 (negative and solvent [0.013 mL/L acetone] controls), 0.2, 2, and 20 µg a.i./L; mean-measured concentrations were <0.02 (<LOQ, controls), 0.2, 1.8, and 18 µg a.i./L. The test system was maintained at 24 to 25°C and a pH of 6.8 to 8.3.

No differences in all endpoints were observed between negative and solvent control groups in this study. All effects are reported based on comparison to the negative control. There were no significant differences ($p>0.05$) between survival of fish in the negative control and treated groups. Clinical signs of toxicity were not reported. Female body weight was significantly increased by 17 and 16% in the low and high treatment groups relative to the negative control; there was 10% body weight increase in the mid treatment group that was not significantly different ($p>0.05$) from the negative control group. Female body length was significantly increased by 7 and 5% in the low and high treatment groups, respectively, compared to the negative control. Male body weights and lengths were not significantly different ($p>0.05$) from the negative control.

Spawning did not occur at least every four days in three and two of the four replicates for the negative and solvent control groups, respectively. Fecundity in the negative and solvent controls averaged 10 (range: 3-15 in replicates) and 13 (range: 7-19 in replicates) eggs/female/reproductive day, respectively. Fertilization was 96 and 95% for the negative and solvent controls, respectively. There was no significant difference ($p>0.05$) in spawning frequency and fecundity between the negative control and treatment groups. Fecundity was 9, 14 and 8 eggs/female/reproductive day for the low, mid, and high treatment groups, respectively. While not statistically different ($p>0.05$) from the negative control, there was a 30% increase in the fecundity in the solvent control. This increase may be due to the lower fecundity observed in the negative control; the overall response of the treatment groups compared to the negative control varied from a 38% increase (high treatment) to a 23% decrease (low treatment) and did not appear to be treatment-dependent. Given the observed increase in fecundity in the solvent control, there is uncertainty as to whether the use of the solvent interfered with the response of the fish.

There were no significant effects ($p>0.05$) on male gonado-somatic indices (GSI) or on male nuptial tubercle scores; tubercles were not noted for females. Female GSI was significantly decreased by 25% only in the low treatment group compared to the negative control. Female vitellogenin (VTG) was significantly increased by 58% at the high treatment level relative to the negative control; however, this increase appears to be due to one female. Plasma VTG of males in treated groups was not significantly different ($p>0.05$) from that of males in the negative control. While not statistically different ($p>0.05$) due to the high variability observed, there were approximate 480 and 1390% increases in average male VTG for the mid and high treatment groups, respectively, compared to the negative control. This observed increase was due to higher VTG levels in two males in the mid treatment group and one male in the high treatment group, as opposed to a response from the population of fish in those treatments. Sex steroids were not measured in this study. Dorsal nape pad observations/measurements were not reported.

Regarding histological effects, a notable delay in ovarian maturation was observed in female fish exposed to the high treatment level, with approximately 60% of females exhibiting a lower developmental stage (2 vs. 3) than the controls and lower treatment groups; one individual with indeterminate sex in the high treatment group displayed a juvenile gonad. Other histological findings not associated with treatment (because they were equally visible across all control and propargite-treated groups) included increased oocyte atresia, testicular degeneration, and potential microsporidia infection. Increased oocyte atresia ranged between 43 and 87% of the females in the control and treatment groups, and testicular degeneration was observed in 33 to 43% of males in the control and treatment groups. It is noted that these findings were minimal or mild (except for

oocyte atresia that was moderate in 4 fish); however, the incident rate of these findings are noteworthy.

In summary, there were no differences in survival, fecundity, fertilisation success, nuptial tubercle score, body weights, blood plasma vitellogenin (VTG) and gonadosomatic index (GSI). The treatment-related lesion observed was a shift in ovary maturation from stage 3 to stage 2 at the highest concentration. However, the effects on ovary maturation may not be considered as population relevant. Propargite was not EAS active.

Amphibian Metamorphosis Assay (OECD TG 231, OCSPP 890.1100, level 3)

In the preliminary test, the 96 hour LC50 was determined to be 24 µg a.i./L with a confidence interval of 21 to 27 µg a.i./L, calculated using the Spearman-Karber method.

The 21-day AMA assay of propargite on amphibian metamorphosis of the African clawed frog (*Xenopus laevis*) was studied under flow-through conditions. Tadpoles, stage 51 and 12 days old post fertilisation at exposure initiation were exposed to propargite at measured concentrations of 0.088, 0.87 and 8.7 µg a.i./L. The study was conducted at 21 to 23 °C using FETAX solution as dilution water. The percentages of late-stage frogs (>NF stage 60) at Day 21 were 33, 34, 36, and 19% for the control, low, mid, and high treatment groups, respectively. These late-stage frogs were not included in the analysis of the Day 21 growth measurements. However, a separate analysis was conducted on the growth data for the late-stage frogs. There were no significant effects (Dunnett; $p>0.05$) on body weight, snout-vent length (SVL), or hind-limb length (HLL) compared to the negative control.

No significant increase or delay ($p>0.05$) of median NF developmental stage was observed. Further, no asynchronous development was observed. Propargite significantly reduced ($p=0.02$, Jonckheere-Terpstra test) Day 7 normalized (for SVL) HLL by 7% in the high treatment group. In the low treatment group, Day 7 SVL was significantly increased ($p=0.04$, Dunnett test) by 7% and Day 7 wet body weight was significantly increased ($p=0.01$, Dunnett test) by 15.5% relative to the negative control. Day 7 wet body weight was also significantly increased ($p=0.02$, Dunnett test) by 14.5% in the mid treatment group compared to the negative control. No significant effects ($p>0.05$) on Day 7 SVL and body weight were observed in the high treatment group. By Day 21, there were no significant effects on HLL, SVL, or body weight at all treatments.

Effects on thyroid gland histopathology included a concentration-dependent increase in the incidence of mild follicular cell hyperplasia and mild follicular cell hypertrophy. In the high treatment group, additional histopathology effects included mild colloid depletion and changes in colloid quality.

Overall, a dose-dependent change in thyroid follicular cell hypertrophy and hyperplasia and in colloid depletion was reported, indicating that propargite interferes with the thyroid pathway.

Pubertal Female Assay (Rat, OCSPP 890.1450, level 4)

Range finding of 0, 50, 75, 100, 125, and 150 mg/kg/day for 10 days via oral gavage showed a significant decrease (21%) in BW at the highest dose. In a Female Pubertal Assay, 16 Sprague Dawley rats/dose group were treated daily via oral gavage (5 mL/kg) with propargite in corn oil at doses of 0 (vehicle), 62.5, or 125 mg/kg/day from post-natal day (PND) 22 to 42 (half the rats in each group) or PND 43 (remaining rats in each group). Animals were examined for vaginal opening (VO) daily beginning on PND 22, and age and weight at day of attainment was recorded. Animals were also examined for estrous cyclicity beginning on day of VO. After sacrifice on PND 42 or 43, total serum levels of thyroxine (T4) and thyroid stimulating hormone (TSH) levels were determined by radioimmunoassay; serum was also analyzed for selected clinical chemistry parameters. Adrenal, liver, pituitary, thyroid, and urogenital organs were weighed, and microscopic examinations were conducted on the ovaries, uterus, thyroid, and kidneys.

At 62.5 mg/kg/day (low dose), relative (to body) kidney weights were increased ($p<0.05$) by 8% and absolute pituitary weights were decreased ($p<0.05$) by 14%. In the male pubertal assay, relative pituitary weight was increased. A closer examination of the

pituitary data in the male and female assays showed that the pituitary weight changes seen in opposite directions (i.e., increase in males and the decrease in females) are likely an artifact due to abnormal control values. Therefore, the pituitary weight changes were not considered to be treatment-related changes in either sex. Additionally, increases ($p<0.05$) were observed in sorbitol dehydrogenase (l7%), and decreases ($p<0.05$) were noted in alkaline phosphatase (31 %) and total protein (14%). No changes in the 62.5 mg/kg/day group were noted in the age or weight at VO, date of first estrus, estrous cyclicity, or uterus and ovary weights. The only microscopic findings in the low-dose group was an increase in the incidence of moderate interstitial cell hyperplasia in the ovaries (7/16 rats vs. 0/16 in control).

In the 125 mg/kg/day (high-dose) group, one rat was observed with piloerection, diarrhea, thinness, hunched posture, and/or a distended abdomen on Days 10 to 15; this rat was euthanized on Day 15. Another rat was found dead on Day 19. All remaining rats survived until scheduled sacrifice, and no clinical signs of toxicity were observed in any of the surviving rats. Final body weights were decreased ($p<0.01$) by 14%, resulting in a 22% decrease ($p<0.01$) in overall (PND 22 to 42) body weight gain. Relative (to body) liver and kidney weights were increased ($p<0.01$) by 16% and 12%, respectively, and absolute and relative pituitary weights were decreased ($p<0.05$, 25% and 16%, respectively). Increased ($p<0.05$) levels of total bilirubin (↑100, and sorbitol dehydrogenase (42%) were observed, and decreased ($p<0.05$) levels of alkaline phosphatase (25%), total protein (9%) and albumin (4%) were noted.

Several reproductive tract/pubertal findings were also observed in the high-dose animals. Mean age at first vaginal estrus (PND 39.1 treated vs. PND 34.7 controls) and age at VO (PND 41.1 treated vs. PND 34.3 controls) were delayed ($p<0.05$), and a 12% increase ($p<0.05$) in weight at day of VO was noted. At termination, 8/14 rats attained VO compared to 14/16 control animals. Decreased ($p<0.05$) weights for the ovary (28%) and uterus (wet and blotted unadjusted for PND 21 weight, 54% and 43%, respectively; blotted adjusted, 42%) were observed. Microscopically, moderate interstitial cell hyperplasia in the ovaries was increased in incidence (10/16 rats versus 0/16 control), moderate to marked uterine atrophy was found in 3/14 rats compared to 0/16 control animals, increases ($p<0.05$) in the number of small follicles (51%) and follicular cysts (7-fold) in the ovary were noted, and the number of corpora lutea was decreased ($p<0.05$) by 63%.

Finally, at the high dose, serum T4 levels were increased ($p<0.05$) by 23%, and thyroid follicular cell height was increased with a corresponding decrease in the colloid area of thyroid follicles. Similar, though reduced, effects were also noted at the low dose. The doses tested were determined to be adequate based on the results of the dose range finding study. Based on these findings, propargite may disrupt the HPG axis and affect thyroid function.

Pubertal Male Assay (Rat, OCSPP 890.1500, level 4)

In a male pubertal assay, 16 Sprague Dawley rats/dose group were treated daily via oral gavage (5 mL/kg) with propargite in corn oil at doses of 0 (vehicle), 62.5, or 125 mg/kg/day from post-natal day (PND) 23 to 53 (half the rats in each dose group) or PND 54 (remaining rats in each dose group). Animals were examined for preputial separation (PPS) daily beginning on PND 30, and age and weight at day of attainment was recorded. Following sacrifice on PND 53 or 54, total serum testosterone, thyroxine (T 4), and thyroid stimulating hormone (TSH) levels were determined by radioimmunoassay; serum was also analyzed for levels of selected clinical chemistry parameters. Adrenal, liver, pituitary, thyroid, and urogenital organ weights were recorded and microscopic examinations of the testes, epididymides, thyroid, and kidneys were performed.

All rats survived to scheduled termination. The following systemic findings were noted at 62.5 mg/kg/day. Salivation prior to dosing was seen in one rat on PND 38. Serum chloride was slightly increased ($p<0.01$; 0.3%) and levels of alanine transferase and alkaline phosphatase were decreased ($p<0.05$; 21% and 28%, respectively). Relative (to body) kidney (8%) and pituitary (15%) weights were increased ($p<0.05$). Additionally, the following microscopic findings were observed in the kidney: minimal to moderate

tubular epithelial cell karyomegaly in 13/16 rats vs. 0 controls; mild hyperplasia and hypertrophy of tubular epithelial cells in 2/16 rats vs. 0 controls; and minimal to mild hyaline droplets in 14/16 rats vs. 1/16 controls (minimal severity).

Additionally at 62.5 mg/kg/day, testosterone levels were decreased ($p<0.01$; 58%). Body weights, body weight gains, and age and weight at PPS were comparable to the control. Serum T4 levels were increased ($p<0.01$; ↑21%), and thyroid gland follicular cell height was increased compared to the control with a corresponding decrease in the colloid area of thyroid follicles.

In the 125 mg/kg/day group, one rat was noted as being thin 24 hours after dose administration from PND 38 until scheduled euthanasia; in addition, this rat was noted as ungroomed on PND 53. Bleeding from the nose was observed in one rat on PND 46 and another rat was noted to have alopecia on the throat on PND 53. Two animals were observed to be thin; one rat on PND 51 and 52 and one rat on PND 54. Final body weights at 125 mg/kg/day were decreased ($p<0.01$) by 23%, resulting in a 29% decrease ($p<0.01$) in overall (PND 23 to 53) body weight gains. Decreases were observed in serum levels of chloride (0.5%), alkaline phosphatase (48%), total protein (7%), and albumin (4%); sorbital dehydrogenase was increased ($p<0.01$; ↑31%). Absolute weights were decreased ($p<0.05$) for the liver (14%), kidney (15%), and adrenals (12%); however, the relative weights of these organs were increased ($p<0.01$; 13%, 11%, and 17%, respectively). Relative pituitary weights were also increased ($p<0.05$; 21%).

Microscopically, the following findings were noted in the kidney: minimal to mild tubular epithelial cell karyomegaly in 16/16 rats vs. 0 controls; mild to moderate hyperplasia and mild hypertrophy of tubular epithelial cells in 16/16 rats vs. 0 controls; and minimal to mild hyaline droplets in 15/16 rats vs. 1/16 controls (minimal severity). Additionally, mean age at PPS was delayed ($p<0.01$) to PND 50.3 vs. PND 45.2 in the controls; body weight at PPS was comparable to the control. Testosterone concentrations were decreased ($p<0.01$; 70%). The weights of the following organs were decreased ($p<0.05$): seminal vesicles (with and without fluid; ↓40% and 35%); ventral prostate (31%); dorsolateral prostate (34%); and levator ani/bulbocavernosus (LABC; 38%). Serum T4 levels were increased ($p<0.01$; ↑34%), but thyroid weights were decreased ($p<0.05$; ↓16%). Thyroid gland follicular cell height was increased with a corresponding decrease in the colloid area of thyroid follicles. Based on these findings, propargite may disrupt the HPG axis and affect thyroid function.

Summary of in vivo results

EATS endocrine activity has been investigated in 6 *in vivo* assays, corresponding to levels 3 and 4 of the OECD CF. EAS activity is tested in the Uterotrophic Assay, Hershberger Assay, Fish Short-term Reproduction Assay, and male and female pubertal assays. Disruption of EAS activity was found in the Hershberger Assay and two pubertal assays. Disruption of the thyroid pathway is showed in two pubertal assays in mammals and one amphibian assay.

Conclusions on the EATS activity

Endocrine activity	EDSP21 /ToxCast	EDSP in vitro assays	TG440	TG441	TG229	TG231	Male pubertal assay	Female pubertal assay
EAS activity	Inconsistent results	negative	negative	Anti-AR	negative		positive	positive
T-activity	Inconsistent results	negative				positive	positive	positive

As shown in the above table, inconsistent EAS activities have been reported in the High-Throughput Screening (HTS) of the EDSP21/ToxCast tests. Test guideline *in vitro* EDSP Tier 1 assays, however, show that propargite is inactive. In contrast, the Hershberger Assay and two pubertal assays showed that propargite disrupted EAS pathways.

Inconsistent results for the thyroid activity were observed in EDSP21 and ToxCast tests. Disruption of the thyroid pathway was observed in one amphibian assay and two rat studies. It is concluded that propargite has potential to induce thyroid activity.

Adverse Affects

Propargite has been investigated in fish, amphibian, and avian toxicity tests. These apical tests are corresponding to levels 3, 4 and 5 assays in the OECD Conceptual Framework. The results of these tests are summarised as follows. Mammalian toxicity tests have been performed in more than 15 different assays, corresponding to OECD CF levels 4 and 5. These test results will be summarised in the human health section and will not be presented here.

Fish

Fish acute toxicity tests have not been included in the OECD CF. For this case, however, information of acute toxicity tests is of help for understanding concentration settings in different chronic toxicity tests. Therefore, the acute toxicity tests are summarized here too.

Acute fish toxicity test (OECD TG 203, bluegill sunfish)

The acute toxicity of propargite to bluegill sunfish was assessed by determining the LC50 over a 96 hour period under continuous-flow conditions. Propargite was added to the test system at nominal concentrations of 0, 0.0625, 0.125, 0.25, 0.5 and 1.0 ppm (respective mean measured concentrations are 0, 0.04, 0.06, 0.181, 0.241 and 0.399 ppm) with a solvent and non-solvent (acetone) control also included. Observations on test fish were made at 1, 3, 6 and 24 hours after test initiation and every 24 hours thereafter. Water quality parameters were measured at test initiation and at 24 hour intervals in all tanks; all quality parameters were within acceptable limits. LC50 values were measured by maximum likelihood estimation compared to the probit model. The 96 hour LC50 value was determined to be 0.081 ppm (mg/L), i.e. 81 µg/L.

Fish, prolonged toxicity test (OECD TG 204, rainbow trout)

The acute toxicity of the test material to rainbow trout was tested under flow-through conditions during a 21 day exposure period. In duplicate test aquaria, twenty organisms were exposed to five concentrations of the test material (18, 27, 42, 65 and 100 µg/L), a dilution water and solvent controls. Concentrations of the test material were maintained in the exposure vessels by introducing approximately 6.3 aquarium volumes per day of newly prepared test solution via an intermittent-flow proportional diluter apparatus. Each replicate solution was sampled and analysed for test material concentration on days 0, 7, 14 and 21 of the exposure period. Based on the results of these analyses, the mean measured test concentrations were 14, 21, 32, 52 and 100 µg/L. Throughout the exposure period, no undissolved test material was observed in any of the exposure vessels.

Biological observations were recorded at test initiation and every 24 hours thereafter. At 96 hour exposure, 100 % mortality was observed in the highest test concentration. The 96 hour LC50 was estimated to be 43 µg/L (95 % C.I. 38-49 µg/L). The LC50 values at 24, 48 and 72 hours were estimated to be >100 µg/L, 84 µg/L (95 % C.I. 70-110 µg/L) and 53 µg/L (95 % C.I. 46-62 µg/L), respectively.

Following 96 hours of exposure, 100 % mortality was observed at the highest test concentration (100 µg a.i./L). Mortalities in the remaining treatments were 85, 20 and 0 %, respectively (52, 32, 21 and 14 µg a.i./L). By test termination, 100 % mortality was also observed at the 52 and 32 µg a.i./L treatment levels while 20 % of the organisms exposed to the 21 µg a.i./L treatment level had died. No mortality was observed in the remaining test concentration of 14 µg a.i./L, however, sublethal effects (e.g. partial or complete loss of equilibrium, darkened pigmentation, erratic swimming and lethargy) were observed among surviving fish in this treatment level. The 21 day LC50 was

estimated by nonlinear interpolation to be 24 µg/L with a 95 % C.I. calculated by binomial probability of 21-32 µg/L. The NOEC was determined to be <14 µg/L.

Fish early-life stage toxicity (OECD TG 210, fathead minnow)

In an early-life stage study with fathead minnow (*Pimephales promelas*), fish were exposed to propargite for 35-days in a flow-through test system. Fish were exposed as fertilized embryos through hatch and early larval development. Nominal test concentrations were 1.8, 3.5, 7.8, 15 and 30 µg/L including both a negative and solvent (acetone) control, with mean measured concentrations of 1.9, 3.2, 7.5, 16 and 28 µg/L. Hatch was 78% or greater in control and treatments and no significant differences were observed. No larvae were remaining at test termination in 28 µg/L treatment group; survival was not affected in the other treatment groups. Wet weight and body length were also not significantly different in the treatment groups (excluding 28 µg/L due to 100% mortality) compared to control at test termination. The NOEC was determined to be 16 µg/L.

Fish full life cycle toxicity test (EPA OPP 72-5, fathead minnow)

Fathead minnow were continuously exposed to five concentrations of propargite, a dilution water control and a solvent (acetone) control for a complete life-cycle (272 days). In addition, their F_1 progeny were continued in exposure for 30 days post-hatch. The nominal concentrations of propargite for this study were 1.8, 3.5, 7.0, 14 and 28 µg/L (mean measured exposure concentrations were 1.4, 2.8, 5.7, 11 and 27 µg/L, respectively, which ranged from 76 to 95 % of the nominal concentrations). Statistical comparisons to determine the significant toxicant effects were made using the pooled data from the dilution water and solvent controls for all endpoints except eggs per female and second generation (F_1) hatching success. For these two endpoints, comparison was made to the solvent control. Dichotomous data were analysed using the appropriate contingency table test, and the continuous data were analysed using Williams' test.

Exposure at 27 µg/L significantly reduced F_0 30 and 59 day post-hatch survival (26 %) as compared to the pooled control survival which was 90 and 91 % on days 30 and 59 post-hatch, respectively. After 59 days of exposure, there was no apparent effect on the length or weight of the exposed fish at any concentration tested below 27 µg/L compared to the controls. At test termination, F_0 survival at 27 µg/L was 20 % compared to pooled control survival (92 %) and was significantly reduced. F_0 growth at all test concentrations below 27 µg/L was comparable to the control. The number of eggs per spawn and spawns per female were also reduced at 27 µg/L. However, no significant difference was established at any test concentration for eggs per female compared to the solvent control.

The number of live F_1 fry at hatch was statistically determined to be reduced at 27 µg/L (66 %) compared to the solvent control (89 %) and following 30 days post-hatch exposure, F_1 larval survival at this treatment level was reduced (0 %) compared to the pooled control (89 %). An effect on the growth (total length and wet weight) of F_1 larval fish at 11 µg/L was statistically established based on comparison to the pooled control. Statistical analysis indicated no significant difference in the total length of larval fish exposed to test concentrations at or below 5.7 µg/L. However, a significant reduction in wet weight was indicated at 2.8 and 5.7 µg/L. The weight difference at 2.8 µg/L was not considered toxicant related as the response did not follow the concentration gradient. At 5.7 µg/L, the mean wet weight was 0.23 g compared to 0.24 g with the pooled control (4 % reduction). This difference was considered biologically insignificant as it is highly unlikely that a 0.1 g reduction in weight would have any impact on the fathead minnow population. The most sensitive indicator of toxicity was the reduced F1 generation growth (total length and wet weight). Based on these data, the NOEC was estimated to be 5.7 µg/L.

Fish Short-term Reproduction Assay (OECD TG 229, fathead minnow)

This study is summarized in the above "in vivo EATS assays".

Summary of fish toxicity tests

Three chronic fish toxicity studies have tested propargite at concentrations between 0.2 and 28 µg/L. Propargite affected survival of fish at concentration of 27 and 28 µg/L in FFLC and in ELS, respectively. Fecundity was not influenced at the high concentration of 27 µg/L in the FFLC. In the FSTRA, propargite influenced ovary histology but not fecundity at the concentration of 18 µg/L. The most sensitive indicator of toxicity was the reduced growth (total length and wet weight) at 11 µg/L in F1 generation. The NOEC was estimated to be 5.7 µg/L.

fish	exposure	Measured cons (µg/L)	endpoints	LC50/NOEC(µg/L)
bluegill sunfish	96h	40, 60, 181, 241, 399	mortality	81
Rainbow trout	21d	14, 21, 32, 52,100	mortality	43 (4d); 24 (21d)
Fathead minnow	35d	1.9, 3.2, 7.5, 16, 28	survival, growth, hatching	16 (survival)
Fathead minnow	21d	0.20, 1.7, 18	survival, fecundity fertilisation success, SSC, BW, VTG, GSI, histology	18
Fathead minnow	272d	1.4, 2.8, 5.7, 11, 27	survival, growth, fecundity, hatching	5.7 (growth)

Amphibian Metamorphosis Assay (OECD TG 231)

The detail of this study is summarized in the above section of EATS endocrine activity. Following information is on adversity only.

No significant increase or delay of median NF developmental stage was observed. Further, no asynchronous development was observed. Propargite significantly reduced Day 7 normalized HLL by 7% in the high treatment group. In the low treatment group, Day 7 SVL and wet body weight were significantly increased by 7% and by 15.5%, respectively. Day 7 wet body weight was also significantly increased by 14.5% in the mid treatment group. No significant effects on Day 7 SVL and body weight were observed in the high treatment group. By Day 21, there were no significant effects on HLL, SVL, or body weight at all treatments.

Avian toxicity studies

Avian Reproduction Text (mallards)

In a one-generation avian reproduction test with mallard ducks, propargite was administered *ad libitum* in the diet of young adult mallards (28 weeks old at test initiation 16 pairs male/female/group) approaching their first breeding season. Diets containing propargite at nominal concentrations of 0, 30, 100 or 300 ppm (measured concentrations <2.0, 43.2, 84.7 and 288.7 ppm) were fed to the adults for 18 weeks. The mallards were observed daily for mortality, abnormal behaviour and signs of toxicity. All adult birds found dead during the study were necropsied. In addition, necropsies were performed on all adults surviving until study termination. Eggs were collected daily and set weekly for incubation beginning at week 12. Weekly throughout the laying period, eggs were collected from every other pen for egg shell thickness measurement. In

addition, effects upon egg production and quality and hatchling health and survivability were also examined.

There were four adult mortalities during the exposure phase; one in the control, one at 30 ppm and two at 300 ppm. The mortalities in the control and 30 ppm groups were not considered to be treatment-related as indicated by findings of a gross necropsy (egg yolk, visceral and intestinal lesions). The same was true for one of the 300 ppm mortalities (egg yolk, air sacculities, body cavity lesions and regressing ovary). However, in the second 300 ppm mortality, necropsy indicated the absence of body fat, inactive ovary, small liver, distended gall bladder, bile stained gizzard and haemorrhagic intestinal lining/contents. This single mortality appeared to be treatment-related. There were no overt signs of toxicity observed in any surviving adults at any concentration. A general observations of some birds appearing thin was made at week 16 in the 300 ppm group. Other non treatment-related signs associated with pen wear and interaction with pen mates included high wing carriage, lower limb weakness and lethargy noted at various concentrations. At necropsy, there was a treatment-related increase in the number of hens exhibiting a regressed ovary at 300 ppm. Also in the 300 ppm group, all females and 11/14 males had atrophied pancreases. Since this lesion was not observed in any of the control birds, this was attributed to treatment. There was no effect on body weight of males in the 300 ppm group or on the males in the 100 ppm group. There was a statistically significant reduction in body weight of 100 ppm females during week 6 and at study termination. There was also a statistically significant reduction in body weight of 300 ppm females at termination (body weight was also reduced by three-fold in 300 ppm males although this was not statistically significant). There were no treatment-related effects on food consumption.

There were no apparent treatment-related effects on reproductive parameters in the 30 and 100 ppm groups. At 100 ppm, there was a slight reduction in the number of hatchlings as a percentage of live three week embryos. The effect was minor and not statistically significant. At 300 ppm there was a marked effect on reproductive performance. Only 53 eggs were laid compared to 626 eggs in the control group. Only 8/14 hens in this group laid and of those eight, only three laid more than ten eggs. Of the 53 eggs laid, two were cracked and the remainder were either soft shelled or abnormal resulting in no eggs being available to set for this group. There were no effects on body weight of hatchlings or 14 day old offspring in the 30 and 100 ppm groups. There were no offspring from the 300 ppm group. The NOAEL was determined to be 84.7 ppm, with a LOAEL of 288.7 ppm, based on the decreases in reproductive parameters in the high-dose group.

Avian reproduction test (bobwhite quail)

A one-generation bobwhite reproduction study was conducted on propargite in compliance with EPA OPP 71-4. Propargite was administered ad libitum in the diet of young adult bobwhite (18 weeks old at test initiation) approaching their first breeding season. Diets containing propargite at nominal concentrations of 0, 100, 300 or 1000 ppm (measured <2.0, 84.7, 288.7 and 949.6 ppm) were fed to the 16 pairs (male/female/group) for 20 weeks. The bobwhite was observed daily for mortality, abnormal behaviour and signs of toxicity. All adult birds found dead during the study were necropsied. In addition, necropsies were performed on all adults surviving until study termination. Eggs were collected daily from the onset of egg production and set weekly for incubation beginning at week 13. Weekly throughout the laying period, eggs were collected from every other pen for egg shell thickness measurement. In addition, effects upon egg production and quality and hatchling health and survivability were also examined.

There were no treatment-related mortalities in adults in any test group. One incidental mortality occurred in each of the 100 and 1000 ppm groups and the control but these were attributed to physical injuries unrelated to treatment. There were no overt signs of toxicity observed in adults at any test concentration. Clinical signs unrelated to treatment included wing droop and ruffled feathers associated with pen wear and interaction with pen mates. At necropsy of adults, no treatment-related lesions were observed. There was

no effect on body weight of adult birds at 100 and 300 ppm nor on males of the 1000 ppm group. However, there was a slight (statistically significant) weight reduction among females of the 1000 ppm group at week 8 and upon termination. There was no treatment-related effects on feed consumption.

There were no apparent treatment-related effects on reproductive parameters in the 100 and 300 ppm groups. At 1000 ppm diet, there was a significant reduction in survivability of offspring (14 day old hatchlings). There was a slight reduction in body weight of hatchlings and 14 day survivors at 1000 ppm. In addition, there was a very slight reduction in egg shell thickness of eggs from the 1000 ppm group. The NOEC was determined to be 300 ppm.

Summary of the chronic avian reproduction tests

Two chronic avian reproduction toxicity tests are available. One study showed that the highest test concentration decreased body weights and there was a profound effect upon reproductive performance in mallard ducks. The NOEC was determined to be 100 ppm (equivalent to 13.5 mg/kg bw/day). In another study in bobwhite quail, there was a slight decrease in the survivability of offspring. The NOEC was determined to be 300 ppm (equivalent to 142 mg/kg bw/day).

Species	Doses (ppm)	Body weight (m/f)	Food consumption	# hens laying eggs	# eggs/female	Eggs cracked %	14d-surviors/chicks hatched%
Duck	30	1127/1157	168	16	41	3	99
Duck	100	1122/1059*	147	16	38	2	98
Duck	300	1106/995*	157	8*	4*	4	0*
Quail	100	203	27	16	38	4	94
Quail	300	195	29	16	38	4	91
Quail	1000	197	28	15	35	3	83*

*, significant difference ($p < 0.05$)

Conclusions on adversity

Three chronic fish toxicity tests, corresponding to levels 3, 4 and 5; one amphibian metamorphosis assay (level 3), and two avian reproduction toxicity tests (level 4) are available. In addition to the effects on survival in fish and birds, propargite decreased growth/body weight in fish, amphibians, and birds. Effects on reproduction have been observed in birds.

7.10.2. Endocrine disruption - Human health

Similar to the above section of endocrine disruption – Environment, the basis of this assessment for human health is the WHO definition on endocrine disruptor with reference to the ECHA/EFSA guidance on endocrine disruptor for pesticides and biocides. The sources of data are:

1. registration dossier in the ECHA website
2. EFSA evaluation reports
3. US EPA EDSP21 Dashboard and ToxCast database
4. literature search in pubmed

EATS Endocrine activity
Details can be found in the the section of endocrine disruption – Environment.

Adverse effects
Propargite has been extensively investigated in mammalian tests at levels 4 and 5. These mammalian tests were performed before 2000. Some of EATS-mediated endpoints were not included in the earlier version of mammalian test guidelines. The following summary focuses on the adverse effects relevant to the ED identification only.

Female Pubertal Assay (Rat, OCSPP 890.1450, level 4, performed in 2011)

Brief summary can be found in the above section of in vivo EATS activity. Overall, propargite induced adverse effects on ovary at low and high dose. At the high dose, it decreased uterus and body weights, delayed age at first vaginal estrus and opening, induced changes in thyroid gland histology and T4.

Pubertal Male Assay (Rat, OCSPP 890.1500, level 4, performed in 2011)

Brief summary can be found in the section of in vivo EATS activity. In summary, changes were observed in pubertal development including delayed PPS, decreases in weights in most, but not all, of the androgen dependent tissues (i.e., seminal vesicle plus coagulating gland with and without fluid, ventral prostate, dorso-lateral prostate, and LABC) along with a decrease in serum testosterone (at 62.5 and 125 mg/kg propargite). There was an increase in circulating T4 concentration with no corresponding change in TSH. Histopathological changes that occurred in the thyroid gland in both the low (62.5) and high (125) dose groups are a sensitive indicator of thyroid gland toxicity.

90-day repeated dose oral studies (OECD TG 408, rats, level 4, performed in 1987)

Rats were fed diets containing 0, 100, 1000 or 2000 ppm (around 8.3, 83, and 166 mg/kg bw/d) propargite for 13 weeks. There were no deaths during the 13 week feeding period. Dose dependent male and female body weights were observed for 1000 and 2000 ppm. Food consumption for males in the 1000 ppm group and males and females in the 2000 ppm group were significantly lower than those of controls for the entire study. Males in the 100 and 2000 ppm groups had significantly higher red blood cell count, while 2000 ppm males had significantly higher haemoglobin. Glucose was significantly reduced in males and females receiving 1000 and 2000 ppm. Urea nitrogen was significantly increased, while creatinine was significantly reduced in the 2000 ppm males and females, although these differences were small. Total protein, albumin and globulin were significantly lower in 2000 ppm males and 1000 and 2000 ppm females. The albumin to globulin ratio was significantly higher in males and females administered 2000 ppm. Calcium was lower in males in females in the 2000 ppm group, although the difference was only significant in the females. Animals administered 1000 and 2000 ppm

had significantly lower terminal body weights and tended to have corresponding lower absolute organ weights. Statistically, however, only the 2000 ppm rats had significantly reduced kidney weights, while significant lower liver and testis weights were only seen in this group's males. Organ to body weight percentages for all organs were significantly higher in animals from the 1000 and 2000 ppm groups. There were no treatment-related macro- or microscopic findings. The NOAEL was determined to be 100 ppm, which is considered to be equivalent to 7.1 mg/kg/day in males and 8.3 mg/kg/day in females.

Repeated dose toxicity test in dogs (non-guideline study)

Groups of three male and three female beagle dogs were administered propargite in the diet at 0 and 2000-2500 mg/kg for a period of 13 weeks (2000 mg/kg during weeks 1-3 and 2500 mg/kg during weeks 4-13). Weight of thyroid, heart, liver, spleen, kidneys, adrenals and testes were measured and a microscopic examination was carried out on a range of tissue types. Signs of apparent propargite effects encountered among the test animals were decreased appetite and body weight loss of 0.7 to 3.6 kg. The test animals were generally comparable with the controls regarding appearance, behaviour, elimination, results of clinical laboratory studies, organ weights, organ/body weight ratios and gross necroscopy findings. Histopathological examination revealed increased amount of pigment in the reticuloendothelial cells of the livers and increased haemosiderosis of the spleen among the treated animals. Based on the reductions in body weights compared to initial values, it can be concluded that the NOAEL is 2000 ppm (approximately equivalent to <50 mg/kg bw/day).

Developmental toxicity study (OECD TG 414, rabbits)

Two rabbit developmental toxicity tests are available. In one test, New Zealand White rabbits were dosed with 0, 2, 4, 6, 8 and 10 mg/kg/day propargite by oral gavage as a single daily dose on days 7 to 19 of gestation. Caesarean examinations were performed on all surviving females on gestation day 29 followed by teratologic examinations. 8 and 10 mg/kg/day does exhibited evidence of maternal toxicity with respect to abortions at the 10 mg/kg/day level and body weight inhibition/loss during the treatment period at both levels (details see Annex II). There were malformed (fused) sternebrae in 2 and 9 kits respectively in the 8 and 10 mg/kg/day groups. This was the only evidence of developmental toxicity. The NOEL was determined to be 6 mg/kg/day for both maternal and developmental toxicity.

In another rabbit developmental toxicity test, rabbits were received propargite by oral intubation at 2, 6, 10 and 18 mg/kg bw/day from day 6 to day 18 of gestation. Maternal, ovarian, uterine, litter and foetal data were evaluated for evidence of treatment-related effects. A dose-related pattern of weight loss was noted in the 6, 10 and 18 mg/kg bw/day groups for days 6-18 and 0-18; this difference was statistically significant for the highest-dose group, with the mean body weight of 3933 and 3066 g in control and the highest dose group, respectively at day 18. The mean implantation efficiency (as a percent) was lower in all treated groups and appeared to be dose-related. The mean incidence of resorptions (as percent) was twice as great in the 10 and 18 mg/kg bw/day groups as compared to the control group. The mean number of live foetuses per litter was slightly to moderately lower in all treated groups; the incidence of foetal viability (as a percent) was lower in the 10 and 18 mg/kg bw/day groups. No statistical differences were noted in the live foetal weights and lengths; however, male and female body weights and the length of the female foetuses of the 18 mg/kg bw/day group were lower as compared to controls. These findings are consistent with foetotoxicity of the test material. Increased visceral and skeletal findings were noted in the three highest dose groups and included the following statistically significant findings: hydrocephaly in the highest-dose group, lagging ossification in the skull in the 6 and 10 mg/kg bw/day groups and maligned or fused sternebrae in the 10 mg/kg bw/day group. The absence of statistical findings for the 18 mg/kg bw/day group in the latter two instances is considered to be due to the small number of foetuses for examination. Under the

conditions of this study, a NOEL was observed at 2 mg/kg bw/day. It is noted that thyroid gland weight and histology, hormones were not investigated in this study.

Developmental toxicity study (OECD TG 414, rats)

Two rat developmental toxicity tests are available. In one test, mated female rats were dosed with 6, 12, 18, 25 and 105 mg/kg/day propargite orally by gavage as a single daily dose on days 6 through 15 of gestation. The control group received vehicle only on a comparable regime. On gestation day 20, cesarean section examinations were performed on 20 gravid females from each group followed by teratologic examinations. The remaining animals were allowed to deliver. These females and pups were observed until lactation day 21 and subsequently were necropsied.

Maternal toxicity occurred at 105 mg/kg/day and manifested as anogenital and body staining and significantly inhibited body weight gains during treatment. Body weight was also significantly reduced on gestation days 9, 12, 16 and 20 (2.5-5.5 %). Body weight was also significantly reduced in this group on day 29, after removal of the uterus). Cesarean sections parameters, malformations and developmental variations were all comparable between treatment and control groups. Post-natal pup mortality by litter was increased significantly at 105 mg/kg/day on day 7 compared to controls but this effect did not endure and all treatment groups were comparable to the controls at weaning. The NOEL was determined to be 25 mg/kg/day for maternal and developmental toxicity. It is noted that thyroid gland weight and histology, hormones were not investigated in this study.

In another rat developmental toxicity test, propargite had no dose-related effects on implantation, numbers of live and dead foetuses or numbers of resorption sites per dam. Propargite exhibited an increase in maternal toxicity and mortality at 105 mg/kg but showed no effect on dam body weights or weight gains during gestation. No dose-related visceral abnormalities in foetuses were ascribed to the test material. Skeletal examinations of the foetuses showed a significant increase in the percentage of litters with incomplete vertebrate and incomplete skull closure at 105 mg/kg/day as well as an increase in missing sternebrae and retarded hyoid development at both 25 and 105 mg/kg/day.

Chronic toxicity/Carcinogenicity

There are several chronic feeding studies in rats, mice and dogs which will not be decribed in further details as they did not show any ED related effects relevant for the scope of this substance evaluation.

Two-generation reproductive study in rats (OECD TG 416, performed in 1998)

Dose levels were selected based on results from a chronic study in rats in which 800 ppm was shown to be the maximum tolerated dose, and minimal effects were seen at 100 ppm. Groups of 25 male and 25 female immature albino rats (F0 animals) were fed diets that contained 0, 80, 400 or 800 ppm (around 0, 4, 20, 40 mg/kg bw/day) for 10 weeks premating and throughout mating, gestation, lactation and weaning of the F1a pups (note, the F0 generation had the F1a and F1b litter; the F1b generation had the F2a and F2b litters).

Body weights and cumulative body weight gains were significantly lower than those of the controls at the 400- and 800-ppm dose levels during both generations for males and females premating, for males postmating, and for females during gestation and lactation. Body weights for males and females in the 400-ppm groups were generally 5 to 10 % lower than those of the controls. When body weights for animals in the 800-ppm groups were compared with those of the controls, F0 males were 9 to 19 % lower, F0 females were 5 to 18 % lower, F1b males were 26 to 29 % lower and F1b females were 15 to 22 % lower.

During the F0 generation, food consumptions were significantly (approximately 7 %) lower than those of the controls for the 400-ppm males (Weeks 0 to 1, 4 to 5, and 8 to 9) and for the 400-ppm females (Weeks 6 to 7). Food consumptions for the 800-ppm F0 males and females were significantly (approximately 10 to 20 %) lower than those of the controls throughout most of the premating phase. During the F1b generation, food consumptions were significantly (approximately 7 %) lower than those of the controls for the 400-ppm males (Weeks 2 to 10) and significantly lower than those of the controls for the 400-ppm females (9 to 19 %) and 800-ppm males (19 to 25 %) and females (17 to 31 %) throughout most of the premating phase.

There were no adverse significant differences from controls in mating or male or female fertility indices during breeding for the F1a, F1b, F2a, and F2b litters. There were no significant differences from controls in female gestation indices or mean days to mate for the F1a, F1b, F2a, and F2b litters.

- During the F1a, F1b, F2a, and F2b litters, there were no significant differences from controls for number of pups per litter or for pup (male and female) sex ratios. In general, the mean pup weights for most litters were significantly (approximately 10 %) lower than those of the controls at the 400-ppm dose level for Lactation Days 7, 14, and 21 and significantly lower than those of the controls at the 800-ppm dose level for Lactation Days 0, 4, 7, 14, and 21. Pup weights in the 800-ppm group on Lactation Day 21 were 36 to 43 % lower than those of the controls.

There were no test material-related macroscopic or microscopic changes. It is noted that thyroid gland weight and histology, hormones were not investigated in this study.

When the test material was administered to rats continuously in the diet through 2 generations (2 litters per generation) at doses up to and including 800 ppm, the only treatment-related effects were decreased body weights, body weight gains and food consumptions in males and females at 400 and 800 ppm of the F0 and F1b generations.

Summary of adversity

Toxicity tests at level 4 and 5 are available. Two level 4 tests, male and female pubertal assays, have studied EATS-mediated endpoints. They showed that propargite induced adverse effects on pubertal development in females (ovary, uterus and vaginal estrus and opening and body weight) and in males (PPS, seminal vesicle plus coagulating gland with and without fluid, ventral prostate, dorso-lateral prostate, and LABC, and testosterone). These tests showed also that propargite decreased thyroid gland weight, altered thyroid gland histology and increased T4 and therefore gives a strong indication that propargite is an endocrine disruptor. In the other available level 4 and 5 tests no clear signs for ED-related adversity were observed. However, it is to be noted that t majority of these studies did not investigate changes in hormones e.g. T3/T4/TSH, did not include thyroid gland histology/weights .

7.10.3. Conclusion on endocrine disrupting properties

ED for environment

As the above adverse effects observed in two pubertal assays are not population relevant, the available evidence in mammals is not enough for the identification of endocrine disruptor for the environment. Propargite has been tested in three chronic fish toxicity tests, one amphibian test and two avian reproduction tests. In contrast to the observations in mammals, there are no observations in fish indicating anti-androgenicity and disruption of the HPG axis. It is noted that the fish test may have limitation in detecting anti-androgenicity. Propargite induced population relevant effects on survival and growth in fish and birds as well as reproduction effects in birds. These endpoints are considered as "sensitive to, but not diagnostic of, EATS". Thyroid-related effects were observed in the absence of systematic toxicity in the amphibian metamorphosis assay (AMA). The population relevant adverse effects on growth have been only observed at

day 7 but not at day 21 in this study. These results in the AMA suggest that the adverse effects on growth induced by propargite may be mediated by the thyroid pathway.

ED properties of propargite have been evaluated in the US EDSP. It is concluded that there is a lack of convincing evidence for potential interaction with the EAS pathways for the environment; there is evidence for potential interaction with the thyroid pathways for the environment. Larval Amphibian Growth and Development Assay (LAGDA) is recommended for further testing because no long term studies are available for potential adverse effects on amphibians. This substance was discussed in the ECHA ED expert group on 7 October 2019. The group considered that a weight of evidence approach may be enough for the ED identification. LAGDA could be considered if there was still a need to confirm adversity. The eMSCA therefore considers that a Larval Amphibian Growth and Development Assay (LAGDA) would provide definitive information to allow conclusions to be drawn about the potential for ED-mediated adverse population-relevant effects in amphibians. However, as stated above, propargite is only produced and formulated at one facility in Europe, at which risk mitigating measures are in place which, according to the chemical safety report of the registrant, are sufficient to avoid emission to water and air. The potential emission to soil is very low. In Europe it is prohibited to place propargite on the market or use plant protection products containing propargite. All the production is exported outside Europe. Consequently, under these circumstances no risk can be identified in Europe that would require further testing. Should there be new registrations, new uses for propargite (change of circumstances) or should the local inspectors report that the emissions are substantial and contrary to the low environmental exposure reported in the chemical safety report, the substance can be put again in the CoRAP to obtain further information on the endocrine disruption potential for the environment.

ED for human health

Propargite has been sufficiently tested for EATS endocrine activity. These tests include EDSP21/ToxCast assays, *in vitro* and *in vivo* assays (levels 2, 3 and 4). Two tests, male and female pubertal assays, have studied EATS-mediated endpoints. They showed that propargite induced adverse effects on pubertal development in females (ovary, uterus and vaginal estrus and opening and body weight) and in males (PPS, seminal vesicle plus coagulating gland with and without fluid, ventral prostate, dorso-lateral prostate, and LABC, and testosterone). These effects give a stong indication that propargite is an endocrine disruptor via disruption of EAS modalities. These two tests showed also that propargite decreased thyroid gland weight, altered thyroid gland histology and increased T4 and therefore gives a strong indication that propargite is an endocrine disruptor.

No reproductive effects have been observed in the two-generation toxicity test at doses up to 40 mg/kg bw/day. However, in these tests numerous EATS mediated parameters, e.g. thyroid hormones and thyroid histology, have not been examined. Consequently, the potential adversity of the endocrine disrupting mode of actions identified is still not fully investigated, such as developmental neurotoxicity. This information could be obtained in performing an OECD TG 426 in which also higher doses can be tested as done in the available two-generation study.

Propargite is only produced and formulated at one facility in Europe. In Europe it is prohibited to place propargite on the market or use plant protection products containing propargite. The total production is exported outside Europe. Consequently, there is no exposure to consumers, but the workers may be exposed. According the CSR, for the production and formulation several RMMs are in place to minimize the exposure to workers. Considering that the production and formulation is restricted to one site, further testing is not considered proportionate. Nevertheless, the evaluating Member State strongly recommends that the registrant seeks for further reduction of the exposure when feasible and monitors that the instructions for personal protection are followed by the workers, in view of the strong indications for endocrine disruptive properties. Should there be new registrations or new uses for propargite (change of circumstances) the

substance can be put again in the CoRAP to obtain further substantiate the endocrine disruption potential for the human health.

7.11. PBT and VPVB assessment

In sections 7.7 and 7.8, it was concluded that propargite meets the T and vP criteria. For bioccumulation, no conclusions can be drawn in absence of reliable data. The eMSCA therefore considers that a new bioaccumulation study according to OECD guideline 305 would provide definitive information to allow conclusions to be drawn about the bioaccumulation potential of propargite. However, propargite is only produced and formulated at one facility in Europe, at which risk mitigating measures are in place that, according to the chemical safety report of the registrant, are sufficient to avoid emission to water and air. The potential emission to soil is very low. In Europe it is prohibited to place propargite on the market or use plant protection products containing propargite. All the production is exported outside Europe. Consequently, under these circumstances no risk can be identified in Europe that would require further testing. Should there be new registrations, new uses for propargite (change of circumstances) or should the local inspectors report that the emissions are substantial and contrary to the low environmental exposure reported in the chemical safety report, the substance can be put again in the CoRAP to obtain further information on the potential PBT/vPvB properties.

7.12. Exposure assessment

See section 7.10.3 and 7.11

7.13. Risk characterisation

Not applicable (See section 7.10.3 and 7.11)

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7.15. Abbreviations

AMA	Amphibian metamorphosis assay
AR	Androgen receptor
CLP	Classification and labelling
CoRAP	Community rolling action plan
CCH	Compliance Check
DMSO	Dimethyl sulfoxide
DFOP	Double First-Order in Parallel
ELS	Early-life stage
ED	Endocrine disruption/disruptor
EDSP	Endocrine Disruption Screening Program
EATS	Estrogenic, androgenic, thyroidal and steroidogenic
ER	Estrogen receptor
FFLC	Fish full life cycle
FSTRA	Fish short term reproduction assay
GSI	Gonado-somatic indices
HTS	High-Throughput Screening
HLL	Hind-limb length
LABC	Levator ani/bulbocavernosus muscle complex
LAGDA	Larval Amphibian Growth and Development Assay
LSC	Liquid scintillation counting
OECD	Organisation for Economic Co-operation and Development
OECD CF	OECD Conceptual Framework
PND	Post-natal days
RMM	Risk management measure
TBPC	p-tertiobutylphenoxycyclohexan-1-ol
SFO	single first-order
SVL	Snout-vent length

s.c.	Subcutaneous
SVHC	Substances of very high concern
TG	Test guideline
TP	Testosterone propionate
T4	Thyroxine
TSH	Thyroid stimulating hormone
VTG	Vitellogenin
VO	Vaginal opening