Biocidal Products Committee (BPC)

Opinion on the application for approval of the active substance:

Willaertia magna C2c Maky

Product type: 11

ECHA/BPC/376/2023

Adopted

5 June 2023

Opinion of the Biocidal Products Committee

on the application for approval of the active substance Willaertia magna C2c Maky for product type 11

In accordance with Article 89(1) of Regulation (EU) No 528/2012 of the European Parliament and of the Council 22 May 2012 concerning the making available on the market and use of biocidal products (BPR), the Biocidal Products Committee (BPC) has adopted this opinion on the non-approval in product type 11 of the following active substance:

Common name:	Willaertia magna C2c Maky
Chemical name:	Not applicable
EC No.:	Not applicable
CAS No.:	Not applicable
New active substance	

This document presents the opinion adopted by the BPC, having regard to the conclusions of the evaluating Competent Authority. The assessment report, as a supporting document to the opinion, contains the detailed grounds for the opinion.

Process for the adoption of the BPC opinion

Following the submission of an application by Amoéba SA on 8 August 2019, the evaluating Competent Authority Malta submitted an assessment report and the conclusions of its evaluation to the ECHA on 17 June 2022. In order to review the assessment report and the conclusions of the evaluating Competent Authority, the Agency organised consultations via the BPC (BPC-47) and its Working Groups (WG-MO, 5 December 2022). Revisions agreed upon were presented and the assessment report and the conclusions were amended accordingly.

Adoption of the BPC opinion

Rapporteur: Malta

The BPC opinion on the application for approval of the active substance *Willaertia magna* C2c Maky in product type 11 was adopted on 5 June 2023.

The BPC opinion was adopted by consensus.

The opinion is published on the ECHA webpage at: http://echa.europa.eu/regulations/biocidal-products-regulation/approval-of-active-substances/bpc-opinions-on-active-substance-approval.

Detailed BPC opinion and background

1. Overall conclusion

The overall conclusion of the BPC is that *the Willaertia magna* C2c Maky in product type 11 may not be approved. The detailed grounds for the overall conclusion are described in the assessment report.

2. BPC Opinion

2.1. BPC Conclusions of the evaluation

a) Presentation of the active substance including the classification and labelling of the active substance

This evaluation covers the use of *Willaertia magna* C2c Maky in product type 11 (preservative for liquid-cooling and processing systems).

The physico-chemical properties of the active substance and biocidal product have been evaluated and are deemed acceptable for the appropriate use, storage and transportation of the active substance and biocidal products BIOMEBA 3%, BIOMEBA 10% and BIOMEBA 30%.

Analytical methods for detection and identification of the active substance as manufactured are available. As a result the identity of the active substance is demonstrated. The demonstration of the identity of the strain level using the Restriction Fragment Length Polymorphism (RFLP) method is inconclusive, however this strain level identity can be specifically demonstrated by the use of a method based on the quantitative Polymerase Chain Reaction (qPCR) upon validation of the method. The presence of living and dead active substance is demonstrated by use of the Malassez counting method with Trypan blue vital staining.

A new 5-batch analysis study is provided but it was not GLP compliant as prescribed by the TAB guidelines. Furthermore, additional critical data and observations to support the analysis are missing or questionable. Specifications for the reference source can therefore not be established.

The description of the method on production has shortcomings. The consistent quality of the active substance and biocidal product produced by described manufacturing process is questionable in regard to concentration, viability and lifecycle stage.

As the technical grade of the active substance and the biocidal products does not contain viable and/or non-viable residues that are toxicologically, ecotoxicologically or environmentally relevant, an analytical method for the detection, identification and quantification of *Willaertia magna* C2c Maky in the matrices soil, air, water and animal and human body fluids and tissues is not required. Similarly, an analytical method for monitoring of the active substance in food and feeding stuff is not required. Analytical methods for impurities are not relevant since there are no impurities in the active substance as manufactured.

There is no classification and labelling for *Willaertia magna* C2c Maky according to Regulation (EC) No 1272/2008 (CLP Regulation) as microorganisms are not in the scope of the CLP regulation. However, all microbial active substances are regarded based on the precautionary principle as potential skin and respiratory sensitisers and the labels will require the following phrase “Microorganisms may have the potential to provoke sensitising reactions”. The active

substance is not included in the list of biological agents from Directive 2000/54/EC on the protection of workers from risks related to exposure to biological agents at work[1].

b) Intended use, target species and effectiveness

Willaertia magna C2c Maky is intended to be used by professionals to prevent the growth of *Legionella pneumophila* in industrial processing water systems.

Phagocytosis and elimination of *Legionella pneumophila* is claimed as mode of action, but was not sufficiently investigated in this application.

The assessment of the efficacy data as was presented in this application indicates that, although the active substance under investigation *Willaertia magna* C2c Maky shows different behaviour towards several *Legionella pneumophila* strains than other Free Living Amoeba (FLA) (e.g. *Willaertia magna* Z503 of the same genus) in some studies it is not unequivocally demonstrated that active substance *Willaertia magna* C2c Maky phagocytises and eliminates/kills *Legionella pneumophila* nor that *Legionella pneumophila* cannot resist digestion by *Willaertia magna* C2c Maky and will reside alive inside the amoebe or even grows.

The latter, so called reservoir- or Trojan Horse effect, cannot be excluded for *Willaertia magna* C2c Maky because determining whether cultured *Legionella pneumophila* came from within the amoebe or not was not explicitly shown due to missing essential study controls. However, regardless of whether the *Legionella pneumophila* measured was present intra- or extracellular in the co-cultures tested, *Willaertia magna* C2c Maky, as was used in the efficacy tests was not able to control total *Legionella pneumophila* growth in some cases, nor eliminate them fully from the culture in others. Therefore the second part of the claimed mode of action for this active substance being "elimination" of *Legionella pneumophila* present, was not substantiated in this submission.

Different Multiplicity of Infection – ratio's (MOI; *Legionella pneumophila* / *Willaertia magna* C2c Maky ratio) were tested in the studies and this led to the conclusion that the efficacy of *Willaertia magna* C2c Maky to eliminate *Legionella pneumophila* is MOI dependent. A specific dose-response effect, which is a requirement for active substance approval, was however not demonstrated. No reasoning was put forward for why the BIOMEBA *Willaertia magna* C2c Maky concentrations were chosen for the field trial applications.

The design of the laboratory studies was poor and was not reported in sufficient detail by the applicant. Minimal (if any) efficacy was seen which was then not substantiated by proper controls. Also *Willaertia magna* C2c Maky batches used were of variable origin and life cycle stage (e.g. Trophozyte/cysts ratio not indicated) and were often not cultured consistently throughout all experiments nor linked to manufactured batches of this submission. Most of the studies were not performed in suspension co-cultures (mimicking active substance use situation) but rather with *Willaertia magna* C2c Maky adhered to a surface. Overall, efficacy was not convincingly demonstrated and therefore insufficient for an active substance admittance.

In conclusion, innate efficacy of *Willaertia magna* C2c Maky was not sufficiently demonstrated in the laboratory studies submitted, main points being:

- *Willaertia magna* C2c Maky, as was used in the efficacy tests was not able to control total *Legionella pneumophila* growth, nor eliminate them fully from the culture and in some cases even favor bacterial growth.

[1] OJ L 262, 17.10.2000 p.21.

- No dose-response to determine optimal *Willaertia magna* C2c Maky concentration for efficacy is presented in this application. Therefore no application rate could be established

During evaluation of the submitted field trial studies it was noticed that the reports were not complete representations of the results obtained and decisions made on when and with how high a dose the active substance was added was not explained. Weekly measurements planned at the start were not all carried out or were not all reported. The applicant stated that long-term monitoring using qPCR as well as the traditional culture methods should be performed to observe valid trends, but in the reports submitted these data were often not shown, nor provided to the evaluators when asked.

For the three Field-trials that could be reviewed, no sufficient data was presented on the reasoning for correction measures taken or the test period was too short to conclude any lasting effects. Also, it was unclear whether the sites originally had a *Legionella pneumophila* problem as that data was not shown.

In conclusion, innate efficacy of *Willaertia magna* C2c Maky was not sufficiently demonstrated in the field trial studies submitted.

The data on *Willaertia magna* C2c Maky and the representative biocidal product have not demonstrated sufficient innate efficacy against the target species *Legionella pneumophila.* Furthermore, limitation of efficacy including resistance was not sufficiently investigated.

c) Overall conclusion of the evaluation including need for risk management measures

Human health

Willaertia magna C2c Maky is not considered to be hazardous based on the available studies. However, using the precautionary principle, all microorganisms may be considered to be potential sensitisers and should be treated as such. For a brief description on the assessment of effects on human health see the follow table.

Endpoint	**Brief description**
Toxicokinetics	Assessment not required for micro-organisms
Acute toxicity	No evidence on pathogenicity, infectivity, mortality or clinical signs of toxicity when tested at the maximum recommended dose (1E+08 *W. magna* C2c Maky/animal) following a single dose via oral gavage (2 mL at 5E+10 *W. magna* C2c Maky/animal) in a study performed according to OPPTS 885.3050. A single application of *W. magna* C2c Maky at 2 mL/kg bw of suspension of *W. magna* C2c Maky at 5E+08 *W. magna* C2c Maky /mL had no effect on the skin of New Zealand white rabbits in a study performed according to OPPTS 885.3100. A single intranasal instillation of a suspension of 1E+08 *W. magna* C2c Maky was not toxic to rats. No evidence of pathogenicity, infectivity, mortality or clinical signs of toxicity were observed in the study performed according to OPPTS 885.3150. Based on this *W. magna* C2c Maky is not considered to be acutely toxic.

Endpoint	Brief description
Corrosion and irritation	A single application of 0.5 mL of 5E+07 *W. magna* C2c Maky/Litre suspension was not irritant/corrosive for the skin of the New Zealand white rabbit in a study performed according to OECD TG 404. A single instillation of 0.1 mL of 5E+07 *W. magna* C2c Maky/Litre suspension is not irritant/corrosive to the eye of the New Zealand White rabbit in a study performed according to OECD TG 405. Based on this *W. magna* C2c Maky is not considered to be irritant/corrosive to the skin or eyes.
Sensitisation	5E+07 *W. magna* C2c Maky / litre suspension was found to be a non sensitiser in the Guinea pig in a study performed according to OECD TG 406. Based on the Ig analysis of serum of rats used in both the acute oral and acute pulmonary pathogenicity study show no specific or non-specific immune response induced by the administration of high concentration of *W. magna* C2c Maky by intranasal and by oral route. Using the precautionary principle, all microorganisms may be considered to be potential sensitisers and should be treated a such.
Repeated dose toxicity	Assessment not required for micro-organisms
Genotoxicity	Assessment not required for micro-organisms
Carcinogenicity	Assessment not required for micro-organisms
Reproductive toxicity	Assessment not required for micro-organisms
Neurotoxicity	Assessment not required for micro-organisms
Immunotoxicity	Assessment not required for micro-organisms
Disruption of the endocrine system	Assessment not required for micro-organisms
Other effects	No other effects were identified in additional information provided.

The table below summarises the exposure scenarios assessed.

Summary table: human health scenarios			
Scenario	**Primary or secondary exposure[2] and description of scenario**	**Exposed group**	**Conclusion**
Loading of biocidal product into the injection cabinet	By loading the product cubitainer into the injection cabinet (injection pump), the water treatment operator may be in dermal contact with a small volume (milliliters) of the biocidal product.	Professionals	Acceptable with gloves, goggles, mask and appropriate clothing
Maintenance of the industrial water system	By maintenance of the industrial water system, cleaning the dispensing pump, maintenance of the equipment, monitoring the system and waste disposing, industrial staff can be exposed by dermal contact and/or by inhalation (when an aerosol is generated) via treated water.	Professionals	Acceptable with gloves, goggles, mask and appropriate clothing and RPE when aerosols are generated.
Atmospheric emission from cooling system	Around cooling towers, bystanders can be exposed to the plume generated through dermal or inhalation exposure.	Bystanders	Not acceptable

Industrial uses

BIOMEBA 3%, BIOMEBA 10% and BIOMEBA 30% biocidal products can be used in cooling towers on industrial sites or on buildings. Therefore, industrial exposure and professional exposure will be identical. Please see professional exposure section below.

Professional uses

The risk from the industrial use of *Willaertia magna* C2c Maky in the biocidal products BIOMEBA 3%, BIOMEBA 10% and BIOMEBA 30% is acceptable when the products are used in accordance with the instructions for use for the prevention of *Legionella pneumophila* growth in cooling water systems.

As all microorganisms are considered potential sensitizers, the use of personal protective equipment is necessary to prevent exposure of the professional operators. Furthermore, due to possible aerosol forming during maintenance activities the use of respiratory equipment is necessary.

The risk for professional users is considered acceptable with the use of personal protective equipment (gloves, goggle, and RPE when aerosols are generated). The use of these protective equipment should be part of the instructions for use.

Secondary (indirect exposure as a result of use)

Exposure of the general public to *Willaertia magna* C2c Maky is possible via the plume generated by the cooling towers. The applicant states that it is a common practice to equip the cooling towers with the drift eliminators retaining the droplets with size above 36 µm. This would reduce a chance of exposure to *Willaertia magna* C2c Maky in its trophozoite form when it has the size that was previously indicated by the applicant (50 - 100 µm). New

[2] See document: Terminology primary and secondary exposure (available from https://webgate.ec.europa.eu/s-circabc/d/a/workspace/SpacesStore/80f71044-fce2-43b3-a73c-e156effc9fcb/Terminology%20primary%20and%20secondary%20exposure.pdf)

information however shows sizes of cultivated amoeba much smaller than 50 µm (ca. 20 µm), which implies that the drift eliminator would not be able to retain the trophozoite form and exposure cannot be ruled out. The extent of the exposure cannot be quantified. As all microorganisms are considered potential sensitizers, general public that is potentially exposed dermally and/or via inhalation might upon exposure suffer from allergic reactions.

Exposure to the cyst form (size 18-21 µm) would also be possible. However, according to the conclusion of the ECHA Working Group – Microorganisms, the conditions in the cooling towers (water temperature, presence of nutrients) do not favour the encystement process.

Finally, the potential impact of the Trojan horse effect on human health needs to be addressed. As discussed in section A.1.6.8, the Trojan horse effect cannot be excluded as it not proven that *Willaertia magna* C2c Maky kills *Legionella pneumophila* after phagocytosis nor that *Legionella pneumophila* cannot multiply within the amoebe. The impact of the Trojan horse effect on the human health is a concern which was not discussed by the Applicant. The concern thus remains and the issue is not resolved.

Environment

There is potential release of *Willaertia magna* C2c Maky to all three environmental compartments (air, water, soil) and the STP via the air plumes of the cooling tower and via discharge of cooling water into receiving waters or into STP treating wastewater from the cooling water system. At the environmental conditions, which are generally unfavorable for *Willaertia magna* C2c Maky and due to competition for space and nutrients with the resident bacteria, it is unlikely that *Willaertia magna* C2c Maky trophozoite form will persist and proliferate in environmental compartments. However, it remains unsure what the fate of the amoeba is following contineous releases into the environmental compartments. Cysts also can be formed in environmental compartments due to harsh conditions and could revert to the vegetative form if conditions become favorable. The Applicant did not discuss the extent of formation of cysts and their persistence in the environment. The concerns as specified below thus also might apply to the cyst form.

Proliferation of *Willaertia magna* C2c Maky in environmental organisms is not expected based on the infectivity / pathogenicity studies showing absence of infectivity in all the tested mammalian and other non-target organisms. Furthermore, *Willaertia magna* C2c Maky does not produce secondary metabolites such as toxins.

For the hazard assessment, several tests were carried out according to OECD or other accepted test guidelines and showed no adverse effects of *Willaertia magna* C2c Maky to the tested organisms. It should be noted that the guidelines have been developed for chemicals and there are no known specific adaptations which can be applied to amoeba. Uncertainties remain on the impact of the experimental conditions (e.g. temperature) as well as the form and size of the *Willaertia magna* C2c Maky (throphozite or cyst). Performing further standard chronic ecotoxicity testing is not requested as the impact of amoebae on other organisms is primarily expected on microorganisms and not on the standard test organisms such as fish and invertebrates. Indeed, the impact of amoebae on other microorganisms from repeated exposure remains unknown.

For the exposure assessment, the Guidance on the BPR: Volume IV Environment, Part B proposes models which are not adapted to micro-organisms. Not all formula’s in the exposure models are easily translated in terms of microorganisms. These models are nevertheless used in a semi-quantitative approach to derive the estimated environmental density (EED) of microorganisms.

In the lack of specific guidance, it was agreed at the Partner Expert Group Meeting on the Guidance on Active Micro-organisms and Biocidal product (27 April 2016), that no PNEC should be derived for microorganism substances. Therefore, endpoints from the available ecotoxicity tests were directly compared to estimated environmental densities (EEDs).

The calculated EED's were also compared to natural densities from literature. This is not considered relevant due to the large overall diversity of protozoan organisms as well as high variations/fluctuations in their densities.

Even though comparison of the EED's with the different available ecotoxicity endpoints resulted in low acute and chronic risks for the environmental compartments, the above stated uncertainties lead to remaining concerns on the full impact of a continuous release into the environment from use of this new biocidal product, especially on microbial populations.

The table below summarises the exposure scenarios assessed.

Summary table: environment scenarios		
Scenario	**Description of scenario including environmental compartments**	**Conclusion**
large open recirculating systems	Direct emission to surface water. Direct emission to air due to evaporation and spray and wind drift, subsequent deposition on soil.	Risk based on available data is low but concerns remain
small open recirculating systems with emission of wastewater directly to surface water	Direct emission to air, surface water and soil through air deposition.	Risk based on available data is low but concerns remain
small open recirculating systems with emission of wastewater to STP	Direct emission to air, soil through air deposition. Emission to surface water, soil via STP	Risk based on available data is low but concerns remain

Another concern is that a Trojan horse effect cannot be excluded as it is not proven that *Willaertia magna* C2c Maky kills *Legionella pneumophila* after phagocytosis nor that *Legionella pneumophila* cannot multilply within the amoebe. A Trojan horse effect can result in unacceptable distribution of *Legionella pneumophila* to surrounding environments.

Consequently, there are too many uncertainties in the environmental risk assessment to conclude on acceptable risks for the environment by the use of *Willaertia magna* C2c Maky.

Overall conclusion

Analytical methods for detection and identification of the active substance as manufactured are available. The demonstration of the identity of the strain level using the Restriction Fragment Length Polymorphism (RFLP) method is inconclusive, however this strain level identity can be specifically demonstrated by the use of a method based on the quantitative Polymerase Chain Reaction (qPCR) upon validation of the method.

Regarding the efficacy and the risk to human health or to the environment, several concerns are identified in consequence of the hazard and exposure assessment for the active substance when considering the intended use and are listed in each relevant section as mentioned above.

The major concerns are described below:

- The consistent quality of the active substance and biocidal product during manufacturing is questionable in regard to concentration, viability and lifecycle stage;

- In laboratory studies, the efficacy of Willaertia magna C2c Maky was not sufficiently demonstrated in the laboratory studies submitted, main points being: (1) *Willaertia magna* C2c Maky, as was used in the efficacy tests was not able to control total Legionella pneumophila growth, nor eliminate them fully from the culture and in some cases even favor bacterial growth. (2) No dose-response to determine optimal *Willaertia magna* C2c Maky concentration for efficacy is presented in this application. Therefore no application rate could be established.

- In addition innate efficacy of *Willaertia magna* C2c Maky was also not sufficiently demonstrated in the field trial studies submitted.

- *Willaertia magna* C2c Maky can act as a reservoir of certain pathogenic strains either in trophozoite or cyst form which leads to a potential Trojan horse effect of the active substance. Considering that the exposure of the general public and the surrounding environment to cysts and trophozoites with a size <36 µmcannot be excluded and that the Trojan horse effect still remains as a concern, it is concluded that the risk is considered as not acceptable for the general public and the environment. A safe use is therefore not demonstrated. In addition, as all microorganisms are considered potential sensitizers, general public that is potentially exposed dermally and/or via inhalation might upon exposure suffer from allergic reactions.

For these reasons it is concluded that a safe use cannot be identified.

2.2. Exclusion, substitution and POP criteria

2.2.1. Exclusion and substitution criteria

The table below summarises the relevant information with respect to the assessment of exclusion and substitution criteria:

Property		**Conclusions**	
CMR properties	Carcinogenicity (C)	Not applicable*	*W. magna* C2c Maky does not fulfil criterion (a), (b) and (c) of Article 5(1)
	Mutagenicity (M)	Not applicable*	
	Toxic for reproduction (R)	Not applicable*	
PBT and vPvB properties	Persistent (P) or very Persistent (vP)	Not applicable **	*W. magna* C2c Maky does not fulfil criterion (e) of Article 5(1) and does not fulfil criterion (d) of Article 10(1)
	Bioaccumulative (B) or very Bioaccumulative (vB)	Not applicable **	
	Toxic (T)	Not applicable**	
Endocrine disrupting properties	Section A of Regulation (EU) 2017/2100: ED	Not applicable ***	W. magna C2c Maky does not

Property		Conclusions	
	properties with respect to humans		fulful criterion (d) of Article 5(1)and does not fulfil criterion (a) of Article 10(1)
	Section B of Regulation (EU) 2017/2100: ED properties with respect to non-target organisms	Not applicable ***	
	Article 57(f) and 59(1) of REACH	Not applicable ***	
	Intended mode of action that consists of controlling target organisms via their endocrine system(s)	Not applicable ***	
Respiratory sensitisation properties	No data indicate respiratory sensitization and therefore no classification is required. Based on the precautionary principle all microorganisms may be considered as potential sensitisers and should be treated as such. *Willaertia magna* C2c maky does not fulfil criterion (b) of Article 10(1).		
Concerns linked to critical effects other than those related to endocrine disrupting properties	Unknown *Willaertia magna* C2c maky does not fulfil criterion (e) of Article 10(1).		
Proportion of non-active isomers or impurities	Not relevant *Willaertia magna* C2c maky does not fulfil criterion (f) of Article 10(1).		

* The active substance *Willaertia magna* C2c maky as a microorganism is not in the scope of Regulation (EC) No 1272/2008 (CLP Regulation)

** The active substance *Willaertia magna* C2c maky as a microorganism is excluded from the PBT assessment based on Annex XIII of the REACH Regulation 1907/2006.

*** The active substance *Willaertia magna* C2c maky as a microorganism is excluded from an ED assessment based on Regulation (EU) No 2017/2100 and (EU) No 2022/1439.

Consequently, the following is concluded:

Willaertia magna C2c Maky does not meet the exclusion criteria laid down in Article 5 of Regulation (EU) No 528/2012.

Willaertia magna C2c Maky does not meet the conditions laid down in Article 10 of Regulation (EU) No 528/2012 and is therefore not considered as a candidate for substitution. The exclusion and substitution criteria were assessed in line with the "Note on the principles for

taking decisions on the approval of active substances under the BPR"[3], "Further guidance on the application of the substitution criteria set out under article 10(1) of the BPR"[4] and "Implementation of scientific criteria to determine the endocrine-disrupting properties of active substances currently under assessment[5]" agreed at the 54th, 58th and 77th meeting respectively, of the representatives of Member States Competent Authorities for the implementation of Regulation 528/2012 concerning the making available on the market and use of biocidal products. This implies that the assessment of the exclusion criteria is based on Article 5(1) and the assessment of substitution criteria is based on Article 10(1)(a, b, d, e and f).

2.2.2. POP criteria

POP assessment is not relevant for active substance *Willaertia magna* C2c Maky.

2.3. BPC opinion on the application for approval of the active substance *Willaertia magna* C2c Maky in product type 11

In view of the conclusions of the evaluation, it is proposed that *Willaertia magna* C2c Maky shall not be approved and included in the Union list of approved active substances.

As all microorganisms are considered as potential sensitisers, based on the precautionary principle, the active substance may not fulfil the criteria according to Article 28(2) to enable inclusion in Annex I of Regulation (EU) 528/2012.

It is noted that the BPC adopted an opinion on the same active substance PT combination in 2018 (ECHA/BPC/206/2018). This opinion was based on an application of the same applicant in 2014. The current opinion differs from the one in 2018 in the additional data submitted on all aspects (e.g. efficacy, batch analysis, environment) . This data did not lead to conclusions, as represented in this opinion, that differ from the ones of 2018.

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[3] See document: Note on the principles for taking decisions on the approval of active substances under the BPR (available from https://circabc.europa.eu/d/a/workspace/SpacesStore/c41b4ad4-356c-4852-9512-62e72cc919df/CA-March14-Doc.4.1%20-%20Final%20-%20Principles%20for%20substance%20approval.doc).
[4] See document: Further guidance on the application of the substitution criteria set out under article 10(1) of the BPR (available from https://circabc.europa.eu/d/a/workspace/SpacesStore/dbac71e3-cd70-4ed7-bd40-fc1cb92cfe1c/CA-Nov14-Doc.4.4%20-%20Final%20-%20Further%20guidance%20on%20Art10(1).doc).
[5] See document: Implementation of scientific criteria to determine the endocrine –disrupting properties of active substances currently under assessment (available from https://circabc.europa.eu/sd/a/48320db7-fc33-4a91-beec-3d93044190cc/CA-March18-Doc.7.3a-final-%20EDs-%20active%20substances%20under%20assessment.docx).