Justification for the selection of a substance for CoRAP inclusion

Substance Name (Public Name):	propargite
Chemical Group:	
EC Number:	219-006-1
CAS Number:	2312-35-8
Submitted by:	Bureau REACH, RIVM, the Netherlands
Date:	17/03/2015

Note

This document has been prepared by the evaluating Member State given in the CoRAP update.

Contents

1 IDENTITY OF THE SUBSTANCE

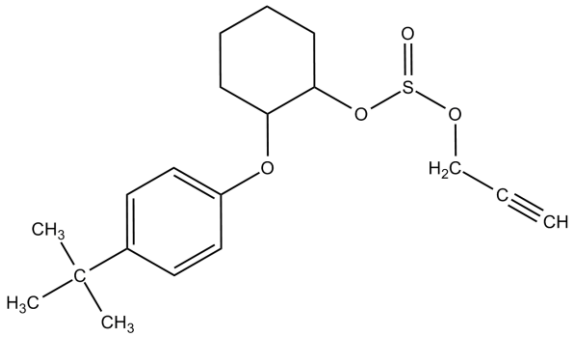
1.1 Other identifiers of the substance

Table 1: Substance identity

EC name:	propargite
IUPAC name:	2-(4-tert-butylphenoxy)cyclohexyl prop-2-ynyl sulphite
Index number in Annex VI of the CLP Regulation	607-151-00-7
Molecular formula:	C19H26O4S
Molecular weight or molecular weight range:	350.5
Synonyms/Trade names:	Omite and Comite

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

Structural formula:



1.2 Similar substances/grouping possibilities

none

2 CLASSIFICATION AND LABELLING

2.1 Harmonised Classification in Annex VI of the CLP

Table 2: Harmonised classification

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	2-(4-tert-butylphenoxy) cyclohexyl prop-2-ynyl sulphite	219-006-1	2312-35-8	Skin Irrit 2 Eye Dam. 1 Acute Tox. 3 Carc. 2 Aquatic Acute 1 Aquatic Chronic 1	H315 H318 H331 H351 H400 H410	M=10	

2.2 Self classification

- In the registration: None. The harmonised 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

2.3 Proposal for Harmonised Classification in Annex VI of the CLP

Not relevant

3 INFORMATION ON AGGREGATED TONNAGE AND USES

From ECHA dissemination site		
☐ 1 – 10 tpa	☐ 10 – 100 tpa	☒ 100 – 1000 tpa
1000 – 10,000 tpa	☐ 10,000 – 100,000 tpa	☐ 100,000 – 1,000,000 tpa
☐ 1,000,000 – 10,000,000 tpa	☐ 10,000,000 – 100,000,000 tpa	☐ > 100,000,000 tpa
☐ <1 . . . . . >+ tpa (e.g. 10+ ; 100+ ; 10,000+ tpa)		☐ Confidential

☐ Industrial use	☒ Professional use	☐ Consumer use	☐ Closed System
The substance is used in formulation of plant protection products.			

4 OTHER COMPLETED/ONGOING REGULATORY PROCESSES THAT MAY AFFECT SUITABILITY FOR SUBSTANCE EVALUATION

☐ Compliance check, Final decision	☐ Dangerous substances Directive 67/548/EEC
☐ Testing proposal	☐ Existing Substances Regulation 793/93/EEC
☒ Annex VI (CLP)	☒ Plant Protection Products, Regulation (EC) No 1107/2009 (repealing Regulation 91/414/EEC)
☐ Annex XV (SVHC)	☐ Biocidal Products Directive 98/8/EEC ; Biocidal Product Regulation (Regulation (EU) 528/2012)
☐ Annex XIV (Authorisation)	☐ Other (provide further details below)
☐ Annex XVII (Restriction)	
The index number for CLP is 607-151-00-7. Propargite is an insecticide used to control mites on a variety of field, fruit, and vegetable crops, as well as ornamentals. The substance has not been approved as active substance under Regulation (EC) no 1107/2009 and is hence banned for pesticide use in EU (cfr. Commission Regulation (EU) no 73/2013)	

5 JUSTIFICATION FOR THE SELECTION OF THE CANDIDATE CoRAP SUBSTANCE

5.1 Legal basis for the proposal

☒ Article 44(2) (refined prioritisation criteria for substance evaluation)

☐ Article 45(5) (Member State priority)

5.2 Selection criteria met (why the substance qualifies for being in CoRAP)

☐ Fulfils criteria as CMR/ Suspected CMR

☐ Fulfils criteria as Sensitiser/ Suspected sensitiser

☒ Fulfils criteria as potential endocrine disrupter

☒ Fulfils criteria as PBT/vPvB / Suspected PBT/vPvB

☐ Fulfils criteria high (aggregated) tonnage (*tpa > 1000*)

☐ Fulfils exposure criteria

☐ Fulfils MS's (national) priorities

5.3 Initial grounds for concern to be clarified under Substance Evaluation

Hazard based concerns		
CMR ☐C ☐M ☐R	Suspected CMR[1] ☐C ☐M ☐R	☒ Potential endocrine disruptor
☐ Sensitiser	☐ Suspected Sensitiser[1]	
☐ PBT/vPvB	☒ Suspected PBT/vPvB[1]	☐ Other (please specify below)
Exposure/risk based concerns		
☐ Wide dispersive use	☐ Consumer use	☐ Exposure of sensitive populations
☐ Exposure of environment	☐ Exposure of workers	☐ Cumulative exposure
☐ High RCR	☐High (aggregated) tonnage	☐ Other (please specify below)

It is noted that propargite is included in the List of Chemicals for Initial Tier 1 Screening in the US EPA endocrine disrupting screening program (EDSP) in 2009.

Propargite is a data-rich substance, with the production in Italy. Except a few studies absent, the dossier contains physical and chemical information, toxicological information and ecotoxicological information required at tonnage of 1000 tpa (Annex X). A few studies are not available, which, however, does not influence the evaluation. For example, a reproductive/developmental toxicity screening test (OECD 421 or 422 is not available in the dossier of propargite. However, both a two-generation reproductive toxicity test and a developmental toxicity test are available in the dossier.

Physical-Chemical Properties

Propargite is an oily, viscous liquid with a strong, sweet odour and a brownish yellow colour at room temperature. Decomposed at 210ºC (727.4 torr) without any evidence of boiling, the substance solidified on cooling but exhibited no distinct freezing point above -70ºC. Measured partition coefficient between octanol and water (log K_{ow}) is 5.7. Vapour pressure is determined to be < 4.04 x 10E-5 Pa at 20ºC. Measured water solubility is 0.215 mg/L at 20 °C.

PBT assessment

Propargite is not readily biodegradable in the modified Sturm Test (OECD 301B). In the simulation tests, the overall DT50 was determined to be 18.3-22.5 days. Given the chemical structure, we have some doubts on the outcome of the simulation study. It is concluded that Propargite may be P and further evaluation of the simulation studies is needed.

Propargite has a log Kow of 5.7. The tested BCF value is 1840. The substance is considered borderline B. Propargite is considered as T according to the CLP. In summary, Propargite is considered to be a potential PBT substance.

[1] CMR/Sensitiser: known carcinogenic and/or mutagenic and/or reprotoxic properties/known sensitising properties (according to CLP harmonized or registrant self-classification or CLP Inventory)
Suspected CMR/Suspected sensitiser: suspected carcinogenic and/or mutagenic and/or reprotoxic properties/suspected sensitising properties (not classified according to CLP harmonized or registrant self-classification)
Suspected PBT: Potentially Persistent, Bioaccumulative and Toxic

Human Health

Toxicokinetics

Toxicokinetics were based on 16 mouse and rats studies. Propargite is rapidly and extensively absorbed, metabolised and eliminated from the bodies of rats and mice. At low dose levels, peak urinary excretion is typically within 0-24 hours of dosing and accounts for around 50-60% of administered dose, whereas peak faecal excretion typically occurs within 0-48 hours and accounts for around 35-60% of administered dose. Urinary and faecal elimination is usually near complete (>93%) by 48 and 72 hours post-dose respectively. The actual extent/rate/route of absorption and elimination is dependent upon sex, dose level and species.

Acute toxicity, irritation and sensitization

The oral and dermal LD50 of the substance was 2800 mg/kg bw in rats and >4000 mg/kg bw in rabbits, respectively. The LC50 after inhalation exposure is 0.89 mg/L in rats. There are one GLP compliant standardised skin irritation study and one standardised eye irritation test. Propargite was determined to be irritating to skin and eyes. Two studies using guinea pig are available for skin sensitization. Propargite was determined to be non-sensitising.

Repeated dose toxicity

Five oral and one dermal repeated dose toxicity tests are available for propargite. The details are as follows:

The key study was done by Atkinson et al. Propargite was administered orally at dose levels of 160, 1250 and 2500 ppm (5.3, 38, 44 mg/kgbw/day) for a period of 12 months to six dogs per sex per group. The high-dose level was reduced to 1875 ppm at week 9 as a result of excessive body weight loss. Physical observations, ophthalmoscopic examinations, body weight, food consumption measurements, hematology, clinical chemistry and urinanalysis were performed on all animals pretest and at selected intervals throughout the study. At the end of the study, all survivors were sacrificed, selected organs were weighed and organ/body weight ratios calculated. Complete gross post-mortem examinations and histopathological examinations of selected tissues were conducted on all animals.

Treatment with the test material at doses up to 1875 ppm for one year did not produce any ocular abnormalities or differences in clinical chemistry or urinanalysis parameters. Two high-dose animals died during the study; the deaths were attributed to marked body weight loss and this was considered to be treatment-related. Physically the high-dose animals were thin over the majority of the study period and were frequently noted as dehydrated over the last three months of the study. Marked decreases in group mean body weight and body weight gain were noted in the mid- and high-dose groups compared to the controls. Controls gained approximately 2 kg over the study period, the mid-dose group gained very little weight (<0.3 kg) while high-dose males and females lost 2.9 and 2.6 kg respectively. The decreased weight gain is most likely due to decreased food consumption. Erythrocyte count and associate hematocrit and haemoglobin levels were significantly decreased compared to controls in high-dose males and females at months 3, 6 and 12 and in mid-dose males at months 6 and 12. Platelet counts were elevated from controls in the 1250 and 1875 ppm females at all intervals and in high-dose males at 6 and 12 months. Organ to body weight ratios were increased from controls predominantly in the high-dose animals and occasionally in the mid-dose animals. The differences were attributed to low body weights. Microscopic examination of tissues revealed treatment-related findings in the lungs, thymus and bone marrow. Red/tan/white foci were noted in the lung of high-dose males. Microscopic examination revealed these foci to be areas of congestion or aerosol subacute/chronic inflammation. Involution of the thymus occurred with slightly greater severity and incidence than controls in mid-dose females and high-dose males and females. Erythroid/myleoid depletion/atrophy of the bone marrow also occurred with a greater incidence and severity in high-dose animals compared to controls. The NOAEL was determined to be 160 ppm (equivalent to 5 mg/kg/day).

In one supporting study, propargite was fed to three male and three female dogs at a dietary levels of 2000 (week 1-3) and 2500 ppm (wees 4-13) for 13 weeks. Decreased appetite and body weight loss were observed. 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. However, the test animals showed a slight trend towards an elevated serum glutamic-oxaloacetic transaminase and liver/body weight ratios for the test animals tended to be slightly elevated in comparison with the controls. Histopathological examination revealed increased amount of pigment in the reticuloendothelial cells of the livers and increased hemosiderosis of the spleen among the treated animals.

In another supporting study, the repeated-dose toxicity (oral) of propargite was determined in a feeding study. Dogs were administered propargite for two years in the diet at 0, 100, 300 and 900 mg/kg. Under the conditions of the test, there were no treatment related effects on dogs. Appearance, behaviour, survival, growth, haematology and blood/urine chemistry, organ weights, lesions observed at gross necropsy and during microscopic examination were all comparable to the control animals. No tumours were found in any dogs. The NOEL was determined to be 900 mg/kg diet.

In the rat supporting study, rats were fed diets containing 0, 100, 1000 or 2000 ppm test material for 13 weeks. Body weights, food consumption and overt signs of toxicity were recorded during the study; blood was collected before necropsy for clinical pathology evaluation. Gross changes in the tissues and in the weights of selected organs were recorded at necropsy. Selected tissues were examined microscopically from all animals in the control and high dose groups. In addition, lungs, liver and kidneys were examined for rats treated at 100 and 1000 ppm.

There were no deaths during the 13 week feeding period or during the kinetic phase. All of the animals in the 2000 ppm dose group had a rough hair coat throughout the study; many of these animals were classified as being thin and having a hunched posture, alopecia and rhinorrhea. Body weights for 1000 and 2000 ppm males and females were significantly lower than those of controls. Body weights for 1000 ppm males and females at week 13 were 30% and 31% lower, respectively, than those of the controls. For 2000 ppm males and females, body weights were 69% and 52% lower, respectively, than those of the controls. Male and female cumulative body weight gains in the 1000 and 2000 ppm groups were significantly lower throughout the study. At the end of the study, the 2000 ppm males and females had gained only 31% and 48%, respectively, of the weight gained by the controls. Food consumption for males in the 1000 ppm group (except week 12) and males and females in the 2000 ppm group were significantly lower than those of controls for the entire study. There were statistically significant differences for several clinical pathology variables between control and treated animals. Nearly all of the differences represented treatment-related effects. The effects occurred at 1000 or 2000 ppm or both and, in general, males and females were affected similarly. Most of the effects were considered to be associated with decreased food consumption and body weight. Animals treated at 1000 or 2000 ppm tended to have lower terminal body weights. Correspondingly these animals tended to have lower absolute organ weights and higher organ-to-body weight percentages. There were no treatment-related macroscopic or microscopic findings. The NOAEL was determined to be 100 ppm.

In another rat supporting study, rats were administered propargite for two years in the diet at 0, 100, 300 and 900 mg/kg and 2000 mg/kg for 1.5 years (this dose was added to the study when it had been in progress for six months with the specific intention of inducing an effect). Offspring were administered the test material for approximately 9 months at 100 mg/kg, for the F_1 generation, and at 300 mg/kg for the F_2 and F_3 generations.

Under the conditions of the test, the only significant effect on growth occurred at the highest dose level of 2000 mg/kg. Survival of males in this group was also reduced at 1.5 years, although it is not clear if this is directly treatment related. Dietary concentrations of up to 900 mg/kg had no effect on appearance, behaviour, survival, growth, haematology and blood/urine chemistry, fertility or reproductive performance. Patterns in organ weights were variable, with no consistent relation to dose level. Lesions observed during gross necropsy and microscopic examination of tissues, including benign and malignant tumours, were observed in both test and control groups, considered normal, and attributed to the extended age of the test animals at study termination. The NOEL was determined to be 900 mg/kg diet (equivalent to 45 mg/kg bw/day).

Mutagenicity

Propargite is not mutagenic as evidenced by the findings of five in vitro tests (Ames test, two mammalian cell gene mutation assays, mammalian chromosome aberration test, DNA damage/repair assay) and one in vivo micronucleus study. The results of these tests are all negative indicating that exposure to this substance does not lead to cellular mutations, damage to chromosomes/DNA or interference with cell mitosis.

Carcinogenicity

Propargite has a harmonised classification as a category 2 carcinogen with the associated hazard phrase 'H351: Suspected of causing cancer'. This classification is based on two key studies and six supporting studies.

Reproduction toxicity—rats, 2-gen study

Groups of 25 male and 25 female rats were fed diets that contained 0, 80, 400 or 800 ppm test material for 10 weeks premating and throughout mating, gestation, lactation and weaning of the F1a pups. After weaning of the F1a litters, the F1a pups were sacrificed and discarded and the F0 animals were then remated to produce F1b litters. After weaning the F1b animals were then assigned to four groups (25/sex/group) and the F0 adults sacrificed and necropsied. The selected F1b animals were fed diets that contained 0, 80, 400 or 800 ppm test material for at least ten weeks premating, and throughout gestation, lactation and weaning of the F2a pups. After weaning of the F2a litters, the F2a pups were sacrificed and discarded and the F1b animals were then remated to produce F2b litters. After weaning of the F2b litters, the F2b pups were sacrificed and discarded and the F1b adults were sacrificed and necropsied. Test diets were fed continuously throughout the study. Clinical observations, body weights and food consumption, reproduction data and litter data were recorded. All F0 and F1b adults were examined macroscopically; microscopic examinations were done on reproductive organs for 0 and 800 ppm animals.

The results of the study are summarised as:

- Survival of the F0 generation was 100% for males and females at all doses except for 80 ppm males (96%), 0 ppm females (96%) and 80 ppm females (92%). Survival of the F1b generation was 100% for males and females at all doses except for 800 ppm males (96%) and 80 and 400 ppm females (96%).

- There were no test material-related clinical observations for F0 or F1b adults.

- In general, body weights and cumulative body weight gains were significantly lower than those of the controls at 400 and 800 ppm 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. 800 ppm F0 males were 9 to 19% lower, 800 ppm F0 females were 5 to 18% lower, 800 ppm F1b males were 26 to 29% lower and 800 ppm F1b females were 15 to 22% lower than the controls.

- During the F0 generation, food consumption was significantly lower than those of the controls for 400 ppm males (weeks 0 to 1, 4 to 5 and 8 to 9) and for 400 ppm females (weeks 6 to 7). Food consumption for the 800 ppm F0 males and females was significantly lower than those of the controls throughout most of the premating phase. During the F1b generation, food consumption was significantly lower that the controls for the 400 ppm males (weeks 2 to 10) and the 400 ppm females and 800 ppm males and females 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 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 litters or for pup (male and female) sex ratios. In general, the mean pup weights for most litters were significantly lower than those of the controls at 400 ppm for lactation days 7, 14 and 21 and significantly lower than those of the controls at 800 ppm 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 microscopic or macroscopic changes.

The NOAEL was determined to be 80 ppm for systemic effects and 800 ppm for male and female reproduction performance.

Developmental toxicity

Key study--rabbits

New Zealand White rabbits were dosed with 0, 2, 4, 6, 8 and 10 mg/kg/day test material 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. 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.

Supporting study 1--rats

Mated female rats were dosed with 6, 12, 18, 25 and 105 mg/kg/day test material 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. 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.

Supporting study 2—rats

The test material was administered by gavage to pregnant rats from days 6 to 15 of gestation at 0, 6, 25 and 105 mg/kg bw/day. On day 20 of gestation, all animals were killed and subject to uterine examination. Foetuses were examined for skeletal and visceral abnormalities. The test material had no dose-related effects on implantation, numbers of live and dead foetuses or numbers of resorption sites per dam. The test material 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.

Supporting study 3--- rabbits

Four groups of seventeen does each received the test material by oral intubation at 2, 6, 10 and 18 mg/kg bw/day from day 6 to day 18 of gestation. A fifth group of seventeen does served as the control. Maternal, ovarian, uterine, litter and foetal data were evaluated for evidence of treatment-related effects. Lower survival of pregnant and non-pregnant does dosed at 10 and 18 mg/kg bw/day was noted. The survival of pregnant does was lower in the 6, 10 and 18 mg/kg bw/day groups; this difference was statistically significant in the 18 mg/kg bw/day group. Clinical observations of adipsia and anorexia were noted more frequently in the 6, 10 and 18 mg/kg bw/day groups while depression was noted more frequently in the two higher-dose groups. 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. These findings noted during the in-life phase of the study are attributed to maternal toxicity of the test material. 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. With the exception of two instances of hydrocephaly in the high-dose group, the remaining findings are considered related to the maternal toxicity of the test material. Due to the small number of litters available for examination, and the fact that both findings of hydrocephaly were noted in the same litter, it cannot be ascertained whether this finding is related to maternal toxicity or to a direct teratogenic effect.

MoA considerations

Propargite was screened by ECHA as a potential endocrine disrupting substance without further indicating the mode of action (MOA). In vitro transcriptional assay showed that propargite has no antiandrogenic activity negative results (Orton et al. 2011). The substance is in the List of Chemicals for Initial Tier 1 Screening in the US EPA endocrine disrupting screening program (EDSP) in 2009. The Tier 1 Screening tests of 11 assays have been finished and the US EPA is currently analyzing the results. It is therefore important to explore the MOAs by analyzing these results.

According to the OECD conceptual framework, apical endpoints of tests at level 4 and 5 could be used to determine adverse effects. For human health, repeated dose toxicity tests, carcinogenicity tests, reproduction and developmental toxicity tests could be used for this purpose. For ecotoxicity tests, long term fish and daphnia tests could also be used.

It is noted that in the life cycle fathead minnow test, fish were examined externally and internally to verify sex and gonadal condition. But the results were not presented. The endpoints of sex ratio and secondary sex characteristics (SSC) are important for the causal relationship of adverse effects and MOA. It is suggested that results of SSC, sex ratio and GSI (gonado-somatic index) should be included in the report.

Orton F., Rosivatz E., Scholze M., Kortenkamp A., Widely used pesticides with previously unknown endocrine activity revealed as in vitro antiandrogen. Environ Health Perspect. 2011 119: 794–800.

Conclusion

Based on the observations in repeated dose, reproductive and developmental toxicity tests, there are no clear indications that propargite has endocrine disrupting properties.

Aquatic toxicity

Short-term toxicity to fish

There are one key study and one supporting study on fish. The key study was carried out in rainbow trout under flow-through conditions during a 21 day exposure to propargite at 18, 27, 42, 65 and 100 µg/L. Throughout the exposure period, no undissolved test material was observed in any of the exposure vessels. The mean measured test concentrations were 14, 21, 32, 52 and 100 µg/L. 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 (95% C.I. 70-110 µg/L) and 53 µg/L (95% C.I. 46-62 µg/L), respectively.

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 control also included. The 96 hour LC50 value was determined to be 0.081 ppm.

Long-term toxicity to fish

There are one key study and two supporting studies on fish.

Key study

Fathead minnow were continuously exposed to five concentrations of propargite, a dilution water control and a solvent control at the completion of hatching 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 the test material 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).

Exposure at 27 µg/L significantly reduced F_0 on 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 significantly 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). The NOEC and LOEC were estimated to be 5.7 µg/L and 11 µg/L, respectively.

Supporting study 1—rainbow trout

Details on exposure of rainbow trout can be found in the acute toxicity fish. After 96 hour exposure, 100% mortality was observed in the highest test concentration. By test termination, 100% mortality was also observed in the 32 and 52 µg/L treatment levels with 20% mortlaity in the 21 µg/L treatment level. No mortality was observed in the 14 µg/L treatment level, however, sublethal effects (e.g. partial or complete loss of equilibrium, darkened pigmentation) were observed among surviving fish at 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.

Supporting study 2—fathead minnow (ELS)

A flow-through 35 day early life stage toxicity study on fathead minnow was performed at the nominal test concentrations of 1.8, 3.5, 7.8, 15 and 30 µg/L (corresponding to mean measured concentrations of 1.9, 3.2, 7.5, 16 and 28 µg/L). Hatchability of fathead minnow eggs was not significantly affected by exposure to the test material at the test concentrations. Survival of fry between hatch and day 35 was significantly affected at 28 µg/L when compared to controls. Length and weight data were not available for statistical analysis for the 28 µg/L test concentration since no fish remained at the termination of the study. All remaining test concentrations did not show a significant decrease in length and weight of the fish after 35 days exposure. Based on these data, the NOEC is 16 µg/L.

Short-term toxicity to Daphnia

The EC50 for immobilsation of *Daphnia* exposed to propargite was determined over a 48 hour period in a study conducted in line with standardised guidelines OECD 202. The nominal concentrations of propargite tested were 0, 0.00625, 0.0125, 0.025, 0.05 and 0.1 ppm with the corresponding overall mean measured concentrations being 0.000, 0.004, 0.013, 0.015, 0.051 and 0.080 ppm, respectively. The EC50 for immobilsation was 0.014 ppm (=14 µg/L).

Long-term toxicity to Daphnia

A 21 day life cycle toxicity study of propargite to Daphnia magna was conducted at 2.5, 4.1, 9.0, 14 and 38 µg/L. The mean measured exposure levels remained consistent throughout the study and all results were based on these values.

The daphnid lengths at 14 µg/L were significantly different from the control. Length analysis of the 38 µg/L concentration could not be performed since no adults survived after 21 days. Statistical analysis of survival indicated that 38 µg/L was significantly different from the control. The mean young/adult/reproduction day was significantly affected at 38 µg/L. The NOEC was estimated to be 9 µg/L.

Toxicity to algae

The acute toxicity of propargite to freshwater algae was assessed by determining the EbC50 over a 96 hour period. Propargite was added to the test system at nominal concentrations of 0, 0.25, 0.5, 1, 2 and 4 mg/L (respective mean measured concentrations are 0, 0.14, 0.21, 0.38, 1.01 and 1.08 mg/L) with a solvent and non-solvent control also included. Observations on the reduction in average growth rate over 96 hours (based on cell density) relative to the control were made every 24 hours. Exposure to propargite did not cause any adverse effects on growth. On this basis, adverse effects on algae are not expected at concentrations equal to or below the water solubility of propargite. EbC50 values could not be calculated due to the lack of consistent dose-response data.

Toxicity to micro-organisms

A GLP study was performed to assess the effect of propargite on the respiration of activated sewage sludge following standard guideline OECD 209. Activated sewage sludge was exposed to an aqueous dispersion of the test material at concentrations of 10, 100 and 1000 mg/L (three replicates for highest concentration) for a period of 3 hours at 20 ± 2ºC with the addition of a synthetic sewage as a respiratory substrate. The rate of respiration was determined after 3 hours contact time and compared to a control and reference substance. The EC50 was determined to be >1000 mg/L. It was subsequently considered unnecessary to test at concentrations >1000 mg/L.

Conclusion

Propargite showed adverse effects in the long-term toxicity tests in fish and Daphnia. These are no data on the end points (e.g. sex ratio) indicating mode of action of the substance. Due to lack of information, it is not possible to conclude whether or not the substance has endocrine disrupting properties.

Given the missing information on environmental ED and remaining concern for PBT properties (focusing on P) makes the substance a candidate for CoRAP.

5.4 Preliminary indication of information that may need to be requested to clarify the concern

☒ Information on toxicological properties	☐ Information on physico-chemical properties
☒ Information on fate and behaviour	☐ Information on exposure
☒ Information on ecotoxicological properties	☐ Information on uses
☒ Information ED potential	☐ Other (provide further details below)

For human health, repeated dose toxicity tests, carcinogenicity tests, reproduction and developmental toxicity tests could be used for this purpose. For ecotoxicity tests, long term fish and daphnia tests could also be used.

It is noted that in the life cycle fathead minnow test, fish were examined externally and internally to verify sex and gonadal condition. But the results were not presented. The endpoints of sex ratio and secondary sex characteristics (SSC) are important for the causal relationship of adverse effects and MOA. Results of SSC, sex ratio and GSI (gonado-somatic index) can be used.

The substance is in the List of Chemicals for Initial Tier 1 Screening in the US EPA endocrine disrupting screening program (EDSP) in 2009. The Tier 1 Screening tests of 11 assays have been finished and the US EPA is currently analyzing the results. It is therefore important to explore the MOAs by analyzing these results. This may mean that the SEV on ED aspects may need to be postponed to maximize the benefit of the EPA program.

5.5 Potential follow-up and link to risk management

☐ Harmonised C&L	☒ Restriction	☒ Authorisation	☐ Other (provide further details)

Harmonised C&L is available for propargite. If the substance is identified as an endocrine disruptor (awaiting ED test results), it may be listed as a SVHC.