Data Requirements and Scientific Criteria for the Determination of Endocrine Disrupting Properties of Active Substances Contained in Plant Protection Products or Biocidal Products in the European Union, and the Assessment of Endocrine Disrupting Properties of Active Substances after the Implementation of the New Criteria

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After the Plant Protection Product (PPP) Directive 91/414/EEC and the Biocidal Product (BP) Directive 98/8/EC were replaced by the PPP Regulation 1107/2009 and the BP Regulation 528/2012, respectively, an active substance (AS) having endocrine disrupting properties that may cause adverse effects in humans or in non-target organisms may not be approved in principle. However, new scientific criteria for the determination of endocrine disrupting properties of active substances were set out and applied in 2018. In this article, the data requirements on endocrine disrupting properties, the criteria set out temporarily, the specific scientific criteria laid down, and the assessment procedure after the introduction of new scientific criteria, *etc*. are summarised.

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Introduction

In the European Union (EU), the European Commission has had a Strategy on Endocrine Disruptors since 1999, and subsequent revisions to EU legislation took this strategy into account. The Plant Protection Product (PPP) Directive concerning the placing of PPPs on the market, which was for the products used for agricultural purposes, and the Biocidal Product (BP) Directive concerning the placing of BPs on the market, which was for the products used for non-agricultural purposes, were replaced by the PPP Regulation and the BP Regulation, respectively. These Regulations set out so-called cut-off criteria or exclusion criteria, which are related to the criteria for the approval of an active substance (AS), and having endocrine disrupting properties that may have adverse effects in humans or in non-target organisms was included in those criteria.

Data on endocrine disrupting properties has been additionally included in data requirements for chemical ASs under the PPP Regulation and the BP Regulation. However, until new scientific criteria were set out and applied in 2018, interim criteria were applied to determine whether an AS had endocrine disrupting properties. The Guidance for the Identification of Endocrine Disruptors was developed for the implementation of the new scientific criteria. In addition, provisions were set out on the assessment procedure as regards endocrine disrupting properties of a chemical AS for which an application for approval or renewal of approval of the AS was submitted before the application of the new scientific criteria.

Sumika Technoservice Corporation has been investigating regulatory information on approval/renewal of approval of ASs used in PPPs or BPs in the EU for many years and providing support in the process of approval/renewal of approval. Because whether ASs have endocrine disrupting properties has become an important factor in the decision on the approval/renewal of approval of ASs, we have been collecting information on data requirements related to endocrine disrupting properties, the cases of determination of endocrine

disrupting properties based on the interim criteria and the new scientific criteria, and the cases of assessing endocrine disrupting properties of chemical ASs for which applications for approval or renewal of approval had already been submitted before the application of the new scientific criteria. Based on our accumulated experience, this article will give an overview of the data requirements on endocrine disrupting properties of chemical ASs under the PPP Regulation and the BP Regulation, the cases of determination of endocrine disrupting properties based on the interim criteria and the new scientific criteria, the assessment procedure as regards endocrine disrupting properties of chemical ASs for which applications for approval or renewal of approval had already been submitted before the application of the new scientific criteria, and the potential impacts when a chemical AS is determined to have endocrine disrupting properties.

Provisions on endocrine disrupting properties under the PPP/BP Directives in the EU

Directive 91/414/EEC concerning the placing of PPPs on the market[1], which was for the products used for agricultural purposes, was published in the Official Journal (OJ) on 19 August 1991. Directive 98/8/EC concerning the placing of BPs on the market[2], which was for the products used for non-agricultural purposes, was published in the OJ on 24 April 1998.

Because it was 1999 when the Community Strategy for Endocrine Disrupters[3] was adopted, this strategy, adopted in 1999, was not reflected in the PPP Directive or the BP Directive.

Annex VI to the PPP Directive 91/414/EEC specified the uniform principles for the evaluation of PPPs, but endocrine disrupting properties were not included.

The data requirements for chemical ASs specified in Annex IIA did not include data requirements on endocrine disrupting properties, either.

With respect to the BP Directive 98/8/EC, 'Common principles for the evaluation of dossiers (documents and data package of the application) for BPs' in Annex VI referred to endocrine effects as effects on the environment to be considered. However, the data requirements for chemical ASs specified in Annex IIA and Annex IIIA did not include data requirements on endocrine disrupting properties.

Point 6.3 'Long-term action' of the strategy adopted in 1999 indicated that the European Commission would consider the adaptation of the PPP Directive and the BP Directive to take account of substances on the endocrine disruptors (ED) priority list which fell within the category of PPPs or BPs. On the implementation of the strategy adopted in 1999, the progress of the work was reported at regular intervals in 2001[4], 2004[5], 2007[6], and 2011[7].

According to the report made in 2004, because of the need for having a test procedure which could confirm whether or not substances were endocrine disrupting substances, as soon as agreed test methodologies were endorsed by the Organisation for Economic Co-operation and Development (OECD), these could be integrated into the assessment process under the PPP Directive 91/414/EEC. In the meantime, where substances were being evaluated and where there was a suspicion of endocrine disrupting potential of a substance, additional testing had been requested. Several substances had so far been tested according to a specific protocol called 'fish full life cycle test'. The report stated that although the Technical Notes for Guidance on data requirements had been adopted under the BP Directive 98/8/EC, there were no clear defined or standardised test methods for several endpoints as at the time the report was prepared.

According to the report made in 2007, the issue of possible endocrine disrupting properties of ASs used in PPPs was not yet fully incorporated in the risk assessment procedures under the PPP Directive 91/414/EEC because of lack of harmonised and internationally-agreed test protocols. In the meantime, where substances were being evaluated and where there was a suspicion of endocrine disrupting potential of a substance, additional testing had been requested, and several substances had so far been tested according to a specific protocol called 'fish full life cycle test'. The report stated that the new proposal for a PPP Regulation replacing the PPP Directive 91/414/EEC included provisions that prohibited the use of ASs that had been identified as endocrine disruptors, unless the exposure of humans to the AS in a PPP, under realistic proposed conditions of use, was negligible and that consideration of endocrine disrupting properties of ASs would receive greater priority in decision-making.

According to the report made in 2011, substances identified as having endocrine disrupting properties that may cause adverse effects in humans could not be authorised under the new PPP Regulation. By December 2013, the European Commission was required to

present a draft of the measures concerning specific scientific criteria for the determination of endocrine disrupting properties to be adopted. With regard to the ecological impacts, substances having endocrine disrupting properties that may have adverse effects on non-target organisms, could also not be authorised under the PPP Regulation. However, in contrast to the situation with human health impacts, there was no obligation upon the European Commission to present criteria for the determination of endocrine disrupting properties in relation to non-target organisms.

Provisions similar to the provisions of the new PPP Regulation described above were to be included in new BP Regulation replacing the BP Directive.

Under the PPP Directive 91/414/EEC, the three AS Approval Directives (Directive 2006/132/EC[8], Directive 2006/133/EC[9] and Directive 2006/134/EC[10]) published in the OJ on 12 December 2006 required the submission of further studies to address potential endocrine disrupting properties as the conditions of approval. However, the deadline for the submission was specified as within two years of the adoption of the Test Guidelines (TGs) on endocrine disruption by the OECD.

With respect to the AS Approval Directives that required submission of further studies to address potential endocrine disrupting properties as the conditions of approval, there was a case (Directive 2009/77/EC[11]) where fish full life cycle test was required. In the first case where this study was required, the deadline for the submission was specified as 31 December 2011, within two years after the date of the approval of the AS, 1 January 2010.

Development of test methods for endocrine disrupting properties by the OECD

According to the OECD document titled 'OECD work on Endocrine Disrupting Chemicals'[12], in 1996, an Advisory Group (AG) on Endocrine Disrupters Testing and Assessment (EDTA) was set up at the OECD to develop new or update existing OECD TGs to identify chemicals with endocrine disrupting properties. The 'Conceptual Framework (CF) for Testing and Assessment of Endocrine Disrupters' was developed by the AG.

The Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption[13] published as OECD Series on Testing and Assessment No. 150 in 2012 showed the original version of the Conceptual Framework for Testing and Assessment of Endocrine Disrupters and the version modified/updated by the EDTA AG in 2011. The revised version included additional assays that were considered relevant to assessment of EDs. The CF as revised in 2011 listed the OECD TGs and standardised test methods available, under development or proposed that could be used to evaluate chemicals for endocrine disruption.

In the context of this Guidance Document, an endocrine disruptor has been defined according to the 'Global assessment of the state-of-the-science of endocrine disruptors'[14] published by the World Health Organisation (WHO) in 2002, and guidance on how to interpret the results from the assays included in the Conceptual Framework was provided.

The Guidance Document published in 2012 was later updated and published as the 'Revised Guidance Document 150 on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption'[15] in 2018.

Provisions on endocrine disrupting properties under the PPP/BP Regulations in the EU

The PPP Directive 91/414/EEC was replaced by the PPP Regulation 1107/2009[16] published in the OJ on 24 November 2009, and the BP Directive 98/8/EC was replaced by the BP Regulation 528/2012[17] published in the OJ on 27 June 2012. These new Regulations set out so-called cut-off criteria or exclusion criteria, which are part of criteria for the approval of ASs, and these criteria include having endocrine disrupting properties that may cause adverse effects in humans (Point 3.6.5 of Annex II to Regulation 1107/2009 and Article 5(1)(d) of Regulation 528/2012). Under the PPP Regulation 1107/2009, having endocrine disrupting properties that may cause adverse effects on non-target organisms is included in the cut-off criteria (Point 3.8.2 of Annex II to Regulation 1107/2009). Under the BP Regulation 528/2012, being identified in accordance with Articles 57(f) and 59(1) of Regulation 1907/2006[18] concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as having endocrine disrupting properties (Article 5(1)(d) of Regulation 528/2012) is included in the exclusion criteria.

Both under the PPP Regulation 1107/2009 and under the BP Regulation 528/2012, there are certain provisions and if the conditions set out in the provisions are

met, even when an AS has endocrine disrupting properties and thereby meets the cut-off criteria or exclusion criteria, the AS may be approved for a limited period.

Under the PPP Regulation 1107/2009, even if an AS has endocrine disrupting properties that may cause adverse effects in humans or on non-target organisms and thereby meets the cut-off criteria, if all the conditions set out in Article 4(7) are met, the substance may be approved for a limited period not exceeding five years by way of derogation (Article 4(7) of Regulation 1107/2009). Under the BP Regulation 528/2012, even if an AS has endocrine disrupting properties that may cause adverse effects in humans and thereby meets the exclusion criteria, if at least one of the conditions set out in Article 5(2) is met, the substance is considered a Candidate for Substitution (CfS) and may only be approved for an initial period not exceeding five years, and each renewal shall be for a period not exceeding seven years (Article 5(2), Article 4(1) and Article 10(1)(a) and (4) of Regulation 528/2012).

When the PPP Regulation 1107/2009 and the BP Regulation 528/2012 were published in the OJ, scientific criteria for the determination of endocrine disrupting properties had not yet been developed. Pending the adoption of scientific criteria, substances that were or had to be classified, in accordance with the provisions of the CLP Regulation 1272/2008[19], as carcinogenic category 2 and toxic for reproduction category 2, were considered to have endocrine disrupting properties. In addition, substances such as those that were or had to be classified as toxic for reproduction category 2 and which had toxic effects on the endocrine organs, may be considered to have such endocrine disrupting properties.

With respect to scientific criteria for the determination of endocrine disrupting properties, the PPP Regulation 1107/2009 provided that by 14 December 2013, the European Commission should present a draft of the measures, and the BP Regulation 528/2012 provided that by no later than 13 December 2013, the European Commission should adopt the delegated acts.

The data requirements for chemical ASs used in PPPs were specified in Part A of the requirements for the dossier to be submitted for the approval of an AS (inclusion of an AS in Annex I) in Annex II to the PPP Directive 91/414/EEC.

Certain provisions set out in the Annexes to the PPP Directive 91/414/EEC were to be transferred into separate legal instruments to be adopted by the European Commission within 18 months after the entry into force of the PPP Regulation 1107/2009, and the provisions on the data requirements for ASs were to be adopted as a Regulation on data requirements for ASs by 14 June 2011 (Article 84(b) of Regulation 1107/2009). The content of Annex II to the PPP Directive 91/414/EEC was succeeded to by the AS Data Requirements Regulation 544/2011[20] published in the OJ on 11 June 2011 without any substantial modification.

In accordance with the provisions on amendments to the Regulations on data requirements taking into account current scientific and technical knowledge (Article 78 (1) (b) of Regulation 1107/2009), the AS Data Requirements Regulation 544/2011 was replaced by the AS Data Requirements Regulation 283/2013[21] published in the OJ on 3 April 2013.

Under the AS Data Requirements Regulation 283/2013, the data requirements for chemical ASs are specified in Part A of the Annex. Endocrine disrupting properties have been added to the data requirements in Part A, such as Point 5.8.3 under Point 5.8 'Other toxicological studies' in Section 5 'Toxicological and metabolism studies' and Points 8.1.5 and 8.2.3 under Point 8.1 'Effects on birds and other terrestrial vertebrates' and under Point 8.2 'Effects on aquatic organisms', respectively, in Section 8 'Ecotoxicological studies'.

The AS Data Requirements Regulation 544/2011 specified the test guidelines under each data requirement point. However, the AS Data Requirements Regulation 283/2013 does not include the information on test methods or guidance documents relevant for each data requirement point. Such information was to be published in the OJ as different type of document from Regulation. The information on test methods and guidance documents corresponding to data requirements for ASs was published in the OJ as Communication 2013/C95/01[22] on 3 April 2013, which was the same day as the publication of the AS Data Requirements Regulation 283/2013.

The test methods recommended for Points 5.8.3, 8.1.5 and 8.2.3, which are data requirements on endocrine disrupting properties, are those included in the Conceptual Framework presented in the 'Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption' published in 2012 as OECD Series on Testing and Assessment No. 150. These test methods are shown in **Table 1**.

The AS Data Requirements Regulation 283/2013 entered into force on 23 April 2013, the twentieth day

Table 1 Test methods for the determination of endocrine disrupting properties of ASs indicated in Communication 2013/C 95/01 (OJ 2013.04.03)

Reference to Part A of the Annex to Regulation 283/2013	Test methods	Included in the OECD CF	Level of the OECD CF
5.8.3. Endocrine disrupting properties	H295R Steroidogenesis assay (OECD TG 456)	○	Level 2
	Hershberger bioassay in Rats, A short-term screening assay for (anti) androgenic properties (OECD TG 441)	○	Level 3
	Stably transfected human estrogen receptor-alpha transcriptional activation assay for detection of estrogenic agonist-activity of chemicals (OECD TG 455)	○	Level 2
	Uterotrophic bioassay in rodents, A short-term screening test for oestrogenic properties (OECD TG 440)	○	Level 3
	Pubertal development and thyroid function in intact juvenile/peripubertal male rats assay (US EPA TG*1 890.1500)	○	Level 4
	Pubertal development and thyroid function in intact juvenile/peripubertal female rats assay (US EPA TG*1 890.1450)	○	Level 4
	15-day intact adult male rat assay (US EPA 2007)	○	Level 4
8.1.5. Endocrine disrupting properties	–	–	–
8.2.3. Endocrine disrupting properties	Fish short term reproduction assay (OECD TG 229)	○	Level 3
	21-day fish assay: A short-term screening for oestrogenic and androgenic activity, and aromatase inhibition (OECD TG 230)	○	Level 3
	Amphibian metamorphosis assay (OECD TG 231)	○	Level 3
	Fish sexual development test (OECD TG 234)	○	Level 4

*1 US EPA Series 890 Endocrine Disruptor Screening Program Test Guidelines. The acronym 'OPPTS' or 'OCSPP', which is included as part of the guideline's number is omitted. The guidelines issued before 2010.04.22, refer to 'OPPTS', whereas those issued after that day, refer to 'OCSPP', because the office name changed from 'Office of Prevention, Pesticides and Toxic Substances' and 'OPPTS' to 'Office of Chemical Safety and Pollution Prevention' and 'OCSPP'. This name change did not otherwise affect the guidelines.

following that of its publication in the OJ on 3 April 2013 and applied from 1 January 2014 (Article 5(1) and (2) of Regulation 283/2013).

According to the 'Guidance Document for Applicants on preparing Dossiers for the Approval of a Chemical New Active Substance and for the Renewal of Approval of a Chemical Active Substance according to Regulation (EU) No 283/2013 and Regulation (EU) No 284/2013[23),24)], the guidance document for preparing dossiers in accordance with the AS Data Requirements Regulation 283/2013 and the PPP Data Requirements Regulation 284/2013 should be used for dossiers prepared for ASs covered by the Renewal Procedure Regulation 844/2012[25)], which means ASs belonging to Annex I Inclusion Renewal (AIR) Group 3, so-called AIR3, 3rd group of ASs which approval (former 'Annex I inclusion') to be renewed and subsequent groups, and for ASs for which an application for the approval has been submitted as from 1 January 2014.

This means that if a dossier submitted as from 1 January 2014 for the approval of a chemical AS or for the renewal of approval of a chemical AS belonging to AIR3 or a subsequent group, it is necessary to submit data on endocrine disrupting properties or justification for non-submission of data.

The PPP Regulation 1107/2009 entered into force on 14 December 2009, the twentieth day following that of its publication in the OJ on 24 November 2009 and applied from 14 June 2011 (Article 84 of Regulation 1107/2009).

With respect to chemical ASs belonging to AIR2, of which dossiers for the renewal of approval were submitted after the application date of the PPP Regulation 1107/2009, and chemical ASs for which an application for the approval was submitted by 31 December 2013, submitted dossiers were prepared in accordance with the AS Data Requirements Regulation 544/2011, therefore data of studies specific to endocrine disrupting properties were not included in principle in those dossiers at the time of submission.

With respect to data requirements for chemical ASs used in BPs Annex IIA to the BP Directive 98/8/EC specified the Common Core Data Set, and Annex IIIA specified the Additional Data Set. The Annexes to the BP Directive 98/8/EC contained only the titles of points of the data requirements. However, the 'Guidance on data requirements for active substances and biocidal products'[26] dated October 2000 set out the detailed content of data requirements.

Under the BP Regulation 528/2012, data requirements for chemical ASs are specified in Title 1 of Annex II. In Title 1 of Annex II, the Common Core Data Set for chemical ASs specified in Annex IIA and the Additional Data Set specified in Annex IIIA to the BP Directive 98/8/EC are included in the same table.

Data requirements on endocrine disrupting properties have been added, such as Point 8.13.3 'Endocrine disruption' under Point 8.13 'Additional studies' in Point 8 'Toxicological Profile for Human and Animal including Metabolism' and Point 9.10 'Identification of endocrine activity' in Point 9 'Ecotoxicological studies'.

The details of each data requirement under the BP Regulation 528/2012 are provided in the four guidance documents each of which contains Part A, corresponding to the information requirements, of each of four volumes, Volume I to Volume IV by major areas, as shown in **Table 2**.

The Guidance on information requirements Version 1.0 dated July 2013[27] does not provide any specific test guidance with regard to Point 8.13.3. With respect to Point 9.10, OECD TG 229 'Fish Short Term Reproduction Assay', OECD TG 230 '21-day Fish Assay' and OECD TG 234 'Fish Sexual Development Test' were referred. The test methods are those included in the Conceptual Framework presented in the 'Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption' published in 2012 as OECD Series on Testing and Assessment No. 150.

The BP Regulation 528/2012 entered into force on 17 July 2012, the twentieth day following that of its publication in the OJ on 27 June 2012 and applied from 1 September 2013 (Article 97 of Regulation 528/2012).

The data requirements for chemical ASs specified in Title 1 of Annex II to the BP Regulation 528/2012 were partially amended by the Amendment Regulation 2021/525[28] published in the OJ on 26 March 2021. Several data requirements including Point 8.13.3 'Endocrine disruption' and Point 9.10 'Endocrine disruption' (previously titled 'Identification of endocrine activity') were modified by this Amendment Regulation. The new test methods which are included in the revised edition of OECD Series on Testing and Assessment No. 150 published in 2018 and also included in the EFSA/ECHA 'Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009'[29] mentioned later, were introduced under the points related to endocrine disruption.

Assessment of endocrine disrupting properties according to the interim criteria

Until the new scientific criteria were set out and applied in 2018, the aforementioned interim criteria,

Table 2 ECHA Guidances which describe how to fulfil the information requirements set by the BP Regulation 528/2012

Volume number	Part(s) covered	Title
Volume I	Parts A+B+C	Identity of the active substance/physico-chemical properties/analytical methodology-Information requirements, evaluation and assessment
Volume II	Part A	Efficacy - Information requirements
Volume III	Part A	Human health - Information requirements
Volume IV	Part A	Environment - Information requirements

namely 'being classified as carcinogenic category 2 and toxic for reproduction category 2, or being classified as toxic for reproduction category 2 and having toxic effects on the endocrine organs', applied when determining whether an AS had endocrine disrupting properties under either the PPP Regulation 1107/2009 or the BP Regulation 528/2012.

The Dangerous Substances Directive (DSD) 67/548/EEC[30], in which provisions relating to the classification and labelling of chemical substances were set out, was replaced by the CLP Regulation 1272/2008 published in the OJ on 31 December 2008, which changed the evaluation procedure for setting/revising classification and labelling. In addition, an AS used in PPPs or BPs is normally subject to EU Harmonised Classifications and Labelling (CLH) (Article 36(2) of Regulation 1272/2008).

Among the chemical ASs used in PPPs or BPs on which non-approval or non-renewal of approval was decided before the application of the new scientific criteria, there were some cases where the reasons for non-approval or non-renewal of approval included ASs'meeting the interim criteria for the determination of endocrine disrupting properties. With respect to chemical ASs used in PPPs for which Non-renewal of approval Regulations 2016/871[31], 2016/872[32], 2017/244[33], 2017/1496[34], and 2017/2091[35] as shown in **Table 3** were published, ASs' meeting the interim criteria for the determination of endocrine disrupting properties was indicated in the recital of each Regulation. Among those cases where the chemical ASs were considered to meet the interim criteria for the determination of endocrine disrupting properties, there were cases where the determination was not made according to the Harmonised Classifications and Labelling adopted by the European Chemicals Agency (ECHA)'s Committee for Risk Assessment (RAC) but the previous EU hazard classification under the DS Directive or the proposed hazard classification indicated in the European Food and Safety Authority (EFSA) Conclusion of the ASs. However, there was no case where the non-renewal of approval was decided solely on the basis of meeting the interim criteria for the determination of endocrine disrupting properties. For all the chemical ASs meeting the interim criteria, concerns other than endocrine disrupting properties were identified, so the non-renewal of approval was to be decided regardless of whether the interim criteria for the determination of endocrine disrupting properties were met.

Among the chemical ASs that were considered to meet the interim criteria for the determination of endocrine disrupting properties, the evaluation of data concerning necessity and the assessment of negligible exposure were conducted on some chemical ASs to determine whether the conditions for derogation were met and the ASs may be approved.

Table 3 PPP ASs that were considered to have endocrine disrupting properties pursuant to the interim provisions of the fourth paragraph of Point 3.6.5 of Annex II to the PPP Regulation 1107/2009

Active substance	EFSA Conclusion	Necessity/Negligible exposure	Former EU CLH*1	RAC	OJ
Amitrole	Repr.1B (2014.06.19)	–	Repr.2	–	Repr.2 + EO*2 (2016.06.02)
Isoproturon	Carc.2 + Repr.2 (2015.07.28)	–	Carc.2	Carc.2 (2016.06.03)	Carc.2 + Repr.2 (2016.06.02)
Linuron	Carc.2 + Repr.1B (2016.06.01)	–	Carc.2 + Repr.1B	–	Carc.2 + Repr.1B (2017.02.11)
Flupyrsulfuron-methyl	Carc.2 + Repr.2 (2014.10.22)	(2017.03.16)/ withdrawn	(no CMR*3)	–	Carc.2 + Repr.2 (2017.08.24)
Iprodione	Carc.1B + Repr.2 (2016.10.14)	–	Carc.2	–	Carc.1B + Repr.2 (2017.11.15)
Pymetrozine	Carc.2 + Repr.2 (2014.08.22)	(2017.12.06)/(2016.12.12)	Carc.2	Carc.2 + Repr.2 (2018.03.09)	Not finalised (2018.10.10)
Isoxaflutole	Carc.2 + Repr.2 (2016.02.16)	(2017.06.13)/(2017.02.08)	Repr.2	Repr.2 (2013.03.08)	Not ED (2019.05.10)

Carc.: Carcinogenicity, Repr.: Reproductive toxicity

*1 Harmonised classifications and labelling arising from translation of the classifications listed in Annex I to the DSD 67/548/EEC

*2 EO : Endocrine organs

*3 CMR : Carcinogenic, Mutagenic or toxic for Reproduction

With respect to the chemical ASs used in PPPs that were considered to meet the interim criteria for the determination of endocrine disrupting properties, ASs' meeting the interim criteria for the determination of endocrine disrupting properties was not indicated in recital of Non-renewal of approval Regulations published after the establishment of the new scientific criteria, such as the Non-renewal of approval Regulation 2018/1501[36] published in the OJ on 10 October 2018. In the Non-renewal of approval Regulation 2018/1501, it was stated that the EFSA concluded that the chemical AS caused adverse effects on endocrine organs, however the scientific assessment for potential endocrine disrupting properties could not be finalised.

Among the chemical ASs that were once considered to meet the interim criteria for the determination of endocrine disrupting properties, the approval of some ASs was renewed because a decision on their renewal or non-renewal of approval was made after the application of the new scientific criteria, based on which they were considered to not have endocrine disrupting properties. An example is Isoxaflutole, of which approval was renewed under the Renewal of approval Regulation 2019/717[37] published in the OJ on 10 May 2019.

For ASs used in BPs, the Opinion on the application for approval of the AS prepared by the Biocidal Products Committee (BPC) shows the table summarising the relevant information with respect to the assessments of exclusion criteria and CfS criteria in which whether the relevant AS meets the interim criteria for the determination of endocrine disrupting properties is indicated. With respect to applications for approval of AS/Product Type (PT) of BP, Chlorophene/PT3, which was not approved as provided by the Non-approval Decision 2018/622[38], fulfils the interim criteria as an AS with endocrine disrupting properties due to the classification as Carc.2 and Repr.2 according to the table shown in Point 2.2.1 'Exclusion and substitution criteria' in the BPC Opinion dated 3 October 2017[39]. In the case of ASs used in BPs even if an AS is considered as having endocrine disrupting properties that may cause adverse effects in humans, it may be approved as derogation, if it is shown that at least one of the prescribed conditions is met (Article 5(2) of Regulation 528/2012). However, in the case of Chlorophene/PT3, the scenarios evaluated in the human health risk assessment identified unacceptable risks and non-approval was proposed in view of the conclusions of the evaluation, so there was no need to examine whether the conditions for derogation were met. In the recital of the Non-approval Decision 2018/622 published in the OJ on 23 April 2018 after the application of new scientific criteria, AS's meeting the interim criteria for the determination of endocrine disrupting properties was not mentioned as a reason for non-approval. The reason for non-approval was that the scenarios evaluated in the human health risk assessment had identified unacceptable risks; therefore, it was not appropriate to approve Chlorophene/PT3.

According to the BPC Opinion dated 13 December 2017[41], Cholecalciferol/PT14 approved as provided by the Approval Regulation 2019/637[40] was a pro-hormone and therefore met the new scientific criteria laid down in the Regulation the Regulation 2017/2100 setting out scientific criteria for the determination of endocrine disrupting properties[42], published in the OJ on 17 November 2017, to be considered as having endocrine disrupting properties that may cause adverse effects in humans. In the case of Cholecalciferol/PT14, though the AS was considered as having endocrine disrupting properties that may cause adverse effects in humans, one of the conditions for approval as derogation was satisfied so it was approved for a period of five years, which was a shorter period compared with most of the approved ASs. In the recital of the Approval Regulation 2019/637 published in the OJ on 24 April 2019 it was stated that Cholecalciferol met the new scientific criteria laid down in Regulation 2017/2100 to be considered as having endocrine disrupting properties that may have adverse effects in humans and therefore met the exclusion criterion, but one condition for derogation set out in Article 5(2)(c) of the BP Regulation 528/2012 was met, it was therefore appropriate to approve Cholecalciferol/PT14. The condition set out in Article 5(2)(c) of the BP Regulation 528/2012 is 'not approving the AS would have a disproportionate negative impact on society when compared with the risk to human health, animal health or the environment arising from the use of the AS' (Article 5(2)(c) of Regulation 528/2012).

New scientific criteria for the determination of endocrine disrupting properties

With respect to scientific criteria for the determination of endocrine disrupting properties, the PPP Regulation 1107/2009 provided that by 14 December 2013, the European Commission should present a draft of the

measures, and the BP Regulation 528/2012 provided that by no later than 13 December 2013, the European Commission should adopt the delegated acts. However, a draft act setting out scientific criteria was not prepared even after those deadlines. It was 15 June 2016 when the European Commission presented draft acts setting out scientific criteria for the determination of endocrine disrupting properties in the context of the PPP and the BP Regulations[43].

At the same time as the presentation of those drafts, the European Commission published the 'Communication from the Commission to the European Parliament and the Council on endocrine disruptors and the draft Commission acts setting out scientific criteria for their determination in the context of the EU legislation on plant protection products and biocidal products'[44]. This Communication indicated that endocrine disruptors would be defined in accordance with the WHO document published in 2002, as defined in the OECD Guidance published in 2012.

The new scientific criteria for the determination of endocrine disrupting properties were set out by the Amendment Regulation 2018/605[45] published in the OJ on 20 April 2018 for ASs used in PPPs, and by the Regulation 2017/2100 setting out scientific criteria for the determination of endocrine disrupting properties, published in the OJ on 17 November 2017 for ASs used in BPs.

The new scientific criteria for the determination of endocrine disrupting properties under the PPP Regulation are almost identical to those under the BP Regulation, except a single difference. The difference is a provision that exists only in the criteria under the BP Regulation (Section B(3) of Annex to Regulation 2017/2100). Because of disagreement with this provision an earlier draft Amendment Regulation setting out the criteria under the PPP Regulation submitted to the Committee could not achieve qualified majority, so the draft was revised by removing the provision. The criteria under the PPP Regulation were published in the OJ several months later than the criteria under the BP Regulations because the adopted draft was the revised version taking into account of the disagreement with that provision.

The new scientific criteria applied as of 10 November 2018 with regard to the PPP Regulation (Article 2 of Regulation 2018/605) and as of 7 June 2018 with regard to the BP Regulation (Article 2 of Regulation 2017/2100). With respect to the Guidance for the identification of EDs developed by the EFSA/ECHA, comments on the draft Guidance[46] were invited by launching public consultation[47] on 7 December 2017 and after the end of public consultation on 31 January 2018 the Guidance was adopted on 5 June 2018 just in time for application of the criteria as of 7 June 2018.

This Guidance for the identification of EDs was developed in parallel to the update of Series on Testing and Assessment No. 150, of which the revised version was published in 2018. This guidance reflects the content of the updated OECD Conceptual Framework for Testing and Assessment of Endocrine Disrupters presented in the revised version of Series on Testing and Assessment No. 150. However, the focus of this guidance for the identification of EDs is on vertebrate organisms and invertebrate non-target organisms are not specially covered. The guidance is also focused on estrogenic, androgenic, thyroidal and steroidogenic (EATS) modalities for which there is currently the most knowledge available.

Since the new scientific criteria for the determination of endocrine disrupting properties and the guidance on identifying EDs were developed and applied as of 10 November 2018 under the PPP Regulation 1107/2009, in case that the deadline for the submission of studies to address the potential endocrine disrupting properties as the conditions of approval was provided in the Approval/Renewal of approval Directives/Regulations under the PPP Directive 91/414/EEC or the PPP Regulation 1107/2009 and the deadline was specified as within two years after the adoption of the OECD TGs on endocrine disruption or, alternatively, of test guidelines agreed at EU level, the deadline was identified as by 10 November 2020, two years from the date of application of the criteria,10 November 2018.

With respect to Fluopyram, approved as provided by the Approval Regulation 802/2013[48], two pieces of confirmatory information were required as the conditions for approval. One of them was information on its potential endocrine disrupting properties, required to be submitted within two years after adoption of the corresponding OECD TGs on endocrine disruption. The other was required to be submitted by 1 February 2016, two years after the date of approval (Annex to Regulation 802/2013). The minutes of the meeting of 'Standing Committee on Plants, Animals, Food and Feed (SCoPAFF) – Section Phytopharmaceuticals – Legislation' held from 24 to 25 January 2019[49] stated that Member States took note of a revised version of

the review report containing the evaluation of first confirmatory information submitted by the deadline, and that the amended review report also confirmed that information to address the point related to endocrine disrupting properties must be submitted by 10 November 2020.

Some OECD TGs on endocrine disruption were published before the Guidance for the identification of EDs. However, because there was no guidance for identifying a proper testing strategy, the required information on the potential endocrine disrupting properties had not been submitted with regard to many approved ASs including Fluopyram.

In relation to OECD TGs on endocrine disruption, **Table 4** shows the test methods included in the OECD Conceptual Framework for Testing and Assessment of Endocrine Disrupters published in 2018, data requirements for ASs under the EU PPP and BP Regulations and the test methods covered in the Guidance for the identification of EDs.

Assessment of endocrine disrupting properties after the application of the new scientific criteria

After the publication of the new scientific criteria for the determination of endocrine disrupting properties in the OJ and the publication of the Guidance for the

Table 4 Test methods contained within the OECD Conceptual Framework (CF) for Testing and Assessment of Endocrine Disrupting Chemicals and whether they are referred to in the data requirements for ASs of PPP/BP and/or in the ECHA/EFSA ED GD

(a) OECD CF Level 2 Mammalian and Non mammalian toxicology

Test method	Original Adoption	Most Recently Updated	CF 2012	CF 2018	PPP AS Data req. Point	BP AS Data req. Point	BP AS Data req. Point in GD	ED GD
Estrogen receptor binding affinity (OECD TG 493)	2015.07.28	–	○	○	–	–	–	*In-vitro*/A[*2]
Androgen receptor binding affinity (US EPA TG[*1] 890.1150)	2009.10	–	○	○	–	–	–	*In-vitro*/A[*2]
Estrogen receptor transactivation (OECD TG 455, ISO 19040-3)	2009.09.07	2021.06.14	○	○	5.8.3	8.13.3.1 (b) (i)	8.13.3.1 (b) (i)	*In-vitro*/A[*2]
Estrogen receptor transactivation (OECD TG 457)	2012.10.02	Deletion 2018.01.29	–	○	–	–	–	*In-vitro*/-[*3]
Yeast estrogen screen (ISO 19040-1 & 2)	2018.08	–	–	○	–	–	–	*In-vitro*/-[*3]
Androgen receptor transactivation (OECD TG 458)	2016.07.29	2020.06.26	○	○	–	8.13.3.1 (b) (ii)	8.13.3.1 (b) (ii)	*In-vitro*/A[*2]
Thyroid transactivation (If/when TGs are available)	–	–	○	–	–	–	–	*In-vitro*/-[*3]
Steroidogenesis *in vitro* (OECD TG 456)	2011.07.28	2022.06.30	○	○	5.8.3	8.13.3.1 (b) (iii)	8.13.3.1 (b) (iii)	*In-vitro*/A[*2]
MCF-7 cell proliferation assays (ER ant/agonist)	–	–	○	–	–	–	–	*In-vitro*/-[*3]
Aromatase assay (US EPA TG[*1] 890.1200)	2009.10	–	○	○	–	8.13.3.1 (b) (iv)	8.13.3.1 (b) (iv)	*In-vitro*/A[*2]
Thyroid disruption assays (*e.g.* thyroperoxidase inhibition, transthyretin binding)	–	–	–	○	–	–	–	*In-vitro*/-[*3]
Retinoid receptor transactivation assays	–	–	–	○	–	–	–	*In-vitro*/-[*3]
Other hormone receptors assays as appropriate	–	–	–	○	–	–	–	*In-vitro*/-[*3]
High-throughput screens	–	–	–	○	–	–	–	*In-vitro*/-[*3]

*1 US EPA Series 890 Endocrine Disruptor Screening Program Test Guidelines. The acronym 'OPPTS' or 'OCSPP', which is included as part of the guideline's number is omitted. The guidelines issued before 2010.04.22, refer to 'OPPTS', whereas those issued after that day, refer to 'OCSPP', because the office name changed from 'Office of Prevention, Pesticides and Toxic Substances' and 'OPPTS' to 'Office of Chemical Safety and Pollution Prevention' and 'OCSPP'. This name change did not otherwise affect the guidelines.

*2 A : Tests included in the Table 12 of the ED GD.

*3 - : Tests that are mentioned in the ED GD, but not included in the Table 12 of the ED GD.

Table 4 Test methods contained within the OECD Conceptual Framework (CF) for Testing and Assessment of Endocrine Disrupting Chemicals and whether they are referred to in the data requirements for ASs of PPP/BP and/or in the ECHA/EFSA ED GD

(b) OECD CF Level 3 Mammalian toxicology

Test method	Original Adoption	Most Recently Updated	CF 2012	CF 2018	PPP AS Data req. Point	BP AS Data req. Point	BP AS Data req. Point in GD	ED GD
Uterotrophic assay (OECD TG 440)	2007.10.16	-	○	○	5.8.3	8.13.3.1(c)	8.13.3.1(c)	Mammal/A*1
Hershberger assay (OECD TG 441)	2009.09.07	-	○	○	5.8.3	8.13.3.1(c)	8.13.3.1(c)	Mammal/A*1

*1 A : Tests included in the Table 13 of the ED GD.

(c) OECD CF Level 3 Non mammalian toxicology

Test method	Original Adoption	Most Recently Updated	CF 2012	CF 2018	PPP AS Data req. Point	BP AS Data req. Point	BP AS Data req. Point in GD	ED GD
Amphibian metamorphosis assay (AMA) (OECD TG 231)	2009.09.07	-	○	○	8.1.4 / 8.2.3	9.10.2	9.10#	Amphibian/A*1
Fish short-term reproduction assay (FSTRA) (OECD TG 229)	2009.09.07	2012.10.02	○	○	8.2.3	9.10.1	9.10	Fish/A*1
21-day fish assay (OECD TG 230)	2009.09.07	-	○	○	8.2.3	9.10.1	9.10	Fish/A*1
Androgenized female stickleback screen (AFSS) (OECD GD 148)	2011.08.18	2017.08.08	○	○	-	-	-	Fish/B*2
EASZY assay. Detection of endocrine active substances, acting through estrogen receptors using transgenic tg (cyp19a1b: GFP) zebrafish embryos (draft OECD TG → OECD TG 250)	2021.06.14	-	-	○	-	-	-	Fish/B*2
Xenopus embryonic thyroid assay (XETA) (draft OECD TG → OECD TG 248)	2019.06.14	-	○	○	-	-	-	Amphibian/B*2
Juvenile medaka anti-androgen screening assay (JMASA) (draft OECD TG)	-	-	-	○	-	-	-	Fish/B*2
Short-term juvenile hormone activity screening assay using *Daphnia magna* (draft OECD TG)	-	-	-	○	-	-	-	-/-*3
Rapid androgen disruption activity reporter (RADAR) assay (draft OECD TG → OECD TG 251)	2022.06.30	-	-	○	-	-	-	Fish/B*2

TG numbers are not clearly indicated.

*1 A : Established tests validated and published as OECD TGs when the ED GD is issued.

*2 B : Tests not yet received full validation by OECD, or are in the process of OECD validation when the ED GD is issued.

*3 -/- : Tests that are not mentioned in the ED GD.

identification of EDs developed by the EFSA/ECHA, the procedures to conclude the assessment of the endocrine disrupting properties after the application of the new scientific criteria for the determination of endocrine disrupting properties were developed under the PPP Regulation 1107/2009 and the BP Regulation 528/2012, respectively.

Under the PPP Regulation 1107/2009, the Amendment Regulation 2018/1659[50] amending the Renewal Procedure Regulation 844/2012 was published in the OJ on 8 November 2018 and applied from 10 November 2018, which was the date of application of the new scientific criteria for the determination of endocrine disrupting properties.

This Amendment Regulation introduced the provisions in relation to the ASs of which application for renewal of approval had been submitted before 10 November 2018 that the applicant may have opportunity to submit additional studies on endocrine disrupting properties and/or additional information, as necessary,

Table 4 Test methods contained within the OECD Conceptual Framework (CF) for Testing and Assessment of Endocrine Disrupting Chemicals and whether they are referred to in the data requirements for ASs of PPP/BP and/or in the ECHA/EFSA ED GD

(d) OECD CF Level 4 Mammalian toxicology

Test method	Original Adoption	Most Recently Updated	CF 2012	CF 2018	PPP AS Data req. Point	BP AS Data req. Point	BP AS Data req. Point in GD	ED GD
Repeated dose 28-day study (OECD TG 407)	1981.05.12	2008.10.03	○	○	5.3.1	8.9.1#/ 8.13.3(a)(i)	8.9.1/ 8.13.3(a)(i)	Mammal/A*2
Repeated dose 90-day study (OECD TG 408)	1981.05.12	2018.06.25	○	○	5.3.2	8.9.2#/ 8.13.3(a)(ii)	8.9.2/ 8.13.3(a)(ii)	Mammal/A*2
One-generation reproduction toxicity study (OECD TG 415)	1983.05.26	Deleted 2017.10.09 (Effective until 2019.04.09)	○	–	–	–	–	Mammal/A*2
Pubertal development and thyroid function assay in peripubertal male rats (PP male assay) (US EPA TG*1 890.1500)	2009.10	–	○	○	5.8.3	8.13.3.1(d)	8.13.3.1(d)	Mammal/B*3
Pubertal development and thyroid function assay in peripubertal female rats (PP female assay) (US EPA TG*1 890.1450)	2009.10	–	○	○	5.8.3	–	–	Mammal/B*3
Intact adult male endocrine screening assay	–	–	○	–	5.8.3	–	–	–
Prenatal developmental toxicity study (OECD TG 414)	1981.05.12	2018.06.25	○	○	5.6.2	8.10.1/ 8.13.3(a)(iv)	8.10.1/ 8.13.3(a)(iv)	Mammal/A*2
Carcinogenicity studies (OECD TG 451)	1981.05.12	2018.06.25	○	○	5.5	8.11.1#/ 8.13.3(a)(vii)	8.11.1/ 8.13.3(a)(vii)	Mammal/A*2
Chronic toxicity studies (OECD TG 452)	1981.05.12	2018.06.25	○	○	5.5	8.9.3#/ 8.13.3(a)(vii)	8.9.3/ 8.13.3(a)(vii)	Mammal/A*2
Combined chronic toxicity and carcinogenicity studies (OECD TG 453)	1981.05.12	2018.06.25	○	○	5.5	8.9.3#/8.11.1#/ 8.13.3(a)(vii)	8.9.3/8.11.1/ 8.13.3(a)(vii)	Mammal/A*2
Reproduction/developmental toxicity screening test (OECD TG 421)	1995.07.27	2016.07.29	○	○	(5.6.1/ 5.6.2)$	(8.10.1/8.10.2/ 8.10.3/8.13.3)$	(8.10.1/8.10.2/ 8.10.3/8.13.3)$	Mammal/A*2
Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422)	1996.03.22	2016.07.29	○	○	(5.6.1/ 5.6.2)$	(8.10.1/8.10.2/ 8.10.3/8.13.3)$	(8.10.1/8.10.2/ 8.10.3/8.13.3)$	Mammal/A*2
Developmental neurotoxicity (OECD TG 426)	2007.10.16	–	○	○	5.6.2	8.10.3/ 8.13.3(a)(vi)	8.10.3/ 8.13.3(a)(vi)	Mammal/A*2
Repeated dose dermal toxicity: 21/28-day study (OECD TG 410)	1981.05.12	–	–	○	5.3.3	8.9.1#	8.9.1	Mammal/-*4
Subchronic dermal toxicity: 90-day study (OECD TG 411)	1981.05.12	–	–	○	5.3.3	8.9.2#	8.9.2	Mammal/-*4
28-day (subacute) inhalation toxicity study (OECD TG 412)	1981.05.12	2018.06.25	–	○	5.3.3	8.9.1#	8.9.1	Mammal/-*4
Subchronic inhalation toxicity: 90-day study (OECD TG 413)	1981.05.12	2018.06.25	–	○	5.3.3	8.9.2#	8.9.2	Mammal/-*4
Repeated dose 90-day oral toxicity study in non-rodents (OECD TG 409)	1981.05.12	1998.09.21	–	○	5.3.2	8.9.2#/ 8.13.3(a)(iii)	8.9.2/ 8.13.3(a)(iii)	Mammal/-*4

$ Since the TGs are for screening test, other TGs for full studies are indicated under the Data Requirement Points in parentheses. If studies conducted according to the TGs exist, they might be submitted to address the Data Requirement Points in parentheses.
# TG numbers are not clearly indicated.
⋆1 US EPA Series 890 Endocrine Disruptor Screening Program Test Guidelines. The acronym 'OPPTS' or 'OCSPP', which is included as part of the guideline's number is omitted. The guidelines issued before 2010.04.22, refer to 'OPPTS', whereas those issued after that day, refer to 'OCSPP', because the office name changed from 'Office of Prevention, Pesticides and Toxic Substances' and 'OPPTS' to 'Office of Chemical Safety and Pollution Prevention' and 'OCSPP'. This name change did not otherwise affect the guidelines.
⋆2 A : Established tests validated and published as OECD TGs when the ED GD is issued.
⋆3 B : Tests not yet received full validation by OECD, or are in the process of OECD validation when the ED GD is issued.
⋆4 - : Tests that are mentioned in the ED GD, but not included in the tables indicating tests and their main investigated parameters.

Table 4 Test methods contained within the OECD Conceptual Framework (CF) for Testing and Assessment of Endocrine Disrupting Chemicals and whether they are referred to in the data requirements for ASs of PPP/BP and/or in the ECHA/EFSA ED GD

(e) OECD CF Level 4 Non mammalian toxicology

Test method	Original Adoption	Most Recently Updated	CF 2012	CF 2018	PPP AS Data req. Point	BP AS Data req. Point	BP AS Data req. Point in GD	ED GD
Fish sexual development test (FSDT) (OECD TG 234)	2011.07.28	–	○	○	8.2.3	9.10.1	9.10	Fish/A*1
Larval amphibian growth & development assay (LAGDA) (OECD TG 241)	2015.07.28	–	○	○	(8.1.4)‡ (8.1.5)‡ (8.2.3)‡	9.10.2	9.10#	Amphibian/A*1
Avian reproduction assay (OECD TG 206)	1984.04.04	–	○	○	8.1.1.3	9.4.3#	9.4.3	Bird/A*1
Fish early life stage (FELS) toxicity test (OECD TG 210)	1992.07.17	2013.07.26	○	○	8.2.2.1	9.1.6.1#	9.1.6	Fish/–*2
New guidance document on harpacticoid copepod development and reproduction test with *Amphiascus tenuiremis* (OECD GD 201)	2014.07.11	–	○	○	(8.2.5.2)‡	(9.1.6.2)+	(9.1.6)+	–/–*3
Potamopyrgus antipodarum reproduction test (OECD TG 242)	2016.07.29	–	○	○	(8.2.5.2)‡	(9.1.6.2)+	(9.1.6)+	–/–*3
Lymnaea stagnalis reproduction test (OECD TG 243)	2016.07.29	–	○	○	(8.2.5.2)‡	(9.1.6.2)+	(9.1.6)+	–/–*3
Sediment-water chironomid toxicity using spiked sediment (OECD TG 218)	2004.04.13	–	○	○	8.2.5.4	9.1.6.2# 9.1.9#	9.1.6 9.1.9	–/–*3
Sediment-water chironomid toxicity using spiked water (OECD TG 219)	2004.04.13	–	○	○	8.2.5.3	9.1.6.2# 9.1.9#	9.1.6 (9.1.9)+	–/–*3
Daphnia magna reproduction test (with male induction) (OECD TG 211)	1998.09.21	2012.10.02	○	○	8.2.5.1	9.1.6.2#	9.1.6	–/–*3
Earthworm reproduction test (OECD TG 222)	2004.04.13	2016.07.29	○	○	8.4.1	9.3.1#	9.3.1	–/–*3
Enchytraeid reproduction test (OECD TG 220)	2004.04.13	2016.07.29	○	○	(8.4.2)+	9.3.1#	9.3.1	–/–*3
Sediment water *Lumbriculus* toxicity test using spiked sediment (OECD TG 225)	2007.10.16	–	○	○	(8.2.5.4)+	9.1.9#	9.1.9	–/–*3
Predatory mite reproduction test in soil (OECD TG 226)	2008.10.03	2016.07.29	○	○	8.4.2.1	(9.5.2)+	(9.5.2)+	–/–*3
Collembolan reproduction test in soil (OECD TG 232)	2009.09.07	2016.07.29	○	○	8.4.2.1	(9.5.2)+	(9.5.2)+	–/–*3
Fish reproduction partial lifecycle test (when/If TG is Available)	–	–	○	–	–	–	–	–/–*3
Mollusc partial lifecycle assays (when TG is available)	–	–	○	–	–	–	–	–/–*3

‡ When the PPP AS Data Requirement Regulation 283/2013 was published those TGs had not yet adopted as new OECD TGs, therefore, if studies conducted according to the TGs exist, they might be submitted to address the Data Requirement Points in parentheses.

+ If studies conducted according to the TGs exist, they might be submitted to address the Data Requirement Points in parentheses. Under the Data Requirement Points in parentheses, other TGs of similar studies on the different species of the same taxonomic groups are indicated.

TG numbers are not clearly indicated.

*1 A : Established tests validated and published as OECD TGs when the ED GD is issued.

*2 - : Tests that are mentioned in the ED GD, but not included in the tables indicating tests and their main investigated parameters.

*3 -/- : Tests that are not mentioned in the ED GD.

Table 4 Test methods contained within the OECD Conceptual Framework (CF) for Testing and Assessment of Endocrine Disrupting Chemicals and whether they are referred to in the data requirements for ASs of PPP/BP and/or in the ECHA/EFSA ED GD

(f) OECD CF Level 5 Mammalian toxicology

Test method	Original Adoption	Most Recently Updated	CF 2012	CF 2018	PPP AS Data req. Point	BP AS Data req. Point	BP AS Data req. Point in GD	ED GD
Extended one-generation reproductive toxicity study (EOGRTS) (OECD TG 443)	2011.7.28 (Corrected in 2012, 2018)	–	○	○	5.6.1	8.10.2 8.10.3 8.13.3(a)(v)	8.10.2 8.10.3 8.13.3(a)(v)	Mammal/A[*1]
Two-generation reproduction toxicity study (OECD TG 416, most recent update)	1983.5.26	2001.01.22	○	○	5.6.1	8.10.2 8.13.3(a)(v)	8.10.2 8.13.3(a)(v)	Mammal/A[*1]

∗1 A : Established tests validated and published as OECD TGs when the ED GD is issued.

(g) OECD CF Level 5 Non mammalian toxicology

Test method	Original Adoption	Most Recently Updated	CF 2012	CF 2018	PPP AS Data req. Point	BP AS Data req. Point	BP AS Data req. Point in GD	ED GD
Fish life cycle toxicity test (FLCTT) (US EPA TG OPPTS 850.1500)	1996.04	–	○	○	8.2.2.2	9.10.1(b)	9.10[#]	Fish/B[*2]
Medaka extended one-generation reproduction test (MEOGRT) (OECD TG 240)	2015.07.28	–	○	○	–	9.10.1(a)	9.10[#]	Fish/A[*3]
Avian two-generation toxicity test in the Japanese quail (ATGT) (US EPA TG[*1] 890.2100)	2015.07	–	○	○	–	–	–	Bird/B[*2]
Sediment water chironomid life cycle toxicity test (OECD TG 233)	2010.07.22	–	○	○	–	–	–	–/–[*4]
Daphnia multigeneration test for assessment of EDCs (draft OECD TG)	–	–	○	○	–	–	–	–/–[*4]
Zebrafish extended one-generation reproduction test (ZEOGRT) (draft OECD TG)	–	–	–	○	–	–	–	Fish/–[*5]
Mysid life cycle toxicity test (when TG is available)	–	–	○	–	–	–	–	–/–[*4]
Copepod reproduction and development test (when TG is available)	–	–	○	–	–	–	–	–/–[*4]
Mollusc full lifecycle assays (when TG is available)	–	–	○	–	–	–	–	–/–[*4]

TG numbers are not clearly indicated.

∗1 US EPA Series 890 Endocrine Disruptor Screening Program Test Guidelines. The acronym 'OPPTS' or 'OCSPP', which is included as part of the guideline's number is omitted. The guidelines issued before 2010.04.22, refer to 'OPPTS', whereas those issued after that day, refer to 'OCSPP', because the office name changed from 'Office of Prevention, Pesticides and Toxic Substances' and 'OPPTS' to 'Office of Chemical Safety and Pollution Prevention' and 'OCSPP'. This name change did not otherwise affect the guidelines.

∗2 B : Tests not yet received full validation by OECD, or are in the process of OECD validation when the ED GD is issued.

∗3 A : Established tests validated and published as OECD TGs when the ED GD is issued.

∗4 -/- : Tests that are not mentioned in the ED GD.

∗5 - : In the ED GD the test method is mentioned 'A similar guideline to TG 240 is currently under validation by OECD on zebrafish (ZEOGRT) and could be used instead of the MEOGRT, once validated. The choice between those two test guidelines should be made based on the species sensitivity and the chemicals being test.'

where the information available is not sufficient to conclude the assessment, and provisions on alternative procedures associated with the request of additional studies/information. The new scientific criteria for the determination of endocrine disrupting properties do not apply where the Standing Committee has voted on a draft Regulation concerning the renewal or non-renewal of the approval of an AS by 10 November 2018, the date of application of the new scientific criteria (Article 2 of Regulation 2018/605).

Where the information available in the submitted dossiers is not sufficient for the Rapporteur Member State (RMS) to conclude the assessment on whether the approval criteria are met and, where applicable, whether application of the derogation under Article 4(7) of the PPP Regulation 1107/2009 is justified, if the Renewal Assessment Report (RAR) for the AS has not been submitted by 10 November 2018, the RMS shall specify in the RAR the additional information which is necessary in order to make the assessment concerned (Article 11a of Regulation 844/2012 and Article 1(1) of Regulation 2018/1659).

Where the information available in the submitted dossiers is not sufficient for the EFSA to conclude the assessment on whether the approval criteria are met, if an EFSA Conclusion is not yet adopted by 10 November 2018, the EFSA shall, in consultation with the RMS, set a period for the submission of the additional information (Article 13(3a) of Regulation 844/2012 and Article 1(2) of Regulation 2018/1659). The period for the submission of the additional information shall be at least three months, and shall not exceed 30 months.

Where the EFSA, in consultation with the RMS, is able to conclude without requesting additional information that the scientific criteria for the determination of endocrine disrupting properties are met, it shall inform the applicant. Within three months after being informed by the EFSA, the applicant may submit additional information to address the approval criteria concerning endocrine disrupting properties, and/or documentary evidence showing that the conditions for the application of the derogation under Article 4(7) of Regulation 1107/2009 are met (Article 13(3a) of Regulation 844/2012 and Article 1(2) of Regulation 2018/1659).

Even where an EFSA Conclusion is adopted before 10 November 2018, if the Standing Committee had not yet voted on a draft Regulation concerning the renewal or non-renewal of the AS by that date, the European Commission may consider that additional information is necessary to assess whether the approval criteria concerning endocrine disrupting properties are met, and in such cases, shall request the EFSA to reassess. When requested by the European Commission, the EFSA may, in consultation with the RMS, decide whether additional information is required (Article 14(1a) of Regulation 844/2012 and Article 1(4) of Regulation 2018/1659). The period for the submission of the additional information shall be at least of three months, shall not exceed 30 months.

The Guidance for the identification of EDs, which applied under the PPP Regulation as of 10 November 2018 together with the scientific criteria for the determination of endocrine disrupting properties, provided the Excel template for reporting the available information relevant for ED assessment as Appendix E. The dossiers for chemical ASs to be submitted after 10 November 2018 should include ED assessment in accordance with the Guidance for the identification of EDs. The information provided with the dossiers which is useful for the ED assessment should be entered in the template provided as Appendix E and submitted together with the dossiers. Though a dossier was submitted before 10 November 2018, the RMS assessment report to be submitted to the EFSA after 10 November 2018 needs to include completed Appendix E spreadsheet. With respect to EFSA Conclusions to be adopted after 10 November 2018, where the assessment of the endocrine disrupting properties is necessary to decide whether to approve or renew the approval, if completed Appendix E has not been submitted to the EFSA together with the assessment report prepared by the RMS, the EFSA will request the applicant to submit completed Appendix E. Where the approval of an AS is renewed based on an EFSA Conclusion adopted before 10 November 2018, submission of confirmatory information concerning endocrine disrupting properties, such as the assessment of endocrine disrupting properties according to the new scientific criteria, including completed Appendix E, may be required.

The 'Administrative guidance on submission of dossiers and assessment reports for the peer-review of pesticide active substances'[51] prepared by the EFSA, whose first version was adopted on 27 March 2019, applied for dossiers submitted on or after 1 October 2019[52]. This guidance provided the 'Template for presentation of assessment of endocrine disrupting properties' as Appendix I.

The revised version adopted on 11 February 2021 that reflected the 'Regulation on the transparency and sustainability of the EU risk assessment in the food chain: Transparency Regulation 2019/1381'[53] is titled 'Administrative guidance on submission of dossiers and assessment reports for the peer-review of pesticide active substances and on the maximum residue level (MRL) application procedure'[54] and applies to the dossiers submitted as of 27 March 2021[55]. Under this

revised version adopted on 11 February 2021, the dossiers for approval (including amendment of approval conditions) or renewal of approval of ASs to which Regulation 2019/1381 applies, are prepared using the International Uniform Chemical Information Database (IUCLID) software package, and Appendix I is deleted from the Appendices to the revised version of the guidance. However, according to the 'IUCLID Active Substance application Manual (IUCLID 6 VERSION 6.X)'[56], the template for presentation of assessment of endocrine disrupting properties provided as Appendix I has been included in the IUCLID.

With respect to the ASs under evaluation for renewal of approval where the information available in the submitted dossier is not sufficient to conclude the assessment of endocrine disrupting properties, the review period has been extended as a result of setting a period for conducting additional studies and/or submitting additional information.

The Renewal Procedure Regulation 2020/1740[57] published in the OJ on 23 November 2020 reflected the Transparency Regulation 2019/1381 and replaced the Renewal Procedure Regulation 844/2012. For the ASs of which procedure for the renewal of approval to which this Regulation applies, provisions that set a period for conducting additional studies and/or submitting additional information were not set out anymore. Because the deadline for submitting dossiers for the ASs to which the Renewal Procedure Regulation 2020/1740 applies is more than two years after the date of application of the new scientific criteria, 10 November 2018, the applicants can conduct tests on endocrine disrupting properties that are considered to be necessary in light of the new scientific criteria and the Guidance for the identification of EDs, and submit the information in the renewal dossiers.

As shown in **Table 4**, some tests which could potentially provide information to be used for assessment of endocrine disrupting properties were already included in the data requirements for chemical ASs before the development of the Guidance for the identification of EDs. In addition, as shown in **Table 5**, the website

Table 5 US EPA Series 890 Endocrine Disruptor Screening Program (EDSP) Test Guidelines and the comparable test methods indicated in OECD Conceptual Framework (CF)

US EPA Series 890		Comparable test method indicated in OECD CF	Level in OECD CF
Group A - EDSP Tier 1 Test Guidelines			
	890.1100 – Amphibian metamorphosis (Frog)	Amphibian metamorphosis assay (OECD TG 231)	Level 3
	890.1150 – Androgen receptor binding (Rat prostate)	Androgen receptor binding affinity (US EPA TG*1 890.1150)	Level 2
	890.1200 – Aromatase (Human recombinant)	Aromatase assay (US EPA TG*1 890.1200)	Level 2
	890.1250 – Estrogen receptor binding	Estrogen receptor binding affinity (OECD TG 493)	Level 2
	890.1300 – Estrogen receptor transcriptional activation (Human cell line HeLa-9903)	Estrogen receptor transactivation (OECD TG 455)	Level 2
	890.1350 – Fish short-term reproduction	Fish short-term reproduction assay (FSTRA) (OECD TG 229)	Level 3
	890.1400 – Hershberger (Rat)	Hershberger assay (OECD TG 441)	Level 3
	890.1450 – Female pubertal (Rat)	Pubertal development and thyroid function assay in peripubertal female rats (PP female assay) (US EPA TG*1 890.1450)	Level 4
	890.1500 – Male pubertal (Rat)	Pubertal development and thyroid function assay in peripubertal male rats (PP male assay) (US EPA TG*1 890.1500)	Level 4
	890.1550 – Steroidogenesis (Human cell line – H295R)	Steroidogenesis *in vitro* (OECD TG 456)	Level 2
	890.1600 – Uterotrophic (Rat)	Uterotrophic assay (OECD TG 440)	Level 3
Group B - EDSP Tier 2 Test Guidelines			
	890.2100 – Avian two-generation toxicity test in the Japanese quail	Avian two-generation toxicity test in the Japanese quail (ATGT) (US EPA TG*1 890.2100)	Level 5
	890.2200 – Medaka extended one generation reproduction test	Medaka extended one-generation reproduction test (MEOGRT) (OECD TG 240)	Level 5
	890.2300 – Larval amphibian growth and development assay (LAGDA)	Larval amphibian growth & development assay (LAGDA) (OECD TG 241)	Level 4

*1 US EPA Series 890 Endocrine Disruptor Screening Program Test Guidelines. The acronym 'OPPTS' or 'OCSPP', which is included as part of the guideline's number is omitted. The guidelines issued before 2010.04.22, refer to 'OPPTS', whereas those issued after that day, refer to 'OCSPP', because the office name changed from 'Office of Prevention, Pesticides and Toxic Substances' and 'OPPTS' to 'Office of Chemical Safety and Pollution Prevention' and 'OCSPP'. This name change did not otherwise affect the guidelines.

containing Series 890 'Endocrine Disruptor Screening Program (EDSP) Test Guidelines'[58], issued as the test guidelines of the United States Environmental Protection Agency (US EPA), displays the test guidelines either under Group A EDSP Tier 1 Test Guidelines or under Group B EDSP Tier 2 Test Guidelines, which are comparable to the test methods included in the OECD Conceptual Framework for Testing and Assessment of Endocrine Disrupters. Therefore, renewal of approval of some ASs was decided without conducting additional studies or submitting additional information on the basis that the ASs are not considered as having endocrine disrupting properties because necessary test data were already available and submitted before the preparation of the assessment report by the RMS.

With respect to some chemical ASs which have issues as a critical areas of concern other than their endocrine disrupting properties and may not meet the approval criteria, setting a period for conducting additional studies and/or submitting additional information on endocrine disrupting properties is regarded as unnecessary, so the non-renewal of approval of the ASs is decided without a conclusion on endocrine disrupting properties.

The EFSA Conclusions adopted after 10 November 2018 contain the assessment of endocrine disrupting properties with regard to chemical ASs. With regard to chemical ASs for which endocrine disrupting properties are assessed according to the new scientific criteria, the EFSA Conclusions adopted after 2021 contain the list as Appendix A titled 'Consideration of cut-off criteria for 'AS' according to Annex II of Regulation (EC) No 1107/2009 of the European Parliament and of the Council', in which a summary of the conclusion on assessment of endocrine disrupting properties is provided. **Table 6** shows the conclusion on cut-off criteria related to toxicity and ecotoxicity from the list indicated in Appendix A to the EFSA Conclusion on pesticides peer review of Clofentezine adopted on 28 July 2021[59] as part of the procedure of the renewal of approval of the AS.

The provisions that set a period for conducting additional studies and/or submitting additional information apply to the chemical ASs of which application for renewal of approval had been submitted before 10 November 2018 and reviewed under the Renewal Procedure Regulation 844/2012. Even when an application for approval or renewal of approval had been submitted before 10 November 2018, the provisions that set a period for conducting additional studies and/or submitting additional information do not apply to the chemical ASs that are reviewed in accordance with the procedures set out in the PPP Regulation 1107/2009 or the chemical ASs belonging to AIR2 that are reviewed under the Renewal Procedure Regulation 1141/2010[60].

In case of Flumioxazin belonging to AIR2, for which the Renewal of approval Regulation 2022/43[61] was published in the OJ on 14 January 2022, the EFSA Conclusion published on 29 September 2020 recommended additional studies to address the endocrine disrupting properties. However, a period for conducting additional studies was not set, and renewal of the approval of the

Table 6 Conclusion on CMR and endocrine disrupting properties related cut-off criteria indicated in Appendix A 'Consideration of cut-off criteria for Clofentezine according to Annex II of Regulation 1107/2009' to EFSA Conclusion on pesticides peer review of Clofentezine

Properties		Conclusion*
CMR	Carcinogenicity (C)	Clofentezine is not considered to be carcinogenic according to point 3.6.3 of Annex II of Regulation 1107/2009 (confirmed in RAC Opinion adopted on 11 June 2020 (ECHA, 2020)).
	Mutagenicity (M)	Clofentezine is not considered to be mutagenic according to point 3.6.2 of Annex II of Regulation 1107/2009 (confirmed in RAC Opinion adopted on 11 June 2020 (ECHA, 2020)).
	Toxic for Reproduction (R)	Clofentezine is not considered to be toxic for reproduction according to point 3.6.4 of Annex II of Regulation 1107/2009 (confirmed in RAC Opinion adopted on 11 June 2020 (ECHA, 2020)).
Endocrine disrupting properties		Clofentezine is considered to meet the criteria for endocrine disruption for humans for the T modality according to point 3.6.5 of Annex II of Regulation 1107/2009, as amended by Commission Regulation 2018/605. The endocrine disrupting properties of Clofentezine for non-target organisms according to point 3.8.2 of Annex II to Regulation 1107/2009, as amended by Regulation 2018/605 could not be concluded.

*Origin of data to be included where applicable (*e.g.* EFSA, ECHA RAC, Regulation).

AS was decided based on the assessment of available information. As one of the conditions for renewal of approval, the applicant was requested to submit further information to confirm the absence of endocrine disrupting properties as confirmatory information by 1 March 2024, two years after the application of Renewal of approval Regulation 2022/43 on 1 March 2022 (Annexes I and II to Regulation 2022/43).

Unlike under the PPP Regulation 1107/2009, no specific Amendment Regulation was prepared under the BP Regulation 528/2012, with regard to the procedures for assessing endocrine disrupting properties after the application of the new scientific criteria. Under the BP Regulation 528/2012, the Note agreed by Member States' Competent Authorities for Biocidal Products dated March 2018 'Implementation of scientific criteria to determine the endocrine-disrupting properties of active substances currently under assessment'[62] provides two separate procedures depending on whether the first draft Competent Authority Report (CAR) prepared by the Evaluating Competent Authority (eCA) in charge of the assessment of the dossier had been submitted before 1 September 2013 (the application date of the BP Regulation).

If the first draft CAR had been submitted before 1 September 2013, the approval criteria under the BP Directive 98/8/EC, in which exclusion criteria were not provided, shall apply. Therefore, whether an AS has endocrine disrupting properties in humans does not result in the non-approval of the AS, and even if the opportunity to submit additional data in order to conclude on endocrine disrupting properties of the AS is given, the applicant does not have the obligation to perform additional studies. The examination of whether to approve an AS/PT can be completed even when no conclusion could be drawn on the endocrine disrupting properties.

If the first draft CAR had been submitted after 1 September 2013, it is necessary to draw a conclusion on endocrine disrupting properties to present a decision on the approval or renewal of the approval of an AS. If no conclusion can be drawn, the applicant is given the opportunity to submit additional information. This request for additional information can occur both during the evaluation phase by the eCA and during the peer review process in the BPC. Where considered appropriate, the eCA may ask advice of the ECHA's Endocrine Disruptor Expert Group (ED EG) on the endocrine disrupting properties of the AS.

An AS used in BPs is considered as having endocrine disrupting properties which results in meeting exclusion criteria for the approval, if it is considered as having endocrine disrupting properties that may cause adverse effects in humans or being identified in accordance with Articles 57(f) and 59(1) of the REACH Regulation 1907/2006 as having endocrine disrupting properties (Article 5(1)(d) of Regulation 528/2012). The exclusion criteria for approval of ASs used in BPs do not include the cases where ASs are considered as having endocrine disrupting properties that may cause adverse effects on non-target organisms in accordance with the scientific criteria for the determination of endocrine disrupting properties.

The Note dated March 2018 provides that if an AS/PT is considered as having endocrine disrupting properties that may cause adverse effects on non-target organisms based only on Section B of the Annex to the Regulation 2017/2100, which sets out scientific criteria for the determination of endocrine disrupting properties, or having an intended biocidal mode of action that consists of controlling target organisms via their endocrine system(s), the AS/PT is not subject to non-approval, but it must be considered a CfS under Article 10(1)(e) of the BP Regulation 528/2012. Article 10(1)(e) of the BP Regulation 528/2012 specifies a condition that there are reasons for concern linked to the nature of the critical effects which, in combination with the use patterns, amount to use that could still cause concern, even with very restrictive risk management measures.

With respect to the assessment of endocrine disrupting properties of ASs in the context of AS/PT approval, the ECHA document titled 'Principles for the assessment of endocrine disrupting properties in active substance approval'[63] was agreed on 26 April 2018. This ECHA document describes in more detail the principles for the determination of the endocrine disrupting properties of the ASs provided in the aforementioned Note agreed by Member States' Competent Authorities for Biocidal Products dated March 2018.

Where necessary, the eCA may ask for scientific advice from the ED EG. All CARs submitted after 7 March 2018 by the eCA to ECHA need to include an ED assessment. However, an ED conclusion is not required if the eCA is proposing non-approval. The advice of the ED EG is envisaged to be sought during the eCA evaluation or at the request of the BPC Working Group (WG).

Table 7 indicates how the endocrine disrupting properties are included in the BPC Opinion template with respect to the assessment of exclusion and CfS criteria as described under Point 2.5 'Biocidal Products Committee' in this ECHA document.

With respect to the literature review required in order to conclude on the endocrine disrupting properties where the first draft CAR had been submitted before 1 September 2013, the ECHA document titled 'ED assessment for active substances where the CAR was submitted before entry into force of the BPR: literature review'[64] was agreed on 26 February 2019. Because endocrine disrupting properties were not specifically mentioned in the data requirements under the BP Directive, for CARs submitted before entry into force of the BP Regulation on 1 September 2013, the dossiers are expected to be unlikely to contain sufficient information to enable concluding on the endocrine disrupting properties. This ECHA document describes the following procedures:

The eCA should inform the applicant that a literature review is required in order to conclude on the endocrine disrupting properties. The applicant does not have the obligation to submit this information but can choose to provide it if they wish.

The applicant shall inform the eCA of its decision as soon as possible.

The eCA can proceed without having received information of the applicant.

If the applicant does not perform a systematic literature review, the eCA should perform a systematic literature review if the likely outcome of the eCA's assessment is that the AS should be considered to have endocrine disrupting properties.

The Annex to this ECHA document shows the list of ASs/PTs for which the first draft CAR was submitted before 1 September 2013 and to which the assessment procedures described in the ECHA document apply.

For the ASs/PTs subject to BPC Opinions on the application for approval of AS/PT adopted before 7 June 2018, the date of application of the new scientific criteria for the determination of endocrine disrupting properties under the BP Regulation 528/2012, but not being voted on the approval of ASs/PTs before 7 June 2018, the ECHA was requested by the European Commission to make the previously adopted opinions updated only on the part in relation to the assessment of the endocrine disrupting properties in order to contain the

Table 7 Template to be included in the BPC Opinions to indicate the endocrine disrupting properties with respect to the assessment of exclusion and substitution criteria based on the endocrine disrupting properties

Property		Conclusions	
Endocrine disrupting properties	Section A of Regulation (EU) 2017/2100: ED properties with respect to humans	Yes/No	Conclusion on fulfilling Article 5 (1) (e) or on fulfilling Article 10 (1) (e)
	Section B of Regulation (EU) 2017/2100: ED properties with respect to non- target organisms	Yes/No	
	Article 57(f) and 59(1) of REACH	Yes/No	
	Intended mode of action that consists of controlling target organisms *via* their endocrine system(s).	Yes/No	

Table 8 Information indicated on the endocrine disrupting properties included in the BPC Opinion on the application for approval of Carbendazim/PT9 with respect to the assessment of exclusion and substitution criteria based on the endocrine disrupting properties

Property		Conclusions
Endocrine disrupting properties	Section A of Regulation (EU) 2017/2100: ED properties with respect to humans	An assessment of the endocrine disrupting properties according to Regulation (EU) 2017/2100 was not conducted. Consequently, no conclusion can be drawn whether carbendazim fulfils criterion (d) of Article 5(1) for human health or criterion (e) of Article 10(1) for the environment.
	Section B of Regulation (EU) 2017/2100: ED properties with respect to non-target organisms	
	Article 57(f) and 59(1) of REACH	
	Intended mode of action that consists of controlling target organisms *via* their endocrine system(s).	

assessment of the endocrine disrupting properties according to the new scientific criteria[65),66)].

For the BPC Opinions on the application for approval of AS/PT prepared after 7 June 2018, the row on the endocrine disrupting properties in the table indicating whether the AS fulfils the exclusion criteria and/or the CfS criteria concerning the approval of the AS under Point 2.2.1 'Exclusion and substitution criteria' was revised. **Table 8** shows part of the information in the table contained in the BPC Opinion on the application for approval of Carbendazim/PT9 adopted on 27 February 2019[67)]. Because Carbendazim was classified as mutagenicity category 1B and toxic for reproduction category 1B, it met the exclusion criteria regardless of whether it had endocrine disrupting properties. With respect to Carbendazim/PT9, the first draft CAR had been submitted before 1 September 2013, so Carbendazim/PT9 could be approved even though it met the exclusion criteria based on hazard classification of the AS. In addition, it was not necessary to draw a conclusion on the endocrine disrupting properties. The conclusion indicated in the table states that an assessment of the endocrine disrupting properties was not conducted and no conclusion can be drawn whether the AS fulfils criterion (d) of Article 5(1) for human health, corresponding to having endocrine disrupting properties that may have adverse effects in humans, or criterion (e) of Article 10(1) for the environment, corresponding to having endocrine disrupting effects that may have adverse effects on non-target organisms, of the BP Regulation 528/2012. However, in the case of Carbendazim/PT9, the risk assessment identified unacceptable risks to the environment and no safe use could be identified, therefore, the BPC Opinion proposed non-approval.

For Carbendazim/PT7 and Carbendazim/PT10, the first draft CAR had been submitted before 1 September 2013, so it was not necessary to draw a conclusion on the endocrine disrupting properties of the AS. The risk assessment of PT7 and PT10 did not identify unacceptable risks for a certain use. Therefore, the BPC Opinions on the application for approval of Carbendazim/PT7[68)] and Carbendazim/PT10[69)] adopted on 10 December 2019 proposed approval. As shown in **Table 9**, the form of the table under Point 2.2.1 'Exclusion and substitution criteria' of these Opinions is slightly different from the table included in the Opinion adopted for Carbendazim/PT9. As no conclusion on the endocrine disrupting properties of the AS can be drawn based on the available data, the conclusion in the table states that no conclusion can be drawn whether the AS fulfils criterion (d) of Article 5(1) and/or criterion (e) of Article 10(1) of the BP Regulation 528/2012.

With respect to ASs/PTs still under review for approval where the first draft CAR had not been submitted before 1 September 2013, the BPC is normally required to draw a conclusion on the endocrine disrupting properties of the ASs. Like the case of ASs used in PPPs, part of the tests related to the assessment of the endocrine disrupting properties were the ones which were already included in the data requirements for chemical ASs before the development of the Guidance for the identification of EDs.

For this reason, some chemical ASs/PTs were considered as not having endocrine disrupting properties without the submission of additional information, and so were approved. On the other hand, for some chemical ASs, the applicants were given the opportunity to submit additional information to determine whether the ASs have endocrine disrupting properties and additional studies were conducted. With respect to the

Table 9 Information indicated on the endocrine disrupting properties included in the BPC Opinion on the application for approval of Carbendazim/PT7 or PT10 with respect to the assessment of exclusion and substitution criteria based on the endocrine disrupting properties

Property		Conclusions	
Endocrine disrupting properties	Section A of Regulation (EU) 2017/2100: ED properties with respect to humans	No conclusion can be drawn based on the available data	No conclusion can be drawn whether carbendazim fulfils criterion (d) of Article 5(1) and/or criterion (e) of Article 10(1)
	Section B of Regulation (EU) 2017/2100: ED properties with respect to non- target organisms	No conclusion can be drawn based on the available data	
	Article 57(f) and 59(1) of REACH	No	
	Intended mode of action that consists of controlling target organisms *via* their endocrine system(s).	No	

chemical ASs for which additional studies are being conducted, the discussions at the BPC cannot be scheduled until the results are obtained.

With respect to ASs/PTs subject to renewal of approval, the 'Guidance on the data requirements and assessment of applications for renewal of approval of active substances under BPR'[70] dated November 2020 was prepared and published by the ECHA. This guidance states that the applicant needs to anticipate the generation of data on endocrine disrupting properties on their AS. For ASs/PTs approved before June 2018 or for which the CARs were submitted before 1 September 2013, the endocrine disrupting properties were not assessed in accordance with the new scientific criteria, or no conclusion was drawn on the endocrine disrupting properties. The applicant should provide either an assessment of endocrine disrupting properties, if not assessed previously, or a justified statement that the conclusions of the latest assessment are still valid. The applicant should also indicate whether they have generated or considered any new information for this purpose. The assessment of endocrine disrupting properties should be included in the relevant section of the RAR.

For carcinogenic/mutagenic/reproductive toxic substances that meet the exclusion criteria, assessment of endocrine disrupting properties is still required. Applicants should anticipate and discuss with the eCA well before the deadline on the need to generate new data to investigate endocrine disrupting properties.

For Creosote/PT8, whose approval was renewed under the Renewal of approval Regulation 2022/1950[71], an application for the renewal of approval was submitted on 27 October 2016. The BPC Opinion on the application for renewal of approval adopted on 4 December 2020[72] states that no conclusion on the endocrine disrupting properties either with respect to humans or with respect to non-target organisms can be drawn based on the available data. Because exclusion criteria other than endocrine disrupting properties have already been met and Creosote containing biocidal products are used only by professionals, it was decided to not proceed further with the evaluation of the endocrine disrupting properties of Creosote. The recital of the Renewal of approval Regulation 2022/1950 states that Creosote is classified as carcinogen category 1B and meets exclusion criteria other than endocrine disrupting properties, but no specific information on the conclusion of the assessment of endocrine disrupting properties is provided.

With respect to biocidal ASs/PTs other than Creosote/PT8 for which approval is renewed, the BPC Opinion on the application for renewal of approval of Propiconazole/PT8 adopted on 9 March 2022[73] was published. This Opinion concluded that Propiconazole/PT8 has endocrine disrupting properties both in humans and on non-target organisms. Propiconazole is classified as toxic for reproduction category 1B and meets the exclusion criteria, and the proposal in the Opinion states that the AS should normally not be approved unless one of the conditions for derogation is met as the exclusion criteria are met.

Identification for endocrine disrupting properties is currently performed by the EFSA under the PPP Regulation 1107/2009 and by the BPC under the BP Regulation 528/2012. On 19 December 2022, the European Commission adopted the Amendment Regulation to introduce new hazard classes concerning endocrine disrupting properties and others under the CLP Regulation 1272/2008. As the next step, the European Commission announced that the EU will chair a new United Nations (UN) informal working group to develop global criteria for the newly adopted hazard classes[74].

The document titled 'Proposal for new work on unaddressed hazard classes in the programme of work for the biennium 2023-2024 - Transmitted by the European Union' dated 15 September 2022[75] issued by the UN Sub-Committee of Experts on the Globally Harmonized System of Classification and Labelling of Chemicals described that at the 42nd session of the Sub-Committee, the representative of the EU highlighted some hazards currently not identified at global level, limiting adequate measures to protect users, consumers and the environment, and informed the Sub-Committee about their intention to submit a proposal for new items to be included in the programme of work for the biennium 2023-2024. The document also described the proposed scope and organisation of the work and the workplan. In Annex III 'Programme of work of the Sub-Committee for 2023-2024' to the Report of the Sub-Committee of Experts on its 43rd session held from 7 to 9 December 2022[76], the proposal from the EU was listed as 'Potential hazard issues and their presentation in the GHS' which was slightly modified from the title of the document transmitted by the EU.

When an Amendment Regulation that introduces new hazard classes concerning endocrine disrupting

properties and others is published in the OJ and the application date is confirmed, endocrine disrupting properties are to be assessed by the ECHA's RAC which proposes the classification and labelling, and whether the new hazard class including hazard category is necessary is to be proposed to classify ASs after the application date.

The CLH reports to be submitted to the ECHA's RAC are prepared using the common report template intended to be used for assessment reports prepared by RMS for ASs used in PPPs or by eCA for ASs used in BPs. The RAC Opinion proposing harmonised classification and labelling of an AS is, in principle, adopted before the adoption of the EFSA Conclusion or BPC Opinion of the AS. This means that in the future, the assessment of endocrine disrupting properties during the evaluation process for approval or renewal of approval of ASs will be conducted ahead of the conclusion on whether the AS meets the approval criteria and approval or renewal of approval can be decided.

Possible impact when chemical ASs are considered to have endocrine disrupting properties

If a chemical AS used in a PPP is considered as having endocrine disrupting properties that may cause adverse effects in humans or on non-target organisms or if a chemical AS in a BP is considered as having endocrine disrupting properties that may cause adverse effects in humans, the AS satisfies the cut-off criteria under the PPP Regulation or the exclusion criteria under the BP Regulation, so approval or renewal of approval of the AS becomes difficult. If the AS meets the condition set out in Article 4(7) of the PPP Regulation 1107/2009 or at least one of the conditions set out in Article 5(2) of the BP Regulation 528/2012, the AS may be approved or the approval of the AS may be renewed. However, even if approval or renewal of approval is decided, the AS is approved for a shorter period as a CfS, and comparative assessment is performed when evaluating an application for authorisation of a product containing the AS (Article 50 of Regulation 1107/2009 and Article 23 of Regulation 528/2012).

If a chemical AS used in BPs is considered as having endocrine disrupting properties that may cause adverse effects only on non-target organisms, the AS does not meet the exclusion criteria under the BP Regulation, but it meets the CfS criteria. Therefore, comparative assessment is performed when evaluating an application for authorisation of a product containing the AS.

If a chemical AS used in PPPs is considered as having endocrine disrupting properties that may cause adverse effects in humans, exposure of humans to the AS must be negligible to fulfil the conditions for approval as derogation. The draft Commission Notice dated May 2015 'Technical guidance on the interpretation of points 3.6.3. to 3.6.5, and 3.8.2 of Annex II to Regulation (EC) No 1107/2009, in particular regarding the assessment of negligible exposure to an active substance in a plant protection product under realistic conditions of use'[77], which is used to determine whether derogation can be granted and the AS can be approved, states that the Maximum Residue Level(s) (MRL(s)) shall be set as 0.01 mg/kg, which is the default value, or as the Limit of Quantitation (LOQ), and shall not be exceeded.

Because non-approval or non-renewal of approval of ASs results in the revocation of authorisation of the relevant PPPs, if the MRLs are specified in Annex II or III to the MRL Regulation 396/2005, Amendment Regulation to Annex II or III needed to delete the MRLs by lowering MRLs to the relevant Limit of Detection (LOD), following the revocation of existing authorisations for PPPs may be adopted without seeking the opinion of the EFSA (Article 17 of Regulation 396/2005).

The MRLs corresponding to Codex MRLs (CXLs), which are internationally agreed standards covering pesticide residues, set out based on uses in third-countries, or import tolerances (ITs), which are the MRLs set out based on uses in the exporting country or region, are normally maintained because they are irrelevant to the withdrawal of authorised use due to the revocation of authorisation for products in the EU. However, if ASs or their metabolites are toxic, particularly when they meet the cut-off criteria with respect to human health, the MRLs including those corresponding to the CXLs and those set as the ITs are lowered to the relevant LOD.

If an AS is considered as having endocrine disrupting properties that may cause adverse effects in humans, MRLs exceeding the LOD cannot be set either for commodities produced in the EU or for commodities produced outside the EU and imported into the EU, regardless of whether approval or renewal of approval of the AS is decided. This makes it difficult for commodities to which products containing the AS concerned are

applied outside the EU to be exported to the EU.

If a chemical AS used in a BP is considered as having endocrine disrupting properties that may cause adverse effects in humans and non-approval or non-renewal of approval of the AS is decided, treated articles that were treated with the BPs containing the AS cannot be placed on the market in the EU. Under the BP Regulation 528/2012 which applied from 1 September 2013, a treated article shall not be placed on the market unless all ASs contained in the BPs that it was treated with or incorporates are approved for the relevant PT and use (Article 58 of Regulation 528/2012). Therefore, if a chemical AS used in a BP in the EU is considered as having endocrine disrupting properties that may cause adverse effects in humans, it is difficult to place treated articles that were treated with the BPs containing the AS on the market in the EU.

Conclusion

Under the initial EU legislation for PPP/BP data requirements and scientific criteria for endocrine disrupting properties of chemical ASs were not set out. In parallel with the development of test methods for endocrine disrupting properties at OECD, data requirements were set out and having endocrine disrupting properties that may have adverse effects in humans or on non-target organisms was included in so-called cut-off criteria or exclusion criteria for the approval of ASs set out under the PPP Regulation and the BP Regulation. The new scientific criteria for the determination of endocrine disrupting properties applied in 2018, so proper assessment of endocrine disrupting properties has only recently started.

In order to ensure approval or renewal of approval of chemical ASs used in PPPs/BPs, it is necessary to be familiar with the new scientific criteria for the determination of endocrine disrupting properties and the Guidance for the identification of EDs.

If a chemical AS used in PPPs/BPs is considered as having endocrine disrupting properties that may cause adverse effects in humans, approval or renewal of approval of the AS cannot be normally decided in the EU; therefore, the AS, in principle, cannot be authorised for use. In addition, this may affect the use of PPPs or BPs containing the chemical AS in non-EU countries. In one example, as it becomes difficult to set the IT for the chemical AS in the EU, it may become difficult to export to the EU the commodities to which PPPs containing the chemical AS are applied. For another example, as the treated articles that are treated with or incorporate a BP containing the chemical AS not approved under the BP Regulation cannot be placed on the market in the EU, it may become difficult to export to the EU such treated articles. Continuous information collection is necessary to determine the possible endocrine disrupting properties of a chemical AS earlier and make a decision on whether to proceed with product development. We would be pleased if this article is of assistance in dealing with such work. For the content of the article, the URLs linked to the referenced documents are also provided in the section 'Reference', to the extent that valid URLs currently exist on the Internet, so that the details can be confirmed with the contents of the document.

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