WHO SPECIFICATIONS AND EVALUATIONS

FOR PUBLIC HEALTH PESTICIDES

ICARIDIN *

1-piperidinecarboxylic acid 2-(2-hydroxyethyl)-1-methylpropylester

WORLD HEALTH ORGANIZATION

GENEVA

* Also known as hydroxyethyl isobutyl piperidine carboxylate (INCI common name).

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WHO specifications are developed with the basic objective of promoting, as far as practicable, the manufacture, distribution and use of pesticides that meet basic quality requirements.

Compliance with the specifications does not constitute an endorsement or warranty of the fitness of a particular pesticide for a particular purpose, including its suitability for the control of any given pest, or its suitability for use in a particular area. Owing to the complexity of the problems involved, the suitability of pesticides for a particular purpose and the content of the labelling instructions must be decided at the national or provincial level.

Furthermore, pesticides which are manufactured to comply with these specifications are not exempted from any safety regulation or other legal or administrative provision applicable to their manufacture, sale, transportation, storage, handling, preparation and/or use.

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Additionally, WHO wishes to alert users to the fact that improper storage, handling, preparation and/or use of pesticides can result in either a lowering or complete loss of safety and/or efficacy.

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[1] This disclaimer applies to all specifications published by WHO.

INTRODUCTION

WHO establishes and publishes specifications* for technical material and related formulations of public health pesticides with the objective that these specifications may be used to provide an international point of reference against which products can be judged either for regulatory purposes or in commercial dealings.

From 2002, the development of WHO specifications follows the **New Procedure**, described in the 1st edition of Manual for Development and Use of FAO and WHO Specifications for Pesticides (2002). This **New Procedure** follows a formal and transparent evaluation process. It describes the minimum data package, the procedure and evaluation applied by WHO and the experts of the "FAO/WHO Joint Meeting on Pesticide Specifications" (JMPS).

WHO Specifications now only apply to products for which the technical materials have been evaluated. Consequently, from the year 2002 onwards the publication of WHO specifications under the **New Procedure** has changed. Every specification consists now of two parts, namely the specifications and the evaluation report(s):

Part One: The Specification of the technical material and the related formulations of the pesticide in accordance with chapters 4 to 9 of the 1st edition of the "FAO/WHO Manual on Pesticide Specifications."

Part Two: The Evaluation Report(s) of the pesticide, reflecting the evaluation of the data package carried out by WHO and the JMPS. The data are provided by the manufacturer(s) according to the requirements of chapter 3 of the "FAO/WHO Manual on Pesticide Specifications" and supported by other information sources. The Evaluation Report includes the name(s) of the manufacturer(s) whose technical material has been evaluated. Evaluation reports on specifications developed subsequently to the original set of specifications are added in a chronological order to this report.

WHO specifications under the **New Procedure** do not necessarily apply to nominally similar products of other manufacturer(s), nor to those where the active ingredient is produced by other routes of manufacture. WHO has the possibility to extend the scope of the specifications to similar products but only when the JMPS has been satisfied that the additional products are equivalent to that which formed the basis of the reference specification.

Specifications bear the date (month and year) of publication of the current version. Dates of publication of the earlier versions, if any, are identified in a footnote. Evaluations bear the date (year) of the meeting at which the recommendations were made by the JMPS.

* Footnote: The publications are available on the Internet under (http://www.who.int/whopes/quality/en/).

PART ONE

SPECIFICATIONS

ICARIDIN

INFORMATION

Common name

Icaridin (proposed ISO)

Synonyms

Hydroxyethyl isobutyl piperidine carboxylate (INCI*), Bayrepel™, Propidine, Pikaridin.

Chemical name

CA: 1-piperidinecarboxylic acid 2-(2-hydroxyethyl)-1-methylpropylester

CAS Registry number

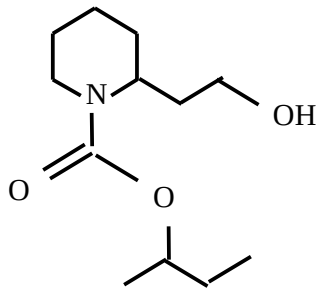
119515-38-7

CIPAC number

740

(note: the INCI name hydroxyethyl isobutyl piperidine carboxylate was allocated CIPAC number 668, whereas CIPAC number 740 refers to the ISO common name, icaridin)

Structural formula



Icaridin is a mixture of two diastereoisoimers in an approximate 1 : 1 ratio, each being a recemate.

Empirical formula

$C_{12}H_{23}NO_3$

Relative molecular mass

229.3

Identity tests

GC (relative retention time), IR, MS (reference spectra deposited with WHO)

* INCI is the International Nomenclature of Cosmetic Ingredients, a system developed by the European Cosmetic, Toiletry and Perfume Association (COLIPA).

ICARIDIN TECHNICAL MATERIAL (TC)

WHO specification TC/740 (October 2004*)

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose name is listed in the evaluation report 740/2004. It should be applicable to relevant products of this manufacturer but it is not an endorsement of those products, nor a guarantee that they comply with the specification. The specification may not be appropriate for the products of other manufacturers. The evaluation report 740/2004, as PART TWO, forms an integral part of this publication.

1 **Description** (Note 1)

The material shall consist of icaridin together with related manufacturing impurities, in the form of a colourless and nearly odourless liquid, free from visible extraneous matter and added modifying agents.

2 **Active ingredient**

2.1 **Identity tests** (740/TC/M/2, CIPAC Handbook K, p. 64, 2003)

The active ingredient shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

2.2 **Icaridin content** (740/TC/M/3, CIPAC Handbook K, p. 64, 2003)

The icaridin content shall be declared (not less than 970 g/kg) and, when determined, the mean measured content shall not be lower than the declared minimum content.

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*Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: http://www.who.int/whopes/quality/en/.

PART TWO

EVALUATION REPORTS

ICARIDIN

WHO SPECIFICATIONS AND EVALUATIONS FOR
PUBLIC HEALTH PESTICIDES

ICARIDIN

EVALUATION REPORT 740/2004

Explanation

The data on icaridin were evaluated for review of an existing WHO interim specification. The interim specification was developed before the ISO name of icaridin became available and was originally based on the INCI* name of hydroxyethyl isobutyl piperidine carboxylate.

Icaridin is under patent in Denmark, Norway, Finland, Hungary, Zambia, South Africa, Turkey, Thailand, Philippines, Japan, Brazil, Venezuela, Australia, New Zealand and Mexico until 2008; in the USA until 2009; in Canada until 2011; and in Argentina until 2014. The European Patent Office patent is valid until 2008.

Icaridin was evaluated for efficacy by the WHOPES programme (WHO 2001a). It was also evaluated by the WHO/PCS (WHO 2001a). Data on icaridin were earlier evaluated by WHOPES in support of an interim specification for icaridin TC (WHO 2001b).

The supporting data for the existing interim specification provided by Bayer AG, Germany in 2000, with additional information provided in 2004.

Uses

Icaridin is an insect repellent, for application to human or animal skin. It also shows repellent activity when applied to surfaces. It is used in public health applications, to repel biting insects such as mosquitoes and biting flies (WHO 2001a).

Identity

Common name

Icaridin (proposed ISO)

Synonyms

Hydroxyethyl isobutyl piperidine carboxylate (INCI), Bayrepel™, Propidine, Pikaridin.

Chemical name

CA: 1- piperidinecarboxylic acid 2-(2-hydroxyethyl)-1-methylpropylester

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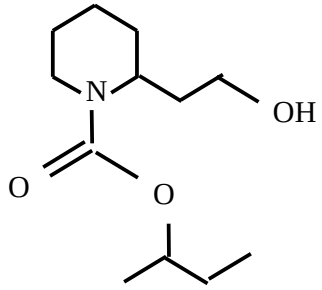

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Relative molecular mass

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Identity tests

GC (relative retention time), IR, MS (reference spectra deposited with WHO).

Physical and chemical properties of icaridin

Table 1. Physico-chemical properties of pure icaridin.

Parameter	Value(s) and conditions	Purity %	Method reference
Vapour pressure:	3.4×10^{-2} Pa at 20°C 5.9×10^{-2} Pa at 25°C 0.7 Pa at 50°C.	97%	OECD 104
Freezing point, boiling point = and thermal stability:	Freezing point: below -170°C Boiling point: 296°C by extrapolation of vapour pressure curve. Thermally stable at ambient temperature in air. DTA: stable in air up to 160°C; stable in nitrogen up to 260°C; no exothermic reaction until 400°C. TGA: weight loss, starting 120°C.	97%	EU- Method A1 OECD 113
Solubility in water:	8.2 g/l at 20°C at pH 4-9: 8.6 g/l at 20°C in unbuffered water	97%	OECD 105
Octanol/water partition coefficient:	log P_{ow} 2.11 at 20°C, unbuffered log P_{ow} 2.23 at 20 °C at pH 4-9	97%	OECD 117
Hydrolysis characteristics:	No hydrolysis products observed after 7 days at 50°C and after 30 days at 25°C at pH 5, 7 and 9	97%	EPA Pesticide Assessment Guideline, Subdivision N, Section 161-1, 1982
Photolysis characteristics:	No absorption at UV and visible wavelengths		

Parameter	Value(s) and conditions	Purity %	Method reference
Dissociation characteristics:	No acidic or basic properties in aqueous solution	97%	OECD 112
Flammability	Not flammable	98.9%	EU A.9, A.12, A13
Explosive properties	No explosive properties	98.9%	EU A.14
Auto-ignition temperature	375°C	98.9%	EU A15/A16

Table 2. Chemical composition and properties of icaridin 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: 988-997 g/kg (2000, 6-batch data) and 999-1000 g/kg (Reubke 2001, 5-batch data), including unknowns (totals of 3-12 g/kg in 2000 and <1 g/kg in 2001[1]).
Declared minimum icaridin content:	970 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:	None.
Melting or boiling temperature range	Melting point: below -170°C Boiling point: 296°C (calculated from vapour pressure). No exothermic reaction until 400°C.

Toxicological summaries

Notes.

(i) The proposer confirmed that the toxicological and ecotoxicological data included in the summary below were derived from icaridin having impurity profiles similar to those referred to in Table 2.

(ii) The conclusions expressed in the summary below are those of the proposer, unless otherwise specified.

Table 3. Toxicology profile of the technical material, based on acute toxicity, irritation and sensitization.

Species	Test	Duration and conditions or guideline adopted	Result
Rat, m	Oral, fasted	OECD 401	LD_{50} = 2236 mg/kg bw (approximate), NOEL = 100 mg/kg bw.
Rat, m	Oral, non-fasted	OECD 401, EPA-FIFRA 81-1, purity 99.1%	LD_{50} = 4743 mg/kg bw (approximate), NOEL = 100 mg/kg bw.
Rat, m	Dermal	OECD 402	LD_{50} = >5000 mg/kg bw, NOEL = 5000 mg/kg bw
Rat, m/f	Dermal	EPA-FIFRA 81-2, USEPA TSCA No. 798.1100, OECD 402, JMAFF 59 NohSan No. 4200, purity 98.5%	LD_{50} = >2000 mg/kg bw, NOEL = 5000 mg/kg bw

[1] The current manufacturing specification for unknowns is a maximum of 1 g/kg, each, although this includes a known impurity, occurring at very low levels (Koch 2004d).

Species	Test	Duration and conditions or guideline adopted	Result
Rat, m	Inhalation	Exposure: 1 x 4 hours, OECD 403, purity 99.1%	LC_{50} = >4364 mg/m^3 air, NOEL = 2153 mg/m^3 air
Rabbit, m	Skin irritation	OECD 404, purity 99.4%	Non-irritant
Rabbit, m	Eye irritation	OECD 405, purity 99.4%	Slightly irritant
Guinea pig, m	Skin sensitization	OECD 406, EU- 84/449/EEC, purity 99.4%	Non sensitizing

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

Species	Test	Duration and conditions or guideline adopted	Result
Rat	Sub-chronic oral	OECD 411, 90 days, purity 99.2-99.3%	NOAEL = 80mg/kg bw/d NOEL = 80mg/kg bw/d
Rat	Sub-chronic dermal	13 weeks EPA FIFRA 82-3, OECD 411, JMAFF 59 NohSan No. 4200	LOEL = 500mg/kg bw/d NOEL = 200mg/kg bw/d
Dog	Intravenous	28 day, purity 99.2-99.3%	NOEL = 0.4 mg/kg bw/d
Dog	Sub-chronic oral	28 day, purity 99.2-99.3%	NOEL = 10 mg/kg bw/d
Dog	Chronic dermal (started as sub-chronic study)	1 year EPA FIFRA 83-1, 82-2, US EPA TSCA No. 798.3320, OECD 453, JMAFF 59 NohSan No. 4200	NOEL = 200 mg/kg bw/d (highest dose studied)
Rat	Combined chronic toxicity/carcinogenicity dermal	2 years EPA FIFRA No. 83-5, OECD 453, TSCA 798.3320, JMAFF 59 NohSan No. 4200	LOEL = 200 mg/kg bw/d NOEL = 100 mg/kg bw/d Not carcinogenic
Mouse	Carcinogenicity dermal	13 months EPA FIFRA No. 83-2, OECD 451, TSCA 798.3300, JMAFF 59 NohSan No. 4200	NOEL = 200 mg/kg bw/d (highest dose studied) Not carcinogenic
Rat	2-generation dermal	2 generations EPA FIFRA No. 83-4, OECD 416, TSCA 798.4700, JMAFF 59 NohSan No. 4200, EU 87/302/EEC	NOEL = 200 mg/kg bw/d (highest dose studied) No effects on reproduction
Rat	Teratogenicity and developmental toxicity, oral	GD 0-20 EPA FIFRA No. 83-3, OECD 414, TSCA 798.4900, JMAFF 59 NohSan No. 4200, EU 87/302/EEC	NOEL = 400 mg/kg bw/d NOEL = 200 mg/kg bw/d Not foetotoxic or teratogenic
Rat	Teratogenicity and developmental toxicity, dermal	OECD 414	NOEL dams = 200 mg/kg bw/d NOEL foetus = 400 mg/kg bw/d (highest dose studied) Not teratogenic
Rat	Teratogenicity and developmental toxicity, dermal	OECD 414	NOEL dams = 250 mg/kg bw/d NOEL foetus = 1000 mg/kg bw/d (highest dose studied) Not teratogenic

Species	Test	Duration and conditions or guideline adopted	Result
Rabbit	Teratogenicity and developmental toxicity, oral	GD 0-20 EPA FIFRA No. 83-3, OECD 414, JMAFF 59 NohSan No. 4200, EU 87/302/EEC	LOEL = 200 mg/kg bw/d NOEL = 100 mg/kg bw/d Not foetotoxic or teratogenic
Rabbit	Teratogenicity and developmental toxicity, dermal	OECD 414	NOEL dams = 100 mg/kg bw/d NOEL foetus = 200 mg/kg bw/d (highest dose studied) Not teratogenic
Rat	Sub-chronic neurotoxicity dermal	13 weeks US EPA FIFRA 82-5(b)	NOEL = 200 mg/kg bw (highest dose studied)

Table 5. Mutagenicity profile of icaridin technical material, based on *in vitro* and *in vivo* tests.

Species	Test	Conditions	Result
Salmonella typhimurium	Salmonella microsome test, *in vitro*	OECD 471, EPA FIFRA 84-2, 8-5000 µg/plate, with and without metabolic activation, purity 99.1%	Negative
Hamster ovarian cells	CHO-HGPRT assay, *in vitro*	EU 87/302/EEC, OECD 475, EPA FIFRA PB 84-233295 125-1500 µg/ml, with and without metabolic activation, purity 99.0%	Negative
V79 cells	V79/HPRT test, *in vitro*	EU 88/302/EEC, OECD 476, EPA FIFRA OPPTS 870.5300	Negative
Chinese hamster ovary cells	Chromosome aberration test, cytogenetics, *in vitro*	EU 79/831/EEC, OECD 473, EPA FIFRA 84-2 125-1500 µg/ml, with and without metabolic activation	Slightly positive within the toxic range (≥800 µg/ml with, and ≥1200 µg/ml with, metabolic activation)
Mouse	Micronucleus test, *in vivo*	EU 92/69/EEC, OECD 474, EPA FIFRA PB 84-233295	Negative
Rat primary hepatocytes	Unscheduled DNA synthesis assay, *in vitro*	EU 87/302/EEC, OECD 482, EPA FIFRA PB 84-233295 10-600 µg/ml, with and without metabolic activation	Negative

Table 6. Ecotoxicology profile of icaridin technical material.

Species	Test	Duration and conditions	Result
Daphnia magna (water flea)]	Acute toxicity	48h, static, 20 ± 1ºC OECD 202 USEPA FIFRA 72-2 purity 97.9%	EC_{50}: calculation not possible NOEC = 103 mg/l (highest test conc.)
Bacteria (mixed population)	Toxicity	88/302/EEC, EC L 133, Part 3 (corresponds in most parts to OECD 209) purity 97.9%	EC_{50} at 0.5 h = 1110 mg/l; no effect on the bacterial population
Oncorrhynchus mykiss (rainbow trout)	Acute toxicity,	96 h, static OECD 203 USEPA FIFRA 72-1 EG L 383 A/163 purity 97.9%	LC_{50} = 173 mg/l LC_{100} = 240 mg/l NOEC = 50.1 mg/l
Brachydanio rerio Hamilton Buchanan (zebra danio)	Bioaccumulation	OECD 305	No potential for bioaccumulation in fish
Scenedesmus subspicatus (green alga)	Effect on growth	72h, 23 ± 2ºC EEC Directive 79/831/E Rev.Vs.383A/179 ISO 8692 (1989) OECD 201 (1984) purity 97.9%	EC_{50} biomass = 71.5 mg/l EC_{50} growth = 87.3 mg/l NOEC biomass = 54.8 mg/l NOEC growth = 54.8 mg/l
Earthworm	-	-	Not applicable due to use pattern
Apis mellifera (honey bee)	-	-	Not applicable due to use pattern
Colinus virgianus (bobwhite quail)	Five-day dietary toxicology	USEPA FIFRA 71-2 OECD 205	LC_{50} = >5000 ppm a.i. in diet NOEC = ≥5000 ppm a.i. in diet
Bacteria	28-day bacterial degradation of 20 mg/l 28-day bacterial degradation of 101.5 mg/l	OECD C.4-B, aniline reference OECD 302 B, sodium benzoate reference	1% degradation, not toxic to the bacteria (94% degradation of reference) 6% mineralization (100% degradation of reference)
Brachydanio rerio	Bioconcentration factor	OECD 305 flow-through	Whole body = 1.8 Lipid = 19

The hazards and risks associated with icaridin were considered by the WHO/PCS secretariat (WHO 2001b), with the conclusion that the intended uses of the material posed no unacceptable risks to users, treated animals or to the environment.

Icaridin has not been evaluated by the FAO/WHO JMPR, nor by IPCS.

Based on the information available on acute toxicity, WHO/PCS concluded that icaridin would fall into the WHO hazard classification category: Class III, “slightly hazardous”.

Two potential impurities of icaridin, *sec*-butyl chloroformate and *sec*-butyl carbonic anhydride, have strong skin sensitizing properties, although they do not sensitize skin to icaridin (Diesing 1991). In practice, these potentially relevant impurities were not detectable in the technical material.

Formulations

The main formulation types available are alcohol-based liquids, aerosols, emulsions (body lotions), sticks (such as deodorant sticks). These formulations are registered and sold in many countries throughout the world.

Methods of analysis and testing

The analytical method for determination of the quantity and identity of the active ingredient is based on capillary GC with FID and internal standardization with dimethylphthalate. The method was validated by collaborative study, adopted by CIPAC in 2002 and adopted and published as a full CIPAC method in 2003. The identity of the active ingredient may be established by comparing GC relative retention time, IR or MS spectra with those of an authentic reference material.

The methods for determination of impurities were based on GC with FID. The material accountability study was performed according to the US Environmental Protection Agency's, Pesticide Assessment Guidelines, Subd. D; Series 62.

Physical properties

Test methods used to determine the physical properties of technical active ingredient were OECD, EPA, EU or Ph. Eur.

Containers and packaging

The active ingredient and its formulations can be stored in containers of polyethylene or high density polyethylene.

Expression of the active ingredient

The active ingredient is expressed as icaridin.

Appraisal

Icaridin, formerly known by its INCI name of hydroxyethyl isobutyl piperidine carboxylate, is a patented active ingredient, for which an interim WHO specification exists for the technical material.

The molecule has two chiral centres and the active ingredient exists as a mixture of two diastereoisoimers in an approximate 1 : 1 ratio, each being a recemate.. The diastereomers are not readily separated by gas chromatography. The compound is moderately soluble in water, somewhat hygrosopic and very soluble in a wide range of organic solvents but it is not classified as fat soluble. It has no appreciable acidic or basic characteristics. Measurable hydrolysis does not occur in water at pH 5, 7 and 9, after 7 days at 50°C or after 30 days at 25°C. Photolysis is unlikely as it has no appreciable absorption at UV wavelengths.

Confidential information on the manufacturing process and impurities present at or above 1 g/kg, was provided by the proposer for evaluation of the existing interim specification. Mass balances were high, at 988-997 g/kg in a 1997 series of 5 batches used to produce a blended batch for toxicity testing (Koch 2004a) and 997-999 g/kg in a 2001 series of 5 batches (Koch 2004b).

The manufacturing specification submitted in support of registration of icaridin in Germany in 1996 (BAUA 2004) was in the form of typical upper and lower values for the components. A slightly different manufacturing specification, initially provided to WHO in support of the existing interim specification, was based on the five batches analyzed in 1997. Rigorous studies of accountability and the analytical methods conducted in 2001 (Reubke 2001a and 2001b) revealed more detail of the minor impurities but also indicated that determination of some impurities is analytically challenging. The 2001 data, together with a slight change in manufacturing process to exclude an impurity and a change in purity of a starting material, led to a further slight change to produce the current manufacturing specification (Koch 2004c, with a further minor amendment in Koch,2004d).

Two impurities were common solvents but no toxicological and ecotoxicological data were available for three other impurities which, in the 1997 profile, had manufacturing limits >1 g/kg. The purity of the TC was high throughout (minimum 970 g/kg) and the WHO/PCS opinion (WHO 2001b) was that there was no evidence to suggest that the other impurities are more toxic than the active ingredient. The toxicological and ecotoxicological data submitted for registration in Germany were identical to those provided to WHO, although additional data were also provided to WHO. Although the profiles submitted for registration in Germany and in support of the current draft WHO specification were not identical, nor strictly equivalent according to the JMPS guidelines (FAO/WHO 2002), the Meeting considered that the differences were not significant. The Meeting agreed that the current (2004) manufacturing specification should form the reference profile for WHO specifications.

Synthesis of icaridin has the potential to produce *sec*-butyl chloroformate and, hypothetically, *sec*-butyl carbonic anhydride as impurities. Both are reactive compounds and very readily hydrolyzed. Both compounds have strong skin sensitizing properties, although they do not sensitize skin to icaridin. In principle, both impurities could be considered as relevant. No other hazardous impurities, such as nitrosamines, are known to be associated with the synthesis of icaridin.

The existing interim specification for icaridin identified *sec*-butyl chloroformate as a relevant impurity, with a limit of 1 g/kg. The toxicological data available did not permit estimates of the LOAEL and NOAEL for sec-butyl chloroformate but a concentration nominally 5 times higher than the limit did not induce a reaction in sensitized animals in a guinea pig maximization test. The proposer confirmed that technical icaridin, complying with the 1 g/kg limit, showed no skin sensitization properties. The proposer also stated that the manufacturing process had been designed to minimize the possibility of occurrence of *sec*-butyl chloroformate and that, in practice, this impurity was not detectable (<0.05 g/kg). The sensitivity of *sec*-butyl chloroformate to hydrolysis is evident from the fact that, during analysis, great care is required to avoid hydrolysis by trace levels of water in the dichloromethane solvent used to dissolve the icaridin sample (Reubke 2001b) and therefore it seems unlikely to occur in practice, particularly in formulations.

The toxicological data available (Diesing 1991) did not permit estimates of the LOAEL and NOAEL for *sec*-butyl carbonic anhydride. The existing interim specification for icaridin TC did not identify it as a relevant impurity and the proposer stated that, in practice, it had never been detected in the synthesis and manufacture of icaridin. The proposer observed that this impurity would not survive the conditions employed for isolation of the active ingredient and it had not been necessary to

optimise the manufacturing process to eliminate or minimise occurrence of this impurity. The analytical method used for the determination of other impurities (Reubke 2001b) was not validated for the determination of *sec*-butyl carbonic anhydride but, if present in the TC, it should be detectable by this method and validation data for the other impurities suggested that "not detected" may be interpreted as <0.1 g/kg.

In 2003, the JMPS aligned decisions on sensitizing materials with the globally harmonized system (GHIS) for classification and labelling of chemicals (UN 2003) and adopted 10 g/kg as a guideline maximum limit for sensitizing impurities[1]. However, the JMPS had also previously adopted the general principles: (i) that, wherever practicable, limits for relevant impurities should be set below the maximum acceptable; and (ii) that an otherwise relevant impurity should not be subject to specification limits if detectable levels do not occur in practice. In the case of icaridin, the manufacturing data and available analytical methods indicated that 1 g/kg limits would be practical for both impurities but there was no evidence to suggest that either of them would be detected in practice (<0.1 g/kg for *sec*-butyl carbonic anhydride and <0.05 g/kg for *sec*-butyl chloroformate). As these analytical limits were <1% and <0.5% of the maximum level acceptable for sensitizing compounds, the Meeting concluded that neither of the compounds should be specified as a relevant impurity in the proposer's products. Nonetheless, the Meeting noted that clauses limiting the two potentially relevant impurities may be required if the specification for icaridin TC is extended to other manufacturers in future.

Another possible impurity, 2-acetylpyrroline, is known to taint wine (Mottram 1998). However, in the view of WHO/PCS (Aitio 2004), the limit applied (0.02 mg/kg) to the TC (Koch 2004d) and the pattern of icaridin use make it unlikely that taint would occur in practice. Therefore the Meeting agreed that it should not be defined as a relevant impurity.

Icaridin had not been evaluated by IPCS or JMPR but national registration authorities had done so. The data submitted were considered by the WHO/PCS secretariat, with the conclusion that the intended uses of the material posed no unacceptable risks to users, treated animals or to the environment (WHO 2001b). Based on acute toxicity, WHO/PCS concluded that icaridin would fall into the WHO hazard classification category: Class III, "slightly hazardous".

The analytical method for determination of the active ingredient is a full CIPAC method. Identity tests are based on GC relative retention time, IR and MS spectra.

Physical and toxicological test methods followed internationally recognised protocols. Specifications for icaridin formulations were not submitted to the Meeting.

Recommendations

The meeting recommended that:

(i) the existing interim specification for icaridin should be withdrawn by WHO;

(ii) the proposed specification, as amended, for icaridin TC should be adopted by WHO;

1 A limit of 1g/kg may be adopted is certain cases, in accordance with GHIS recommendations.

(iii) if the specification is extended in future to include the products of other manufacturers, the evaluation must consider the need for clauses to limit the content of *sec*-butyl carbonic anhydride, *sec*-butyl chloroformate and/or 2-acetylpyrroline. If the present manufacturer changes the process such that detectable levels of these impurities occur, the manufacturer must inform WHO so that the specification can be reviewed.

References

Aitio 2004 — Re: Icaridin. Aitio A., WHO/PCS, two e-mails, dated 8 October 2004 to Zaim M, WHO, and Hill A.

BAUA 2004 — Full notification report 96-04-0885-00 under EU Directive 92/32 EEC, dated 21 November 1996, provided by Dr Böhlen, Bundesanstalt für Arbeitsschutz and Arbeitsmedizin with accompanying letter dated 7 April 2004.

Diesing 1991 — Diesing L. Components of KBR 3023: study for skin sensitising effect on guinea pigs. Bayer AG report No. 20046, 1991. Unpublished.

FAO/WHO 2002 — Manual on development and use fof FAO and WHO specifications for pesticides, first edition. FAO plant production and protection paper 173. FAO, Rome, 2002.

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