TECHNICAL REPORT

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Outcome of the consultation with Member States, the applicant and EFSA on the pesticide risk assessment for thiabendazole in light of confirmatory data

European Food Safety Authority (EFSA)

Abstract

The European Food Safety Authority (EFSA) was asked by the European Commission to provide scientific assistance with respect to the risk assessment for an active substance in light of confirmatory data requested following approval in accordance with Article 6(1) of Directive 91/414/EEC and Article 6(f) of Regulation (EC) No 1107/2009. In this context EFSA's scientific views on the specific points raised during the commenting phase conducted with Member States, the applicant and EFSA on the confirmatory data and their use in the risk assessment for thiabendazole are presented. The current report summarises the outcome of the consultation process organised by the rapporteur Member State, Spain, and presents EFSA's scientific views and conclusions on the individual comments received.

Keywords: thiabendazole, peer review, confirmatory data, risk assessment, pesticide, fungicide

Requestor: European Commission

Question number: EFSA-Q-2020-00278

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Summary

The approval of the active substance thiabendazole was renewed on 1 April 2017 in accordance with Regulation (EC) No 1107/2009 by Commission Implementing Regulation (EU) 2017/157 of 30 January 2017. It was a specific provision of the renewal of the approval that the applicant was required to submit to the European Commission further studies on the potential for endocrine-mediated effects of thiabendazole by 31 March 2019.

In accordance with the specific provision, the applicant, Syngenta Ltd, submitted an updated dossier in March 2019, which was evaluated by the designated rapporteur Member State (RMS), Spain, in the form of an addendum to the renewal assessment report. In compliance with the guidance document SANCO 5634/2009-rev.6.1, the RMS distributed the addendum to Member States, the applicant and EFSA for comments on 18 November 2019. The RMS collated all comments in the format of a reporting table, which was submitted to EFSA on 2 April 2020. EFSA added its scientific views on the specific points raised during the commenting phase in column 4 of the reporting table.

The current report summarises the outcome of the consultation process organised by the RMS, Spain, and presents EFSA's scientific views and conclusions on the individual comments received.

The confirmatory data requirements have not been addressed neither for human health nor for non-target organisms. Therefore, in line with the ECHA/EFSA Guidance on the identification of endocrine disruptors, additional data are required before concluding on the endocrine disrupting properties of thiabendazole.

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1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

The approval of the active substance thiabendazole was renewed in accordance with Regulation (EC) No 1107/2009[1] by Commission Implementing Regulation (EU) 2017/157[2] of 30 January 2017. EFSA previously finalised a Conclusion on this active substance on 23 October 2014 (EFSA, 2014).

It was a specific provision of the renewal of the approval that the applicant was required to submit to the European Commission further studies on the potential for endocrine-mediated effects of thiabendazole by 31 March 2019. New criteria to identify endocrine disrupters (Commission Regulation (EU) 2018/605[3]) and a guidance document (ECHA, EFSA, 2018) apply from 10 November 2018. Therefore, as confirmed by the Commission, the assessment carried out by the Rapporteur Member State and reviewed by EFSA and the other Member States had to take into account the scientific criteria for identifying endocrine disruptors and the guidance document mentioned above.

In accordance with the specific provision, the applicant, Syngenta Ltd, submitted an updated dossier in March 2019, which was evaluated by the designated rapporteur Member State (RMS), Spain, in the form of an addendum to the renewal assessment report (Spain, 2019a). In compliance with the guidance document SANCO 5634/2009-rev.6.1 (European Commission, 2013), the RMS distributed the addendum to Member States, the applicant and the EFSA for comments on 18 November 2019. The RMS collated all comments in the format of a reporting table, which was submitted to EFSA on 2 April 2020. EFSA added its scientific views on the specific points raised during the commenting phase in column 4 of the reporting table.

The current report summarises the outcome of the consultation process organised by the RMS, Spain, and presents EFSA's scientific views and conclusions on the individual comments received.

1.2. Interpretation of the Terms of Reference

On 22 December 2014 the European Commission requested EFSA to provide scientific assistance with respect to the risk assessment of confirmatory data following approval of an active substance in accordance with Article 6(1) of Directive 91/414/EEC and Article 6(f) of Regulation (EC) No 1107/2009. EFSA's scientific views on the specific points raised during the commenting phase conducted with Member States, the applicant and EFSA on the risk assessment of confirmatory data for thiabendazole are presented.

To this end, a technical report containing the finalised reporting table is being prepared by EFSA. The deadline for providing the finalised report is 2 May 2020.

On the basis of the reporting table, the European Commission may decide to further consult EFSA to conduct a full or focused peer review and to provide its conclusions on certain specific points.

1 Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ L 309, 24.11.2009, p. 1-50.

2 Commission Implementing Regulation (EU) 2017/157 of 30 January 2017 renewing the approval of the active substance thiabendazole in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market, and amending the Annex to Commission Implementing Regulation (EU) No 540/2011. OJ L 25, 31.1.2017, p. 5–9.

3 Commission Regulation (EU) 2018/605 of 19 April 2018 amending Annex II to Regulation (EC) No 1107/2009 by setting out scientific criteria for the determination of endocrine disrupting properties. OJ L 101, 20.4.2018, p. 33–36.

2. Assessment

The comments received on the pesticide risk assessment for the active substance thiabendazole in light of confirmatory data and the conclusions drawn by the EFSA are presented in the format of a reporting table.

The comments received are summarised in column 2 of the reporting table. The RMS' considerations of the comments are provided in column 3, while EFSA's scientific views and conclusions are outlined in column 4 of the table.

The finalised reporting table is provided in Appendix A of this report.

Documentation provided to EFSA

1. Spain, 2019a. Addendum to the assessment report on thiabendazole, Vol 3 B6, B9, confirmatory data, November 2019, updated in April 2020. Available online: www.efsa.europa.eu.

2. Spain, 2019b. Reporting table, comments on the pesticide risk assessment for thiabendazole in light of confirmatory data, November 2019.

References

ECHA (European Chemicals Agency) and EFSA (European Food Safety Authority) with the technical support of the Joint Research Centre (JRC), Andersson N, Arena M, Auteri D, Barmaz S, Grignard E, Kienzler A, Lepper P, Lostia AM, Munn S, Parra Morte JM, Pellizzato F, Tarazona J, Terron A and Van der Linden S, 2018. Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009. EFSA Journal 2018;16(6):5311,135 pp. https://doi.org/10.2903/j.efsa.2018.5311. ECHA-18-G-01-EN

EFSA (European Food Safety Authority), 2011. Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009. EFSA Journal 2011;9(2):2092, 49 pp. doi:10.2903/j.efsa.2011.2092

EFSA (European Food Safety Authority), 2014. Conclusion on the peer review of the pesticide risk assessment of the active substance thiabendazole. EFSA Journal 2014;12(11):3880, 57 pp. doi:10.2903/j.efsa.2014.3880

EFSA (European Food Safety Authority), 2020. Technical report on the outcome of the pesticides peer review meeting on general recurring issues in mammalian toxicology. EFSA supporting publication 2020:EN-1837. 26 pp. doi:10.2903/sp.efsa.2020.EN-1837

European Commission, 2013. Guidance document on the procedures for submission and assessment of confirmatory information following approval of an active substance in accordance with Regulation (EC) No 1107/2009. SANCO 5634/2009-rev. 6.1

Abbreviations

AMA	Amphibian Metamorphosis Assay
AOP	adverse outcome pathway
AR	androgen receptor
a.s.	active substance
BW	body weight
BWG	body weight gain
DAR	draft assessment report
GAP	good agricultural practice
EAS	oestrogen, androgen, steroidogenic modalities
ECHA	European Chemicals Agency
ED	endocrine disruption
EU	European Union
FSTRA	Fish Short-Term Reproduction Assay
LAGDA	Larval Amphibian Growth and Development Assay
MEOGRT	Medaka Extended One Generation Test
MIE	Molecular Initiating Event
MS	Member State
MoA	mode of action
MTD	maximum tolerable dose
OECD	Organisation for Economic Co-operation and Development
RMS	rapporteur Member State
RAR	renewal assessment report
T	thyroid
ToxCAST	(US EPA) Toxicity Forecaster
TPO	thyroid peroxidase
TSH	thyroid-stimulating hormone (thyrotropin)

Appendix A – Collation of comments from Member States, applicant and EFSA on the pesticide risk assessment for the active substance thiabendazole in light of confirmatory data and the conclusions drawn by EFSA on the specific points raised

2. Effects on human and animal health (Endocrine Disruption)

Mammalian Toxicology (Endocrine Disruption)				
No.	Column 1 Reference to Assessment Report (vol., point, page)	Column 2 Comments from Member States, EFSA, applicant or public	Column 3 Evaluation by (RMS) rapporteur and	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
2(1)	B.6.8.3.4.4 Conclusions on endocrine disrupting proprieties	Applicant: Syngenta believe that the below studies may be required to conclude on the endocrine disrupting potential of thiabendazole in mammals. EAS modalities: Hershberger assay (OECD TG 441) AR transactivation assay in vitro (OECD TG 458) H295R steroidogenesis assay (OECD TG 456) Aromatase inhibition assay (OCSPP 890.1200) T modality: *In vitro* assessment of thyroid hormone clearance in primary human and rat hepatocytes	**RMS**: It agrees with this comment. The conclusions on endocrine disrupting properties have been modified accordingly. With regards T-modality, the relevance of the effects to humans cannot be ruled out. The postulated MoA involves hepatic enzyme induction and subsequent increases in hepatic clearance of T4 from the circulation; this would cause an increment of pituitary secretion of TSH, which may result in an increase of the thyroid activity, and subsequently, the detected microscopical lesions (as follicular cell hypertrophy) would appear. The applicant proposes to conduct a study to determine whether the proposed MoA is applicable to humans: An *in vitro* assessment of species differences in thyroid hormone clearance using human and rat primary hepatocytes. RMS deems necessary to undertake the proposed study (including	**Data gap:** Regarding **T-modality**, T-mediated adversity has been consistently observed across several studies, mainly in rat, and the available evidence is indicative of thyroid disruption and considered human relevant unless there is proof of the contrary according to the ECHA/EFSA (2018) ED Guidance (refer to its Appendix A). The applicant proposes to perform an *in vitro* assessment of thyroid hormone clearance in primary human and rat hepatocytes to evaluate the human relevance of thyroid findings. This information, according to Appendix A of the ECHA/EFSA (2018) ED Guidance, is considered informative to evaluate the human relevance of thyroid

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		(Additional information in column 3 of reporting table)	dog hepatocytes). If this study is not performed, based on observed effects in available toxicological studies, thiabendazole should be considered to have endocrine disrupting properties for T-modality. **Data requirement** The following tests are considered a data requirement (in a stepwise approach): - OECD TG 458 for A modality; - OECD TG 456 for S modality and - OPPTS 890.1200 for S modality. ->If OECD TG 456 and 458 and OPPTS 890.1200 are negative, OECD TG 441 should be performed. ->In case of positive result/s based on the previous studies for at least one modality, OECD TG 443 with the inclusion of cohort 1B or OECD TG 416 latest version should be conducted. An additional testing to evaluate the human relevance of the thyroid findings (i.e. *in vitro* assessment of species differences in	findings. However, as commented by the RMS, thyroid hormone clearance should also be evaluated in dog hepatocytes to provide additional useful information for the weight of evidence analysis. Moreover, the human relevance should be evaluated according to the Appendix A of the ECHA/EFSA (2018) ED Guidance and therefore the exclusion of other MIEs should also be performed and assessed. Regarding **EAS-modalities**, as commented by the RMS, the following data, in line with the ECHA/EFSA (2018) ED Guidance, are required before concluding: - OECD TG 458 for A modality; - OECD TG 456 and OPPTS 890.1200 for S modality. If OECD TG 456 and 458 and OPPTS 890.1200 are negative, OECD TG 441 should be performed. In case of positive result/s based on the previous studies for at least one modality, OECD TG 443 with the inclusion of cohort 1B or OECD TG 416 latest version should be conducted.

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			thyroid hormone clearance in primary human, rat and dog hepatocytes).	In case level 5 studies are conducted, based on the recently published (6th April 2020, 10.2903/sp.efsa.2019.EN-1837) "*Outcome of the pesticides peer review meeting on general recurring issues in mammalian toxicology*" (EFSA, 2020), it is recommended to include the following parameters even if they are triggered and/or not mandatory: - anogenital distance of each F1 and F2 pups, - presence and number of nipples/areolae in all male F1 and F2 pups, - histopathological assessment of the mammary gland in P0 and F1 adult males and females, - sperm parameters measured always by default regardless if they have also been tested in the 90-days. This was considered as a best scientific practice and would allow a comprehensive evaluation of relevant level 5 studies.

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				Refer also to 2(11, 12, 17, 18, 19, 20, 21, 22, 23)
2(2)	Annex B, Addendum I, General comment	DE: The review of this ED assessment is somewhat challenging. The extent of the reported relevant data for the OECD CF Level 4 and 5 studies is currently limited, e.g. minimal information on body weight (% reduction or gain) or statistical analysis, which makes it difficult to assess if the reported ED effects were observed above or below the MTD. Please refer to Column 3 for further explanations. It would be very beneficial if the assessment could be presented in accordance with "Appendix I" of the EFSA's "Administrative guidance on submission of dossiers and assessment reports for the peer-review of pesticide active substances" (published in April 2019). *(Additional information in column 3 of reporting table)*	**RMS**: All relevant data for this ED assessment have been included in the revised addendum. The information from them is collected in the corresponding tables. Furthermore, the methodology followed for the search/review of the literature has been included, as well as the approach for evaluating the relevant data (criteria to assess the reliability and relevance). Regarding submission of ED assessment in accordance to "Appendix I" of the EFSA's "Administrative guidance on submission of dossiers and assessment reports for the peer-review of pesticide active substances" (published in April 2019), as indicated in the Commission implementation schedule (SANTE-10914-2019 rev. 0, of 22 March 2019), EFSA Guidance should apply "*For (supplementary) dossiers submitted to Member States and EFSA on or after 1 October 2019*". The confirmatory data dossier was submitted to RMS well before this date. Hence, the assessment has not been presented in this format.	A more detailed description would be needed in the RMS addendum in order to facilitate the ED assessment according to the comment made by DE. Particularly, information on BW and BWG changes is very important in order to assess if the reported ED effects were observed above or below the MTD.

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			Fulfilled.	
2(3)	Appendix E table, General comment	DE: We found a few inconsistencies in the Appendix E table that should be double-checked. - Study ID 7 (rat carcinogenicity study): According to the DAR, "*Statistical analysis of liver and thyroid weight data showed a significantly ($P \leq 0.05$) higher liver to body weight ratio for the high-dose males and a thyroid to body weight ratio for the high-dose females as compared to the values for the respective control groups.*" In the table, it is indicated "no effect" for both liver and thyroid weights. - Study ID 35 (mouse carcinogenicity study): The reported doses for the effects are incorrect, e.g. decreased ovary weight starting at 0.005 (should it rather be 0.5% instead?).	**RMS**: Appendix E table has been corrected accordingly. Fulfilled.	Addressed
2(4)	Annex B, Addendum I, B.6.8.3.2, p. 6	DE: Please provide more information on the "unusable" studies (e.g. definition of unusable, how many of such studies were excluded). We see that this information is given in the ED assessment provided by the applicant.	**RMS**: A study was classified as "unusable" according to the CEFIC EMSG framework, where the weight or significance assigned to a study is derived from a combination of its reliability/repeatability and relevance scores. If relevance and reliability are low,	Addressed

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			the study is classified as unusable. It is also a measure of the significance which can be ascribed to a study in reaching a conclusion about endocrine disruption. It is also the parameter which is ultimately used in the evaluation of the endocrine disrupting potential for the combined dataset for a particular substance. CEFIC EMSG assigns the significance of *in vitro* and *in vivo* studies as High, Indicative, Low or Unusable according to the criteria. Following these considerations, a total of 8 publications were considered as "unusable" and, therefore, were not included in the Addendum I. Fulfilled.	
2(5)	Annex B, Addendum I, B.6.8.3.2, p. 9	DE: Correct the reference for ToxCast Estrogen Receptor (ER) model. The current reference ("point B.6.8.3.2.2.1") refers to the open literature on androgenic activity.	**RMS**: Done. Fulfilled.	Addressed
2(6)	Annex B, Addendum I, B.6.8.3.2.1.2.2, p. 9 B.6.8.3.2.2.2.1, p. 11 B.6.8.3.2.3.2.1, p. 14	DE: It might be good to mention the version of the ToxCast database used and/or update the presentation of the ToxCast data.	**RMS**: Data provided by the notifier was considered updated and acceptable at the time of the evaluation of the Confirmatory Data started. Furthermore, when the	The RMS did not check if additional relevant data are available in the most recent version of ToxCast and eventually this information would

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	B.6.8.3.2.4.2.1, p. 18	The data provided in the assessment seem to be extracted from an older version of ToxCast as the most recent version (3.0.9 as of August 2019) contains additional screening data for all EATS modalities that are not mentioned in the assessment (e.g. "TOX21_TSHR_Agonist_ratio" for the thyroid modality).	mentioned version of ToxCast was published, the assessment was already ongoing (in an advanced stage). The E-modality was sufficiently investigated. For A and S modality level 2 studies are required to allow the sufficiency of data to conclude on endocrine activity according to the ECHA/EFSA Guidance on ED identification. Update of Addendum I and Excel matrix is not considered necessary. The screening results for the T-modality included in the mentioned 3.0.9 version have been consulted and showed negative results for 8 assays. Taking into account the gaps for T-modality as stated in comment 2(1), it is not necessary to include these data in Addendum I and Excel matrix. Fulfilled.	need to be reported in the excel file and in the ED assessment. Please note that according to the recently published "*Outcome of the pesticides peer review meeting on general recurring issues in mammalian toxicology*" (EFSA, 2020), a screenshot or a stand-alone pdf-printout with all the relevant ToxCast data, including the date of data collection, should be made available. This will be necessary to keep track of any possible changes in ToxCast over time. At least a summary containing all relevant information from ToxCast provided by the applicant and checked by the RMS, should be included in the Volume 3 together with an evaluation by the RMS.
2(7)	Annex B, Addendum I, B.6.8.3.4.1.2, p. 72	DE: Please provide some further information on the significant decrease in body weight gain. Is ovarian atrophy observed above the MTD (no more than 10 % decrease in body weight gain relative to control)?	**RMS**: Addressed. This information has been included.	Addressed

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		This point applies also for the other reported adversities (e.g. preputial gland adenomas in rats and testicular and pituitary gland adenomas in mice).	Fulfilled.	
2(8)	Annex B, Addendum I, B.6.8.3.4.1.4, p. 72	DE: It would be helpful to have the incidence of pituitary histological findings in the 3 treated groups to see any dose-response relationship.	**RMS**: Addressed. Data on incidence has been included. Fulfilled.	Addressed
2(9)	Annex B, Addendum I, B.6.8.3.4.3, p. 75	DE: The study description of Prince et al., 2004 (regarding increased hepatic enzyme activity) is neither found in the assessment nor in the DAR/RAR. Please provide this in the RAR for the ED assessment. This study is relevant for the review of the T-mediated modality.	**RMS**: Addressed. A summary of the study has been included in the Addendum I, B.6.8.3.3.1. Also, the Excel file and lines of evidence have been updated Fulfilled.	Addressed
2(10)	Annex B, Addendum I, B.6.8.3.4.4, p. 78	DE: Agree with the RMS that the E-mediated endocrine activity is sufficiently investigated.	**RMS**: Noted. Fulfilled.	Addressed
2(11)	Annex B, Addendum I, B.6.8.3.4.4, p. 78	DE: For the A- and S-mediated modalities, we agree that there are data gaps regarding activity. Please briefly summarise here the observed endocrine effects (e.g. preputial gland adenomas in rats, testicular adenomas in mice), which might be mediated by A- or S-modality. Currently,	**RMS**: See comment 2(1) for data requirements. **RMS**: point B.6.8.3.4.4 has been amended to add a brief summary of the observed endocrine effects which might be mediated by A- or S- modality.	Addressed See data gap at 2(1)

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		there is nothing described about adversity. Also, a proposed test strategy (tiered approach) for filling the gaps should be presented here. We suggest that Level 2 assays, such as androgen receptor transactivation (OECD TG 458) and H295R steroidogenesis *in vitro* (OECD TG 456) assays, should be conducted first before deciding whether an *in vivo* Hershberger assay is required (in consideration of the 3R principle). *(Additional information in column 3 of reporting table)*	See comment 2(1)	
2(12)	Annex B, Addendum I, B.6.8.3.4.4, p. 78	DE: For the T-mediated modality, we also agree with the RMS's approach of requesting data from an *in vitro* comparative metabolism study in primary hepatocytes (with particular focus on liver enzyme induction and nuclear receptor activation; see next column for further explanation) in order to better understand and assess the mode of action of thiabendazole leading to thyroid effects. Hepatocytes from rats, humans as well as dogs should be assessed and compared as thyroid effects were observed in rats and dogs.	**RMS**: See comment 2(1)	See data gap at 2(1)

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2(13)		FR: this section was not reviewed.	**RMS**: Noted. Fulfilled.	Addressed
2(14)	B.6.8.3.4.1 Lines of Evidence for Endocrine Disrupting Potential Relevant to Humans	AT: It is not clear if the effects described in the lines of evidence occurred in the presence or absence of systemic toxicity for the *in vivo* studies (e.g. thyroid weight and histopathology or preputial gland adenomas in the 2 a rat study with F344 strain). It is essential to distinguish between effects that were observed above, at or below the MTD, because according to COMMISSION REGULATION (EU) 2018/605 "adverse effects that are non-specific secondary consequences of other toxic effects shall not be considered for the identification of the substance as endocrine disruptor".	**RMS**: Lines of evidence have been updated with additional data in order to properly correlate adverse effects with the presence or absence of systemic toxicity. Fulfilled.	Addressed
2(15)	B.6.8.3.4.1 Lines of Evidence for Endocrine Disrupting Potential Relevant to Humans	AT: All relevant and reliable data for the ED assessment should be included into the Excel file as well as into the lines of evidence (e.g. Prince et al. 2004).	**RMS**: Noted. Excel file and lines of evidence have been updated accordingly. Fulfilled.	Addressed
2(16)	B.6.8.3.4.1 Lines of Evidence for Endocrine Disrupting Potential Relevant to Humans	AT: In the Excel sheet a study (ID 40) is mentioned showing TPO inhibition (*in vivo*), while in the lines of evidence only an *in vitro* study showing no inhibition of TPO is quoted.	**RMS**: Noted. Excel file and lines of evidence have been updated accordingly. Fulfilled.	Addressed

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2(17)	B.6.8.3.4.3 MOA Analysis – Human Health	AT: No hepatic phase induction was observed at 10 and 30 mg/kg bw/d, while thyroid follicular cell hypertrophy was observed form 30 mg/kg bw/d onwards (2-year rat study). Even if studies of the same duration (i.e. 28 days) are compared, thyroid follicular hypertrophy occurs at 50 mg/kg bw/d, whereas hepatic phase I/II induction is only observed at 90 mg/kg bw/d. Therefore, the dose and temporal concordance between the proposed KE1, KE 3 and KE5 is not very strong. Furthermore, also the data on dogs should be included in this assessment.	**RMS:** Although temporal concordance between KE is not sufficiently strong, the whole available data indicates a MoA via liver enzyme induction. Additionally it has to be noted that while it is true that dose and temporal concordance are important elements which must be addressed when determining the empirical support for KERs, according to the EFSA/ECHA guidance, biological plausibility of each of the KERs in the MoA is the most influential consideration in assessing weight of evidence or degree of confidence in an overall postulated MoA for establishing the link between the adverse effect and the molecular initiating event. With respect to data on dogs, the main information found in this species supporting this MoA (KE5) was the increased in follicle size or follicular cell hypertrophy (2 females and 1 male of the highest group observed in the study of 53 weeks of duration). Data on dog have been included on table 6.8.3.4.3-2.	See data gap at 2(1)

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			Fulfilled.	
2(18)	B.6.8.3.4.3 MOA Analysis – Human Health	AT: It should be distinguished if the proposed MoA is via liver enzyme induction or liver toxicity. In the latter case a comparative MoA analysis is considered necessary.	**RMS**: A MoA via liver enzyme induction has been considered. Fulfilled.	Addressed See also data gap at 2(1)
2(19)	B.6.8.3.4.4 Conclusions on endocrine disrupting proprieties	AT: According to the "Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009" for EAS an OECD TG 456, OPPTS 890.1200 and OECD TG 458 should be requested. If these tests are negative an OECD TG 441 should be conducted. However, it is noticed that the level 2 tests of the OECD CF were already requested, but not submitted as confirmatory information. In case, a comparative enzyme activity study is conducted for the T-modality, all relevant test species (at least human, rat and dog) should be included. However, as the proposed MoA lacks a clear dose and temporal concordance (earlier KEs should be observed at doses below or similar to the doses of later KEs) other MIE should be also taken into account. It is not considered sufficient to rely solely on ToxCast data.	**RMS**: See comment 2(1) for data requirements. With respect to alternative MoA for the T-modality, it has to be noted that available data indicate that thiabendazole does not inhibite thyroid peroxidase (TPO) (Paul Friedman K *et al.,* 2016) and the sodium-iodide symporter (NIS) (Wang J *et al.*, 2018). Additionally, the RMS agrees that is not sufficient to rely solely on Toxcast data. See comment 2(1)	See data gap at 2(1)

Mammalian Toxicology (Endocrine Disruption)				
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2(20)	Vol. 3, Addendum I, confirmatory data, B.6.8.3, Endocrine disruption	SE: We agree with the proposed MoA but disagree that this is a non-endocrine MoA. Adverse effects on the thyroid that are secondary to liver enzyme induction leading to enhanced hormone metabolism should be considered as an endocrine MoA. This is explicitly stated in the JRC report "Key scientific issues relevant to the identification and characterisation of endocrine disrupting substances" from 2013 and the ECHA/EFSA guidance, including Appendix A, does not indicate otherwise. *(Additional information in column 3 of reporting table)*	**RMS**: Noted. A pattern of effects indicative of adversity for T modality cannot be excluded. Therefore, based on the available evidences, the postulated MoA can be considered as an endocrine MoA. The relevance of the effects in thyroid for humans should not be dismissed; however, as previously stated, an additional testing to evaluate species differences in thyroid hormone clearance in primary human, rat and dog hepatocytes should be performed. RMS's comments at this point have been modified to make it clearer. Fulfilled.	See data gap at 2(1)
2(21)	Vol. 3, Addendum I, confirmatory data, B.6.8.3, Endocrine disruption	SE: EAS-mediated adversity has not sufficiently investigated for Thiabendazole; the included 2-generation study predates 2001. However, available mechanistic data indicates that there is no E- or S-activity. We agree with RMS that addition of the Hershberger assay would be an appropriate next step to generate missing mechanistic data for A-activity.	**RMS**: See comment 2(1)	See data gap at 2(1)

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2(22)	Vol. 3, Addendum I, confirmatory data, B.6.8.3, Endocrine disruption	SE: Can RMS please clarify the comment "*The postulated MoA is considered plausible, although a conclusion cannot be reached in the absence of further assessment of uncertainties*" on p 78? Which uncertainties are you referring to and how should they be assessed?	**RMS**: Identified uncertainties for the postulated MoA are summarised and commented in Table 6.8.3.4.3-3 (Conclusions on the biological plausibility of the link between the adverse outcome and the key events for a postulated MoA). To address this issue, additional testing to evaluate the human relevance of the thyroid findings (i.e. *in vitro* assessment of species differences in thyroid hormone clearance in primary human, rat and dog hepatocytes) has been requested. See comment 2(1). Fulfilled.	See data gap at 2(1)
2(23)	Confirmatory data addendum – mammalian toxicology	EFSA: EFSA notes that the applicant has not provided the OECD level 2 tests requested in the EFSA conclusion. Particularly, regarding EAS-modalities, EFSA agrees with RMS and applicant that the E-modality is sufficiently investigated based on the available ToxCast ER prediction model. However, EFSA agrees with RMS that the statement made by the applicant that ToxCast data allow to sufficiently investigate the endocrine activity of A- and	**RMS**: Agree. See comment 2(1)	See data gap at 2(1)

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		S-modalities is not in line with the ECHA-EFSA Guidance on the ED identification. Therefore, additional data are needed. Precisely, considering that the dataset for adversity is not sufficiently investigated (i.e. lack of OECD TG 416 performed with latest version or OECD TG 443) and that no EAS-mediated adversity has been observed, the following tests are requested: OECD TG 458 for A modality; OECD TG 456 and OPPTS 890.1200 for S modality. If OECD TG 456 and 458 and OPPTS 890.1200 are negative, OECD TG 441 should be performed. In case of positive result/s based on the previous studies for at least one modality, OECD TG 443 with the inclusion of cohort 1B or OECD TG 416 latest version should be conducted. Regarding T-modality, T-mediated adversity has been consistently observed across several studies, mainly in rat. EFSA notes that the applicant commented that likely the observed effects on the thyroid are not specific effects on the endocrine system but secondary to liver toxicity. EFSA notes that a comparative		

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		MoA analysis to evaluate if thyroid effects are secondary to liver effects is missing and therefore, based on the available data, this cannot be proven. EFSA also acknowledges that the applicant suggested to perform additional testing to evaluate the human relevance of the thyroid findings (i.e. *In vitro* assessment of species differences in thyroid hormone clearance in primary human and rat hepatocytes). EFSA agrees that this information, in line with the ECHA-EFSA Guidance, will be informative for the assessment of ED towards T-modality, although EFSA considers that the addition of dog hepatocytes would provide additional useful information for the weight of evidence analysis. Overall, EFSA notes that, based on the available evidences, a MoA can be postulated but a thorough evaluation of the hazard, in line with the EFSA-ECHA guidance was not performed. Therefore, based on the available evidences, a pattern of effects indicative of adversity for T modality cannot be excluded.		

5. Ecotoxicology (Endocrine Disruption)

Ecotoxicology (Endocrine Disruption)				
No.	Column 1 Reference to Assessment Report (vol., point, page)	Column 2 Comments from Member States, EFSA, applicant or public	Column 3 Evaluation by (RMS) rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(1)	B.9.6.2 RMS conclusions	Applicant: Syngenta agrees with RMS proposal for testing to further evaluate endocrine disrupting potential in non-target organisms (according to scenario 2a(iii) of the assessment strategy in the ECHA-EFSA Guidance): EAS modalities: 21-d fish screening assay (OECD TG 230) T modality: Amphibian metamorphosis Assay (OECD TG 231)	RMS: According to the EFSA criteria (se comment 5(9)) a test in line with OECD 229 give a valuable information with regards to fecundity and gonad histopathological examination which are not included in OECD 230. Furthermore, EFSA/ECHA Guidance states that to consider the E, A, S modalities for non-target organism other than mammals sufficiently investigated, preferably a OECD TG 229 should be conducted; however, the assay OECD 230 is acceptable as well. Therefore, RMS is of the opinion that a "Fish short term reproduction assay" in line with OECD 229 should be conducted. Furthermore, RMS agrees with the applicant that to study T modality and Amphibian metamorphosis Assay should be performed. **Data requirement**	See 5(6)

Ecotoxicology (Endocrine Disruption)				
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			Applicant to conduct the below studies: • Fish short term reproduction assay (OECD TG 229) • Amphibian metamorphosis Assay (OECD TG 231)	
5(2)	Vol. 3, Addendum I Endocrine disruption, B.9, Ecotoxicology ED	DE: The EATS modality is not sufficiently investigated and we agree with the proposed test strategy to assess the EATS modality in non-target organisms other than mammals.	RMS: Noted. Thanks for the comment. Fulfilled.	See 5(6)
5(3)	General comment	EFSA: the study summaries are too short to allow for an in-depth and independent evaluation	RMS: Noted. RMS agrees that the applicant should submitted further summaries of the available studies to allow a better evaluation of them. **Data requirement** Applicant to include further summaries of the available studies to allow a better evaluation of them.	A more detailed description of the studies would be needed in the RMS addendum in order to facilitate the evaluation of the studies and the ED assessment.

Ecotoxicology (Endocrine Disruption)				
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5(4)	General comment	EFSA: the study summaries are too short to allow for an in-depth and independent evaluation	RMS: Noted. RMS agrees that the applicant should submitted further summaries of the available studies to allow a better evaluation of them. **Data requirement** Applicant to include further summaries of the available studies to allow a better evaluation of them.	See 5(3)
5(5)	Vol. 3, B.9.6.1, Invertebrates	FR: Further details on the available data on invertebrates would be welcome. Indeed, even if these organisms could not be directly used in the assessment scheme of the EFSA/ECHA guidance (June 2018), the available results on them should be presented as they can be used as supportive data to support the overall conclusion.	RMS: According to EFSA-ECHA guidance, the below invertebrates toxicity test are considered as "relevant" according to OECD Conceptual Framework and OECD GD 150 for testing and assessment of Endocrine Disrupting Chemicals. Level 3: • OECD TG 242 (*Potamopyrgus antipodarum* reproduction test). • OECD TG 243 *(Lymnaea stagnalis* reproduction test). • OECD TG 218-219 (Chironomid toxicity test).	Addressed

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			• OECD TG 211 (*Daphnia magna* reproduction test). • OECD TG 222 (Earthworm reproduction test). • OECD TG 220 (Enchytraeid reproduction test). • OECD TG 225 (Sediment water *Lumbriculus* toxicity test • OECD TG 226 Predatory mite reproduction test in soil. • OECD TG 232 (Collembolan reproduction test in soil). Level 4: • OECD TG 233 (Sediment water chironomid life cycle toxicity test. • Draft OECD TG (*Daphnia* multigeneration test for assessment of endocrine disrupting chemicals). However, due to the scarce knowledge on the endocrinology for non-target invertebrates, the EFSA/ECHA guidance (June 2018) does not specifically cover those organisms and therefore the generation of specific data will not be triggered by applying the strategy developed in this guidance.	

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			It is noted that no information with regards these studies has included in Thiabendazole Vol. 3 B9 (May/October 2013). Furthermore, the applicant stated that "No ecotoxicology studies within the scope of the Guidance and relevant to identification of ED properties were retrieved in these searches". RMS also found no information on open scientific literature regarding to invertebrates endpoints of thiabendazole. Therefore, further details on invertebrates have not been included. Fulfilled.	
5(6)	Vol. 3, B.9.6.1, Data review	FR: A literature search on the potential effects of thiabendazole on the endocrine system should have been provided and included in this addendum for confirmatory data according to the EFSA/ECHA guidance (June 2018). Without this literature search a data gap should be concluded on this issue.	RMS: According to the EFSA/ECHA guidance the first step in the ED assessment strategy is "Gather all relevant information". It includes "all available relevant scientific data: Scientific data generated in accordance with internationally agreed study protocols and other scientific data selected applying a systematic review methodology".	**Data gap** A literature search in line with EFSA (2011) and the recommendations in ECHA/EFSA Guidance (2018) should be provided.

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			The systematic literature review should be conducted in line with EFSA Guidance on submission of scientific peer-reviewed open literature for the approval of pesticide active substances (EFSA 2011). The systematic review should include all relevant published scientific information. The applicant should submitted further information regarding the literature search on the potential effects of thiabendazole on the endocrine system. It includes detailes information databases, search strategy, relevance criteria,.. Therefore, a data requirement has been described to include a literature search according to the EFSA/ECHA guidance. **Data requirement** Applicant to include a literature search according to the EFSA/ECHA guidance and EFSA guidance (EFSA 2011).	
5(7)	Vol. 3, B.9.6.2, RMS conclusion	FR: FR agrees that the available data set is not sufficient to conclude on the potential	RMS: Noted.	**Data gap**

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		endocrine disruption of thiabendazole for EATS modalities. The testing strategy of the EFSA/ECHA guidance (June 2018) should be followed to produce the further tests to complete the dataset. Moreover, an evaluation and a conclusion for wild mammals should also presented pending the results from the further tests considered required by the Toxicology section.	The endocrine disruption assessment for wild mammals is based upon the data package for mammals, which has been evaluated and discussed under the point B.6.8. In contrast to the human health assessment, the assessment for wild mammals (non-target organisms) concentrates on those endpoints and effects with the potential for being relevant at the population level, meaning the affecting survival, reproduction, growth and development. Further test required by the Toxicology section will be evaluated when are available. **Open point** RMS to evaluated further test required by toxicology section.	With the available information, it is not possible to draw a conclusion on the ED properties of thiabendazole for non-target organisms. The following studies should be requested in line with the ECHA/EFSA (2018) Guidance: • An AMA test according to OECD TG 231 (for T-modality); • A FSTRA test according to OECD TG 229 (for EAS-modalities). If one of those assays is positive, a mode of action analysis should be performed and further data might be needed to investigate adversity (i.e. LAGDA according to OECD TG 241 and/or MEOGRT according to OECD TG 240). Although T-mediated adversity was observed in mammals, this is not considered relevant for wild mammal populations as the effects on thyroid histopathology were observed in isolation, without impairment of

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				growth/development and/or reproduction. See also data gap 5(6)
5(8)	Vol. 3, Addendum I, confirmatory data, B.9, Endocrine disruption	SE: Referring to our comment in the toxicology section above, we do not agree to the proposed non-ED mode of action for the T-modality in mammals. From our point of view, the ED criteria for the T-modality is fulfilled based on the mammalian data. Depending on the outcome of the discussion on T-modality for mammals, however, further data on amphibians may be needed to exclude this modality for non-mammalian NTO.	RMS: Noted. T-mediated adversity has been consistently observed across several studies (mainly in rat), although no evidence for a direct interaction with the thyroid could be found in the in vitro mechanistic studies. The relevance of the effects in thyroid for humans should not be dismissed; however, as previously stated, an additional testing to evaluate species differences in thyroid hormone clearance in primary human, rat and dog hepatocytes should be performed. Since a T-modality in mammals could not be excluded, RMS is of the opinion that further data on amphibians (AMA, OECD 231) would be necessary to exclude this modality for non-target organisms other than mammals. Addressed.	See 5(7)

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5(9)	Vol. 3, Addendum I, confirmatory data, B.9, Endocrine disruption	SE: The RMS proposed that an OECD TG 230 screening test should be requested. According to the EFSA/ECHA guidance document, the OECD TG 229 would be a better choice, since this test includes also fecundity and gonad histopathology, which gives valuable information to address endocrine activity.	RMS: Agree. Fulfilled. See response to comment 5(1).	See 5(7)
5(10)	Assembled lines of evidence - non-target organisms	EFSA: the lines of evidence are presented according to the ECHA/EFSA Guidance. However, for endocrine activity, it is stated that no information is available. This is not considered the case for thiabendazole where information from TOXcast is available and can be considered also for non-target vertebrates other than mammals, although supportive only in many cases. As explained in the guidance in vitro data using mammalian cells are considered	RMS: According to the EFSA/ECHA ED Guidance (2018) many of the in vitro assays that are designed to provide information on an endocrine MoA utilise human or mammalian cell lines can also provide information to other vertebrates. It is due to the high level of conservation of the endocrine system and receptor homology across the vertebrates. The EFSA/ECHA ED Guidance (2018) states that the ToxCast Estrogen Receptor (ER) model is described as an example of a particular defined approach, which combines test and no-test methods. It integrates 18 high-throughput ToxCast screening in vitro assays (Judson et al., 2015) that provide comprehensive pathway coverage for the biology of the ER signalling pathway (Browne et al., 2015). The EFSA-ECHA guidance refers to this model as part of the testing strategy to evaluate the endocrine activity (Level 2). Data provided by the notifier was considered updated and acceptable at the time of the	Addressed See 2(1)

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			evaluation of the Confirmatory Data started, furthermore, when the most recent version of ToxCast (3.0.9 as of August 2019) was published the assessment was already ongoing (in an advanced stage).The information from ToxCast has been considered by RMS. The adverse effects under E, A, S-mediated evaluation was considered negative. E-modality can be concluded for Thiabendazole, since Level 2 ToxCast ER Bioactivity Model was provided, with negative effects. With regards to the A-, S-modalities, the EFSA-ECHA guidance (2018) includes the 'Hershberg bioassay in rats' (OECD TG 441) to consider the AS-related endocrine activity as sufficiently investigated. Regarding T-modality, no evidence for a direct interaction with the thyroid *in vitro* has been observed. However, *in vivo* effects on thyroid hormone levels has been seen, although no evidence for a direct interaction with the thyroid could be found. Therefore, based on the available evidences, a pattern of effects indicative of adversity for T modality cannot be excluded. Addressed.	

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5(11)	Integrated lines of evidence for adversity	EFSA: it is considered more informative to call the line of evidence by specifying the parameter 'body weight' instead of growth. Similarly, the lines of evidence should be called hatching success instead of development. This is mainly due to the fact that growth and development can refer to more than one parameter.	RMS: Noted. RMS agrees with EFSA with regards to consider more informative call the line of evidence by specifying the parameter: "body weight" instead of Growth and "Hatching success" instead of Development. Thiabendazole Addendum I (Confirmatory Data) on Endocrine Disruption B9 (Ecotoxicology) has been updated taking into account the criteria of EFSA. Fulfilled.	Addressed
5(12)	Conclusion of the RMS for E,A,S modalities	EFSA: the RMS has suggested, in order to consider the endocrine activity as sufficiently investigated, to conduct a test in line with OECD 230. Although, this is mentioned in the ECHA/EFSA Guidance, a test in line with OECD 229 should always be preferred. The difference between the 2 tests is given by the inclusion in the OECD 229 of gonad histopathological examination which are not included in OECD 230. Gonad histopathology is, however, considered, very informative and crucial for a proper interpretation of the findings in some cases.	RMS: According to the EFSA/ECHA Guidance to consider the E, A, S modalities for non-target organisms other than mammals sufficiently investigated, a test in line with OECD 230 (Fish short term reproduction assay) should be provided, however the 21-day fish assay OECD 230 is acceptable as well. However, RMS agrees with EFSA that OECD 229 give a valuable information with regards to fecundity gonad histopathological examination which are not included in	See 5(7)

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			OECD 230. This information gives useful information to address endocrine activity. Therefore, the applicant should provide a "Fish short term reproduction assay" in line with OECD 229 to study E, A, S modalities for non-target organisms other than mammals. **Data requirement** Applicant to provide a "Fish short term reproduction assay" in line with OECD 229 to study E, A, S modalities for non-target organisms other than mammals.	

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5(13)	Conclusion of the RMS for E,A,S modalities	EFSA: The assessment of the RMS is agreed. However, before performing new studies, the population relevance of the adverse effects observed in rats for wild mammals should be discussed. If the population relevance cannot be established, additional tests with non-target vertebrates other than mammals should be performed. It is agreed that an AMA is in this case the kind of test to be performed.	RMS: Noted. According to the EFSA/ECHA ED Guidance (2018) "t*o consider the E, A, S modalities for non-target organisms other than mammals sufficiently investigated, preferably the 'Fish short term reproduction assay' (FSTRA; OECD TG 229) should have been conducted…; however the 21-day fish assay OECD TG 230 (OECD, 2009b) is acceptable as well…*". Therefore, RMS is of the opinion that this test should be conducted. Regarding Amphibian Metamorphosis Assay (AMA OECD 231) should be submitted sin T-mediated adversity cannot not be ruled out (See comments 5(1) and 5(9)). See Data Requirement in point 5(1)	See 5(7)