Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products

Evaluation of active substances

Assessment Report

Icaridin

Product-type 19
(Repellents and attractants)

December 2019

DK

CONTENTS

1. STATEMENT OF SUBJECT MATTER AND PURPOSE

1.1. Procedure followed

This assessment report has been established as a result of the evaluation of the active substance icaridin as product-type 19 (repellents and attractants), carried out in the context of the work programme for the review of existing active substances provided for in Article 89 of Regulation (EU) No 528/2012, with a view to the possible approval of this substance.

Icaridin (CAS no. 119515-38-7) was notified as an existing active substance, by Saltigo GmbH, hereafter referred to as the applicant, in product-type 19.

Commission Regulation (EC) No 1062/2014 of 4 August 2014[1] lays down the detailed rules for the evaluation of dossiers and for the decision-making process.

On 20 April 2006, the Danish competent authorities received a dossier from Saltigo GmbH. The Rapporteur Member State accepted the dossier as complete for the purpose of the evaluation on 4 July 2006.

On 14 January 2011, the Rapporteur Member State submitted to the Agency (ECHA) and the applicant a copy of the evaluation report, hereafter referred to as the competent authority report.

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 the "Agency" (ECHA). Revisions agreed upon were presented at the Biocidal Products Committee and its Working Groups meetings and the competent authority report was amended accordingly.

1.2. Purpose of the assessment report

The aim of the assessment report is to support the opinion of the Biocidal Products Committee and a decision on the approval of icaridin for product-type 19, and to facilitate the authorisation of individual biocidal products. 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.

For the implementation of the common principles of Annex VI, the content and conclusions of this assessment report, which is available from the Agency web-site shall be taken into account.

[1] COMMISSION DELEGATED REGULATION (EU) No 1062/2014 of 4 August 2014 on the work programme for the systematic examination of all existing active substances contained in biocidal products referred to in Regulation (EU) No 528/2012 of the European Parliament and of the Council. OJ L 294, 10.10.2014, p. 1

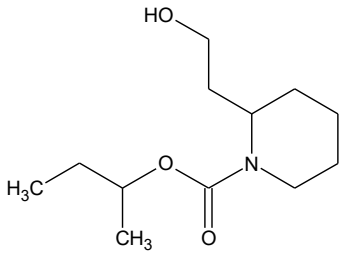
However, where conclusions of this assessment report are based on data protected under the provisions of Regulation (EU) No 528/2012, such conclusions may not be used to the benefit of another applicant, unless access to these data for that purpose has been granted to that applicant.

2. OVERALL SUMMARY AND CONCLUSIONS

2.1. Presentation of the Active Substance

2.1.1. Identity, Physico-Chemical Properties & Methods of Analysis

CAS-No.	119515-38-7
EINECS-No.	423-210-8
Other No. (CIPAC, ELINCS)	CIPAC No. 740
IUPAC Name	*(RS)*- *sec*-butyl *(RS)*-2-(2-hydroxyethyl)piperidine-1-carboxylate
C.A. Name	1-piperidinecarboxylic acid, 2-(2-hydroxyethyl)-1-methylpropylester
Common name, Synonyms	Icaridin Bayrepel KBR 3023 Picaridin Propidine
Molecular formula	$C_{12}H_{23}NO_3$

Structural formula	
SMILES:	C1C (N (CCC1) C (OC (C) CC) =O) CCO
Molecular weight (g/mol)	229.3
Purity	≥ 97%
Impurities	Confidential information. See confidential annex. None of the manufacturing impurities are considered to be of potential concern.

Icaridin is a colourless and odourless liquid. No freezing, melting, crystallisation or glass transition was observed in a temperature range between -170 °C and 20 °C. The boiling point of icaridin is 296 °C at 1013 hPa, its density 1.07 g/mL at 20 °C and its vapour pressure 3.4×10^{-2} Pa at 20 °C.

The water solubility of icaridin is 8.2 g/L in one study and 10.6 g/L in another study, both at 20 °C. It is not influenced by the pH in the range pH 4 to pH 9 but by temperature in the range 10 °C to 30 °C. The log Pow of icaridin is 2.23 at 20 °C. This parameter is not influenced by the pH in the range pH 4 to pH 9 but shows slight temperature dependence between 20 °C and 50 °C.

The surface tension is 49 mN/m at 20 °C and icaridin is regarded as surface active. Its viscosity is 0.104 Pa×s at 23 °C and a shear rate from 0 to 100 s^{-1}.

The flash point is 142 °C at 1007 hPa and 151 °C at 1027 hPa.

Icaridin does not have oxidising, pyrophoric or explosive properties.

The methods of analysis for the active substance as manufactured, and for the determination of impurities, have been validated. The methods for analysis in soil have been validated and shown to be sufficiently sensitive with respect to the levels of concern. The method for icaridin in water is not sufficiently validated and the method for icaridin-acid in water is not acceptable as it uses derivatisation with diazomethane, which is toxic and

carcinogenic. The method for air is not acceptable as carbon tetrachloride is used as solvent and as the method is not sufficiently validated. However, air is not a compartment of concern for icaridin due to the short half-life of the compound in the atmosphere (DT50 = 6.87 hours) and the low vapour pressure (3.4×10^{-2} Pa at 20 °C). The RMS therefore suggests not requiring an analytical method for determining icaridin residues in air.

Further data on analytical methods for determining icaridin and icaridin-acid residues in surface water and groundwater is thus a data requirement and the RMS suggests requiring these data at the product authorisation stage. Furthermore, an analytical method for determining icaridin-acid residues in soil is lacking.

For icaridin no analytical method is required for the determination of residues in animal and human body fluids and tissues or residues in food or feedstuff.

2.1.2. Intended Uses and Efficacy

The assessment of the biocidal activity of the active substance demonstrates that it has a sufficient level of efficacy against the target organism(s) *Culex quinquefasciatus* 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.

Icaridin and Autan formulations have been examined for efficacy in a wide range of field and laboratory tests.
Performance of icaridin containing repellent products depends on the level of icaridin in the formulated product rather than on the composition of the co-formulants.
However, the risk assessment for human health and the environment has only been performed for Autan Pump Spray 20% against mosquitoes.
Thus, for the inclusion of icaridin the evaluation has been performed with Autan Pump Spray 20% against mosquitoes. Products with different compositions or against other target organisms than *Culex quinquefasciatus* will need to be assessed at Member State level at product authorisation stage.
The evaluation of all the efficacy studies is kept in the CA report in order to help MS at the product authorisation stage.

1. In the context of applying 3 g 20% icaridin product to cover 64% (10890 cm^2) of the body (equivalent to 0.275 mg product per cm^2), equivalent to 0.055 mg active ingredient (icaridin) per cm^2. An arm-in cage studies demonstrating efficacy at dose rate of 0.055 mg icaridin/cm^2 was requested by the eCA DK. The tests were performed with pump spray products containing 10% or 20% icaridin, respectively, with *Culex quinquefasciatus* as target organism (Gundalai, 2016a and 2016b). The arm-in-cage tests resulted in a protection time of 4.9 hours (the lowest CPT ought to be used to cover as many users as possible) for 0.055 mg icaridin/cm^2. Thus, the requirements for authorization against mosquitoes in Europe and the tropics are not fulfilled. Arm-in-cage test with 0.055 mg/cm^2 should be requested from representative species from *Aedes*, *Anopheles* and *Culex*. If Europe is the only intended market *Anopheles* can be omitted, but then it should be clearly stated on the label that the product is not intended for use in the tropics, because it is not tested against mosquitoes able to transmit malaria. This has to be taken into consideration in European countries where Malaria may occur.

Autan Pump Spray 20% (3g) are to be applied used on face, neck, arms, hands, legs and feet which is the proper use, i.e. use in compliance with the conditions on the label, once a day for adults and children (2-11 years).

Use on small children younger than 2 years should be prevented.

The below mentioned relevant risk mitigation measures should be implemented e.g.

- that a bittering agent should be included in the recipe of the product,
- Autan Pump Spray 20% is not to be used on children under the age of 2,
- that the daily number of application should be considered carefully in relation to the concentration of the product
- The label shall include information that the product should only be applied to arms, neck, hands, legs and feet and that contact to eyes should be avoided and that hands should be washed after use.
- The protection time derived from efficacy testing should always be stated on the product label.

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

2.1.3. Classification and Labelling

Classification and labelling of the active substance
No current classification and labelling of icaridin are given in accordance with the CLP Regulation 1272/2008.

No proposed classification / labelling for icaridin results from its physico-chemical, toxicological, environmental and ecotoxicological properties.

A harmonized classification and labelling according to Regulation (EC) No 1272/2008 is not available for icaridin. A CLH dossier will be submitted in spring 2020.

Classification of the product

Regarding its physico-chemical properties, the representative product Autan Pump Spray containing 20% icaridin would be classified / labelled according to Regulation 1272/2008 as given in the tables below. No classification results from the toxicological and ecotoxicological properties

Proposed classification of the representative product according to Regulation 1272/2008

Hazard symbol:	GHS02, GHS07 
Signal Word:	Warning
Hazard Class and Category	Eye irrit.2 Flam. Liq. 3
Hazard statements	H319: Category 2: Causes serious eye irritation H226: Flammable liquid and vapour
Precautionary statements	P305 + P351 + P338: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses if present and easy to do – continue rinsing. P337 + P313: If eye irritation persists get medical advice/attention. P101: If medical advice is needed, have product container or label at hand. P102: Keep out of reach of children. P210: Keep away from open flames. — No smoking. P501: Dispose of contents/container to [*in accordance with local/regional/national/international regulation* (to be specified)].

2.2. Summary of the Risk Assessment

2.2.1. Human Health Risk Assessment

2.2.1.1. Hazard identification and effects assessment

The toxicity data for the active substance icaridin has been generated with focus on the dermal route of exposure. Thus, repeated-dose toxicity, carcinogenicity, and reproductive toxicity testing has been conducted by the dermal route. A number of the dermal studies show no effects at the highest dose level. Studies performed with other animals than rats and human volunteers are not accompanied by dermal absorption data.
The absorption, metabolism and excretion of icaridin were investigated in rats and in human volunteers following dermal exposure. No data on ADME though oral route were available.
Both humans and rats predominantly excreted icaridin via the urine following dermal exposure. More than 93% of the dose absorbed by human volunteers was recovered from urine collected during the first 24 h after dosing. In rats, the majority of absorbed radioactivity was excreted within the first two days after treatment.
The metabolic pathway was similar in both species. Phase-I reactions included hydroxylation of the piperidine ring and the isobutyl moiety as well as oxidation of the terminal carbon in the hydroxy-ethyl side chain was the major metabolism pathway in rats. In humans, Phase-II metabolism was the major pathway. The vast majority of the metabolites appear both in rat and man, however in different concentrations. It was remarked that the radioactivity measured in rat and human plasma contains a mixture of the parent compound and the metabolites, not the parent compound itself for which the clearance should be derived. No metabolites are regarded to be of toxicological concern.
In the dermal ADME-study in rats by Ecker and Weber (1997) dermal absorption was investigated after single and repeated exposure (15 days) to a dose of 20 mg/kg, as well as single exposure to a high dose of 200 mg/kg bw. The results showed that dermal absorption was depending on the dose level but independent of sex. The amount absorbed through the skin ranged from 40-63% of the applied dose: The mean dermal absorption (skin and urine and organs) was 61% after a single dose of 20 mg/kg and 61% after repeated exposure to 20 mg/kg.bw/day. These results indicate that single dose administration compared to a repeated dose administration (pre-treated dose group) has no impact on the absorption fraction. After a single dose of 200 mg/kg the mean dermal absorption was 47%. Thus, the absorbed fraction decreased from low dose groups to high dose groups.
In an *in vivo* dermal penetration study by Warren & Sturdivant (1997) in rats, the average dermal absorption values (both sexes) after 8 hours exposure for applied icaridin doses of 8, 40 and 200 mg/kg bw/day were 23%, 19% and 17%, respectively.
The mean dermal absorption value of 47% from exposure over 24h to 200 mg/kg bw dose reported in the Ecker and Weber (1997) is used for the calculation of the internal dose in the subchronic dermal study in the rat (Sheets, 1995).
In human volunteers, the dermal penetration by icaridin was less than 4%. The uptake of dermally applied 14C-icaridin was investigated in 6 human volunteers (Selim,1994). The subjects were dosed for 8 hours with undiluted icaridin or a 15% solution of icaridin in ethanol.
The mean absorbed doses including tape stripping were 1.7% and 3.8% for the undiluted substance and the 15% formulation, respectively, after a 120-hour monitoring period. The mean value of 4% dermal penetration is used in the calculation of the internal exposure in humans.
Icaridin is of low acute oral, dermal and inhalatory toxicity and no classification is warranted. Icaridin is not irritating to the skin but slightly irritating to the eye fulfilling the criteria for a classification as Eye Irrit. 2, H319. Icaridin was not sensitising in the Maximisation test on guinea pigs.

Repeated administration of icaridin to rats via the dermal or oral route revealed effects on liver and kidney manifested as increased organ weights and the microscopic correlates, hepatocellular hypertrophy and degenerative nephropathy. The liver effects were not associated with functional changes and all effects were fully reversible within a 4-week post-exposure period. Therefore, these effects were appraised as being non-adverse. The kidney effects are only observed in male rats and therefore suggestive of a α2-microglobulin effect. However, as this mechanism was not shown, the effects on the kidney are taken into considered when setting NOAEL in repeated dose toxicity studies.

Repeated dermal exposure of rats to icaridin caused scab formation, acanthosis and hyperkeratosis at all doses in a dose-dependent relationship. Since the use of the substance is as a dermally applied repellent, contact with the skin over a prolonged period is expected and it could be argued that the skin reactions are relevant for the risk assessment the effect may therefore be relevant. However, the dosing regime in all repeated-dose dermal studies with icaridin in the rat featured continuous exposure to the test substance as no wiping or washing off prior to the next dosing was used. This exposure pattern thus differs from the intermittent pattern of consumer use of repellent products. In addition, this effect is not observed in the one year dog study or the chronic mouse study. It is therefore doubtful that the findings on rat skin are relevant for the human user. Therefore, the effect is regarded not to be relevant to the human risk assessment.

It could also be speculated whether acanthosis in the rat could have an impact on the dermal absorption in the dermal studies by decreasing the dermal absorption, but this was not apparent in a comparison of single-dose versus repeated-dose dermal absorption (both ~60%) in the ADME study by Ecker and Weber (1997). As the local effects were deemed of lesser relevance for humans, no risk characterisation for local effects was performed.

In the dermal one-year studies in rats and dogs, the high-dose level was set to 200 mg/kg/day. At nominally 200 mg/kg in male rats, an increased incidence of cystic liver degeneration with a clear dose-response relationship was observed at 200 mg/kg bw/day, with no effect on liver weight. The toxicological significance of the finding is unclear. No other systemic effects were seen in this study.

Icaridin was non-mutagenic in bacteria and in majority of the *in vitro* mammalian cells test. Clastogenic effects in a mammalian cell line were detected and overall the test was considered positive. Icaridin did not induce DNA-repair activity in primary rat hepatocytes. Icaridin was negative in an *in-vivo* micronucleus test in mice which was confirm in the ad hoc follow up group WG12017 where the majority of the members agreed with the eCA that the in vivo micronucleus test is acceptable and negative even though the test was not fully compliant with the OECD guideline (2016). Overall, the weight of evidence suggests that icaridin is of no genotoxic concern.

The combined chronic/carcinogenicity studies in rats and mice were also conducted using dermal exposure to icaridin. The highest nominal dose level was 200 mg/kg bw/day in both species. No adverse systemic effects were reported. The incidence of neoplastic lesions in rats was not affected by icaridin at any tested dose. In mice no skin tumours were observed under the condition of the cancer study. However, as no signs of toxicity were reported in the study at any dose level, no conclusion on long term or carcinogenic effects could be drawn.

Teratogenicity studies with dermal exposure to icaridin were conducted in rats and rabbits. In rats, the highest nominal dose tested was 400 mg/kg bw/day. As expected from the 90-day dermal toxicity study in rats, the dams in the high-dose group responded with increased liver weights. Embryotoxic effects in rats at maternally toxicity levels were noted as delayed ossification at 400 mg/kg/day in the dermal study. The study on rabbits included a high-dose level of 200 mg/kg/day. Neither does nor foetuses were affected by icaridin at any dose level. Dermal absorption of icaridin in rabbits is low (5.5%) and no data is available on serum levels of icaridin in the doe or the foetus. Therefore, the study is not valid for risk assessment purposes of the endpoint of teratogenicity.

In the oral dose range finding teratogenicity study in the rat (single dose of 500 mg/kg bw/day) for embryotoxic effects foetal ossifications were

noted. The embryotoxic effect correlated with maternal toxicity.
An oral developmental toxicity study in rabbits was conducted at the request of the RMS. The new oral rabbit study revealed maternal and foetal toxicity at 300 and 1000 mg/kg bw/day but no specific teratogenic effects on the foetuses. Maternal toxicity was seen as reduced feed intake, bw loss, clinical signs and abortion. Embryotoxicity were seen as reduced weights and retarded ossification at several sites.
The dermal two-generation reproduction study on rats found no treatment-related effects up to and including the highest nominal dose level of 200 mg/kg/day. However, identification of long-term or reproductive effects is generally not technically feasible on the basis of dermal studies alone, which indeed has been shown here.

A study focusing on potential neurotoxic effects in rats during subchronic exposure to icaridin found no effects at doses up to and including 200 mg/kg bw/day. Acute neurotoxicity testing found no substance-related neurotoxicological effects at the highest dose tested (2000 mg/kg bw).
As discussed above the inherent systemic toxicological properties of icaridin might not be fully covered by this dossier. However due to the specific application of icaridin as a repellent on the skin the dermal studies are relevant for the assessment of the dermal toxicity of icaridin in doses comparable to doses used on humans. The RMS considers the dossier acceptable for the risk assessment of icaridin because the foreseeable route of systemic exposure for this insect repellent is through the dermal route. However, this implies that the dossier is only sufficient to approve icaridin as an active substance in dermally applied insect repellents, and restriction to this use should be retained as the dossier does not cover all potential inherent systemic effects of the substance.

Table 2-1: Summary of LOAEL and NOAEL settings

Study	Species	Nominal doses [mg(kg bw/day]	End point	LOAEL [mg/kg bw/day]	NOAEL [mg/kg bw/day]	Reference
5-week oral	Rat	0,90/121,152/189,308/360 or1034/1141	Increased weights of the liver associated with histopathology, reduced BWG and nephropathy (♂)	308	152	[redacted], 2001a
14-week oral	Rat	0,100,150,300 or 1000	Reduced BW and BWG, increased kidney weights (♀+♂)	1033	301	[redacted], 2001b
13-week dermal	Rat	0,80,200,500 or 1000	Dose dependent change in liver	500	200	[redacted] 1995

Study	Species	Nominal doses [mg(kg bw/day]	End point	LOAEL [mg/kg bw/day]	NOAEL [mg/kg bw/day]	Reference
			weight associated with histopathology, renal tubular degeneration and chronic inflammation (♂)			
One-year dermal	Rat	0,50,100 or 200	Liver effects (cystic degeneration) (♂)	200	100	[redacted], 1996a
	Dog	0,50,100 or 200	No effects	> 200	200	[redacted], 1995
Chronic/carcinogenicity, dermal	Rat	0,50,100 or 200	No systemic effects/ No neoplastic effects	> 200	200	[redacted]n, 1996a
	Mouse	0,50,100 or 200	No systemic effects/ No skin tumours observed	> 200	200	[redacted], 1996b
Teratogenicity, dermal	Rat	0,50,200 and 400	Maternal liver weight ↑	400	200	[redacted], 1996b
			Delayed foetal ossification	400	200	
Teratogenicity, oral	Rabbit	0,100,300 or 1000	Maternal Bw and feed intake ↓, clinical signs and abortions	300	100	[redacted], 2008
			Foetal Bw ↓, delayed ossification	300	100	
	Rat		Parental: No effects	> 200	200	[redacted], 1996c

Study	Species	Nominal doses [mg(kg bw/day]	End point	LOAEL [mg/kg bw/day]	NOAEL [mg/kg bw/day]	Reference
Two-generation, dermal		0,50,100 or 200	Offspring: No effects	> 200	200	
Neurotoxicity, subchronic, dermal	Rat	0, 50,100 or 200	No effects	> 200	200	[redacted], 1996b

2.2.1.1. Reference value setting

2.2.1.1.1.1. *Assessment factor*

The TNsG on Annex I inclusion recommends that the risk characterisation be performed using an AOEL (AEL) approach. eCA DK is still of the view together with an independent expert from Danish National Food Institute, that the overall quality of the available database for icaridin does not give reason for reducing the default assessment factor of 100. The limited database of icaridin which mostly consist of dermal studies and as such might not elucidate the systemic intrinsic properties of the active substance due to the fact that doses in the dermal studies were generally low and technically not possible to increase due to the nature of the studies. In general, few effects were detected at the high doses, which might indicated low systemic dosing. The absent of dermal absorption studies for other species than rats gives rise to questions on how much of the active substance is actually absorbed and available to systemic metabolism and distribution. Furthermore the premises and criteria in the WHO paper are not fulfilled for using a CSAF (chemical specific assessment factor= reducing the default assessment factors) for icaridin.

However, this was overruled by Ad hoc group (after WG I 2017), which found the available toxicokinetics studies, human and rat kinetic data sufficient to reduce the interspecies kinetic factor from 4 to 1.34 resulting in an overall assessment factor of 2.5 x 2 x 1.34 x 10 = 67 for dermal studies but to keep default 100 for oral studies. From the minutes of the ad hoc follow up group:

"*Some members noted limitations in the proposal from the applicant to reduce the interspecies AF for toxicokinetics from 4 to 1.34, based on WHO/IPCS paper on chemical specific assessment factor. The following deficiencies were pointed out: the active chemical moiety has not been identified, and the assumption that the metabolism in humans differs from the rat quantitatively was not sufficiently proven. Therefore, it was reiterated that the reduction of the interspecies factor is not justified.*

Other members considered that the WHO/IPCS approach on chemical specific assessment factor should be applied with flexibility. Moreover, the identified limitations were not regarded as sufficient to reject the reduction of the AF. To take into account the limitations, it was proposed to apply an additional AF of 2 to the original applicant proposal. The other members accepted this approach."

Legal basis:
When a dossier has been submitted before 1st September 2013, the respective Biocidal Product Directive 98/8/EC provisions apply. Consequently, the provisions of the Biocidal Product Directive do not exclude that historical human data can be used to lower the margins of safety resulting from tests on vertebrates for the purpose of the risk assessment of such active substance.

The situation is different for dossiers submitted after 1st September 2013, by a member state, as the Biocidal Product Regulation (EU) No 528/2012 provisions apply, and human data therefore cannot be used to lower the margins of safety, resulting from tests on vertebrates for the purpose of the risk assessment of such active substances. The same apply for granting product authorisations under the Biocidal Product Regulation (EU) No 528/2012.

In the case of icaridin, as the draft competent authority report was submitted before 1st September 2013, human data can be used to lower the margins of safety resulting from tests on vertebrates for the purpose of this risk assessment.

The Commission informed eCA DK in February 2019 that the AEL value set at the approval stage (using human data because the draft CAR was submitted before 1st September 2013) can also in this case be used for product assessment provided that no re-assessment of AEL value would be needed at the BP authorisation stage (e.g. due to new data submitted).

2.2.1.1.1.2. *AEL derivations*

AELs for short-term, medium-term and long-term exposure are calculated by applying an assessment factor to the internal NOAEL on the critical effect divided by the relevant assessment factor.

The 5-week oral NOAEL of 152 mg /kg bw/day is used for the derivation of the $AEL_{short\ term}$. In lack of information as to the oral absorption, 100% is assumed, and no correction for oral absorption is included in the calculation of $AEL_{short\ term}$:

$AEL_{short\ term}$ derivation			
AEL short term			
NOAEL 5-week oral, rat (*Wahle 2001a)*	oral absorption, default	Assessment factor	$AEL_{short\ term}$
152 mg/kg bw/day	100%	100	1.5 mg/kg bw/day

The most relevant NOAEL for icaridin in repellent products is the dermal 13-week NOAEL of 200 mg/kg bw/day. This value needs to be corrected for the estimated dermal penetration over rat skin of 47% in order to calculate the systemically available dose. As a result, the following $AEL_{medium\ term}$ is derived:

$AEL_{medium\ term}$ derivation			
AEL medium term			
NOAEL 13-week dermal, rat (*Sheets, 1995)*	Dermal absorption, rat	Assessment factor	$AEL_{medium\ term}$
200 mg/kg bw/day	47%	67	1.4 mg/kg bw/day

A long term AEL is derived on the basis of the one year dermal study in the rat (NOAEL 100 mg/kg bw/day) with correction for the dermal availability (*Ecker and Weber*, 2007), in order to calculate the systemically available dose. As a result, the following AEL $_{\text{long term}}$ is derived:

AEL$_{\text{long term}}$ derivation			
AEL long term			
NOAEL 1 year dermal, rat (*Wahle and Christenson 1996a)*	Dermal absorption, rat	Assessment factor	AEL $_{\text{long term}}$
100 mg/kg bw/day	47%	67	0.7 mg/kg bw/day

ADI/ARfD

The Ad hoc follow up group January 2017 agreed to the following reference values.

The ADI is 0.75 mg/kg bw/d based on the NOAEL of the 14-week feeding study, rounded to 150 mg/kg bw/d, and the default AF of 100 and an additional AF of 2 for duration extrapolation.

An ARfD is not derived. Icaridin is not acute toxic.

2.2.1.1. Exposure assessment and risk characterisation

Repellents are applied on uncovered skin: on the head, hands, arms, legs and feet, which corresponds to 64 % [2]of the total skin area (HEEG opinion on "Default human factor values for use in exposure assessments for biocidal products" and recommendations of Technical Notes for Guidance (TNsG) – Human Exposure to Biocidal Products (2002) as revised by User Guidance version 2 (April 2007). It is considered that the exposed body surface area of an adult represents 64% of the total body surface (Pest Control Products Fact Sheet). This corresponds to the situation when a short-sleeved shirt (i.e. T-shirt) and shorts are worn. Exposure takes place dermally and orally. Repellents are applied on the uncovered skin: on the head, hands, arms, legs and feet. Exposure takes place dermally and orally. The primary exposure path is the dermal path, as insect repellents are

[2] The use of 64% treated body surface area was agreed with ECHA and accepted by the WG HH at the time of evaluation (January 2017). A new treated body surface of 55% was established in the revised HEAdhoc Recommendation end of 2017.

usually applied by direct spraying onto skin and then spread by hand. Hand-to-mouth contact may occur, leading to the ingestion of some of the repellent. Exposure due to hand-mouth contact will mainly be important for children. It is evaluated that exposure via inhalation normally is low or absent due to the use outdoors, and because use indoors mainly takes place in the summer in situations where there is generally a high ventilation rate. Indirect exposure may occur through drinking water contamination.
Calculation of exposure in a Tier I is based on TNsG default assumptions on use pattern for insect repellents, e.g. area of body treated and application rates. In a Tier II, refinement of the exposure calculation was introduced in accordance with the proposed label requirements for the representative product that exclude the use of the product for children under the age of 2, so that children of 10.5 mths are excluded from the calculations. Also, the addition of a bittering agent to the product and product specific data on application rate and frequency are included. In Tier III, the treated surface of the body is corrected in accordance with an EPA survey.
Calculation of drinking water levels showed negligible levels of icaridin.
A summary of the results of the calculation of the exposure to icaridin through the use of Autan Pump Spray 20% following the recommendations of the Technical Notes for Guidance (TNsG) – Human Exposure to Biocidal Products (2002) as revised by User Guidance version 2 (April 2007), HEEG Opinion on "Default human factor values for use in exposure assessments for biocidal products" and values on bodyweight and body part surface areas for children (3-6 years and 2-3 years) from RIVM report General Fact Sheet General default parameters for estimating consumer exposure - Updated version 2014 is shown below in Table 2.2.

Table 2-2: Assumptions and results of combined exposure assessment (dermal and oral exposure). For the primary exposure Tier I dermal is 2 application while Tier II dermal is 1 application. Secondary Tier I oral (one application).

Tier	Population	Body weight [kg]	Amount b.p. per application [mg]	Number of applications [1/day]	Dermal uptake	Oral uptake	Total systemic dose [mg/kg bw/day]
Tier II dermal, Tier I oral	Adult	60.0	3000	1	0.40	Not relevant[1]	0.40
	Children (6-11 years)	23.9	1604	1	0.54	Not relevant[1]	0.54
	Children (2-6 years)	15.7	1193	1	0.61	Not relevant[1]	0.61
					0.64		
	Toddlers	10.0	828	1	0.66	1.32[2]	1.98
	Infants	8.0	707	1	0.71	1.41[2]	2.12
Tier I dermal, Tier I oral	Adult	60.0	3000	2	0.80	Not relevant[1]	0.80
	Children	23.9	1604	2	1.08	Not relevant[1]	1.08

Tier	Population	Body weight [kg]	Amount b.p. per application [mg]	Number of applications [1/day]	Dermal uptake	Oral uptake	Total systemic dose [mg/kg bw/day]
	(6-11 years)						
	Children (2-6 years)	15.7	1193	2	1.22	Not relevant[1]	1.22
	Toddlers	10.0	828	2	1.33	1.32[2]	2.65
	Infants	8.0	707	2	1.42	1.41[2]	2.83

[1] Oral exposure by hand-to-mouth transfer is not considered to be a significant and relevant route of exposure of adults and children between 2-11 years since Bitrex strongly discourages oral uptake.

[2] The hand to mouth behaviour is more frequent in small children and based on concerns that Bitrex may not be sufficiently effective in protecting small children. Bitrex has been demonstrated effective at deterring product ingestion by children 18-47 months (Berning et al., 1982).

2.2.1.1. Risk characterisation for human health

AEL approach

The internal dose following dermal primary exposure to the icaridin-containing repellent product, Autan Pump Spray 20%, and the comparison with the relevant $AEL_{medium\ term}$, is summarised in Table 2.2-3.

Table 2.2-3: AEL approach: Risk assessment for exposure to Autan Pump Spray 20%[3]. Tier I dermal (2 application per day) & Tier II dermal (1 application per day). Secondary oral exposure Tier I (1 application) $AEL_{medium\ term}$ of 1.4 mg/kg bw/day using human data to reduce the assessment factor to 67.

[3] Risk characterisation according to Technical Notes for Guidance (TNsG) – Human Exposure to Biocidal Products (2002) as revised by User Guidance version 2 (April 2007), HEEG Opinion on "Default human factor values for use in exposure assessments for biocidal products" and values on bodyweight and body part surface areas for children (3-6 years and 2-3 years) from RIVM report General Fact Sheet General default parameters for estimating consumer exposure - Updated version 2014 and compared with recently revised Recommendation 11 (Jan 2018)

Table 2-3: Assumptions and results of combined exposure assessment (dermal and oral exposure). For the primary exposure Tier I dermal is 2 application while Tier II dermal is 1 application. Secondary Tier I oral (one application).

Tier	Population	Body weight [kg]	Amount b.p. per application [mg]	Number of applications [1/day]	Dermal uptake	Oral uptake	Total systemic dose [mg/kg bw/day]
Tier II dermal, Tier I oral	Adult	60.0	3000	1	0.40	Not relevant[1]	0.40
	Children (6-11 years)	23.9	1604	1	0.54	Not relevant[1]	0.54
	Children (2-6 years)	15.7	1193	1	0.61	Not relevant[1]	0.61
					0.64		
	Toddlers	10.0	828	1	0.66	1.32[2]	1.98
	Infants	8.0	707	1	0.71	1.41[2]	2.12
Tier I dermal, Tier I oral	Adult	60.0	3000	2	0.80	Not relevant[1]	0.80
	Children (6-11 years)	23.9	1604	2	1.08	Not relevant[1]	1.08
	Children (2-6 years)	15.7	1193	2	1.22	Not relevant[1]	1.22
	Toddlers	10.0	828	2	1.33	1.32[2]	2.65
	Infants	8.0	707	2	1.42	1.41[2]	2.83

[1] Oral exposure by hand-to-mouth transfer is not considered to be a significant and relevant route of exposure of adults and children between 2-11 years since Bitrex strongly discourages oral uptake.

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Tier* / Parameter	Tier I dermal, Tier I oral						Tier II dermal, Tier I oral					
	Adults	Child (6-11y)	Child (2-6y)	Child (2-3y)	Toddler (1-2y)	Infant (6-12 m)	Adults	Child (6-11y)	Child (2-6y)	Child (2-3y)	Toddler (1-2y)	Infant (6-12 m)
Total systemic exposure [mg/kg bw/day]	0.8	1.08	1.22	2.56	2.65	2.83	0.4	0.54	0.61	1.92	1.98	2.12
AEL medium term [mg/kg bw/day]	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4
AEL consumption	**57%**	**77 %**	**87 %**	**183 %**	**189%**	**202 %**	**29%**	**39 %**	**44 %**	**137 %**	**141%**	**151 %**

Conclusion on the Risk Characterisation

Risk characterisation for human health for icaridin was based upon the representative product Autan Pump Spray 20%, when comparing the effects on human health with exposure levels. The overall outcome of the risk assessment for humans which covers use of the product Autan Pump Spray 20% on face, neck, arms, hands, legs and feet which is the proper use, i.e. use in compliance with the conditions on the label, shows acceptable use for adults and children (2-11 years) applying Autan Pump Spray 20% twice a day. However due to the environment risk assessment an overall use of once per day is currently only acceptable. Use on small children younger than 2 years should be prevented.

The risk characterisation is based on the assessment of the realistic worst case as presented by the applicant and referring to the TNsG on human exposure. The use of the representative product twice a day is considered acceptable for adults and children (2-11 years), based on the calculations above. Furthermore, the assessment demonstrated that for children below 2[5]

[4] Risk characterisation according to Technical Notes for Guidance (TNsG) – Human Exposure to Biocidal Products (2002) as revised by User Guidance version 2 (April 2007), HEEG Opinion on "Default human factor values for use in exposure assessments for biocidal products" and values on bodyweight and body part surface areas for children (3-6 years and 2-3 years) from RIVM report General Fact Sheet General default parameters for estimating consumer exposure - Updated version 2014 and compared with recently revised Recommendation 11 (Jan 2018)

[5] *"At the time of the exposure calculations and WGI2017 of Icaridin no age group between 2 - 6 years was stated in Recommendation 115. Therefore eCA used default values from RIVM General Factsheet from children between 2-3 years and 3-6 years. However it was commented in the Final consolidated RCOM (Dec 2016) to the CAR discussed at WGI2017 that a bodyweight of 12-13 kg from the RIVM General Factsheet is more applicable for a 2-year old child than a 3 year old and therefore the risk characterisation is for "Child, 2 yrs", not "Child, 3 yrs". The eCA agreed to amend and change the reference to child age from 3 years to 2 years. The restriction on the use of icaridin product should be on children under the age of 2 instead of the age of 3. This should have been amended but was mistakenly not done. In November 2017 a revision of Recommendation 11 added a new age group "Children (2 to*

years, toddlers and infants the exposure after dermal and oral exposure resulted in unacceptable risk from the use of Autan Pump Spray 20% as an insect repellent due to exceedance of the AEL.
Overall, it is concluded that an unacceptable risk has been identified for children below 2 years from the use of Autan Pump Spray 20%.

The below mentioned relevant risk mitigation measures should be implemented e.g.

- that a bittering agent should be included in the recipe of the product.
- Autan Pump Spray 20% is not to be used for children under the age of 2.
- that the daily number of application should be considered carefully in relation to the concentration of the product
- Autan Pump Spray 20% should not be applied on the trunk, additional labelling should include the phrase "Only apply to face, arms, neck, hands, legs and feet. The label shall include information that the product should only be applied to face, arms, neck, hands, legs and feet and that contact to eyes should be avoided and that hands should be washed after use.

<6 years, 15.6 kg)" and this was agreed upon (publication date Jan 2018). This was commented by ECHA during the commenting period (Nov 2018). The default values used in icaridin for age category from 3 to < 6 years old (i.e. body weight, body surface area) corresponded however quite well to the default values for the age category 2 to < 6 years old stated in the revised HEAdhoc Recommendation. Therefore exposure assessment in the CAR will be adapted from group 3 < 6 years old to 2 to < 6 years old. However the former calculation from Child (2-3 years) will not be deleted in the CAR at this late stage."

Secondary (indirect) exposure via food:

Icaridin is used in repellent products that are applied directly onto the skin. Icaridin is not used for and/or during food production, or in rooms where food is produced processed or stored. Contamination of food and feeding stuff has generally been considered to be negligible for PT19 products (in line with previously evaluated PT19). Recent measurements in some food items (e.g. berries and mushrooms) for another dermally applied repellents however suggest a possible transfer. Therefore a*n assessment of the risk in food and feed areas may be required at product authorisation where use of the product may lead to contamination of food and feeding stuffs."*

2.2.2. Environmental Risk Assessment

2.2.2.1. Fate and distribution in the environment

Considering the hydrolytic stability of icaridin determined under environmental relevant pH and temperature conditions, it is not expected that hydrolytic processes will contribute to the degradation of icaridin in the environment.
Due to its lack of UV absorbance in the sunlight region icaridin is not degradable by direct photodegradation in water.

The calculation indicates a rapid degradation of icaridin when entering the atmosphere. Hence, air will not be an environmental compartment of concern for the compound used in repellents.

Based on the Modified OECD Screening Test, icaridin is concluded to be not ready biodegradable. Based on the results of the Zahn-Wellens/EMPA-Test, icaridin is also not inherently biodegradable.

Biodegradation of icaridin in freshwater has a DT_{50} value at 12°C of 6.1 days; however icaridin-acid has a DT_{50} value of 545 days at 12°C, suggesting that icaridin is not persistent but that icaridin-acid is a P/vP substance. This is confirmed by degradation data in the sediment where a DT_{50} value at 12°C of 4.1 days for icaridin and a DT_{50} value of 1000 days at 12°C for icaridin-acid is derived.

Degradation of icaridin in both compartments of a water sediment system proceeded via formation of icaridin-acid. The results reveal that no further metabolite at amounts > 5% were formed during the study in the water phase. Icaridin-acid could also be found in the sediment; however, no further stable metabolites were determined in the sediment. No volatile, organic transformation products were formed during the test duration.

It should be noted that there is a remarkable difference between the degradation rate in the water/sediment study compared to degradation rate in soil. The reason could be the difference in oxygen availability; however, the rate of biodegradation in surface water, soil and sediment is related to the structure and concentration of substances, microbial number, organic content and temperature. Hence, not only the oxygen content, but a variety of factors influences the degradation behaviour of a compound in water/sediment and soil systems. The degradation of icaridin in soil incubated under aerobic conditions proceeds primarily via the formation of icaridin-acid and of bound residues (6.7% at test termination). The half-lives of icaridin is 0.05 days at 12°C but for icaridin-acid a DT_{50} (12°C) of 3.3 days is calculated.

Based on the estimated K_{oc} value of 85.11 L/kg icaridin can be assumed to have a high potential for mobility in soils. The K_{oc} value of icaridin-acid is estimated to 401 L/kg and therefore this metabolite has a significant lower leaching potential; however icaridin-acid is still considered to have a moderate-high potential for mobility in soils.

2.2.2.2. Hazard identification and effects assessment

A base data set of effect studies is available for the environmental effect assessment for icaridin. QSAR modelling with VEGA v1.1.3, ECOSAR v 1.11 and OECD QSAR Toolbox 3.4.0 estimates the aquatic toxicity of icaridin to be significantly higher that the results from experimental data reveal. Furthermore, icaridin-acid is a factor of 2 more toxic than icaridin itself in most cases. Thus, the toxicity of the metabolite icaridin-acid is estimated to be in the same range as icaridin based on the QSAR estimation. However, if the QSAR outcomes for the metabolite (being worst case) is used to calculate the PNECwater a value of 60.8 ug/L occur which is about a factor of 5 lower than the experimental values of icaridin (PNEC water 314.2 ug/L).

Based on the uncertainty of the QSAR results it was decided at the Env WG-I-2017 to set up an ad-hoc follow-up working group to discuss the effects assessment of the metabolite icaridin-acid. The conclusions from the ad-hoc follow up group were to assume that the metabolite is 5 times more toxic than the parent. Consequently, the PNEC for icaridin-acid will be derived from the ecotoxicity data on icaridin by using a factor of 5 to account for the observed uncertainty. The same approach is followed in the PNEC derivation for STP, water (and sediment) and soil, and the risk assessment of icaridin-acid has been revised with the updated PNEC values.

The ad hoc follow-up group also agreed that no further effect data on icaridin-acid will be requested at this stage.

Aquatic compartment

Icaridin:

One valid acute study with fish was provided for icaridin. The study revealed a LC_{50} of 173 mg test substance/L based on measured concentrations. When recalculated to reflect the content of icaridin in the test substance (97.9%) this equals 169.4 mg a.s./L. Under the test conditions icaridin was stable, resulting in mean measured concentrations between 97 % and 101 %. Two other acute toxicity tests with fish were performed; however, the results of these studies are based on static tests with nominal concentrations and the tests are a pre-test and an orientating test respectively. These results can be regarded as additional information.

One valid chronic toxicity study with zebrafish was provided (an Early-Life stage Study according to OECD Guideline 210). For a test duration of 32 days, the overall NOEC was determined to be 3.14 mg a.s./L.

One valid acute study with *Daphnia magna* was provided. No effects of the test substance on the daphnids were observed at the highest concentration tested (103 mg a.s./L). Thus, the EC_{50} > 103 mg a.s./L. The measured test substance concentrations at the end of the 48 hours exposure period were not lower than at the beginning of the test.

A valid chronic toxicity test with Daphnia magna is available determining the influence of icaridin on development, reproductive capacity and behaviour over 21 days under static-renewal exposure. The overall NOEC of 50 mg a.s./L is based on a decreased final body length of parental animals exposed to the highest tested concentration of 100 mg/L and a distinctly lower number of offspring from these adults.

One 72 h growth study with the green alga *Scenedesmus subspicatus* was performed. The growth-rate based E_rC_{50} was 87.3 mg a.s./L. The NOEC was determined to be 54.8 mg a.s./L. Analytical analyses showed good agreement between mean measured concentrations and nominal concentrations; which was; however only measured at the beginning of the test. Thus, the nominal concentrations were used for all calculations. In this case it was accepted to use

the algae endpoints based on nominal concentration because icaridin is stable to hydrolysis, not degraded by direct photodegradation in water, and is neither readily nor inherently biodegradable. Furthermore, in both the acute fish test and the acute daphnia test, the measured concentration at the end of the exposure period was not lower than at the beginning of the test.

The lowest NOEC value (Zebra fish) of 3.14 mg a.s./L is considered for the PNEC calculation. Since long-term NOECs are available from all three trophic levels, an assessment factor of 10 was applied to the lowest of three long-term NOEC values. A **$PNEC_{water}$ of 0.314 mg icaridin/L has been derived based on the available data.**

Icaridin-acid:

$PNEC_{water}$ = 0.314 mg icaridin-acid/L /5 = 0.063 mg icaridin-acid/L.

Sediment:

Icaridin:

No data for effects on sediment organisms are available. According to BPR guidance Vol. IV Part B Section 3.5.2 an effect assessment for sediment should be considered in cases where log Kow $\geq$ 3 applies; however for icaridin a log Kow of 2.11 and log Koc of 1.93 was found. Therefore, the equilibrium partition method (EPM) has been applied to identify a potential risk to sediment organisms as a screening approach. The calculated **$PNEC_{sed,EPM}$** for icaridin is **0.84 mg icaridin/kg wwt.**

Icaridin-acid:

For the sediment no toxicity data are available. The PNEC value has been calculated based on the equilibrium partitioning method and $PNEC_{water}$.

$PNEC_{sed}$ = 0.596 mg icaridin-acid/kg wwt

Inhibition of microbial activity:

Icaridin:

Icaridin showed only a slight inhibitory effect on activated sludge in a valid test. 50% inhibition of microbial activity was determined resulting in an EC_{50} = 1087 mg a.s./L. An assessment factor of 100 was applied to calculate the $PNEC_{STP}$.

$PNEC_{STP}$ = 10.87 mg icaridin/L.

Icaridin-acid:

$PNEC_{STP}$ = 10.87 mg icaridin-acid/L / 5

= 2.17 mg icaridin-acid/L

Terrestrial Compartment

Icaridin:

A 21-day study was performed with icaridin in a growth chamber under controlled test conditions with three plant species: *Brassica napa*, *Glycine max*, *Avena sativa*. The test was performed in accordance with OECD Draft Guideline 208. *Brassica napus* was the most sensitive plant to icaridin. EC_{50} based on reduction in fresh weight was 97.79 mg a.s./kg and NOEC based on reduction in shoot height was < 12.35 mg a.s./kg.

The effect of icaridin on earthworms was studied on *Eisenia fetida*. The test was carried out according to OECD Guideline 207 (1984). For earthworms the acute LC_{50} is 985 mg a.s./kg dwt soil).

No data has been submitted for evaluation of the toxicity to terrestrial micro-organisms and no data has been required for this endpoint. Furthermore, the aquatic tests demonstrate that micro-organisms most likely not are among the most icaridin-sensitive species.

Acute toxicity of icaridin to birds is not available and was not required.

One subacute toxicity test of icaridin to birds was submitted. The five-day LC_{50} for Bobwhite quail was determined to be > 5000 mg a.s./kg diet and the NOEC ≥ 5000 mg a.s./kg diet. Based on the results, icaridin can be considered as non-toxic to birds.

For the effects assessment of the soil compartment an acute earthworm test and results for terrestrial plants are available:

- Earthworm *(Eisenia fetida*), acute: LC_{50} (14 days) approx. 985 mg Icaridin/kg dwt soil,
- Terrestrial plants: Lowest relevant EC_{50} (21 days): 97.79 mg icaridin/kg soil and NOEC: <12.35 mg icaridin/kg dwt soil

The calculation of the $PNEC_{soil}$ is based on the test with non-target plants (EC_{50} value = 97.79 mg icaridin/kg dwt soil. An assessment factor of 1000 is applied to the LC_{50} value of the acute test with terrestrial plants according to table 16 of the TGD.

$PNEC_{soil}$ = 97.79 mg icaridin/kg dwt soil / 1000

= 0.0978 mg icaridin/kg dwt soil

= 0.087 mg icaridin/kg wwt soil

Icaridin-acid:

For the metabolite icaridin-acid the PNEC value/5 for soil will be used.

$PNEC_{soil}$ = 0.017 mg icaridin-acid/kg wwt soil

Atmosphere:

Icaridin:

Due to the low vapour pressure (3.4 x 10-2 Pa at 20°C) and the Henry´s Law constants (9.1 x 10-4 $Paxm^3xmol^{-1}$ at 20°C) only low volatilisation and transfer to the atmosphere is expected. Additionally, the tropospheric half-lives of icaridin in air was estimated using the AOPWIN program to 6.87 hours. Hence, air will not be an environmental compartment of concern for icaridin used in repellents and accumulation and long-range transport of icaridin in the atmosphere followed by wet or dry deposition is not expected.

Non compartment specific effects relevant to the food chain (secondary poisoning):

Icaridin:

The log K_{OW} is 2.11, suggesting a low bioaccumulation potential. Measured BCF values range between 0.9 and 1.8 L/kg related to wet weight and 10 to 19 L/kg related to lipid content, but since the depuration is rapid no risk for bioaccumulation is anticipated. The risk of secondary poisoning is therefore expected to be low via ingestion of potentially contaminated food (e.g., fish, earthworms) by birds or mammals.

Icaridin-acid:

For icaridin-acid a Log Kow of 3.08 is estimated by EPIWIN, however the BCF was estimated to 47 L/kg. Therefore, the B criterion is not fulfilled.

2.2.2.3. Exposure assessment and risk characterisation

Exposure assessment

For the environmental exposure estimation data about one representative biocidal product containing 20% a.s. is provided by the applicant. An application rate of 2.92 g product, corresponding to 0.584g icaridin, per person per day has been used for the environmental exposure assessment.

According to the intended use emission to the environment are expected only for the life-cycle step "non-professional use". Two different models were applied to estimate the emissions to the environment. First, a consumption-based assessment was conducted incorporating specific information about the product and the intended use. The second model applied is a tonnage-based model, which is more generic approach estimating emission from the EU-produced and/or imported tonnage of the assessed active substance.

For the environmental exposure the emission scenario document endorsed by the Environment Working Group in March 2015 has been used (ECHA, 2015). Emissions arising from the use of insect repellents from human skin are based on those for human hygiene biocidal products (PT 1, Aa van der & Balk, 2004). PEC calculations were performed in EUSES.

Furthermore, PEC values were calculated based on a tonnage approach.

Consumption Scenario

The main emissions of this use to the environment occur during the removal phase of the insect repellent. Removal of the product from human skin can either take place:

1. Via showering or bathing of humans who have used an insect repellent and/or washing of the clothes treated with the repellent formulation. Sewage treatment plants are the primary compartment for emissions whereas surface water bodies (including sediment) as well as the soil compartment (including groundwater) are secondary exposed compartments for remnants via STP effluents and sewage sludge applications, respectively.

2. Via direct release to surface water if people with treated skin go swimming in outdoor surface waters (only for human skin repellents).

Insect repellents are employed by non-professional users of the general public. The product may stay on the human skin for a longer period after the application. During this period of 'service life' the product may evaporate or be dermally absorbed, transfer to the clothing and is removed when clothing is washed. Remains of the product on the human skin are removed during showering or bathing.

The product is directly released with wastewater at washing and bathing after application or indirectly when substances that have been transferred to clothing are removed at washing. Hence, a conceivable route of intake for Icaridin into surface water bodies is the release of STP effluents containing Icaridin (and/or its degradation products).

Lakes used for bathing may also contain icaridin residues due to icaridin-treated people going swimming. Due to the use pattern of icaridin, potential direct contamination of soil is considered negligible, but sludge from STP might be applied to agricultural land. Therefore, the STP sludge concentration and the concentrations in soil and pore water have been calculated.

Other potential routes of emission are those to the atmosphere, either due to the volatilisation of the compound from the skin surface or as a result of volatilisation from the sewage treatment plant.

The potential emission to soil by wet and dry exposition from the atmosphere is assessed to be insignificant due to the short atmospheric half-life of icaridin.

In summary, the environmental compartments exposed from the use of icaridin within the representative product are the aquatic environment including STP, surface water (via STP) and sediment, soil and groundwater and the air compartment. A determination of regional concentrations for the proposed use pattern of icaridin has not been made since the insect repellent use is not considered to be of sufficiently large scale to warrant such prediction.

Tonnage Scenario

The tonnage-based environmental exposure has been assessed applying the EU Technical Guidance Document (TGD) on Risk Assessment (2003). These calculations were performed in EUSES. Since the assessment is based on confidential data, the calculations and PECs can be found in the confidential annex.

Summary of PECs

The PECs for the Consumption Scenario and the Tonnage Scenario have been estimated for the aquatic compartment including STP, surface water, and sediment, and for the terrestrial compartment including soil and groundwater. As the $PEC_{groundwater}$ estimation for icaridin-acid according to the pore-water calculation model of the TDG resulted in unacceptable risks for the groundwater after sewage sludge application, the groundwater risk assessment was refined by using FOCUS model PEARL.

Risk characterisation

Stages of the product's life-cycle considered as relevant for the Consumption Scenario are surface application to human skin for non-professional use. Sewage treatment plants are the primary compartment for emissions whereas surface water bodies (including sediment) as well as the soil compartment (including groundwater) are secondary exposed compartments for remnants via STP effluents and sewage sludge applications, respectively. However direct release to surface water is also expected if people with treated skin go swimming in outdoor surface waters.

The same environmental emission pathway applies to the Tonnage Scenario; however, as the

consumption-based approach yielded higher emissions compared to the tonnage approach (the tonnage based PEC/PNEC ratios are all below 1) the consumption evaluation represent the realistic worst case.

Aquatic Compartment

PEC/PNEC ratios for icaridin for different exposure situations concerning the hydrosphere

Exposure scenario	Environmental compartment	PEC	PNEC	PEC / PNEC
Via post-consumer release scenario	STP	287 µg/L	10 870 µg/L	0.026
	Surface water	29 µg/L	314.2 µg/L	0.092
	Sediment	76 µg/kg wwt	840 µg/kg wwt	0.090
Based on the swimming scenario	STP	-	-	-
	Surface water	3.7 µg/L	314.2 µg/L	0.012
	Sediment	9.7 µg/kg wwt	840 µg/kg wwt	0.012

PEC/PNEC ratios for icaridin-acid for different exposure situations concerning the hydrosphere

Exposure scenario	Environmental compartment	PEC	PNEC	PEC / PNEC
Via post-consumer release scenario	STP	301 µg/L	2170 µg/L	0.139
	Surface water	30 µg/L	63 µg/L	0.476
	Sediment	286 µg/kg wwt	596 µg/kg wwt	0.480
Based on the swimming scenario	STP	-	-	-
	Surface water	4.1 µg/L	63 µg/L	0.065
	Sediment	39 µg/kg wwt	596 µg/kg wwt	0.065

Estimated PEC/PNEC ratios for STP, surface water and sediment are < 1. Thus, it is considered that there is no risk for the aquatic environment caused by icaridin dermally applied in repellent product in the concentrations evaluated.

Terrestrial Compartment including Groundwater

Due to the use-pattern of icaridin, direct contamination of the environment via the pathway soil is negligible. However, STP sludge might be applied to soils. Therefore, the STP sludge concentration and the concentrations in agricultural soil averaged over 30 days were

calculated.

PEC/PNEC ratios for different exposure situations concerning the terrestrial compartment

Exposure scenario	Environmental compartment	PEC	PNEC	PEC / PNEC
Icaridin Via post-consumer release scenario	Soil-30 days	0.00003 mg/kg wwt	0.087 mg/kg wwt	0.0003
	Groundwater (porewater of agricultural)	0.003 µg/L	0.1 µg/L	acceptable
Icaridin-acid Via post-consumer release scenario	Soil-30 days	0.009 mg/kg wwt	0.017 mg/kg wwt	0.529
	Groundwater (porewater of agricultural soil)	0.2 µg/L	0.1 µg/L	**Not acceptable**

Estimated PEC/PNEC ratios for soils are < 1 for both icaridin and icaridin-acid. The EUSES calculation gave concentrations in porewater/groundwater exceeding the legal drinking water limit for single pesticide substances of 0.1 µg/L for icaridin-acid but not for icaridin. However, the Tier 2 calculations for icaridin and icaridin-acid with FOCUS PEARL resulted in 80th percentile PEC_{gw} below 0.1 µg/L for all 9 scenarios. A risk arising for humans through drinking water is therefore not likely.

Secondary Poisoning

The log K_{OW} is 2.11, suggesting a low bioaccumulation potential. Measured BCF values range between 0.9 and 1.8 L/kg related to wet weight and 10 to 19 L/kg related to lipid content, but since the depuration is rapid no risk for bioaccumulation is anticipated. The risk of secondary poisoning is therefore expected to be low via ingestion of potentially contaminated food (e.g., fish, earthworms) by birds or mammals. For icaridin-acid a Log Kow of 3.08 is estimated by EPIWIN, however the BCF was estimated to 47 L/kg. Therefore, the B criterion is most likely not fulfilled.

Furthermore, FOCUS PEARL calculations revealed groundwater concentrations of icaridin and Icaridin-acid below 0.1 µg/L. A significant exposure of humans through drinking water is therefore not likely.

2.2.2.4. PBT and POP assessment

The PBT assessment was performed in line with the REACH legislation (Guidance on Information Requirements and Chemical Safety Assessment Part C: PBT/vPvB assessment, and Chapter R.11: PBT/vPvB assessment, Version 2.0), following the PBT and vPvB criteria laid down in Annex XIII of the REACH Regulation (EC) No 1907/2006. In addition, exclusion criteria according to Article 5(1) of the BPR were assessed according to ECHA Guidance on BPR Vol. IV Part B. The PBT assessment presented covers both icaridin and icaridin-acid.

P Assessment

P criterion: Half-life > 40 d freshwater or >120 d in freshwater sediment or > 120 d in soil

vP criterion: Half-life > 60 d water or > 180 d in freshwater sediment or >180 d in soil

Icaridin is not ready or inherently biodegradable but based on a water/sediment study is not persistent. Based on an aerobic water/sediment study icaridin-acid can be considered as P and vP (DT_{50} value of 545 days at 12°C for freshwater and 1000 days for sediment. The degradation of icaridin in soil incubated under aerobic conditions proceeds primarily via the formation of icaridin-acid and of bound residues. A fast degradation in soil was seen for both icaridin and icaridin-acid (hours to a few days)

B-Assessment

B-criterion: BCF > 2000 L/kg wwt

vB-criterion: BCF > 5000 L/kg wwt

The bioaccumulation for fish indicate that icaridin does not fulfil the B criteria (measured BCF values range between 0.9 and 1.8 L/kg related to wet weight and 10 to 19 L/kg related to lipid content). For icaridin-acid a Log Kow of 3.08 is estimated by EPIWIN, however the BCF was estimated to 47 L/kg. Therefore, the B criterion is not fulfilled.

T-Assessment

T-criterion: Chronic NOEC < 0.01 mg/L or CMR or endocrine disrupting effects

Based on acute and chronic data icaridin is not fulfilling the T criteria (lowest NOEC value is 3.1 mg/L). For icaridin-acid it is assumed that the toxicity is 5 times higher than for icaridin as a conservative approach (based on QSAR data), corresponding to a chronic NOEC of 0.6. Therefore, icaridin-acid does not fulfil the criteria for T. Also considering that neither CMR properties are reported nor criteria for endocrine-disrupting effects (see next section) are met for the a.s., it can be concluded on the basis of the provided effect that neither icaridin or icaridin-acid are fulfilling the T criteria.

POP

Icaridin does not fulfil any of the PBT criteria and the long-range transport criterion according to the Stockholm convention (half-life in air of more than two days). Therefore, icaridin does not fulfil the POP criteria.

2.2.3. Assessment of endocrine disruptor properties

Human health

Since the specific scientific criteria for the determination of endocrine-disrupting properties were finalized in Reg. (EU) 2017/2100, evaluation of available information was performed.

All the *in vivo* tests (Level 4) submitted in the data package for this active substance were evaluated. No relevant observed adverse effects were identified under the experimental conditions of the submitted studies.
The available *in vivo* studies did not cover all EATS-mediated parameters.

A comprehensive battery of testing on Level 1(the OECD Conceptual Framework) is available from ToxCast1 (TOXCAST ER and AR prediction model) covering E, T & A modalities. These tests were negative.

In-depth assessment based on a literature search was conducted. The results from this search do not indicate any relevant concern regarding the interaction of icaridin or icaridin-acid and the respective receptors.

In conclusion, the available *in vivo* data and *in vitro* data (Tox21 data; QSAR) as well as the published literature indicates that Icaridin does not perturb any of the pathways E, A and T related to endocrine activity based on the ED assessment performed for vertebrates.

WoE suggests that a pattern of T-mediated adversity was not observed. T modality is considered sufficiently investigated. Therefore, the ED criteria are not met for this modality according to Scenario 1a.

WoE suggests for E modality the ED criteria are not met because no E mediated endocrine activity was observed (TOXCAST ER and AR prediction model). Therefore, the ED criteria are not met for E modality according to Scenario 2a (ii).

Regarding the A and S-modality: The available *in vivo* dossier studies (Level 4) showed no indication of effects on E-or A-sensitive tissues, adrenal or other relevant apical endpoints, however level 5 has not been investigated properly. Furthermore, the data for the S-modality, on endocrine activity is insufficient according to ED guidance and a Steroidogenesis Assay (OECD TG 456) should be performed.

The A and S-modality follows Scenario 2a (iii) with next step "Generate missing level 2 and 3 information. Alternatively, generate missing "EATS-mediated" parameters. Depending on the outcome move to corresponding scenario".

For the A and S modalities, although adversity was not observed, the dataset was neither sufficient for adversity nor endocrine activity. Therefore, further data need to be generated before a conclusion can be drawn on whether the ED criteria are met for the A and S modalities.

WGIV2019 conclusion:
The WG agreed that based on the available data, it is not possible to reach a conclusion on meeting the ED criteria due to missing information on the A and S modalities.
The WG noted that there are no indications of ED properties in the available data.

Non-target organisms

Based on the available data, there is no evidence that icaridin has/not has ED properties with regard to non-target organisms. However, sufficient data to be able to conclude on any of the modalities E, A, T and S with regard to non-target organisms was not available (please note that the Guidance for the identification of endocrine disruptors in the context on Regulations (EU) No 528/2012 and (EC) No 1107/2009 (EDGD) states: "…further investigation of the endocrine activity is always required when no adversity based on EATS-mediated parameters is observed on the basis of an insufficient data set" (p.32)). Accordingly, additional information is needed to conclude on the ED properties of icaridin with respect to non-target organisms.

Please refer to Doc IIA for the complete assessment of endocrine disrupting properties of icaridin with respect to non-target organisms.

Overall conclusion regarding endocrine disrupting properties

The available information relevant for the assessment of endocrine disrupting properties for icaridin does not indicate any endocrine disrupting properties for humans or for other non-target organisms.

However, following the Guidance for the identification of endocrine disruptors in the context on Regulations (EU) No 528/2012 and (EC) No 1107/2009, no conclusion can be drawn as insufficient data is available for the assessment. Additional information on the A and S modalities with respect to humans and mammals as non-target organisms and on the E, A, S and the T modalities with respect to other non-target organisms is needed in order conclude on the ED properties of icaridin.

As the first draft CAR for icaridin was submitted to the COM in 2011, i.e. before 1/9 2013, the applicant is not obliged to provide new studies, but has the opportunity to do so. Also due to the submission date of the CAR, the BPC does not need to come to a conclusion based on the available data according to the CA note "Implementation of scientific criteria to determine the endocrine-disrupting properties of active substances currently under assessment" (CA-March18.Doc.7.3a-Final).

2.3. Overall conclusions

The outcome of the assessment for icaridin is that icaridin in product type 19 should be approved. An acceptable use for both the HH and the ENV has been demonstrated with one application per day. This corresponds to an application rate of 0.584 g icaridin per person per day and ensuring efficacy for 4.9 hours protection time.

The outcome of the assessment for icaridin in product-type 19 is specified in the BPC opinion following discussions at the 28th and the 33rd meeting of the Biocidal Products Committee (BPC). The BPC opinion is available from the ECHA website.

2.4. List of endpoints

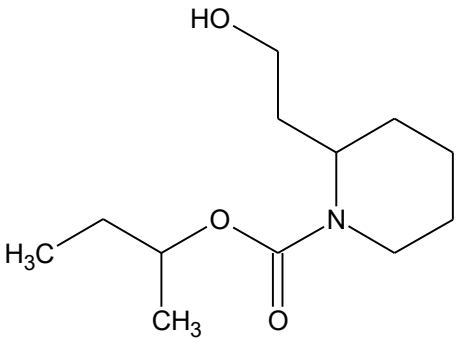
The most important endpoints, as identified during the evaluation process, are listed in Appendix I.

Appendix I: List of endpoints

Chapter 1:Identity, Physical and Chemical Properties, Classification and Labelling

Active substance (ISO Name)	Icaridin
Product-type	19 – Repellents and attractants

Identity

Chemical name (IUPAC)	(RS)-sec-butyl (RS)- 2-(2-hydroxyethyl)piperidine-1-carboxylate
Chemical name (CA)	1-piperidinecarboxylic acid, 2-(2-hydroxyethyl)-1-methylpropylester
CAS No	119515-38-7
EC No	423-210-8
Other substance No.	CIPAC No. 740
Minimum purity of the active substance as manufactured (g/kg or g/l)	≥ 97%
Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (g/kg)	The identity of the impurities of Icaridin is confidential. This information is provided in the confidential part of the dossier.
Molecular formula	C12H23NO3
Molecular mass	229.3 g/mol
Structural formula	

Physical and chemical properties

Melting point (state purity)	No freezing, melting, crystallisation or glass transition was observed in a temperature range between -170 °C and 20 °C. A sample kept at -20 °C for 4 weeks did not solidify. (Purity: 98.9%)
Boiling point (state purity)	296 °C at 1013 hPa; (purity: 98.9%)
Thermal stability / Temperature of decomposition	DTA: no exothermic reaction in sealed glass and in open containers until 400 °C; TGA: weight loss starting above 120 °C under air and under nitrogen. Icaridin was classified as thermally stable at ambient temperature under air.

Appearance (state purity)	Colourless and odourless liquid; (purity: 98.9%)
Relative density (state purity)	Density: 1.07 g/ml at 20 °C; (purity: 98.9%)
Surface tension (state temperature and concentration of the test solution)	49 mN/m at 20 °C, surface active (1g/L)
Vapour pressure (in Pa, state temperature)	3.4 × 10-2 Pa at 20 °C, 5.9 × 10-2 Pa at 25 °C, 7.1 × 10-1 Pa at 50 °C
Henry's law constant (Pa m^3 mol^{-1})	9.1 × 10-4 Pa×m3×mol-1 at 20 °C
Solubility in water (g/l or mg/l, state temperature)	Results at 20 °C: unbuffered water: 8.6 g/L, buffered water, pH 4-9: 8.2 g/L The solubility in water is not influenced by pH in the range pH 4 to pH 9. Results at different temperatures: 12.9 g/L at 10 °C, 10.6 g/L at 20 °C, 8.9 g/L at 30 °C The solubility in water is influenced by temperature in the range 10 °C to 30 °C.
Solubility in organic solvents (in g/l or mg/l, state temperature)	Results at 10 °C and 20 °C: Acetone, Acetonitrile, Dichloromethane, Ethylacetate, n-Heptane, 1-Octanol, Polyethyleneglycol 400, 2-Propanol, Xylene: > 250 g/L A determination of the solubility of Icaridin in dimethylsulfoxide at 10 °C was not possible since the mixture was frozen. The solubility of Icaridin in dimethylsulfoxide is > 250 mg/L at 20 °C.
Stability in organic solvents used in biocidal products including relevant breakdown products	Icaridin as manufactured does not include an organic solvent. Therefore, the stability in organic solvents is not applicable.
Partition coefficient (log P_{OW}) (state temperature)	Results of log Pow at 20 °C: unbuffered water: 2.11; buffered water, pH 4-9 (salt concentration = 0.1 mol/L): 2.23 Results of log Pow at pH 7 and different temperatures: 30 °C: 2.3 40 °C: 2.4 50 °C: 2.5 The log Pow-values showed slight temperature dependence.
Dissociation constant	Icaridin has no acidic or basic properties in aqueous solutions. It is not possible to specify dissociation constants for water.

UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	No absorption was observed.
Flammability or flash point	Icaridin does not liberate gases in hazardous amounts and has no pyrophoric properties. It exhibits an auto ignition temperature of 375 °C.
Explosive properties	Icaridin is not explosive.
Oxidising properties	Icaridin is not oxidising.
Auto-ignition or relative self-ignition temperature	Icaridin is not pyrophoric.

Classification and proposed labelling

with regard to physical hazards	No classification / labelling results from the physico-chemical properties.
with regard to human health hazards	Eye Irrit 2, H319
with regard to environmental hazards	No classification / labelling results from the ecotoxicological properties.

Chapter 2:Methods of Analysis

Analytical methods for the active substance

Technical active substance (principle of method)	Icaridin is separated by means of gas chromatography using flame ionisation detection after dissolving samples in dichloromethane. The quantitative evaluation is carried out according to the method of the internal standard.
Impurities in technical active substance (principle of method)	The analytical methods for the determination of the impurities in the active substance Icaridin are confidential. This information is provided in the confidential part of the dossier.

Analytical methods for residues

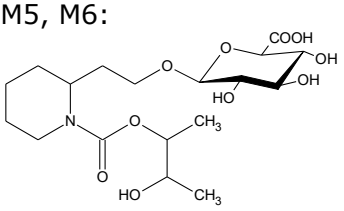
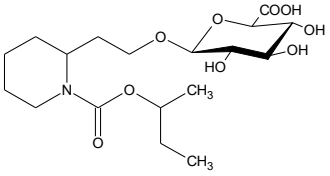
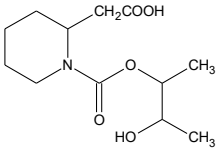
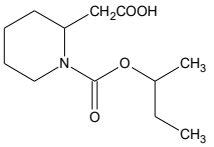
Soil (principle of method and LOQ)	LC-MS/MS; LOQ = 0.005 mg/kg
Air (principle of method and LOQ)	Not required.
Water (principle of method and LOQ)	Ground and tap water: GC-MS; LOQ = 0.3 µg/L. Not validated at sufficiently low concentration. Surface water: No sufficient validated method is submitted for icaridin. Proposed method for icaridin-acid is not acceptable.
Body fluids and tissues (principle of method and LOQ)	Not applicable since Icaridin is not classified as toxic or highly toxic.

Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	Not relevant since Icaridin is not used in a manner which may cause contact with food or feedstuffs, or intended to be placed on, in or near soils in agricultural or horticultural use.
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	Not relevant since Icaridin is not used in a manner which may cause contact with food or feedstuffs, or intended to be placed on, in or near soils in agricultural or horticultural use.

Chapter 3:Impact on Human Health

Absorption, distribution, metabolism and excretion in mammals

Rate and extent of oral absorption:	100% (default value)
Rate and extent of inhalation	100% (default value)
Rate and extent of dermal absorption*:	**4%** (Selim *et al.* 1994) in vivo human, exposure period 8 hours. Rat, 200 mg/kg, 24-h exposure: 47%
Distribution:	-
Potential for accumulation:	No evidence for accumulation
Rate and extent of excretion:	100% (default value)

Toxicologically significant metabolite(s)	<u>Human:</u> M5, M6:  M14, M15:  <u>Rat:</u> M8, M9:  M16: 

* Read-across from this study (4% dermal absorption) to actual products at the product authorisation phase required comparison of the compositions in questions for the read-across to be justified and use of the specific conditions stated in the EFSA GD.

Acute toxicity

Rat LD_{50} oral	2236 mg/kg bw (♂)
Rat LD_{50} dermal	> 2000 mg/kg bw (♂ +♀)
Rat LC_{50} inhalation	> 4364 mg/m³ (♂ +♀)

Skin corrosion/irritation	Not irritating
Eye irritation	Irritating to eyes, Eye Irrit.2, H319
Respiratory tract irritation	-

Skin sensitisation (test method used and result)	No classification – OECD 406 Maximisation test
Respiratory sensitisation (test method used and result)	-

Repeated dose toxicity

Short term

Species / target / critical effect	Rat/ liver and kidney/Increased liver weights associated with histopathology, reduced body weight gain and nephropathy (♂)
Relevant oral NOAEL / LOAEL	152 / 308 mg/kg bw/day; 5-week oral study in rats 149/382 mg/kg bw/day, 14 weeks oral rat study (NOAEL rounded to 150 mg/kg bw/day)
Relevant dermal NOAEL / LOAEL	-
Relevant inhalation NOAEL / LOAEL	-

Subchronic

Species/ target / critical effect	Rat /kidney/ weight increase and degenerative nephropathy
Relevant oral NOAEL / LOAEL	149 / 301 mg/kg bw/day, 14- week oral study
Relevant dermal NOAEL / LOAEL	200 / 500 mg/kg bw/day, 13-week dermal study
Relevant inhalation NOAEL / LOAEL	-

Long term

Species/ target / critical effect	Increased incidence of cystic degeneration in liver (♂) with clear dose response
Relevant oral NOAEL / LOAEL	–
Relevant dermal NOAEL / LOAEL	100/200 mg/kg bw/day, 1 year dermal rat study
Relevant inhalation NOAEL / LOAEL	–

Genotoxicity	Based on the weight of evidence icaridin is unlikely to be genotoxic.

Carcinogenicity

Species/type of tumour	Not tumorigenic in rats or mice in dermal chronic carcinogenicity studies at the highest dose tested (200 mg/kg bw/day). Icaridin is unlikely to pose a risk to humans.
Relevant NOAEL/LOAEL	

Reproductive toxicity

Developmental toxicity

Species/ Developmental target / critical effect	Rabbit, oral Maternal: BW decrease and abortions. Offspring: delayed ossification
Relevant maternal NOAEL	100 mg/kg bw/day
Relevant developmental NOAEL	100 mg/kg bw/day

Fertility

Species/critical effect	Rat, dermal. No reproductive effects in 2 generation study.
Relevant parental NOAEL	≥ 200 mg/kg bw/day
Relevant offspring NOAEL	≥ 200 mg/kg bw/day
Relevant fertility NOAEL	≥ 200 mg/kg bw/day

Neurotoxicity

Species/ target/critical effect	Rat / no neurotoxicity observed in acute or subchronic dermal neurotoxicity study. NOAEL ≥ 200 mg/kw bw /day (highest tested dose)

Developmental Neurotoxicity

Species/ target/critical effect	No study.

Immunotoxicity

Species/ target/critical effect	No study.

Developmental Immunotoxicity

Species/ target/critical effect	No study.

Other toxicological studies

No further studies available. No indications for concern

Medical data

No reports on clinical cases or poisoning incidents. Photoirritation testing on human volunteers was negative.

Summary

	NOAEL	Value	Study	Safety factor
$AEL_{long\text{-}term}$	100 mg/kg bw/day	0.70 mg/kg bw/day	1 year dermal, rat ([redacted] *1996a)*	1.34x2x2.5x10=67
$AEL_{medium\text{-}term}$	200 mg/kg bw/day	1.4 mg/kg bw/day[6]	13-week dermal rat study ([redacted], *1995*)	1.34x2x2.5x10=67
$AEL_{short\text{-}term}$	152 mg/kg bw/day	1.5 mg/kg bw/day	5-week oral rat study ([redacted] *2001a*)	10x10=100
ADI[7]	150 mg/kg bw/day	0.75 mg/kg bw/day	14-week rat feeding study, ([redacted], *2001b*)	200
ARfD	Not allocated			

MRLs

Relevant commodities	Not relevant

Reference value for groundwater

According to BPR Annex VI, point 68	0.1 µg/L (Directive 98/83/EC)

Dermal absorption

Study (*in vitro/vivo*), species tested	Human: [redacted] 1994, dermal absorption *in vivo* Rats [redacted], *in vivo* **4%** ([redacted] 1994) in vivo human, exposure period 8 hours. Rat, 200 mg/kg, 24-h exposure: 47%

[6] Adjusted to a systemic value using 47% dermal absorption for rat skin.
[7] If residues in food or feed.

Formulation (formulation type and including concentration(s) tested, vehicle)	Please refer to CAR.
Dermal absorption values used in risk assessment[8]	Human: 4% Rat: 47%

[8] Read across to actual products at BP stage should be justified and EFSA GD on dermal absorption should be followed.

Chapter 4: Fate and Behaviour in the Environment

Route and rate of degradation in water

Hydrolysis of active substance and relevant metabolites (DT_{50}) (state pH and temperature)	
pH 5	Icaridin was stable under acidic (pH 5 conditions at 25 and 50 °C.
pH 9	Icaridin was stable under alkaline (pH 9) conditions at 25 and 50 °C.
Other pH: *[indicate the value]*	Icaridin was stable under neutral (pH 7) conditions at 25 and 50 °C.
Photolytic / photo-oxidative degradation of active substance and resulting relevant metabolites	It was proven by an UV spectrum in water, that Icaridin shows no light absorption at wavelengths λ > 290 nm.
Readily biodegradable (yes/no)	No, neither readily nor inherently biodegradable.
Inherent biodegradable (yes/no)	No
Biodegradation in freshwater	Aerobic: DT_{50} for Icaridin at 12°C: 6.1 days DT_{50} for Icaridin-acid at 12°C: 545 days Anaerobic: DT_{50} for Icaridin at 12°C: 5.3 days DT_{50} for Icaridin-acid at 12°C: 878 days
Biodegradation in seawater	Not relevant since Icaridin is not used or released in the marine environment at considerable amounts. Therefore, a seawater biodegradation test is not required.
Non-extractable residues	In an anaerobic water/sediment study up to 4.8% NER was found in sediment
Distribution in water / sediment systems (active substance)	Aerobic. For the total system: DT_{50} for Icaridin at 12°C: 6.5 days Anaerobic. For the total system: DT_{50} for Icaridin at 12°C: 5.5 days Aerobic sediment: DT_{50} for Icaridin at 12°C: 4.1 days Anaerobic sediment: DT_{50} for Icaridin at 12°C: 4.7 days

Distribution in water / sediment systems (metabolites)	Aerobic. For the total system: DT_{50} for Icaridin-acid at 12°C: 829 days Anaerobic. For the total system: DT_{50} for Icaridin-acid at 12°C: 1475 days Aerobic sediment: DT_{50} for Icaridin-acid at 12°C: persistent; 1000 days Anaerobic sediment: DT_{50} for Icaridin-acid at 12°C: persistent; 1000 days.

Route and rate of degradation in soil

Mineralization (aerobic)	At the end of the test (21-31 days) a mineralization of 84.6%-95.8% of the applied is observed
Laboratory studies (range or median, with number of measurements, with regression coefficient)	
DT_{50lab} (20°C, aerobic):	DT_{50lab} (20.25°C, aerobic); geometric mean: 0.028 days, corresponding to 0.05 days at 12°C.
DT_{90lab} (20°C, aerobic):	
DT_{50lab} (10°C, aerobic):	
DT_{50lab} (20°C, anaerobic):	
degradation in the saturated zone:	-
Field studies (state location, range or median with number of measurements)	-
DT_{50f}:	
DT_{90f}:	
Anaerobic degradation	-
Soil photolysis	-
Non-extractable residues	At the end of the test the amount of bound residues varied between 2.6-6.7 % of the applied radioactivity
Relevant metabolites - name and/or code, % of applied a.i. (range and maximum)	Icaridin-acid: DT50lab (20.25°C, aerobic); geometric mean: 1.68 days, corresponding to 3.26 days at 12°C
Soil accumulation and plateau concentration	

Adsorption/desorption

Ka , Kd Ka_{oc} , Kd_{oc} pH dependence (yes / no) (if yes type of dependence)	Koc = 85.11 L/kg, log Koc = 1.93

Fate and behaviour in air

Direct photolysis in air	Not relevant because there is no relevant release of the compound to the air compartment
Quantum yield of direct photolysis	Not relevant because there is no relevant release of the compound to the air compartment
Photo-oxidative degradation in air	Latitude: ..... Season: ..... DT_{50} DT_{50} 6.87 hours
Volatilization	Not relevant because there is no relevant release of the compound to the air compartment

Reference value for groundwater

According to BPR Annex VI, point 68	0.01 µg/L

Monitoring data, if available

Soil (indicate location and type of study)	Not available
STP	Two WWTP in Germany (Wiesbaden and Stockstadt) were monitored. Wiesbaden in 2000, 2004 and 2005 and Stockstadt in 2005. Maximum influent conc. was 6.4 µg/L. No icaridin could be detected in the effluent. Icaridin was transformed to icaridin-acid in the STP. Maximum conc. of icaridin-acid in the effluent was 2.1 µg/L.
Surface water (indicate location and type of study)	No acceptable data available
Ground water (indicate location and type of study)	Five tap- and four groundwater samples were taken in August and September 2005 (area Frankfurt/Wiesbaden) and analysed for residues of icaridin and icaridin-acid. None of the samples contained residues above the limit of determination (0.01 µg/L)
Air (indicate location and type of study)	Not available

Chapter 5: Effects on Non-target Species

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

Species	Time-scale	Endpoint	Toxicity
Fish			
Oncorhynchus mykiss	96 hours	Mortality	LC_{50} = 169.4 mg/L
Danio rerio	32 days	Growth, mortality, weight, behaviour	NOEC = 3.14 mg/L
Invertebrates			
Daphnia magna	48 hours	Mortality	LC_{50}: > 103 mg/L
Daphnia magna	21 days	Reproduction, growth	NOEC = 50 mg/L
Algae			
Scenedesmus subspicatus	72 hours	Growth inhibition	E_rC_{50} = 87.3 mg/L NOEC = 54.8 mg/L
Microorganisms			
Activated sludge	3 hours	Inhibition of respiratory rate	EC50 = 1087 mg/L

Effects on earthworms or other soil non-target organisms

Acute toxicity to earthworms	LC_{50} (14 days) ≈ 985 mg/kg
Reproductive toxicity to terrestrial plants	EC_{50} (fresh weight) = 97.79 mg/kg

Effects on soil micro-organisms

Nitrogen mineralization	No study available
Carbon mineralization	No study available

Effects on terrestrial vertebrates

Acute toxicity to mammals	LC_{50} 2236 mg/kg bw (♂)
Acute toxicity to birds	No study available
Dietary toxicity to birds	LC_{50} > 5000 mg/kg
Reproductive toxicity to birds	No study available

Effects on honeybees

Acute oral toxicity	No study available
Acute contact toxicity	No study available

Effects on other beneficial arthropods

Acute oral toxicity	No study available
Acute contact toxicity	No study available
Acute toxicity to ……..	No study available

Bioconcentration

Bioconcentration factor (BCF)	BCF = 0.9 – 1.8 L/kg (wet weight); 10-19 L/kg (lipid content) in fish.
Depuration time (DT_{50})	No depuration time has been calculated, but during the examined depuration period (44 h) the measured icaridin concentration in fish tissue decreased below the detection limit (100 µg/kg wet weight).
Depuration time (DT_{90})	
Level of metabolites (%) in organisms accounting for > 10 % of residues	No metabolites identified

Chapter 6: Other End Points

None

Appendix II: List of Intended Uses

Object and/or situation	Product Name	Organisms controlled	Formulation		Application			Applied amount per treatment			Remarks:
			Type (d-f)	Conc. of a.s. (i)	method kind (f-h)	number min max	interval between applications (min)	g a.s./L min max	water L/m² min max	g a.s./m² min max	
Mosquito repellent	representative product	*Culex quinquefasciatus*	Liquid	20%	Applied on skin	1 per day	4.9 hours	3 g of 20% icaridin	0.55 µL b.p./cm²	0.055 mg a.s./cm²	The tested product (10.2% icaridin) showed an average protection time of 4.9 h (range 4-8 h, n=10) against the common house mosquito *Culex quinquefasciatus* under worst-case laboratory conditions with a low application rate of 0.055 mg/cm².

Appendix III: List of studies

Data protection is claimed by the applicant in accordance with Article 60 of Regulation (EU) No 528/2012.

(Sub)Section / Annex point	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A2.8 (01) IIA, II 2.8	Boddenberg, A.	2016	Justification of specification (impurity profile)	Saltigo GmbH, Leverkusen, Germany	-	No	No	Yes	SALTIGO GmbH
A2.8 (02) IIA, II 2.8	Neuland, M.	2016a	Determination of specified main and minor components of 5 batches (plant 1) of Icaridin/Saltidin ®	Currenta GmbH & Co OHG. Analytik, Leverkusen, Germany	2016/0110/01	Yes	No	Yes	SALTIGO GmbH
A2.8 (03) IIA, II 2.8	Neuland, M.	2016b	Determination of specified main and minor components of 5 batches (plant 5) of Icaridin/Saltidin ®	Currenta GmbH & Co OHG. Analytik, Leverkusen, Germany	2016/0111/01	Yes	No	Yes	SALTIGO GmbH

(Sub)Section / Annex point	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A3.1.1(01) IIA, III 3.1 also filed: A3.1.2(01) also filed: A3.1.3(01) also filed: A3.2(01) also filed: A3.3(01) also filed: A3.5(01) also filed: A3.6(01) also filed: A3.7(01) also filed: A3.9(01) also filed: A3.10(01) also filed: A3.13(01)	Krohn, J.	1996	Physical and chemical properties of KBR 3023. Date: 1996-09-25	Bayer AG, Leverkusen, Germany	14 120 0904	Yes	No	Yes	SALTIGO GmbH
A3.1.1(02) IIA, III 3.1	Feldhues, E.	2006	Statement freezing point / melting point of KBR 3023. Date: 2006-01-31	Bayer Industry Services BIS-SUA-PUA I, Leverkusen, Germany	--	No	No	Yes	SALTIGO GmbH

(Sub)Section / Annex point	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A3.1.2(01) IIA, III 3.1 also filed: A3.1.1(01) also filed: A3.1.3(01) also filed: A3.2(01) also filed: A3.3(01) also filed: A3.5(01) also filed: A3.6(01) also filed: A3.7(01) also filed: A3.9(01) also filed: A3.10(01) also filed: A3.13(01)	Krohn, J.	1996	Physical and chemical properties of KBR 3023. Date: 1996-09-25	Bayer AG, Leverkusen, Germany	14 120 0904	Yes	No	Yes	SALTIGO GmbH

(Sub)Section / Annex point	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A3.1.3(01) IIA, III 3.1 also filed: A3.1.1(01) also filed: A3.1.2(01) also filed: A3.2(01) also filed: A3.3(01) also filed: A3.5(01) also filed: A3.6(01) also filed: A3.7(01) also filed: A3.9(01) also filed: A3.10(01) also filed: A3.13(01)	Krohn, J.	1996	Physical and chemical properties of KBR 3023. Date: 1996-09-25	Bayer AG, Leverkusen, Germany	14 120 0904	Yes	No	Yes	SALTIGO GmbH

(Sub)Section / Annex point	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A3.2(01) IIA, III 3.2 also filed: A3.1.1(01) also filed: A3.1.2(01) also filed: A3.1.3(01) also filed: A3.3(01) also filed: A3.5(01) also filed: A3.6(01) also filed: A3.7(01) also filed: A3.9(01) also filed: A3.10(01) also filed: A3.13(01)	Krohn, J.	1996	Physical and chemical properties of KBR 3023. Date: 1996-09-25	Bayer AG, Leverkusen, Germany	14 120 0904	Yes	No	Yes	SALTIGO GmbH

(Sub)Section / Annex point	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A3.3(01) IIA, III 3.3 also filed: A3.1.1(01) also filed: A3.1.2(01) also filed: A3.1.3(01) also filed: A3.2(01) also filed: A3.5(01) also filed: A3.6(01) also filed: A3.7(01) also filed: A3.9(01) also filed: A3.10(01) also filed: A3.13(01)	Krohn, J.	1996	Physical and chemical properties of KBR 3023. Date: 1996-09-25	Bayer AG, Leverkusen, Germany	14 120 0904	Yes	No	Yes	SALTIGO GmbH
A3.4(01) IIA, III 3.4	Erstling, K.	2005	Identity and spectral data of KBR 3023. Date: 2005-04-26	Bayer Industry Services GmbH & Co. OHG, BIS-SUA-Analytics, Leverkusen, Germany	G 04/0079/00 LEV	Yes	No	Yes	SALTIGO GmbH

(Sub)Section / Annex point	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A3.5(01) IIA, III 3.5 also filed: A3.1.1(01) also filed: A3.1.2(01) also filed: A3.1.3(01) also filed: A3.2(01) also filed: A3.3(01) also filed: A3.6(01) also filed: A3.7(01) also filed: A3.9(01) also filed: A3.10(01) also filed: A3.13(01)	Krohn, J.	1996	Physical and chemical properties of KBR 3023. Date: 1996-09-25	Bayer AG, Leverkusen, Germany	14 120 0904	Yes	No	Yes	SALTIGO GmbH
A3.5(02) IIA, III 3.5	Jungheim, R.	2006 a	Determination of the water solubility (flask method) of KBR 3023 at 10 °C, 20 °C, and 30 °C. Date: 2006-01-03	Bayer Industry Services GmbH & Co. OHG, Leverkusen, Germany	G 04/0079/03 LEV	Yes	No	Yes	SALTIGO GmbH

(Sub)Section / Annex point	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A3.6(01) – also filed: A3.1.1(01) also filed: A3.1.2(01) also filed: A3.1.3(01) also filed: A3.2(01) also filed: A3.3(01) also filed: A3.5(01) also filed: A3.7(01) also filed: A3.9(01) also filed: A3.10(01) also filed: A3.13(01)	Krohn, J.	1996	Physical and chemical properties of KBR 3023 Date: 1996-09-25	Bayer AG, Leverkusen, Germany	14 120 0904	Yes	No	Yes	SALTIGO GmbH

(Sub)Section / Annex point	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A3.7(01) IIIA, III.1 also filed: A3.1.1(01) also filed: A3.1.2(01) also filed: A3.1.3(01) also filed: A3.2(01) also filed: A3.3(01) also filed: A3.5(01) also filed: A3.6(01) also filed: A3.9(01) also filed: A3.10(01) also filed: A3.13(01)	Krohn, J.	1996	Physical and chemical properties of KBR 3023 Date: 1996-09-25	Bayer AG, Leverkusen, Germany	14 120 0904	Yes	No	Yes	SALTIGO GmbH
A3.7(02) IIIA, III.1	Jungheim, R.	2006 b	Solubility of KBR 3023 in different organic solvents at 10 °C. Date: 2006-01-13	Bayer Industry Services GmbH & Co. OHG, Leverkusen, Germany	G04/0079/04 LEV	Yes	No	Yes	SALTIGO GmbH

(Sub)Section / Annex point	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A3.9(01) IIA, III 3.6 also filed: A3.1.1(01) also filed: A3.1.2(01) also filed: A3.1.3(01) also filed: A3.2(01) also filed: A3.3(01) also filed: A3.5(01) also filed: A3.6(01) also filed: A3.7(01) also filed: A3.10(01) also filed: A3.13(01)	Krohn, J.	1996	Physical and chemical properties of KBR 3023. Date: 1996-09-25	Bayer AG, Leverkusen, Germany	14 120 0904	Yes	No	Yes	SALTIGO GmbH

(Sub)Section / Annex point	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A3.9(02) IIA, III 3.6	Jungheim, R.	2005	Determination of the partition coefficient (n-octanol/water) at 30 °C, 40 °C, and 50 °C, High performance liquid chromatography (HPLC) method of KBR 3023. Date: 2005-07-20	Bayer Industry Services GmbH & Co. OHG, Leverkusen, Germany	G04/0079/05 LEV	Yes	No	Yes	SALTIGO GmbH

(Sub)Section / Annex point	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A3.10(01) IIA, III 3.7 also filed: A3.1.1(01) also filed: A3.1.2(01) also filed: A3.1.3(01) also filed: A3.2(01) also filed: A3.3(01) also filed: A3.5(01) also filed: A3.6(01) also filed: A3.7(01) also filed: A3.9(01) also filed: A3.13(01)	Krohn, J.	1996	Physical and chemical properties of KBR 3023. Date: 1996-09-25	Bayer AG, Leverkusen, Germany	14 120 0904	Yes	No	Yes	SALTIGO GmbH
A3.11(01) IIA, III 3.8 also filed: A3.12(01) also filed: A3.15(01)	Mix, K.-H.	1996	Determination of safety-relevant parameters of KBR 3023. Date:1996-09-04	Bayer AG, Leverkusen, Germany	96/00298	Yes	No	Yes	SALTIGO GmbH

(Sub)Section / Annex point	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A3.11(02) IIA, III 3.8 also filed: A3.12(02)	Heitkamp, D.	2001	Determination of safety-relevant parameters of KBR 3023. Date:2001-04-05	Bayer AG, Leverkusen, Germany	01/00080	Yes	No	Yes	SALTIGO GmbH
A3.12(01) IIA, III 3.9 also filed: A3.11(01) also filed: A3.15(01)	Mix, K.-H.	1996	Determination of safety-relevant parameters of KBR 3023. Date: 1996-09-04	Bayer AG, Leverkusen, Germany	96/00298	Yes	No	Yes	SALTIGO GmbH
A3.12(02) IIA, III 3.9 also filed: A3.11(02)	Heitkamp, D.	2001	Determination of safety-relevant parameters of KBR 3023. Date:2001-04-05	Bayer AG, Leverkusen, Germany	01/00080	Yes	No	Yes	SALTIGO GmbH

(Sub)Section / Annex point	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A3.13(01) IIA, III 3.10 also filed: A3.1.1(01) also filed: A3.1.2(01) also filed: A3.1.3(01) also filed: A3.2(01) also filed: A3.3(01) also filed: A3.5(01) also filed: A3.6(01) also filed: A3.7(01) also filed: A3.9(01) also filed: A3.10(01)	Krohn, J.	1996	Physical and chemical properties of KBR 3023. Date: 1996-09-25	Bayer AG, Leverkusen, Germany	14 120 0904	Yes	No	Yes	SALTIGO GmbH
A3.14(01) –	Jungheim, R.	2006 c	Determination of the viscosity of KBR 3023. Date: 2006-01-24	Bayer Industry Services GmbH & Co. OHG, Leverkusen, Germany	2006/0005/01 LEV	Yes	No	Yes	SALTIGO GmbH

(Sub)Section / Annex point	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A3.15(01) IIA, III 3.11 also filed: A3.11(01) also filed: A3.12(01)	Mix, K.-H.	1996	Determination of safety-relevant parameters of KBR 3023. Date: 1996-09-04	Bayer AG, Leverkusen, Germany	96/00298	Yes	No	Yes	SALTIGO GmbH
A3.16(01) IIA, III 3.12	Koch, F.	2006	Icaridin / Oxidising properties. Date: 2006-01-19	SALTIGO GmbH, Leverkusen, Germany	--	No	No	Yes	SALTIGO GmbH
A3.17(01) IIA, III 3.13	Lindel, H.	2005	Icaridin: Reactivity towards container material. Date: 2005-02-02	SALTIGO GmbH, Dormagen, Germany	--	No	No	Yes	SALTIGO GmbH
A4.1(01) IIA, IV 4.1	Jungheim, R	2009	Validation of GC-method for the determination of KBR3023 and significant impurities in KBR3023	Currenta GmbH & Co OHG Services Analytik, Leverkusen, Germany	2009/0004/01	Yes	No	Yes	SALTIGO GmbH
A4.1(01) IIA, IV 4.1	Neuland, M.	2017	Re-Validation of en existing GC method for the determination of 2 impurities in Icaridin/Saltidin ®	Currenta GmbH & Co OHG. Analytik, Leverkusen, Germany	2017/0027/01	Yes	No	Yes	SALTIGO GmbH

(Sub)Section / Annex point	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A4.1(01) IIA, IV 4.1	Nonn, E.	1998 a	2-(2-Hydroxyethyl)-piperidine-1-carboxylic acid-1-methylpropylester (KBR 3023), Assay and By-products – Capillary Gas Chromatography. Date: 1998-11-25	Bayer AG, Zentrale Analytik Dormagen, Germany	Analytical Method No.: 2201-0311702-98	No	No	Yes	SALTIGO GmbH
A4.1(02) IIA, IV 4.1	Nonn, E.	1998 b	2-(2-Hydroxyethyl)-piperidine-1-carboxylic acid-1-methylpropylester (KBR 3023), Assay and By-products – Capillary Gas Chromatography. Date: 1998-11-25	Bayer AG, Zentrale Analytik Dormagen, Germany	Method Validation No.: 2201-0311702-98	No	No	Yes	SALTIGO GmbH

(Sub)Section / Annex point	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A4.2(01) IIA, IV 4.2	Weber, H. and Anspach, Th.	2001	Enforcement method for the determination of the residues of KBR 3023 in soil – Validation of DFG Method S 19 (extended revision) combined with a detection by LC-MS/MS. Date: 2001-05-22	Dr. Specht & Partner, Chemische Laboratorien GmbH, Hamburg, Germany	BAY-0105V, Az. G01-0008	Yes	No	Yes	SALTIGO GmbH
A4.2(02) IIA, IV 4.2	Eben, A.	1989	KBR 3023 Concentration determination in the test atmosphere after spraying. Date: 1989-11-13	Bayer AG, Toxicology Department, Wuppertal, Germany Bayer AG	18510	Yes	No	Yes	SALTIGO GmbH
A4.2(03) IIA, IV 4.2	Knepper, T.P.	2004	Analysis and mass spectrometric characterization of the insect repellent Bayrepel and its main metabolite Bayrepel-acid.	Europe University for Applied Science Fresenius, Idstein, Germany *Journal of Chromatography A* 1046, pp. 159-166	--	No	Yes	No	–

(Sub)Section / Annex point	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A4.2(04) IIA, IV 4.2	Knepper, T.P.	2005	Monitoring of Bayrepel and its metabolite Bayrepel-acid in wastewater influents and effluents, ground and tap water. Date: 2005-10-10	Europa Fachhochschule Fresenius, Idstein, Germany	--	No	No	Yes	SALTIGO GmbH
A5.3(01) IIA, 5.3	World Health Organisation (WHO)	2001	Review of IR 3535; KBR 3023; (RS)-Methoprene 20% EC; Pyriproxyfen 0.5% GR and Lambda-cyhalothrin 2.5% CS	Report of the Fourth WHOPES Working Group Meeting, WHO/HQ, Geneva, 4-5 December 2000	WHO/CDS/WHOPES/2001.2	--	Yes	No	--
A5.3(02) IIA, 5.3	Barnard, D.R.	2000	Field Evaluation of DEET and KBR 3023 for Repellency to *Aedes taeniorhynchus* in the Everglades National Park, Flamingo, Florida, USA	Center for Medical, Agricultural and Veterinary Entomology, Agricultural Research Service, US Department of Agriculture, Gainsville, Florida, USA	--	--	No	Yes	SALTIGO GmbH SC Johnson & Son, Inc.

(Sub)Section / Annex point	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A5.3(03) IIA, 5.3	Costantini, C. and E. Ilboudo-Sanogo	1999	WHOPES Evaluation of Insect Repellent KBR 3023 in Burkina Faso. Final Report for WHO Project V2.181.276	Institute of Parasitology, University of Rome "La Sapienza", Italy in cooperation with Centre National De Lutte Contre Le Paludisme (CNLP), Ouagadougou, Burkina Faso	--	--	No	Yes	SALTIGO GmbH SC Johnson & Son, Inc.
A5.3(04) IIA, 5.3	Boeckh, J., et al.	1996	Acylated 1,3-Aminopropanols as Repellents against Bloodsucking Arthropods	--	Pesticide Science, 48, pp. 359-373	--	Yes	No	Published
A5.3 (05) IIA5.3	Carroll, S.C.	2008	Efficacy test of KBR 3023 (Picaridin; Icaridin) – based Personal Insect Repellents (20 % cream and 20 % spray) with Mosquitoes under Field Conditions.	Carroll-Loye Biological Research, Davis, CA, USA	LNX-001	Yes	No	Yes	SALTIGO GmbH

(Sub)Section / Annex point	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A5.3 (06) IIA5.3	Carroll, S.C.	2010	Efficacy test of KBR 3023 (Picaridin; Icaridin) – based Personal Insect Repellents (20 % cream and 20 % spray) with Ticks under Laboratory Conditions.	Carroll-Loye Biological Research, Davis, CA, USA	LNX-003	Yes	No	Yes	SALTIGO GmbH
B5.10(09)	Gundalai, E.	2016 a	Repellent Efficacy of a Product on Human Arms against House mosquito, Culex quinquefasciatus.	BioGenius GmbH, Bergisch Gladbach, Germany	BIO004-16	Yes	No	Yes	Saltigo GmbH.
B5.10(10)	Gundalai, E.	2016 b	Repellent Efficacy of a Product on Human Arms against House mosquito, Culex quinquefasciatus.	BioGenius GmbH, Bergisch Gladbach, Germany	BIO004-17	Yes	No	Yes	Saltigo GmbH.
A6.1.1(01) IIA, VI 6.1.1	[redacted]	1988 a	Investigation of acute oral toxicity in rats	[redacted]	17133	Yes	No	Yes	SALTIGO GmbH
A6.1.2(01) IIA, VI 6.1.2		1991	Acute Dermal Toxicity Study with Technical Grade KBR3023 in Rats		90-022-GD	Yes	No	Yes	SALTIGO GmbH

(Sub)Section / Annex point	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A6.1.3(01) IIA, VI 6.1.3	[redacted]	1990	Study for Acute Inhalation Toxicity in the Rat to OECD Guideline No.403	[redacted]	19220	Yes	No	Yes	SALTIGO GmbH
A6.1.4(01) IIA, VI 6.1.4		1997 a	Primary Dermal Irritation Study in Rabbits with Technical Grade KBR 3023		107638	Yes	No	Yes	SALTIGO GmbH
6.1.4(02) IIA, VI 6.1.4		1988	KBR 3023 – Studies on the local irritant / corrosive effect on skin and eyes (rabbits) in accordance with OECD Guideline No. 404 and 405		17019	Yes	No	Yes	SALTIGO GmbH
A6.1.4(03) IIA, VI 6.1.4		1997 b	Primary Eye Irritation Study in Rabbits with Technical Grade KBR 3023		107637	Yes	No	Yes	SALTIGO GmbH
A6.1.5(a), 6.1.5(b) IIA; VI 6.1.5		1991	Study for skin-sensitising effect on guinea pigs		20623 amended by Report No.: 20623A	Yes	No	Yes	SALTIGO GmbH

(Sub)Section / Annex point	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A6.1.5 (02) IIA VI.6.1.5	[redacted]	2007	Icaridin – Study for Skin-Sensitising Effect in Guinea Pigs.	[redacted]	AT04065	Yes	No	Yes	SALTIGO GmbH
A6.2(01) IIA, VI 6.2		1997	[Hydroxyethyl-1-^{14}C]KBR 3023: Rat Metabolism Study After Intravenous Injection And After Dermal Application		PF 4178	Yes	No	Yes	SALTIGO GmbH
A6.2(02) IIA, VI 6.2		1997	[Hydroxyethyl-1-^{14}C]KBR 3023: Human Volunteer Metabolism Study After Dermal Application		PF 4187	Yes	No	Yes	SALTIGO GmbH

(Sub)Section / Annex point	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A6.2(03) IIA, VI 6.2	[redacted]	1994	A Single Dose Open Label Study to Investigate the Absorption and Excretion of a ^{14}C-Labelled Insect Repellent (KBR 3023) from two Different Formulations after Dermal Application to Healthy Volunteers	[redacted]	P1092004	Yes	No	Yes	SALTIGO GmbH
A6.2(04) IIA, VI 6.2		1997	Dermal Absorption of Technical KBR 3023		107488	Yes	No	Yes	SALTIGO GmbH
6.3.1(01) IIA, VI 6.3		2001 a	Technical Grade KBR 3023: A Subchronic Toxicity Testing Study in the Rat (5-Week Interval)		110222	Yes	No	Yes	SALTIGO GmbH

(Sub)Section / Annex point	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
6.4.1(01) IIA, VI 6.4	[redacted]	2001 b	Technical Grade KBR 3023: A Subchronic Toxicity Testing Study in the Rat (14-Week Interval)	[redacted]	110223	Yes	No	Yes	SALTIGO GmbH
6.4.2(01) IIA, VI 6.4.2		1995	A Repeated Dose 90-Day Dermal Toxicity Study with Technical Grade KBR 3023 in Rats		90-122-HC	Yes	No	Yes	SALTIGO GmbH
6.5(01) IIA, VI 6.5		1995	Technical Grade KBR 3023: A Chronic Percutaneous Toxicity Study in the Beagle Dog		107155	Yes	No	Yes	SALTIGO GmbH
A6.5+6.7(a); 6.5+ 6.7(b) IIA, VI, 6.5/6.7		1996 a	Technical Grade KBR 3023: A Combined Chronic Toxicity/Oncogenicity Testing Study in the Rat		107432 amended by Report No. 107432-1	Yes	No	Yes	SALTIGO GmbH
A6.6.1(01) IIA, VI 6.6.1	Herbold, A.	1990	KBR 3023 – Salmonella/ Microsome Test	Bayer AG, Toxicology, Wuppertal, Germany	18917	Yes	No	Yes	SALTIGO GmbH

(Sub)Section / Annex point	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A6.6.2(01) IIA, VI 6.6.2	Gahlmann, R.	1996	KBR 3023 –In Vitro Mammalian Chromosome Aberration Test with Chinese Hamster Ovary (CHO) Cells	Bayer AG, Toxicology, Wuppertal, Germany	25019	Yes	No	Yes	SALTIGO GmbH
A6.6.2(02) IIA, VI 6.6.2	Gudi, R. and Schadly, E.H.	1997	Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells	Microbiological Associates, Inc., Rockville, MD, USA	107777	Yes	No	Yes	SALTIGO GmbH
A6.6.2(03) IIA, VI 6.6.2	[redacted]	1992	KBR 3023 – Mutagenicity Test on Unscheduled DNA Synthesis in Rat Liver Primary Cell Cultures in Vitro	[redacted]	21314	Yes	No	Yes	SALTIGO GmbH
A6.6.3(01)	Herbold, B.	1991	KBR 3023 – V79/HPRT-Test in Vitro for the Detection of Induced Forward Mutations	Bayer AG, Toxicology, Wuppertal, Germany	29220	Yes	No	Yes	SALTIGO GmbH
A6.6.4(01) IIA, VI 6.6.4	[redacted]	1994	KBR 3023 – Micronucleus Test on the Mouse	[redacted]	23291	Yes	No	Yes	SALTIGO GmbH

(Sub)Section / Annex point	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A6.7(a); 6.7(b) IIA, VI 6.7	[redacted]	1996 b	Technical Grade KBR 3023: An Oncogenicity Dermal Toxicity Study in the Mouse	[redacted]	107433 amended by Report No. 107433-1	Yes	No	Yes	SALTIGO GmbH
A6.8.1(01) IIA, VI 6.8.1		1996 b	A Developmental Toxicity Study with KBR 3023 Technical in the Sprague-Dawley Rat		95-622-DI	Yes	No	Yes	SALTIGO GmbH
A6.8.1(02) IIA, VI 6.8.1		1996	Developmental Toxicity Study in Rabbits after Dermal Application		24928	Yes	No	Yes	SALTIGO GmbH
A6.8.1(03) IIA, VI 6.8.1		2008	Icaridin – Developmental Toxicity Study in Rabbits after Oral Administration		AT05042	Yes	No	Yes	SALTIGO GmbH

(Sub)Section / Annex point	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A6.8.2(01) IIA, VI 6.8.2	[redacted]	1996c	A Two Generation Reproductive Toxicity Study with KBR 3023 Technical in the Bayer Corporation, Agriculture Division, Toxicology, Stilwell, KS, USA Sprague-Dawley Rat	[redacted]	107489	Yes	No	Yes	SALTIGO GmbH
A6.9(01) IIIA, VI 1		1996a	An Acute Dermal Neurotoxicity Screening Study with Technical Grade KBR 3023 in Fischer 344 Rats		107467	Yes	No	Yes	SALTIGO GmbH
A6.9(02) IIIA, VI 1		1996b	Subchronic Dermal Neurotoxicity Screening Study with Technical Grade KBR 3023 in Fischer 344 Rats		107466	Yes	No	Yes	SALTIGO GmbH

(Sub)Section / Annex point	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A6.12.4(01) IIA, VI 6.9.4	[redacted]	1996	Controlled Intra-Individual Comparative Study of the Phototoxicity of the Repellent KBR 3023	[redacted]	107792	No	No	Yes	SALTIGO GmbH
A6.12.6 IIA VI.6.9.6	Corazza, M. *et al.*	2005	Allergic Contact Dermatitis due to an Insect Repellent: Double Sensitization to Picaridin and Methyl Glucose Dioleate.	Dept. of Dermatology, University of Ferrara, Italy	--	No	Yes	No	--
A6.12.7(01) IIA, VI 6.9.7	Röder, K.	2000	Bayrepel (KBR 3023) containing products – Human poisoning, first aid, medical treatment and antidot	Bayer AG, Leverkusen, Germany	--	--	No	--	SALTIGO GmbH

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A7.1.1.1.1(01) IIA, 7.6.2.1	Hellpointner, E.	1996	Hydrolysis of [14C]KBR 3023 in sterile aqueous buffers	Bayer AG, Crop Protection Development, Institute for Metabolism Research and Residue Analysis, Leverkusen, Germany	MR 842/96 (PF No. 4185)	Yes	No	Yes	SALTIGO GmbH
A7.1.1.2.1(01) IIA, 7.6.1.1	Caspers, N. and Mueller, G.	1997	Investigation of the ecological properties of KBR 3023	Bayer AG, Institute of Environmental Analysis, Leverkusen, Germany	573 A/96	Yes	No	Yes	SALTIGO GmbH
A7.1.1.2.2(01) IIA, 7.6.1.1	Mueller, G.	1999	Investigation of the ecological properties of KBR 3023. Inherent Biodegradability	Bayer AG, Institute of Environmental Analysis, Leverkusen, Germany	799 A/98	Yes	No	Yes	SALTIGO GmbH
A7.1.2.2.2(01)	Fiebig, S. and Goller, St.	2014	Aerobic transformation in aquatic sediment systems using 14C-labelled test item	Dr Noack Laboratorien, Sarstedt, Germany	NAT15260	Yes	No	Yes	SALTIGO GmbH

(Sub)Section / Annex point	Authors (s)	Year	Title	Testing Company	Report No.	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Data Owner
A7.1.2.2.2(02)	Fiebig, S. and Goller, St.	2014	Anaerobic transformation in aquatic sediment systems using 14C-labelled test item	Dr Noack Laboratorien, Sarstedt, Germany	NAN15260	Yes	No	Yes	SALTIGO GmbH
A7.1.3(01) IIA, 7.7	Jungheim	2001	Bayrepel – Adsorption/Desorption	Bayer AG, ZF-Zentrale Analytik, Leverkusen, Germany	N-01/0026/00 LEV	Yes	No	Yes	SALTIGO GmbH
A7.2.1(01)	Fiebig, S. and Goller, St.	2014	Aerobic transformation in soil	Dr Noack Laboratorien, Sarstedt, Germany	NAB15260	Yes	No	Yes	SALTIGO GmbH
A.7.3.1(01) IIIA, VII 5	Beiell, U.	2005	Icaridin (KBR 3023): Calculation of Photodegradation Date: 2005-02-18	Dr. Knoell Consult GmbH, Mannheim, Germany	--	--	No	Yes	SALTIGO GmbH
A7.4.1.1(01) IIA, VII 7.1	[redacted]	1996	KBR 3023 techn. – Acute Toxicity (96 hours) to Rainbow Trout *(Oncorhynchus mykiss)* in a Static Test	[redacted]	DOM 96024	Yes	No	Yes	SALTIGO GmbH

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A7.4.1.2(01) IIA, VII 7.2	Heimbach, F.	1996	Acute Toxicity of KBR 3023 (tech.) to Water Fleas *(Daphnia magna)*	Bayer AG, Crop Protection Development, Institute for Environmental Biology, Leverkusen, Germany	HBF/Dm 162	Yes	No	Yes	SALTIGO GmbH
A 7.4.1.3(01) IIA, VII 7.3	Anderson, J.P.E.	1996	Influence of KBR 3023 Technical on the Growth of the Green Alga *Scenedesmus subspicatus*	Bayer AG, Crop Protection Development, Institute for Environmental Biology, Leverkusen, Germany	107689 (AJO/146496)	Yes	No	Yes	SALTIGO GmbH
A7.4.1.4(01) IIA, VII 7.4	Mueller, G.	1997	Investigation of the ecological properties of KBR 3023. Influence on Microbial Activity	Bayer AG, Institute of Environmental Analysis, Leverkusen, Germany	610 N/96	Yes	No	Yes	SALTIGO GmbH
A7.4.2(01) IIA, VII 7.5	[redacted]	2000	Bioconcentration : Flow-through Fish Test of KBR 3023	[redacted]	746 A/98 BA	Yes	No	Yes	SALTIGO GmbH

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7.4.3.2(01) IIIA, XIII 2.2	[redacted]	2003	Early-Life Stage Toxicity Test with Zebrafish (*Danio rerio*) under Flow-Through Conditions	[redacted]	FSZ86881	Yes	No	Yes	SALTIGO GmbH
7.4.3.4(01) IIIA, XIII 2.4	Dorgerloh, M.	2003	Influence of KBR 3023 (techn.) on Development and Reproductive Output of the Water Flea Daphnia magna in a Static Renewal Laboratory Test System	Bayer CropScience AG, BCS-Development, Ecotoxicology, Leverkusen, Germany	DOM 22039	Yes	No	Yes	SALTIGO GmbH
A7.5.1.2(01) IIIA, XIII 3.2	Lechelt Kunze, C.	2002	KBR 3023 (techn.): Acute Toxicolgy to Earthworms (*Eisenia fetida*)	Bayer CropScience AG, Development – Environmental Biology, Monheim, Germany	LKC/Rg 408/02	Yes	No	Yes	SALTIGO GmbH

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7.5.1.3(01) IIIA, XIII 3.4	Spatz, B.	2002	Effects of KBR 3023 (technical) on Terrestrial (Non-Target) Plants: Seedling Emergence and Seedling Growth Test	IBACON GmbH, Rossdorf, Germany	14671084	Yes	No	Yes	SALTIGO GmbH
7.5.3.1.2(01) IIIA, XIII 1.2	[redacted]	1997	Five Day Dietary Toxicity of KBR 3023 on Bobwhite Quail (*Colinus virginianus*) Five Day Dietary Toxicity of KBR 3023 on Bobwhite Quail (*Colinus virginianus*)	[redacted]	107844	Yes	No	Yes	SALTIGO GmbH
A8.1(01) IIA, VIII 8.1 also filed: A8.2(01) also filed: A8.3(01) also filed: A8.4(01) also filed: A8.5(01)	Anonymous	2005	KBR 3023 Safety Data Sheet. Date: 2005-01-24	SALTIGO GmbH, Leverkusen, Germany	SDS No.: 710303/06	No	No	–	SALTIGO GmbH

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A8.2(01) IIA, VIII 8.2 also filed: A8.1(01) also filed: A8.3(01) also filed: A8.4(01) also filed: A8.5(01)	Anonymous	2005	KBR 3023 Safety Data Sheet. Date: 2005-01-24	SALTIGO GmbH, Leverkusen, Germany	SDS No.: 710303/06	No	No	–	SALTIGO GmbH
A8.3(01) IIA, VIII 8.3 also filed: A8.1(01) also filed: A8.2(01) also filed: A8.4(01) also filed: A8.5(01)	Anonymous	2005	KBR 3023 Safety Data Sheet. Date: 2005-01-24	SALTIGO GmbH, Leverkusen, Germany	SDS No.: 710303/06	No	No	–	SALTIGO GmbH
A8.4(01) IIA, VIII 8.4 also filed: A8.1(01) also filed: A8.2(01) also filed: A8.3(01) also filed: A8.5(01)	Anonymous	2005	KBR 3023 Safety Data Sheet. Date: 2005-01-24	SALTIGO GmbH, Leverkusen, Germany	SDS No.: 710303/06	No	No	–	SALTIGO GmbH

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A8.5(01) IIA, VIII 8.5 also filed: A8.1(01) also filed: A8.2(01) also filed: A8.3(01) also filed: A8.4(01)	Anonymous	2005	KBR 3023 Safety Data Sheet. Date: 2005-01-24	SALTIGO GmbH, Leverkusen, Germany	SDS No.: 710303/06	No	No	–	SALTIGO GmbH