# Cyproconazole

## Product-type 8

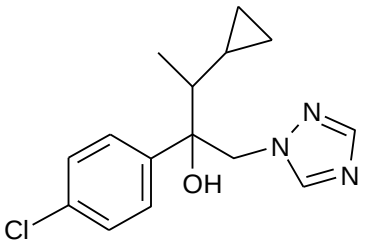
## List of endpoints – updated June 2016

### following the submission of data after active substance approval

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

| | |
|---|---|
| Active substance (ISO Common Name) | Cyproconazole |
| Function (*e.g.* fungicide) | PT 8 (Wood preservative) |

**Identity**

| | |
|---|---|
| Chemical name (IUPAC) | (2RS,3RS;2RS,3SR)-2-(4-chlorophenyl)-3-cyclopropyl-1-(1H-1,2,4-triazol-1-yl)butan-2-ol |
| Chemical name (CA) | alpha-(4-chlorophenyl)-alpha-(1-cyclopropyl-ethyl)-1H-1, 2, 4-triazole-1-ethanol |
| CAS No. | 94361-06-5 |
| EC No. | Not available |
| Other substance No. | CIPAC 600 |
| Minimum purity of the active substance as manufactured (g/kg or g/l) | Min. 940 g/kg<br>Cyproconazole has two diastereomers.<br>(Diastereoisomer A: 430 – 500 g/kg,<br>Diastereoisomer B: 470 – 550 g/kg).<br><br>Diastereomer A: enantiomeric pair, where the 3-hydroxy group and the 2-hydrogen are located on the same side (2S, 3S and 2R, 3R).<br><br>Diastereomer B: enantiomeric pair, where the 3-hydroxy group and 2-hydrogens are located on opposite sides (2R, 3S and 2S, 3R).<br><br>Technical cyproconazole is *ca.* 1:1 mixture of the two diasteriomers, each of which is exactly a 1:1 mixture of the enantiomers. |
| Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (g/kg) | 1-methyl-2-pyrrolidone (max. 4 g/kg) |
| Molecular formula | $C_{15}H_{18}ClN_3O$ |
| Molecular mass | 291.8 g/mol |
| Structural formula |  |

**Physical and Chemical Properties**

| | |
|---|---|
| Melting point (state purity) | 106.2 - 106.9°C ± 0.4°C (99.7%) |
| Boiling point (state purity) | Due to the thermal decomposition of the test substance it was not possible to determine the boiling point under normal pressure (99.7%) |
| Temperature of decomposition | 299 °C (99.7%) |
| Appearance (state purity) | White, fine powder (99.7%) |
| Relative density (state purity) | 1.25 (99.7%) |
| Surface tension | 65.2 mN/m at 20 °C (90 % saturated solution) (96.6%) |
| Vapour pressure (in Pa, state temperature) | 2.6 x $10^{-5}$ Pa at 25 °C (99.7%) |
| Henry's law constant (Pa $m^3$ $mol^{-1}$) | 5.0 x $10^{-5}$ Pa $m^3$ $mol^{-1}$ |
| Solubility in water (g/l or mg/l, state temperature) | 93 mg/L at 22 °C (pH 7.1) (98.9%) |
| Solubility in organic solvents (in g/l or mg/l, state temperature) | Solubility (g/L) at 25 °C (96.6%):<br>Acetone: 360<br>Dichloromethane: 430<br>Ethyl acetate: 240<br>Hexane 1.3<br>Methanol 410<br>Octanol: 100<br>Toluene: 100 |
| Stability in organic solvents used in biocidal products including relevant breakdown products | Not applicable because the active substance as manufactured does not include an organic solvent and is not formulated in organic solution in the biocidal product. |
| Partition coefficient (log $P_{OW}$) (state temperature) | log $P_{O/W}$ = 3.09 at 25 °C (pH 7.2) (99.7%) |
| Hydrolytic stability ($DT_{50}$) (state pH and temperature) | <u>Cyproconazole</u><br>No degradation observed at pH 4, 5, 7 or 9 (50°C, 5 days)<br><u>1,2,4 triazole(CGA 71019)</u><br>No degradation observed at pH 5, 7 or 9 (25°C, 30 days) |
| Dissociation constant | pKa = Cyproconazole will not dissociate in water at environmental pH, therefore no pKa value has been calculated.<br>(98.9%) |
| UV/VIS absorption (max.) (if absorption > 290 | pH 5 solution (99.7 %): |

| | |
|---|---|
| nm state ε at wavelength) | $\lambda_{max}$ 295 (nm); ε = 0.4 (L.mol$^{-1}$.cm$^{-1}$)<br><br>pH 7 solution (99.7 %):<br>$\lambda_{max}$ 295 (nm); ε = 0.7 (L.mol$^{-1}$.cm$^{-1}$)<br><br>pH 9 solution (99.7 %):<br>$\lambda_{max}$ 295 (nm); ε = 0.8 (L.mol$^{-1}$.cm$^{-1}$) |

| | |
|---|---|
| Photostability ($DT_{50}$) (aqueous, sunlight, state pH) | Not relevant |
| Quantum yield of direct phototransformation in water at Σ > 290 nm | Not determined/not required |
| Flammability | Non-flammable (95%) |
| Explosive properties | Non-explosive (95.7%) |
| Oxidising properties | Non-oxidising (95%) |

**Classification and Proposed Labelling**

| | |
|---|---|
| With regard to physical/chemical data | Directive 67/548/EEC – No classification required<br>Regulation 1272/2008 – No classification required |
| With regard to toxicological data | Directive 67/548/EEC<br>R22: Harmful if swallowed<br>Carc. Range Cat 3: R40: Limited evidence of a carcinogenic effect<br>Repr. Cat 2: R61: May cause harm to the unborn child<br>Regulation 1272/2008<br>Acute Tox 4 H302: Harmful if swallowed<br>Carc. Cat 2 H351: Suspected of causing cancer<br>Repr. Cat 1B H360: May damage the unborn child |
| With regard to fate and behaviour data | Directive 67/548/EEC – No classification required<br>Regulation 1272/2008 – No classification required |
| With regard to ecotoxicological data | Directive 67/548/EEC<br>R50: Very toxic to aquatic organisms<br>R53: May cause long-term adverse effects in the aquatic environment<br>Regulation 1272/2008<br>H410 (Chronic Cat.1): 'Very toxic to aquatic life with long lasting effects' |

## CHAPTER 2: METHODS OF ANALYSIS

### Analytical Methods for the Active Substance

| | |
|---|---|
| Technical active substance (principle of method) | CIPAC 600 –<br>Analysis by HPLC with UV detection following dissolution by methanol.<br><br>Identity confirmed by MS |
| Impurities in technical active substance (principle of method) | Analysis by HPLC with UV detection/GC with FID detection following dissolution in methanol.<br><br>Identity confirmed by MS |

### Analytical Methods for Residues

| | |
|---|---|
| Soil (principle of method and LOQ) | HPLC-MS/MS<br>LOQ = 0.01 mg/kg for parent cyproconazole. |
| Air (principle of method and LOQ) | The HPLC-MS/MS method for air was not fully validated, however no further will be required before Annex I inclusion because cyproconazole is considered to be non-volatile and the exposure to cyproconazole in air is considered to be negligible for the supported use. (professional spray application). In the event that additional modes of application are requested in the future, the discussion surrounding a requiremenmt for a fully validated cyrpoconazle monitoring method may have to be reviewed. |
| Water (principle of method and LOQ) | Method REM 200.01<br>Following the addition of methanol, the water specimen is sucked through a solid phase extraction column for concentration of the analyte. The eluate is evaporated and cyproconazole is quantified in the final extract by GC/MSD using the selected ion mode (SIM). The ion at 292 m/z is used for confirmation and the ions at 139 and 222 m/z are used for quantitation.<br>This method of analysis has proven to be suitable for the determination of cyproconazole in surface water and drinking water with LOQ values of 0.05 µg/L and 0.1 µg/L, respectively. |
| Body fluids and tissues (principle of method and LOQ) | High Performance Liquid Chromatography with Tandem Mass Specific Detection (HPLC-MS/MS).<br>This method of analysis has proven to be suitable for the determination of cyproconazole in animal fluids and tissues (blood, milk, fat, muscle/meat, organs – liver/kidney, eggs) with LOQ values of 0.01 mg/kg for all matrices. |
| Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes) | Not applicable |
| Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes) | Not applicable |

## CHAPTER 3: TOXICOLOGY

### Absorption, Distribution, Metabolism and Excretion in Mammals

| | |
|---|---|
| Rate and extent of oral absorption: | Rapidly absorbed, > 85 % within 144 hours, based on urinary and biliary excretion and carcass residues |
| Rate and extent of dermal absorption: | 1.0% for the undiluted product (A-9898A 5.175% w/w))<br>10% for multiple application of spray strength solutions (0.02% - 0.4%) |
| Distribution: | Widely distributed, highest residues associated with the organs of elimination (kidney, liver, pancreas) |
| Potential for accumulation: | No potential for accumulation upon repeated oral administration |
| Rate and extent of excretion: | Major route is biliary excretion for males (75 %) and females (59 %), followed by with renal (26.7 % and 9.5 % respectively); < 5 % faecal excretion |
| Toxicologically significant metabolite(s) | M21/M21a (NOA 405870)<br>M36 (NOA 405872)<br>Triazole alanine (TA or CGA 131013) |

### Acute Toxicity

| | |
|---|---|
| Rat $LD_{50}$ oral | Rat: 350 mg/kg bw<br>Mouse: 200 & 218 mg/kg bw, males & females respectively; 270 mg/kg bw (males)<br>Rabbit: 460 mg/kg bw (females) |
| Rat $LD_{50}$ dermal | Rat: >2000 mg/kg<br>Rabbit: >2000 mg/kg bw |
| Rat $LC_{50}$ inhalation | >5.65 mg/L, 4 hours, nose-only exposure |
| Skin irritation | Non-irritating |
| Eye irritation | Non-irritating |
| Skin sensitization (test method used and result) | Non-sensitising (M & K) and Beuhlar |

### Repeated Dose Toxicity

| | |
|---|---|
| Species/ target / critical effect | Liver toxicity and reduced weight gain in rats, mice and dogs. |
| Lowest relevant oral NOAEL / LOAEL | 90-day, rat: 6.4 mg/kg bw/day<br>90-day mouse: 2.2 mg/kg bw/day, LOAEL 43.8 mg/kg bw/day<br>1-year dog: 3.2 mg/kg bw/day |
| Lowest relevant dermal NOAEL / LOAEL | 10 mg/kg/d (28 day dermal, rat) based on changes in clinical chemistry. |

| | |
|---|---|
| Lowest relevant inhalation NOAEL / LOAEL | 4.9 mg/kg/d (16 day inhalation, rat) |
| **Genotoxicity** | Cyproconazole is unlikely to be genotoxic |
| **Carcinogenicity and long term toxicity** | |
| Target/critical effect | Reduced body weight gain in male and female rats and mice.<br>Liver: Liver change consistent with adaptive response and hepatotoxicity in rats and mice. |
| Relevant NOAEL | 1.84 mg/kg bw/day; 18-month mouse<br>2.22 mg/kg bw/day; 2-year rat |
| Carcinogenicity | Liver tumours (adenoma and carcinoma) in mice at 13.17 mg/kg bw/day |
| **Reproductive Toxicity** | |
| **Reproduction** | |
| Reproduction target / critical effect | Maternal: Increased liver weight.<br>Offspring: Slightly increased pre/peri- and post natal mortality.<br>Reproductive: No effect on reproduction/ fertility |
| Relevant parental NOAEL | 20 ppm: 2.0 mg/kg bw/day |
| Relevant reproductive NOAEL | 8.3 mg/kg bw/day |
| Relevant offspring NOAEL | 20 ppm: 2.0 mg/kg bw/day |
| **Developmental toxicity** | |
| Developmental target/critical effect | Maternal (rabbit): ↓mean body weight<br>Developmental (rabbit): Increased post-implantation loss; Increased foetal malformations<br><br>Maternal (rat) ↓mean body weight gain.<br>Developmental: Reduced foetal body weight teratogenicity (cleft palate, hydrocephaly) in the rat at maternally toxic doses. |
| Relevant maternal NOAEL | 10 mg/kg bw/day (rabbit) |
| Relevant developmental NOAEL | 2 mg/kg bw/day (rabbit) |
| **Neurotoxicity/Delayed Neurotoxicity** | |
| Acute neurotoxicity | No data - not required |
| Delayed neurotoxicity | No data - not required |
| **Other Toxicological Studies** | |
| *Mechanistic studies* | |
| Liver cell proliferation study; rat<br>mouse | Hepatocyte proliferation not induced.<br>Transient, early increase in proliferation (LEL = 15 ppm/2.2 mg/kg bw/day) |

| | | |
|---|---|---|
| Rat and mouse liver enzyme induction | | Strong induction of phase I and II enzymes in rat. Induction of NCPR, Cyp1A, GST and UDPGT in mice |
| C3H Mouse CAR studies | | Evidence of CAR interaction |
| *Studies on metabolites* | | |
| M21/M21A | Acute oral (rat) LD50<br>Ames test | >2000 mg/kg bw<br>Negative<br>(not toxicologically relevent) |
| M36 | Acute oral (rat) LD50<br>Acute oral (mouse) LD50<br>Genotoxicity | >2000 mg/kg bw<br>>2000 mg/kg bw<br>Not likely to be genotoxic<br>(not toxicologically relevent) |
| Triazole alanine | | No hazard discernible from toxicological profile (not toxicologically relevant) |

**Medical Data**

| | |
|---|---|
| No adverse effects reported | |

**Summary**

| | Value | Study | Safety factor |
|---|---|---|---|
| **Professional user** | | | |
| AEL $_{\text{long term}}$ | 0.02 mg/kg bw/day | Feeding studies, rat and mouse | 100x |
| AEL $_{\text{medium term}}$ | 0.02 mg/kg bw/day | Rat and rabbit developmental toxicity studies. | 100x |
| AEL $_{\text{short term}}$ | 0.02 mg/kg bw/day | Rat and rabbit developmental toxicity studies. | 100x |
| **Professional user** | | | |
| Reference value for inhalation (proposed OEL) | 100% | - | - |
| Reference value for dermal absorption | 1% (concentrate -15 mg a.s./ml)<br>10% (dilution) – 0.25 mg a.s./ml) | | |

**Acceptable Exposure Scenarios (including method of calculation)**

| | |
|---|---|
| Professional users | See intended uses. |
| Production of active substance | Not applicable |
| Formulation of biocidal product | Not applicable |
| Intended uses | **Industrial use: Double-vacuum and vacuum-pressure impregnation (TNsG 2002 handling model 1).**<br>Tier (2) Double Vacuum treatment exposure 0.05 mg/kg bw day MOE 40Unacceptable<br>Tier (1) Vacuum Pressure treatment exposure 0.013 mg/kg bw day MOE 153 Acceptable<br>**Industrial use : dipping and deluge/flood (TNsG 2002** |

| | |
|---|---|
| | **Dipping model 1).**<br>Tier (2) Deluge/flood Dipping model 1 0.004 mg/kg bw day MOE 500 Acceptable<br>**Industrial use : spraying (TNsG 2002 spray model 2).**<br>Tier (2)Spraying 0.006 mg/kg bw day MOE 333 Acceptable<br>**Tier (1)Cleaning of equipment (Applicants model)**<br>0.0033 mg/kg bw day MOE 606 Acceptable |
| Secondary exposure | See indirect exposure |
| Indirect exposure as a result of use | TNsG 2002) Adult sanding treated wood exposure 0.0002 mg/kg bw day MOE 10000<br>(TNsG 2002) Adult sanding treated wood 6 hours exposure 0.0013 mg/kg bw day MOE 1538<br>(TNsG 2002) Infant chewing wood off-cut exposure 0.00085 mg/kg bw day MOE 166.67<br>Inhalation of volatilised residues (infant) 0.00085 mg/kg bw day MOE 2352.94<br>Inhalation of volatilised residues (Child) 0.0008 mg/kg bw day MOE 2500<br>Inhalation of volatilised residues (Adult) 0.0005 mg/kg bw day MOE 4000<br>(TNsG 2002) Child playing on treated structure 0.0002 mg/kg bw day MOE 10000<br>(TNsG 2002) Infant playing on treated structure 0.002 mg/kg bw day MOE 1000 |
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| | |

**Chapter 4: Fate and Behaviour in the Environment**

**Route and rate of degradation in water** (Annex IIA, point7.6, IIIA, point XII.2.1, 2.2))

| | |
|---|---|
| Hydrolysis of active substance and relevant metabolites ($DT_{50}$) (state pH and temperature) | Cyproconazole<br>No degradation observed at pH 4, 5, 7 or 9 (50°C, 5 days)<br>1,2,4 triazole(CGA 71019)<br>No degradation observed at pH 5, 7 or 9 (25°C, 30 days) |
| Photolytic/photo-oxidative degradation of active substance and resulting relevant metabolites | Stable - molar absorption coefficients (ε) are < 10 L $mol^{-1}$ $cm^{-1}$ at wavelengths ≥ 290 nm |
| Readily biodegradable (yes/no) | No |
| Biodegradation in seawater | Not assessed/not required |
| Non-extractable residues | 3.8 (river system)-10.0 % (pond system) after 259 d |
| Distribution in water / sediment systems (active substance) | Cyproconazole<br>Water: 8.6-18.1% after 105 days (n=2)<br>6.4-16.1% after 259 days (n=2)<br>Sediment: 74.6 – 79.2% after 105 days (n=2)<br>72.4-73.2 % after 259 days ( n= 2) |
| Distribution in water / sediment systems (metabolites) | No identified metabolites<br>No unidentified metabolites in sediment or water > 3%<br>U1 reached a maximum of 4.6 % in the entire system |

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

| | |
|---|---|
| Mineralization (aerobic) | $^{14}$C-phenyl labelled cyproconazole<br>Up to 11%, day 112 d, n=1.<br>$^{14}$C-benzyl labelled cyproconazole<br>26.8-32.9%, day 112, n=2.<br>$^{14}$C-triazole labelled cyproconazole (140 d, n=1)<br>Less than 1%, 140 d, n=1 |

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

| Soil type | pH | t. ºC / actual soil moisture % | $DT_{50}$ / $DT_{90}$ (d) | $r^2$ | $DT_{50}$ (d) 12°C (TGD) | Model |
|---|---|---|---|---|---|---|
| **Rate of degradation studies** | | | | | | |
| Loam, Flaach 2/88 | 7.3 W | 22/40 | 89/295 | 0.93 | 198 | SFO |
| Sandy loam; Hatzenbühl | 5.0 | 22/40 | 192/638 | 0.94 | 427 | SFO |
| Loamy sand; Neuhofen | 5.0 | 22/40 | 132/438 | 0.91 | 294 | SFO |
| Loam; Flaach 2/89 | 7.6 | 22/40 | 72.4/240 | 0.98 | 161 | SFO |
| **Rate of degradation under varying incubation conditions (temperature, moisture, application rate).** | | | | | | |
| Loam; Flaach 2/89 | 7.6 | **12**/40 | 347/>1,000 | 0.72 | 347(M) | SFO |
| | 7.6 | 20/**20** | 219/727 | 0.82 | 415 | SFO |
| Loam; Flaach 2/89 (low app. dose) | 7.6 | 22/40 | 44.8/148 | 0.99 | 100 | SFO |
| **Route of degradation studies with kinetic information** | | | | | | |
| Sandy clay loam; Flaach 2/92) | 7.2 | 20/40 | 148/491 | 0.91 | 281 | SFO |
| Sandy clay loam; Flaach 2/90 (Benzyl radiolabel) | 7.0 | 22/75 % 1/3 bar | 124/412 | 0.72 | 276 | SFO |
| Silt loam; Louisiana 90 | 4.30 | 22/75 % 1/3 bar | 150.7/500.6 | 0.42 | 335 | SFO |
| Loamy sand; N. Carolina | 5.30 | 22/75 % 1/3 bar | Excluded | | --- | --- |
| Sandy clay loam Flaach 2/90 (Phenyl radiolabel) open system | 7.0 | 20/40 | 82/272 | 0.97 | 156 | SFO |
| Sandy clay loam Flaach 2/90 (Phenyl radiolabel) closed system | 7.0 | 20/40 | 193/642 | 0.95 | 366 | SFO |
| **Geomean**[#] | | | | | **298** | **SFO** |

The geomean was calculated in the following way: first the geomean values for sandy clay loam Flaach soils and loam Flaach soils were calculated, giving two separate values. At the next step these values were combined with the remaining kinetic endpoints to give the final geometric mean values. M= measured value

| | |
|---|---|
| | $DT_{50lab}$ (12°C, aerobic): (calculated from half-life at 12°C TGD)<br>Cyproconazole: 298 days<br>1,2,4 triazole (CGA 71019): 18.09 days |
| | $DT_{50lab}$ (20°C, anaerobic):<br>Cyproconazole: Negligible degradation<br>1,2,4 triazole (CGA 71019): 81 days (n = 1, $r^2 > 0.8$) |
| | Degradation in the saturated zone: No data supplied. |
| Field studies (state location, range or median with number of measurements) | $DT_{50f}$: 28.97 d(DFOP) – 162 d(SFO), n =5 |
| | $DT_{90f}$: 306.92 d(SFO)- >1,000 d(DFOP) n =5 |
| Anaerobic degradation | Negligible degradation |
| Soil photolysis | Negligible degradation |
| Non-extractable residues | Laboratory studies<br>$^{14}$C-phenyl labelled cyproconazole<br>20.8-21.5 % AR, day 140<br><br>$^{14}$C-benzyl labelled cyproconazole<br>13-23.9 %AR, day 112<br><br>$^{14}$C-triazole labelled cyproconazole (140 d, n=1)<br>16 %, day 140 |
| Relevant metabolites - name and/or code, % of applied a.i. (range and maximum) | 1,2,4 triazole (CGA 71019) – maximum 17.36%, day 140 |
| Soil accumulation and plateau concentration | Accumulation studies suggest no accumulation after 5 years of treatment, residues generally <LOQ 1 year after last treatment. However, these were carried out with a plant protection product. Consequently, they do not reflect the proposed use of cyproconazole as a wood preservative. For situations involving a daily flux of cyproconazole into soil, such as leaching from treated wood, the level of cyproconazole will tend towards a plateau. The level at which at the plateau is established, and the time to reach it, depend on the amount of cyproconazole in soil when the flux begins (if any), the daily flux rate and the dissipation rate of cyproconazole in soil. The release pattern for use as a plant protection product is different. Consequently, the CA is considering these accumulation studies as supportive information |

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

| | |
|---|---|
| Ka , Kd<br><br>$Ka_{oc}$ , $Kd_{oc}$ | <u>Freundlich normalised distribution coefficient ($K_{foc}$)</u><br>Cyproconazole: 364 L/kg (range 173 – 711, mean, n = 5)<br>1,2,4-triazole: 89 L/kg (range 43– 120, mean, n = 4)<br><br><u>Normalised distribution coefficient</u><br><u>Cyproconazole:</u><br>Mean: 473 L/kg (n = 5)<br>Median: 433.3 L/kg (n = 5)<br>Range: 174-904.35 L/kg,<br><br><u>1,2,4-triazole</u><br>Mean: 124 L/kg (n = 4)<br>Median: 115 L/kg (n = 4)<br>Range: 83-183 L/kg, |
| pH dependence (yes / no) (if yes type of dependence) | 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 determined/not required |
| Photo-oxidative degradation in air | $DT_{50}$: ~1 d (Atkinson calculation)<br><u>Calculation assumptions:</u><br>The calculation assumes a 24 hr time period and a [OH] radical concentration of 5 x $10^5$ molec $cm^{-3}$ |
| Volatalization | from plant surfaces: 17% in 24 hours |
| | from soil: < 1% in 24 hours |

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

| | |
|---|---|
| Soil (indicate location and type of study) | None available |
| Surface water (indicate location and type of study) | None available |
| Ground water (indicate location and type of study) | None available |
| Air (indicate location and type of study) | None available |

## 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 (mg a.i./L) |
|---|---|---|---|
| **Fish** | | | |
| **Cyproconazole technical** | | | |
| Rainbow trout | 96 h | $LC_{50}$ | 19 (m) |
| Bluegill sunfish | 96 h | $LC_{50}$ | 21 (m) |
| Carp | 96 h | $LC_{50}$ | 20 (n) |
| Sheepshead minnow (salt water) | 96 h | $LC_{50}$ | 21 (m) |
| Rainbow trout | 21 day | NOEC | 5.04 (growth) (m)<br>0.65 (behaviour) (m) |
| Rainbow trout | 89 day | NOEC<br>LOEC<br>89 day NOEC<br>59 day NOEC | 0.58 (survival) (m)<br>0.16 (fry growth) (m)<br><0.16 (fry growth) (m)<br>0.16 (fry growth) (m) |
| Fathead minnow | 357 day | NOEC | 0.5 (n) |
| **Metabolite CGA 71019** | | | |
| Rainbow trout | 96 h | $LC_{50}$ | 498 mg CGA 71019/L (m) |
| Rainbow trout | 28 day | NOEC | 100 mg CGA 71019/L (growth) (n) |
| **Invertebrates** | | | |
| **Cyproconazole technical** | | | |
| *Daphnia magna* | 48 h | $EC_{50}$ | >22 (m) |
| *Daphnia magna* | 48 h | $EC_{50}$ | 26 (m) |
| *Daphnia magna* | 21 day | NOEC | 0.29 (reproduction) (m) |
| *Daphnia magna* | 21 day | NOEC | 0.023 (reproduction) (m) |
| *Mysidopsis bahia* (Mysid shrimp) | 96 h | $EC_{50}$ | 9.6 (m) |
| *Crassostrea virginica* (Eastern oyster) | 96 h | $EC_{50}$ | 2.6 (m) |
| **Metabolite CGA 71019** | | | |
| *Daphnia magna* | 48 h | $EC_{50}$ | >100 mg CGA 71019/L (growth) (n) |
| **Algae** | | | |
| **Cyproconazole technical** | | | |
| *Scenedesmus subscipatus* | 72 h<br>96 h<br>96 h | $E_bC_{50}$<br>$E_bC_{50}$<br>NOEC | 0.099 (m)<br>0.077 (m)<br>0.021 (m) |
| *Chlorella vulgaris* | 72 h<br>72 h | $E_bC_{50}$<br>NOEC | 0.66 (m)<br>0.392 (m) |
| **Metabolite CGA 71019** | | | |
| *Selenastrum capricornutum* | 72 h<br>96 h<br>96 h | $E_bC_{50}$<br>$E_bC_{50}$<br>NOEC | 13 mg CGA 71019/L (m)<br>14 mg CGA 71019/L (m)<br>6.8 mg CGA 71019/L (m) |
| **Sediment dwellers** | | | |
| **Cyproconazole technical** | | | |
| *Chironomus riparius* | 28 day | NOEC (development rate) | 5.0 mg/L (via water column) (n)<br>50 mg ai/kg dwt sediment dwt (via sediment) (n)<br>10.9 mg a.i./kg wwt |

| Sewage sludge | | | |
|---|---|---|---|
| **Cyproconazole technical** | | | |
| Activated sludge | 3 hours | $EC_{50}$<br>NOEC | >100 (n)<br>≥ 100 (n) |

*m=measured concentration; n=nominal concentration

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

| | |
|---|---|
| Acute toxicity to earthworms<br>(Annex IIIA, point XIII.3.2) | Technical ai: 14 day $LC_{50}$ 335 mg ai/kg dwt soil (n)<br>CGA 71019: 14 day $LC_{50}$ >1000 mg ai/kg dwt soil (n) |
| Reproductive toxicity to earthworms and collembola<br>(Annex IIIA, point XIII.3.2) | CGA 71019: 56 day earthworm NOEC 0.0708(1) g ai/ha dwt (n)<br>CGA 71019: 56 day earthworm NOEC 1.0 mg a.i./L dwt (n)<br>CGA 71019: 28 day *F. candida* NOEC 1.8 mg ai/kg dwt (n)CGA A-9898 A: 28 day *F. candida* NOEC 55.8 mg ai/kg dwt (n) |

(1) Highest rate tested

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

| | |
|---|---|
| Nitrogen mineralization | Technical ai: <25% effect at 2.5 mg mg ai/kg dwt<br><25% effect at 2.0 mg mg ai/kg wwt<br>CGA 71019: <25% effect at 0.353 mg ai/kg dwt<br><25% effect at 0.31 mg ai/kg wwt |
| Carbon mineralization | Technical ai: <25% effect at 2.5 mg mg ai/kg dwt<br><25% effect at 2.0 mg mg ai/kg wwt<br>CGA 71019: <25% effect at 0.353 mg ai/kg dwt<br><25% effect at 0.31 mg ai/kg wwt |

**Effects on terrestrial vertebrates**

| | | |
|---|---|---|
| Acute toxicity to mammals<br>(Annex IIIA, point XIII.3.3) | **Cyproconazole technical** | |
| | Rat $LD_{50}$ oral | 1290 mg a.i./kg (male and female) |
| | Rat $LD_{50}$ dermal | >2000 mg a.i./kg |
| | Rat $LC_{50}$ inhalation | >5.65 mg a.i./L |
| Acute toxicity to birds<br>(Annex IIIA, point XIII.1.1) | **Cyproconazole technical** | |
| | *Anas platyrhynchos*<br>(Mallard duck) | $LD_{50}$ ≥2000 mg a.i./kg bw |
| | *Colinus virginianus*<br>(Bobwhite quail) | $LD_{50}$ 94 mg a.i./kg bw |
| | *Colinus virginianus*<br>(Bobwhite quail) | $LD_{50}$ 183 mg a.i./kg bw |
| Dietary toxicity to birds<br>(Annex IIIA, point XIII.1.2) | **Cyproconazole technical** | |
| | *Anas platyrhynchos*<br>(Mallard duck) | $LC_{50}$ 851 mg a.i./kg food |
| | *Colinus virginianus*<br>(Bobwhite quail) | $LC_{50}$ 1292 mg a.i./kg food |
| | *Colinus virginianus*<br>(Bobwhite quail) | $LC_{50}$ 567 mg a.i./kg food |

| | | |
|---|---|---|
| Reproductive toxicity to birds (Annex IIIA, point XIII.1.3) | **Metabolite CGA 131013** | |
| | *Anas platyrhynchos* (Mallard duck) | $LC_{50}$ >5000 mg CGA 131013/kg food |
| | *Colinus virginianus* (Bobwhite quail) | $LC_{50}$ >5000 mg CGA 131013/kg food |
| | **Cyproconazole technical** | |
| | *Anas platyrhynchos* (Mallard duck) | NOEC = 10 mg a.i./kg food (n) |
| | *Colinus virginianus* (Bobwhite quail) | NOEC = 50 mg a.i./kg food (n) |
| | **Metabolite CGA 71019** | |
| | *Cortunix cortunix japonica* (Cortunix quail) | NOEC= 316 mg CGA 71019/kg bw (m) |

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

| | |
|---|---|
| Acute oral toxicity | Technical ai: 24-h $LD_{50}$ >1000mg ai/bee (n) |
| Acute contact toxicity | Technical ai: 24-h $LD_{50}$ >100 mg ai/bee (n) |

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

| Species | Mortality effects | Sub-lethal effects |
|---|---|---|
| **Cyproconazole technical** | | |
| *Typhlodromus pyri* | $LR_{50}$ 35.6 g ai/ha (n)<br>Corrected mortalities 0, 2.1, 0, 0, 71.5, 85.7, 100, 97.9% | 13% and 34% reduction in fecundity at 10 and 20 g ai/ha, respectively |
| *Aphidius rhopalosiphi* | $LR_{50}$ <80 g ai/ha (n)<br>Mortality –100% | - |
| *Aphidius rhopalosiphi* | $LR_{50}$ >200 g ai/ha(n)<br>0, 0% mortality | No significant effects on fecundity at any rates |
| *Chrysoperla carnea* | $LR_{50}$ >200 g ai/ha(n)<br>Corrected mortality up to 20% | No significant effects on fecundity at any rate |
| *Poecilus cupreus* | $LR_{50}$ >160 g ai/ha(n)<br>No mortality at any rate | No significant effects upon feeding behaviour |
| *Orius laevigatus* | $LR_{50}$ >200 g ai/ha (n) Corrected mortality 0, 3.9, 0, 0% | No adverse effects on fecundity at any rate |
| **Formulation A-9961 B** | | |
| *Typhlodromus pyri* | $LR_{50}$ 29.4 g ai/ha(n)<br>Corrected mortalities 0, 0, 44.4, 61.1, 63, 74.1, 100% | No significant effects on fecundity at 4.9 to 133.3 mL A-9898 A/ha |
| *Typhlodromus pyri* | Fresh residues<br>$LR_{50}$ 51 g ai/ha (n)<br>Corrected mortalities 12.5, 57.1, 76.8, 100%<br>Aged residues (7 d)<br>$LR_{50}$ 94.3 g ai/ha (n)<br>Corrected mortalities 9.3, 44.4, 61.1% | No significant effects on fecundity with fresh and aged residues at all treatment rates |

**Bioconcentration** (Annex IIA, point 7.5)

| | |
|---|---|
| Bioconcentration factor (BCF) Fish | 28 |
| Depuration time ($DT_{50}$)<br>($DT_{90}$) | 0.87 days<br>Elimination almost complete in 4 - 7 days |
| Level of metabolites (%) in organisms accounting for >10% of residues | Not determined |
| Calculated BCF earthworm | 16 |

**Effects on terrestrial plants**

| | |
|---|---|
| 21 days-seedling emeregence<br><br>16 days-vegetative vigour | A-9961 B applications up to 400 g formulation/ha did not have an adverse effect on seedling emergence or vegetative vigour in *Brassica napus, Glycine max, Avena fatua* or *Allium cepa*. Applications of 200-400 g/ha caused negligible effects (<12.5%) in seedling emergence and vegetative vigour of and *Zea mays*. Applications of 200-400 g/ha caused <37.5% effects on seedling emergence and a 25% reduction in growth of *Beta vulgaris*. |

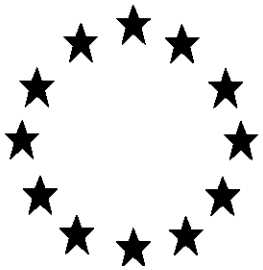
**Chapter 6: Other End Points**

**None**

**Regulation (EU) n°528/2012 concerning the making available on the market and use of biocidal products**

***Evaluation of active substances***

Assessment Report



# Cyproconazole

# Product-Type 8

# (Wood preservative)

March 2014

RMS: IRELAND

# Assessment Report

## Finalised in the Standing Committee on Biocidal Products at its meeting on 13 March 2014

CONTENTS

# 1. STATEMENT OF SUBJECT MATTER AND PURPOSE

## 1.1. PRINCIPLE OF EVALUATION

This assessment report has been established as a result of the evaluation of Cyproconazole as product-type 8 (wood preservatives), carried out in the context of the work programme for the review of existing active substances provided for in Article 16(2) of Directive 98/8/EC concerning the placing of biocidal products on the market[1], with a view to the possible inclusion of this substance into Annex I or IA to the Directive.

The evaluation has therefore been conducted in the view to determine whether it may be expected, in light of the common principles laid down in Annex VI to Directive 98/8/EC, that there are products in product-type 8 containing Cyproconazole that will fulfil the requirements laid down in Article 5(1) b), c) and d) of that Directive.

## 1.2. PURPOSE OF THE ASSESSMENT

The aim of the assessment report is to support a decision on the approval of Cyproconazole for product-type 8, and should it be approved, to facilitate the authorisation of individual biocidal products in product-type 8 that contain Cyproconazole. In the evaluation of applications for product authorisation, the provisions of Regulation (EU) No 528/2012 shall be applied, in particular the provisions of Chapter IV, as well as the common principles laid down in Annex VI.

The conclusions of this report were reached within the framework of the uses that were proposed and supported by the applicant (see Appendix II). Extension of the use pattern beyond those described will require an evaluation at product authorisation level in order to establish whether the proposed extensions of use will satisfy the requirements of Regulation (EU) No 528/2012.

For the implementation of the common principles of Annex VI, the content and conclusions of this assessment report shall be taken into account.

However, where conclusions of this assessment report are based on data protected under the provisions of Regulation (EU) No 528/2012, such conclusions may not be used to the benefit of another applicant, unless access to these data has been granted.

## 1.3. PROCEDURE FOLLOWED

This assessment report has been established as a result of the evaluation of Cyproconazole as product-type 8 (wood preservatives), carried out in the context of the work programme for the review of existing active substances provided for in Article 16(2) of Directive 98/8/EC concerning the placing of biocidal products on the market.

[1] Directive 98/8/EC of the European Parliament and of the Council of 16 February 1998 concerning the placing of biocidal products on the market. OJ L 123, 24.4.98, p.1.

Cyproconazole (CAS no. 94361-06-5) was notified as an existing active substance, by Syngenta Crop Protection AG who was replaced as the participant by Lanxess Deutschland GmbH on 6 April 2011, hereafter referred to as the applicant, in product-type 8.

Commission Regulation (EC) No. 1451/2007 of 4 December 2007[2] lays down the detailed rules for the evaluation of dossiers and for the decision-making process in order to include or not an existing active substance into Annex I or IA to the Directive.

In accordance with the provisions of Article 7(1) of that Regulation, Ireland was designated as Rapporteur Member State to carry out the assessment on the basis of the dossier submitted by the applicant. The deadline for submission of a complete dossier for Cyproconazole as an active substance in product-type 8 was 28th March 2004, in accordance with Annex V of Regulation (EC) No. 2032/2003.

On 16 September 2005, the Irish competent authorities received a dossier from the applicant. The Rapporteur Member State accepted the dossier as complete for the purpose of the evaluation on 18 September 2006.

On 30th May 2012, the Rapporteur Member State submitted, in accordance with the provisions of Article 14(4) and (6) of Regulation (EC) No 1451/2007, to the Commission and the applicant a copy of the evaluation report, hereafter referred to as the competent authority report. The Commission made the report available to all Member States by electronic means on 7th June 2012. The competent authority report included a recommendation for the inclusion of Cyproconazole in Annex I to the Directive for PT 8.

In accordance with Article 16 of Regulation (EC) No 1451/2007, the Commission made the competent authority report publicly available by electronic means on 12 September 2013. This report did not include such information that was to be treated as confidential in accordance with Article 19 of Directive 98/8/EC.

In order to review the competent authority report and the comments received on it, consultations of technical experts from all Member States (peer review) were organised by the Commission. Revisions agreed upon were presented at technical and competent authority meetings and the competent authority report was amended accordingly.

In accordance with Article 15(4) of Regulation (EC) No 1451/2007, the present assessment report contains the conclusions of the Standing Committee on Biocidal Products, as finalised during its meeting held on 13 March 2014.

[2] Commission Regulation (EC) No 1451/2007 of 4 December 2007 on the second phase of the 10-year work programme referred to in Article 16(2) of Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market. OJ L 325, 11.12.2007, p. 3

# 2. OVERALL SUMMARY AND CONCLUSIONS

## 2.1. PRESENTATION OF THE ACTIVE SUBSTANCE

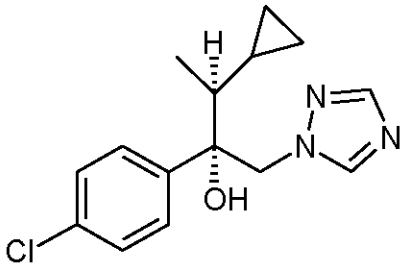
### 2.1.1. Identity, Physico-Chemical Properties and Methods of Analysis

| | |
|---|---|
| CAS-No.: | 94361-06-5 |
| EINECS-No.: | not available |
| CIPAC: | CIPAC 600 |
| IUPAC Name: | (2RS,3RS;2SR,3SR)-2-(4-chloro-phenyl)-3-cyclopropyl-1-(1H-1,2,4-triazol-1-yl)butan-2-ol |
| CA Name: | alpha-(4-chlorophenyl)-alpha-(1-cyclopropyl-ethyl)-1H-1,2,4-triazole-1-ethanol |
| Common name, synonym: | Cyproconazole |
| Molecular formula: | $C_{15}H_{18}ClN_3O$ |
| Purity: | Min. 94% w/w<br>(Diastereoisomer A: 430 – 500 g/kg, Diastereoisomer B: 470 – 550 g/kg)<br>The enantiomers are in a 1:1 ratio in the technical material as manufactured. |

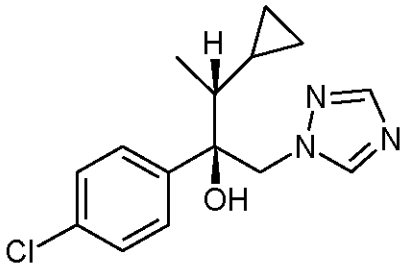
Structural formula:

Cyproconazole is a mixture of four stereoisomers: two diasteriomeric pairs of enantiomers, which means there are two enantiomers for each of the diasteriomers.
Diasteriomer A: enantiomeric pair, where the 2-hydroxy group and the 3-hydrogen are located on the same side (2S, 3S and 2R, 3R).
Diasteriomer B: enantiomeric pair, where the 2-hydroxy group and 3-hydrogen are located on opposite sides (2R, 3S and 2S, 3R).

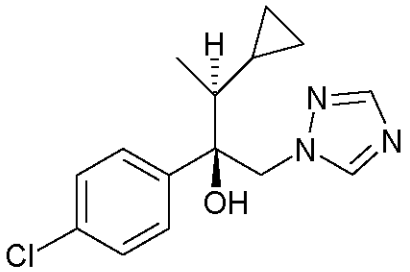
Cyproconazole, 2S, 3S – enantiomer (diastereomer A)



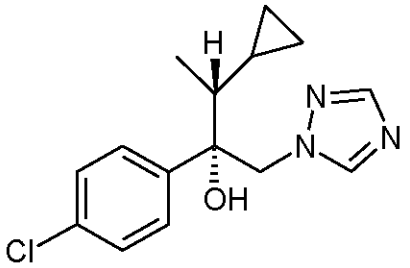
Cyproconazole, 2R, 3R – enantiomer (diastereomer A)




Cyproconazole, 2S, 3R – enantiomer (diastereomer B)




Cyproconazole, 2R, 3S – enantiomer (diastereomer B)




Molecular weight (g/mol): 291.8

Cyproconazole is a white fine powder with a faint aromatic odour. The purified active substance has a melting point range of 106.2 – 106.9 °C and has a low vapour pressure (2.6 x $10^{-5}$ Pa). The active substance is readily soluble in acetone, dichloromethane, ethyl acetate, methanol, octanol and toluene. The active substance was found to be slightly soluble in hexane. It is moderately-soluble in water (93 ± 18 mg/L at pH 7.1). Cyproconazole can be described as being borderline between fat/non-fat soluble with a $Log_{10}$ $K_{ow}$ value of 3.09. Cyproconazole is assumed to be photolytically stable as there was no absorption above 290nm. The technical material was found to be non-flammable, non-explosive and non-oxidising.
Cyproconazole does not classify from a Phys./Chem. point of view.

The representative product is EVIPOL® 60 SL and contains 5.175 % w/w cyproconazole.

### *2.1.1.1. Analysis of the active substance as manufactured*

CIPAC Method 600 (HPLC-UV) is available to analyse the Cyproconazole content in the TGAI.

Method No.SB-43/1 (GC-FID and HPLC-UV) is available to analyse impurities in the TGAI.

The identity of the active ingredient and impurities in the technical material as manufactured has been confirmed by MS.

#### *2.1.1.2. Formulation analysis*

A HPLC-UV method of analysis is available for the determination of Cyproconazole in the biocidal product EVIPOL 60 SL. However, data requirements in relation to method validation remain outstanding. The outstanding data should be provided at product authorisation stage.

#### *2.1.1.3. Residue analysis*

The residue definition for monitoring in environmental matrices is considered parent cyproconazole only.

Suitable methods of analysis are available for monitoring residues of Cyproconazole in drinking and surface water. The GC-MS method of analysis provided LOQs of 0.10 and 0.05 µg/L in surface and drinking water respectively.

There is a suitable HPLC-MS/MS method available for monitoring residues of cyproconazole in soil. The LOQ = 0.01 mg/kg.

The applicant provided a HPL-MS/MS method of analysis for cyproconazole residue in air. The HPLC-MS/MS method was not fully validated, however no further will be required before Annex I inclusion because cyproconazole is considered to be non-volatile and the exposure to cyproconazole in air is considered to be negligible for the supported use.

In the event that additional modes of application are requested in the future, the discussion surrounding a requiremenmt for a fully validated cyrpoconazle monitoring method may have to be reviewed.

It is considered that methods of analysis for residues of cyproconazole in food of plant and animal origin are not applicable for this submission.

A method of analysis for the determination of cyproconazole in body fluids and tissues remains outstanding.

### 2.1.2. Intended Uses and Efficacy

The assessment of the biocidal activity of cyproconazole demonstrates that it has a sufficient level of efficacy against the target organism(s) and the evaluation of the summary data provided in support of the efficacy of the accompanying product, establishes that the product may be expected to be efficacious.

In addition, in order to facilitate the work of granting or reviewing authorisations, the intended uses of cyproconazole, as identified during the evaluation process, are listed in Appendix II.

#### *2.1.2.1. Field of use envisaged / Function and organism(s) to be controlled*

MG02: Preservative.
PT08: Wood Preservative
Fungicide: (Control of wood rotting fungi, wood staining fungi and moulds)

Cyproconazole containing products are used for industrial wood preservation or for use by the industrial users for wood preservation. Cyproconazole can be used both in stand-alone and in combination products in both solvent and water-based products for industrial, superficial or penetrative applications for use classes up to 4a (UC 2, 3, 4a). The biocidal products can be either concentrates or ready-to-use products.

Organisms to be controlled are wood destroying fungi, including:

- *Basidiomycetes*
- *Poria placenta*
- *Lentinus lepideus*
- *Coriolus versicolor*
- *Serpula lacrymans*
- *Coniophora puteana*
- *Gloeophyllum trabeum*

#### *2.1.2.2. Effects on target organism(s)*

Cyproconazole inhibits fungal growth and has no obvious effect on spore germination or penetration of the pathogen.

The applicant has provided three key studies in support of the efficacy of the active substance against wood rotting fungi. These are Zgraggen and Graf, 1996a; Zgraggen and Graf, 1996b and Zgraggen and Graf, 1996c. Data were generated using SAN 619F (5% w/w cyproconazole in toluene). The results provide a useful indication of the activity of cyproconazole against the wood decaying fungal pathogens used in the standard effectiveness testing of wood preservatives.

All three studies were conducted to the European test standard EN 113, with ageing (EN 73), and ageing and leaching (EN 84) methods included in studies b & c respectively. The EN 113 test standard is a laboratory test to determine the toxic values of wood preservatives against wood destroying basidiomycetes cultured on agar medium. The EN 73 and EN 84 standards were used as pre-treatments prior to fungal testing. The test uses small blocks with a range of preservative concentrations. In the studies, the concentrations of cyproconazole tested on the Scots pine sapwood blocks were 0.00 - 0.004 – 0.008 - 0.016 -0.032 - 0.064% w/w. Concentrations tested on beech timber blocks were 0.00 – 0.00625 – 0.0125 – 0.025 – 0.050 – 0.1 % w/w.

All three studies investigated and confirmed the innate activity of cyproconazole against the brown rot fungi *Coniophora puteana*, *Poria placenta*, *Gloeophyllum trabeum* on pine sapwood and the white rot fungus *Coriolus versicolor* on beech. In each case pure cultures of basidiomycetes were used to determine the toxic values of the preservative.

In summary effective doses ranged from 20.2-384.7 g a.s./m³ of wood product.

Based on the efficacy studies submitted the IE CA considers the results from all three studies as demonstrating the effectiveness of cyproconazole against decay fungi (basidiomycetes), and considers the data to be acceptable for the purposes of the assessment of the active substance.

From the data submitted in the standard tests for wood preservatives of the product (EN 113 'Test method for determining the protective effectiveness against wood destroying basidiomycetes – determination of the toxic values') carried out either with accelerated ageing of treated wood prior to biological testing (EN 73 'Evaporative ageing procedure') or leaching (EN 84 'Leaching procedure'), the minimum effective dose of the product (EVIPOL® 60 SL) across the two representative wood types; Scots Pine (softwood) and Beech (hardwood) against the representative range of fungal pathogens (*Poria placenta, Coriolus versicolor, Coniophora puteana* and *Gloeophyllum trabeum*) was 1.49 kg of product/m³ (75 g cyproconazole/m³) of wood product. This application rate (75 g a.s./m³) is deemed to provide a robust dose under all circumstances, on softwood and hardwood, against the range of wood decaying fungi which may be encountered. The two further proposed organisms (*Lentinus lepideus* and *Serpula lacrymans*) included in section 2.2 above were not tested, however, the Applicant maintains that these are likely to have similar toxic values to those tested.

The proposed product label suggests a dose range for pressure impregnation treatment of 65-75 g cyproconazole/m³. The range is based on the highest mid toxic value and the highest upper toxic value derived from the two studies using the product) this is equivalent to 1.3-1.5 kg product/m³ of wood product (or 1.3-1.5 l/product/m³ of wood product, based on the product density of 0.99g/ml). This range of doses ensures that all types of wood product will be adequately protected against the full range of fungal pathogens, but does not exceed the minimum effective dose for the most difficult to control species *Coniophora puteana* (i.e. 75 g a.s./m³ of wood product). The product is intended to be used preventatively, as prior exposure to wood decaying fungi could lead to reduced effectiveness.

The proposed doses for surface treatment (industrial dipping and automated spraying) are 130-150 mg cyproconazole/m² of wood product (0.13-0.15 g a.s./m²). This is equivalent to approximately 2.6-3.0 mls product/m² of wood product. No efficacy testing was undertaken using surface applied treatments, but the proposed dose range is in line with the guidance provided for extrapolation of a dose per volume to a dose per surface area provided in EN 599-1:1996, 'Durability of wood and wood based products – Performance of preventative wood preservatives as determined by biological tests – part 1: Specification according to hazard class', section 5.3.11 (2 x g a.s./m³ = 1 x mg a.s./m²).

#### *2.1.2.3. Humaneness*

Not applicable.

#### *2.1.2.4. Resistance*

The Applicant has proposed the following reasoning in support of their position that resistance of the proposed wood decaying fungi to cyproconazole is unlikely:

The development of resistance against wood protection fungicides, especially azole fungicides, is highly unlikely because:

1. Treatments are preventive. Curative treatment of decaying wood is not the recommended practice. Wood attacked by fungi has to be removed and replaced, according to standard procedure. As a result, there is no treatment of already established fungal populations from which less sensitive mutants might be selected. Only single fungal spores being dispersed from natural sources are inhibited when contacting the treated wood.

2. In industrial treatment, wood is treated only once, which happens before it is put to use. There are no repeated industrial treatments. When treatments are repeated, this happens at most once in five years. This situation contrasts sharply with agricultural practice, where several treatments per season on the same crop are common practice. Several successive treatments with the same type of fungicide are known to be the main cause of resistance development.

3. Wood is mostly being treated by specialised industrial professionals, who use sufficiently high doses to entirely prevent fungal growth. The use of suboptimal doses that allow some fungi to survive treatment, as sometimes performed by individuals in an agricultural context, is another important cause of resistance development.

4. Wood used in construction is necessarily rather widely spaced in places were fungal attack is possible, not only in the constructions themselves, but also over the surface of the earth. In contrast, in an agricultural context (also in post-harvest treatment of produce), the substrate for fungal attack is densely packed on fields or in storage spaces. In such situations, disease pressure and the probability of resistance development is much higher than in the wood protection business. In the only instances where wood is densely packed, in sawmills, professional industrial treatment is performed and the wood is kept dry, avoiding fungal attack. It has to be added that most wood decay fungi seldom produce sporulating fruiting bodies before the wood is totally decayed. By that time the damaged wood has long been removed and replaced.

5. Decades of experience have proven that, when resistance against sterol demethylase inhibiting azole fungicides occurs, it is never the result of a single mutation in the target enzyme. Resistance against these fungicides typically develops as the result of the gradual accumulation of several (10 or more) genes being mutated, resulting in an increase of the number of membrane pumps removing the fungicides from the fungal cells being treated. As stated on http://www.frac.info/frac/index.htm (SBI means sterol biosynthesis inhibitors): "Problems with SBI performance typically became obvious only after several years of intensive use with efficacy degrading stepwise. Following reduced selection pressure, a partial recovery in sensitivity is often observed. The mechanism of resistance is mostly controlled by the accumulation of several independent mutations and is generally referred to as 'continuous selection', 'quantitative resistance' or 'shifting'". As a result, development of resistance against these fungicides is unlikely, and when it occurs it is gradual, slow and incomplete. In combination with the three previous arguments, we can state that the development of fungicide resistance is not an important issue in wood protection.

Under these circumstances, the risk of the target organisms developing resistance to cyproconazole containing products is considered to be low.

The IE CA agrees with the Applicant's reasoning, it is unlikely that resistance problems will become a concern when used as described above. There are no specific resistance cases to cyproconazole reported for wood destroying basiodiomycetes. It is therefore recommended to report the competent authorities any new information on the development of fungal resistance to cyproconazole.

### 2.1.3. Classification and Labelling

The current classification and labelling of the active substance Cyproconazole is shown below.

According to Annex I of Council Directive 67/548/EEC:

**Table 2.1.3-1 Current classification / labelling of cyproconazole**

| | |
|---|---|
| **Hazard symbol:** |  |
| **Indication of danger:** | Xn: Harmful<br>N: Dangerous for the Environment |
| **R-phrases:** | R22: Harmful if swallowed<br>Cat3; R63: Possible risk of harm to the unborn child<br>R50: Very toxic to aquatic organisms<br>R53: May cause long-term adverse effects in the aquatic environment |
| **S-phrases:** | S2: Keep out of the reach of children<br>S36/37: Wear suitable protective clothing and gloves<br>S46: If swallowed, seek medical advice immediately and show this container or label.<br>S60: This material and its container must be disposed of as hazardous waste<br>S61: Avoid release to the environment. Refer to special instructions/Safety data sheet |

Accordng to CLP Reg 1272/2008:

| | | |
|---|---|---|
| **Pictogram** | |  |
| **Signal word** | Warning | |
| **H-Statements** | Acute Tox 4; H302: Harmful if swallowed<br>Repr. Cat 2; H361: Suspected of damaging the unborn child<br>H410 (Chronic Cat. 1): Very toxic to aquatic life with long lasting effects | |
| **P-Statements** | P102: Keep out of reach of children<br>P201: Obtain special instructions before use<br>P281: Use personal protective equipment as required<br>P301+P310: IF SWALLOWED: Immediately call a Poison Center or Doctor/Physician<br>P273: Avoid release to the environment<br>P391: Collect spillage<br>P501: Dispose of contents/container to… | |
| **M-Factor** | Acute M-factor: 10 (based on $0.01 < E_bC_{50} \leq 0.1$: $E_bC_{50} = 0.077$ mg a.i./L)<br>Chronic M-factor: 10 (based on 0.001< NOEC ≤ 0.01 mg/l: Chronic NOEC=0.021 mg a.i./L) and cyproconazole is non-rapidly degradable. | |

#### *2.1.3.1. Proposal of the RMS Ireland for the classification and labelling of the active substance*

The proposals for the active substance outlined below are to be determined ultimately following discussions by the Risk Assessment Committee (RAC) of ECHA following submission of the cyproconazole CLH report.

**Proposed classification based on Directive 67/548/EEC:**

| | |
|---|---|
| **Hazard symbol:** |  |
| **Indication of danger:** | T: Toxic<br>N: Dangerous for the Environment |
| **R-phrases:** | R22: Harmful if swallowed<br>Cat 3; R40: Limited evidence for a carcinogenic effect<br>Cat 2; R61: May cause harm to the unborn child<br>R50: Very toxic to aquatic organisms<br>R53: May cause long-term adverse effects in the aquatic environment |
| **S-phrases:** | S2: Keep out of the reach of children<br>S36/37: Wear suitable protective clothing and gloves<br>S46: If swallowed, seek medical advice immediately and show this container or label.<br>S60: This material and its container must be disposed of as hazardous waste<br>S61: Avoid release to the environment. Refer to special instructions/Safety data sheet |

**Proposed classification based on CLP Regulation:**

| | |
|---|---|
| **Pictogram** |  |
| **Signal word** | Danger |
| **H-Statements** | Acute Tox 4; H302: Harmful if swallowed<br>Carc. Cat 2 H351: Suspected of causing cancer<br>Repr. Cat 1B; H360D: May damage the unborn child<br>H400 (Acute Cat 1): Very toxic to aquatic life<br>H410: Very toxic to aquatic life with long lasting effects |
| **P-Statements** | P102: Keep out of reach of children<br>P201: Obtain special instructions before use<br>P281: Use personal protective equipment as required<br>P301+P310: IF SWALLOWED: Immediately call a Poison Center or Doctor/Physician<br>P273: Avoid release to the environment<br>P391: Collect spillage<br>P501: Dispose of contents/container to… |
| **M-Factor** | Acute M-factor: 10 (based on $0.01 < E_bC_{50} \leq 0.1$: $E_bC_{50} = 0.077$ mg a.i./L)<br>Chronic M-factor: 10 (based on 0.001< NOEC ≤ 0.01 mg/l: Chronic NOEC=0.021 mg a.i./L) and cyproconazole is non-rapidly degradable. |

## Justification for the proposal:

**Physical-Chemical Properties:**
The molecule will not classify as flammable, explosive or oxidising. No classification required.

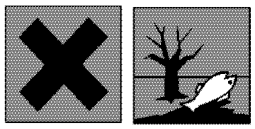
**Human Health:**

The RMS classification proposal is in line with that agreed following the 91/414 review (PRAPeR 81, September 2010) and is as below. It was agreed at the TM that this is a borderline case and the question should be resolved by the RAC. It is intended to forward the proposal for harmonised classification and labelling to ECHA's Risk Assessment Committee. Please see classification section of Document IIA.

**Environment:**

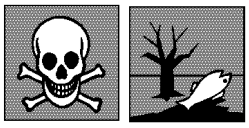
Cyproconazole is classified as N Dangerous for the environment, and R50 as it is very toxic to algae as indicated by the 96 hr $E_bC_{50}$value of 0.077 mg a.i./L for *Scenedesmus subspicatus*. Cyproconazole is assigned R53 as it is not readily biodegradable. Under the CLP Regulation the R50 translates into Acute Category 1. Since Cyproconazole is not readily biodegradable and the lowest chronic NOEC of 0.021 mg a.i./L *Scenedesmus subscipatus* it also classifies as Chronic Category 1.

### *2.1.3.2. Classification and labelling of the product EVIPOL® 60 SL (concentrate) based on current classification of cyproconazole and on acute toxicity tests with the biocidal product*

| | | |
|---|---|---|
| **Hazard symbol:** (for labelling) | Xn, N |  |
| **Indication of danger:** | Harmful<br>Dangerous for the Environment | |
| **Risk Phrases:** (for labelling) | R22: Harmful if swallowed<br>R63 Possible risk of harm to the unborn child<br>R41: Risk of serious damage to the eyes<br>R50: Very toxic to aquatic organisms<br>R53: May cause long-term adverse effects in the aquatic environment | |
| **Safety Phrases:** (for labelling) | S2: Keep out of the reach of children<br>S26 In case of contact with eyes, rinse immediately with plenty of water and seek medical advice<br>S36/37: Wear suitable protective clothing and gloves<br>S46: If swallowed, seek medical advice immediately and show this container or label.<br>S60: This material and its container must be disposed of as hazardous waste<br>S61: Avoid release to the environment. Refer to special instructions/Safety data sheet | |

### *2.1.3.3. Proposal of the RMS for the classification and labelling of the product EVIPOL® 60 SL*

Proposed classification for the biocidal product EVIPOL® 60SL according to Directive 99/45/EC

| | | |
|---|---|---|
| **Hazard symbol:** (for labelling) | |  |
| **Indication of danger:** | T: Toxic<br>N: Dangerous for the Environment | |

| | |
|---|---|
| **Risk Phrases:** (for labelling) | R22 Harmful if swallowed<br>R41 Risk of serious damage to eyes<br>Cat 3; R40 Limited evidence for a carcinogenic effect<br>Cat 2; R61 May cause harm to the unborn child<br>R50: Very toxic to aquatic organisms<br>R53: May cause long-term adverse effects in the aquatic environment |
| **Safety Phrases:** (for labelling) | S 2 Keep out of the reach of children<br>S26 In case of contact with eyes, rinse immediately with plenty of water and seek medical advice<br>S36/37/39 Wear suitable protective clothing and gloves<br>S46: If swallowed, seek medical advice immediately and show this container or label.<br>S60: This material and its container must be disposed of as hazardous waste<br>S61: Avoid release to the environment. Refer to special instructions/Safety data sheet |

Proposed classification for the biocidal product EVIPOL® 60SL according to CLP Regulation (EC) No 1272/2008

| | | |
|---|---|---|
| **Pictogram:** (for labelling) | |  |
| **Signal word:** | Danger | |
| **Hazard Statement:** (for labelling) | Acute Tox 4 H302: Harmful if swallowed<br>Cat 1 H318: Causes serious eye damage<br>Carc. Cat 2 H351: Suspected of causing cancer<br>Repr. Cat 1B H360: May damage the unborn child<br>H410 (Chronic Cat. 1): Very toxic to aquatic life with long lasting effects | |
| **Precautionary Statement:** (for labelling) | P102: Keep out of reach of children<br>P201+P202: Obtain special instructions before use. Do not handle until all safety precautions have been read and understood.<br>P281: Use personal protective equipment as required<br>P301+P310: IF SWALLOWED: Immediately call a Poison Center or Doctor/Physician<br>P305+P351+P338: IF IN EYES: Rinse continuously with water for several minutes. Remove contact lenses if present and easy todo – continue rinsing.<br>P273: Avoid release to the environment<br>P391: Collect spillage<br>P501: Dispose of contents/container to… | |

## Justification for the proposal:

**Physical-Chemical Properties:**
Note: The phys.chem. classification of the product EVIPOL 60SL remains open due to outstanding data. The data should be provided at product authorisation.

**Human Health**
The RMS classification proposal is in line with that agreed following the 91/414 review (PRAPeR 81, September 2010). It was agreed at TM that the proposed classification for carcinogenicity was a

borderline case and that relevancy to man needs to be discussed in the light of additional mechanistic information provided. Please see classification section of Document IIA.

**Environment**

In order to classify the biocidal product in relation to the concentration of the active substance an M-Factor should be applied to the concentration limits set out by Directive 99/45/EC ($C_n \geq 25$ %). An acute M-Factor of 10 was established based on the 96 hr $E_bC_{50}$value of 0.077 mg a.i./L for *Scenedesmus subspicatus*, a chronic M-Factor of 10 was established based on the NOEC of 0.021 mg a.i./L for *Scenedesmus subspicatus*. This results in a concentration limit of 2.5%. As the biocidal product contains 5.175 % (w/w) active substance, the classification of the active substance has to be assigned to the biocidal product. Consequently, the biocidal product should be classified as N, R50/R53. This translates into acute category 1 and chronic category 1 under the CLP regulation.

## 2.2. SUMMARY OF THE RISK ASSESSMENT

### 2.2.1. Human Health Risk Assessment

#### *2.2.1.1. Hazard Identification and Effects Assessment*

*ADME*

Cyproconazole was found to be rapidly and extensively absorbed with a total bioavailability of > 86%. Cyproconazole was rapidly distributed and had an extensive volume of distribution following either single or repeated administration. Residues were predominately associated with the organs of elimination (kidney, liver and pancreas) as well as the spleen and adrenal glands. Based on the absorption studies provided there was no evidence of accumulation in any tissues of the rat.

Cyproconazole is extensively metabolised, with a greater number of metabolites identified in the urine compared to the faeces. In the faeces parent cyproconazole and the identified metabolite NOA421152 are the major components. The metabolite pattern was almost identical after multiple dosing with slight quantitative differences. Pre-treatment with a larger dose of cyproconazole was also found to have no effect on the metabolism profile. Further analysis of the metabolism profile revealed 35 metabolites of which 13 were considered significant. Based on the metabolite profile the predominant metabolism reactions in the rat were a) oxidative elimination of the triazole ring, b) hydroxylation of the carbon bearing the methyl group, c) oxidation of the methyl group to the carbinol and further to the carboxylic acid and d) reductive elimination of the carbon bearing the methyl group, yielding a benzyl alcohol which is further oxidised to the corresponding ketone.

There were no clear differences in metabolism either between sexes, species (rat and goat) dosages or due to pre-treatment for the rat.

Major route of elimination of cyproconazole in the rat was the bile, accounting for approximately 75% in males and 59% in females. Elimination *via* the urine occurred to a greater extent in females (26.8%) than males (9.5%). Faecal elimination accounted for less than 5% of the administered dose. The majority of the test substance was eliminated *via* the urine and bile within the first 48 hours post administration irrespective of the route of administration. However some of the test substance may be reabsorbed from the bile and excreted via the urine. Over 85% of cyproconazole was eliminated within 144 hours. Repeated administration had no significant effect upon the routes and rates of elimination compared to a single oral dose. The elimination from most tissues occurred rapidly, following monophasic kinetics.

**Absorption**

*Oral:* Cyproconazole was found to be rapidly and extensively adsorbed at the low dose levels and slightly slower but equally extensive adsorption occurred at a high dose level. Maximal blood concentrations were reached within 24- 48 hours. A total bioavailability of > 86% was estimated (including data from a bile duct cannulation experiment). 100% oral absorption is therefore assumed for risk assessment purposes.

*Dermal:* The dermal absorption of Cyproconazole in humans has been estimated based on a series of studies conducted with a 100SL formulation (water based) designed for agricultural uses, using *in vivo* (rat) and *in vitro* (human and rat) data. Results are reported in Doc IIIA and the conclusion on estimated dermal absorption is outlined in Doc IIA. It was recommended to assume a dermal absorption for humans of not more than 1% for multiple exposures to an undiluted product and a 10% dermal absorption can be used for assessments of human exposure to the diluted product. In addition, as a very worst case, a dermal absorption of 16% (estimated in the rat *in vivo* study for a high dilution rate of 1:1600) might be used in circumstances where such high dilution rates were employed.

***Acute toxicity***

The acute oral toxicity of cyproconazole was tested in the rat, mouse and rabbit. The test substance was found to be harmful via the oral route in the rat. There were no adverse effects *via* the dermal and inhalation routes. The test substance was not irritating to the skin or eyes and not a dermal sensitiser.

***Short-term toxicity***

The toxicological properties of cyproconazole upon short-term treatment were investigated in rat, mouse and dog. In all species investigated, liver was the target organ for cyproconazole. Evidence for a disturbance of lipid metabolism was found in all species. A maximum tolerated dose (MTD) was found in rats at 1000 ppm after 28 days of treatment and at 350 ppm after 90 days of treatment, based on body weight effects and functional and structural changes in the liver. The dose of 300 ppm was an MTD in the 90-day mouse study, based on body weight effects and structural liver changes.
The lowest NOAEL among short-term toxicity studies was at 6.4 mg/kg bw from the 1st 90-day rat study and was considered to be the relevant overall NOAEL for the rat short-term studies. The lowest oral NOAEL among all investigated species was 2.2 mg/kg bw, obtained in the mouse 90-day study.
The target organ at non-lethal concentrations in the 16-day inhalation study in rats was the liver, indicated by slight, reversible changes in liver enzymes and hepatocellular hypertrophy.
The NOAEL was 4.9 mg/kg bw/day (corresponds to 0.017 mg/L).

Dermal application of cyproconazole technical to rats at dose levels up to 1000 mg/kg over a 28-day period was well tolerated up to 100 mg/kg bw/day without any signs of overt toxicity. Above 10 mg/kg there were changes in haematological parameters and clinical chemistry findings including increassed cholesterol, protein and globulin. The NOAEL for systemic toxicity in this study was therefore at 10 mg/kg bw per day.

***Genotoxicity***
The genotoxicity of cyproconazole was extensively investigated in a wide range of test systems both *in vitro* and *in vivo*. All relevant endpoints were addressed. The test substance was negative in all tests reported.

***Long-term toxicity and carcinogenicity***
The long term toxicity and carcinogenic potential of cyproconazole was assessed in a 2-year feeding study in KFM Wistar rats and an 18-month feeding study in CD-1 mice. Both studies were considered acceptable though the dose intervals used in the chronic rat study were not ideal.

*Long-term toxicity - Rat*
The main target organ in the rat was the liver, with evidence of cytotoxic hepatic changes in males at 350 ppm (equivalent to 15.59 and 21.76 mg/kg/day in males and females respectively) comprising an increase in the incidence and severity of fatty change. However, these fatty changes were not associated with any degenerative lesions. Most of the other hepatic changes were consistent with cyproconazole's ability to induce xenobiotic-metabolising enzymes in rodent liver.
Daily administration of cyproconazole at 350 ppm (equivalent to 15.59 and 21.76 mg/kg/day in males and females respectively also caused a significant reduction in body weight gain in rats (both sexes) after only two weeks of treatment, the effect being more pronounced in females.

*Long-term toxicity - Mouse*
Similar to the rat, the liver was also the main target organ for cyproconazole in mice, though the mouse appears to be more sensitive to the hepatotoxic effects (possibly due to differences in ratios of enzyme activity resulting in a reduced capacity of the mouse liver to metabolise and eliminate cyproconazole compared to the rat. Cytotoxic changes including focal hepatocytic inflammation and single cell hepatocytic necrosis were observed in males at doses as low as 100 ppm (equivalent to 13.17 mg/kg bw/day), and were accompanied by effects associated with enzyme induction (significant increases in relative liver weight, significant increase in the incidence of hepatic accentuated lobular pattern, diffuse hepatocytic hypertrophy). Significant cytoxic changes in the livers of female mice at 100 ppm and above (equivalent to 17.65 mg/kg bw/day) comprised centriacinar and periacinar vacuolation, as well as single cell hepatocytic necrosis. Relative and absolute liver weights were also significantly increased relative to controls in females at this dose level and there was a significant increase in the incidence of hepatic accentuated lobular pattern.

Similar to the rat, body weight development in the mouse was also effected by cyproconazole, though in this case, the effect was more apparent in males. A clear retardation in bodyweight development, relative to controls was observed in both sexes at 100 and 200 ppm, in males from week 13 onwards, in females, after 26 –52 weeks of treatment.

Other treatment-related changes of possible toxicological significance included testicular germinal epithelial deficit, aspermia and possibly an increase in skin wounds at 100 and 200 ppm in males and an increased incidence of aortic arteritis and lymphoid hyperplasia in the mesenteric lymph modes at 200 ppm in females.

*Carcinogenicity - Rat*
There were no treatment-related neoplasms observed in male or female rats even at the highest dose level of 350 ppm (equivalent to 15.59 and 21.76 mg/kg/day in males and females respectively). Thus cyproconazole was not considered to be carcinogenic in rats.

*Carcinogenicity – Mouse*
Cyproconazole was carcinogenic in mice. Long-term administration of cyproconazole at doses of 100 ppm (equivalent to 13.17 mg/kg bw/day) and above caused a significant increase in the incidence of hepatocytic adenomas and carcinomas in males. In females these neoplastic changes were observed at doses of 200 ppm (equivalent to 36.30 mg/kg/day ).
Supplementary investigative studies suggest a cytotoxic mode of action in mice by which continuous treatment with cyproconazole leads to a well-defined sequence of events, starting with a perturbation of hepatic homeostasis and resulting in degenerative lesions with subsequent liver cell proliferation leading to preneoplastic lesions and finally hepatocellular tumours. Although several of these events were also observed in rats treated with cyproconazole, the incidence of liver tumours did not increase. There was not sufficient mechanistic evidence provided to suggest the mechanism of tumour induction, as observed in the mouse, was not relevant to man. Therefore, it is proposed that cyproconazole should be classified as a Category 3 carcinogen according to council Directive 67/548/EEC (Categroy 2 according to CLP Regulation 1272/2008) and labelled accordingly.

*Overall long-term NOAEL:*
Based on the various non-neoplastic and neoplastic effects as observed in the liver of male and female mice at 100 ppm, the overall long-term and oncogenic NOAEL for cyproconazole in rodents is considered to be 15 ppm, equivalent to 1.84 mg/kg and 2.56 mg/kg in male and female mice, respectively.

***Reproductive toxicity***
The reproductive toxicity of cyproconazole was investigated in a 2-generation breeding study in the rat. Developmental toxicity was investigated in the rat and rabbit.

There was no effect on fertility or reproductive performance in a single 2 generation study in the rat conducted with up to 120 ppm (8-13 mg/kg bw/day ) cyproconazole. Minimal parental toxicity was recorded in F0 males only in this study. There was evidence of feototoxicity/embryotoxicity at the highest dose, in that there was a slight decrease in implantation number and an increase in pre/peri natal loss. The NOEL for development was 20 ppm (approx. 2 mg/kg bw/day).

Cyproconazole treatment resulted in significant embryo/foetal toxicity in the rat from $\geq$ 24 mg/kg bw/day (increased post implantation loss, reduced foetal body weight and reduced and/or delayed ossification). Cyproconazole was clearly shown to induce serious malformations at the higher doses in the rat developmental toxicity studies. Hydrocephalus and palatoschisis occurred in all three rat studies and was seen from 20 mg/kg bw/day (Machera, 1996). At dose levels where malformations occurred, maternal toxicity was recorded as reduced weight gain/mean body weight loss during days 6 – 11 of gestation, specifically from days 6-8. Mean weight gain thereafter was generally similar to controls.

Early reduced mean weight gain/body weight loss was seen in pregnant rabbits at 50 mg/kg bw/day. In the first study, post implantation loss was increased at ≥10 mg/kg bw/day. This was not apparent in the second study where there was an increase in skeletal malformations at 50 mg/kg bw/day and possible at 10 mg/kg bw/day.

Overall the NOEL for developmental toxicity was 1.7 mg/kg bw/day based on the two-generation study (and 2 mg/kg in the rabbit developmental studies). The parental NOEL was 2 mg/kg bw/day in the 2-generation study and was 10 mg/kg bw/day in the rabbit developmental studies.

Therefore, it is proposed that cyproconazole should be classified as Category 2 reproductively toxic according to council Directive 67/548/EEC (Categroy 1B according to CLP Regulation 1272/2008) and labelled accordingly.

***Relevant metabolites of cyproconazole***

Metabolites M21/M21a and M36 (also named NOA 405870 and NOA 405872, respectively) were found in the milk and in the urine of lactating goats. They were found in the rat at minor amounts only (0.02-0.06% of applied dose in urine). Therefore, the toxicological profile of these metabolites was investigated.

Metabolite M21/21a was investigated in an acute oral toxicity study in the rat at a dose level of 2000 mg/kg bw. This dose was found to be non-toxic to rats. The oral LD50 for rats is therefore greater than 2000 mg/kg bw. In a bacterial reverse mutation assay (Ames test) no evidence for a mutagenic potential was found.

For metabolite NOA 405872 an oral LD50 value of greater than 2000 mg/kg bw was obtained for rat and mouse. In 3 tests (*in vitro* Ames test and mouse lymphoma cell assay plus *in vivo* mouse micronucleus assay) NOA 405872 showed no evidence for a mutagenic potential. Although NOA 405872 showed apparent clastogenic potential in one *in vitro* system (CHO cells), since this finding was not confirmed *in vivo*, this finding is considered to be of no relevance for humans. A subchronic (28-day) feeding study in rats resulted in deaths at the test limit dose of 20,000 ppm but minimal toxicity only below this dose level. The NOEL in this study was at 1500 ppm and therefore considerably above the respective value of the parent compound cyproconazole (100 ppm).

In summary, the two major metabolites in goat milk show favourable toxicological profiles. Acute and subchronic toxicity studies indicate a significantly lower toxicity than the parent compound. Therefore, the two metabolites are unlikely to contribute to the toxicity of cyproconazole.

Triazole alanine, (TA or CGA 131013) is the major crop metabolite for many triazole derivatives. It can be assumed that TA is a conjugate of 1,2,4-triazole that is taken up by the plants from the soil.

CGA 131013 is rapidly absorbed and excreted, mainly as the unchanged parent compound in the urine. A small proportion is excreted as the N-acetyl metabolite. CGA131013 is of very low acute oral toxicity in rats and mice. No specific adverse effects on organs were noticed following repeated oral administration of CGA 131013. In 90-day feeding studies in rats and dogs, retarded body weight development (at high dose levels only) was found to be the most sensitive parameter. There was no evidence of genotoxicity in *in vitro* and *in vivo* assays. CGA131013 is not a teratogen. Overall, no specific hazard is discernible from the toxicological profile of CGA 131013; the lowest NOAEL of 100 mg/kg bw/day was observed in reproductive toxicity studies in rats. CGA 131013 (triazole alanine) is considered of no toxicological relevance

***Summary of Further Toxicological Studies***

To further investigate the mode of action for liver oncogenicity in mice, the proliferative behaviour of rat and mouse liver cells as well as the inducibility of phase I and II xenobiotic-metabolising liver

enzymes upon short term treatment were assessed. Generally, the pathological responses as observed in the liver cell proliferation study were similar in rats and mice with centrilobular hepatocyte hypertrophy being the major change in both species. Hepatocyte vacuolation was found in both rats and mice but the distribution showed differences between the species. In the rat study, the low dose group of 20 ppm (1.5 mg/kg/day) was found to be the no-effect level. In the mouse study a no-effect level could not be established and 15 ppm (2.2 mg/kg/day) was set as a low-effect level for hepatic cell proliferation, enlargement and vacuolation.

Liver cell proliferation after treatment with cyproconazole showed distinct species differences. In the mouse study there was an increase in cell proliferation beginning at day two of treatment. In the rat study there was no consistent evidence for an increase in cell proliferation during the comparable period. Thus, the species difference observed may reflect the species difference in the oncogenic potential of cyproconazole.

Cyproconazole was found to be a strong phenobarbital-type inducer of xenobiotic-metabolising enzymes in rat and mouse. In the mouse this comprises an induction of cytochrome P450 isoenzymes of subfamily CYP2A, CYP2B and CYP3A and the phase II enzymes microsomal epoxide hydrolase, microsomal UDP-glucuronosyltransferase and cytosolic glutathione S-transferase. Likewise, a mode of action of cyproconazole as a polycyclic aromatic hydrocarbon- or peroxisome-type inducer can be excluded as cytochrome P450 isoenzymes of subfamily CYP1A and CYP4A were not or only slightly induced.

**Additional mechanistic studies have been submitted to the RMS in the context of the 91/414 review:**

1. Milburn G, (2006a). Cyproconazole (SAN619) And Phenobarbital: 14 Day Dietary Study for the Evaluation of Liver Effects in Three Strains of Mice. Syngenta Report Number: XM7470-TEC
2. Milburn G, (2006b). Exposure of Wild-Type and CAR null C3H Male Mice via the Oral (Dietary) Route for 7 Days. Syngenta Report Number: XM7573-TEC
3. Milburn G, (2006c). Phenobarbital: Exposure of Wild-type and CAR null C3H Male Mice via the Oral (Dietary) Route for 3 and 7 days. Syngenta Report Number: XM7584-TEC-R2

It was concluded that there was clear evidence in the mouse for involvement of CAR activation, altered expression of genes involved in cell cycle and apoptosis regulation, hepatocyte proliferation, suppression of apoptosis, liver growth, and single cell necrosis. However, cyproconazole is also cytotoxic to the liver, resulting in degenerative lesions (necrosis, vacuolation) and subsequent liver cell proliferation. These conditions may create an environment where spontaneously mutated liver cells have a proliferative advantage, leading to clonal expansion and the development of pre-neoplastic foci after long-term treatment to form tumours. It was clearly shown in these additional studies that PB and CCZ share a common initial event which is CAR receptor activation, and that the expression of certain genes is similar, but a causal link to liver tumourigenesis is not proven in these studies though they do support the notion that CCZ may act in a similar manner to PB. Other events downstream of this system or CAR-independent events influenced by CCZ and PB exposure may also be operating. Overall, the data is not conclusive enough to fully eliminate concern for the role of CCZ in the promotion of liver carcinogenesis that was seen in the mouse and the proposal of Cat 3; R40 (CLP Cat 2; H351).

*AEL derivation*

**$AEL_{LONG-TERM}$**

The NOAELs from all sub-chronic studies conducted in mouse, rat and dog and the NOAELs from the long-term and reproductive toxicity studies were considered. The most consistent toxicological findings, which were observed in long term studies with mouse, rat and dog, were changes in the

liver. Both rat and mice revealed similar NOAELs at around 2 mg/kg bw. The NOAEL of the 1-year dog study was at 3.2 mg/kg. In the 2-generation reproduction study a NOAEL of 1.4 mg/kg was found for males, based again on liver findings. As the respective value for males in the 2-year study was slightly higher (2.2 mg/kg/bw/day), the value from the reproduction study is not considered to be relevant for AEL setting. The NOAEL for females was at 1.8 mg/kg based on increased pre-/peri- and post natal losses. To sum up, all relevant NOAELs from mouse and rat are at approximately 2 mg/kg bw., which is below the NOAEL from the dog. Therefore, $AEL_{long\ term}$ calculation is based on a NOAEL of 2 mg/kg bw. using a safety factor of 100, which gives a value of 0.02 mg/kg bw/day.

**$AEL_{ACUTE}$**

The calculation of the $AEL_{acute}$ may be based on the NOAEL from a suitable acute or subchronic toxicity study, including reproductive toxicity data, with the application of an appropriate Safety Factor (SF) for human exposure.
Cyproconazole was found to be teratogenic in the rat at maternally toxic doses, i.e., 20 mg/kg bw/day. In addition, adverse effects were seen on embryo/foetal development in a slight increase in pre-/peri- and postnatal losses in the rat 2-generation study at 120 ppm (equivalent to approximately 10 mg/kg bw/day) and an increase in post-implantation loss was seen in the rabbit developmental study at 10 mg/kg bw/day. The NOAEL in both cases is approximately 2 mg/kg bw/day. Therefore, the ARfD is calculated using a safety factor of 100, as 0.02 mg/kg bw/day.

**$AEL_{MEDIUM}$**

The $AEL_{medium}$ is defined on the basis of short-term toxicity studies in animals,(including reproductive toxicity) , applying a Safety Factor (SF) for human exposure. As operators are exposed to pesticides mainly via the dermal route, available information on systemic toxicity upon dermal exposure and on dermal absorption has to be taken into consideration apart from toxicity data upon oral exposure. The use of short-term toxicity data including reproductive toxicity data, is appropriate for operator risk assessment.

The lowest NOAEL was obtained in the 2-generation study in male F0 rats (20 ppm; 1.4 mg/kg bw/day ). A slight (statistically significant) increase in relative liver weight was associated with a marginally increased incidence in liver fatty change. This observation is of questionable significance as no toxicity was seen in $F_0$ females or $F_1$ males and females. In addition, the 90-day rat studies indicated that the NOEL for liver effects was in excess of 80 ppm (6.4 mg/kg bw/day ).

Overall, the most sensitive endpoint was developmental toxicity with some adverse effects on pre-/peri- and postnatal loss in the 2-generation study conducted in the rat and increased post-implantation loss in the rabbit developmental toxicity study. The NOAELS for these effects were 1.7 mg/kg bw/day in the female rat and 2 mg/kg bw/day in the rabbit leading to an overall NOAEL of 2 mg/kg bw/day.

Application of a safety factor of 100 gives a medium term AEL of 0.02 mg/kg bw/day.

### *2.2.1.2. Exposure Assessment*

The exposure assessment for industrial direct exposure was carried out as described in the following tables.

| Exposure path | Industrial use | Via the environment |
|---|---|---|
| Inhalation | *Yes* | *Yes* |

| | | |
|---|---|---|
| Dermal | *Yes* | *Yes* |
| Oral | *No* | *Yes* |

**Summary of Main Paths of direct Human Exposures**

***Industrial use: double-vacuum and vacuum-pressure impregnation***

| Exposure path | **Industrial use : double-vacuum and vacuum-pressure impregnation** | | | |
|---|---|---|---|---|
| | Mixing/loading | Application | Post application | Maintenance/ cleaning |
| Inhalation | No exposure | No significant exposure (exposure calculation covered by post application) | Exposure expected. Modelled with TNsG handling model 1. | No exposure |
| Dermal | No exposure | No significant exposure (exposure calculation covered by post application) | Exposure expected. Modelled with TNsG handling model 1. | Exposure when cleaning |
| Oral | No exposure | No exposure | No exposure | No exposure |

***Industrial use: dipping and deluge/flood***

| Exposure path | **Industrial use : dipping and deluge/flood** | | | |
|---|---|---|---|---|
| | Mixing/loading | Application | Post application | Maintenance/ cleaning |
| Inhalation | No exposure | No significant exposure (exposure calculation covered by post application) | Exposure expected. Modelled with TNsG dipping model 1 | No exposure |
| Dermal | No exposure | No significant exposure (exposure calculation covered by post application) | Exposure expected. Modelled with TNsG dipping model 1 | Exposure when cleaning |
| Oral | No exposure | No exposure | No exposure | No exposure |

***Industrial use: spraying***

| Exposure path | **Industrial use : spraying** | | | |
|---|---|---|---|---|
| | Mixing/loading | Application | Post application | Maintenance/ cleaning |
| Inhalation | Exposure modelled using TNsG mix and load model | Exposure modelled using spray model 2 | No exposure | No exposure |
| Dermal | Exposure modelled using TNsG mix and load model | Exposure modelled using spray model 2 | Very limited exposure compared to application no exposure calculation | Exposure when cleaning |
| Oral | No exposure | No exposure | No exposure | No exposure |

**Indirect or secondary exposure**

The exposure assessment for indirect exposure was carried out as described below.

| **Indirect exposure scenarios modelled.** | |
|---|---|
| Model taken from TNsG 2002 | Adult sanding treated wood |
| Model taken from TNsG 2002 | Adult sanding treated wood 6 hours |
| Model taken from TNsG 2002 | Infant chewing wood off-cut |
| Model taken from TNsG 2002 | Inhalation of volatilised residues (infant) |
| Model taken from TNsG 2002 | Inhalation of volatilised residues (Child) |
| Model taken from TNsG 2002 | Inhalation of volatilised residues (Adult) |
| Model taken from TNsG 2002 | Child playing on treated structure |
| Model taken from TNsG 2002 | Infant playing on treated structure |

### *2.2.1.3. Risk Characterisation*

**Professional industrial Use**

The possibility that an industrial operator is exposed to EVIPOL® 60 SL during normal usage has been considered. In view of the repeated exposures involved, it is appropriate to characterize the resulting risk to the operator based on an MOE approach as follows:

| **Assessment** | **Default values used** | **Systemic exposure (mg/kg bw/day)** | **Systemic NOAEL medium term/long term mg/kg bw/day** | **MOE** |
|---|---|---|---|---|
| Tier (1) Double Vacuum treatment | Active conc 0.4%, 4 cycles, 100% penetration for coveralls ,10% dermal absorption, 60kg body wt. | 0.26 mg/kg bw day | 2.0 mg/kg bw/day | 7 |

| | | | | |
|---|---|---|---|---|
| Tier (2) Double Vacuum treatment | Active conc 0.4%, 4 cycles, 10% penetration for treated coveralls ,10% dermal absorption, 60kg body wt. | 0.05 mg/kg bw day | 2.0 mg/kg bw/day | 40 |
| Total exposure including application, repair and cleaning | | 0.05363 | 2.0 mg/kg bw/day | 37 |
| Tier (1) Vacuum Pressure treatment | Active conc 0.02%, 4 cycles, 100% penetration for coveralls , 10% dermal absorption, 60kg body wt. | 0.013 mg/kg bw day | 2.0 mg/kg bw/day | 153 |
| Tier (2) Vacuum Pressure treatment | Active conc 0.02%, 3 cycles, 10% penetration for treated coveralls , 10% dermal absorption, 60kg body wt. | 0.0027 mg/kg bw day | 2.0 mg/kg bw/day | 740 |
| Total exposure including application, repair and cleaning | | 0.00633 | 2.0 mg/kg bw/day | 316 |
| Tier (1) Deluge/flood<br><br>Dipping model 1 | Active conc 0.2%, 30 min cycle, 100% penetration for coveralls , 10% dermal absorption, 60kg body wt. | 0.02 mg/kg bw day | 2.0 mg/kg bw/day | 100 |
| Tier (2) Deluge/flood<br><br>Dipping model 1 | Active conc 0.2%, 30 min cycle, 10% penetration for treated coveralls , 10% dermal absorption, 60kg body wt. | 0.004 mg/kg bw day | 2.0 mg/kg bw/day | 500 |
| Total exposure including application, repair and cleaning | | 0.00763 | 2.0 mg/kg bw/day | 262 |

| | | | | |
|---|---|---|---|---|
| Tier (1) | Mix and load Active conc 5.2%, 100% penetration for coveralls , 10% dermal absorption, 60kg body wt. | 0.017 | 2.0 mg/kg bw/day | 117 |
| Tier (2) | Mix and load Active conc 5.2%, 10% penetration for treated coveralls , 10% dermal absorption, 60kg body wt. | 0.0018 | 2.0 mg/kg bw/day | 1111 |
| Tier (1)Spraying | Active conc 0.2%, 40 mins, 100% penetration for coveralls , 10% dermal absorption, 60kg body wt. | 0.03 mg/kg bw day | 2.0 mg/kg bw/day | 67 |
| Tier (2)Spraying | Active conc 0.2%, 40 mins, 10% penetration for coveralls , 10% dermal absorption, 60kg body wt. | 0.006 mg/kg bw day | 2.0 mg/kg bw/day | 333 |
| Total exposure including application, repair and cleaning | | 0.01143 | 2.0 mg/kg bw/day | 175 |
| Maintenance/repair of the spray equipment | Active conc 0.2%, exposure to 1 ml., 100% penetration through gloves , 10% dermal absorption, 60kg body wt. | 0.0033 mg/kg bw day | 2.0 mg/kg bw/day | 606.06 |
| Tier (1)Cleaning of equipment | Active conc 0.2%, exposure to 1 ml., 100% penetration through gloves , 10% dermal absorption, 60kg body wt. | 0.0033 mg/kg bw day | 2.0 mg/kg bw/day | 606.06 |

| | | | | |
|---|---|---|---|---|
| Tier (2)Cleaning of equipment | Active conc 0.2%, exposure to 1 ml., 10% penetration through gloves , 10% dermal absorption, 60kg body wt. | 0.00033 mg/kg bw day | 2.0 mg/kg bw/day | 6060.6 |

MOE values over 100 are considered acceptable in relation to their risk.

Characterization of the resulting risk to the operator based on an Exposure/AEL quotient approach is as follows:

| **Assessment** | **Default values used** | **Systemic exposure (mg/kg bw/day)** | **Systemic AEL medium term/long term**<br><br>**mg/kg bw/day** | **Exposure/AEL** |
|---|---|---|---|---|
| Tier (1) Double Vacuum treatment | Active conc 0.4%, 4 cycles, 100% penetration for coveralls ,10% dermal absorption, 60kg body wt. | 0.26mg/kg bw day | 0.02 mg/kg bw/day | 13 |
| Tier (2) Double Vacuum treatment | Active conc 0.4%, 64cycles, 10% penetration for treated coveralls ,10% dermal absorption, 60kg body wt. | 0.05 mg/kg bw day | 0.02 mg/kg bw/day | 2.5 |
| Total exposure including application, repair and cleaning | | 0.05363 | 0.02 mg/kg bw/day | 3 |
| Tier (1) Vacuum Pressure treatment | Active conc 0.02%, 3 cycles, 100% penetration for coveralls , 10% dermal absorption, 60kg body wt. | 0.013 mg/kg bw day | 0.02 mg/kg bw/day | 0.65 |

| | | | | |
|---|---|---|---|---|
| Tier (2) Vacuum Pressure treatment | Active conc 0.02%, 4 cycles, 10% penetration for treated coveralls , 10% dermal absorption, 60kg body wt. | 0.0027 mg/kg bw day | 0.02 mg/kg bw/day | 0.135 |
| Total exposure including application, repair and cleaning | | 0.00633 | 0.02 mg/kg bw/day | 0.32 |
| Tier (1) Deluge/flood | Active conc 0.2%, 30 min cycle, 100% penetration for coveralls , 10% dermal absorption, 60kg body wt. | 0.02 mg/kg bw day | 0.02 mg/kg bw/day | 1 |
| Dipping model 1 | | | | |
| Tier (2) Deluge/flood | Active conc 0.2%, 30 min cycle, 10% penetration for treated coveralls , 10% dermal absorption, 60kg body wt. | 0.004 mg/kg bw day | 0.02 mg/kg bw/day | 0.2 |
| Dipping model 1 | | | | |
| Total exposure including application, repair and cleaning | | 0.00763 | 0.02 mg/kg bw/day | 0.38 |
| Tier (1) | Mix and load Active conc 5.2%, 100% penetration for coveralls , 10% dermal absorption, 60kg body wt. | 0.017 | 0.02 mg/kg bw/day | 0.85 |
| Tier (2) | Mix and load Active conc 5.2%, 10% penetration for treated coveralls , 10% dermal absorption, 60kg body wt. | 0.0018 | 0.02 mg/kg bw/day | 0.09 |

| | | | | |
|---|---|---|---|---|
| Tier (1)Spraying | Active conc 0.2%, 40 mins, 100% penetration for coveralls , 10% dermal absorption, 60kg body wt. | 0.03 mg/kg bw day | 0.02 mg/kg bw/day | 1.5 |
| Tier (2)Spraying | Active conc 0.2%, 40 mins, 10% penetration for coveralls , 10% dermal absorption, 60kg body wt. | 0.006 mg/kg bw day | 0.02 mg/kg bw/day | 0.3 |
| Total exposure including application, repair and cleaning | | 0.01143 | 0.02 mg/kg bw/day | 0.57 |
| Maintenance/repair of the spray equipment | Active conc 0.2%, exposure to 1 ml., 100% penetration through gloves , 10% dermal absorption, 60kg body wt. | 0.0033 mg/kg bw day | 0.02 mg/kg bw/day | 0.165 |
| Tier (1)Cleaning of equipment | Active conc 0.2%, exposure to 1 ml., 100% penetration through gloves , 10% dermal absorption, 60kg body wt. | 0.0033 mg/kg bw day | 0.02 mg/kg bw/day | 0.165 |
| Tier (2)Cleaning of equipment | Active conc 0.2%, exposure to 1 ml., 10% penetration through gloves , 10% dermal absorption, 60kg body wt. | 0.00033 mg/kg bw day | 0.02 mg/kg bw/day | 0.0165 |

A ratio value that is < or = to 1 is considered acceptable in relation to their risk.

**Overall Assessment Of The Risk For The Use Of The Active Substance In Biocidal Products**

The calculations above detail the systemic dose (dermal, inhalation and oral, as appropriate) and compare it to the $AEL_{medium}$ (0.02 mg/kg bw/day) to establish a Margin of Exposure (MOE (MOS)). It

has been determined that a number of normal wood treatment process are not safe when cyproconazole formulated as EVIPOL® 60 SL is applied.

Deluge/flood was found to be safe with PPE.

However, a safe use for double vacuum treatment was not found. Exposure to double vacuum treatment operators wearing PPE was estimated at 0.05 mg/kg bw day equating to a margin of exposure of 40. This suggests a risk to operators using EVIPOL® 60 SL in a double vacuum process.

Safe uses were found for single vacuum pressure and spray applications. Exposure to spray and single vacuum treatment operators wearing PPE was estimated at 0.006 mg/kg bw day (tier 2) and 0.0027 mg/kg bw day (tier 1), respectively, equating to a margin of exposure of greater than 100. These values suggest an acceptable use pattern to operators using EVIPOL® 60 SL in single vacuum and spray processes.

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## Risk characterisation for product type 8 indirect exposure

Determination of Margin of Exposure (MOE) (Impregnation – from double vaccum and vaccum pressure application)

| Assessment | Inhalation exposure | Dermal exposure | Oral exposure | Total systemic exposure | Systemic NOAEL (medium/long term or acute) | MOE |
|---|---|---|---|---|---|---|
| Adult sanding treated wood | 0.000002mg/kg bw/day | 0.0002 mg/kg bw day | Negligible | 0.0002 mg/kg bw day | 2.0 mg/kg bw/day | 10000 |
| Adult sanding treated wood 6 hours | 0.000012mg/kg bw day | 0.0016 mg/kg bw day | Negligible | 0.0013 mg/kg bw day | 2.0 mg/kg bw/day | 1538 |
| Infant chewing wood off-cut | Negligible | Negligible | 0.012 mg/kg bw/day | 0.012 mg/kg bw/day | 2.0 mg/kg bw/day | 166.67 |
| Inhalation of volatilised residues (infant) | 0.00085 mg/kg bw day | Negligible | Negligible | 0.00085 mg/kg bw day | 2.0 mg/kg bw/day | 2352.94 |
| Inhalation of volatilised residues (Child) | 0.0008 mg/kg bw day | Negligible | Negligible | 0.0008 mg/kg bw day | 2.0 mg/kg bw/day | 2500.00 |
| Inhalation of volatilised residues (Adult) | 0.0005 mg/kg bw day | Negligible | Negligible | 0.0005 mg/kg bw day | 2.0 mg/kg bw/day | 4000.00 |
| Child playing on treated structure | Negligible | 0.0002 mg/kg bw day | Negligible | 0.0002 mg/kg bw day | 2.0 mg/kg bw/day | 10000 |
| Infant playing on treated structure | Negligible | 0.001 mg/kg bw day | 0.001 mg/kg bw day | 0.002 mg/kg bw day | 2.0 mg/kg bw/day | 1000.00 |

Determination of Exposure/AEL (Impregnation – from double vaccum and vaccum pressure application)

| Assessment | Inhalation exposure | Dermal exposure | Oral exposure | Total systemic exposure | Systemic AEL (medium/long term or acute) | Exposure/AEL |
|---|---|---|---|---|---|---|
| | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Adult sanding treated wood | 0.000002mg/kg bw/day | 0.0002 mg/kg bw day | Negligible | 0.0002 mg/kg bw day | 0.02 mg/kg bw/day | 0.01 |
| Adult sanding treated wood 6 hours | 0.000012mg/kg bw day | 0.0016 mg/kg bw day | Negligible | 0.0013 mg/kg bw day | 0.02 mg/kg bw/day | 0.065 |
| Infant chewing wood off-cut | Negligible | Negligible | 0.012 mg/kg bw/day | 0.012 mg/kg bw/day | 0.02 mg/kg bw/day | 0.6 |
| Inhalation of volatilised residues (infant) | 0.00085 mg/kg bw day | Negligible | Negligible | 0.00085 mg/kg bw day | 0.02 mg/kg bw/day | 0.0425 |
| Inhalation of volatilised residues (Child) | 0.0008 mg/kg bw day | Negligible | Negligible | 0.0008 mg/kg bw day | 0.02 mg/kg bw/day | 0.04 |
| Inhalation of volatilised residues (Adult) | 0.0005 mg/kg bw day | Negligible | Negligible | 0.0005 mg/kg bw day | 0.02 mg/kg bw/day | 0.025 |
| Child playing on treated structure | Negligible | 0.0002 mg/kg bw day | Negligible | 0.0002 mg/kg bw day | 0.02 mg/kg bw/day | 0.01 |
| Infant playing on treated structure | Negligible | 0.001 mg/kg bw day | 0.001 mg/kg bw day | 0.002 mg/kg bw day | 0.02 mg/kg bw/day | 0.1 |

Determination of Margin of Exposure (MOE) (Surface application - from spraying)

| **Assessment** | **Inhalation exposure** | **Dermal exposure** | **Oral exposure** | **Total systemic exposure** | **Systemic AEL (medium/long term or acute)** | **Exposure/AEL** |
|---|---|---|---|---|---|---|
| **Adult sanding treated wood (Surface treatment)** | **0.000002mg/kg bw/day** | **0.00004 mg/kg bw day** | **Negligible** | **0.00004 mg/kg bw day** | **2 mg/kg bw/day** | **50000** |

| | | | | | | |
|---|---|---|---|---|---|---|
| Adult sanding treated wood 6 hours (Surface treatment) | 0.000012mg/kg bw day | 0.00025 mg/kg bw day | Negligible | 0.00025 mg/kg bw day | 2 mg/kg bw/day | 8000 |
| Child playing on treated structure (Surface treatment) | Negligible | 0.000035 mg/kg bw day | Negligible | 0.000035 mg/kg bw day | 2 mg/kg bw/day | 57142.8571 |
| Infant playing on treated structure (Surface treatment) | Negligible | 0.00012 mg/kg bw day | 0.0012 mg/kg bw day | 0.0013 mg/kg bw day | 2 mg/kg bw/day | 1538.46154 |

Determination of Exposure/AEL (Surface application)

| Assessment | Inhalation exposure | Dermal exposure | Oral exposure | Total systemic exposure | Systemic AEL (medium/long term or acute) | Exposure/AEL |
|---|---|---|---|---|---|---|
| Infant playing newly treated wet structure | Negligible | 0.003mg/kg bw day | 0.06 mg/kg bw day | 0.063 mg/kg bw day | 0.02 mg/kg bw/day | 3.15 |
| Adult sanding treated wood (Surface treatment) | 0.000002mg/kg bw/day | 0.00004 mg/kg bw day | Negligible | 0.00004 mg/kg bw day | 0.02 mg/kg bw/day | 0.002 |
| Adult sanding treated wood 6 hours (Surface treatment) | 0.000012mg/kg bw day | 0.00025 mg/kg bw day | Negligible | 0.00025 mg/kg bw day | 0.02 mg/kg bw/day | 0.0125 |
| Child playing on treated structure (Surface treatment) | Negligible | 0.000035 mg/kg bw day | Negligible | 0.000035 mg/kg bw day | 0.02 mg/kg bw/day | 0.00175 |
| Infant playing on treated structure (Surface treatment) | Negligible | 0.00012 mg/kg bw day | 0.0012 mg/kg bw day | 0.0013 mg/kg bw day | 0.02 mg/kg bw/day | 0.065 |

The processes considered are industrial only and expected to be carried out in an industrial setting. On this basis exposure of a child to wet treated wood has not been considered.

**Overall Assessment Of The Risk For The Use Of The Active Substance In Biocidal Products**

## Indirect exposure

The processes considered are industrial only and expected to be carried out in an industrial setting. On this basis exposure of a child to wet treated wood has not been considered.

Results from indirect exposure modelling suggest that post application exposure to cyproconazole applied as EVIPOL® 60 SL will not result in exposure above the $AEL_{(acute/medium-term/long-term)}$ of 0.02mg/kg bw/day. The model "infant chewing a wood cut-off" leads to the highest realistic expected indirect exposure. However, infant exposure remains below the AEL when "infant chewing a wood cut-off" is combined with exposure modelled for the infant playing on a treated structure.

The above calculations suggest that exposure in excess of the AEL will not result from indirect/secondary exposure to the active substance.

#### *2.2.1.4. Combined exposure*

Exposure in excess of the AEL has been modelled for industrial double vacuum application. Combined exposure from cleaning equipment and vacuum pressure, spray or dipping applications with PPE yield exposures less than the AEL. On this basis industrial processes with their associated cleaning steps are safe with the exception of double vacuum pressure.

## 2.2.2. Environmental Risk Assessment

### *2.2.2.1. Fate and Distribution in the Environment*

The degradation of cyproconazole has been studied in a number of laboratory studies and is well understood. Degradation in soil is principally mediated by microorganisms under aerobic conditions. Soil photolysis and studies under sterile or anaerobic conditions demonstrate little or no degradation of cyproconazole.

Cyproconazole is stable to hydrolysis and is expected to be stable to direct photolysis in water (at $\lambda > 290$ nm UV adsorption $\varepsilon < 10$ $L^{-1}$ $mol^{-1}$ $cm^{-1}$). Cyproconazole is considered not readily biodegradable. Degradation in two dark water/sediments at 20°C was very slow ($DT_{50}$ >> 1 year). The main dissipation process from the water phase is partition to sediment. Only minor metabolites were found (max. 4.6 % AR after 259 d). Mineralization was negligible, and unextractable radioactivity amounted to 3.8 – 10 % AR after 259 days. The ratio of the cyproconazole diasteroisomers did not change during the course of the study. However, enantiomeric ratios were not checked during these experiments.

The route of degradation of cyproconazole in soil under dark aerobic conditions at 20 – 22 °C was investigated in three studies with $^{14}C$ triazole-labelled cyproconazole (one soil: pH 7.2), $^{14}C$-benzyl-labelled cyproconazole (three soils: pH 4.3 – 7.0), and $^{14}C$-phenyl-labelled cyproconazole (one soil: pH 7). In all these studies degradation of cyproconazole was slow, and considerable amounts of radioactivity remained as unmodified cyproconazole at the end of the respective experiments. In the study performed with $^{14}C$-triazole-labelled cyproconazole, the metabolite 1,2,4-triazole (max. 17.36 % AR after 140 days, end of the study) was identified as the only major metabolite in soil (≥ 10%AR). Mineralization of the triazole ring was negligible, and non-extracted radioactivity amounted to 16 % AR at the end of the study (140 days). In the studies performed with the $^{14}C$-benzyl and the $^{14}C$-phenyl-labelled cyproconazole no major metabolites were identified and only very minor (< 3 % AR) polar fractions were observed as a consequence of cyproconazole degradation. Substantial mineralization was only observed in two of the experiments performed with cyproconazole $^{14}C$ labelled in the benzyl position. Non-extracted radioactivity amounted to 13- 23.9 % AR (after 112 days) and 20.8-21.5 % AR (after 140 days) in the experiments performed with the $^{14}C$-benzyl and $^{14}C$-phenyl-labelled cyproconazole, respectively. Only slight variations were observed on the diasteromeric ratios during the experiments. These variations are not significant and consistent enough to consider that diasteromeric degradation occurs. However, enantiomeric ratios were not tested during these experiments.

The degradation of cyproconazole in soil under dark anaerobic conditions was investigated in two studies that show that cyproconazole is stable under anaerobic conditions.

Photolysis of cyproconazole in soil was investigated under simulated sunlight (Xe lamp filtered for $\lambda < 290$ nm). Cyproconazole was stable in the dark control, and only very slight degradation was observed in the irradiated experiment. It may be considered that photolysis will not contribute to the environmental dissipation of cyproconazole.

Persistence of cyproconazole in soil under dark aerobic conditions was investigated in the several studies. Under laboratory conditions, the $DT_{50}$ ranged from 100 d to 427 d at 12°C. The geomean $DT_{50lab}$ was 298 d. A number of field dissipation studies were submitted (1 in UK (4 sites), 5 in France, and 5 in Germany). For some of the field trials the data had to be fitted to DFOP kinetics in order to obtain reliable results. Residues of the major soil metabolite 1,2,4-triazole were not measured in any of the field studies. In field trials the $DT_{50}$ ranged from 28.97 d (DFOP) to 162 d(SFO). The corresponding $DT_{90}$ ranged from 306.92 d(SFO) to >1,000 days(DFOP).

The rate of degradation of the major soil metabolite 1,2,4-triazole under dark aerobic conditions at 20 °C was investigated in one study with three soils. Under these conditions 1,2,4-triazole was low to moderately persistent in soil ($DT_{50lab}$ 6.8-12.04 d, 20 °C). At 12°C the geomean $DT_{50}$ was 18.09 d.

Cyproconazole is moderately adsorbed to soil ($K_{foc}$ 364 L/kg, n = 5, $K_{doc}$ = 473 L/kg). The major soil metabolite, 1,2,4-triazole is mobile in soil ($K_{foc}$ 89 L/kg, n = 4, $K_{doc}$ = 124 L/kg). Photochemical oxidative degradation of cyproconazole was estimated with the AOPWIN software. The photochemical half-life of cyproconazole in the atmosphere was determined to be around 1 day, and therefore cyproconazole is not expected to persist in the atmosphere.

### *2.2.2.2. Effects Assessment*

Cyproconazole has been evaluated for its use as a wood preservative (Product type 8). An environmental exposure assessment was submitted by the applicant to support cyproconazole use (Evipol® 60 SL).

The co-formulants (i.e. water, surfactant and co-solvents) for the industrial use product EVIPOL® 60SL (containing 5.175% w/w cyproconazole) do not include any environmental classification in their MSDS's. However ecotoxicity information are available for the formulation EVIPOL® 60SL (acute fish $LC_{50}$ is 35.36 mg/L) which indicates that the formulation is of similar acute toxicity to the active substance alone (fish $LC_{50}$ 19-26 mg/L). Given that there is no significant increased toxicity of the formulation compared to the active substance alone, it is considered that any risk associated with the use of the product is covered by the assessment of the active substance. Especially since chronic data for the active substance exist for both the aquatic and terrestrial compartments.

There is one major metabolite, CGA 71019 (1,2,4-triazole), for which a risk assessment has been conducted in the relevant compartments.

#### *2.2.2.2.1Aquatic compartment*

***Surface water***

Cyproconazole (a.i.) is of moderate acute toxicity to fish (96 h $LC_{50}$ = 19 mg a.i./L), increasingly toxic to aquatic invertebrates (96 h $EC_{50}$ Eastern oyster = 2.6 mg a.i./L) and very toxic to green algae (96 h $E_bC_{50}$ = 0.077 mg a.i./L). The lowest effect value in a long-term laboratory study was obtained for green algae (96 h NOEC = 0.021 mg a.i./L) when compared to the values for fish (21 d NOEC < 0.16 mg a.i./L) and daphnids (lowest 21 d NOEC = 0.023 mg a.i./L) . A $PNEC_{aquatic}$ of 0.0021 mg a.i./L was obtained from the available studies (AF=10).

The metabolite, CGA 71019 (1,2,4-triazole), is of low toxicity to fish (96 h $LC_{50}$ = 498 mg CGA 71019/L; 28 d NOEC = >100 mg CGA 71019/L) and daphids (48 h $EC_{50}$ = >100 mg CGA 71019/L). Green algae exhibited the greatest sensitivity to the metabolite (72 h $E_bC_{50}$ = 13 mg CGA 71019/L; 96 h NOEC = 6.8 mg CGA 71019/L). $PNEC_{aquatic}$ of 0.136 mg CGA 71019/L was obtained from the available studies (AF=50).

***Sediment***

Based on the available toxicity data for sediment dwelling Chironomus riparius (28 d NOEC = 50 mg a.i./kg sediment dwt) a $PNEC_{sed}$ of 0.109 mg a.i./kg wwt was derived (AF=100). The PNECsed for the metabolite CGA 71019 (1,2,4-triazole) was derived using the equilibrium partitioning method based on the lack of experimental data. The $PNEC_{sed}$ was determined to be 0.37 mg CGA 71019/kg wwt.

***STP microorganisms***

Cyproconazole is of low toxicity to microbes in sewage sludge ($EC_{50}$ = > 100 mg a.i./L). The $PNEC_{STP}$ = 1 mg a.i./L (AF=100). Based on the proposed use of the biocidal product, exposure of sewage treatment plant to CGA 71019 is unlikely, thereby obviating the need to conduct a risk assessment in this instance.

### *2.2.2.2.2Terrestrial compartment*

Tests with earthworms, collembolans, plants and soil microorganisms have been provided. Cyproconazole had a low acute toxicity to earthworms (14 d $LC_{50}$ = 335 mg a.i./kg; NOEC = 125-250 mg a.i./kg), plants, collembola (28 d $LC_{50}$ = 94.1 mg a.i./kg; NOEC = 55.8 mg a.i./kg) and field soil microorganisms (>100 mg a.i./ha). The most sensitive test using technical cyproconazole was the laboratory test on carbon and nitrogen metabolism. While the test indicated that treatment with the active ingredient had very little impact on soil respiration and nitrification, the highest concentration tested was quite low resulting in a low and highly conservative NOEC value (>>2.25 mg a.i./kg dry wt.). The resulting PNEC for soil were therefore found to be >>0.02 mg cyproconazole/kg (wet wt.). Similarly, in the case of the metabolite the lowest NOEC value was derived from a laboratory earthworm study where no effect was observed at even the highest concentration tested. Therefore the low and highly conservative (NOEC >>0.024 mg/kg dry wt.) value resulted in a PNEC of >>0.00042 mg CGA 71019/kg (wet wt.).

### *2.2.2.3. PBT and POP Assessment*

**PBT Assessment**

***Persistence***

In soil the $DT_{50}$ for cyproconazole ranged from 100 d to 427 d at 12°C. The geomean $DT_{50lab}$ was 298 d. In field trials the $DT_{50}$ ranged from 28.97 d (DFOP) to 162 d (SFO). The corresponding $DT_{90}$ ranged from 306.92 d(SFO) to 1,000 days (DFOP). Consequently, cyproconazole meets the very persistent criterion in soil ($DT_{50}$ >180 d). An aquatic dissipation study in two dark water/sediments at 20°C is available. Degradation in both systems was very slow ($DT_{50}$ >> 1 year).

In light of this cyproconazole fulfils the criteria for very persistentin aquatic systems. The metabolite, triazole does not fulfil the persistence criteria.

***Bioaccumulation***

With an experimentally determined bioconcentration factor in fish (BCF) of 28 L/kg, cyproconazole has a low bioaccumulation potential in fish and other aquatic organisms.The octanol/water partition coefficient of the cyproconazole metabolite, CGA 71019 (log $P_{ow}$) is –1, indicating that the compound is unlikely to bioaccumulate in fish or other aquatic organisms. Specific studies on the bioaccumulation of CGA 71019 are therefore not considered necessary.

The BCF for earthworms, calculated using the equation as described by Jager (1998), is 16 L/kg indicating that cyproconazole has a low bioaccumulation potential in earthworms and other terrestrial organisms. Furthermore results of the toxicokinetic studies with laboratory rats, goats and hens showed a rapid elimination of the product in all animals. The octanol/water partition coefficient of the cyproconazole metabolite, CGA 71019 (log $P_{ow}$) is –1, indicating that the compound is unlikely to bioaccumulate in earthworms or other terrestrial

organisms. Specific studies on the bioaccumulation of CGA 71019 are therefore not considered necessary.

Additionally, the log $P_{ow}$ of 3.1 for cyproconazole also indicates a low potential for biomagnification. In accordance with the Technical Guidance Document on Risk Assessment Part II the biomagnifications factor of 1.

Therefore, neither cyproconazole nor its metabolite, triazole, fullfill the bioaccumulation or B criteria.

***Toxicity***

Since none of the NOECs for aquatic or avian studies are <0.01 mg/L cyproconazole does not fulfil the toxicity criterion (T) from an ecotoxicology perspective. However, the aquatic metabolites are not considered to be toxic in the context of this PBT assessment. The metabolite, triazole does not fulfil the T criteria from an environment point-of-view.

The mammalian toxicity data (see Doc IIA Section 3) proposes the classification of the active substance, cyproconazole, as follows: *Xn, R22 – Harmful if swallowed*; *Xn, Carc. Cat.3, R40 – limited evidence of a carcinogenic effect,* and T, *Repr. Cat. 2, R61 – may cause harm to unborn child.*

Thus, cyproconazole fulfils the toxicity criterion for mammalian toxicity based on its classification which includes *T Repr. Cat. 2, R61.*

**POP Assessment**

***Persistence***

According to the Stockholm Convention a substance is defined as persistent when the half-life of the chemical in water is greater than two months, or when its half-life in soil is greater than six months, or when its half-life in sediment is greater than six months; or if the chemical is otherwise sufficiently persistent to justify its consideration within the scope of the Convention. In soil the $DT_{50}$ for cyproconazole ranged from 100 d to 427 d at 12°C. The geomean $DT_{50lab}$ was 298 d. In field trials the $DT_{50}$ ranged from 28.97 d (DFOP) to 162 d (SFO). The corresponding $DT_{90}$ ranged from 306.92 d(SFO) to 1,000 days (DFOP). Consequently, cyproconazole meets the very persistent criterion in soil ($DT_{50}$ >180 d). An aquatic dissipation study in two dark water/sediments at 20°C is available. Degradation in both systems was very slow ($DT_{50}$ >> 1 year).

Cyproconazole fulfils the screening criteria for persistence as laid out in the Stockholm Convention.

*Bioaccumulation*

The BCF in fish is 28 L/kg. Non-edible tissue 41 L/kg, whole fish 22 L/kg, edible tissue 6.1 L/kg. A bioconcentration study in terrestrial organisms was not performed, however, for completeness the $BCF_{earthworm}$ has been modelled using the equation as described by Jager (1998) that is recommended in TGD Part II and the estimated BCF for earthworm (terrestrial) = 16 L/kg. Therefore cyproconazole does not fulfil the bioaccumulation criteria.

The octanol/water partition coefficient of the cyproconazole metabolite, CGA 71019 (log $P_{ow}$) is –1, indicating that the compound is unlikely to bioaccumulate in earthworms or other terrestrial organisms. Specific studies on the bioaccumulation of CGA 71019 are therefore not considered necessary as it does not fulfil the bioaccumulation criteria.

*Long-range environmental transport*

Cyproconazole has a vapour pressure of $2.6 \times 10^{-5}$ Pa at 25°C and Henry law constant of $5.0 \times 10^{-5}$ Pa $m^3$ $mol^{-1}$. Consequently, cyproconazole should not vaporise in significant quantities to the atmosphere. Any cyproconazole reaching the atmosphere will undergo photolysis with hydroxyl radicals ($DT_{50}$ 1 day –AOPWIN). Consequently, cyproconazole should not undergo long-range transport ($DT_{50}$ < 2 d). The criteria for long-range transport have not been met.

*Adverse effects (includes ED Asseessment)*

On the basis of the evaluation by the Irish CA for Biocides of toxicology/eco-toxicology studies using cyproconazole, no determination of endocrine disruption effects could be ascertained in the test organisms dosed with cyproconazole.

However, work carried out under the EU Strategy for Endocrine Disruptors has included cyproconazole in Group III (Cat. 3b for both human health and wildlife) of a list of 564 candidate substances with the potential to be substances that cause endocrine disruption in both humans and animals. With this in mind, further information may be required to assess the potential for endocrine disruption of cyproconazole when EU harmonised guidelines are established for test methods and risk assessment. The 1,2,4-triazole metabolite is not on the afore mentioned list, However, it should be noted that while the azole group is suspected of endocrine disrupting properties there is not sufficient data availale about this potential.

**Summary of PBT and POP Assessment**

*PBT conclusion*

Following the outlined assessment it has been demonstrated that, cyproconazole, and its major metabolite (CGA 71019) in the aquatic environment, do not meet the complete set of PBT or vPvB-criteria and therefore should not be classified as PBT substances.

Overall, the active substance is considered to fulfil the P (and vP) and T criteria of the PBT assessment. Cyproconazole does not fulfil the B criterion.

The metabolite, triazole is not considered to fulfil the P, B or T criteria.

*POP conclusion*

The criterion for persistence has been met by cyproconazole. However, neither criteria for bioaccumulation nor long-range environmental transport have been met. Therefore,

cyproconazole is not a POP candidate. Further information may be required to assess the potential for endocrine disruption of cyproconazole when EU harmonised guidelines are established for test methods and risk assessment.

#### *2.2.2.4. Exposure Assessment*

Cyproconazole has been evaluated for its use as a wood preservative (Product type 8). Evipol ® 60 SL is an industrial wood preservative containing 5.175% w/w cyproconazole.

Evipol® 60 SL is intended to be used as wood preservative for the treatment of wood from use class 2 (wood above ground (wetting, protected from the weather), 3 (above ground exposed to weathering but not in ground contact) and 4a (in permanent contact with the ground and permanently exposed to wetting), as a fungicide against wood destroying fungi and blue stain. Cyproconazole is not used as such for the treatment of wood in contact with fresh water (wood class 4b) and wood permanently exposed to salt water (wood class 5).
Evipol ® 60 SL should be used only in an industrial environment. This should include use by personnel on industrial premises, but should not cover use by professional personnel for *in-situ* treatments.

Penetration and surface treatment processes are both included in the exposure assessment. A volume application rate of 75 g a.s./$m^3$ was used for impregnated wood, based on results from efficacy tests. Surface application rates were derived from this volume application rate using the appropriate wood area to wood volume ratios specified in the ESD for different types of wooden items. This resulted in surface application rates of 1.9 g a.s./$m^2$ (house, fence, fence post and noise barrier), 1.4 g a.s./$m^2$ (bridge) and 4.7 g a.s./$m^2$ (transmission pole).

Potential exposure of environmental compartments to wood preservatives can occur from two stages of their life cycle:

- application
- treated wood in service

For industrial treatments emissions can also occur during storage the storage of treated wood.

Several emission scenarios have been identified based on exposure type and the potential exposures and routes of exposure are dependant on these. In the case of *application*, the relevant emission scenarios for industrial preventive processes using Evipol ® 60 SL (5.175 % w/w cyproconazole) are:

- Automated spraying process;
- Vacuum pressure;
- Double vacuum pressure;
- Dipping / immersion process;

During these treatment processes exposure to surface water and sediment may occur through the release of application solution from industrial wood treatment to faculty drains connected to sewer systems. Mitigation against emissions from the industrial treatment processes by prevention of the emission to the faculty drain, with no connection to the sewer system or STP, is recommended. This was taken into account in higher tier calculations.

In uncovered and unpaved storage areas leaching from the treated wood may occur during a rainfall event. In the absence of reliable leaching data it was conservatively assumed that the entire amount of active is leached from the treated wood during the assessment period. Leached material can subsequently runoff into surface water or be washed off into the soil

compartment in the immediate area of the storage vicinity during a rainfall event. Groundwater contamination may then occur. These assumptions were made in Tier 1 calculations. In Tier 2, it was assumed that suitable mitigation measures are put in place e.g. the storage area is covered and on a non-permeable surface.

In the case of treated *wood in service,* the relevant emission scenarios considered are:

- House (UC 3)
- Noise barrier (Class 3)
- Transmission pole (Class 4a)
- Fence post (Class 4a)
- Bridge over pond (UC 3)

The service life of the wood depends on the treatment application method or process used. The values used were those agreed at the EU leaching workshop on wood preservatives, namely 20 years (vacuum pressure/double vacuum), 15 years (spraying, dipping, flow coat) and 5 years (brushing).

No calculations were provided for the bridge over the pond scenario for UC 3 by the applicant. This scenario is used to evaluate the use phase of treated wood in order to describe the emission pathway into open water bodies. The CA deems it necessary to include this scenario, as the applicant does not know where the treated wood will be used. Cyproconazole is not used as such for the treatment of wood in contact with fresh water (wood class 4b) and wood permanently exposed to salt water (wood class 5). Therefore the emission scenarios *"jetty in lake"* and *"wharf"* are not included. The Reviewer notes it can be assumed that planks of a jetty may be composed of wood in hazard belonging to hazard class 3. However, the bridge over pond scenario is assumed to represent the realistic worst-case emission to surface water with respect to emitting wood area and volume of receiving watercourse. Hazard Class 3 wood is unlikely to be used in harbour wharfs consequently it not necessary to consider use Class 5.

In summary, potential exposure to surface water and sediment may occur via industrial preventative treatment processes, if not contained or by leaching from treated wood during storage, if wood is not stored under cover and on an impermeable surfaces. However, both these potential exposure routes can be mitigated against. Exposure to air can only occur during the application stage via the industrial preventative treatment processes. The foreseeable routes of exposure to soil are by leaching from industrially treated wood during storage, if wood is not stored under cover and on an impermeable surface (however this is mitigated against) or via leaching from treated wood in service over the service life of the treated wood. Estimations of the expected concentrations of active substance in the affected compartments are detailed in **Document IIB, Section 3**

*Metabolites*

Cyproconaozle has one metabolite greater than 10 % in soil (1,2,4-triazole). This degrades faster than cyproconazole and has a lower molar mass. In the exposure assessment the concentrations of this compound is assumed to be lower than the cyproconazole concentration in soil. Therefore, concentrations of cyproconazole in soil are used in the risk assessment of this degradation product. This is a worst-case assumption.

#### *2.2.2.5. Risk Characterisation*

***Evipol® 60 SL***

APPLICATION

The risk assessments for cyproconazole arising in sewage treatment plants from industrial preventive processes and the wood in service '*noise barrier*' scenario indicated that there is no unacceptable risk to STP microorganisms following treatment with Evipol® 60 SL. Mitigation measures against emissions from the industrial treatment processes by containment of the emissions to the facility drain and subsequent storage under cover on an impermeable surface are recommended. When applied, these measures reduce the risk to STP microorganisms to zero. No corresponding risk assessment is required for the CGA 71019 (1,2,4-triazole) metabolite since exposure to treatment plants is considered unlikely.

The risk assessment for cyproconazole arising in surface water and sediment from emissions arising from industrial processes of Evipol ® 60 SL application indicated a risk to aquatic organisms in surface water for each treatment process and, in the case of sediment, for the automated spraying (large plant) and dipping/immersion treatment processes. However, when mitigation measures against emissions from the industrial treatment processes, such as containment of the emissions to the facility drain and subsequent storage under cover on an impermeable surface, are applied, the risk associated with all treatment processes for both surface water and sediment is reduced to zero.

WOOD IN SERVICE

*Risk characterization for surface water and sediments*

A risk assessment for the two scenarios where leaching of cyproconazole from treated wood *in-service* may occur was conducted for both surface water and sediment. In the case of the '*noise barrier*' scenario no risk is identified for sediment dwelling organisms following any treatment process at each assessment period. A slight risk is identified for surface water at the 30 d assessment time for each treatment process (PEC/PNEC=2.98). However, for the longer respective 15/20 year assessment periods, no unacceptable risk is determined for each of the treatment processes. Therefore, the leaching of cyproconazole from wood in service via STP for the '*noise barrier*' scenario, poses no unacceptable risk.

For the '*bridge over pond*' scenario an unacceptable risk was determined for both surface water and sediment dwelling organisms following treatment with Evipol® 60 SL for each treatment process and assessment period. For all treatment processes and the associated assessment periods the risk to surface water organisms, via leaching of cyproconazole from the treated wood, was greater than that for sediment dwelling organisms. It should be noted that in the absence of an acceptable leaching study on cyproconazole the PEC values are generated assuming that 100% of the applied amount of active substance leaches over the assessment period. Therefore, the PEC values can be considered to be very conservative. In order to reduce the risks identified to an acceptable level suitable mitigation measures must be identified and applied in order to develop a safe use of Evipol 60 ® SL in the '*bridge over pond*' scenario. However, with respect to this scenario, the CA notes according to the Manual of Technical Agreements Version 4 2010 (MOTA) "*…the current bridge over pond scenario represents a worst case scenario. A new scenario covering the risk from in-situ application (e.g. brushing) as well as the leaching from the treated timber near or above static water bodies is currently under development for the revised PT08 ESD"*

No risk is identified for the metabolite CGA 71019 (1,2,4-triazole) for surface water and sediment dwelling organisms following emissions from industrial processes since at the Tier 2 level of assessment, with mitigation measures in place, no emissions will occur. No risk is identified for the metabolite for the *in-service* '*noise barrier*' scenario, even when worst case

PEC values were applied, for all of the treatment processes over all of the assessment periods for surface water and sediment dwelling organisms. However, a risk has been identified for the in service '*bridge over pond*' scenario for both surface water and sediment dwelling organisms for all treatment processes and the associated assessment periods. As was seen with the parent active ingredient, cyproconazole, the risk posed by the metabolite is greater for surface water than that for sediment dwellers.

No marine risk assessment was necessary based on the intended uses of cyproconazole in Evipol 60 ® SL. The appropriate use of Evipol 60 ® SL will not result in PECs greater than or equal to 0.1 µg/L for both cyproconazole and CGA 71019 (1,2,4-triazole) which is the maximum permissible concentration of 0.1 µg/l given for groundwater in Directive 80/778/EEC (amended by 98/83/EC). No further assessment on the effect of Evipol 60 ® SL on groundwater used as drinking water was required. Emission of cyproconazole to air is not considered relevant based on its physical chemical properties, therefore obviating the need for any further risk assessment.

*Risk characterisation for soil compartment*

Cyproconazole may arise in the soil compartment including industrial, agricultural and grassland soils, during application and storage of wood treated with Evipol 60 ® SL for industrial preventative processes. At the Tier 2 level of assessment, with mitigation measures in place, specifically, the containment of the emission to the faculty drain and subsequent storage under cover on an impermeable surface, emissions to all soils will be zero. Therefore, with mitigation measures, no risk to soil organisms is identified for cyproconazole or its metabolite, CGA 71019 (1,2,4-triazole), following the use of Evipol 60 ® SL for industrial preventative processes.

The risk assessment for soil dwelling organisms exposed to cyproconazole due to emissions from Evipol 60 ® SL treated wood *in-service* included '*house*', '*fence post*', '*transmission pole*' and '*noise barrier*' scenarios. The $PNEC_{soil}$ for cyproconazole was derived from the highest concentration tested in a laboratory study on its impact carbon and nitrogen metabolism in soil. The PNEC is considered to be highly conservative as there was no effect seen at even the highest rate tested, and so the NOEC does not definitively describe the risk ($PNEC_{soil}$ >>0.-02 mg a.i./kg (wet wt.)). In the case of the '*house*', '*fence post*', and '*transmission pole*' scenarios the PEC/PNEC ratios exceed 1 for each assessment period (30 d and 15/20 y) even when dissipation is taken into account. This risk exists for both superficial and penetration treatments for each scenario. The $PNEC_{soil}$ for the metabolite, CGA 71019 (1,2,4-triazole), is derived from an earthworm study where the NOEC used to derive the PNEC is the highest concentration tested, which was rather low. Therefore, the NOEC does not definitively describe the risk ($PNEC_{soil}$ >>0.00048 mg CGA 71019/kg (wet wt.)). In applying the worst-case emission scenario for (i.e. $PEC_{soil}$ for cyproconazole), and considering that the PNEC for the metabolite is an order of magnitude less than that of the parent cyproconaozole it is clear that a risk to soil dwelling organisms would also be identified for the metabolite. In order to reduce the risks identified to an acceptable level suitable mitigation measures must be identified and applied in order to develop a safe use of Evipol 60 ® SL treated wood in service for '*house*', '*fence post*', '*transmission pole*' and '*noise barrier*' scenarios

For the '*noise barrier*' scenario, a risk is identified for both application scenarios at Times 1 and 2 as described in Doc IIC. In order to reduce the risk identified to an acceptable level for the '*noise barrier*' scenario suitable mitigation measures must be identified and applied in order to develop a safe use of Evipol 60 ® SL treated wood in service for the '*noise barrier*' scenario.

To conclude, no safe use has been identified for any of the treated wood in-service scenarios that were assessed, i.e. the '*house*' (UC 3), '*fence post*' (UC 4a), '*transmission pole*' (UC 4a) and '*noise barrier*' (UC 3) scenarios as described above, since a risk to soil was identified in each case. A risk to surface water and sediment was also identified for the 'bridge over pond' scenario (UC 3).

Environmentally safe uses could be expected for products for use on wood that will not be exposed to weathering, i.e. Use Classes 1 and 2 (situations in which wood is under cover and fully protected from the weather, e.g. framing, roof timbers etc.), since in these cases the potential emissions from treated wood to the outer environment are considered negligible.

*Risk characterization for groundwater used as drinking water*

The groundwater concentrations of cyproconazole and the major soil metabolite 1,2,4-triazole were calculated using FOCUS-PEARL 3.3.3 with the assumption that 35 wooden houses are treated with cyproconazole per hectare. 3 of the 9 FOCUS scenarios (Jokioinen, Porto and Sevilla) gave groundwater concentrations less than the maximum permissible concentration of 0.1 µg/L specified for groundwater in Directive 80/778/EEC (amended by 98/83/EC). All metabolite concentrations were less than 0.1 µg/L.

*Risk of secondary poisoning*

The risk of secondary poisoning by cyproconazole in the aquatic and terrestrial compartments is considered negligible considering the BCF values for both compartments, 28 L/kg and 16L/kg respectively. The rapid and almost complete elimination of incorporated cyproconazole further supports this conclusion. The low Log Kow of the metabolite of concern indicates a very low potential to bioaccumulate, thereby obviating the requirement for further assessment of effects of Evipol® 60SL on secondary poisoning.

*Waste disposal stage*

According to the product labels, spent containers of Evipol® 60SL should be disposed of via an incinerator approved for chemicals, and any spillages contained and disposed of, in accordance with Local Authority regulations. All disposal is therefore expected to be in accordance with local, state or national legislation avoiding release to the environment. For these reasons, it is expected that the waste disposal stage of the life cycle will not contribute significantly to the environmental exposure in comparison to the emissions from the in-use phases of the life cycle and general risk management measures based on EU waste legislation are sufficient to ensure sufficient protection of man and the environment

### *2.2.2.6. Overall Summary and Conclusion*

The use of Evipol® 60SL for industrial treatment processes is not considered to pose a risk to STP, surface water or sediment when appropriate risk mitigation measures are in effect. These mitigation measures secure against emissions from such industrial treatment processes by containment of the emission to the facility drain and subsequent storage under cover on an impermeable surface. Emissions thereby collected in the facility drain must be treated as hazardous waste amd adequate waste treatment options have to be applied. Leaching of cyproconazole from treated wood to the water body and sediment via STP for the '*noise barrier*' scenario is not considered to pose a risk when the 15/20 year assessment period is considered. However, a risk is identified for the '*bridge over pond*' scenario due to leaching from treated wood to the water body and sediment. The risk is considerable, being greater for

surface water than for sediment. Due to the absence of an acceptable leaching study on cyproconazole the PEC values are generated assuming that 100% of the applied amount of active substance leaches over the assessment period. This is highly conservative, but must be applied in this instance. It is unclear as to what kind of appropriate risk mitigarion measure could be applied in order to reduce this risk identified for the '*bridge over pond*' scenario. The possibility of the application of a 'top coating' is discussed below. There is no definitive conclusion regarding this potential risk mitigation measure. In light of this therefore, it is not possible to recommend the use of Evipol® 60SL treated wood in any '*bridge over pond*' scenario. However, with respect to this scenario, the CA notes according to the Manual of Technical Agreements Version 4 2010 (MOTA) "*…the current bridge over pond scenario represents a worst case scenario. A new scenario covering the risk from in-situ application (e.g. brushing) as well as the leaching from the treated timber near or above static water bodies is currently under development for the revised PT08 ESD"*

Considering the service life of pre-treated timber for all relevant emission scenarios (house, noise barrier, transmission pole and fence) a risk to the soil compartment was identified. Therefore, the Irish CA has concluded that the risks to the terrestrial compartment from use of timber pre-treated with the wood preservative product EVIPOL® 60SL containing up to 5.175% w/w cyproconazole for outdoor constructions are considered unacceptable. Appropriate risk mitigation measures to protect the soil compartment are required for wood in use class 3. In view of the risk identified for the soil compartment, appropriate risk mitigation measures have to be taken to protect that compartment. When assessing ready for use products containing the active substance together with fixatives and additives it is important to reassess the emission behaviour via experimental leaching tests.

Up to now it is unclear what kind of appropriate risk mitigation measures to protect the soil compartment will be required at the product authorisation stage. It seems questionable whether 'top coating' is a feasible risk mitigation measure to prevent losses from treated wood under use class 3. When assessing the environmental risk for ready for use products containing fixatives as a 'top coating', lower leaching rates might be expected. The Irish CA has some reservations to this measure, which requires discussion at TM.

### 2.2.3. List of Endpoints

In order to facilitate the work of Member States in granting or reviewing authorisations the most important endpoints, as identified during the evaluation process, are listed in Appendix I.

# 3. PROPOSED DECISION

## 3.1. BACKGROUND TO THE PROPOSED DECISION

Cyproconazole (CAS 94361-06-5) is a mixture of four stereoisomers: two diasteriomeric pairs of enantiomers, which means there are two enantiomers for each of the diasteriomers. Diasteriomer A: enantiomeric pair, where the 3-hydroxy group and the 2-hydrogen are located on the same side (2S, 3S and 2R, 3R). Diasteriomer B: enantiomeric pair, where the 3-hydroxy group and 2-hydrogen are located on opposite sides (2R, 3S and 2S, 3R).

Cyproconazole is a white fine powder with a faint aromatic odour. The purified active substance has a melting point range of 106.2 – 106.9 °C and has a low vapour pressure (2.6 x $10^{-5}$ Pa). The active substance is readily soluble in acetone, dichloromethane, ethyl acetate, methanol, octanol and toluene. The active substance was found to be slightly soluble in hexane. It is moderately-soluble in water (93 ± 18 mg/L at pH 7.1). Cyproconazole can be described as being borderline between fat/non-fat soluble with a $Log_{10}$ $K_{ow}$ value of 3.09. Cyproconazole is assumed to be photolytically stable as there was no absorption above 290nm. The technical material was found to be non-flammable, non-explosive and non-oxidising.

The assessment of the biocidal activity of cyproconazole demonstrates that it has a sufficient level of efficacy against the target organism(s) and the evaluation of the summary data provided in support of the efficacy of the accompanying product, establishes that products containing cyproconazole may be expected to be efficacious against wood destroying fungus.

For industrial users, deluge/flood was found to be safe only when PPE was worn and a safe use for double vacuum treatment was not found. Exposure to double vacuum treatment operators wearing PPE was estimated at 0.057 mg/kg bw day equating to a margin of exposure of 35.
This suggests a risk to operators using EVIPOL® 60 SL in a double vacuum process.

Safe uses were found for single vacuum pressure and spray applications. Exposure to spray and single vacuum treatment operators wearing PPE was estimated at 0.006 mg/kg bw day (tier 2) and 0.0027 mg/kg bw day (tier 1), respectively, equating to a margin of exposure of greater than 100. These values suggest an acceptable use pattern to operators using EVIPOL® 60 SL in single vacuum and spray processes.

Results from indirect exposure modelling suggest that post application exposure to cyproconazole applied as EVIPOL® 60 SL will not result in exposure above the $AEL_{(acute/medium-term/long-term)}$ of 0.02mg/kg bw/day. The model "infant chewing a wood cut-off" leads to the highest expected indirect exposure. However, infant exposure remains below the AEL when "infant chewing a wood cut-off" is combined with exposure modelled for the infant playing on a treated structure. Exposure in excess of the AEL will not result from indirect/secondary exposure to the active substance.

Cyproconazole was found to be rapidly and extensively absorbed with a total bioavailability of > 86%. Cyproconazole was rapidly distributed and had an extensive volume of distribution following either single or repeated administration. Residues were predominately associated with the organs of elimination (kidney, liver and pancreas) as well as the spleen and adrenal glands. Based on the absorption studies provided there was no evidence of accumulation in any tissues of the rat.

Cyproconazole was found to be rapidly and extensively adsorbed at the low dose levels and slightly slower but equally extensive adsorption occurred at a high dose level. Maximal blood concentrations were reached within 24- 48 hours. A total bioavailability of > 86% was estimated (including data from a bile duct cannulation experiment). 100% oral absorption is therefore assumed for risk assessment purposes.

The dermal absorption of Cyproconazole in humans has been estimated based on a series of studies conducted with a 100SL formulation (water based) designed for agricultural uses, using *in vivo* (rat) and *in vitro* (human and rat) data. It was recommended to assume a dermal absorption for humans of not more than 1% for multiple exposures to an undiluted product and a 10% dermal absorption can be used as a worst case value for assessments of human exposure to the diluted product

The acute oral toxicity of cyproconazole was tested in the rat, mouse and rabbit. The test substance was found to be harmful via the oral route in the rat. There were no adverse effects *via* the dermal and inhalation routes. The test substance was not irritating to the skin or eyes and not a dermal sensitiser.

Based on the various non-neoplastic and neoplastic effects as observed in the liver of male and female mice at 100 ppm, the overall long-term and oncogenic NOAEL for cyproconazole in rodents is considered to be 15 ppm, equivalent to 1.84 mg/kg and 2.56 mg/kg in male and female mice, respectively. Cyproconazole should be classified as a Category 3 carcinogen according to council Directive 67/548/EEC (Categroy 2 according to CLP Regulation 1272/2008).

Overall the NOEL for developmental toxicity was 1.7 mg/kg bw/day based on the two-generation study (and 2 mg/kg in the rabbit developmental studies). The parental NOEL was 2 mg/kg bw/day in the 2-generation study and was 10 mg/kg bw/day in the rabbit developmental studies. Cyproconazole should also be classified as Category 2 reproductively toxic according to council Directive 67/548/EEC (Categroy 1B according to CLP Regulation 1272/2008).
The genotoxicity of cyproconazole was extensively investigated in a wide range of test systems both *in vitro* and *in vivo*. All relevant endpoints were addressed. The test substance was negative in all tests reported.

Cyproconazole is stable to hydrolysis and is expected to be stable to direct photolysis in water (at $\lambda\perp >$ 290 nm UV adsorption $\varepsilon < 10$ $L^{-1}$ $mol^{-1}$ $cm^{-1}$). Cyproconazole is considered not readily biodegradable. Degradation in two dark water/sediments at 20°C was very slow ($DT_{50}$ >> 1 year). The main dissipation process from the water phase is partition to sediment.

The photochemical half-life of cyproconazole in the atmosphere was determined to be around 1 day.

The route of degradation of cyproconazole in soil under dark aerobic conditions at 20 – 22 °C was investigated in three studies with $^{14}C$ triazole-labelled cyproconazole (one soil: pH 7.2), $^{14}C$-benzyl-labelled cyproconazole (three soils: pH 4.3 – 7.0), and $^{14}C$-phenyl-labelled cyproconazole (one soil: pH 7). In all these studies degradation of cyproconazole was slow, and considerable amounts of radioactivity remained as unmodified cyproconazole at the end of the respective experiments. In the study performed with $^{14}C$-triazole-labelled cyproconazole, the metabolite 1,2,4-triazole (max. 17.36 % AR after 140 days, end of the study) was identified as the only major metabolite in soil (≥ 10%AR).

Persistence of cyproconazole in soil under dark aerobic conditions was investigated in the several studies. Under laboratory conditions, the $DT_{50}$ ranged from 100 d to 427 d at 12°C. The geomean $DT_{50lab}$ was 298 d. A number of field dissipation studies were submitted (1 in UK (4 sites), 5 in France, and 5 in Germany). In field trials the $DT_{50}$ ranged from 28.97 d (DFOP) to 162 d(SFO). The corresponding $DT_{90}$ ranged from 306.92 d(SFO) to >1,000 days(DFOP).

Cyproconazole is moderately adsorbed to soil ($K_{foc}$ 364 L/kg, n = 5, $K_{doc}$ = 473 L/kg). The major soil metabolite, 1,2,4-triazole is mobile in soil ($K_{foc}$ 89 L/kg, n = 4, $K_{doc}$ = 124 L/kg).

The use of Evipol® 60SL for industrial treatment processes is not considered to pose a risk to STP, surface water or sediment when appropriate risk mitigation measures are in effect. These mitigation

measures secure against emissions from such industrial treatment processes by containment of the emission to the facility drain and subsequent storage under cover on an impermeable surface.

Due to the absence of an acceptable leaching study on cyproconazole the PEC values are generated assuming that 100% of the applied amount of active substance leaches over the assessment period. This is highly conservative, but must be applied in this instance to the in-service scenarios. As a result no safe use has been identified for any of the treated wood in-service scenarios i.e. the '*house*', '*fence post*', '*transmission pole*', "*bridge over pond*" and '*noise barrier*' scenarios.

The risk of secondary poisoning by cyproconazole in the aquatic and terrestrial compartments is considered negligible considering the BCF values for both compartments, 28 L/kg and 16L/kg respectively. The rapid and almost complete elimination of incorporated cyproconazole further supports this conclusion. The low Log Kow of the metabolite of concern indicates a very low potential to bioaccumulate, thereby obviating the requirement for further assessment of effects of Evipol® 60SL on secondary poisoning.

Following the outlined assessment it has been demonstrated that, cyproconazole, and its major metabolite (triazole) in the aquatic environment, do not meet the complete set of PBT or vPvB-criteria and therefore should not be classified as PBT substances.

Overall, the active substance is considered to fulfil the P (and vP) and T criteria of the PBT assessment. Cyproconazole does not fulfil the B criterion.

The metabolite, triazole is not considered to fulfil the P, B or T criteria.

In relation to endocrine disruption the evaluation by the Irish CA for Biocides of toxicology/eco-toxicology studies using cyproconazole, no determination of endocrine disruption effects could be ascertained in the test organisms dosed with cyproconazole.

However, work carried out under the EU Strategy for Endocrine Disruptors has included cyproconazole in Group III (Cat. 3b for both human health and wildlife) of a list of 564 candidate substances with the potential to be substances that cause endocrine disruption in both humans and animals. With this in mind, further information may be required to assess the potential for endocrine disruption of cyproconazole when EU harmonised guidelines are established for test methods and risk assessment. The 1,2,4-triazole metabolite is not on the afore mentioned list, However, it should be noted that while the azole group is suspected of endocrine disrupting properties there is not sufficient data availale about this potential.

## 3.2. PROPOSED DECISION

The overall conclusion from the evaluation of Cyproconazole for use in product-type 8 (Wood preservatives), is that it may be possible to issue authorisations of products containing Cyproconazole in accordance with the conditions laid down in Article 5(1) b), c) and d) of Dir. 98/8/EC.

The report concludes that cyproconazole meets the criteria for being classified as toxic for reproduction category 1B in accordance with Regulation (EC) No 1272/2008 of the European

Parliament and of the Council[3], and for being very persistent (vP) and toxic (T) according to Annex XIII to Regulation (EC) No 1907/2006. Notwithstanding the fact that the existing harmonised classification of cyproconazole should be revised pursuant to Article 37 of Regulation (EC) No 1272/2008, those intrinsic properties should be taken into account for the purpose of determining the period of approval, Since the conditions of the first subparagraph of Article 90(2) of Regulation (EU) No 528/2012 are not met, the current practice under Directive 98/8/EC should be followed. The period of approval should therefore be five years.

However, for the purpose of authorising products in accordance with Article 23 of Regulation (EU) No 528/2012, cyproconazole shall be considered as a candidate for substitution pursuant to Article 10(1)(a) and (d) of that Regulation.

It is therefore proposed to approve Cyproconazole as an active substance for use in product-type 8 (Wood preservatives), subject to the following specific conditions:

Cyproconazole is considered a candidate for substitution in accordance with Article 10(1)(a) and (d) of Regulation (EU) No 528/2012.

The product assessment shall pay particular attention to the exposures, the risks and the efficacy linked to any uses covered by an application for authorisation, but not addressed in the Union level risk assessment of the active substance.

Authorisations are subject to the following conditions:

1) For industrial users, safe operational procedures and appropriate organizational measures shall be established. Where exposure cannot be reduced to an acceptable level by other means, products shall be used with appropriate personal protective equipment.
2) Products shall not be authorised for industrial use by double vaccum impregnation, unless data is submitted to demonstrate that the product will not present unacceptable risks, if necessary by the application of appropriate mitigation measures.
3) Appropriate risk mitigation measures shall be taken to protect the soil and aquatic compartments. In particular :
    a. Labels and, where provided, safety data sheets of products authorised shall indicate that industrial application shall be conducted within a contained area or on impermeable hard standing with bunding, that freshly treated timber shall be stored after treatment under shelter or on impermeable hard standing, or both, to prevent direct losses to soil or water, and that any losses from the application of the product shall be collected for reuse or disposal.
    b. Products shall not be authorised for industrial treatment of wood that will be exposed to weathering, or for treatment of wood that will be used for outdoor constructions, unless data is submitted to demonstrate that the product will not present unacceptable risks, if necessary by the application of appropriate mitigation measures.

[3] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006 (OJ L 353, 31.12.2008, p. 1)

## 3.3. ELEMENTS TO BE TAKEN INTO ACCOUNT WHEN AUTHORISING PRODUCTS

- For the purpose of authorising products in accordance with Article 23 of Regulation (EU) No 528/2012, cyproconazole shall be considered as a candidate for substitution pursuant to Article 10(1)(a) and (d) of that Regulation.

- Only the use for industrial use has been assessed for the purpose of the approval. Other uses will have to be considered at the product auithorisation stage if requested by the applicant.

- Wastewater from industrial wood treatment must not be released directly to surface water or indirectly via a sewage treatment plant. Application solutions shall be collected and reused or disposed as hazardous waste.[4]

- Freshly treated wood at industrial wood treatment plants must be stored under cover and on a non-permeable surface prior to transportation. The leachate/run-off water should be collected and recycled into the wood treatment process.

- In-situ application by brush or spray in the vicinity of watercourses has not been considered in the current exposure assessment.

- The dossier submitted for the review program of cyproconazole as a wood preservative in wood for Use Class 3 as required in Article 5(1)(b)(iv) of Directive 98/8/EC has demonstrated potential risks to the environment. At product authorisation it is required that a suitable leaching study from treated wood and appropriate risk mitigation measures are considered, e.g. additional treatment with a cyproconazole-free coating (top-coat) or co-formulant fixative in the product, to characterise and reduce the leaching of cyproconazole from treated wood in Use Class 3.

- Where applications are made for the authorisation of products in use-classes 4a, 4b or 5 additional efficacy data will be required for assessment of the treated wood under these conditions of use.

- When Member States are authorising products containing cyproconazole the potential of cyproconazole to cause endocrine disruption will need to be further analysed and considered once guidance is available. This is because cyproconazole may have the potential to cause endocrine disruption based on suspected properties. However, in the submitted studies there were no effects in the test animals which could be related to possible endocrine disruption. Therefore, it has been agreed that cyproconazole should be further assessed with regards to its potential endocrine disruptor properties once further guidance is available and preferably before the product authorisation stage. The conclusion of that assessment might lead to review the active substance approval.

## 3.4. REQUIREMENT FOR FURTHER INFORMATION

It is considered that the evaluation has shown that sufficient data have been provided to verify the outcome and conclusions, and permit the proposal for the approval of Cyproconazole in accordance with Article 9 of Regulation (EU) No 528/2012.

However, notwithstanding the above statement the following data requirements have been identified:

[4] These requirements may actually be determined in detail in the environmental permits on the basis of IPPC Directive (96/61/EC) but should be listed in the instructions for use of a biocidal product.

**Identity of the active substance**

Not applicable.

**Physical and chemical properties of the active substance**

- No requirements for the active substance

**Physical and chemical properties of the biocidal product**

The following information should be provided at product authorisation stage for the product EVIPOL 60SL:

- A GLP study to test EVIPOL 60 SL' autoflammability should be conducted.
- A GLP study to test the flammability of the product when in contact with water is required (please use method EC A.12).
- A pH study (conducted to GLP) is required using a 1% dilution in water.
- Three new storage stability studies are required:

(1) Accelerated storage
(2) 2 year storage at ambient temperature
(3) Cold storage stability

- Persistent foaming study required in accordance with CIPAC MT 47.2.
- The notifier is required to provide a surface tension study.
- A new viscosity study is required. The new study should be conducted in line with OECD 114.

**Methods of analysis**

- A fully validated method of analysis for monitoring cyproconazole in body fluids and tissues is required. This data has to be preferably submitted at least 6 months before the date of approval of cyproconazole to the original Rapporteur Member State (Ireland).
- The HPLC-MS/MS method for air was not fully validated, however no further will be required before Annex I inclusion because cyproconazole is considered to be non-volatile and the exposure to cyproconazole in air is considered to be negligible for the supported use. (industrial spray application). In the event that additional modes of application are requested in the future, the discussion surrounding a requiremenmt for a fully validated cyrpoconazle monitoring method may have to be reviewed.
- The applicant also needs to provide a method of analysis for 1-methyl-2-pyrrolidone in the biocidal product. The impurity is considered relevant from a tox. point of view. The method can be provided at product authorisation stage.

## Human health

Not applicable.

## Environment

- At product authorisation a leaching test will be required for each general application method (penetration and superficial) by which the wood preservative is to be applied. In addition, a leaching test will also be required for each formulation type (water and solvent based) of the wood preservative.

## 3.5. UPDATING THIS ASSESSMENT REPORT

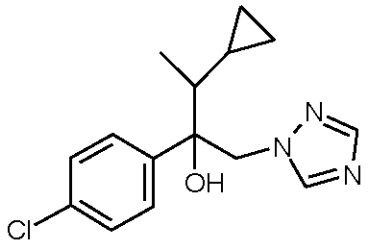
This assessment report may need to be updated periodically in order to take account of scientific developments and results from the examination of any of the information submitted in relation with Regulation (EU) No 528/2012. Such adaptations will be examined and finalised in connection with any amendment of the conditions for the approval of Cyproconazole.

# APPENDIX I: LIST OF ENDPOINTS

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

| | |
|---|---|
| Active substance (ISO Common Name) | Cyproconazole |
| Function (*e.g.* fungicide) | PT 8 (Wood preservative) |

**Identity**

| | |
|---|---|
| Chemical name (IUPAC) | (2RS,3RS;2RS,3SR)-2-(4-chlorophenyl)-3-cyclopropyl-1-(1H-1,2,4-triazol-1-yl)butan-2-ol |
| Chemical name (CA) | alpha-(4-chlorophenyl)-alpha-(1-cyclopropyl-ethyl)-1H-1, 2, 4-triazole-1-ethanol |
| CAS No. | 94361-06-5 |
| EC No. | Not available |
| Other substance No. | CIPAC 600 |
| Minimum purity of the active substance as manufactured (g/kg or g/l) | Min. 940 g/kg<br>Cyproconazole has two diastereomers.<br>(Diastereoisomer A: 430 – 500 g/kg,<br>Diastereoisomer B: 470 – 550 g/kg).<br><br>Diastereomer A: enantiomeric pair, where the 3-hydroxy group and the 2-hydrogen are located on the same side (2S, 3S and 2R, 3R).<br><br>Diastereomer B: enantiomeric pair, where the 3-hydroxy group and 2-hydrogens are located on opposite sides (2R, 3S and 2S, 3R).<br><br>Technical cyproconazole is *ca.* 1:1 mixture of the two diasteriomers, each of which is exactly a 1:1 mixture of the enantiomers. |
| Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (g/kg) | 1-methyl-2-pyrrolidone (max. 4 g/kg) |
| Molecular formula | $C_{15}H_{18}ClN_3O$ |
| Molecular mass | 291.8 g/mol |
| Structural formula |  |

**Physical and Chemical Properties**

| | |
|---|---|
| Melting point (state purity) | 106.2 - 106.9°C ± 0.4°C (99.7%) |
| Boiling point (state purity) | Due to the thermal decomposition of the test substance it was not possible to determine the boiling point under normal pressure (99.7%) |
| Temperature of decomposition | 299 °C (99.7%) |
| Appearance (state purity) | White, fine powder (99.7%) |
| Relative density (state purity) | 1.25 (99.7%) |
| Surface tension | 65.2 mN/m at 20 °C (90 % saturated solution) (96.6%) |
| Vapour pressure (in Pa, state temperature) | 2.6 x $10^{-5}$ Pa at 25 °C (99.7%) |
| Henry's law constant (Pa $m^3$ $mol^{-1}$) | 5.0 x $10^{-5}$ Pa $m^3$ $mol^{-1}$ |
| Solubility in water (g/l or mg/l, state temperature) | 93 mg/L at 22 °C (pH 7.1) (98.9%) |
| Solubility in organic solvents (in g/l or mg/l, state temperature) | Solubility (g/L) at 25 °C (96.6%):<br>Acetone: 360<br>Dichloromethane: 430<br>Ethyl acetate: 240<br>Hexane 1.3<br>Methanol 410<br>Octanol: 100<br>Toluene: 100 |
| Stability in organic solvents used in biocidal products including relevant breakdown products | Not applicable because the active substance as manufactured does not include an organic solvent and is not formulated in organic solution in the biocidal product. |
| Partition coefficient (log $P_{OW}$) (state temperature) | log $P_{O/W}$ = 3.09 at 25 °C (pH 7.2) (99.7%) |
| Hydrolytic stability ($DT_{50}$) (state pH and temperature) | Cyproconazole<br>No degradation observed at pH 4, 5, 7 or 9 (50°C, 5 days)<br>1,2,4 triazole(CGA 71019)<br>No degradation observed at pH 5, 7 or 9 (25°C, 30 days) |
| Dissociation constant | pKa = Cyproconazole will not dissociate in water at environmental pH, therefore no pKa value has been calculated.<br>(98.9%) |
| UV/VIS absorption (max.) (if absorption > 290 | pH 5 solution (99.7 %): |

| | |
|---|---|
| nm state ε at wavelength) | $\lambda_{max}$ 295 (nm); ε = 0.4 (L.mol$^{-1}$.cm$^{-1}$)<br><br>pH 7 solution (99.7 %):<br>$\lambda_{max}$ 295 (nm); ε = 0.7 (L.mol$^{-1}$.cm$^{-1}$)<br><br>pH 9 solution (99.7 %):<br>$\lambda_{max}$ 295 (nm); ε = 0.8 (L.mol$^{-1}$.cm$^{-1}$) |
| Photostability ($DT_{50}$) (aqueous, sunlight, state pH) | Not relevant |
| Quantum yield of direct phototransformation in water at Σ > 290 nm | Not determined/not required |
| Flammability | Non-flammable (95%) |
| Explosive properties | Non-explosive (95.7%) |
| Oxidising properties | Non-oxidising (95%) |

**Classification and Proposed Labelling**

| | |
|---|---|
| With regard to physical/chemical data | Directive 67/548/EEC – No classification required<br>Regulation 1272/2008 – No classification required |
| With regard to toxicological data | Directive 67/548/EEC<br>R22: Harmful if swallowed<br>Carc. Range Cat 3: R40: Limited evidence of a carcinogenic effect<br>Repr. Cat 2: R61: May cause harm to the unborn child<br>Regulation 1272/2008<br>Acute Tox 4 H302: Harmful if swallowed<br>Carc. Cat 2 H351: Suspected of causing cancer<br>Repr. Cat 1B H360: May damage the unborn child |
| With regard to fate and behaviour data | Directive 67/548/EEC – No classification required<br>Regulation 1272/2008 – No classification required |
| With regard to ecotoxicological data | Directive 67/548/EEC<br>R50: Very toxic to aquatic organisms<br>R53: May cause long-term adverse effects in the aquatic environment<br>Regulation 1272/2008<br>H400 (Acute Cat 1): 'Very toxic to aquatic life';<br>H410 'Very toxic to aquatic life with long lasting effects' |

## CHAPTER 2: METHODS OF ANALYSIS

### Analytical Methods for the Active Substance

| | |
|---|---|
| Technical active substance (principle of method) | CIPAC 600 –<br>Analysis by HPLC with UV detection following dissolution by methanol.<br><br>Identity confirmed by MS |
| Impurities in technical active substance (principle of method) | Analysis by HPLC with UV detection/GC with FID detection following dissolution in methanol.<br><br>Identity confirmed by MS |

### Analytical Methods for Residues

| | |
|---|---|
| Soil (principle of method and LOQ) | HPLC-MS/MS<br>LOQ = 0.01 mg/kg for parent cyproconazole. |
| Air (principle of method and LOQ) | The HPLC-MS/MS method for air was not fully validated, however no further will be required before Annex I inclusion because cyproconazole is considered to be non-volatile and the exposure to cyproconazole in air is considered to be negligible for the supported use. In the event that additional modes of application are requested in the future, the discussion surrounding a requiremenmt for a fully validated cyrpoconazle monitoring method may have to be reviewed. |
| Water (principle of method and LOQ) | Method REM 200.01<br>Following the addition of methanol, the water specimen is sucked through a solid phase extraction column for concentration of the analyte. The eluate is evaporated and cyproconazole is quantified in the final extract by GC/MSD using the selected ion mode (SIM). The ion at 292 m/z is used for confirmation and the ions at 139 and 222 m/z are used for quantitation.<br>This method of analysis has proven to be suitable for the determination of cyproconazole in surface water and drinking water with LOQ values of 0.05 µg/L and 0.1 µg/L, respectively. |
| Body fluids and tissues (principle of method and LOQ) | Open. |
| Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes) | Not applicable |
| Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes) | Not applicable |

## CHAPTER 3: TOXICOLOGY

### Absorption, Distribution, Metabolism and Excretion in Mammals

| | |
|---|---|
| Rate and extent of oral absorption: | Rapidly absorbed, > 85 % within 144 hours, based on urinary and biliary excretion and carcass residues |
| Rate and extent of dermal absorption: | 1.0% for the undiluted product (A-9898A 5.175% w/w))<br>10% for multiple application of spray strength solutions (0.02% - 0.4%)<br>16% for very dilute formulations (<1:1000) |
| Distribution: | Widely distributed, highest residues associated with the organs of elimination (kidney, liver, pancreas) |
| Potential for accumulation: | No potential for accumulation upon repeated oral administration |
| Rate and extent of excretion: | Major route is biliary excretion for males (75 %) and females (59 %), followed by with renal (26.7% and 9.5 %, respectively); < 5 % faecal excretion |
| Toxicologically significant metabolite(s) | M21/M21a (NOA 405870)<br>M36 (NOA 405872)<br>Triazole alanine (TA or CGA 131013) |

### Acute Toxicity

| | |
|---|---|
| Rat $LD_{50}$ oral | Rat: 350 mg/kg bw<br>Mouse: 200 & 218 mg/kg bw, males & females respectively; 270 mg/kg bw (males)<br>Rabbit: 460 mg/kg bw (females) |
| Rat $LD_{50}$ dermal | Rat: >2000 mg/kg<br>Rabbit: >2000 mg/kg bw |
| Rat $LC_{50}$ inhalation | >5.65 mg/L, 4 hours, nose-only exposure |
| Skin irritation | Non-irritating |
| Eye irritation | Non-irritating |
| Skin sensitization (test method used and result) | Non-sensitising (M & K) and Beuhler |

### Repeated Dose Toxicity

| | |
|---|---|
| Species/ target / critical effect | Liver toxicity and reduced weight gain in rats, mice and dogs. |
| Lowest relevant oral NOAEL / LOAEL | 90-day, rat: 6.4 mg/kg bw/day<br>90-day mouse: 2.2 mg/kg bw/day, LOAEL 43.8 mg/kg bw/day<br>1-year dog: 3.2 mg/kg bw/day |
| Lowest relevant dermal NOAEL / LOAEL | 10 mg/kg/d (28 day dermal, rat) based on changes in clinical chemistry. |
| Lowest relevant inhalation NOAEL / LOAEL | 4.9 mg/kg/d (16 day inhalation, rat) |

| | |
|---|---|
| **Genotoxicity** | Cyproconazole is unlikely to be genotoxic |

**Carcinogenicity and long term toxicity**

| | |
|---|---|
| Target/critical effect | Reduced body weight gain in male and female rats and mice.<br>Liver: Liver change consistent with adaptive response and hepatotoxicity in rats and mice. |
| Relevant NOAEL | 1.84 mg/kg bw/day; 18-month mouse<br>2.22 mg/kg bw/day; 2-year rat |
| Carcinogenicity | Liver tumours (adenoma and carcinoma) in mice at 13.17 mg/kg bw/day |

**Reproductive Toxicity**

**Reproduction**

| | |
|---|---|
| Reproduction target / critical effect | Maternal: Increased liver weight.<br>Offspring: Slightly increased pre/peri- and post natal mortality.<br>Reproductive: No effect on reproduction/ fertility |
| Relevant parental NOAEL | 20 ppm: 2.0 mg/kg bw/day |
| Relevant reproductive NOAEL | 8.3 mg/kg bw/day |
| Relevant offspring NOAEL | 20 ppm: 2.0 mg/kg bw/day |

**Developmental toxicity**

| | |
|---|---|
| Developmental target/critical effect | Maternal (rabbit): ↓mean body weight<br>Developmental (rabbit): Increased post-implantation loss; Increased foetal malformations<br><br>Maternal (rat) ↓mean body weight gain.<br>Developmental: Reduced foetal body weight teratogenicity (cleft palate, hydrocephaly) in the rat at maternally toxic doses. |
| Relevant maternal NOAEL | 10 mg/kg bw/day (rabbit) |
| Relevant developmental NOAEL | 2 mg/kg bw/day (rabbit) |

**Neurotoxicity/Delayed Neurotoxicity**

| | |
|---|---|
| Acute neurotoxicity | No data - not required |
| Delayed neurotoxicity | No data - not required |

**Other Toxicological Studies**

| | | |
|---|---|---|
| Mechanistic studies | | |
| Liver cell proliferation study; rat<br>mouse | | Hepatocyte proliferation not induced.<br>Transient, early increase in proliferation (LEL = 15 ppm/2.2 mg/kg bw/day) |
| Rat and mouse liver enzyme induction | | Strong induction of phase I and II enzymes in rat. Induction of NCPR, Cyp1A, GST and UDPGT in mice |
| C3H Mouse CAR studies | | Evidence of CAR interaction |
| Studies on metabolites | | |
| M21/M21A | Acute oral (rat) LD50<br>Ames test | >2000 mg/kg bw<br>Negative<br>(not toxicologically relevent) |
| M36 | Acute oral (rat) LD50<br>Acute oral (mouse) LD50<br>Genotoxicity | >2000 mg/kg bw<br>>2000 mg/kg bw<br>Not likely to be genotoxic<br>(not toxicologically relevent) |
| Triazole alanine | | No hazard discernible from toxicological profile (not toxicologically relevant) |

**Medical Data**

| |
|---|
| No adverse effects reported |

**Summary**

| | Value | Study | Safety factor |
|---|---|---|---|
| **Professional industrial user** | | | |
| AEL $_{\text{long term}}$ | 0.02 mg/kg bw/day | 2-year Feeding studies, rat and mouse | 100x |
| AEL $_{\text{medium term}}$ | 0.02 mg/kg bw/day | Rat and rabbit developmental toxicity studies. | 100x |
| AEL $_{\text{short term}}$ | 0.02 mg/kg bw/day | Rat and rabbit developmental toxicity studies. | 100x |
| **Professional industrial user** | | | |
| Reference value for inhalation (proposed OEL) | 100% | - | - |
| Reference value for dermal absorption | For water-based formulations:<br>1% (concentrate -15 mg a.s./ml)<br>10% (dilution – 0.25 mg a.s./ml)<br>16% (very dilute formulations, <1:1000) | | |

**Acceptable Exposure Scenarios (including method of calculation)**

| | |
|---|---|
| Professional users | See intended uses. |
| Production of active substance | Not applicable |
| Formulation of biocidal product | Not applicable |
| Intended uses | **Industrial use: vacuum-pressure impregnation (TNsG 2002 handling model 1).**<br>Tier (1) Vacuum Pressure treatment exposure 0.013 mg/kg bw day MOE 153 Acceptable<br>**Industrial use : dipping and deluge/flood (TNsG 2002 Dipping model 1).**<br>Tier (2) Deluge/flood Dipping model 1 0.004 mg/kg bw day MOE 500 Acceptable<br>**Industrial use : spraying (TNsG 2002 spray model 2).**<br>Tier (2)Spraying 0.006 mg/kg bw day MOE 333 Acceptable<br>**Tier (1)Cleaning of equipment (Applicants model)**<br>0.0033 mg/kg bw day MOE 606 Acceptable |
| Secondary exposure | See indirect exposure |
| Indirect exposure as a result of use | TNsG 2002) Adult sanding treated wood exposure 0.0002 mg/kg bw day MOE 10000<br>(TNsG 2002) Adult sanding treated wood 6 hours exposure 0.0013 mg/kg bw day MOE 1538<br>(TNsG 2002) Infant chewing wood off-cut exposure 0.00085 mg/kg bw day MOE 166.67<br>Inhalation of volatilised residues (infant) 0.00085 mg/kg bw day MOE 2352.94<br>Inhalation of volatilised residues (Child) 0.0008 mg/kg bw day MOE 2500<br>Inhalation of volatilised residues (Adult) 0.0005 mg/kg bw day MOE 4000<br>(TNsG 2002) Child playing on treated structure 0.0002 mg/kg bw day MOE 10000<br>(TNsG 2002) Infant playing on treated structure 0.002 mg/kg bw day MOE 1000 |
| | |
| | |
| | |

**Chapter 4: Fate and Behaviour in the Environment**

**Route and rate of degradation in water** (Annex IIA, point7.6, IIIA, point XII.2.1, 2.2))

| | |
|---|---|
| Hydrolysis of active substance and relevant metabolites ($DT_{50}$) (state pH and temperature) | Cyproconazole<br>No degradation observed at pH 4, 5, 7 or 9 (50°C, 5 days)<br>1,2,4 triazole(CGA 71019)<br>No degradation observed at pH 5, 7 or 9 (25°C, 30 days) |
| Photolytic/photo-oxidative degradation of active substance and resulting relevant metabolites | Stable - molar absorption coefficients (ε) are < 10 L $mol^{-1}$ $cm^{-1}$ at wavelengths ≥ 290 nm |
| Readily biodegradable (yes/no) | No |
| Biodegradation in seawater | Not assessed/not required |
| Non-extractable residues | 3.8 (river system)-10.0 % (pond system) after 259 d |
| Distribution in water / sediment systems (active substance) | Cyproconazole<br>Water: 8.6-18.1% after 105 days (n=2)<br>6.4-16.1% after 259 days (n=2)<br>Sediment: 74.6 – 79.2% after 105 days (n=2)<br>72.4-73.2 % after 259 days ( n= 2) |
| Distribution in water / sediment systems (metabolites) | No identified metabolites<br>No unidentified metabolites in sediment or water > 3%<br>U1 reached a maximum of 4.6 % in the entire system |

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

| | |
|---|---|
| Mineralization (aerobic) | $^{14}$C-phenyl labelled cyproconazole<br>Up to 11%, day 112 d, n=1.<br>$^{14}$C-benzyl labelled cyproconazole<br>26.8-32.9%, day 112, n=2.<br>$^{14}$C-triazole labelled cyproconazole (140 d, n=1)<br>Less than 1%, 140 d, n=1 |
| Laboratory studies (range or median, with | |

| | pH | t. °C / actual soil moisture % | $DT_{50}$ / $DT_{90}$ (d) | $r^2$ | $DT_{50}$ (d) 12°C (TGD) | Model |
|---|---|---|---|---|---|---|
| Soil type | | | | | | |

number of measurements, with regression coefficient)

| | | | | | | |
|---|---|---|---|---|---|---|
| **Rate of degradation studies** | | | | | | |
| Loam, Flaach 2/88 | 7.3 W | 22/40 | 89/295 | 0.93 | 198 | SFO |
| Sandy loam; Hatzenbühl | 5.0 | 22/40 | 192/638 | 0.94 | 427 | SFO |
| Loamy sand; Neuhofen | 5.0 | 22/40 | 132/438 | 0.91 | 294 | SFO |
| Loam; Flaach 2/89 | 7.6 | 22/40 | 72.4/240 | 0.98 | 161 | SFO |
| **Rate of degradation under varying incubation conditions (temperature, moisture, application rate).** | | | | | | |
| Loam; Flaach 2/89 | 7.6 | **12**/40 | 347/>1,000 | 0.72 | 347(M) | SFO |
| | 7.6 | 20/**20** | 219/727 | 0.82 | 415 | SFO |
| Loam; Flaach 2/89 (low app. dose) | 7.6 | 22/40 | 44.8/148 | 0.99 | 100 | SFO |
| **Route of degradation studies with kinetic information** | | | | | | |
| Sandy clay loam; Flaach 2/92) | 7.2 | 20/40 | 148/491 | 0.91 | 281 | SFO |
| Sandy clay loam; Flaach 2/90 (Benzyl radiolabel) | 7.0 | 22/75 % 1/3 bar | 124/412 | 0.72 | 276 | SFO |
| Silt loam; Louisiana 90 | 4.30 | 22/75 % 1/3 bar | 150.7/500.6 | 0.42 | 335 | SFO |
| Loamy sand; N. Carolina | 5.30 | 22/75 % 1/3 bar | Excluded | | --- | --- |
| Sandy clay loam Flaach 2/90 (Phenyl radiolabel) open system | 7.0 | 20/40 | 82/272 | 0.97 | 156 | SFO |
| Sandy clay loam Flaach 2/90 (Phenyl radiolabel) closed system | 7.0 | 20/40 | 193/642 | 0.95 | 366 | SFO |
| **Geomean**[#] | | | | | **298** | **SFO** |
| The geomean was calculated in the following way: first the geomean values for sandy clay loam Flaach soils and loam Flaach soils were calculated, giving two separate values. At the next step these values were combined with the remaining kinetic endpoints to give the final geometric mean values. M= measured value | | | | | | |

$DT_{50lab}$ (12°C, aerobic): (calculated from half-life at 12°C TGD)

| | |
|---|---|
| | Cyproconazole: 298 days<br>1,2,4 triazole (CGA 71019): 18.09 days |
| | $DT_{50lab}$ (20°C, anaerobic):<br>Cyproconazole: Negligible degradation<br>1,2,4 triazole (CGA 71019): 81 days (n = 1, $r^2 > 0.8$) |
| | Degradation in the saturated zone: No data supplied. |
| Field studies (state location, range or median with number of measurements) | $DT_{50f}$: 28.97 d(DFOP) – 162 d(SFO), n =5 |
| | $DT_{90f}$: 306.92 d(SFO)- >1,000 d(DFOP) n =5 |
| Anaerobic degradation | Negligible degradation |
| Soil photolysis | Negligible degradation |
| Non-extractable residues | Laboratory studies<br>$^{14}$C-phenyl labelled cyproconazole<br>20.8-21.5 % AR, day 140<br><br>$^{14}$C-benzyl labelled cyproconazole<br>13-23.9 %AR, day 112<br><br>$^{14}$C-triazole labelled cyproconazole (140 d, n=1)<br>16 %, day 140 |
| Relevant metabolites - name and/or code, % of applied a.i. (range and maximum) | 1,2,4 triazole (CGA 71019) – maximum 17.36%, day 140 |
| Soil accumulation and plateau concentration | Accumulation studies suggest no accumulation after 5 years of treatment, residues generally <LOQ 1 year after last treatment. However, these were carried out with a plant protection product. Consequently, they do not reflect the proposed use of cyproconazole as a wood preservative. For situations involving a daily flux of cyproconazole into soil, such as leaching from treated wood, the level of cyproconazole will tend towards a plateau. The level at which at the plateau is established, and the time to reach it, depend on the amount of cyproconazole in soil when the flux begins (if any), the daily flux rate and the dissipation rate of cyproconazole in soil. The release pattern for use as a plant protection product is different. Consequently, the CA is considering these accumulation studies as supportive information |

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

| | |
|---|---|
| Ka , Kd<br><br>$Ka_{oc}$ , $Kd_{oc}$ | <u>Freundlich normalised distribution coefficient ($K_{foc}$)</u><br>Cyproconazole: 364 L/kg (range 173 – 711, mean, n = 5)<br>1,2,4-triazole: 89 L/kg (range 43 – 120, mean, n = 4)<br><br><u>Normalised distribution coefficient</u><br><u>Cyproconazole:</u><br>Mean: 473 L/kg (n = 5)<br>Median: 433.3 L/kg (n = 5)<br>Range: 174-904.35 L/kg,<br><br><u>1,2,4-triazole</u><br>Mean: 124 L/kg (n = 4)<br>Median: 115 L/kg (n = 4)<br>Range: 83-183 L/kg, |
| pH dependence (yes / no) (if yes type of dependence) | 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 determined/not required |
| Photo-oxidative degradation in air | $DT_{50}$: ~1 d (Atkinson calculation)<br><u>Calculation assumptions:</u><br>The calculation assumes a 24 hr time period and a [OH] radical concentration of 5 x $10^5$ molec $cm^{-3}$ |
| Volatalization | from plant surfaces: 17% in 24 hours |
| | from soil: < 1% in 24 hours |

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

| | |
|---|---|
| Soil (indicate location and type of study) | None available |
| Surface water (indicate location and type of study) | None available |
| Ground water (indicate location and type of study) | None available |
| Air (indicate location and type of study) | None available |

## 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 (mg a.i./L) |
|---|---|---|---|
| **Fish** | | | |
| **Cyproconazole technical** | | | |
| Rainbow trout | 96 h | $LC_{50}$ | 19 (m) |
| Bluegill sunfish | 96 h | $LC_{50}$ | 21 (m) |
| Carp | 96 h | $LC_{50}$ | 20 (n) |
| Sheepshead minnow (salt water) | 96 h | $LC_{50}$ | 21 (m) |
| Rainbow trout | 21 day | NOEC | 5.04 (growth) (m)<br>0.65 (behaviour) (m) |
| Rainbow trout | 89 day | NOEC<br>LOEC<br>89 day NOEC<br>59 day NOEC | 0.58 (survival) (m)<br>0.16 (fry growth) (m)<br><0.16 (fry growth) (m)<br>0.16 (fry growth) (m) |
| Fathead minnow | 357 day | NOEC | 0.5 (n) |
| **Metabolite CGA 71019** | | | |
| Rainbow trout | 96 h | $LC_{50}$ | 498 mg CGA 71019/L (m) |
| Rainbow trout | 28 day | NOEC | >100 mg CGA 71019/L (growth) (n) |
| **Invertebrates** | | | |
| **Cyproconazole technical** | | | |
| *Daphnia magna* | 48 h | $EC_{50}$ | >22 (m) |
| *Daphnia magna* | 48 h | $EC_{50}$ | 26 (m) |
| *Daphnia magna* | 21 day | NOEC | 0.29 (reproduction) (m) |
| *Mysidopsis bahia* (Mysid shrimp) | 96 h | $EC_{50}$ | 9.6 (m) |
| *Crassostrea virginica* (Eastern oyster) | 96 h | $EC_{50}$ | 2.6 (m) |
| **Metabolite CGA 71019** | | | |
| *Daphnia magna* | 48 h | $EC_{50}$ | >100 mg CGA 71019/L (growth) (n) |
| **Algae** | | | |
| **Cyproconazole technical** | | | |
| *Scenedesmus subscipatus* | 72 h<br>96 h<br>96 h | $E_bC_{50}$<br>$E_bC_{50}$<br>NOEC | 0.099 (m)<br>0.077 (m)<br>0.021 (m) |
| *Chlorella vulgaris* | 72 h<br>72 h | $E_bC_{50}$<br>NOEC | 0.66 (m)<br>0.392 (m) |
| **Metabolite CGA 71019** | | | |
| *Selenastrum capricornutum* | 72 h<br>96 h<br>96 h | $E_bC_{50}$<br>$E_bC_{50}$<br>NOEC | 13 mg CGA 71019/L (m)<br>14 mg CGA 71019/L (m)<br>6.8 mg CGA 71019/L (m) |
| **Sediment dwellers** | | | |
| **Cyproconazole technical** | | | |
| *Chironomus riparius* | 28 day | NOEC (development rate) | 5.0 mg/L (via water column) (n) dwt<br>50 mg ai/kg sediment (via sediment) (n)<br>10.9 mg a.i./kg wwt |
| **Sewage sludge** | | | |

| Cyproconazole technical | | | |
|---|---|---|---|
| Activated sludge | 3 hours | $EC_{50}$<br>NOEC | >100 (n)<br>≥ 100 (n) |

*m=measured concentration; n=nominal concentration

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

| | |
|---|---|
| Acute toxicity to earthworms<br>(Annex IIIA, point XIII.3.2) | Technical ai: 14 day $LC_{50}$ 335 mg ai/kg dwt soil (n)<br>CGA 71019: 14 day $LC_{50}$ >1000 mg ai/kg dwt soil (n) |
| Reproductive toxicity to earthworms and collembola<br>(Annex IIIA, point XIII.3.2) | CGA 71019: 56 day earthworm NOEC 0.0708[(1)]g ai/ha dwt (n)<br>CGA 71019: 28 day *F. candida* NOEC 1.8 mg ai/kg dwt (n)<br>CGA A-9898 A: 28 day *F. candida* NOEC 55.8 mg ai/kg dwt (n) |

(1) Highest rate tested

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

| | |
|---|---|
| Nitrogen mineralization | Technical ai: <15% effect at 2.5 mg ai/kg dwt<br><15% effect at 0.25 mg ai/kg wwt<br>CGA 71019: <15% effect at 0.353 mg ai/kg dwt<br><15% effect at 0.31 mg ai/kg wwt |
| Carbon mineralization | Technical ai: 23% increased in effect at 2.5 mg ai/kg dwt (NOEC = 2.5 mg ai/kg dwt)<br><15% effect at 0.25mg mg ai/kg wwt<br>CGA 71019: <15% effect at 0.353 mg ai/kg dwt<br><15% effect at 0.31 mg ai/kg wwt |

**Effects on terrestrial vertebrates**

| | | |
|---|---|---|
| Acute toxicity to mammals<br>(Annex IIIA, point XIII.3.3) | **Cyproconazole technical** | |
| | Rat $LD_{50}$ oral | 1290 mg a.i./kg (male and female) |
| | Rat $LD_{50}$ dermal | >2000 mg a.i./kg |
| | Rat $LC_{50}$ inhalation | >5.65 mg a.i./L |
| Acute toxicity to birds<br>(Annex IIIA, point XIII.1.1) | **Cyproconazole technical** | |
| | *Anas platyrhynchos*<br>(Mallard duck) | $LD_{50}$ ≥2000 mg a.i./kg bw |
| | *Colinus virginianus*<br>(Bobwhite quail) | $LD_{50}$ 94 mg a.i./kg bw |
| | *Colinus virginianus*<br>(Bobwhite quail) | $LD_{50}$ 183 mg a.i./kg bw |
| Dietary toxicity to birds<br>(Annex IIIA, point XIII.1.2) | **Cyproconazole technical** | |
| | *Anas platyrhynchos*<br>(Mallard duck) | $LC_{50}$ 851 mg a.i./kg food |
| | *Colinus virginianus*<br>(Bobwhite quail) | $LC_{50}$ 1292 mg a.i./kg food |
| | *Colinus virginianus*<br>(Bobwhite quail) | $LC_{50}$ 567 mg a.i./kg food |

| | | |
|---|---|---|
| Reproductive toxicity to birds (Annex IIIA, point XIII.1.3) | **Metabolite CGA 131013** | |
| | *Anas platyrhynchos* (Mallard duck) | $LC_{50}$ >5000 mg CGA 131013/kg food |
| | *Colinus virginianus* (Bobwhite quail) | $LC_{50}$ >5000 mg CGA 131013/kg food |
| | **Cyproconazole technical** | |
| | *Anas platyrhynchos* (Mallard duck) | NOEC = 10 mg a.i./kg food (n) |
| | *Colinus virginianus* (Bobwhite quail) | NOEC = 50 mg a.i./kg food (n) |
| | **Metabolite CGA 71019** | |
| | *Cortunix cortunix japonica* (Cortunix quail) | NOEC= 316 mg CGA 71019/kg bw (m) |

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

| | |
|---|---|
| Acute oral toxicity | Technical ai: 24-h $LD_{50}$ >1000mg ai/bee (n) |
| Acute contact toxicity | Technical ai: 24-h $LD_{50}$ >100 mg ai/bee (n) |

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

| Species | Mortality effects | Sub-lethal effects |
|---|---|---|
| **Cyproconazole technical** | | |
| *Typhlodromus pyri* | $LR_{50}$ 35.6 g ai/ha (n)<br>Corrected mortalities 0, 2.1, 0, 0, 71.5, 85.7, 100, 97.9% | 13% and 34% reduction in fecundity at 10 and 20 g ai/ha, respectively |
| *Aphidius rhopalosiphi* | $LR_{50}$ <80 g ai/ha (n)<br>Mortality –100% | - |
| *Aphidius rhopalosiphi* | $LR_{50}$ >200 g ai/ha(n)<br>0, 0% mortality | No significant effects on fecundity at any rates |
| *Chrysoperla carnea* | $LR_{50}$ >200 g ai/ha(n)<br>Corrected mortality up to 20% | No significant effects on fecundity at any rate |
| *Poecilus cupreus* | $LR_{50}$ >160 g ai/ha(n)<br>No mortality at any rate | No significant effects upon feeding behaviour |
| *Orius laevigatus* | $LR_{50}$ >200 g ai/ha (n) Corrected mortality 0, 3.9, 0, 0% | No adverse effects on fecundity at any rate |
| **Formulation A-9961 B** | | |
| *Typhlodromus pyri* | $LR_{50}$ 29.4 g ai/ha(n)<br>Corrected mortalities 0, 0, 44.4, 61.1, 63, 74.1, 100% | No significant effects on fecundity at 4.9 to 133.3 mL A-9898 A/ha |
| *Typhlodromus pyri* | Fresh residues<br>$LR_{50}$ 51 g ai/ha (n)<br>Corrected mortalities 12.5, 57.1, 76.8, 100%<br>Aged residues (7 d)<br>$LR_{50}$ 94.3 g ai/ha (n)<br>Corrected mortalities 9.3, 44.4, 61.1% | No significant effects on fecundity with fresh and aged residues at all treatment rates |

**Bioconcentration** (Annex IIA, point 7.5)

| | |
|---|---|
| Bioconcentration factor (BCF) | 28 |
| Depuration time ($DT_{50}$)<br>($DT_{90}$) | 0.87 days<br>Elimination almost complete in 4 - 7 days |
| Level of metabolites (%) in organisms accounting for >10% of residues | Not determined |

**Chapter 6: Other End Points**

**None**

## APPENDIX II: LIST OF INTENDED USES

Cyproconazole has been evaluated for its intended use in the preservation of timber.

| | |
|---|---|
| Main group | MG02 - Preservatives |
| Product type | PT8 - Wood preservative |
| Function | Fungicide – Preventative |
| Formulation | EVIPOL® 60SL water-based formulation – 5.175 % w/w |
| Target Organism | Wood rotting Basidiomycetes including:<br>*Poria placenta*<br>*Lentinus lepideus*<br>*Coriolus versicolor*<br>*Serpula lacrymans*<br>*Coniophora puteana*<br>*Gloeophyllum trabeum* |
| Categories of User | Industrial |
| Type of Application | Industrial vacuum pressure impregnation<br>Double vacuum pressure impregnation<br>Manual or mechanized dipping<br>Deluge/flood process |
| Application rate | Industrial vacuum pressure: 65-75 g a.s. m-3<br>Double vacuum; industrial joinery: 65-75 g a.s. m-3<br>Manual or mechanised dipping 130-150 mg a.s. m-2<br>Deluge/flood process: 130-150 mg a.s. m-2 |

| Field of use envisaged | Likely concentration at which the active substance (a.s.) will be used in% weight/weight* | | Effective retention in wood in kilogram a.s./m² or a.s./m³ | | Remarks (e.g. concentrates) Use Class (UC) |
|---|---|---|---|---|---|
| | Water-based | Solvent-based | Water-based | Solvent-based | |
| Vacuum pressure treatment, metal free product (industrial) | 0.02 | Not used- | 0.065-0.075 kg/m³ | Not used | *EVIPOL® 60 SL or* Concentrates up to 5 % UC: 2,3,4a |
| Vacuum pressure treatment, cyproconazole in combination with other actives in the product (industrial) | expected 0.01 | Not used | expected 0.04 – 0.050 kg/m³ | Not used | Concentrates up to 1.0% UC: 2,3,4a |
| Double vacuum treatment (industrial) including Vacuumat | 0.15 | 0.4 | 0.065-0.075 kg/m³ | 0.065-0.075 kg/m³ | *EVIPOL® 60 SL or* Concentrates up to 5 % UC: 2,3,4a |
| Double vacuum treatment (industrial) including Vacuumat, cyproconazole in combination with other actives in the product | expected 0.075 | 0.2 | expected 0.040-0.050 kg/m³ | expected 0.040-0.050 kg/m³ | *EVIPOL® 60 SL or* Concentrates up to 5 % UC: 2,3,4a |
| Automated spraying (industrial) | 0.2 | 0.2 | 0.15 g/m² | 0.15 g/m² | *EVIPOL® 60 SL or* Concentrates up to 5% UC: 2,3 |
| Flow coating (industrial) | 0.2% | 0.2 | 0.15 g/m² | 0.15 g/m² | *EVIPOL® 60 SL or* Concentrates up to 5% UC: 2,3 |
| Dipping of wooden articles (industrial) | 0.2 | 0.2 | 0.15 g/m² | 0.15 g/m² | *EVIPOL® 60 SL or* Concentrates up to 5.0% UC: 2,3 |

For Annex I inclusion, efficacy studies have been submitted based on information of effective retention per m³, but not on retention per m². Cyproconazole concentrations are worst case assumptions and the highest figures have been taken and used in the calculations.

## APPENDIX III: LIST OF STUDIES

Data protection is claimed by the applicant in accordance with Article 12.1(c) (i) and (ii) of Council Directive 98/8/EC for all study reports marked "Y" in the "Data Protection Claimed" column of the table below. It is assumed that the relevant studies are not already protected in any other Member State of the European Union under existing national rules relating to biocidal products. It was however not possible to confirm the accuracy of this information.

### IIIA Reference List by Annex Point

### References: Doc III-A1-A3

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 2.2. | Kettner, R. | 2000a | Chemical composition of SAN 619 tech. (5 representative batches)<br>Novartis Crop Protection AG, Basel, Switzerland<br>Novartis Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 102505<br>GLP<br>Not Published<br>Syngenta File N° SAN619/6948<br>CONFIDENTIAL INFORMATION | Y | SYN |
| IIIA 2.2. | Messerli, Ch. | 1999 | Final report for the analysis of chlorinated dibenzodioxins and -furans in SAN 619 tech.<br>Novartis Crop Protection AG, Basel, Switzerland<br>Labor Dr. Meyer AG, Bern, Switzerland, Report No P2128<br>GLP<br>Not Published<br>Syngenta File N° SAN619/6779<br>CONFIDENTIAL INFORMATION | Y | SYN |
| IIIA 2.2. | Hertner, T. | 2001 | Purity of test material used in toxicity test (including analytical certificates)<br>Syngenta Crop Protection AG, Basel, Switzerland, Report No N/A<br>Not GLP<br>Not Published<br>Syngenta File N° SAN619/7291<br>CONFIDENTIAL INFORMATION | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 2.2. | Kettner, R. | 2000b | Chemical composition of SAN 619 tech. (batch 8507)<br>Novartis Crop Protection AG, Basel, Switzerland<br>Novartis Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 102508<br>GLP<br>Not Published<br>Syngenta File N° SAN619/6949<br>CONFIDENTIAL INFORMATION | Y | SYN |
| IIIA 2.2. | Kettner, R. | 2000c | Chemical composition of SAN 619 tech. (Batch MU809073)<br>Syngenta Crop Protection AG, Basel, Switzerland<br>Novartis Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 74711<br>GLP<br>Not Published<br>Syngenta File N° SAN619/7292<br>CONFIDENTIAL INFORMATION | Y | SYN |
| IIA 2.2 | Oggenfuss, P. | 2000 | Nitrosamines in SAN 619 tech.<br>Novartis Crop Protection AG, Basel, Switzerland<br>Novartis Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 102592<br>GLP<br>Not Published<br>Syngenta File N° SAN619/7425<br>CONFIDENTIAL INFORMATION | Y | SYN |
| IIIA 3.1.1 | Das, R. | 1998 | Report on melting point / melting range<br>Novartis Crop Protection AG, Basel, Switzerland<br>Novartis Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 66837<br>GLP<br>Not Published<br>Syngenta File N° SAN619/0447 | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 3.1.2/01<br>IIIA 3.10/01 | Das, R. | 2000 | Boiling point / boiling range of SAN 619<br>Novartis Crop Protection AG, Basel, Switzerland<br>Novartis Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 77100<br>GLP<br>Not Published<br>Syngenta File N° SAN619/6876 | Y | SYN |
| IIIA 3.1.3/01 | Füldner, H.H. | 1998 | Report on density of solids<br>Novartis Crop Protection AG, Basel, Switzerland<br>Novartis Services AG, Basel, Switzerland, Report No PP-98/96P.DES<br>GLP<br>Not Published<br>Syngenta File N° SAN619/0503 | Y | SYN |
| IIIA. 3.2/01 | Widmer, H. | 1998 | Vapour pressure of SAN 619<br>Novartis Crop Protection AG, Basel, Switzerland<br>Novartis Crop Protection AG, Basel, Switzerland, Report No 98WI32<br>GLP<br>Not Published<br>Syngenta File N° SAN619/0532 | Y | SYN |
| IIIA 3.2/02 | Krohn, J. | 2001a | Vapour pressure curve of 1,2,4-triazole<br>Syngenta Crop Protection AG, Basel, Switzerland<br>Bayer AG, Leverkusen, Germany, Report No 100415<br>Not GLP<br>Not Published<br>Syngenta File N° CGA71019/0049 | Y | SYN |
| IIIA 3.2.1/01 | Burkhard, N. | 1999 | Henry's law constant<br>Syngenta Crop Protection AG, Basel, Switzerland<br>Novartis Crop Protection AG, Basel, Switzerland, Report No N/A<br>Not GLP<br>Not Published<br>Syngenta File N° SAN619/0099 | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 3.3.1/01<br>IIIA 3.3.2/01<br>IIIA 3.3.3/01 | Das, R. | 1999a | General physico-chemical properties of SAN 619<br>Novartis Crop Protection AG, Basel, Switzerland<br>Novartis Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 77101<br>GLP<br>Not Published<br>Syngenta File N° SAN619/6781 | Y | SYN |
| IIIA 3.3.1/02<br>IIIA 3.3.2/02<br>IIIA 3.3.3/02 | Das, R. | 1999b | General physico-chemical properties of SAN 619 tech.<br>Novartis Crop Protection AG, Basel, Switzerland<br>Novartis Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 77102<br>GLP<br>Not Published<br>Syngenta File N° SAN619/6780 | Y | SYN |
| IIIA 3.4/01 | Oggenfuss, P. | 2001 | Spectra of SAN 619<br>Syngenta Crop Protection AG, Basel, Switzerland<br>Syngenta Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 107381<br>GLP<br>Not Published<br>Syngenta File N° SAN619/7060 | Y | SYN |
| IIIA 3.5/01 | Wisson, M. | 1989 | Solubility of the pure active ingredient in redistilled water at pH 3-5, 7 and 9-11 (Final report)<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No 41311<br>GLP<br>Not Published<br>Syngenta File N° SAN619/6125 | Y | SYN |
| IIIA 3.5/02 | Krohn, J. | 2001b | Water solubility and Henry law constant of 1,2,4-triazole<br>Syngenta Crop Protection AG, Basel, Switzerland<br>Bayer AG, Leverkusen, Germany, Report No MO-01-005554<br>Not GLP<br>Not Published<br>Syngenta File N° CGA71019/0050 | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 3.5/03<br>IIIA 3.9/03 | Bates, M. | 1994a | M21a: Determination of the physico-chemical properties according to USA-EPA requirements<br>Novartis Crop Protection AG, Basel, Switzerland<br>Hazleton Europe Ltd., Harrogate, North Yorkshire, United Kingdom, Report No 252/112-1014<br>GLP<br>Not Published<br>Syngenta File N° NOA405870/5005 | Y | SYN |
| IIIA 3.5/04<br>IIIA 3.9/04 | Bates, M. | 1994b | M36: Determination of the physico-chemical properties according to USA-EPA requirements<br>Novartis Crop Protection AG, Basel, Switzerland<br>Hazleton Europe Ltd., Harrogate, North Yorkshire, United Kingdom, Report No 252/113-1014<br>GLP<br>Not Published<br>Syngenta File N° NOA405872/5007 | Y | SYN |
| IIIA 3.6/01 | Gampp, H. | 1989 | Cyproconazole (SAN 619 F) - Dissociation constant in water.<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No 31308<br>GLP<br>Not Published<br>Syngenta File N° SAN619/6138 | Y | SYN |
| IIIA 3.7/01 | Stulz, J. | 1998a | Report on solubility in organic solvents<br>Novartis Crop Protection AG, Basel, Switzerland<br>Novartis Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 69561<br>GLP<br>Not Published<br>Syngenta File N° SAN619/0522 | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 3.9/01 | Stulz, J. | 1998b | Report on octanol / water partition coefficient<br>Novartis Crop Protection AG, Basel, Switzerland<br>Novartis Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 66839<br>GLP<br>Not Published<br>Syngenta File N° SAN619/0518 | Y | SYN |
| IIIA 3.9/02 | Unknown | 1983 | Physico-chemical properties of 1,2,4 triazole (CGA 71019)<br>Syngenta Crop Protection AG, Basel, Switzerland<br>Ciba-Geigy Ltd., Basel, Switzerland, Report No N/A<br>Not GLP<br>Not Published<br>Syngenta File N° CGA71019/0070 | Y | SYN |
| IIIA 3.10/02 | Angly, H. | 2000 | Screening test for thermal stability and stability in air<br>Novartis Crop Protection AG, Basel, Switzerland<br>Institute of Safety and Security, Basel, Switzerland, Report No 2000.4031.TSA<br>GLP<br>Not Published<br>Syngenta File N° SAN619/6950 | Y | SYN |
| IIIA3.11.1/01 | van, Helvoirt J.A. | 1994a | Determination of the flammability of cyproconazole techn.<br>Novartis Crop Protection AG, Basel, Switzerland<br>NOTOX B.V., 'S Hertogenbosch, Netherlands, Report No 128868<br>GLP<br>Not Published<br>Syngenta File N° SAN619/6239 | Y | SYN |
| IIIA 3.11.2/01 | van, Helvoirt J.A. | 1994b | Determination of the relative self-ignition temperature of cyproconazole techn.<br>Novartis Crop Protection AG, Basel, Switzerland<br>NOTOX B.V., 'S Hertogenbosch, Netherlands, Report No 128879<br>GLP<br>Not Published<br>Syngenta File N° SAN619/6240 | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA3.13/01 | Martin, N. | 1999 | Final report on surface tension<br>Novartis Crop Protection AG, Basel, Switzerland<br>Novartis Services AG, Basel, Switzerland, Report No PP-99/01T.SUR<br>GLP<br>Not Published<br>Syngenta File N° SAN619/6767 | Y | SYN |
| IIIA3.15/01 | Krips, H.J. | 1996 | Determination of the explosive properties of cyproconazole techn.<br>Novartis Crop Protection AG, Basel, Switzerland<br>NOTOX B.V., 'S Hertogenbosch, Netherlands, Report No 166286<br>GLP<br>Not Published<br>Syngenta File N° SAN619/5160 | Y | SYN |
| IIIA3.16/01 | Krips, H.J. | 1995 | Determination of the oxidizing properties of cyproconazole techn.<br>Novartis Crop Protection AG, Basel, Switzerland<br>NOTOX B.V., 'S Hertogenbosch, Netherlands, Report No NOTOX 146374<br>GLP<br>Not Published<br>Syngenta File N° SAN619/6238 | Y | SYN |

## References: Doc.III-A4

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 4.1/01 | Kettner, R. | 1999 | SAN 619 tech. - Assay by HPLC<br>Novartis Crop Protection AG, Basel, Switzerland<br>Novartis Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No AW-209/1<br>Not GLP<br>Not Published<br>Syngenta File N° SAN619/6839 | Y | SYN |
| IIIA 4.1/02 | Kettner, R. | 2000 | Validation of analytical method AW-209/1<br>Novartis Crop Protection AG, Basel, Switzerland<br>Novartis Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 102465<br>GLP<br>Not Published<br>Syngenta File N° SAN619/6945 | Y | SYN |
| IIIA 4.2 | Garcia-Alix, M | 2010 | Analytical Method for the Determination of Residues of Cyproconazole in Soil. Final Determination by LC-MS/MS, Analytical Method, Syngenta Ltd unpublished report No. GRM033.05A, Syngenta Task No. TK0024771<br>GLP | Y | SYN |
| IIIA 4.2 | Garcia-Alix, M | 2010 | Validation of Residue Method GRM033.05A for the determination of Cyproconazole in Soil, CEMAS, UK, unpublished report No. CEMR-4826-REG, Syngenta Task No. TK0024771.<br>GLP | Y | SYN |
| IIIA 4.2(a)/01 | Bourry, R., Gasser, A., Hertl, P. | 1996 | A Method for the Determination of Residues of Cyproconazole in human Food, animal Feed and environmental Matrices.<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No BS8058<br>Not GLP<br>Not Published<br>Syngenta File N° SAN619/5107 | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 4.2(a)/02 | Krennhuber, K., Pfarl, Ch. | 1996a | Validation of an Analytical Method for Determination of Residues of Cyproconazole in Human Food, Animal Feed and Environmental Matrices<br>Novartis Crop Protection AG, Basel, Switzerland<br>Agrolinz Agrarchemikalien Gmbh, Leonding, Austria, Report No R 96-98<br>GLP<br>Not Published<br>Syngenta File N° SAN619/0063 | Y | SYN |
| IIIA 4.2(a)/03 | Hargreaves, SL | 2002 | Residue Analytical Method for the Determination of Residues of Cyproconazole in Soil<br>Syngenta Crop Protection AG, Basel, Switzerland, Report No RAM369/01<br>Not GLP<br>Not Published<br>Syngenta File N° SAN619/7163 | Y | SYN |
| IIIA 4.2(b)/01 | Kettner, R., Karapally, J.C., Lauper, M. | 1993 | Determination of Cyproconazole in Air<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No 21302<br>GLP<br>Not Published<br>Syngenta File N° SAN619/5330 | Y | SYN |
| IIIA 4.2(b)/02 | Tribolet, R. | 1999 | Validation of Analytical method BS 3786 for the Determination of Cyproconazole (SAN 619) in Air by analysis of fortified Air sampling tubes and Evaluation of recoveries<br>Novartis Crop Protection AG, Basel, Switzerland<br>Novartis Crop Protection AG, Basel, Switzerland, Report No 211/99<br>GLP<br>Not Published<br>Syngenta File N° SAN619/6768 | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 4.2(b)/03 | Tummon, O. J. | 2004 | Cyproconazole: Validation of an Analytical Method for the Determination of Residues of Cyproconazole in Air<br>Syngenta Crop Protection AG, Basel, Switzerland<br>Syngenta, Jealott's Hill, United Kingdom, Report No RJ3497B<br>GLP<br>Not Published<br>Syngenta File N° SAN619/7478 | Y | SYN |
| IIIA 4.1(c)/01 | Gasser, A. | 2000a | Determination of Cyproconazole by Gas Chromatography (MSD)<br>Syngenta Crop Protection AG, Basel, Switzerland<br>Novartis Crop Protection AG, Basel, Switzerland, Report No REM 200.01<br>Not GLP<br>Not Published<br>Syngenta File N° SAN619/7077 | Y | SYN |
| IIIA 4.2(c)/02 | Gasser, A. | 2000b | Validation of Method REM 200.01 (validation by Analysis of drinking and surface water specimens fortified with Cyproconazole (SAN 619); determination of recoveries<br>Syngenta Crop Protection AG, Basel, Switzerland<br>Novartis Crop Protection AG, Basel, Switzerland, Report No 205/00<br>GLP<br>Not Published<br>Syngenta File N° SAN619/7078 | Y | SYN |
| IIIA 4.2(c)/03 | Gasser, A., Hertl, P., Karapally, J.C. | 1989 | Determination of Cyproconazole in Groundwater<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No CBK 12747/89<br>Not GLP<br>Not Published<br>Syngenta File N° SAN619/6073 | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 4.2(c)/04 | Krennhuber, K., Pfarl, Ch. | 1996b | Validation of an Analytical Method for Determination of Residues of Cyproconazole in Groundwater<br>Novartis Crop Protection AG, Basel, Switzerland<br>Agrolinz Agrarchemikalien Gmbh, Leonding, Austria, Report No 1282<br>GLP<br>Not Published<br>Syngenta File N° SAN619/0051 | Y | SYN |

## References: Doc III-A5 (Efficacy)

| Section No / Reference No | Author(s) | Year | Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA5.3.1 | Zgraggen B. and Graf E. | 1996a | Determination of the Toxic Values for Wood Preservatives against Wood-Destroying Basidiomycetes without any ageing: SAN 619 F, EMPA Switzerland, Report No. 124226P1<br>Not Published | Y | SYN |
| IIIA5.3.2 | Zgraggen B. and Graf E. | 1996b | Determination of the Toxic Values for Wood Preservatives against Wood-Destroying Basidiomycetes after 12 weeks exposure in the wind tunnel: SAN 619 F, EMPA Switzerland, Report No. 124226P3<br>Not Published | Y | SYN |
| IIIA5.3.3 | Zgraggen B. and Graf E. | 1996c | Determination of the Toxic Values for Wood Preservatives against Wood-Destroying Basidiomycetes after leaching: SAN 619 F, EMPA Switzerland, Report No. 124226P2<br>Not Published | Y | SYN |

## References: Doc III-A6 (Toxicology)

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 6.1.1/01 | [redacted] | 1984a | SAN 619 F - Acute oral LD50 in male and female rats.<br>[redacted]<br>No 265/84, CBK I.6168/84<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA6.1.1/01a Non-Key | [redacted] | 2005a | Acute Oral Up and Down Procedure in Rats with Cyproconazole Technical. [redacted]<br>GLP<br>Not Published | Y | SYN |
| IIIA 6.1.1/02 | [redacted] | 1984b | SAN 619 F - Acute oral LD50 in the male and female mouse<br>[redacted] Report<br>No 254/84, CBK I.6157/84<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.1.1/03 | [redacted] | 1987 | SAN 619 F - Acute oral LD50 study in male mice (CD-1 strain)<br>[redacted]<br>No 263/87, CBK I.6828/87<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.1.1/04 | [redacted] | 1985a | SAN 619 F - Acute oral LD50 in the female rabbit.<br>[redacted]<br>No 160/85, CBK I.6405/84<br>GLP<br>Not Published<br>[redacted] | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 6.1.2/01 | [redacted] | 1984c | SAN 619 F - Acute dermal LD50 in male and female rats.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA6.1.2/01a Non-key | [redacted] | 2005b | (2005b), Acute Dermal Toxicity Study in Rats - Limit Test with Cyproconazole Technical. [redacted]<br>GLP<br>Not Published | Y | SYN |
| IIIA 6.1.2/02 | [redacted] | 1985 | SAN 619 F - Acute dermal LD50 in male and female rabbits.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.1.3/01 | [redacted] | 1985 | SAN 619 F - 4-hour acute dust aerosol inhalation toxicity (LC50) study with SAN 619 F in rats.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA6.1.3/01a Non-key | [redacted] | 2005c | Acute Inhalation Toxicity Study in Rats with Cyproconazole Technical. Product Safety [redacted]<br>GLP<br>Not Published | Y | SYN |
| IIIA 6.1.4/01 | [redacted] | 1985b | SAN 619 F - Primary skin irritation test in rabbits.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA6.1.4/01a<br>Non-key | [redacted] | 2005d | Primary Skin Irritation Study in Rabbits with Cyproconazole Technical. [redacted]<br>GLP<br>Not Published | Y | SYN |
| IIIA 6.1.4/02 | [redacted] | 1985c | SAN 619 F - Primary eye irritation test in rabbits. [redacted]<br>GLP<br>Not Published [redacted] | Y | SYN |
| IIIA6.1.4/02a<br>Non-key | [redacted] | 2005e | Primary Eye Irritation Study in Rabbits with Cyproconazole Technical. [redacted]<br>GLP<br>Not Published | Y | SYN |
| IIIA 6.1.5/01 | [redacted] | 1992 | Contact hypersensitivity to Cyproconazole techn. in albino Guinea pigs - Maximization test. [redacted]<br>GLP<br>Not Published [redacted] | Y | SYN |
| IIIA6.1.5/01a<br>Non-key | [redacted] | 2005f | Dermal Sensitization Study in Guinea Pigs (Buehler Method) with Cyproconazole Technical. [redacted]<br>GLP<br>Not Published | Y | SYN |
| IIIA 6.2/01 | [redacted] | 1987a | SAN 619 F - Absorption, distribution and excretion in rats after single and multiple doses of [14C] SAN 619 F. [redacted]<br>GLP<br>Not Published [redacted] | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 6.2/02 | [redacted] | 1987b | SAN 619 F - Quantitative whole-body autoradiography in rats after single oral doses of [14C] SAN 619 F.<br>[redacted]<br>Not GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.2/03 | [redacted] | 2003 | Disposition of [Phenyl-U-14C] SAN 619F in the Rat After Multiple Oral Administrations<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.2/04 | [redacted] | 1992 | Absorption, tissue distribution and excretion of [14C] SAN 619 F following dermal administration to the pig.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.2/05 | [redacted] | 1993 | The dermal absorption of 14C-Cyproconazole (SENTINEL 40 WG) by male Sprague-Dawley rats.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 6.2/06 | [redacted] | 1997 | SAN 1414 F 360 SL 001 BS - Rates of penetration of (14C) - Cyproconazole through human and rat skin using an in vitro system.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.2/07 | [redacted] | 1987a | SAN 619 F - Metabolism in the rat.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.2/08 | [redacted] | 1987b | SAN 619 F - Metabolism of the Diastereomer A and B in the rat.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.2/09 | [redacted] | 1992 | Supplementary Cyproconazole metabolism in the rat.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.2/10 | [redacted] | 1994 | Determination of Cyproconazole M36 metabolite in rats.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 6.2/11 | [redacted] | 1995a | Cyproconazole - Investigations of the in vitro metabolism in the rat and mouse liver.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.2/12 | [redacted] | 1987a | Metabolism of [14C]SAN 619F by a Lactating Goat<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.2/13 | [redacted] | 1991 | Metabolism of Cyproconazole in Lactating Goats<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.2/14 | [redacted] | 1987b | Metabolism of SAN 619 F by Laying Hens<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.2/15 | [redacted] | 2001 | The Metabolism of [U-Phenyl-$^{14}$C] SAN 619 F after Multiple Oral Administration to Laying Hens<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 6.3.1/01 | [redacted] | 1985a | SAN 619 F - 4-Week feeding study in rats.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.3.2/01 | [redacted] | 2000 | SAN 619 tech. - 28-day repeated dose dermal toxicity study in rats<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.3.3/01 | [redacted] | 1988 | SAN 619 F - Subacute (16-day) repeated dose inhalation toxicity study in rats.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.4.1/01 | [redacted] | 1985b | SAN 619 F - 13-Week feeding study in rats.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.4.1/02 | [redacted] | 1999 | SAN 619 F (Cyproconazol) 3-Month oral toxicity study in rats. (Administration in food)<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 6.4.1/03 | [redacted] | 1987 | SAN 619 F - 13-Week dose range finding feeding study in CD-1 mice.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.4.1/04 | [redacted] | 1986 | SAN 619 F - 13-Week feeding study in Beagle dogs.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.4.1/05 | [redacted] | 1988 | SAN 619 F - Chronic oral toxicity by dietary administration to Beagle dogs for one year.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.6.1/01 | [redacted] | 1986 | Mutagenicity evaluation of SAN 619 F in the Ames Salmonella/microsome reverse mutation assay.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 6.6.2/01 | [redacted] | 1988 | Evaluation of the ability of Cyproconazole to induce chromosome aberrations in cultured Chinese Hamster Ovary (CHO) Cells (including multiple fixation times)<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.6.2/02 | [redacted] | 1992 | Slide analysis for chromosome aberrations in cultured Chinese hamster ovary (CHO) cells.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.6.2/03 | [redacted] | 1990 | Mutagenicity test on SAN 619 F technical in an in vitro cytogenetic assay measuring chromosomal aberration frequences in Chinese hamster ovary (CHO) cells.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.6.2/04 | [redacted] | 1988 | SAN 619 F - Unscheduled DNA synthesis in rat primary hepatocytes.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 6.6.2/05 | [redacted] | 1995 | A chromosomal aberration test of Cyproconazole technical in cultured Chinese hamster cells.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.6.2/06 | [redacted] | 1985 | Mutagenicity evaluation of SAN 619 F in the mitotic non-disjunction assay with saccharomyces cerevisiae strain D6.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.6.3/01 | [redacted] | 1985a | SAN 619 F - In vitro hypoxanthine-guanine phosphoribosyl transferase (HGPRT) gene mutation assay using Chinese hamster cell line V79.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.6.3/02 | [redacted] | 1985b | SAN 619 F - In vitro cell transformation assay with Syrian hamster embryo (SHE) cells.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 6.6.4/01 | [redacted] | 1985 | Mutagenicity evaluation of SAN 619 F in the in vivo mouse micronucleus assay.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.6.4/02 | [redacted] | 1999 | SAN 619 A - Chromosome studies on bone marrow of mouse<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.6.6/01 | [redacted] | 1991 | SAN 619 F - Subchronic dominant lethal mutation assay in rats.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.7/01 | [redacted] | 1988 | SAN 619 F - Chronic toxicity / oncogenicity feeding study In rats.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.7/02 | [redacted] | 1989 | SAN 619 F - The potential oncogenicity of SAN 619 F by prolonged dietary administration to mice.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 6.8.1/01 | [redacted] | 1985a | Dose-finding teragenicity study in rats with SAN 619 F.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.8.1/02 | [redacted] | 1985b | Teratogenicity study in rats with SAN 619 F.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.8.1/03 | [redacted] | 1995 | Developmental toxicity of Cyproconazole, an inhibitor of fungal ergosterol biosynthesis in the rat.<br>[redacted]<br>Not GLP<br>Published<br>[redacted] | Y | N/A |
| IIIA 6.8.1/04 | [redacted] | 1986 | Teratogenicity study in rabbits with SAN 619 F.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.8.1/05 | [redacted] | 1991 | SAN 619 F - Oral (gavage) teratogenicity study in the rabbit.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 6.8.2/01 | [redacted] | 1987 | SAN 619 F - 2-Generation reproduction Study in rats.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.10/01 | [redacted] | 1995 | Cyproconazole (SAN 619 F) - 4-Week liver cell proliferation study in rats and mice (with serial sacrifices).<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.10/02 | [redacted] | 1999 | Comparative histopathologic evaluation of the effects of cyproconazole and propiconazole on the liver of male mice.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.10/03 | [redacted] | 1995b | Cyproconazole (SAN 619 F)- Investigations of enzyme induction in the rat and mouse liver.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 6.10/04 | [redacted] | 2001 | SAN 619 A (Cyproconazole) - Effects on biochemical parameters in the liver following dietary administration to male and female mice<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |

## References: Doc III-A7 (Environment, including Eco-toxicology)

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 7.1.1.1.1/01 | Glänzel, A. | 1999 | Hydrolysis of $^{14}$C-triazole labelled SAN 619 F under laboratory conditions<br>Novartis Crop Protection AG, Basel, Switzerland, Report No 99AG04<br>GLP<br>Not Published<br>Syngenta File N° SAN619/6849 | Y | SYN |
| IIIA 7.1.1.1.1/02 | Spare, W.C. | 1983 | Determination of the hydrolysis rate constants of 1,2,4-H-Triazole (CGA 71019)<br>Novartis Crop Protection AG, Basel, Switzerland<br>Ciba-Geigy Corp., Greensboro, United States, Report No 83-E-074<br>Not GLP<br>Not Published<br>Syngenta File N° CGA71019/0033 | Y | TDMG |
| IIIA 7.1.1.1.2/01 | Oliver, S, Hurt, A D | 2002 | Aqueous Photolysis of $^{14}$ C-Triazole labelled SAN619<br>Syngenta Crop Protection AG, Basel, Switzerland, Report No RJ3322B<br>GLP<br>Not Published<br>Syngenta File N° SAN619/7282 | Y | SYN |
| IIIA 7.1.1.2.1/01 | Scholtz, R. | 1996 | Cyproconazole / Testing of Biological Degradability with Fungal and Bacterial Cultures<br>Novartis Crop Protection AG, Basel, Switzerland<br>Brian Christensen Companies, Inc., Minnetonka, United States, Report No BMG569-95<br>Not GLP<br>Not Published<br>Syngenta File N° SAN619/5081 | Y | SYN |
| IIIA 7.1.2.2.2/01 | Blumhorst, M.R. | 1995 | Anaerobic aquatic metabolism of $^{14}$C-Cyproconazole<br>Novartis Crop Protection AG, Basel, Switzerland<br>Epl Bio-Analytical Services Inc., Harristown, United States, Report No 111S16<br>GLP<br>Not Published<br>Syngenta File N° SAN619/6410 | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 7.1.2.2.2/02 | Völkel, W. | 1997 | U-$^{14}$C-Triazol-Cyproconazole: route and rate of degradation in aerobic aquatic systems<br>Novartis Crop Protection AG, Basel, Switzerland<br>RCC Ltd., Itingen, Switzerland, Report No 613001<br>GLP<br>Not Published<br>Syngenta File N° SAN619/0186 | Y | SYN |
| IIIA 7.2.1/01 | Glänzel, A. | 1994 | [U-14C-Triazolyl]-Cyproconazole Laboratory Soil Metabolism Study<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No 41323<br>GLP<br>Not Published<br>Syngenta File N° SAN619/5321 | Y | SYN |
| IIIA 7.2.1/02 | Wisson, M. | 1992 | [14C-Benzyl]-Cyproconazole / Aerobic Degradation in Three Types of Soil (Balance Study)<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No 41321<br>GLP<br>Not Published<br>Syngenta File N° SAN619/5362 | Y | SYN |
| IIIA 7.2.1/03 | Glänzel, A., Wisson, M. | 1994 | [U-14C-Phenyl]-Cyproconazole / Laboratory Soil Metabolism Study<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No 41322<br>GLP<br>Not Published<br>Syngenta File N° SAN619/5288 | Y | SYN |
| IIIA 7.2.2/01 | Blumhorst, M.R. | 1995 | Anaerobic aquatic metabolism of $^{14}$C-Cyproconazole<br>Novartis Crop Protection AG, Basel, Switzerland<br>Epl Bio-Analytical Services Inc., Harristown, United States, Report No 111S16<br>GLP<br>Not Published<br>Syngenta File N° SAN619/6410 | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 7.2.2/02 | Wisson, M. | 1990a | Cyproconazole / Degradation in Soil under Anaerobic Condition (Laboratory Study with a Field Soil)<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No 41'316<br>GLP<br>Not Published<br>Syngenta File N° SAN619/5541 | Y | SYN |
| IIIA 7.2.2/03 | Mamouni, A | 2003 | [$^{14}$C]-CGA71019: Anaerobic soil degradation<br>Syngenta Crop Protection AG, Basel, Switzerland<br>RCC Ltd., Itingen, Switzerland, Report No 798660<br>GLP<br>Not Published<br>Syngenta File N° CGA71019/0062 | Y | TDMG |
| IIIA 7.2.2/04 | Adam, D. | 2000 | Soil photolysis of (U-$^{14}$C)-Phenyl CGA 221949 / SAN 619 under laboratory conditions<br>Novartis Crop Protection AG, Basel, Switzerland, Report No 99DA05<br>GLP<br>Not Published<br>Syngenta File N° SAN619/6887 | Y | SYN |
| IIIA 7.2.2.1/01 | Wisson, M. | 1989a | Cyproconazole (SAN 619F) : Laboratory Metabolism Study in a Field Soil<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No 41309<br>GLP<br>Not Published<br>Syngenta File N° SAN619/6064 | Y | SYN |
| IIIA 7.2.2.1/02 | Wisson, M. | 1990b | Cyproconazole / Degradation in Three Types of Soil under Various Conditions (Laboratory Study with Field Soils)<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No 41'313<br>GLP<br>Not Published<br>Syngenta File N° SAN619/6143 | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 7.2.2.1/03 | Slangen, P.J. | 2000 | Degradation of 1,2,4-triazole in Three Soils under Aerobic Conditions<br>Novartis Crop Protection AG, Basel, Switzerland<br>NOTOX B.V., 'S Hertogenbosch, Netherlands, Report No NOTOX 278336<br>GLP<br>Not Published<br>Syngenta File N° CGA64250/4345 | Y | TDMG |
| IIIA 7.2.2.2/01 | Hertl, P. | 1991 | Dissipation of Cyproconazole in soil following direct application of its formulations to bare soil in Switzerland and Germany during 1985 - 1988.<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No N/A<br>Not GLP<br>Not Published<br>Syngenta File N° SAN619/5458 | Y | SYN |
| IIIA 7.2.2.2/02 | Bourry, R. | 1986a | SAN 619 F - Rückstände in Boden (Obst und Weinbau). Direkte Bodenbehandlung<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No R 8418<br>Not GLP<br>Not Published<br>Syngenta File N° SAN619/6617 | Y | SYN |
| IIIA 7.2.2.2/03 | Bourry, R. | 1986b | SAN 619 F residues in soil (Fruit tree area); Direct soil application.<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No R 8419<br>Not GLP<br>Not Published<br>Syngenta File N° SAN619/6618 | Y | SYN |
| IIIA 7.2.2.2/04 | Bourry, R. | 1988 | SAN 619 F Residues in Soil (Corn-field; Direct soil application). First year of treatment.<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No R-NO. 8416/85<br>Not GLP<br>Not Published<br>Syngenta File N° SAN619/6620 | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 7.2.2.2/05 | Bourry, R. | 1989 | SAN 619 F Residues in Soil.(Direct soil application, second year of treat- ment).<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No R-NO. 9180<br>GLP<br>Not Published<br>Syngenta File N° SAN619/5823 | Y | SYN |
| IIIA 7.2.2.2/06 | Bourry, R. | 1990a | SAN 619 F Residues in Untilled Soil. (mineral heavy soil, treatment of 3rd year, 1988).<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No R-NO. 8979/86<br>GLP<br>Not Published<br>Syngenta File N° SAN619/5804 | Y | SYN |
| IIIA 7.2.2.2/07 | Bourry, R. | 1990b | SAN 619 F - Residues in Soil (corn field); Direct soil application. First year of Treatment.<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No R 8417/1985<br>GLP<br>Not Published<br>Syngenta File N° SAN619/6619 | Y | SYN |
| IIIA 7.2.2.2/08 | Bourry, R. | 1991a | Cyproconazole long term soil dissipation after one application of SAN 709 F 380 EC to bare soil in the FRG, 1988 (degradation curve)<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No R 9470<br>GLP<br>Not Published<br>Syngenta File N° SAN619/5529 | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 7.2.2.2/09 | Bourry, R. | 1991b | Cyproconazole long term dissipation after one application of SAN 709 F 380 EC to bare soil in the FRG, 1988 (degradation curve)<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No R 9469<br>GLP<br>Not Published<br>Syngenta File N° SAN619/5530 | Y | SYN |
| IIIA 7.2.2.2/10 | Bourry, R. | 1991c | Cyproconazole long term soil dissipation after one application of SAN 709 F 380 EC to the bare soil in the FRG, 1988. (degradation curve)<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No R 9472<br>GLP<br>Not Published<br>Syngenta File N° SAN619/5532 | Y | SYN |
| IIIA 7.2.2.2/11 | Bourry, R. | 1991d | Cyproconazole long term soil dissipation after one application of SAN 709 F 380 EC to bare soil in the FRG, 1988. (degradation curve)<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No R 9471<br>GLP<br>Not Published<br>Syngenta File N° SAN619/5531 | Y | SYN |
| IIIA 7.2.2.2/12 | Bourry, R. | 1991e | Cyproconazole Residues in Bare Soil, France (DC)<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No R 9326<br>GLP<br>Not Published<br>Syngenta File N° SAN619/5518 | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 7.2.2.2/13 | Bourry, R. | 1991f | SAN 619 F 100 SL - Cyproconazole Residues in Bare Soil<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No R 9327<br>GLP<br>Not Published<br>Syngenta File N° SAN619/5519 | Y | SYN |
| IIIA 7.2.2.2/14 | Hertl, P. | 1992a | Dissipation of Residues of Cyproconazole from Field Soil after Application of ALTO 100 SL under Field Conditions in France, 1989 (Field Soil Dissipation/Leaching Study).<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No R 9661<br>GLP<br>Not Published<br>Syngenta File N° SAN619/5378 | Y | SYN |
| IIIA 7.2.2.2/15 | Hertl, P. | 1992b | Dissipation of Residues of Cyproconazole from Field Soil after Application of ALTO 100 SL under Field Conditions in France, 1989 (Field Soil Dissipation/Leaching Study).<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No R 9663<br>GLP<br>Not Published<br>Syngenta File N° SAN619/5380 | Y | SYN |
| IIIA 7.2.2.2/16 | Hertl, P., Vogler, F. | 1993a | Dissipation of Cyproconazole from Field Soil after repeated Applications of SAN 619 F 100 SL to Bare Soil in Switzerland, 1989-1993 (Field Soil Dissipation and Accumulation Study).<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No R 9777<br>GLP<br>Not Published<br>Syngenta File N° SAN619/5346 | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 7.2.2.2/17 | Hertl, P., Vogler, F. | 1993b | Dissipation of Cyproconazole from Field Soil after Application of ALTO 100 SL to Bare Soil in Germany, 1991-1992 (Field Soil Dissipation).<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No R 10190<br>GLP<br>Not Published<br>Syngenta File N° SAN619/5342 | Y | SYN |
| IIIA 7.2.2.2/18 | Hertl, P., Gasser, A. | 1993 | Dissipation of Residues of Cyproconazole from Field Soil after Application of ALTO 100 SL under Field Conditions in France, 1989-1991 (Field Soil Dissipation/Leaching Study). FINAL REPORT.<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No R 9662<br>GLP<br>Not Published<br>Syngenta File N° SAN619/5355 | Y | SYN |
| IIIA 7.2.2.2/19 | Bass, R.V. | 1994 | Cyproconazole: Dissipation of Residues from Field Soil after Application of ALTO 100 SL to Bare Soil in United Kingdom<br>Novartis Crop Protection AG, Basel, Switzerland<br>Hazleton Europe Ltd., Harrogate, North Yorkshire, United Kingdom, Report No 707/3-1012<br>GLP<br>Not Published<br>Syngenta File N° SAN619/5277 | Y | SYN |
| IIIA 7.2.2.2/20 | Hertl, P. | 1996 | Dissipation of residues of Cyproconazole from Field Soil after repeated Applications of Alto 100 SL to Bare Soil in Switzerland, 1989-1993. (Field Soil Dissipation and Accumulation Study).<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No R 9776<br>GLP<br>Not Published<br>Syngenta File N° SAN619/5126 | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 7.2.2.2/21 | Wisson, M. | 1989b | SAN 619F F SL 100 - Study on Degradation and Mobility of SAN 619 F in undisturbed Field Columns under Field Conditions (Final Report)<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No 41351<br>GLP<br>Not Published<br>Syngenta File N° SAN619/5920 | Y | SYN |
| IIIA 7.2.2.2/22 | Ali, S. | 1990 | SAN 619 F 40 WG - Storage stability of Cyproconazole in Soil.<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz Agro Inc., Des Plaines, United States, Report No 6-433018<br>Not GLP<br>Not Published<br>Syngenta File N° SAN619/5581 | Y | SYN |
| IIIA 7.2.2.2/23 | Shadrick, B.A, Bloomberg, A.M, Helfrich, K.K | 1999 | Freezer Storage Stability of 1H-1,2,4-Triazole[3,5-$^{14}$C] in Soil<br>Syngenta Crop Protection AG, Basel, Switzerland<br>Bayer Corporation, Kansas City, United States, Report No 108303<br>GLP<br>Not Published<br>Syngenta File N° CGA71019/0068 | Y | TDMG |
| IIIA 7.2.3.1/01 | Skinner, W.S., et, al. | 1985 | Adsorption, Desorption and Mobility of SAN 619 F in Soil<br>Novartis Crop Protection AG, Basel, Switzerland<br>Zoecon Corp., Palo Alto, United States, Report No 3760-24-11-85<br>Not GLP<br>Not Published<br>Syngenta File N° SAN619/6102 | Y | SYN |
| IIIA 7.2.3.1/02 | Hawkins, D.R. | 1988 | Soil adsorption and desorption of 1,2,4-Triazole.<br>Novartis Crop Protection AG, Basel, Switzerland<br>Rohm and Haas, Philadelphia, United States, Report No 34S-88-27<br>GLP<br>Not Published<br>Syngenta File N° CGA71019/0014 | Y | TDMG |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 7.2.3.2/01 | Wisson, M. | 1991 | ALTO 100 SL / Leaching Behaviour in the BBA Standard Soils<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No 41'319<br>GLP<br>Not Published<br>Syngenta File N° SAN619/5512 | Y | SYN |
| IIIA 7.3/01 | Glänzel, A. | 1996 | Estimation of the Photochemical Oxidative Degradation Rate of Cyproconazole in the Atmosphere<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz Agro Ltd., Huningue, France, Report No TDS BS 7210<br>Not GLP<br>Not Published<br>Syngenta File N° SAN619/5173 | Y | SYN |
| IIIA 7.3/02 | Gampp, H. | 1990 | Cyproconazole, volatility from wheat leaves<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No 41317<br>GLP<br>Not Published<br>Syngenta File N° SAN619/5491 | Y | SYN |
| IIIA 7.4.1.1/01 | [redacted] | 1988a | Acute toxicity of SAN 619 F Technical to rainbow trout (*Salmo gairdneri*).<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 7.4.1.1/02 | [redacted] | 1988b | Acute toxicity of SAN 619 F Technical to bluegill sunfish (*Lepomis macrochirus*)<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 7.4.1.1/03 | [redacted] | 1985 | SAN 619 F - Fish toxicity in the carp<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 7.4.1.1/04 | [redacted] | 1993 | Cyproconazole: a 96-hour flow-through acute toxicity test with the sheepshead minnow (*Cyprinodon variegatus*)<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 7.4.1.1/05 | [redacted] | 1983 | Report on the test for acute toxicity of CGA 98032 to rainbow trout.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | TDMG |
| IIIA 7.4.1.2/01 | Surprenant, D.C. | 1986 | Acute Toxicity of SAN 619 F to daphnids (*Daphnia magna*).<br>Novartis Crop Protection AG, Basel, Switzerland<br>Springborn Laboratories Inc., Wareham, MA, United States, Report No BW-86-11-2156<br>GLP<br>Not Published<br>Syngenta File N° SAN619/5937 | Y | SYN |
| IIIA 7.4.1.2/02 | Frazier, S. | 1988 | Acute Toxicity of SAN 619 F to *Daphnia magna*.<br>Novartis Crop Protection AG, Basel, Switzerland<br>ABC Analytical Bio-Chemistry Lab. Inc., Columbia, MO, United States, Report No 36547<br>GLP<br>Not Published<br>Syngenta File N° SAN619/5938 | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 7.4.1.2/03 | Drottar, K.R, Swigert, J.P. | 1993a | Cyproconazole: a 96-hour flow-through acute toxicity test with the saltwater mysid (*Mysidopsis bahia*)<br>Novartis Crop Protection AG, Basel, Switzerland<br>Wildlife International Ltd., Easton, MD, United States, Report No 131A-150<br>GLP<br>Not Published<br>Syngenta File N° SAN619/5045 | Y | SYN |
| IIIA 7.4.1.2/04 | Sved, D.W., Drottar, K., Swigert, J.P. | 1993 | Cyproconazole (SAN 619F): A 96-hour shell deposition test with the eastern oyster (*Crassostrea virginica*)<br>Novartis Crop Protection AG, Basel, Switzerland<br>Wildlife International Ltd., Easton, MD, United States, Report No 131A-149<br>GLP<br>Not Published<br>Syngenta File N° SAN619/5046 | Y | SYN |
| IIIA 7.4.1.2/05 | Bell, G | 1995 | Fluquinconazole technical material 100.8% w/w 1,2,4-triazole: Acute Toxicity to *Daphnia magna*<br>Syngenta Crop Protection AG, Basel, Switzerland<br>Huntingdon Life Sciences Ltd., Huntingdon, UK, Report No ENVIR/95/52<br>GLP<br>Not Published<br>Syngenta File N° CGA169374/2320 | Y | TDMG |
| IIIA 7.4.1.3/01 | Ellgehausen, H. | 1986a | Acute toxicity of SAN 619 to *Scenedesmus subspicatus*<br>Novartis Crop Protection AG, Basel, Switzerland<br>RCC Ltd., Itingen, Switzerland, Report No 075521<br>GLP<br>Not Published<br>Syngenta File N° SAN619/0104 | Y | SYN |
| IIIA 7.4.1.3/02 | Jenkins, C.A. | 1993 | SAN 619 F : Determination of $EC_{50}$ to *Chlorella vulgaris* (72 hour static assay)<br>Novartis Crop Protection AG, Basel, Switzerland<br>Life Science Research Ltd., Eye, UK, Report No 93/SAS049/0830<br>GLP<br>Not Published<br>Syngenta File N° SAN619/5314 | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 7.4.1.3/03 | Palmer, S.J., Kendall, T.Z., Krueger, H.O. | 2001 | 1,2,4-triazole: a 96-hour toxicity test with the freshwater alga (*Selenastrum capricornutum*)<br>Syngenta Crop Protection AG, Basel, Switzerland<br>Wildlife International Ltd., Easton, MD, United States, Report No 528A-101<br>GLP<br>Not Published<br>Syngenta File N° CGA71019/0044 | Y | TDMG |
| IIIA 7.4.1.4/01 | Wallace, S.J. | 2002 | SAN619 (Cyproconazole technical): Effect on the Respiration rate of activated sludge<br>Syngenta Crop Protection AG, Basel, Switzerland<br>Brixham Environmental Laboratory, Brixham, UK, Report No BL7332/B<br>GLP<br>Not Published<br>Syngenta File N° SAN619/7217 | Y | SYN |
| IIIA 7.4.2/01 | [redacted] | 1986 | Uptake, depuration and bioconcentration of $^{14}$C-SAN 619 F to bluegill sunfish (*Lepomis macrochirus*)<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 7.4.3.1/01 | [redacted] | 1989 | SAN 619 F – 21 day rainbow trout toxicity study under flow-through exposure conditions<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 7.4.3.1/02 | [redacted] | 2002 | 1,2,4-triazole: juvenile growth test, fish (*Oncorhychus mykiss*)<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | TDMG |
| IIIA 7.4.3.2/01 | [redacted] | 1993b | Cyproconazole (SAN 619): an early life-stage toxicity test with the rainbow trout (*Oncorhynchus mykiss*)<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 7.4.3.2/02 | [redacted] | 2001 | Cyproconazole tech. (SAN 619): Determination of effects on the life cycle of the fathead minnow (*Pimephales promelas*), including measurements of vitellogenin and gonad histopathology<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 7.4.3.4/01 | Drottar, K.R., Swigert, J.P | 1993c | Cyproconazole (SAN 619 F): a flow-through life-cycle toxicity test with the Cladoceran (*Daphnia magna*)<br>Novartis Crop Protection AG, Basel, Switzerland<br>Wildlife International Ltd., Easton, MD, United States, Report No 131A-152<br>GLP<br>Not Published<br>Syngenta File N° SAN619/5043 | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 7.4.3.5.1/01 | Grade, R. | 1999 | Toxicity test of SAN 619 tech. on sediment-dwelling *Chironomus riparius* (syn. *Chironomus thummi*) under static conditions<br>Novartis Crop Protection AG, Basel, Switzerland<br>Novartis Crop Protection AG, Basel, Switzerland, Report No 983753<br>GLP<br>Not Published<br>Syngenta File N° SAN619/0627 | Y | SYN |
| IIIA 7.5.1.1/01 | Wisson, M. | 1987 | SAN 619 F (technical active ingredient) soil respiration and nitrification<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No 41303<br>GLP<br>Not Published<br>Syngenta File N° SAN619/5955 | Y | SYN |
| IIIA 7.5.1.1/02 | Völkel, W. | 2000 | The effects of CGA 71019 on soil respiration and nitrification<br>Novartis Crop Protection AG, Basel, Switzerland<br>RCC Ltd., Itingen, Switzerland, Report No 763367<br>GLP<br>Not Published<br>Syngenta File N° CGA71019/0042 | Y | TDMG |
| IIIA 7.5.1.2/01 | Ellgehausen, H. | 1986b | SAN 619 F - Acute toxicity ($LC_{50}$) study to earthworms (*Eisenia foetida*)<br>Novartis Crop Protection AG, Basel, Switzerland<br>RCC Ltd., Itingen, Switzerland, Report No RCC 075532<br>GLP<br>Not Published<br>Syngenta File N° SAN619/5954 | Y | SYN |
| IIIA 7.5.1.2/02 | Heimbach, F. | 1986 | Acute toxicity of 1,2,4-triazole (technical) to earthworms.<br>Novartis Crop Protection AG, Basel, Switzerland<br>Bayer AG, Leverkusen, Germany, Report No HBF/RG 59<br>GLP<br>Not Published<br>Syngenta File N° CGA71019/0021 | Y | TDMG |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 7.5.1.3/01 | Wälder, L. | 2000 | Herbicide profiling test to evaluate the phytotoxicity of SAN619 240 EC (A-9961 B) to terrestrial non-target higher plants<br>Novartis Crop Protection AG, Basel, Switzerland<br>Novartis Crop Protection AG, Basel, Switzerland, Report No SMQ 00007<br>Non-GLP<br>Not Published<br>Syngenta File N° SAN619/6980 | Y | SYN |
| IIIA 7.5.2.1/01 | Ehlers, H.A. | 2000 | Effects of 1,2,4-triazole on reproduction and growth of earthworms *Eisenia fetida* (Savigny 1826) in artificial soil<br>Novartis Crop Protection AG, Basel, Switzerland<br>IBACON GmbH, Rossdorf, Germany, Report No 7781022<br>GLP<br>Not Published<br>Syngenta File N° CGA64250/4385 | Y | TDMG |
| IIIA 7.5.2.1/02 | Barth, M | 2001 | Cyproconazole: toxicity of the formulation A-9898 A on the reproduction of the Collembola *Folsomia candida*<br>Syngenta Crop Protection AG, Basel, Switzerland<br>BioChem agrar, Gerichshain, Germany, Report No 01 10 48 040<br>GLP<br>Not Published<br>Syngenta File N° SAN619/7115 | Y | SYN |
| IIIA 7.5.2.1/03 | Meister, A., Klein, S. | 2002 | Effects of SAN 619 formulated as SL 100 (A-9898 A) on the decomposition of organic material enclosed in litter bags in the field<br>Syngenta Crop Protection AG, Basel, Switzerland<br>IBACON GmbH, Rossdorf, Germany, Report No 10741081<br>GLP<br>Not Published<br>Syngenta File N° SAN619/7201 | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 7.5.2.1/03 | Moser T, Scheffczyk A | 2002 | 1,2,4-triazole: acute and reproduction toxicity to the Collembolan species *Folsomia candida*<br>Syngenta Crop Protection AG, Basel, Switzerland<br>ECT Oekotoxikologie GmbH, Flörsheim, Germany, Report No P31CR<br>GLP<br>Not Published<br>Syngenta File N° CGA71019/0053 | Y | TDMG |
| IIIA 7.5.3.1.1/01 | [redacted] | 1991 | SAN 619 F : An acute oral toxicity study with the mallard<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 7.5.3.1.1/02 | [redacted] | 1985a | An acute oral toxicity study with the bobwhite<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 7.5.3.1.1/03 | [redacted] | 1993 | Acute oral toxicity study with cyproconazole in bobwhite quail<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 7.5.3.1.2/01 | [redacted] | 1985b | SAN 619 F - A dietary $LC_{50}$ study with the mallard<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 7.5.3.1.2/02 | [redacted] | 1985c | SAN 619F - A dietary $LC_{50}$ study with the bobwhite<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 7.5.3.1.2/03 | [redacted] | 1991 | SAN 619 F : A dietary $LC_{50}$ study with the northern bobwhite<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 7.5.3.1.2/04 | [redacted] | 1983a | A dietary $LC_{50}$ in the mallard with CGA-131013.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | TDMG |
| IIIA 7.5.3.1.2/05 | [redacted] | 1983b | A dietary $LC_{50}$ in the bobwhite with CGA-131013.<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | TDMG |
| IIIA 7.5.3.1.3/01 | [redacted] | 1993a | Cyproconazole: a reproduction study with the mallard<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 7.5.3.1.3/02 | [redacted] | 1993b | Cyproconazole: a reproduction study with the northern bobwhite<br>[redacted]<br>GLP<br>Not Published<br>[redacted] | Y | SYN |
| IIIA 7.5.3.1.3/03 | [redacted] | 1982 | Effects of 77 chemicals on reproduction in male and female coturnix quail.<br>[redacted]<br>Not GLP<br>Published<br>[redacted] | Y | SYN |
| IIIA 7.5.4.1/01 | Donat, H.J. | 1985 | Laboratory studies on the acute contact and oral toxicities of SAN 619 F (active ingredient) to worker honeybees<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No PB NO. 66562/85a<br>Not GLP<br>Not Published<br>Syngenta File N° SAN619/6426 | Y | SYN |
| IIIA 7.5.4.1/02 | Atkins, E.L. | 1986 | SAN 619F : Acute contact LD50 - Honey bee<br>Novartis Crop Protection AG, Basel, Switzerland<br>University of California, Riverside, CA, United States, Report No N/A<br>Not GLP<br>Not Published<br>Syngenta File N° SAN619/5952 | Y | SYN |
| IIIA 7.5.4.1/03 | Walker, H., Brown, K.C | 2002 | A Tier 1 laboratory study to estimate the median lethal rate of a 100 G $L^{-1}$ SL formulation to the predatory mite *Typhlodromus pyri* (Acari: Phytoseiidae)<br>Syngenta Crop Protection AG, Basel, Switzerland<br>Ecotox, Ltd., Tavistock, Devon, U.K., Report No ER-01-HMA431<br>GLP<br>Not Published<br>Syngenta File N° SAN619/7142 | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 7.5.4.1/04 | Reber, B. | 2001a | Acute dose-response toxicity of SAN 619 EC 240 (A 9961 B) to the predacious mite *Typhlodromus pyri* Scheuten (Acari: Phytoseiidae)<br>Syngenta Crop Protection AG, Basel, Switzerland, Report No 2013614<br>GLP<br>Not Published<br>Syngenta File N° SAN619/7088 | Y | SYN |
| IIIA 7.5.4.1/05 | Reber, B. | 2001b | Toxicity of fresh and aged residues of SAN 619 EC 240 (A 9961 B) to the predacious mite *Typhlodromus pyri* (Acari: Phytoseiidae) under extended laboratory conditions<br>Syngenta Crop Protection AG, Basel, Switzerland, Report No 2003537<br>GLP<br>Not Published<br>Syngenta File N° SAN619/7089 | Y | SYN |
| IIIA 7.5.4.1/06 | Mead-Briggs, M. | 1990 | An evaluation of the residual effects of the fungicides Alto 100 SL and Alto Elite to the parasitic wasp, *Aphidius rhopalosiphi*<br>Novartis Crop Protection AG, Basel, Switzerland<br>Agrochemical Evaluation Unit, The University, Southampton, U.K., Report No SAN-90-1<br>GLP<br>Not Published<br>Syngenta File N° SAN619/0108 | Y | SYN |
| IIIA 7.5.4.1/07 | Mead-Briggs, M. | 1995 | An extended laboratory test to evaluate the side-effects of the fungicide Alto 100 SL on adults of the parasitic wasp *Aphidius rhopalosiphi*, when applied to barley plants<br>Novartis Crop Protection AG, Basel, Switzerland<br>Report No SAN-95-1<br>GLP<br>Not Published<br>Syngenta File N° SAN619/6683 | Y | SYN |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| IIIA 7.5.4.1/08 | Walker, H.M. | 2002a | A Tier II laboratory study to estimate the median lethal rate of a 100 G $L^{-1}$ SL formulation to the green lacewing, *Chrysoperla carnea* (Neuroptera: Chrysopidae)<br>Syngenta Crop Protection AG, Basel, Switzerland<br>Ecotox, Ltd., Tavistock, Devon, U.K., Report No ER-02-HMA432<br>GLP<br>Not Published<br>Syngenta File N° SAN619/7162 | Y | SYN |
| IIIA 7.5.4.1/09 | Beech, P. | 1994 | A laboratory evaluation of the side-effects of the fungicide ALTO 100 SL on adults of the carabid beetle *Poecilus Cupreus*<br>Novartis Crop Protection AG, Basel, Switzerland<br>Report No SAN-94-4<br>GLP<br>Not Published<br>Syngenta File N° SAN619/6684 | Y | SYN |
| IIIA 7.5.4.1/10 | Walker, H.M. | 2002b | SAN 619: a Tier II laboratory study to estimate the median lethal rate of a 100 G $L^{-1}$ SL formulation to the predatory bug, *Orius laevigatus* (Heteroptera: Anthocoridae)<br>Syngenta Crop Protection AG, Basel, Switzerland<br>Ecotox, Ltd., Tavistock, Devon, U.K., Report No ER-02-HMA433<br>GLP<br>Not Published<br>Syngenta File N° SAN619/7141 | Y | SYN |
| IIIA 7.5.4.1/11 | (Anonymous) | 1987 | Effect of SAN 619 F on non-target organisms.<br>Novartis Crop Protection AG, Basel, Switzerland<br>Sandoz AG, Basel, Switzerland, Report No N/A<br>Not GLP<br>Not Published<br>Syngenta File N° SAN619/5953 | Y | SYN |

## IIIB Reference List by Annex Point

### References: Doc III-B1-B3

| Section No / Reference No | Author(s) | Year | Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| B2.2/01 | Not specified | 2005 | - Safety Data Sheet Evipol 60 SL<br>- Janssen Pharmaceutica N.V.<br>Report No.: not applicable<br>- GLP: not applicable<br>Unpublished | N | Janssen |
| B2.2/02 | Not specified | 2004 | - Safety Data Sheet EVIPOL Technical<br>- Janssen Pharmaceutica N.V.<br>Report No.: not applicable<br>- GLP: not applicable<br>Unpublished | N | Janssen |
| B2.2/03 | Not specified | 2002 | - Safety Data Sheet Tridecyl alcohol ethoxylate<br>- Clariant Iberica S.A.<br>Report No.: not applicable<br>- GLP: not applicable<br>Unpublished | N | Clariant |
| B2.2/04 | Not specified | 1999 | - Safety Data Sheet Propylene glycol methyl ether<br>- Dow Europe SA<br>Report No.: not applicable<br>- GLP: not applicable<br>Unpublished | N | Dow |
| B2.2/05 | Not specified | 1999 | - Safety Data Sheet Dipropylene glycol methyl ether<br>- Dow Europe SA<br>Report No.: not applicable<br>- GLP: not applicable<br>Unpublished | N | Dow |
| B2.2/06 | Not specified | 2003 | - Product Recipe Evipol 60 SL<br>- Janssen Pharmaceutica N.V.<br>Report No.: not applicable<br>- GLP: not applicable<br>Unpublished | Y | Janssen |
| B3.1 | Muchow, T. | 2001 | - Evipol 60 SL: Product Chemistry data<br>- Osmose Inc, USA<br>- Osmose Inc.<br>Report No.: OSMOSE-2001-3<br>- GLP, Unpublished | Y | Osmose |
| B3.4 | Fannes, C. | 2005 | - Thermal stability EVIPOL 60 SL<br>- Janssen Pharmaceutica N.V.<br>Report No. 2005/115A<br>- Not GLP, Unpublished | Y | Janssen |
| B3.5 | Verbeeck, G. | 2005 | - Determination of the Density of EVIPOL 60 SL<br>- Janssen Pharmaceutica N.V. | Y | Janssen |

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| | | | Report No.: 05050-TS<br>- Not GLP, Unpublished | | |
| B3.6 | Verbeeck, G. | 2005 | - pH measurement of EVIPOL 60 SL<br>- Janssen Pharmaceutica N.V. Report No.: 05049-TS<br>- Not GLP, Unpublished | Y | Janssen |
| B3.7/01 | Moons, M. and Verbeeck, G. | 2005 | - Accelerated storage stability of EVIPOL 60 SL<br>- Janssen Pharmaceutica N.V. Report No.: 05048 TS<br>- Not GLP, Unpublished | Y | Janssen |
| B3.7/02 | Verbeeck, G. and Van der Flaas, M. | 2005 | - Low temperature stability of EVIPOL 60 SL<br>- Janssen Pharmaceutica N.V. Report No.: 05047 TS<br>- Not GLP, Unpublished | Y | Janssen |

**References: Doc.III-B4**

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| B4.1 | de Ryckel, B. | 2005 | - Validation of an Analytical HPLC Method for the Determination of Active Substance Content in a Formulation Soluble Concentrate (SL) containing R095137<br>- Walloon Agricultural Centre, Pesticides Research Department, Gembloux, Belgium<br>- Janssen Pharmaceutica N.V. Report No.: 20930 Janssen Reference No. AGR 1078<br>- GLP, Unpublished | Y | Janssen |

## References: Doc.III-B5

| Section No / Reference No | Author(s) | Year | Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| B5.10.2/01 | Stevens M. and Van Eetvelde G. | 1997 | Determination of toxic values against wood-destroying fungi of SAN 619 F 60 SL. University of Gent<br>Report No. HT97-BT0408, 8 April 1997.<br><br>Unpublished | Y | Sandoz |
| B5.10.2/02 | Stevens M. and Van Eetvelde G. | 1997 | Determination of toxic values against wood-destroying fungi of SAN 619 F 60 SL. University of Gent<br>Report No: HT97-BT0214, 14 February 1997.<br><br>Unpublished | Y | Sandoz |

## References: Doc.III-B6

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| B6.1.1 | [redacted] | 2001 | Acute Oral Toxicity Study in Rats - Defined $LD_{50}$<br>[redacted]<br>GLP, Unpublished | Y | Janssen |
| B6.1.2 | [redacted] | 2001 | Acute Dermal Toxicity Study in Rats - Limit Test<br>[redacted]<br>GLP, Unpublished | Y | Janssen |
| B6.1.3 | [redacted] | 2001 | Acute Inhalation Toxicity Study in Rats - Limit Test<br>[redacted]<br>GLP, Unpublished | Y | Janssen |
| B6.2/01 | [redacted] | 2001 | Primary Skin Irritation Study in Rabbits<br>[redacted]<br>GLP, Unpublished | Y | Janssen |
| B6.2/02 | [redacted] | 2001 | Primary Eye Irritation Study in Rabbits<br>[redacted]<br>GLP, Unpublished | Y | Janssen |
| B6.3 | [redacted] | 2001 | Dermal Sensitization Study in Guinea Pigs (Buehler Method)<br>[redacted]<br>GLP, Unpublished | Y | Janssen |

**References: Doc.III-B7**

| Section No / Reference No | Author(s) | Year | Title.<br>Source (where different from company)<br>Company, Report No.<br>GLP (where relevant) / (Un)Published | Data Protection Claimed (Yes/No) | Owner |
|---|---|---|---|---|---|
| B7.7 | [redacted] | 2004 | Acute Toxicity of LAg 2000 278 to Fish<br>[redacted]<br>GLP, Unpublished | Y | Janssen |
| B9.4/01 | Not specified | 1997 | Technische fiche<br>10 L stapelbare jerrycan<br>Polimoon N.V.<br>Report No. not applicable<br>Not GLP, Unpublished | N | Polimoon N.V. |
| B9.4/02 | Blümel, P. and Skutnik, M. | 1993 | Zulassungsschein<br>10-Liter Kanister<br>Bundesanstalt für Materialforschung- und Prüfung<br>Report No. : 9539/3H1<br>Not GLP | N | BAM |