WHO SPECIFICATIONS AND EVALUATIONS FOR PUBLIC HEALTH PESTICIDES

DELTAMETHRIN

(*S*)-α-cyano-3-phenoxybenzyl (1*R*,3*R*)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropane carboxylate

World Health Organization

PART TWO

EVALUATION REPORTS

DELTAMETHRIN

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FAO/WHO EVALUATION REPORT 333/2005

Recommendations

The Meeting recommended the following.

(i) The existing (April 2005) WHO specifications for deltamethrin TC, DP, SC, EC WG, and existing (September 2005) WHO specifications for deltamethrin WP, UL, together with the previously unpublished specification for deltamethrin EW (all originally based upon data submitted by Bayer CropScience) should be amended to include a footnote regarding the potentially relevant impurity, becisthemic acid chloride, and extended to encompass the products of Tagros (India) and Argos (South Africa). WHOPES evaluation of the EW having been completed satisfactorily, this specification should now be adopted by WHO.

(ii) The existing (May 2005) FAO specifications for deltamethrin TC, DP, SC, EC and WG, together with the previously unpublished specifications for deltamethrin EW, EG, WP and UL (all based upon data submitted by Bayer CropScience) should be amended to include a footnote regarding the potentially relevant impurity, becisthemic acid chloride[1], and extended to encompass the products of Tagros (India) and Argos (South Africa). Analytical methods for determination of deltamethrin in EW, EG, WP and UL having been adopted by CIPAC, these specifications should now be adopted by FAO.

Appraisal

The Meeting considered data and information submitted by Tagros (India) and Argos (South Africa), for extension of: (i) existing FAO specifications for deltamethrin TC, DP, SC, EC and WG (May 2005); (ii) existing WHO specifications for TC, DP, SC, EC, WG (April 2005); (iii) existing WHO specifications for WP and UL (September 2005); (iv) pending FAO specifications for EG, EW, UL and WP; and (v) a pending WHO specification for EW.

Argos provided written confirmation that their products (currently WP only) contain only deltamethrin sourced from Tagros and therefore the Meeting agreed that decisions and recommendations relating to Tagros would apply also to Argos.

The Meeting was provided by Tagros with commercially confidential information on the manufacturing process and batch analysis data on all detectable impurities. Mass balances were very high (99.91–100.10%), with no unknowns detected. The UK Health & Safety Executive (HSE) confirmed that there were no significant differences between the data submitted to FAO/WHO and those submitted for registration in the UK.

In evaluating the equivalence of Tagros and Bayer TCs, the Meeting considered two potentially relevant impurities, becisthemic acid anhydride [(1*R*,3*R*)-3-(2,2-

[1] The name "becisthemic" is sometimes spelt "bicisthemic" but the common spelling is used here.

the impurity, is applied: a mixture is classified as corrosive if the sum concentration of corrosive components is ≥5% and as an irritant if it is ≥1 but <5%.

Tagros then replaced the company's non-specific titrimetric procedure with an HPLC method, which was more specific for the determination of becisthemic acid chloride and which had a limit of quantification of 0.1 g/kg (Tagros 2006a, 2006b). In consequence, the manufacturer reported that levels of this impurity did not occur at up to 2 g/kg, as previously stated, but were actually <1 g/kg. The Tagros manufacturing specification for this impurity was consequently lowered to <1 g/kg. Although the stability of the impurity during analysis was not reported, the HPLC method did not seem likely to under-estimate the concentration of becisthemic acid chloride and the change in manufacturing specification from 2 to <1 g/kg effectively changed the designation of this impurity to non-relevant. Consequently, there was no requirement for a specification clause to control its concentration. The new data had not been considered by a national registration authority.

The Meeting agreed that a cautionary footnote should be added to specifications, to indicate that becisthemic acid chloride could be a relevant impurity in the products of other manufacturers, if it occurred at ≥1 g/kg deltamethrin.

Overall, Tagros deltamethrin complied with the existing specification for TC but the becisthemic acid anhydride (not becisthemic acid chloride) indicated non-equivalence of the impurity profiles. However, the PCS assessment of this impurity and the available hazard data for Tagros deltamethrin TC showed no evidence to suggest that the Tagros TC presents greater or additional hazards compared with Bayer deltamethrin TC. Thus the Meeting concluded that the two TCs should be considered equivalent.

Tagros and Argos stated their products otherwise complied with the existing (September 2005) FAO and/or WHO specifications for TC, WP, EC and SC. The Meeting noted that development of the specifications for WT, proposed by Bayer and Tagros, cannot be addressed until suitable methods become available to test tablet hardness and friability.

CIPAC methods are available for identification and determination of deltamethrin in the TC and formulations, with the exception of WT for which the CIPAC method status is tentative. A more acceptable method is therefore required to support the proposed specification for WT.

The Meeting noted that WHOPES trials of deltamethrin EW had been successfully completed (WHO 2006).

dibromovinyl)-2,2-dimethylcyclopropane carboxylic anhydride] and becisthemic acid chloride [(1*R*,3*R*)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropane carboxoyl chloride]. Neither impurity occurred in the Bayer TC ≥1 g/kg but, initially, the Tagros manufacturing limits were 10 g/kg and 2 g/kg, respectively. The acute toxicology data submitted by Tagros suggested that these higher limits might be reflected in the classification of the company's TC as a mild irritant of eyes. The data for the acid anhydride were complicated by the fact that the analytical method did not distinguish between the anhydride and becisthemic acid and the analytical method used for determination of becisthemic acid chloride was based on titration and appeared to lack specificity.

WHO/PCS secretariat assessed the results of eye irritation studies conducted (to GLP and according to OECD guidelines 404 and 405) by Tagros and concluded that, as defined by GHS (GHS 2003), the Tagros TC should not be classified as an eye irritant (PCS 2005a). WHO/PCS also concluded that, on the basis of toxicology, the Tagros TC should be considered equivalent to that of Bayer and the Meeting agreed.

No information was available on the toxicity of becisthemic anhydride but WHO/PCS concluded that it should not be considered a relevant impurity (PCS 2005a) . Limited experimental data had indicated that a structural analogue of it, namely chrysanthemic anhydride, is sensitizing to the skin and, applying the precautionary principle, JMPS had previously concluded that the analogue should be considered a relevant impurity in *d*-allethrin (JMPS 2002). However, when assessing the relevance of a chlorine analogue of becisthemic anhydride (namely 2,2-dimethyl-3-(2,2'-dichlorovinyl) cyclopropane carboxylic acid anhydride), it was considered that there was no justification for declaring it a relevant impurity. That is, the structure-activity relationship was not considered to be strong enough to extend the weak data for sensitization from the non-halogenated chrysanthemic anhydride to the dichloro analogue of becisthemic acid anhydride (PCS 2005b). In keeping with this rationale, PCS considered that the structural relationship between chrysanthemic anhydride and becisthemic anhydride does not justify the classification of becisthemic anhydride as sensitizing. The conclusion was supported by the fact that Tagros deltamethrin TC was not sensitizing to the skin of Guinea pigs (studies performed according to the OECD guideline and GLP). The Meeting therefore agreed that becisthemic anhydride is not a relevant impurity in deltamethrin TC.

As in the case of the anhydride, no information was available on the toxicity of becisthemic acid chloride but WHO/PCS secretariat concluded that it should be considered a relevant impurity (PCS 2005a), if it occurred at ≥1 g/kg in the TC. WHO/PCS advised that, based on its chemical structure, becisthemic acid chloride is likely to be irritating (several acid chlorides are corrosive). WHO/PCS noted that, in the GHS classification, substances for which structure-activity or structure-response assessments indicate that they may be corrrosive/irritant, should be classified as corrosive/irritant, in the absence of human or experimental data (GHS 2003). WHO/PCS thus recommended that becisthemic acid chloride should be considered as a relevant impurity. GHS guidelines (GHS 2003) indicate that when classifying a mixture, the data used should be derived primarily from studies on the mixture itself. As Tagros deltamethrin, apparently containing the becisthemic acid chloride at ≤2g/kg, (also and becisthemic acid and anhydride at a sum concentration of ≤10 g/kg), was not irritating, WHO/PCS concluded that this limit could be accepted as the specification limit for becisthemic acid chloride. WHO/PCS noted that the conclusion is the same if the GHS second tier approach, classification by the concentration of

SUPPORTING INFORMATION

FOR

EVALUATION REPORT 333/2005

Physico-chemical properties of deltamethrin

Table 1. Physico-chemical properties of pure deltamethrin (Tagros)

Parameter	Value(s) and conditions	Purity %	Method	References
Vapour pressure	1.24 X 10^{-6} Pa at 20°C	98.0	EEC A4	10803
Melting point	98-101°C	98.0	EEC A1, A2	10761
Temperature of decomposition	>300°C	98.0	EEC A1, A2	10761
Solubility in water, at 20°C	0.16 x 10^{-6} g/l at 20°C	98.0	OECD 105	10760
Octanol/water partition coefficient, at 23°C	log P K_{OW} = 4.61 at 25 ± 1°C	98.0	EEC A8	10806
Hydrolysis characteristics, at 25°C	Negligible hydrolysis at 50°C, pH 4.0 & 7.0 Half-life = 1.75 d at 40°C, pH 9.0 Half-life = 1.85 d at 30°C, pH 9.0	98.0	OECD 111	12430

Table 2. Chemical composition and properties of technical deltamethrin (TC)

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data	Confidential information supplied and held on file by FAO and WHO. Mass balances were 99.91-100.10%, *with no unknowns.*
Declared minimum deltamethrin content	985 g/kg
Relevant impurities ≥ 1 g/kg and maximum limits for them	None.
Relevant impurities < 1 g/kg and maximum limits for them	None
Stabilisers or other additives and maximum limits for them	None
Melting temperature of the TC	98-101°C

Formulations

Tagros deltamethrin TC is registered and sold in Taiwan, China, Korea, Australia South Africa, Ecuador and Spain; the EC formulation in Taiwan, Saudi Arabia, Azerbaijan, Kyrgystan, Cambodia, Turkmenistan, Sri Lanka and Romania; the SC formulation in Taiwan; the WP formulation in Sri Lanka, Azerbaijan and Sudan; and the ULV formulation in Lebanon.. Argos formulations are registered and sold in South Africa.

Methods of analysis and testing

Tagros and Argos confirmed that the existing CIPAC methods for the determination of active ingredient content and for testing physical properties are satisfactory for use with their products.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

Note: Tagros provided written confirmation that the toxicological and ecotoxicological data included in the following summary were derived from deltamethrin having impurity profiles similar to those referred to in Table 2, above.

Table A. Toxicology profile of Tagros deltamethrin technical material, based on acute toxicity, irritation and sensitization

Species	Test	Duration and conditions	Result	References
Rat, Wistar, m	Acute oral	14 d obs., dose: 0, 500, 750 & 1000 mg/kg bw, vehicle vegetable oil, OECD 401, 99.2% purity	(i) LD_{50} = 612 mg/kg bw (ii) LD_{50} = 782 mg/kg bw	7719
Mouse Swiss albino, m & f	Acute oral	14 d obs., dose 0, 50, 100 & 150 mg/kg bw, vehicle vegetable oil, OECD 401, 99.2% purity	LD_{50} = 86 mg/kg bw (m) LD_{50} = 130 mg/kg bw (f)	7720
Rat, Wistar, m & f	Acute dermal	14 d obs., dose 0 & 2000 mg/kg bw OECD 402, 99.2% purity	LD_{50} >2000 mg/kg bw (m,f)	7721
Rat, Wistar, m & f	Acute inhalation	14 d obs., dose 0, 1.63, 3.11 & 4.39 mg/l, OECD 403, 99.2% purity	LC_{50} = 3.16 mg/l	8205
Rabbit	Skin irritation	Observation 1, 24, 48 & 72 h after treatment, dose: 500 mg (4 hours), OECD 404, 99.2% purity	non-irritant	7722
Rabbit	Eye irritation	Observation: 1, 24, 48 & 72 h after treatment, dose: 69 mg, OECD 405, 99.2% purity	mild irritant	7723
Guinea pig, Hartley	Skin sensitization	Observation: 28 d, dose 25 mg, OECD 406, 99.2% purity	non-sensitizer	7724

Deltamethrin has moderate to high acute toxicity when administered orally to the rat or mouse. Dullness, lethargy, mild tremor, salivation, diarrhoea and paralysis were observed in both male and female rats 2 h after treatment and persisted up to 24 h. In the rat, deltamethrin is less toxic by the dermal route but is highly toxic by inhalation. Deltamethrin is a mild-irritant to eye and non-irritant to skin of rabbits. It is not a skin sensitizer in the Guinea pig.

Table B. Toxicology profile of Tagros deltamethrin technical material, based on repeated administration (sub-acute to chronic)

Species	Test	Duration and conditions	Result	References
Rat	90 day oral	90 d, dose 0, 25, 50 & 75 mg/kg bw/d, OECD 408, purity 98%	NOAEL = 50 mg/kg bw/day	10380

Table C. Mutagenicity profile of Tagros deltamethrin technical material, based on *in vitro* and *in vivo* studies

Species	Test	Duration and conditions	Result	References
Salmonella typhimurium (TA 98, TA100, TA1535, TA1537)	Bacterial reverse mutation assay	Gaitonde Committee guideline 6.3.0 (1); dosage 0.5–5000 µg/plate, purity 98.65%	Negative	11270
TK6 human lymphoblastoid cells	Mammalian cell gene mutation test	Dosage 0.005, 0.01, 0.04 & 0.06 mM with S-9 mix; 0.005, 0.01, 0.02 & 0.04 mM without S-9 mix; OECD 476, purity 98.65%	Negative	10401
Human lymphocytes	DNA damage and repair	OECD 482; dosage 250, 500, & 1000 µg/plate, purity 98.65%	Negative	8181
Chinese hamster ovary (CHO) cells	Chromosomal aberration assay	Dosage 6, 7, & 8 µM with S-9 mix, 2, 4 & 6 µM without S-9 mix, OECD 473, purity 98.65%	Negative	10399
Mouse, Swiss Albino (m,f)	Mouse micronucleus assay	Gaitonde Committee guideline 6.3.0.2 (A), dosage 0,7.5,15,30 mg/kg, once or twice orally – 24h apart, purity 98.65%	Negative	11271
Mouse, Swiss Albino bone-marrow cells	Chromosomal aberration	Gaitonde Committee Guideline 6.3.0 (1), dosage: 0, 7.5, 15, 30 mg/kg b.w., once orally, purity 98.65%	Negative	11272
Mouse Swiss Albino (m, germinal cells)	Dominant lethal mutation	Gaitonde Committee Guideline 6.3.0.2 (A), dosage 0, 1.25, 2.5, 5 mg/kg b.w, once orally, purity 98.65%	Negative	11273

Table D. Ecotoxicology profile of Tagros deltamethrin technical material

Species	Test	Duration and conditions	Result	References
Daphnia magna (water flea)	Acute immobilization	Dosage: 1, 2, 4, 8 and 16 µg/l, 24 h, OECD 202, 99.2% purity	EC_{50} = 4.14 µg/l	7739
Poecilia immobiliza (freshwater fish)	Acute toxicity	Dosage: 0, 0.75, 1.13, 1.68, 2.53 and 3.79 µg/l, 96 h, OECD 203, 99.2% purity	LC_{50} = 1.74 µg/l	7737
Chlorella vulgaris (green algae)	Growth	72 h, OECD 201, 98.65% purity	EC_{50} = 22.77 µg/l	11442
Lampito mauritii (earthworm)	Acute toxicity	Dosage 150–1000 mg/kg dry soil, 14 d, OECD No.207, 99.2% purity	LC_{50} >1000 mg/kg dry soil	8321
Apis cerana indica (honey bee)	Acute contact toxicity	Dosage 0.05–1.20 ppm, 24 h, EPPO 170, 99.2% purity	LC_{50} = 0.52 ppm	8320
Coturnix coturnix japonica (Japanese quail)	Dietary toxicity	Dosage 1000, 2000, 3000, 4000 or 5000 ppm, 5 d, OECD 205, 99.2% purity	LC_{50} >5000 ppm	7738

Under laboratory conditions, deltamethrin is highly toxic for fish, aquatic arthropods, and honeybees. However, under field conditions, lasting adverse effects are not likely to occur under recommended conditions of use.

ANNEX 2. REFERENCES

Tagros document number or other reference	Year and title of report or publication details
7719	2000. Acute oral toxicity study with deltamethrin technical in Wistar rat.
7720	2000. Acute oral toxicity study with deltamethrin technical in Swiss albino mice.
7721	2000. Acute Dermal toxicity study with deltamethrin technical in Wistar rat.
7722	2000. A study on primary skin irritation of deltamethrin technical in Himalayan albino rabbits.
7723	2000. A study on irritation on mucous membrane of deltamethrin technical in Himalayan albino rabbits.
7724	2000. Skin sensitization potential of deltamethrin technical in Guinea pigs.
7737	2000. Acute toxicity of deltamethrin technical to freshwater fish, *Poecilia immobiliza*.
7738	2000. Dietary toxicity study with deltamethrin technical in Japanese quails.
7739	2000. Acute immobilization test with deltamethrin technical in *Daphnia magna*.
8181	2000. Mutagenicity evaluation of deltamethrin technical in human lymphocytes (DNA damage and repair – unscheduled synthesis).
8205	2000. Acute inhalation toxicity study with deltamethrin technical in Wistar rats.
8320	2001. Toxicity of deltamethrin technical to honey bee, *Apis indica*.
8321	2001. Toxicity of deltamethrin technical to earthworm, *Lampito mauritii*.
10380	2002. Sub-acute oral toxicity study with deltamethrin technical in Wistar rats.
10399	2002. Mutagenicity evaluation of deltamethrin technical – *in vitro* chromosomal aberration assay.
10401	2002. Mutagenicity evaluation of deltamethrin technical – *in vitro* mammalian cell gene mutation test.
10760	2002. Study on solubility of deltamethrin technical in water.
10761	2002. Study report on melting point, boiling point and relative density of deltamethrin technical.
10803	2002. Study report on vapour pressure of deltamethrin technical.
10806	2002. Study on partition co-efficient (*n*-octanol/water) of deltamethrin technical.
11270	2002. Mutagenicity evaluation of deltamethrin technical by Ames *Salmonella typhimurium* – reverse mutation assay.
11271	2002. Mutagenicity evaluation of deltamethrin technical – in vivo mouse micronucleus assay.
11272	2002. Mutagenicity evaluation of deltamethrin technical – in vivo by mouse bone marrow cytogenetic assay (chromosomal aberration)
11273	2002. Mutagenicity evaluation of deltamethrin technical – in vivo by dominant lethal test in mouse.
11442	2002. Effect of deltamethrin technical on the growth of green alga (*Chlorella vulgaris*).
12430	2002. Study on hydrolysis (abiotic) of deltamethrin technical.
GHS 2003	The Globally Harmonized System of Classification and Labelling of Chemicals (GHS) at: http://www.unece.org/trans/danger/publi/ghs/ghs_rev00/English/GHS-PART-3e.pdf , accessed on 9 September, 2005.
JMPS 2002	WHO Specifications and evaluations for public health pesticides. *d*-Allethrin. accessed at http://www.who.int/whopes/quality/en/dAllethrin_spec_eval_March_04.pdf on 12 September, 2005.
PCS 2005a	14 September 2005. Relevance of impurities in deltamethrin, and equivalence of two deltamethrin products.
PCS 2005b	11 January 2005. Dermal irritation and sensitization of permethrin.
Tagros 2006a	*Method of analysis for the determination of bicisthemic acid content corresponding to* deltamethrin content in deltamethrin technical. Tagros report on study No. 05063. E-mail sent to M. Zaim (WHO) and G Vaagt (FAO) on 24 February 2006.

Tagros document number or other reference	Year and title of report or publication details
Tagros 2006b	ReRe: Deltamethrin specifications E-mail sent to M. Zaim (WHO) and G Vaagt (FAO) on 01 March 2006.
WHO 2006	Report of the Ninth WHOPES Working Group Meeting. Geneva, World Health Organization, 2006 (WHO/CDS/NTD/WHOPES/2006.2).