

WHO SPECIFICATIONS AND EVALUATIONS FOR PUBLIC HEALTH PESTICIDES

d,d,trans-CYPHENOTHRIN ^{1/}

(*S*)-alpha-cyano-3-phenoxybenzyl (1*R*,3*R*)-2,2-
dimethyl-3-(2-methylprop-1-enyl)
cyclopropanecarboxylate

Note: Evaluation report ONLY. The WHO specifications will be published subject to satisfactory validation of the method for determination of the active ingredient content.



**WORLD HEALTH ORGANIZATION
GENEVA**

^{1/} Cyphenothrin is the ISO common name for a racemic mixture of 4 pairs of diastereoisomers. The name *d,d,trans*-cyphenothrin refers to the mixture, comprised mainly of the stereoisomer (*S*)-alpha-cyano-3-phenoxybenzyl (1*R*,3*R*)-2,2-dimethyl-3-(2-methylprop-1-enyl) cyclopropanecarboxylate together with small proportions of the other stereoisomers, which is defined by the WHO specification.

WHO SPECIFICATIONS FOR PUBLIC HEALTH PESTICIDES

***d,d,trans*-CYPHENOTHRIN**

EVALUATION REPORT 761/2003

Explanation

The data for *d,d,trans*-cyphenothrin were evaluated in support of new WHO specifications.

d,d,trans-Cyphenothrin is not under patent.

d,d,trans-Cyphenothrin has not been evaluated by the FAO/WHO JMPR or WHO/IPCS. It is currently under review by the US EPA.

The draft specification and the supporting data were provided by Sumitomo Chemical Company Ltd, Japan, in 2002.

Uses

d,d,trans-Cyphenothrin is synthetic pyrethroid, acting by contact poisoning. It is used in public health against flies, mosquitoes, cockroaches, etc. (Matsuo, 1980).

Identity

ISO common name: Cyphenothrin is the ISO common name for a racemic mixture of 4 pairs of diastereoisomers, designated as (\pm)- α -cyano-3-phenoxybenzyl (\pm)-*cis-trans*- chrysanthemate. The name *d,d,trans*-cyphenothrin refers to an enantio-enriched mixture, comprised mainly of the single stereoisomer (S)- α -cyano-3-phenoxybenzyl (1*R*, 3*R*)-2,2-dimethyl-3-(2-methylprop-1-enyl) cyclopropanecarboxylate, with only small proportions of the other stereoisomers, as defined by the WHO specification.

Synonyms: None

Chemical names:

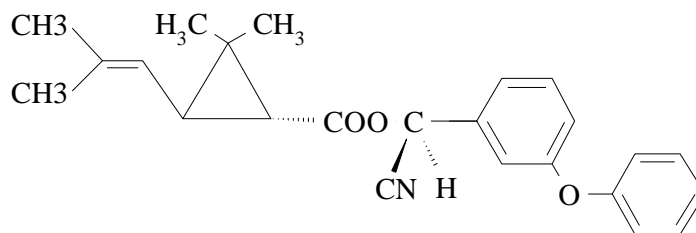
IUPAC: None. IUPAC name for the main stereoisomer present is: (S)- α -cyano-3-phenoxybenzyl (1*R*, 3*R*)-2,2-dimethyl-3-(2-methylprop-1-enyl) cyclopropanecarboxylate.

CA: None. CAS name for cyphenothrin is: cyano(3-phenoxyphenyl)methyl 2,2-dimethyl-3-(2-methyl-1-propenyl) cyclopropanecarboxylate.

CAS No: None. CAS number for cyphenothrin is: 39515-40-7

CIPAC No: 761

Structural formula:



Molecular formula: $C_{24}H_{25}NO_3$

Relative molecular mass: 375.47

Identity tests: GC retention time (cyphenothrin); IR spectrum (cyphenothrin);
enantio-selective HPLC peak pattern (*d,d,trans*-cyphenothrin).

Physical and chemical properties of *d,d,trans*-cyphenothrin

Table 1. Physico-chemical properties of pure *d,d,trans*-cyphenothrin.

Parameter	Value(s) and conditions	Purity %	Method reference
Vapour pressure:	$<7.52 \times 10^{-10}$ Pa at 20, 35 and 45°C	100.2	EPA Guideline 63-9
Melting point and temperature of decomposition:	Melting point: 43.8 °C Decomposition temperature: Not available	Not stated	EPA Guideline 63-5,
Solubility in water:	$<10 \times 10^{-9}$ g/l at 25°C at pH 7	100.2	EPA Guideline 63-8
Octanol / water partition coefficient:	$\log P_{OW} >6$ at 25°C at pH 5.2	100.2	EPA Guideline 63-11
Hydrolysis characteristics:	Not available	-	-
Photolysis characteristics:	Not available	-	-
Dissociation characteristics:	Does not dissociate	-	-

Table 2. Chemical composition and properties of *d,d,trans*-cyphenothrin technical material (TC).

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data.	Confidential information supplied and held on file by WHO. Mass balances were 98.0-98.5%.
Declared minimum <i>d,d,trans</i> -cyphenothrin content:	930 g/kg
Relevant impurities ≥ 1 g/kg and maximum limits for them:	none
Relevant impurities < 1 g/kg and maximum limits for them:	none
Stabilizers or other additives and maximum limits for them:	BHT: 20 g/kg
Melting or boiling temperature range	Boiling point: 154°C at 0.1 mm Hg

Hazard summary

Notes.

- (i) The proposer provided written confirmation that the toxicological and ecotoxicological data included in the summary below were derived from *d,d,trans*-cyphenothrin having impurity profiles similar to those referred to in the table above.
- (ii) The conclusions expressed in the summary below are those of the proposer, unless otherwise specified.

Table 3. Toxicology profile of *d,d,trans*-cyphenothrin technical material, based on acute toxicity, irritation and sensitization.

Species	Test	Duration and conditions	Result
Rat M/F	Oral	EPA Guideline 81-1	LD ₅₀ 188 mg/kg bw (male); 220 mg/kg bw (female)
Rat M/F	Dermal*	EPA Guideline 81-2	LD ₅₀ > 5000 mg/kg bw (male and female)
Rat M/F	Inhalation*	EPA Guideline 81-3	LC ₅₀ > 1850 mg/m ³ (male and female)
Rabbit	Skin irritation*	EPA Guideline 81-5	negative
Rabbit	Eye irritation*	EPA Guideline 81-4	negative
Guinea pig	Skin sensitization*	Buehler method	negative

* The toxicity of *d,d,trans*-cyphenothrin is not expected to differ significantly from that of cyphenothrin (Wilkinson 1996; Kaneko 1984).

Table 4. Toxicology profile of *d,d,trans*-cyphenothrin technical material, based on repeated administration (sub-acute to chronic).

Species	Test	Duration and conditions	Result
Rat M/F	Feeding toxicity*	180-day study, Guideline of Japanese Ministry of Agriculture, Forestry and Fisheries	NOAEL = 300 ppm 16.8 mg/kg bw/day (male) 19.6 mg/kg bw/day (female)
Mouse M/F	Feeding toxicity*	90-day study, EPA Guideline 82-1	NOAEL = 500 mg/m ³ (male, female)
Dog M/F	Feeding, toxicity*	90-day study, EPA Guideline 82-1	NOAEL = 3 mg/kg/day (male, female)
Rat M/F	Inhalation*	28-day study	NOEL = 7.76 mg/m ³ (male, female)
Rat M/F	Feeding, carcinogenicity*	Sumitomo report No. EET-0084. 2-year study, EPA Guideline 83-2	Carcinogenicity: no statistically significant increased incidence of neoplasms associated with treatment compared with the control group. NOEL = 1000 ppm (48 mg/kg/day) (male); 300 ppm (18 mg/kg/day) (female),

Species	Test	Duration and conditions	Result
Mouse M/F	Feeding, carcinogenicity*	Sumitomo report No. EET-0084. 2-year study, EPA Guideline 83-2	Carcinogenicity: no statistically significant increased incidence of neoplasms associated with treatment compared with the control group. NOEL > 1000 ppm (male, female)
Dog M/F	Oral*	[1-year study] EPA Guideline 83-1	NOEL = 3 mg/kg/day
Rat M/F	Feeding, 2-generation reproduction*	Sumitomo report No. EET-0067. EPA Guideline 83-4 Fed S-2703F in diet continuously throughout two successive generations at 0, 100, 300, 1000 ppm; 24 rats/sex/dose both F1 and F2.	No dose related mortalities observed. Statistically significant lower body weight gains observed in F1 high dose females. No additional statistically significant differences found in other adult parameters. No significant differences in any clinical observations in the F1 and F2 pups. Generally gross necropsy and histomorphologic findings of adults and offspring were few and were not considered treatment related. Adult NOEL = 300 ppm (based on decreased body weight gain at 1000 ppm); Developmental NOEL = 1000 ppm (based on no treatment related effects).
Rat M/F	Feeding, teratogenicity and embryotoxicity*	Sumitomo report No. EET-0026. Subcutaneous treatment with S-2703 Forte (cyphenothrin) at 0, 50, 150, 500 mg/kg/day on days 7 to 17 of gestation; 38 female rats/dose.	Significant decrease in maternal weight gain in highest dose group. Maternal NOEL = 150 mg/kg/day (based on decreased weight gain at 500 mg/kg/day). No physiological or developmental effects on fetuses at any dose level. Developmental NOEL = 150 mg/kg/day (based on viability of F1 offspring on 4 th day). No teratogenic effects attributable to cyphenothrin observed.

Species	Test	Duration and conditions	Result
Rabbit M/F	Feeding, teratogenicity and embryotoxicity*	Sumitomo report No. EET-0036. Subcutaneous treatment with S-2703 Forte (cyphenothrin) at 0, 50, 125 mg/kg/day on days 6-18 of gestation and 250 mg/kg/day on days 6-10 of gestation; 15 New Zealand White female rabbits/dose.	Significant decrease in maternal weight gain in the two highest dose groups. Maternal NOEL = 50 mg/kg/day (based on decreased body weight at 125 and 250 mg/kg/day). No physiological or developmental effects on fetuses at any dose level. Developmental NOEL = 250 mg/kg/day (based on no effects). No teratogenic effects attributable to cyphenothrin observed.

* The toxicity of *d,d,trans*-cyphenothrin is not expected to differ significantly from that of cyphenothrin (Wilkinson 1996; Kaneko 1984).

Table 5. Mutagenicity profile of *d,d,trans*-cyphenothrin technical material, based on *in vitro* and *in vivo* tests.

Species	Test	Conditions	Result
<i>Salmonella typhimurium</i> and <i>Escherichia coli</i>	Bacterial reverse mutation*	EPA Guideline 84-2	negative
Mouse bone marrow erythrocytes	Micronucleus test*	EPA Guideline 84-2	negative
Chinese hamster ovary cells	Sister chromatid exchange assay*	EPA Guideline 84-2	negative

* The toxicity of *d,d,trans*-cyphenothrin is not expected to differ significantly from that of cyphenothrin (Wilkinson 1996; Kaneko 1984).

Table 6. Ecotoxicology profile of *d,d,trans*-cyphenothrin technical material.

Species	Test	Duration and conditions	Result
Bobwhite quail	Acute dietary toxicity*	EPA Guideline 71-2	LC ₅₀ >5620 ppm
Rainbow trout	Acute flow-through toxicity	EPA Guideline 72-1; 96 hr	LC ₅₀ = 0.38 µg/l
<i>Daphnia magna</i>	Acute flow-through toxicity	EPA Guideline 72-2; 48 hr	LC ₅₀ = 1.2 µg/l

* The toxicity of *d,d,trans*-cyphenothrin is not expected to differ significantly from that of cyphenothrin (Kent 1996).

Neither WHO/PCS nor FAO/WHO JMPR have evaluated *d,d,trans*-cyphenothrin. The IPCS hazard classification of cyphenothrin (1*R*-isomers) is Class II, moderately hazardous (WHO, 2002).

Formulations

The main formulation types available are EC, OL, for use in public health applications. The EC formulation is registered and sold in Japan, Jordan, Argentina, U.A.E. and other countries.

Methods of analysis and testing

The analytical method for determination of *d,d,trans*-cyphenothrin content (including identity tests) is based on packed column GC with FID and internal standardization with di(2-ethylhexyl) phthalate (Asada 1995). A CIPAC collaborative study of the method with capillary column GC is in progress, the results of the full study are expected to be presented in 2005. The method for determination of identity as *d,d,trans*-cyphenothrin is based on enantio-specific HPLC. (Asada 1995).

Test methods to determine the physical and chemical properties of the technical active ingredient were OECD and USEPA, while those for the formulations were according to the FAO/WHO Manual (FAO/WHO 2002).

Containers and packaging

No special requirements for containers and packing have been identified.

Expression of the active ingredient

The active ingredient is expressed as *d,d,trans*-cyphenothrin, as defined by the WHO specification.

Appraisal

The active ingredient, *d,d,trans*-cyphenothrin, has not previously been the subject of a WHO specification.

The ISO name, cyphenothrin, denotes the mixture of the racemic chrysanthemic acid bound to the racemic cyanhydrin, an α -cyanoalcohol. Cyphenothrin has 3 chiral centres and is therefore comprised of 4 racemic pairs of diastereoisomers, with a total of 8 stereoisomers. The name, *d,d,trans*-cyphenothrin, is the name given by the manufacturer to the esterification product of the *1R-trans* acid moiety and the *S* form of the cyanhydrin. The prefix “*d,d,trans*-” reflects the former designation (*d*, for dextro-rotary) of the configurations of the chiral centres of the chrysanthemic acid moiety and the cyanhydrin. together with the *trans* configuration for the chrysanthemic acid, the form with the highest insecticidal activity (Matsuo *et al.* 1980). The mixture, characterized by the WHO specification as *d,d,trans*-cyphenothrin, contains 97% *trans*-isomer, 95% of the *1R* isomer and 92% of the *S*-isomer in the alcohol moiety. The total content of *d,d,trans*-cyphenothrin can be determined by capillary column GC, whereas the stereoisomer ratios are determined using enantio-selective liquid chromatography, by which all minor and major stereoisomers present can be separated and quantified. The capillary GC method is in process of validation under the auspices of CIPAC, whereas the enantio-selective HPLC method for isomer ratio is in process of peer validation.

d,d,trans-Cyphenothrin is almost insoluble in water but highly soluble in organic solvents, such as hexane, ethanol, acetone, toluene etc. It is of low volatility. It is stable under normal storage conditions but is readily hydrolyzed in water at higher pH and is sensitive to light (Roberts and Hutson 1999). It has a low potential for

bioaccumulation due to hydrolysis, photolysis and metabolism in water, soil and in biota (Roberts and Hutson 1999).

Commercially confidential information on the manufacturing process and on all impurities present at or above 1 g/kg was provided to the meeting, together with limits for impurities in the TC. Limits for impurities were supported by 5 batch analysis data, in which unaccountable material represented 15 to 20 g/kg (mass balances were 98.0 to 98.5%). The declared minimum active ingredient content was 930 g/kg. The proposer stated that no relevant impurities are present in the technical material, either > 1 g/kg maximum or less than 1 g/kg maximum, and the meeting agreed. The proposer stated that 2,6-di-*tert*-butyl-*p*-cresol (BHT, “butylated hydroxytoluene”) is added as a stabilizer, at 20 g/kg, after the final step of the synthesis, to reduce the sensitivity of the TC to degradation by oxygen and light. The meeting accepted that the stabilizer should be present at the concentration recommended by the proposer but decided that these should form a Note to the specification and should not be part of the specification itself.

The impurity data submitted in support of the WHO specification were not derived from TCs produced by the same process as the corresponding data submitted for registration of cyphenothrin by the Swiss Office of Public Health in 1985. The results and manufacturing specifications were nevertheless similar in most respects (cyphenothrin content, amounts of by-products and unaccountable material) and the meeting agreed that there was no significant difference.

The data for toxicology of *d,d,trans*-cyphenothrin partly rely on studies conducted with cyphenothrin. The data package submitted for registration of *d,d,trans*-cyphenothrin in Switzerland included an article on the comparative metabolism of stereoisomers of cyphenothrin in rats (Wilkinson 1996; Kaneko *et al.* 1984). Taking this into account, the meeting agreed that data generated with cyphenothrin were acceptable for the purposes of evaluating *d,d,trans*-cyphenothrin. The active ingredient generally shows low mammalian toxicity and is not a sensitizer in the Buehler and is not irritating to the rabbit eye and skin. There was no evidence of carcinogenicity in the rat or mouse. There was no evidence of mutagenic responses in bacterial, micronucleus or sister chromatid exchange tests. In a 2-generation reproduction study in the rat, no reproductive effects were observed at any dose level. There was no evidence of teratogenicity or developmental effects in rats or rabbits, although there was a decrease in maternal weight gain and a consequential decrease in rat offspring viability at the high dose tested.

d,d,trans-Cyphenothrin is very toxic to *Daphnia magna* and fish but it has a low toxicity to bobwhite quails.

d,d,trans-Cyphenothrin is only used in public health applications against mosquitoes, houseflies, cockroaches and the main formulations are emulsifiable concentrates and oils. With no uses of *d,d,trans*-cyphenothrin in agriculture, it is unlikely that dietary exposure will be of significance.

On the basis of the one-year dog study, a NOEL of 16.8 to 19.6 mg/kg bw/d is established by the Swiss Office of Public Health. The *d,d,trans*-cyphenothrin TC was classified as moderately toxic (Class 3) in Switzerland and, although it has not been

classified by the International Programme on Chemical Safety (IPCS), this organization has classified the closely related cyphenothrin (1*R*-isomers) as Class II, moderately hazardous.

Recommendations

The meeting recommended that the draft specifications for *d,d,trans*-cyphenothrin TC and EC, proposed by Sumitomo Chemical Company Limited and amended as described in the appraisal above, should be adopted by WHO, subject to acceptable validation of the analytical and identity test methods.

References

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