Doc III-A BPR Data set IIA Annex Point 9.10	**Identification of endocrine disrupting properties with regard to non-target organisms**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X]	**Technically not feasible [ ]** **Scientifically unjustified [ ]**	
Limited exposure [ ]	**Other justification [ ]**	
Detailed justification:	The following summary of endocrine assessment for icaridin and icaridin acid with regard to non-target organisms was submitted, reference: **Duft 2019: Assessment of potential endocrine disrupting properties of Icaridin (CAS No. 119515-38-7) with regard to non-target organisms** (this document was prepared in addition to the ED assessment for toxicology (Mostert 2019. Assessment of Endocrine Disruption Potential of Icaridin (CAS No. 119515-38-7)) enclosed at the end of this document) No new studies are submitted for this endocrine assessment. An extensive literature search was performed which included a single concept literature search in the following databases: AGRICOLA, BIOSIS, CABA, CAPLUS, DDFU, EMBASE, ESBIOBASE, FSTA, GEOREF, MEDLINE, PQSCITECH, SCISEARCH and TOXCENTER. Please refer to DocIII 9.10-1. **EXECUTIVE SUMMARY (Excerpt of Duft 2019)** "In the present case of icaridin where no alert for potential endocrine disrupting properties at all has been found from the toxicology and ecotoxicology section and the included comprehensive study package (indeed covered by the related data requirements at the time of dossier submission), by the conducted literature search and evaluation, as well as by the investigated databases related to endocrine disrupting properties, no further data generation regarding vertebrate testing should be requested. As pointed out, the conducted literature search for icaridin outlined in detail above, has shown no hits nor concern with regard to any probable alert regarding endocrine disrupting properties in non-target organisms. Furthermore, there is data investigating endocrine activity from a comprehensive battery of testing on Level 2 of the OECD Conceptual Framework. This data is available from ToxCast, covering potential EATS modalities, and shows no alerts regarding endocrine activity. This is confirmed by	

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	QSAR profiling (see ED assessment for toxicology; Mostert, V. 2019). In addition, there were not only no indications for adverse effects, but also no indications for endocrine activity of icaridin. Following the new ECHA/EFSA ED Guidance, even if the assumption would be "'EATS-mediated' parameters on adverse not sufficiently investigated", and given that there are "no indications for endocrine activity", this would be sufficient to conclude on "ED criteria not met". In conclusion, the overall assessment of the available data (in silico, in vitro and in vivo toxicological and ecotoxicological studies regarding adverse effects and endocrine activity) should be sufficient to give a complete picture in a weight of evidence approach to exclude a concern regarding potential endocrine disrupting properties of icaridin. **Conclusion** From the data available and fulfilling the data requirements at the time of dossier submission, in addition considering the requirements of the new ECHA/EFSA ED Guidance in a weight of evidence approach, it can be concluded that the EU ED criteria are not fulfilled for icaridin."
Undertaking of intended data submission [ ]	–
	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	November 2019
Evaluation of applicant's justification	**Literature search:** eCA DK considers literature search to be comprehensive and valid. However, the eCA does not agree to the applicants evaluation that no publications are relevant to be included in the subsequent ED assessment. The eCA found the study by Almeida et al. (2018) relevant for the assessment of ED properties of Icaridin with regard to non-target organisms (for reference, please refer to the literature search by the applicant (can be found in DocIII 9.10-1)). Therefore this study was included in the eCAs evaluation of ED properties with regard to non-target organisms.

ToxCast and QSAR data:

Please refer to DocIII 8.13.3.

Assessment of endocrine disrupting properties for non-target organisms

According to the EFSA/ECHA ED guidance (EDGD), it is recommended to strive for a conclusion on the ED properties with regard to humans and in parallel, using the same database, to strive for a conclusion on mammals as non-target organisms. Only where, based on this assessment the ED criteria are not met for mammals as non-target organisms, a further assessment of non-mammalian non-target organisms in the environment (e.g. fish and/or amphibians) would be required.

The conclusion of the ED assessment with regard to mammals is that icaridin does not perturb the pathways E and T related to endocrine activity and therefore further consideration of the potential ED properties of icaridin on non-target organisms other than mammals is required for these modalities.

Regarding the A- and S-modalities: 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. Hence, no conclusion could be drawn for the S-modality. According to section 3.4.3 of the EDGD, an OECD TG 456 (H295R Steroidogenesis Assay) should be performed as an initial step in order to conclude on absence of S-related endocrine activity. Therefore, also for the A and S modalities, further consideration on the potential ED properties on non-target organisms other than mammals is required.

ED assessment for the T-modality

For the T-modality, *in vitro* data retrieved from ToxCast, the FELS study on zebrafish and the Almeida et al. (2018) publication on spotted salamander could be of relevance. The avian study according to OECD TG 205 was considered not relevant as no endpoints relevant for ED identification were measured. Please refer to the lines of evidence table for adverse effects and endocrine activity related to the T-modality with regard to NTOs.

No EATS-mediated parameters were investigated in the FELS test. According to OECD GD 150, the FELS test can give indications of damage to the metamorphosis of fish embryos to larvae and could be used to a limited extent as support for a conclusion regarding thyroid disruptors. The study measured egg hatch, swim-up of hatched larvae, length, weight and survival. No effects was observed except for a decrease in mean length and weight at the highest tested concentration (9.54 mg/L).

This effect could be indication of T-related activity, but not diagnostic of such. Additionally, the study author also mention observations of disorders of co-ordination and distortion of spine, however these effects were also observed in the control and not in a dose related manner.

Almeida et al. (2018) examined the developmental stage, body length, tail deformity and survival of salamander larvae exposed to the formulation "Sawyer Premium Insect Repellent" (containing 20% icaridin) at concentrations of 20, 200 and 2000 ng icaridin/L (nominal concentrations) for 25 days. The test substance was applied once at the beginning of the test and no exchange of the test substrate during the testing period was reported. The test design included three replicate 1-liter chambers containing three larvae each, i.e. nine salamanders per test concentration. Developmental stage and body length was assessed at day 4 and 12, mortality and tail deformation was assessed approximately three times per week. Clear effects on all measured parameters was observed at all tested concentrations, however not in a dose related manner (please refer to the lines of evidence table

for adverse effects and endocrine activity related to the T-modality with regard to NTOs). Although developmental stage may be an EATS-mediated parameter, major discrepancies involving the identity of the test substance, no analytical measurements, no renewal of the test substrate, non-standard test organism and a poor test design involving a low number of organisms per concentration makes the study not reliable for the identification of endocrine adversity or activity. In addition, the effects was observed at concentrations above the MTC/lethal doses.

According to the EDGD, section 3.4.2, to consider the T-related endocrine activity sufficiently investigated for non-target organisms, an Amphibian metamorphosis assay (OECD TG 231) should be conducted.

ED assessment for the EAS-modalities

For the EAS-modality, *in vitro* data retrieved from ToxCast and the FELS study on zebrafish could be of relevance. Please refer to the lines of evidence table for adverse effects and endocrine activity related to the EAS-modalities with regard to NTOs.

For the assessment of the FELS study, please refer to the ED assessment for the T-modality in the previous paragraph.

According to the EDGD, section 3.4.2, to consider the EAS-related endocrine activity sufficiently investigated, a Fish short term reproduction assay (FSTRA; OECD TG 229) should be conducted.

ED assessment for non-EATS modalities

An OECD TG 211 (Daphnia magna Reproduction test) was conducted for icaridin. According to the OECD GD 150, the TG 211 can be responsive to juvenile hormone agonists; however, observation of change in number of male neonates was not included in the test. Therefore, this test was considered not relevant for the ED assessment with respect to non-target organisms. No other data was relevant for the assessment of non-EATS modalities.

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Conclusion	Based on the available data, there is no firm evidence that icaridin has/has no 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 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)). In this case, following scenario 2a (iii) in section 3.4.4 of the EDGD, the missing level 2 and level 3 information or alternatively missing EATS-mediated parameters should be generated. The missing information includes: - H295R Steroidogenesis Assay (OECD TG 456) (to investigate S-mediated activity in mammals) - Amphibian Metamorphosis assay (OECD TG 231) (to investigate T-mediated activity in other non-target organisms) - Fish short term reproduction assay (OECD TG 229) (to investigate EAS-mediated activity in other non-target organisms) Depending on the outcome of these tests, additional testing may be needed (in case of positive results). The eCA would suggest to initially complete the level 2 data and secondly perform the AMA test. However, 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).
Remarks	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

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