

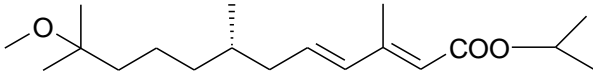
## APPENDIX I: LIST OF ENDPOINTS

CHAPTER 1: IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES,  
CLASSIFICATION AND LABELLING

Active substance (ISO Common Name)	S-Methoprene
Function ( <i>e.g.</i> fungicide)	Insecticide

Rapporteur Member State	Ireland
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**Identity** (Annex IIA, point II.)

Chemical name (IUPAC)	Isopropyl-(2E,4E,7S)-11-methoxy-3,7,11-trimethyl-2,4. – dodecadienoate
Chemical name (CA)	(S)-methoprene
CAS No	65733-16-6
EC No	None
Other substance No.	Not applicable
Minimum purity of the active substance as manufactured (g/kg or g/l)	≥ 950 g/kg
Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (g/kg)	None identified.
Molecular formula	C <sub>19</sub> H <sub>34</sub> O <sub>3</sub>
Molecular mass	310.48
Structural formula	

**Physical and chemical properties** (Annex IIA, point III, unless otherwise indicated)

Freezing point (state purity)	Purity: 98.3% < -22°C
Boiling point (state purity)	Purity: 99.6% 279.9 °C
Temperature of decomposition	Not applicable as the boiling point was estimated.
Appearance (state purity)	Purity: > 95% A transparent pale yellow liquid at 24°C with a faint, fruity, waxy odour.
Relative density (state purity)	Purity: > 95% 0.924 g/ml at 20°C
Surface tension	Purity: 98.3% 50.1 mN/m at 20°C (1 mg/l)
Vapour pressure (in Pa, state temperature)	Purity: 98.1 % 0.623 mPa at 20°C 1.08 mPa at 25°C
Henry's law constant (Pa m <sup>3</sup> mol <sup>-1</sup> )	0.0306 Pa x m <sup>3</sup> /mol at 20°C
Solubility in water (g/l or mg/l, state temperature)	Purity: > 95% 6.85 mg/l at 20 °C
Solubility in organic solvents (in g/l or mg/l, state temperature) (Annex IIIA, point III.1)	Purity: 98.1% Hexane: > 5 10 <sup>5</sup> mg/l Methanol: > 4.5 10 <sup>5</sup> mg/l Acetone: > 5 10 <sup>5</sup> mg/l Temperature: 20 ± 1 °C
Stability in organic solvents used in biocidal products including relevant breakdown products (IIIA, point III.2)	Not required as no organic solvents are present in the technical.
Partition coefficient (log P <sub>ow</sub> ) (state temperature)	LogKow = 6.34 (calculated)
Hydrolytic stability (DT <sub>50</sub> ) (state pH and temperature) (point VII.7.6.2.1)	pH 1.2: 17 hours at 37 ± 0.5°C ----- pH 4: Stable at 25 ± 0.5°C, 37 ± 0.5°C and 50 ± 0.5°C ----- pH 7: Stable at 25 ± 0.5°C, 37 ± 0.5°C and 50 ± 0.5°C ----- pH 9: Stable at 25 ± 0.5°C, 37 ± 0.5°C and 50 ± 0.5°C
Dissociation constant (not stated in Annex IIA or IIIA; additional data requirement from TNsG)	Not required as S-methoprene does not dissociate in water.
UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	Purity: 95% <u>90% Neutral Methanol:</u> λ <sub>max</sub> 264 nm; ε 26,700 <u>90% Acidified Methanol:</u> λ <sub>max</sub> 264 nm; ε 26,600 <u>90% Alkalinized Methanol:</u> λ <sub>max</sub> 266 nm; ε 27,450
Photostability (DT <sub>50</sub> ) (aqueous, sunlight, state pH) (point VII.7.6.2.2)	DT <sub>50</sub> at pH 7: 4.8 hours (continuous irradiation)

Quantum yield of direct phototransformation in water at  $\Sigma > 290$  nm (point VII.7.6.2.2)

1.1

Flammability

263 °C

Explosive properties

The molecular structure of S-Methoprene indicates that the substance has little or no explosive properties.

### Classification and Proposed Labelling

With regard to physical/chemical data

None

With regard to toxicological data

None

With regard to fate and behaviour data

None

With regard to ecotoxicological data

N, R50/53, S35

CLP Labelling: Chronic Category 1, H410, P273, P391, P501

## CHAPTER 2: METHODS OF ANALYSIS

Soil (principle of method and LOQ) (Annex IIA, point 4.2)

Not required

Air (principle of method and LOQ) (Annex IIA, point 4.2)

Not required

Water (principle of method and LOQ) (Annex IIA, point 4.2)

GC-MS  
LOQ: 0.1µg/l

Body fluids and tissues (principle of method and LOQ) (Annex IIA, point 4.2)

S-Methoprene is not classified as being toxic or highly toxic. It is therefore proposed that analytical methods in animal and human body fluids and tissues are not required.

Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes) (Annex IIIA, point IV.1)

Not required

Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes) (Annex IIIA, point IV.1)

Not required

## CHAPTER 3: IMPACT ON HUMAN HEALTH

**Absorption, distribution, metabolism and excretion in mammals** (Annex IIA, point 6.2)

Rate and extent of oral absorption:	Peak plasma concentration: Low dose group 6 hours (male) and 12 hours (female) High dose group 4 hours (male) and 6 hours (female) Indicating S Methoprene is systemically absorbed in 4 to 12 hours Oral absorption 35%
Rate and extent of dermal absorption:	2.86 %
Distribution:	Low dose; stomach, liver, adrenals and white fat . High dose; (after 6 hours) stomach, GI tract, liver, white fat and kidney. Multiple dose; GI tract, liver, stomach, kidney and white fat (highest in males)
Potential for accumulation:	Tissue radioactivity negligible at 96 hours in most tissues with the exception of white fat following single dosing. (1-4% remaining at 96 hours). The same pattern applied to repeat dose group. S-Methoprene does not bioaccumulate
Rate and extent of excretion:	Majority of S-Methoprene excreted within 24-48 hours (34-69% in faeces; 14-28% in expired air; 8-20% in urine).
Toxicologically significant metabolite	Chromatographic analysis of urine, faeces, and bile samples indicated at least 22, 23, and 11 radioactive components, respectively, all more polar than the parent compound.

**Acute toxicity** (Annex IIA, point 6.1)

Rat LD <sub>50</sub> oral	> 5050 mg/kg bw/day
Rat LD <sub>50</sub> dermal	> 5050 mg/kg bw/day
Rat LC <sub>50</sub> inhalation	> 2.38 mg/L
Skin irritation	Not irritating
Eye irritation	Not irritating
Skin sensitization (test method used and result)	Not a sensitizer (Buehler test)

**Repeated dose toxicity** (Annex IIA, point 6.3)

Species/ target / critical effect	Dog 90-day study: Clinical signs such as thin faeces and diarrhoea, increased liver weight in males and females and raised ALKP values in females Rat 104 weeks study: Liver histopathology
Lowest relevant oral NOAEL / LOAEL	Dog: LOAEL = 300 mg/kg bw/day

	NOAEL = 100 mg/kg bw/day Rat: LOAEL = 130.8 mg/kg bw/day NOAEL = 65.4 mg/kg bw/day
Lowest relevant dermal NOAEL / LOAEL	Not relevant
Lowest relevant inhalation NOAEL / LOAEL	Not relevant

**Genotoxicity** (Annex IIA, point 6.6)

Non genotoxic in an *in vitro* bacterial mutation assay, an *in vitro* chromosomal aberration assay and an *in vitro* gene mutation mammalian assay

**Carcinogenicity** (Annex IIA, point 6.4)

Species/type of tumour

Rat / No carcinogenic potential.  
Mouse / No carcinogenic potential.

Lowest dose with tumours

Not relevant

**Reproductive toxicity** (Annex IIA, point 6.8)

Species/ Reproduction target /critical effect

Rat; Reduction in body weight in both parents and offspring

Lowest relevant reproductive NOAEL / LOAEL

LOAEL = 130.8 mg/kg bw/day  
NOEL = 8.15 mg/kg bw/day

Species/Developmental target /critical effect

Rat: Reduction in weight gain (maternal), intrauterine mortality and low pregnancy rate  
Rabbit: Intrauterine foetal growth retardation, maternal death, increase in abortions, reduced activity and vaginal bleeding, decreased weight gain

Lowest relevant developmental NOAEL / LOAEL

LOAEL (rat) = 1000 mg/kg bw/day  
NOAEL (rat) = 250 mg/kg bw/day  
  
LOAEL (rabbit) = 1000 mg/kg bw/day  
NOAEL (rabbit) = 100 mg/kg bw/day

**Neurotoxicity / Delayed neurotoxicity** (Annex IIIA, point VI.1)

Species/ target/critical effect

Not applicable

Lowest relevant developmental NOAEL / LOAEL.

Not applicable

**Other toxicological studies** (Annex IIIA, VI/XI)

Not applicable

**Medical data** (Annex IIA, point 6.9)

Workers producing S-Methoprene for Bábłona

.....	<p>Bioenvironmental Centre Ltd. Over the past 25years have reported no incidences of adverse effects.</p> <p>Workers have reported no incidences of adverse effects, accidents, poisonings or clinical cases during the synthesis of S-Methoprene and the production of the biocidal product.</p> <p>No clinical cases, poisoning or incidents have been reported.</p> <p>No observations of sensitisation or allergenicity have been made following use of S-Methoprene.</p>
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**Summary** (Annex IIA, point 6.10)

ADI (if residues in food or feed)

AOEL (Operator/Worker Exposure)

Drinking water limit

ARfD (acute reference dose)

AEL acute

AEL medium-term

AEL long-term

Value	Study	Safety factor
Not applicable	Not applicable	Not applicable
Not applicable	Not applicable	Not applicable
Not applicable	Not applicable	Not applicable
Not applicable	Not applicable	Not applicable
0.35 mg/kg bw/day	Rabbit developmental study	100
0.35 mg/kg bw/day	90 day dog study	100
0.076 mg/kg bw/day	2-year rat study	100

**Acceptable exposure scenarios** (including method of calculation)

Professional users	<p>Oral and Inhalation exposure are not applicable. Dermal exposure was assessed using reverse reference scenario, as there is no suitable model to assess exposure.</p> <p>To achieve the NOAEL a 60 kg adult would need to be dermally exposed to the contents of 119.8 bait stations/day.</p> <p>Exposure is acceptable</p>
Non-professional users	<p>Oral and Inhalation exposure are not applicable. Dermal exposure was assessed using reverse reference scenario, as there is no suitable model to assess exposure.</p> <p>To achieve the NOAEL a 60 kg adult would need to be dermally exposed to the contents of 119.8 bait stations/day.</p> <p>Exposure is acceptable</p>
Indirect exposure as a result of use	<p>Dermal short-term exposure is considered for infant, children and adults. Oral short-term exposure is considered for infants. Inhalation long-term exposure is considered for infant, children and adults. All exposure to each group was considered acceptable.</p> <p>Indirect exposure to S-Methoprene <i>via</i> the environment i.e. <i>via</i> drinking water or foodstuffs is negligible.</p>

## CHAPTER 4: FATE AND BEHAVIOUR IN THE ENVIRONMENT

## Route and rate of degradation in water (Annex IIA, point 7.6, IIIA, point XII.2.1, 2.2)

Hydrolysis of active substance and relevant metabolites (DT<sub>50</sub>) (state pH and temperature)

S-Methoprene technical was found to be hydrolytically stable at pH 4, 7 and 9 (examined at 25, 37 and 50°C). In strong acid solution (pH 1.2), hydrolysis is rapid with a half-life of 17 hours at 37°C.

Photolytic / photo-oxidative degradation of active substance and resulting relevant metabolites

DT<sub>50</sub> at pH 7: 4.8 hours (15 d continuous irradiation with a Xe lamp, pH 7, sterilised, 22 ± 2 °C)

A number of submitted journal articles indicated that Methoprene rapidly decomposes in aqueous solution when exposed to sunlight. In sterilised water buffered to pH 7 the DT<sub>50</sub> of Methoprene was reported to be between <1 day and 5 days (Quistad et al. 1975, Schooley et al. 1975).

Sixteen transformation products detected, with the methoprene isomer [E,Z]-S-Methoprene and seven unidentified components each individually exceeding 10% of applied radioactivity.

Readily biodegradable (yes/no)

No

Inherent biodegradable (yes/no)

Yes (OECD 302C)

Biodegradation in seawater

Not relevant

Non-extractable residues

Aerobic water-sediment study - two systems presented  
River system: 36.9% @ 100days  
Pond system: 41.0% @ 100days

Distribution in water / sediment systems (active substance)

Aerobic water-sediment study - two systems presented

River system:

Water phase: 95.9% immediately after dosing to <LOQ by day 14; DisT<sub>50</sub> = 1.48d @ T=12°C (SFO)

Sediment phase: max of 16.6% on day 2 to 3.3% by day 49; DisT<sub>50</sub> = 7.09d @ T=12°C (SFO)

Whole system: 95.9% immediately after dosing to 3.3% by day 49; DT<sub>50</sub> = 2.50d @ T=12°C (SFO)

Pond system:

Water phase: 99.1% immediately after dosing to 0.3% by day 49; DT<sub>50</sub> = 1.02d @ T=12°C (SFO)

Sediment phase: max of 20.8% on day 2 to 1.7% by day 49; DT<sub>50</sub> = 12.8d @ T=12°C (SFO)

Whole system: 99.1% immediately after dosing to 2.0% by day 49; DT<sub>50</sub> = 1.65d @ T=12°C (DFOP, k<sub>1</sub> = 0.109, k<sub>2</sub> = 1.223, g = 0.2756)

Note: Comparison of biphasic kinetic parameters with trigger cutoffs is not ideal. Therefore calculation of the DT<sub>50</sub> from the slow phase of the degradation yields a more conservative estimate of degradation:

DT<sub>50</sub> = ln2/k<sub>1</sub> = 0.6931/0.1089 = 6.4 days @ T = 20 °C  
or 12.1 days @ T = 12 °C.

Distribution in water / sediment systems

Aerobic water-sediment study - two systems presented

(metabolites)

Metabolite M2 (River system):

Water phase: max of 7.8% @ day 2 to 1.0% by day 21;  
DT<sub>50</sub> not reported

Sediment phase: max of 1.6% on day 2 to 0.3% by day 49; DT<sub>50</sub> not reported

Whole system: max of 9.4% @ day 2 to 0.3% by day 49;  
DT<sub>50</sub> = 5.40d @ T=12°C (SFO)

Metabolite M2 (Pond system):

Water phase: max of 6.2% @ day 2 to 0.8% by day 21;  
DT<sub>50</sub> not reported

Sediment phase: max of 1.9% on day 2 to 0.6% by day 49; DT<sub>50</sub> not reported

Whole system: max of 8.1% @ day 2 to 0.6% by day 49;  
DT<sub>50</sub> = 9.88d @ T=12°C (SFO)

Metabolite M3 (River system):

Water phase: max of 10.2% @ day 2 to < LOQ by day 14; DT<sub>50</sub> not reported

Sediment phase: max of 2.0% @ day 2 to 0.3% by day 49; DT<sub>50</sub> not reported

Whole system: max of 10.2% @ day 2 to 0.3% by day 49;  
DT<sub>50</sub> = 2.29d @ T=12°C (SFO)

Metabolite M3 (Pond system):

Water phase: max of 5.8% @ day 2 to <LOQ by day 7;  
DT<sub>50</sub> not reported

Sediment phase: max of 1.9% @ day 2 to 0.3% by day 49; DT<sub>50</sub> not reported

Whole system: max of 7.7% @ day 2 to 0.3% by day 49;  
DT<sub>50</sub> = 3.64d @ T=12°C (SFO)

**Route and rate of degradation in soil** (Annex IIIA, point VII.4, XII.1.1, XII.1.4; Annex VI, para. 85)

Mineralisation (aerobic)

Aerobic soil degradation study - four soils, one radiolabel:

Max 51.1% on day 118 for Soil I

Max 61.5% on day 118 for Soil I

Max 52.4% on day 118 for Soil I

Max 52.8% on day 62 for Soil I



Laboratory studies (range or median, with number of measurements, with regression coefficient)

Aerobic soil degradation study - four soils, one radiolabel:

DT<sub>50</sub> values @ 20°C = 0.93 (soil 1), 0.73 (soil 2), 0.79 (soil 3) and 0.83 (soil 4) with correlation values of 0.9888 (soil 1), 0.9922 (soil 2), 0.999 (soil 3) and 0.9691 (soil 4).

DT<sub>50</sub> values @ 12°C = 1.76d (soil 1), 1.38d (soil 2), 1.50d (soil 3) and 1.57d (soil 4). These were calculated from the 20°C above using the equation:

$$DT_{50}(12\text{ }^{\circ}\text{C}) = DT_{50}(20\text{ }^{\circ}\text{C}) \cdot e^{(0.08(20-12))}$$

Geomean DT50 = 1.55 days

Field studies (state location, range or median with number of measurements)

Not relevant

Anaerobic degradation

Not relevant

Soil photolysis

Not relevant

Non-extractable residues

Aerobic soil degradation study - four soils, one radiolabel:

Max 48.6% on day 7 for Soil I

Max 48.8% on day 7 for Soil I

Max 54.3% on day 3 for Soil I

Max 52.2% on day 7 for Soil I

Relevant metabolites - name and/or code, % of applied a.i. (range and maximum)

Not relevant

Soil accumulation and plateau concentration

Not relevant

#### Adsorption/desorption (Annex IIA, point XII.7.7; Annex IIIA, point XII.1.2)

K<sub>a</sub> , K<sub>d</sub>

K<sub>a</sub> adsorption values (L/kg): 5.5, 6.5, 7.9 (mean = 6.6, n = 3 soils)

K<sub>aoc</sub> , K<sub>doc</sub>

Adsorption coefficients (L/kg) of 537, 684 and 1407, with a mean of 876.

pH dependence (yes / no) (If yes, state type of dependence)

pH dependent: No

#### Fate and behaviour in air (Annex IIIA, point VII.3, VII.5)

Direct photolysis in air

Not relevant

Quantum yield of direct photolysis

Not relevant

Photo-oxidative degradation in air

Not relevant

Volatilization

Not relevant

**Monitoring data, if available** (Annex VI, para. 44)

Soil (indicate location and type of study)

No data is provided

Surface water (indicate location and type of study)

No data is provided

Ground water (indicate location and type of study)

No data is provided

Air (indicate location and type of study)

No data is provided

## CHAPTER 5: EFFECTS ON NON-TARGET SPECIES

**Toxicity data for aquatic species (most sensitive species of each group)**

(Annex IIA, point 8.2, Annex IIIA, point 10.2)

Species	Time-scale	Endpoint	Toxicity
<b>Fish</b>			
Zebrafish, <i>Brachydanio rerio</i> ,	96 h	LC <sub>50</sub> NOEC	An LC <sub>50</sub> value of 4.26 mg/l and NOEC value of 1.25 mg/l was determined.
<b>Invertebrates</b>			
<i>Daphnia magna</i>	48 h	EC <sub>50</sub>	A 48-Hour EC <sub>50</sub> value of 0.22mg/l was determined.
<i>Daphnia magna</i>	21d	NOEC	0.019 mg/L measured
<b>Algae</b>			
<i>Selenastrum capricornutum</i>	72 h	ErC <sub>50</sub>	An ErC <sub>50</sub> value of 2.264 mg/l was determined.
<b>Microorganisms</b>			
Activated sewage sludge	3 h	EC <sub>50</sub>	A 3-Hour EC <sub>50</sub> value of 6.85 mg/l was determined.

**Toxicity data for aquatic species (most sensitive species of each group)**

(Annex IIA, point 8.2, Annex IIIA, point 10.2)

Species	Time-scale	Endpoint	Toxicity
<b>Fish</b>			
Zebrafish, <i>Brachydanio rerio</i> ,	96 h	LC <sub>50</sub> NOEC	An LC <sub>50</sub> value of 4.26 mg/l and NOEC value of 1.25 mg/l was determined.
<b>Invertebrates</b>			
<i>Daphnia magna</i>	48 h	EC <sub>50</sub>	A 48-Hour EC <sub>50</sub> value of 0.38 mg/l was determined.
<b>Algae</b>			
<i>Selenastrum capricornutum</i>	72 h	ErC <sub>50</sub>	An ErC <sub>50</sub> value of 2.264 mg/l was determined.
<b>Microorganisms</b>			
Activated sewage sludge	3 h	EC <sub>50</sub>	A 3-Hour EC <sub>50</sub> value of > 100 mg/l was determined.

**Effects on earthworms or other soil non-target organisms**

Acute toxicity to .....

Not relevant

(Annex IIIA, point XIII.3.2)

Reproductive toxicity to Earthworm (*Eisenia fetida*) and Collembola (*Folsomia candida*)  
(Annex IIIA, point XIII.3.2)

Earthworm (*Eisenia fetida*) Reproduction (56 d) NOEC 106 (mg/kg dwt) EC<sub>50</sub> / LC<sub>50</sub> 241 (mg/kg dwt)

Earthworm (*Eisenia fetida*) Mortality (28d) NOEC 213 (mg/kg dwt) EC<sub>50</sub> / LC<sub>50</sub> 404 (mg/kg dwt)

Collembola (*Folsomia candida*) Reproduction (56 d) NOEC 47 (mg/kg dwt) EC<sub>50</sub> / LC<sub>50</sub> 79.85 (mg/kg dwt). EC<sub>10</sub> reproduction (26 day) 24.75 mg/kg dwt (corrected to 16.83 mg/kg dwt)

PNECsoil = (EC<sub>10</sub> 16.83 dwt and AF of 100)  
**PNECsoil 0.168mg/kg dwt (=0.148 mg/kg wwt)**

**Effects on soil micro-organisms** (Annex IIA, point 7.4)

Nitrogen mineralization

Not relevant

Carbon mineralization

Not relevant

**Effects on terrestrial vertebrates**

Acute toxicity to mammals  
(Annex IIIA, point XIII.3.3)

Not relevant

Acute toxicity to birds  
(Annex IIIA, point XIII.1.1)

Not relevant

Dietary toxicity to birds  
(Annex IIIA, point XIII.1.2)

Not relevant

Reproductive toxicity to birds  
(Annex IIIA, point XIII.1.3)

Not relevant

**Effects on honeybees** (Annex IIIA, point XIII.3.1)

Acute oral toxicity

Not relevant

Acute contact toxicity

Not relevant

**Effects on other beneficial arthropods** (Annex IIIA, point XIII.3.1)

Acute oral toxicity

Not relevant

Acute contact toxicity

Not relevant

Acute toxicity to .....	Not relevant
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**Bioconcentration** (Annex IIA, point 7.5)

Bioconcentration factor (BCF)	516
Depration time (DT <sub>50</sub> ) (DT <sub>90</sub> )	Not relevant
Level of metabolites (%) in organisms accounting for > 10 % of residues	Not relevant

**CHAPTER 6: OTHER ENDPOINTS**

No other end points are available for S-Methoprene.