TECHNICAL REPORT

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Scientific assistance on the internal review under Regulation (EC) No 1367/2006 of the Commission Implementing Regulation (EU) 2021/2049 renewing the approval of the active substance cypermethrin as a candidate for substitution in accordance with Regulation (EC) No 1107/2009

European Food Safety Authority (EFSA)

Abstract

Following a request of the European Commission, the European Food Safety Authority (EFSA) reviewed the scientific arguments raised by the non-governmental organisation Pesticide Action Network Europe ('PAN Europe') requesting the review of Commission Implementing Regulation (EU) 2021/2049 renewing the approval of the active substance cypermethrin as a candidate for substitution in accordance with Regulation (EC) No 1107/2009. EFSA's assessment focuses on relevant scientific elements and does not cover legal aspects, as they are not in EFSA's remit and not in the frame of the mandate received from the European Commission. The current report summarises the outcome of the assessment of the scientific arguments raised by PAN Europe following consultation with the rapporteur Member State Belgium.

Keywords: cypermethrin, peer review, risk assessment, pesticide, insecticide

Requestor: European Commission

Question number: EFSA- Q-2022-00203

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Summary

Following a request of the European Commission, the European Food Safety Authority (EFSA) reviewed the scientific arguments raised by the non-governmental organisation Pesticide Action Network Europe ('PAN Europe') requesting the review of Commission Implementing Regulation (EU) No 2021/2049 renewing the approval of the active substance cypermethrin as a candidate for substitution in accordance with Regulation (EC) No 1107/2009. PAN Europe initiated an internal review with a view to replacing this re-approval with a decision not to renew the approval of this active substance.

This request is based on Article 10 of Regulation (EC) No 1367/2006 as amended by Article 1(2)(a) of Regulation (EU) No 2021/1767 of the European Parliament and of the Council of 6 October 2021 amending Regulation (EC) No 1367/2006 on the application of the provisions of the Aarhus Convention on Access to Information, Public Participation in Decision-making and Access to Justice in Environmental Matters to Community institutions and bodies.

EFSA analysed the relevant scientific elements put forward in the review letter of PAN Europe and provided the outcome of the assessment of the relevant scientific arguments in close collaboration with the rapporteur Member State Belgium. In particular EFSA analysed the scientific elements in relation to paragraphs 33, 48 and 49 of the request for internal review(see Appendix A).

The current report does not cover legal aspects, as they are not in EFSA's remit and not in the frame of the mandate received from the European Commission.

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1. Introduction

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

Cypermethrin is a substance covered by the third stage of the renewal programme ('AIR3') in accordance with Regulation (EC) No 844/2012[1].

An application for renewal of the active substance cypermethrin by the Cypermethrin Working Group Task Force (consisting of Arysta LifeScience Benelux sprl (previously Agriphar S.A.) and SBM Développement) was assessed by the rapporteur Member State (RMS), Belgium, and the co-rapporteur Member State (co-RMS), Germany.

Following the submission of the renewal assessment report (RAR) to EFSA (received on 8 May 2017), EFSA initiated a peer review of the RAR in line with the provisions of Regulation (EC) No 844/2012. Following the completion of the peer review, including expert discussion, EFSA published its conclusion on the pesticide peer review for cypermethrin on 30 August 2018 (EFSA, 2018).

The EFSA conclusion on cypermethrin was reached on the basis of the evaluation of the representative uses of cypermethrin as an insecticide on winter and spring cereals, on winter and spring oilseed rape and potato, as proposed by the applicants. The risk assessments in the EFSA conclusion identified as critical areas of concern, for the representative uses assessed, a high risk to aquatic organisms, to bees and to off-field non-target arthropods and that the batches used in the (eco)toxicological studies could not be concluded as representative of the technical specification. Drift mitigation measures up to 95% to reduce exposure for some of these organisms, but not for bees, were considered in the EFSA conclusion, according to indications provided in the guidance currently in place.

In order to verify the possibility to identify additional mitigation measures other than those currently in place based on the agreed guidance document and allowing the identification of a safe use, the European Commission asked EFSA on 15 July 2019 for technical support in identifying conditions of use which are likely to result in an acceptable risk for aquatic organisms, non-target arthropods and bees, considering the risk assessment for the representative uses of cypermethrin. EFSA finalised a statement (EFSA, 2019) considering the options of exposure reduction as proposed by the RMS (BE) and the extent to which a low risk to aquatic organisms, non-target arthropods and bees, could be demonstrated. EFSA considered in particular:

- the off-field risk to aquatic organisms and non-target arthropods;
- the spray drift mitigation for off-field risk to bees;
- whether, and, if so, in which circumstances, the in-field exposure for bees can be expected to be significantly reduced.

The exposure reduction measures prepared by the RMS BE and provided in Annex A of the EFSA, 2019, were used as the basis for this statement.

On 21 January 2022, Commissioner Kyriakides received a request for internal review of the Commission Implementing Regulation (EU) 2021/2049[2] of 24 November 2021 renewing the approval of the active substance cypermethrin as a candidate for substitution in accordance with Regulation (EC) No 1107/2009[3] of the European Parliament and of the Council concerning the placing of plant

[1] Commission Implementing Regulation (EU) No 844/2012 of 18 September 2012 setting out the provisions necessary for the implementation of the renewal procedure for active substances, as provided for in Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market. OJ L 252, 19.9.2012, p. 26–32.

[2] Commission Implementing Regulation (EU) 2021/2049 of 24 November 2021 renewing the approval of the active substance cypermethrin as a candidate for substitution 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 420, 25.11.2021, p. 6–13

[3] 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.

protection products on the market, and amending the Annex to Commission Implementing Regulation (EU) No 540/2011[4].

This request, submitted by a non-governmental organisation under Article 10 of Regulation (EC) No 1367/2006[5] as amended by Article 1 (2) (a) of Regulation 2021/1767[6] of the European Parliament and of the Council of 6 October 2021 amending Regulation (EC) No 1367/2006 on the application of the provisions of the Aarhus Convention, is substantiated by technical arguments referring to EFSA's risk assessment.

In order to address the issues raised by the non-governmental organisation, EFSA was asked for an in-depth analysis of the relevant scientific elements included in the request for internal review.

2. Assessment

EFSA analysed the relevant scientific elements put forward in the review letter of PAN Europe and provides the outcome of the assessment of the relevant scientific arguments with close collaboration with the rapporteur Member State Belgium. In particular EFSA analysed the scientific elements in relation to paragraphs 33, 48 and 49 of the request for internal review (see Appendix A).

The current report does not cover legal aspects, as they are not in EFSA's remit and not in the frame of the mandate received from the European Commission. The relevant scientific arguments and the EFSA's scientific views on the specific points raised are presented in the format of a reporting table.

The arguments raised 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.

[4] Commission Implementing Regulation (EU) No 540/2011 of 25 May 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the list of approved active substances. OJ L 153, 11.6.2011, p. 1–186.

[5] Regulation (EC) No 1367/2006 of the European Parliament and of the Council of 6 September 2006 on the application of the provisions of the Aarhus Convention on Access to Information, Public Participation in Decision-making and Access to Justice in Environmental Matters to Community institutions and bodies. OJ L 264, 25.9.2006, p. 13–19.

[6] Regulation (EU) 2021/1767 of the European Parliament and of the Council of 6 October 2021 amending Regulation (EC) No 1367/2006 on the application of the provisions of the Aarhus Convention on Access to Information, Public Participation in Decision-making and Access to Justice in Environmental Matters to Community institutions and bodies. OJ L 356, 8.10.2021, p. 1–7.

Documentation provided to EFSA

1. Letter from the European Commission to the EFSA Executive Director, dated 18 February 2022 requesting technical and scientific assistance on the internal review under Regulation (EC) No 1367/2006 of Commission Implementing Regulation (EU) 2021/2049 of 24 November 2021 renewing the approval of the active substance cypermethrin as a candidate for substitution in accordance with Regulation (EC) No 1107/2009.

2. PAN Europe's request for internal review of Commission Implementing Regulation (EU) 2021/2049 renewing the approval of the active substance cypermethrin dated 20 January 2022.

References

Belgium, 2018. Revised Renewal Assessment Report (RAR) on cypermethrin prepared by the rapporteur Member State Belgium in the framework of Regulation (EC) No 1107/2009, March 2018. Available online: www.efsa.europa.eu

EFSA (European Food Safety Authority), 2013. EFSA Guidance Document on the risk assessment of plant protection products on bees (Apis mellifera, Bombus spp. and solitary bees). EFSA Journal 2013;11(7):3295, 268 pp. https://doi.org/10.2903/j.efsa.2013.3295

EFSA (European Food Safety Authority), 2018. Conclusion on the peer review of the pesticide risk assessment of the active substance cypermethrin. EFSA Journal 2018;16(8):5402, 27 pp. doi:10.2903/j.efsa.2018.5402

EFSA (European Food Safety Authority), 2019. Statement on risk mitigation measures on cypermethrin. EFSA Journal 2019;17(10):5822, 23 pp. doi:10.2903/j.efsa.2019.5822

Singh D, Irani D, Bhagat S, Vanage G, Cypermethrin exposure during perinatal period affects fetal development and impairs reproductive functions of F1 female rats, Sci Total Environ, 10;707:135945, 2020.

Wang HX, Zhang R, Zheng LZ, Wang LS, Yu Y, Wang Q, Ding Z, Zhang JP, Zhang MR, Xu LC, Cypermethrin induces Sertoli cell apoptosis through mitochondrial pathway associated with calcium, Toxicol Res, 19;10(4):742-750, 2021.

Abbreviations

a.s.	active substance
DAR	draft assessment report
GAP	good agricultural practice
DG SANCO	European Commission Directorate General Health and Consumers
EU	European Union
LC_{50}	lethal concentration, median
LD_{50}	lethal dose, median; dosis letalis media
MRL	maximum residue level
MS	Member State
NESTI	national estimated short-term intake
OSR	oilseed rape
PBI	Plant-back interval
PEC	predicted environmental concentration
PEC_{sed}	predicted environmental concentration in sediment
PEC_{soil}	predicted environmental concentration in soil
PEC_{sw}	predicted environmental concentration in surface water
PRIMo	Pesticide Residue Intake Model
RAR	renewal assessment report
RMS	rapporteur Member State
TMDI	theoretical maximum daily intake

Appendix A – Collation of the relevant scientific arguments provided in the review letter for the active substance cypermethrin and the conclusions drawn by EFSA on the specific points raised

No.	Column 1 Reference to review letter	Column 2 Argument	Column 3 Evaluation by rapporteur Member State	Column 4 EFSA's scientific views on the specific point
1	Paragraph 33, in (2) Lack of knowledge of the scientific criteria for the determination of endocrine disrupting properties laid down in Regulation (EU) 2018/605[7].	33. This is all the more true since the scientific literature has also demonstrated these endocrine disrupting properties since these years (Jin 2011, Marettova 2017, Singh 2020, Wang 2021). In accordance with Article 8 (5) of Regulation 1107/2009, EFSA should also have taken into account that evidence provided by independent scientific literature.	**Jin 2011** • The Jin 2011 study is not fully referenced in the letter, but we assume that the following was meant: Jin et al, Cypermethrin exposure during puberty induces oxidative stress and endocrine disruption in male mice, Chemosphere, 84 (1), 124-130, 2011. • The article has been taken into account in the DRAR of Cypermethrin (Belgium, 2018; Vol 3 B.6 p.443/679). **Marettova 2017** • Marettova E, Maretta M, Legáth J, Effects of pyrethroids on female genital system. Review, Anim Reprod Sci 184:132-138, 2017.	The first two articles (Jin 2011, and Marettova 2017) have already been considered during the peer review (Belgium, 2018): **Jin, 2011**: Effects in adolescent male mice at 20 mg/kg bw per day included decreased serum testosterone levels. **Marettova, 2017**: This article is a review paper, and most publications considered in this review were also evaluated during the peer review (EFSA, 2018). The last two articles (Singh 2020, and Wang 2021), being published after the finalisation of the peer review (EFSA, 2018), could not be taken into account. **Singh, 2020**:

[7] 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.

			• The article has been taken into account in the DRAR of Cypermethrin (Belgium, 2018; Vol 3 B.6 p.478/679). Singh 2020, Wang 2021 :The new studies are even not fully referenced in the letter, and above all cannot be part of the Peer Review as they date from >2020. RMS supposes that the NGO meant to cite: i. **Singh D**, Irani D, Bhagat S, Vanage G, Cypermethrin exposure during perinatal period affects fetal development and impairs reproductive functions of F1 female rats, Sci Total Environ, 10;707:135945, **2020**. In this article, one former publication of Singh et al (2017) is cited in the DAR, which was of course part of the evaluation by the RMS. In this study (Singh 2020), apical effects are reported from 10 mg/kg bw per day onwards (with debatable dose-response), with inconsistent and non-dose responsive effects stated at 1 mg/kg bw per day and above. However, existing multigeneration studies in rats do not suggest untoward reproductive effects at dose	Overall, both studies by Singh et al. (2017 and 2020) are considered not robust enough (with inconsistent effects and/or absence of dose-response relationship) to override the existing guideline studies. **Wang, 2021**: Apoptotic findings were observed in the mouse Sertoli cell line TM4 *after in vitro* exposure to cypermethrin. Since in the EU evaluation, apical reproductive toxicity endpoints were assessed *in-vivo* in rodents, it remains unlikely that the Wang 2021 study would impact on the final EFSA conclusion. See also overall conclusion under point No.2 below.

			levels ≤10 mg/kg bw per day. In addition, as agreed during the peer review, cypermethrin may *perhaps* have anti-androgenic effects *in-vitro*. However, neither the structural properties nor the ToxCast ER model did predict cypermethrin to act as an oestrogen or anti-oestrogen, therefore meaningful effects are not expected for oestrogenicity, leaving the mouse findings (at least at the lowest dose) unexplained. The outcome of both studies does not change the conclusion in our opinion. ii. **Wang HX**, Zhang R, Zheng LZ, Wang LS, Yu Y, Wang Q, Ding Z, Zhang JP, Zhang MR, Xu LC, Cypermethrin induces Sertoli cell apoptosis through mitochondrial pathway associated with calcium, Toxicol Res, 19;10(4):742-750, **2021**. The authors claim that their *in-vitro* study provides «*a new insight into mechanisms involved in cypermethrin-induced male reproductive toxicology*», because of apoptotic findings in the mouse Sertoli cell line TM4 (established cell line culture derived from immature mouse testis). Since in the EU evaluation, apical reprotoxicity endpoints were assessed *in-vivo* in rodents, it remains unlikely	

			that the Wang 2021 study would impact on the final EFSA conclusion.	
2	Paragraph 48, in (2) Lack of knowledge of the scientific criteria for the determination of endocrine disrupting properties laid down in Regulation (EU) 2018/605.	48. For example, the regulatory dossier indicates that no toxicity is observed neurodevelopmental cypermethrin in rodents at a dose of 15 mg/kg body weight. EFSA therefore concluded a no-effect dose of 15 mg/kg (NOAEL: No Observable Adverse Effect Level). However, a 2017 study** indicates an effect of 5 mg/kg. EFSA therefore identified 15 mg/kg as a non-effective dose whereas scientific literature shows one to 5 mg/kg. ** In utero and lactational exposure to low-doses of the pyrethroid insecticide cypermethrin leads to neurodevelopmental defects in male mice - An ethological and transcriptomic study, Laugeray *et al.* 2017	The 2 year rat study ([redacted] et al. **1978**), with NOAEL of 0.5 mg/kg bw per day, was used to derive the ADI of 0.005 mg/kg bw per day, supported by the DNT study. In the DNT study ([redacted], **2011**), the LOAEL of 5 mg/kg bw per day was identified for parental animals based on clinical signs, and the developmental NOAEL of 15 mg/kg bw per day was based on FOB changes and testes/epididymis alterations. This developmental NOAEL was used to derive the ARfD 0.005 mg/kg with UF 3000, the AOEL and AAOEL of 0.0025 mg/kg with UF 3000 (and correcting for oral absorption of 50%). The NOAEL for development was the point of departure supported by the 24 months study. The **Laugeray (2017)** study was described in the RAR (Belgium, 2018, section B.6.6.3.5). The Laugeray 2017 study is not unreliable per se, although shortcomings were identified, but the outcome is without meaningful impact on the overall conclusion. As indicated above the RfD's are orders of magnitude lower than the lowest tested dose, allegedly identified as a LOAEL in this published study (5	**Laugeray 2017:** Considering the different shortcomings in this study, it was agreed during the peer review that the NOAEL of 5 mg/kg bw per day should not be used in the context of quantitative risk assessment. **Overall conclusion**: • Literature studies, with intrinsic limitations, were duly evaluated during the peer review and considered in the weight of evidence. The new studies recently published did not raise additional concern with regard to potential adverse effects of cypermethrin. • On the basis of the available regulatory studies and literature findings, it was acknowledged that cypermethrin has endocrine-mediated activity but the potential for endocrine disruption could not be concluded upon. This is already highlighted as a data gap in the EFSA conclusion

			mg/kg bw/d). Limitations of the study include administration of the a.s. by intranasal bolus 3x/week (not very representative for a normal -oral and even inhalation- exposure route) and difficulties to align the observations and measurements to the adopted OECD guidelines, and therefore considered to provide complementary information only. A tentative LOAEL of 5 mg/kg bw/d is debatable in the framework of a quantitative RA, in the view of the uncertainty of the test protocol used by the authors.	(EFSA, 2018)[8]. • Additionally, considering the difference between the agreed toxicological reference values (0.005 and 0.0025 mg/kg bw (per day)) and the dose levels at which potential effects were observed in these literature studies (min 5 mg/kg bw per day), there is currently no need to change the conclusions of the risk assessment for cypermethrin.
3	Paragraph 49, in (2) Lack of knowledge of the scientific criteria for the determination of endocrine disrupting properties laid down in Regulation (EU) 2018/605.	49. As regards the endocrine disrupting properties of the substance, the scientific literature contains numerous articles indicating that cypermethrin is an endocrine disruptor. For example, in 2009, Wang et al.[9] highlighted that exposure of breastfeeding mice to cypermethrin has a negative impact on the development of the sexual organs of its offspring. Similarly, in 2012, Sangha et al.[10] highlighted the influence of rat	**Wang** *et al.*, Maternal Cypermethrin Exposure During Lactation Impairs Testicular Development and spermatogenesis in Male Mouse Offspring, **2009**. • The article has been taken into account in the DRAR of Cypermethrin (Belgium, 2018; Vol 3 B.6 p.441/679). It is conceivably a publication of	**Wang 2011**: Effects in male mouse offspring at a maternal dose of 25 mg/kg bw per day included decreased tested weight (and histopathological findings), reduced testicular testosterone level at weaning (and not in adulthood). Following mating of these males with control females, no impact on reproductive parameters (fertility and gestation and foetal parameters) was observed.

[8] Please note that the applicant has been requested to provide an updated assessment as regards the ED criteria within two years after publication of the Implementing Regulation renewing the approval of cypermethrin, in line with the updated criteria and guidance (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))

[9] Wang *et al.*, Maternal Cypermethrin Exposure During lactation impairs Testicular Development and spermatogenesis in Male Mouse Offspring, 2009. **EFSA**: please note that the reference has been checked: it was accepted on 6 December 2009, published online on 3 February 2010 (wileyonlinelibrary.com; DOI 10.1002/tox.20566), with the final publication in Environ Toxicol 26: 382–394, 2011.

[10] Sangha *et al.*, Cypermethrin induced Pathological and biochemical changes in reproductive organs of female rats, 2012. **EFSA:** please note that the reference has been checked: it was accepted on 26 May 2012, with the final publication in Journal of Environmental Biology, Vol. 34, 99-105, January 2013.

		exposure to this pesticide on their genital organs. There are many other scientific publications and EFSA and the European Commission seem to have ignored them. These publications should, in addition to the information obtained from the regulatory studies, have led the Commission not to re-approve cypermethrin to protect human health.	2011 and not of 2009. **Sangha** *et al.*, Cypermethrin induced pathological and biochemical changes in reproductive organs of female rats, **2012**. • The article has been cited in the DRAR of Cypermethrin. It is not discussed at length, because this study was performed to investigate the subacute effects of the formulation cypermethrin (25EC) in female rats, and not of the active substance itself. However, the study was fully evaluated in the alpha-cypermethrin dossier (Assessment Report p.144/1013), also evaluated at the same time by RMS BE. We are thus aware of the publication overall, and it was concluded that, since the active substance was administered as a 25% emulsifiable concentrate, it is impossible to attribute the findings to the substance in the first place, as many aromatic solvents may severely interfere with the observations. In valid GLP 28d and 90d studies, no adverse findings on female gonads	**Sangha 2013**: As the contribution of the different co-formulants to the toxicity of the active substance itself cannot be distinguished in this study, the results cannot be relied upon and cannot overrule the valid short term studies performed with cypermethrin (where no adverse effect on female gonads was observed). See also overall conclusion under point No.2 above.

			were reported.	